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Effect of Early Tracheostomy in Mechanically Ventilated Patients

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Objective: To investigate the effect of the timing of tracheostomy in patients who required prolonged mechanical ventilation using two methods: analysis of early versus late tracheostomy and landmark analysis.

Study Design: Retrospective cohort study.

Methods: Patients who were emergently intubated and admitted into the intensive care unit or high dependency unit between January 2011 and August 2016, with or without tracheostomy, were included. In the early and late tracheostomy analysis, all patients were divided into early (≤10 days, n = 88) and late (>10 days, n = 132) groups. In the landmark analysis, 198 patients requiring ventilation for more than 10 days were divided into early tracheostomy (≤10 days, n = 57) and nonearly tracheostomy (>10 days, n = 141) groups. We compared 60-day ventilation withdrawal rate and 60-day mortality.

Results: Early tracheostomy was a significant factor for early ventilation withdrawal, as shown by log-rank test results (early and late tracheostomy: $P = .001$, landmark: $P = .021$). Multivariable analysis showed that the early group was also associated with a higher chance of ventilation withdrawal in each analysis (early and late tracheostomy: adjusted hazard ratio [aHR] = 1.69, 95% confidence interval [CI] = 1.20–2.39, $P = .003$; landmark: aHR = 1.61, 95% CI = 1.06–2.38, $P = .027$). Early tracheostomy, however, was not associated with improved 60-day mortality (early and late tracheostomy: aHR = 0.88, 95% CI = 0.46–1.69, $P = .71$; landmark: aHR = 1.46; 95% CI = 0.58–3.66; $P = .42$).

Conclusion: For patients requiring ventilation, performing tracheostomy within 10 days of admission was independently associated with shortened duration of mechanical ventilation; 60-day mortality was not associated with the timing of tracheostomy.

Key Words: Early tracheostomy, mechanical ventilation, withdrawal, landmark analysis.

Level of Evidence: 2b

INTRODUCTION

Tracheostomy is a well-established procedure for critically ill patients requiring prolonged mechanical ventilation. This procedure is invasive and carries some risk; however, it also has advantages, including decreased tube dead space and breathing effort compared with endotracheal intubation. Clinicians are required to consider the risk-benefit profile for each patient; however, the ideal timing for performing tracheostomy remains unclear. In 1989, the National Association of Medical Directors of Respiratory Care recommended, based on expert opinion alone, that translaryngeal intubation should be reserved for patients requiring <10 days of mechanical ventilation. Furthermore, they recommended that tracheostomy should be performed in patients requiring intubation beyond 21 days.[1] However, to date, there is no recommendation or guideline that has been based on objective evidence.

Recently, the potential advantage of early tracheostomy has attracted considerable attention; several retrospective and prospective studies have suggested a clinical benefit of early tracheostomy on patients requiring prolonged mechanical ventilation.[2–11] However, the design of these trials is insufficient to investigate the effect of early tracheostomy. For example, in retrospective studies, it is difficult to match patients because there are no consistent indication criteria for tracheostomy.

The timing of tracheostomy is affected by various factors, including illness severity, clinical physician preference, patient and family requests, and hospital resources. For example, in patients with a favorable prognosis, clinicians might be more likely to perform early tracheostomy, causing selection bias. Furthermore, as tracheostomy timing is variable, one must consider immortal time bias: patients undergoing tracheostomy must be alive before the surgery is performed. Therefore, the time-to-event for patients undergoing late tracheostomy is necessarily longer than that for patients undergoing early tracheostomy, even if the timing does not affect the event. In addition, patients undergoing late tracheostomy appear to have a longer duration of ventilation dependence. Randomized prospective trials could eliminate the risk of such selection and immortal time biases; however, no criteria or tools are currently available to predict accurately upon admission which of the patients might require prolonged ventilation support, and there is

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a risk of over-treatment with tracheostomy. Such criteria are crucial for safe prospective trials of early tracheostomy; therefore, they are recommended targets for future research.

Evidence-based guidance for tracheostomy timing is long overdue; however, establishing this evidence remains difficult. To address this, we have constructed a double-analysis approach: first, we compared patients undergoing early and late tracheostomy; and second, we performed a landmark analysis using a tertiary referral center cohort of ventilation-dependent critically ill patients. In the tracheostomy analysis, we divided the patients into early (≤10 days) and late (>10 days) tracheostomy groups, and compared the duration of ventilation dependence from time of tracheostomy to withdrawal or death. The landmark analysis included ventilated patients who had not undergone tracheostomy, and we evaluated the effect of early tracheostomy on patients with prolonged mechanical ventilation use (>10 days). Our objective was to determine the benefits of early tracheostomy using these methods.

METHODS

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Teine-Keijinkai Hospital, Sapporo, Japan.

Patient Selection

Between January 2011 and August 2016, the following patients were included in the study: 1) Tracheostomy group: patients emergently intubated in the emergency room (ER) and admitted to an intensive care unit (ICU) or high dependency unit (HDU) who subsequently underwent tracheostomy; and 2) Nontracheostomy group: patients emergently intubated in the ER who were admitted to ICU/HDU without tracheostomy.

TRACHEOSTOMY GROUP. All medical records of the 337 patients who were intubated in the ER because of emergent respiratory distress, and admitted to ICU/HDU and underwent tracheostomy due to prolonged mechanical ventilation, were reviewed retrospectively. The exclusion criteria were as follows: age <20 years, ventilation withdrawal before undergoing tracheostomy, tracheostomy due to control of suctioning, and upper airway obstruction (deep neck infection, neck trauma, or difficulty with laryngeal intubation). After application of the above exclusion criteria, the remaining 220 patients were reviewed retrospectively.

NONTRACHEOSTOMY GROUP. A total of 946 patients were identified who had been intubated in the ER because of emergent respiratory distress, admitted to ICU/HDU, and were withdrawn from ventilation or died without undergoing tracheostomy. The exclusion criteria were as follows: death within 24 hours of intubation; age <20 years; and intubation due to upper airway obstruction or for other investigations, such as bronchoscopy. After application of the exclusion criteria, 563 patients remained. Of these, 110 were chosen at random using a computer algorithm and reviewed retrospectively. A group size of 110 was chosen for the control group because it was half the size of the tracheostomy group, which is suitable for statistical analysis.

Study Analysis

This study consisted of two separate analyses: an early and late tracheostomy analysis and a landmark analysis. We selected patients for each analysis from the tracheostomy and nontracheostomy groups. Study enrollment is detailed in Figure 1.

In the early and late tracheostomy analysis, all the patients in the tracheostomy group were assigned to the early (tracheostomy performed ≤10 days after admission) or late (>10 days after admission) groups, and we compared the outcomes between the groups. However, using this analysis, we were not able to evaluate the patients who required ventilation for a long duration because there was a considerable difference in the median (95% confidence interval [CI]) day of ventilation withdrawal or death from intubation of the patients in our cohort undergoing early (median = 7 days; range = 2–18 days) and late (median = 14 days; range = 5—32 days) tracheostomy. Furthermore, to evaluate effectiveness of the tracheostomy, it was important to include patients who were withdrawn from ventilation without tracheostomy (nontracheostomy group) in our analysis. The nontracheostomy group also showed early ventilation withdrawal or death (median = 3 days; range = 2–7 days).

To avoid any selection bias due to a higher chance of ventilation withdrawal or death among the early tracheostomy and nontracheostomy groups compared with late tracheostomy group (which had a longer time-to-outcome, which is a type of immortal time bias), we performed a landmark analysis by excluding patients in the tracheostomy and nontracheostomy groups who died or were withdrawn from ventilation before the landmark, which was set at day 10 from endotracheal intubation. This type of analysis was introduced by Anderson et al. to match the conditions within each group.[12,13] In this analysis, patients who underwent tracheostomy within 10 days of admission were categorized into the early-tracheostomy (ET) group, while patients who underwent tracheostomy more than 10 days after admission (from the tracheostomy group), or were withdrawn from ventilation or died after 10 days without tracheostomy (from the nontracheostomy group) were categorized into non-ET group.

We used day 10 as the landmark point and for defining early tracheostomy for the following reasons: previous trials[14,15] have defined early tracheostomy as that performed within 7, 10, or 14 days of admission; the median duration from intubation to tracheostomy in our study was 12 days, and we sought to investigate the effect of tracheostomy at days earlier than our current average.

There are currently no set criteria for the timing of tracheostomy; however, the attending physician evaluated whether patients could be weaned from ventilation daily, and tracheostomy was considered via clinical evaluation. Written informed consent for tracheostomy was obtained from the patients or their family. Open tracheostomy was

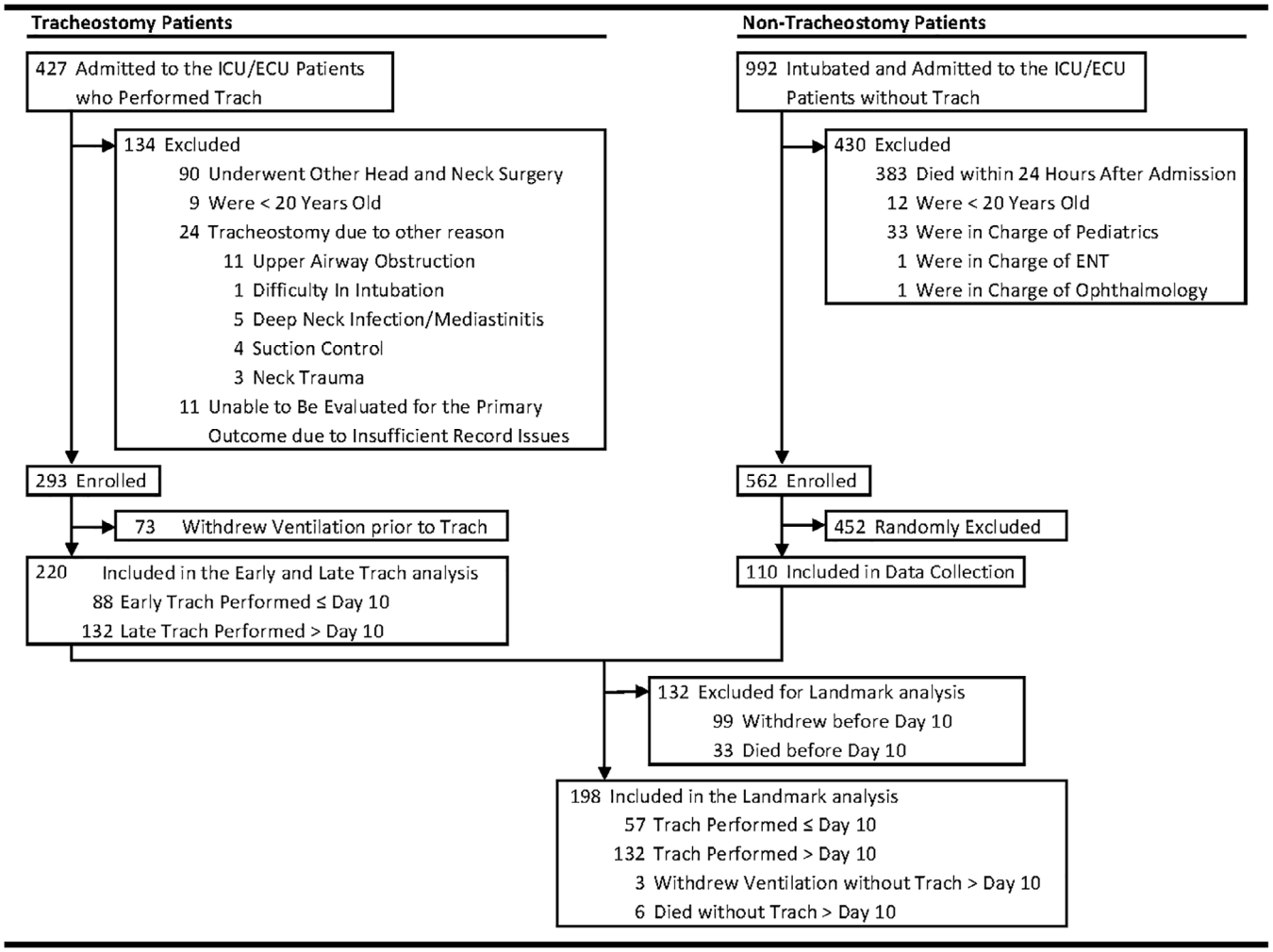

Fig. 1. Flowchart of enrolling patients in the study cohort.

the most common procedure, but percutaneous dilatational tracheostomy was also performed in selected patients.

Variables

We collected the following data from the patients: demographic and clinical data; number of ventilation-dependent days; time to tracheostomy (if performed); number of days with use of intravenous medication, such as opioid analgesics, sedatives, or antibiotics; total ICU/HDU and overall hospital stay; Acute Physiology and Chronic Health Evaluation[16] (APACHE II) score in the first 24 hours of ICU/HDU admission, which estimates severity of disease and risk of death; and Charlson Comorbidity Index[17] (CCI) score, which estimates the risk of death due to a selection of comorbid conditions.

Outcome Measures

The primary outcome was mechanical ventilation withdrawal by day 60. Ventilation withdrawal was defined as maintaining spontaneous breathing for at least 2 days. Day 60 was chosen because of a high withdrawal rate by 60 days from intubation, and effectiveness of tracheostomy timing was not thought to be associated with the cases requiring mechanical ventilation for more than 60 days. The secondary outcome was 60-day survival. In both analyses, we evaluated the primary and secondary outcomes.

Statistical Analysis

Time-to-event data of primary and secondary outcomes were estimated using the Kaplan-Meier method, and group comparisons were performed using a log-rank test. In the early and late tracheostomy analysis, the outcomes were not measured as time postintubation, but as time post-tracheostomy.

In the landmark analysis, the outcomes were measured as time postintubation because the timing of tracheostomy did not interfere with duration of events. For the primary outcome (60-day ventilation withdrawal) measurement, the patients who were lost to follow-up or died within 60 days were censored at the date of last follow-up. For the secondary outcome (60-day survival), only the patients who were lost to follow-up were censored at the date of last follow-up. The patients who were withdrawn from mechanical ventilation or died after 60 days were also censored at day 60.

TABLE I.
Baseline Characteristics of the Patients Included in the Early and Late Tracheostomy and Landmark Analyses.

	Early and Late Trach Analysis			Landmark Analysis		
Characteristics	Early Trach (n = 88)	Late Trach (n = 132)	*P* Value	ET Group (n = 57)	Non-ET Group (n = 141)	*P* Value
Age						
Mean (SD), years	71 (16)	71 (13)	.69	71 (14)	71 (13)	.85
Sex: number (%)						
Male	62 (70)	89 (67)	.74	39 (68)	93 (66)	.87
Female	26 (30)	43 (33)		18 (32)	48 (34)	
APACHE-II score, mean (SD)	22.3 (6.7)	22.1 (7.5)	.86	21.3 (6.8)	22.0 (7.4)	.45
CCI, mean (SD)	2.0 (1.8)	2.2 (1.8)	.47	2.2 (1.7)	2.2 (1.7)	.61
Main reason for admission: number (%)						
Hypoxic encephalopathy	23 (26)	20 (15)	.06	8 (14)	20 (14)	.53
Head trauma and stroke	23 (26)	31 (23)		13 (23)	34 (24)	
Cardiovascular disease	5 (6)	28 (21)		18 (32)	32 (23)	
Respiratory disease	22 (25)	34 (26)		14 (25)	35 (25)	
Infectious disease	15 (17)	19 (14)		4 (7)	20 (14)	
Admission type*						
Medical	56 (64)	86 (65)	.93	32 (56)	94 (67)	.17
Surgical	32 (36)	46 (35)		25 (44)	47 (33)	

*Patients were assigned to the surgical group if they needed surgical procedures, except tracheostomy.
APACHE-II = acute physiology and chronic health evaluation; CCI = Charlson comorbidity index; ET = early tracheostomy; Trach = tracheostomy.

For each analysis, univariate and multivariate Cox proportional hazard regression analyses were constructed. In the multivariate analyses, the hazard ratio (HR) was adjusted for age, sex, APACHE-II score, CCI score, admission diagnosis, hypoxic encephalopathy, head trauma and stroke, cardiovascular disease, respiratory disease (infection or chronic obstructive pulmonary disease), and nonrespiratory infectious diseases.

We compared categorical parameters using Fisher's exact test, and continuous parameters using unpaired *t* test or Mann-Whitney *U* test, where appropriate. Data analysis was performed using EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). This modified version of R commander is designed to add statistical functions frequently used in biostatistics.[18] A significance level of $P < .05$ was used.

RESULTS

Baseline Patient Characteristics

In the early and late tracheostomy analysis, a total of 220 patients in the tracheostomy group were included and divided into early (≤10 days, n = 88) and late (>10 days, n = 132) tracheostomy groups.

The landmark analysis included patients requiring ventilation support for at least 10 days. Patients who were weaned off the ventilator or died before day 10 were excluded from the tracheostomy and nontracheostomy groups. We excluded 132 patients; therefore, the landmark analysis cohort included 198 patients (Fig. 1). In the landmark group, 57 and 141 patients were categorized into the ET and non-ET groups, respectively. The baseline characteristics of both groups were similar in both analyses (Table I).

60-Day Ventilation Withdrawal

In the early and late tracheostomy analysis, median ventilation-dependent time by day 60 was 9 days (95% CI = 5–13) in the early tracheostomy group, which was significantly higher than that in the late tracheostomy group (median = 20 days; 95% CI = 14–40; $P = .001$; Fig. 2a). Multivariate analysis showed that performing tracheostomy within 10 days of admission was associated with a significantly higher chance of mechanical ventilation withdrawal (adjusted hazard ratio [aHR] = 1.69; 95% CI = 1.20–2.39; $P = .003$; Table II).

In the landmark analysis, median ventilation-dependent time by day 60 was 27 days (95% CI = 20–36) in the ET group and 37 days (95% CI = 31–55) in the non-ET group, which was significantly different ($P = .021$, Fig. 2b). After adjusting for covariates, early tracheostomy within 10 days remained a significant positive factor for ventilation withdrawal (aHR = 1.61; 95% CI = 1.06–2.38; $P = .027$; Table II). In the multivariate analysis of early and late tracheostomy, the presence of respiratory disease, including pneumonia and chronic obstructive pulmonary disease, significantly increased ventilation dependence (aHR = 0.48; 95% CI = 0.27–0.85; $P = .012$); however, there was no significant difference in the landmark analysis (aHR = 0.90; 95% CI = 0.45–1.79; $P = .75$; Table II).

60-Day Survival

The Kaplan-Meier curve of 60-day survival of the early and late tracheostomy groups, and landmark analyses

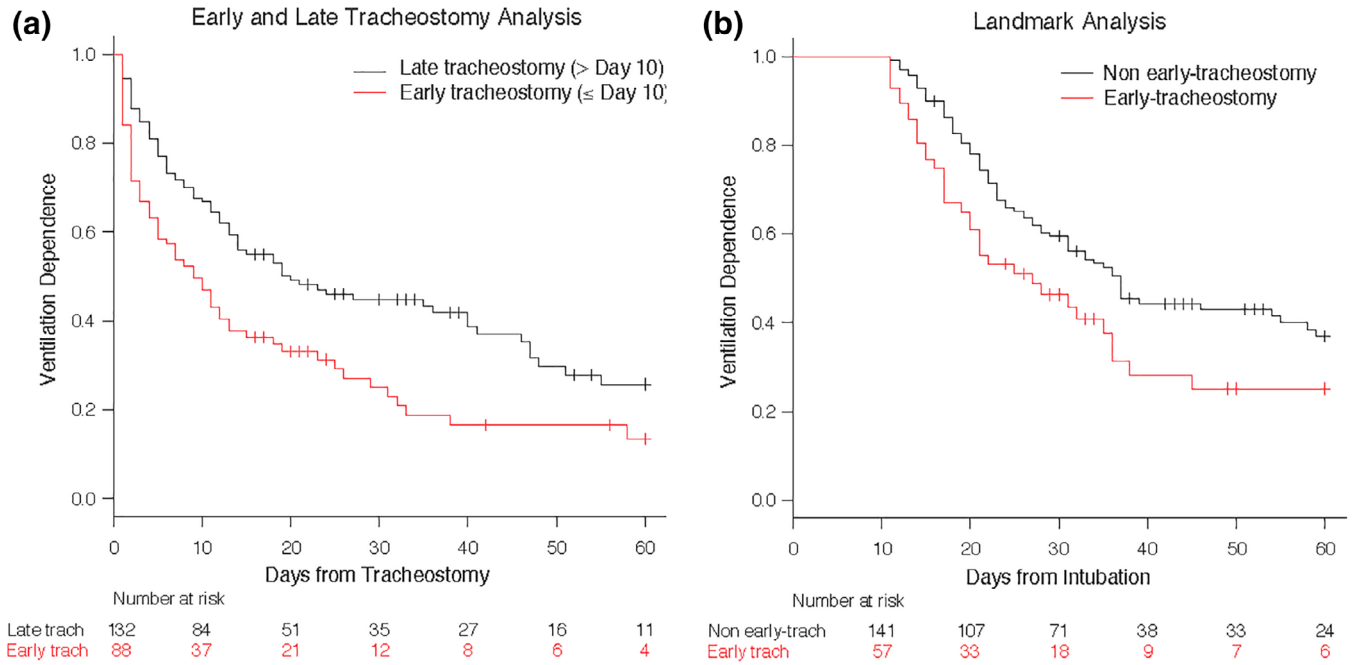

Fig. 2. Kaplan-Meier estimates of ventilation withdrawal according to timing of tracheostomy for patients in the early and late tracheostomy groups, and landmark analysis results. (a) In the early and late tracheostomy analysis, median ventilation-dependent time by day 60 was 9 days (95% confidence interval [CI] = 5–13) in the early tracheostomy group, which was significantly higher than that in the late tracheostomy group (median = 20 days; 95% CI = 14–40; P = .001). (b) In the landmark analysis, median ventilation-dependent time by day 60 was 27 days (95% CI = 20–36) in the early-tracheostomy group, which was significantly higher than that in the nonearly tracheostomy group (median = 37 days; 95% CI = 31–55; P = .021).

showed no significant difference in mean (standard deviation) 60-day survival time (early and late tracheostomy: 39 [21.2] vs. 44 [19.1] days, P = .56; landmark: 45 [16.8] vs. 50 [14.3] days; P = .097, figures not shown). Multivariate analysis showed that performing tracheostomy within 10 days was not associated with an improvement in 60-day survival in either analysis (early and late tracheostomy: aHR = 0.88, 95% CI = 0.46–1.69, P = .71; landmark: aHR = 1.46, 95% CI = 0.58–3.66; P = .42; Table III).

Other Clinical Outcomes

In the early and late tracheostomy analysis, the early tracheostomy group had significantly shorter

TABLE II.
Univariate and Multivariate Analyses of 60-Day Ventilation Withdrawal.

	Early and Late Trach Analysis		Landmark Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Univariate analysis				
Early trach within day 10	1.70 (1.22–2.37)	.002	1.59 (1.06–2.38)	.024
Multivariate analysis				
Early trach within day 10	1.69 (1.20–2.39)	.003	1.61 (1.06–2.46)	.027
Age	0.99 (0.98–1.00)	.086	0.99 (0.97–1.00)	.05
Sex	1.11 (0.76–1.60)	.59	0.96 (0.63–1.45)	.84
APACHE-II score	0.99 (0.97–1.02)	.64	1.00 (0.97–1.04)	.82
CCI	0.96 (0.87–1.06)	.43	0.94 (0.84–1.05)	.26
Main reason for ICU/HDU admission				
Hypoxic encephalopathy	1 (reference)	NA	1 (reference)	NA
Head trauma and stroke	0.74 (0.44–1.24)	.25	1.17 (0.60–2.30)	.65
Cardiovascular disease	0.79 (0.38–1.64)	.53	1.30 (0.55–3.09)	.55
Respiratory disease	0.48 (0.27–0.85)	.012	0.90 (0.45–1.79)	.75
Infectious disease	0.79 (0.45–1.40)	.42	1.36 (0.67–2.74)	.39

APACHE-II = acute physiology and chronic health evaluation; CCI = Charlson comorbidity index; CI = confidence interval; HDU = high dependency unit; HR = hazard ratio; ICU = intensive care unit; Trach = tracheostomy.

TABLE III.
Univariate and Multivariate Analyses of 60-Day Survival.

	Early and Late Trach Analysis		Landmark Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Univariate analysis				
Early trach within day 10	0.83 (0.45–1.55)	.56	0.89 (0.45–1.73)	.71
Multivariate analysis				
Early trach within day 10	0.88 (0.46–1.69)	.71	0.88 (0.44–1.76)	.72
Age	1.03 (1.00–1.06)	.047	1.03 (1.00–1.05)	.056
Sex	0.98 (0.52–1.87)	.96	0.88 (0.47–1.64)	.69
APACHE-II score	0.98 (0.94–1.03)	.50	0.98 (0.94–1.02)	.38
CCI	1.09 (0.95–1.26)	.22	1.15 (1.00–1.32)	.043
Main reason for ICU/HDU admission				
Hypoxic encephalopathy	1 (reference)	NA	1 (reference)	NA
Head trauma and stroke	0.41 (0.11–1.50)	.18	0.43 (0.10–1.76)	.24
Cardiovascular disease	1.30 (0.37–4.54)	.68	1.31 (0.35–4.96)	.69
Respiratory disease	1.27 (0.45–3.60)	.65	1.35 (0.42–4.34)	.62
Infectious disease	1.77 (0.65–4.84)	.27	1.58 (0.50–5.01)	.44

APACHE-II = acute physiology and chronic health evaluation; CCI = Charlson comorbidity index; CI = confidence interval; HDU = high dependency unit; HR = hazard ratio; ICU = intensive care unit; Trach = tracheostomy.

ICU/HDU and overall hospital admission durations, and less medication use than the late tracheostomy group (Table IV).

In the landmark analysis, the ET group tended to have better clinical outcomes, such as shorter hospital admission duration, and less antibiotic use than the non-ET group; however, these differences did not reach statistical significance. Patients in the ET group tended to have fewer complications. No deaths were directly attributed to complications arising from tracheostomy.

DISCUSSION

Several previous trials have evaluated the clinical effect of early tracheostomy; however, the best timing for tracheostomy in patients requiring prolonged ventilation remains to be elucidated. Our analyses revealed that early tracheostomy within 10 days significantly decreased the degree of ventilation dependence at 60 days; however, it did not improve 60-day survival. Our findings are consistent with previous reports. Furthermore, we argue that our analysis is less susceptible to bias, and therefore, makes a significant contribution to the literature.

Prospective trials are hindered by uncertainty regarding inclusion criteria and lack of guidelines. In the TracMan prospective trial, almost half of the patients assigned to the late tracheostomy (≥10 days) group were withdrawn from ventilation without tracheostomy.[15] Based on this result, if the groups were comparable, tracheostomy could have been avoided for half of the patients undergoing early tracheostomy (≤4 days). Similarly, a meta-analysis of 12 randomized controlled trials (RCTs) showed a much higher tracheostomy rate in patients undergoing early tracheostomy (87% vs. 53%).[19] In these trials, the patients may have been excessively treated and exposed to the complications related to this surgery. Although our study reported no life-threatening complications of tracheostomy, avoiding unnecessary treatment is important in clinical practice.

Our approach is unique in that it uses two complementary analyses to reduce selection and immortal-time biases. In the early and late tracheostomy analysis, we defined the time-to-event as the time from tracheostomy to the event, which reduced immortal-time bias. However, this analysis did not include patients who did not undergo tracheostomy. To assess this, we sought to compare the clinical outcomes among patients who were intubated with or without tracheostomy. Therefore, we added the landmark analysis. Comparing outcomes between tracheostomy and nontracheostomy groups can introduce selection bias for different factors from each group; therefore, we included only the patients who required ventilation until the landmark of day 10. Patients who were successfully extubated or died soon after early tracheostomy were excluded. This reduced any biases caused by the time-dependent variable: the timing of tracheostomy. To the best of our knowledge, this is the first report to apply landmark analysis to investigate the effect of early tracheostomy. Furthermore, the primary outcome of early tracheostomy was consistent in both analyses.

In our analysis, early tracheostomy did not improve 60-day survival, which is consistent with the findings of two RCTs and a meta-analysis.[7,20,21] In contrast, another RCT and two meta-analyses have shown a mortality benefit with early tracheostomy.[6,14,19] Thus, the association between early tracheostomy and improved survival remains controversial.

In the early and late analysis performed in the present study, early tracheostomy was significantly associated with shorter ICU/HDU and overall hospital stays, and reduced medication use. We expected that early

TABLE IV.
Clinical Outcomes of the Early and Late Tracheostomy and Landmark Analyses.

Variable	Early and Late Trach Analysis			Landmark Analysis		
	Early Trach (n = 88)	Late Trach (n = 132)	*P* Value	ET Group (n = 57)	Non-ET Group (n = 141)	*P* Value
Duration of trach, days, median (IQR)	7 (5–8)	15 (13–17)		7 (6–9)	15 (13–19)	
Procedure						
Open trach: number (%)	80 (91)	128 (97)	.10	54 (95)	128 (91)	.068
PDT: number (%)	8 (9)	4 (3)		3 (5)	4 (3)	
VAP: number (%)[†]	11 (13)	23 (17)	.36*	6 (11)	23 (16)	.32*
ICU/HDU length of stay, days, median (95% CI)	13 (11–16)	20 (17–23)	.01*	15 (12–19)	19 (17–21)	.31*
Hospital length of stay, days, median (95% CI)	49 (42–58)	70 (62–78)	.002*	58 (46–63)	70 (62–78)	.07*
ICU/HDU mortality: number (%)	6 (7)	15 (11)	.84*	4 (7)	17 (12)	.43*
Hospital mortality: number (%)	16 (18)	36 (27)	.74*	12 (21)	42 (30)	.67*
Transferred to other hospital: number (%)	66 (75)	85 (65)	.13	40 (70)	88 (62)	.38
Discharged to home: number (%)	6 (7)	11 (8)	.88	5 (9)	11 (8)	1
Days free of medication, 60-day, median (95% CI)						
Sedatives[‡]	53 (52–55)	45 (44–47)	<.00001*	52 (50–53)	45 (44–47)	.21
Opioids[‖]	56 (54–58)	51 (48–54)	.008*	54 (53–55)	51 (48–54)	.37
Antibiotics[§]	47 (45–49)	41 (39–44)	.009*	49 (43–NA)	44 (40–48)	.068
All complications with trach: number (%)	7 (8)	22 (11)	.13	7 (12)	24 (17)	.80
Early complications with trach: number (%)	4 (4)	15 (11)	.18	4 (7)	17 (10)	.61
Infection	3 (3)	3 (2)		3 (5)	3 (2)	
Minor necrosis	0	5 (4)		0	5 (4)	
Minor bleeding	0	4 (3)		0	3 (2)	
Major bleeding	1 (1)	3 (2)		1 (2)	3 (2)	
Late complications with trach: number (%)	3 (3)	7 (6)	.74	3 (5)	7 (5)	1
Granulation tissue	1 (1)	5 (4)		1 (2)	5 (4)	
Ulceration	2 (2)	2 (2)		2 (3)	2 (1)	

**P* value was calculated using Kaplan-Meier curve and log-rank methods.
[†]VAP was diagnosed clinically, not based on VAP criteria.
[‡]Sedative medication included propofol, midazolam, and dexmedetomidine.
[§]Opioid medication included fentanyl and ketamine.
[‖]Included antibiotics used for main disease.
CI = confidence interval; ET = early tracheostomy; HDU = high dependency unit; ICU = intensive care unit; IQR = interquartile range; PDT = percutaneous dilational tracheostomy; Trach = tracheostomy; VAP = ventilation associated pneumonia.

tracheostomy would be associated with these outcomes in the landmark analysis also; however, the results were not statistically significant. We hypothesize that the non-ET patients in the landmark analysis who were ventilated for a longer period required intensive care and medication unrelated to early tracheostomy intervention. This suggests that the clinical benefits of early tracheostomy could not be demonstrated in the landmark analysis. Furthermore, in both analyses, the ET group tended to have fewer complications than late tracheostomy or the non-ET group; however, these differences did not reach statistical significance. These outcomes might contribute to improvements in cost-effectiveness and quality of life. Further studies with validated outcome measures for cost-effectiveness, quality of life, and tracheostomy complications would be useful to evaluate the potential benefits of early tracheostomy.

Our findings demonstrated the effectiveness of early tracheostomy for critically ill patients who required prolonged ventilation. However, a tool to prospectively predict the need for prolonged ventilation is yet to be developed. In the present study, 28 of the 88 patients who underwent early tracheostomy were withdrawn from ventilation within 10 days of intubation. We hypothesize that the effectiveness of early tracheostomy in these patients may be limited. To avoid unnecessary early tracheostomy, it is crucial to analyze the indicators for predicting longer ventilation requirements at the time of endotracheal intubation. By applying such tools prospectively, the effect of early tracheostomy might be assessed more accurately.

Our study has several limitations. First, we did not adjust the tracheostomy timing HR for variables such as level of consciousness; ventilator status, such as ventilator settings; and PaO_2/FiO_2 ratio in our multivariable analysis. We adjusted for APACHE-II score in our multivariable analysis, which contained PaO_2 and Glasgow Coma Scale parameters; however, we may have underestimated the contribution of these or other variables. Second, the retrospective nature of this study may have led to selection bias. We performed the landmark analysis to avoid immortal-time bias; however, the analysis itself is limited because patients were excluded to correct for

bias associated with the timing of tracheostomy. However, it is noteworthy that both analyses showed the effectiveness of early tracheostomy for critically ill patients. Third, the timing of tracheostomy was affected by hospital resources, including availability of otorhinolaryngology staff and anesthesiologists. Finally, this was a single-center study; therefore, careful interpretation is required for clinical application.

CONCLUSION

We performed an early and late tracheostomy analysis, and a landmark analysis to avoid selection and immortal-time bias, and to assess the effectiveness of tracheostomy in critically ill patients. Early tracheostomy performed within 10 days of admission was significantly associated with an earlier ventilation withdrawal of patients in both analyses. Further studies are needed to predict which patients require prolonged ventilation support, and to investigate the clinical benefits of early tracheostomy.

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