

ORIGINAL ARTICLE

Early versus Late Percutaneous Tracheostomy in Ventilated Stroke Patients in Indonesia: Pneumonia, Ventilator Liberation and Mortality in a Retrospective Cohort

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ARTICLE INFO

Article history

Received: August 20, 2025
Revised: September 18, 2025
Accepted: October 18, 2025
Available online: October 25, 2025
Published: October 29, 2025

Keywords

Intensive Care Units
Pneumonia, Ventilator-Associated
Respiration, Artificial
Stroke
Tracheostomy

DOI

<https://doi.org/10.37275/jacr.v6i2.988>

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ABSTRACT

Background: The timing of percutaneous dilatational tracheostomy (PDT) in ventilated stroke patients is debated, and observational comparisons are prone to guarantee-time bias.

Objective: To compare outcomes after early (≤ 7 days from intubation) and late (> 7 days) PDT, reporting only effects the data can identify.

Methods: Retrospective cohort of all 70 adults with acute stroke ventilated for more than 48 h who underwent bedside PDT at a tertiary hospital in Malang, Indonesia, in 2024 (early $n=34$; late $n=36$). Group-level counts were analyzed with exact tests; because only group-level data were available, covariate adjustment was replaced by bounds analyses across all datasets compatible with the observed margins.

Results: Ventilator-associated pneumonia (VAP) occurred in 20.6% after early and 44.4% after late PDT (risk difference -23.9 percentage points, 95% CI -42.8 to -1.8 ; Fisher $p=0.043$; exact odds ratio 95% CI $0.10-1.04$); the fragility index was 1 and Holm-adjusted $p=0.217$. Liberation by discharge (50.0% vs 41.7%; $p=0.632$) and in-hospital death (50.0% vs 58.3%; $p=0.632$) did not differ, and procedural complications were rare. Cumulative liberation equaled survival in both groups, and time-to-liberation effects were not identifiable because exposure was defined by the day of the procedure.

Conclusion: Early PDT was associated with less VAP but not with liberation or survival; the VAP association is fragile and may reflect reverse causation. Patient-level timing data are needed before early PDT is recommended for respiratory benefit.

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1. Introduction

Stroke caused 7.3 million deaths in 2021 and remains the third leading cause of death worldwide, and age-standardized incidence, mortality and disability rates have risen in Southeast Asia, where intracerebral hemorrhage makes up a larger share of strokes than in high-income regions.¹ The World Stroke Organization–Lancet Neurology Commission projected a substantial increase in global stroke burden through 2050,² and national analyses from the region report incidence well above the global average.³ Between 4% and 10% of patients hospitalized with stroke receive invasive mechanical ventilation,^{4,5} and their prognosis is poor: in a prospective French cohort, two-thirds of ventilated stroke patients were dead or severely disabled at one year.⁶ For the survivors of the first days, a tracheostomy is frequently the bridge to weaning.

Tracheostomy is thought to help ventilated neurological patients in several ways. It allows lighter sedation and earlier neurological examination, easier suctioning of secretions, a lower resistive load, earlier mobilization and shorter exposure to a translaryngeal tube. Sedative and analgesic use falls within a day of tracheostomy,⁷ coma and delirium days decline afterwards,⁸ and deeper sedation is independently associated with delayed and failed weaning

across 50 countries.⁹ In brain-injured patients, one in five extubation attempts fails and one in five patients receives a tracheostomy without an extubation attempt,¹⁰ and ventilator-associated pneumonia (VAP) develops in about 40% of those ventilated for 48 h or longer.¹¹ Whether bringing the procedure forward converts these mechanisms into better outcomes is a separate question.

The randomized evidence answers that question only in part. In SETPOINT2, tracheostomy within 5 days of intubation did not improve 6-month functional outcome in 382 patients with severe stroke compared with a standard approach from day 10, and one-third of the standard-care group never needed a tracheostomy.¹² Meta-analyses restricted to stroke found no association between timing and mortality,¹³ although tracheostomy within 7 days was associated with shorter ventilation, shorter intensive care unit (ICU) stay and less VAP.¹⁴ Across mixed ICU populations, a Bayesian synthesis of 19 trials gave a 94% probability that early tracheostomy reduces VAP but only a 51% probability of a modest benefit.¹⁵ Observational studies, which make up most of the stroke literature, define exposure by the day of a procedure that only patients who are still alive and ventilated can receive. This creates guarantee-time bias, a form of immortal-time bias in which one group is guaranteed survival and continued ventilation for part of follow-up; when exposures of this kind were

remodeled as time-varying, apparent benefits disappeared.^{16,17}

Evidence from Indonesia is scarce. Stroke services require a larger and more equitably distributed specialist workforce,¹⁸ critical care bed density in lower-middle-income Asian economies is a fraction of that in high-income systems,^{19,20} and an Indonesian surgical intracerebral hemorrhage cohort reported in-hospital mortality of 31.2%.²¹ Indonesian VAP cohorts also report high mortality and multidrug resistance.²² Bed occupancy, sedation practice and infection-prevention resources differ from those of the trial settings, so the balance between the benefits and costs of early tracheostomy may also differ. The applicability of international timing evidence to Indonesian ventilated stroke patients remains uncertain.

The aim of this study was to compare VAP, ventilator liberation, mortality, length of stay and procedural complications after early versus late PDT in critically ill stroke patients at a tertiary hospital in Malang, Indonesia, using only analyses that the available data can support, and to state explicitly which effects remain unidentified.

2. Methods

2.1. Study design and reporting

This was a retrospective, single-center cohort study reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

2.2. Ethical approval

The study protocol was approved by the CMHC Research Center Ethics Committee, Indonesia (Approval No. 2024/8243) in 2024, before data extraction. Because only anonymized data from routine medical records were used, the requirement for individual informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

2.3. Setting

The study was conducted in the ICU of a tertiary referral and teaching hospital in Malang, East Java, Indonesia, which admits adults with ischemic and hemorrhagic stroke from the hospital's emergency department, stroke service and regional referral network. All PDTs were performed at the bedside in the ICU by a trained intensivist or anesthesiologist using the single-step dilatational technique (Ciaglia Blue Rhino®, Cook Medical), frequently with bronchoscopic guidance; the proportion of procedures performed with bronchoscopic guidance in each group was not recorded.

2.4. Participants

All adults (≥18 years) admitted to the ICU between 1 January and 31 December 2024 with a primary diagnosis of acute ischemic or hemorrhagic stroke who required invasive mechanical ventilation for more than 48 h and subsequently underwent PDT were eligible. Patients were excluded if they had a tracheostomy before ICU admission, underwent surgical tracheostomy, had incomplete data on key baseline or outcome variables, or had a pre-existing condition independently mandating tracheostomy, such as advanced neuromuscular disease or an unstable cervical spine injury. The number of ventilated stroke patients screened, the number excluded for each reason and the

number of ventilated stroke patients who never received a tracheostomy were not available for this analysis.

2.5. Exposure

Patients were classified by the interval between initial endotracheal intubation and PDT as early PDT (≤7 days, ≤168 h) or late PDT (>7 days, >168 h), the cut-off used in stroke-specific meta-analyses and published cohorts.^{14,23} The timing of the procedure was chosen by the treating clinicians; the reasons for the choice and the exact procedure day of each patient were not available for analysis.

2.6. Variables and outcome definitions

Baseline variables were age, sex, stroke type (ischemic or hemorrhagic), hypertension, diabetes mellitus and heart failure. Neurological severity at admission was recorded with the Glasgow Coma Scale (GCS; 3–15, lower scores indicating deeper impairment of consciousness) and the National Institutes of Health Stroke Scale (NIHSS; 0–42, higher scores indicating more severe deficit), both documented by trained neurology residents or attending neurologists as part of the standard admission protocol.

Ventilator liberation was defined as discontinuation of invasive mechanical ventilation for at least 48 consecutive hours, and in-hospital death before liberation was regarded as a competing event. Secondary outcomes were ICU and hospital length of stay, ICU and in-hospital death, VAP and procedure-related complications. VAP was diagnosed clinically as a new or progressive infiltrate on chest radiography together with at least two of fever above 38 °C, leukocytosis or leukopenia, and purulent tracheal secretions; tracheal aspirate cultures guided treatment but were not required for the diagnosis. Procedure-related complications were major bleeding, significant desaturation and loss of the airway during or immediately after PDT, as recorded by the treating team. Data were extracted from the medical records with a standardized form. Follow-up for all outcomes ended at hospital discharge or in-hospital death.

2.7. Missing data

Patients with incomplete data on key baseline or outcome variables were excluded at the eligibility stage, so the analyzed cohort had no missing values for the variables reported. Because the number of patients excluded for this reason is unknown, the potential for selection bias cannot be quantified; if exclusion for incomplete records was more frequent among patients with long or complicated ICU stays, it would preferentially remove late-PDT patients with adverse outcomes, make the late group appear healthier than it was and bias the comparisons against early PDT.

2.8. Sources of bias

Two biases are inherent in this design. First, confounding by indication: the decision to perform an early tracheostomy may reflect the clinicians' expectation of prolonged ventilation or of recovery, and patients whose earlier extubation attempts failed are more likely to reach a late tracheostomy. Second, guarantee-time bias: to be classified as late PDT, a patient had to remain alive and ventilated for more than 7 days, a period during which liberation was impossible by definition. Measuring time to liberation from ICU admission therefore adds guaranteed ventilator time to the late group, and measuring it from the procedure discards the late group's pre-procedure

ventilator days. Both favor early PDT irrespective of any causal effect.^{16,17,24} Only a common time-zero at intubation with a landmark design or a clone-censor-weight emulation of a target trial can remove this bias,²⁵ and both require patient-level dates.

2.9. Study size

The study included every eligible patient treated during the 12-month period; no sample size was calculated in advance. Precision is reported for every estimate, and the sample sizes that future studies would need were calculated from the observed proportions and from effect sizes in the literature.

2.10. Statistical analysis

Patient-level linked records were not available for this analysis. All analyses therefore used the group-level counts, medians and interquartile ranges (IQRs) of the cohort, and no patient-level value was imputed or simulated. Analyses were organized in four layers, distinguishing quantities that the data identify from those they do not.

Univariate and bivariate layer. Proportions were reported with 95% Wilson score confidence intervals (CIs). Early and late PDT were compared with two-sided Fisher exact tests, risk differences with Newcombe hybrid score CIs, risk ratios with log-method CIs (0.5 added to zero cells) and conditional maximum-likelihood odds ratios (ORs) with exact CIs; Cohen's h was reported as the effect size. Baseline balance was expressed as standardized differences in proportions, with absolute values below 0.10 indicating negligible imbalance. The family for multiplicity adjustment comprised the five testable secondary binary outcomes (VAP, ICU death, in-hospital death, major bleeding and significant desaturation); loss of airway, with no events, was not testable. P values in this family were adjusted with the Holm procedure. For the only nominally significant contrast, VAP, robustness was examined with alternative tests (Pearson χ^2 , Yates-corrected χ^2 , Fisher mid- p , and Barnard and Boschloo unconditional exact tests computed with SciPy defaults), the fragility index, a two-way misclassification tipping-point analysis, the number needed to treat and the E -value for unmeasured confounding.^{26,27} Because the VAP diagnosis was clinical and unblinded, a probabilistic bias analysis corrected the observed counts for outcome misclassification over 100,000 draws, combining binomial resampling of the counts with sensitivity drawn uniformly from 0.70–0.95 and specificity from 0.85–0.98 (non-differential scenario), and with sensitivity of 0.60–0.80 in the early and 0.85–0.98 in the late group (differential scenario reflecting more intensive surveillance during longer translaryngeal intubation). Reverse causation was examined by excluding from the late group increasing numbers of VAP episodes assumed to have preceded PDT.

Continuous variables. Age, GCS, NIHSS, length of stay and time from PDT to liberation were available only as medians and IQRs. Because the Mann–Whitney U statistic increases monotonically with each observation of one group and decreases with each observation of the other, its attainable range was obtained by placing every unconstrained order statistic at the boundary of its feasible interval and enumerating all integer pairs of order statistics compatible with each interpolated quartile (weighted-average definition, position $(n+1)p$). The range was expressed as the probability that an early-PDT value exceeds a late-PDT value (U/n_1n_2 , 0.50 indicating no difference). No difference

was inferred when this range contained 0.50. The analysis was repeated with the alternative quartile definition (position $1+(n-1)p$) and, for time from PDT to liberation, with denominators of both the liberated patients (17 and 15) and all patients (34 and 36).

Bounds analysis for unobserved joint distributions. The cross-classification of covariates with outcomes within each exposure group was not available. This was treated as a sensitivity analysis over the space of datasets consistent with the observed margins. For every pair of binary variables of interest (VAP and death; stroke type, diabetes and heart failure with VAP or death), all within-group 2×2 tables compatible with the margins were enumerated and pooled, and the attainable ranges of the OR, Cramér's V and risk difference, and the proportion of admissible tables with Fisher $p < 0.05$, were recorded. For covariate adjustment, 4,000 admissible datasets were generated by permuting the labels of each binary variable within each exposure group, which preserves every observed exposure-by-variable count, and Firth-penalised logistic regression of VAP and of in-hospital death on PDT timing, stroke type, sex, hypertension, diabetes and heart failure was fitted to each. To locate the extremes of the adjusted OR, directed hill-climbing (40 restarts of 400 label swaps in each direction) was supplemented by climbs of 6,000 swaps from the most favorable of 20,000 constructed starting configurations; fits with rank-deficient designs, coefficients beyond ± 10 or standard errors above 5 were discarded (random seed 20261013). Because a search cannot prove that no more extreme dataset exists, the values found are reported as the most extreme values found, a lower bound on the attainable range. The percentage of sampled datasets reaching $p < 0.05$ describes the sampled admissible space under within-group independent permutation; it is not a probability that the association is real. Age, GCS and NIHSS could not be included. An association was considered not identifiable when the range found spanned an OR of 1.

External comparison and precision. Verified trials and cohorts published no later than 2025 were used as descriptive benchmarks. Differences in population, endpoint definitions, follow-up and procedural techniques prevent these sources from serving as external control groups; no external-comparison p values or pooled effects are retained. Sample sizes for ± 10 and ± 5 percentage-point precision and for 80% and 90% power at two-sided $\alpha = 0.05$ were calculated with the arcsine approximation for binary endpoints and with the Schoenfeld formula for the cause-specific hazard of liberation.

All tests were two-sided with $\alpha = 0.05$, and p values are reported to three decimal places. Analyses were performed in Python 3.14 with SciPy 1.18 and statsmodels 0.15, and figures were drawn with Matplotlib 3.10; the code is provided in Supplementary File 2.

3. Results

3.1. Participants and baseline characteristics

Seventy patients were analyzed, 34 (48.6%) with early and 36 (51.4%) with late PDT; the flow of patients and the outcomes in each group are shown in Figure 1. All patients were followed to hospital discharge or death. Haemorrhagic stroke accounted for 42 of 70 patients (60.0%; 95% CI 48.3–70.7). Baseline characteristics are detailed in Table 1. The groups were similar in sex (male 58.8% vs 61.1%), stroke type (hemorrhagic 61.8% vs

58.3%), hypertension (73.5% vs 77.8%), diabetes mellitus (35.3% vs 38.9%) and heart failure (17.6% vs 19.4%); all standardized differences were 0.10 or less in absolute value and all Fisher p values were above 0.78. Median age was 60.5 [IQR 51–68] and 59.0 [49–67] years, median admission GCS 7 [5–9] and 7 [5–8], and median NIHSS 22 [18–28] and 24 [19–29]. Because only medians and IQRs

were available for these variables, the attainable probability that an early-PDT value exceeded a late-PDT value ranged from 0.39 to 0.79 for age, 0.34 to 0.72 for GCS and 0.21 to 0.61 for NIHSS; each range contains 0.50, so no difference in these variables can be inferred from the summary statistics.

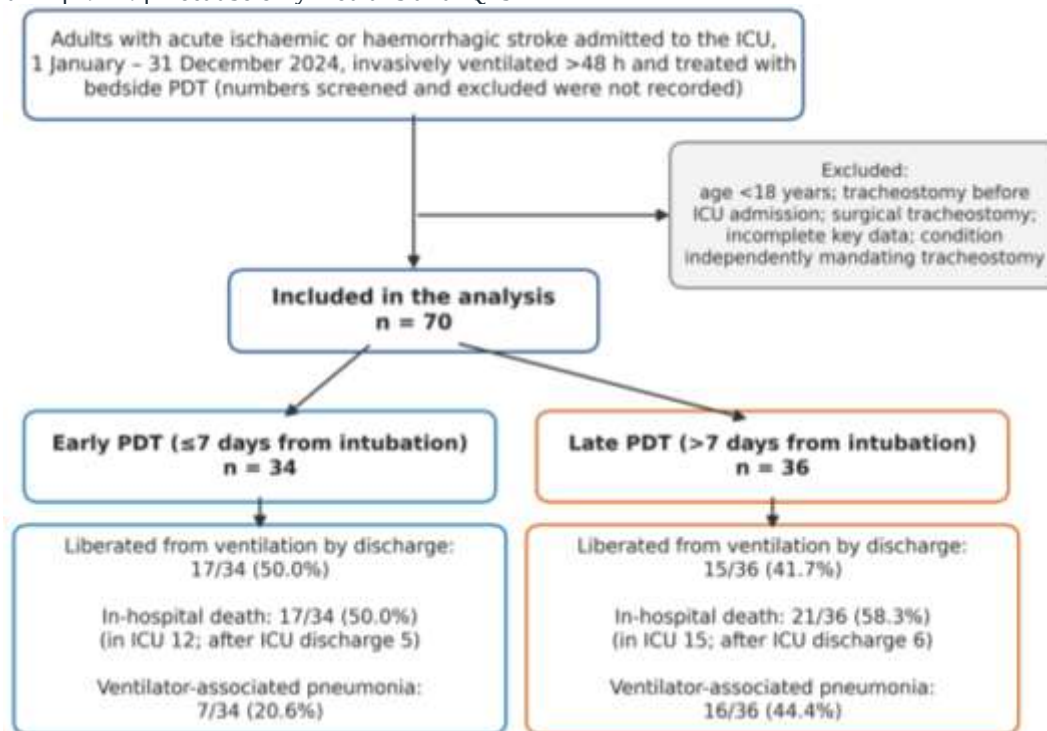


Figure 1. Study flow (STROBE). All 70 patients ventilated for more than 48 h after acute stroke who underwent bedside percutaneous dilatational tracheostomy (PDT) in 2024 were analyzed, 34 with early (≤ 7 days from intubation) and 36 with late (> 7 days) PDT; outcome counts by group are shown in the lower boxes. ICU, intensive care unit.

Table 1. Baseline characteristics of 70 ventilated stroke patients by timing of percutaneous dilatational tracheostomy.

Characteristic	Early PDT (n=34)	Late PDT (n=36)	SMD*	p
Age, years, median [IQR]	60.5 [51–68]	59.0 [49–67]	—	n/i (0.39–0.79)†
Male sex, n (%)	20 (58.8)	22 (61.1)	-0.05	1.000
GCS at admission, median [IQR]	7 [5–9]	7 [5–8]	—	n/i (0.34–0.72)†
NIHSS at admission, median [IQR]	22 [18–28]	24 [19–29]	—	n/i (0.21–0.61)†
Haemorrhagic stroke, n (%)	21 (61.8)	21 (58.3)	0.07	0.811
Ischaemic stroke, n (%)	13 (38.2)	15 (41.7)		
Hypertension, n (%)	25 (73.5)	28 (77.8)	-0.10	0.783
Diabetes mellitus, n (%)	12 (35.3)	14 (38.9)	-0.07	0.808
Heart failure, n (%)	6 (17.6)	7 (19.4)	-0.05	1.000

PDT, percutaneous dilatational tracheostomy; IQR, interquartile range; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; SMD, standardized mean difference; n/i, not identifiable from the summary statistics. *Standardised difference in proportions (early minus late); |SMD| < 0.10 indicates negligible imbalance. p values are two-sided Fisher exact tests. †Only median and IQR are available; the range shown is the attainable probability that an early-PDT value exceeds a late-PDT value across all integer datasets reproducing the observed median and quartiles (0.50 = no difference); because the range contains 0.50, no difference can be inferred.

3.2. Pneumonia, liberation, mortality and procedural complications

Outcomes by group are presented in Table 2 and Figure 2, and the corresponding risk differences in Figure 3. VAP was diagnosed in 23 of 70 patients (32.9%; 95% CI 23.0–

44.5); in 7 of 34 (20.6%; 10.3–36.8) after early PDT and in 16 of 36 (44.4%; 29.5–60.4) after late PDT. The risk difference was –23.9 percentage points (95% CI –42.8 to –1.8), the risk ratio 0.46 (0.22–0.99), the exact OR 0.33 (0.10–1.04) and Cohen's h –0.52 (Fisher p=0.043).

Table 2. Clinical outcomes by timing of percutaneous dilatational tracheostomy.

Outcome	Early PDT, n (%) [95% CI]	Late PDT, n (%) [95% CI]	Risk difference, pp [95% CI]	Risk ratio [95% CI]	Exact OR [95% CI]	Cohen's h	Fisher p
Binary outcomes							
Liberated from ventilation by discharge†	17 (50.0) [34.1–65.9]	15 (41.7) [27.1–57.8]	8.3 [-14.3 to 29.9]	1.20 [0.72–2.00]	1.39 [0.49–4.00]	0.17	0.632
Ventilator-associated pneumonia	7 (20.6) [10.3–36.8]	16 (44.4) [29.5–60.4]	-23.9 [-42.8 to -1.8]	0.46 [0.22–0.99]	0.33 [0.10–1.04]	-0.52	0.043
ICU death	12 (35.3) [21.5–52.1]	15 (41.7) [27.1–57.8]	-6.4 [-27.6 to 15.8]	0.85 [0.47–1.54]	0.77 [0.26–2.23]	-0.13	0.630
In-hospital death	17 (50.0) [34.1–65.9]	21 (58.3) [42.2–72.9]	-8.3 [-29.9 to 14.3]	0.86 [0.55–1.32]	0.72 [0.25–2.03]	-0.17	0.632
Death after ICU discharge	5 (14.7) [6.4–30.1]	6 (16.7) [7.9–31.9]	-2.0 [-19.3 to 15.8]	0.88 [0.30–2.63]	0.86 [0.19–3.82]	-0.05	1.000
Major bleeding	1 (2.9) [0.5–14.9]	1 (2.8) [0.5–14.2]	0.2 [-11.5 to 12.4]	1.06 [0.07–16.27]	1.06 [0.01–85.60]	0.01	1.000
Significant desaturation	2 (5.9) [1.6–19.1]	2 (5.6) [1.5–18.1]	0.3 [-13.0 to 14.1]	1.06 [0.16–7.10]	1.06 [0.07–15.45]	0.01	1.000
Loss of airway	0 (0.0) [0.0–10.2]	0 (0.0) [0.0–9.6]	0.0 [-9.6 to 10.2]	1.06 [0.02–51.84]	—	0.00	1.000
Time outcomes, median [IQR], days							
			P(early > late)‡				
PDT to liberation (liberated patients)	6.0 [4–8]	9.0 [7–12]	0.08–0.42				
ICU length of stay	15.0 [11–22]	19.5 [14–27]	0.20–0.59				
Hospital length of stay	24.0 [17–35]	28.5 [20–41]	0.21–0.59				

Notes: CI, confidence interval (Wilson for proportions, Newcombe hybrid score for risk differences, log method for risk ratios with 0.5 added to zero cells, conditional maximum-likelihood exact for odds ratios); pp, percentage points; OR, odds ratio (early vs late). †Every survivor was liberated by hospital discharge. ‡Attainable range of the probability that an early-PDT value exceeds a late-PDT value across all integer datasets reproducing the observed median and quartiles (0.50 = no difference). For PDT-to-liberation the whole range lies below 0.50, so shorter post-procedure ventilation in the early group holds in every compatible dataset, but its p value ranges from <0.001 to 0.436 and is not identifiable; for ICU and hospital stay the range contains 0.50, so neither direction nor significance is identifiable.

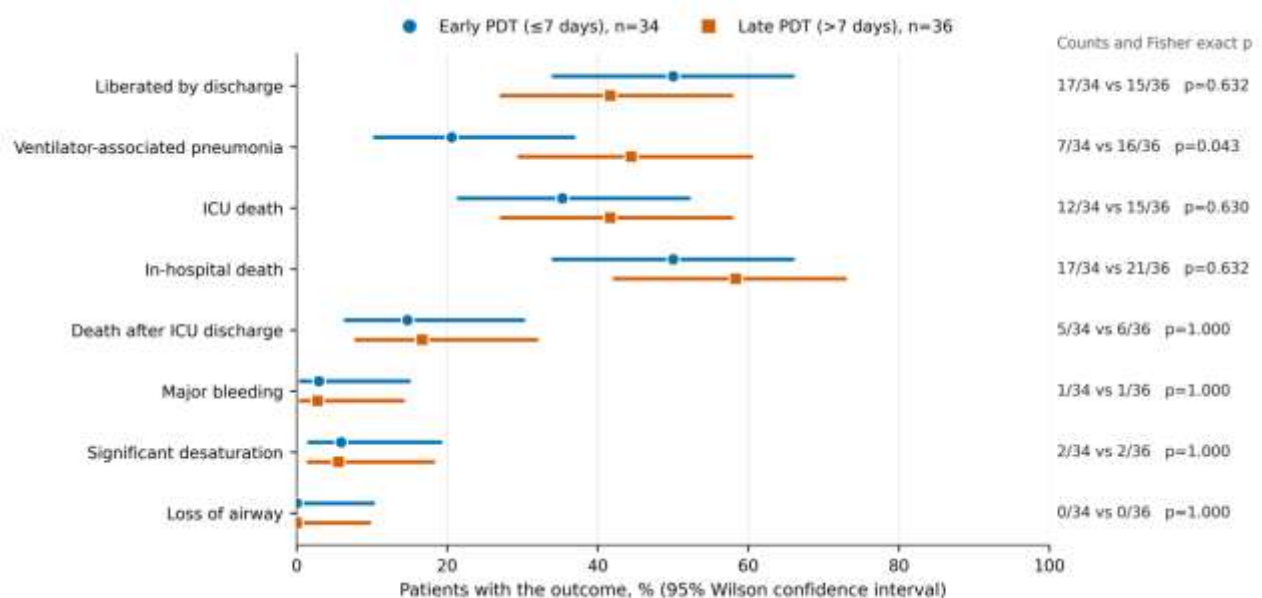


Figure 2. Outcome proportions by timing of tracheostomy. Points show the percentage of patients with each outcome and horizontal lines the 95% Wilson confidence intervals for early (blue circles, n=34) and late (vermillion squares, n=36) PDT; counts and two-sided Fisher exact p values are listed on the right

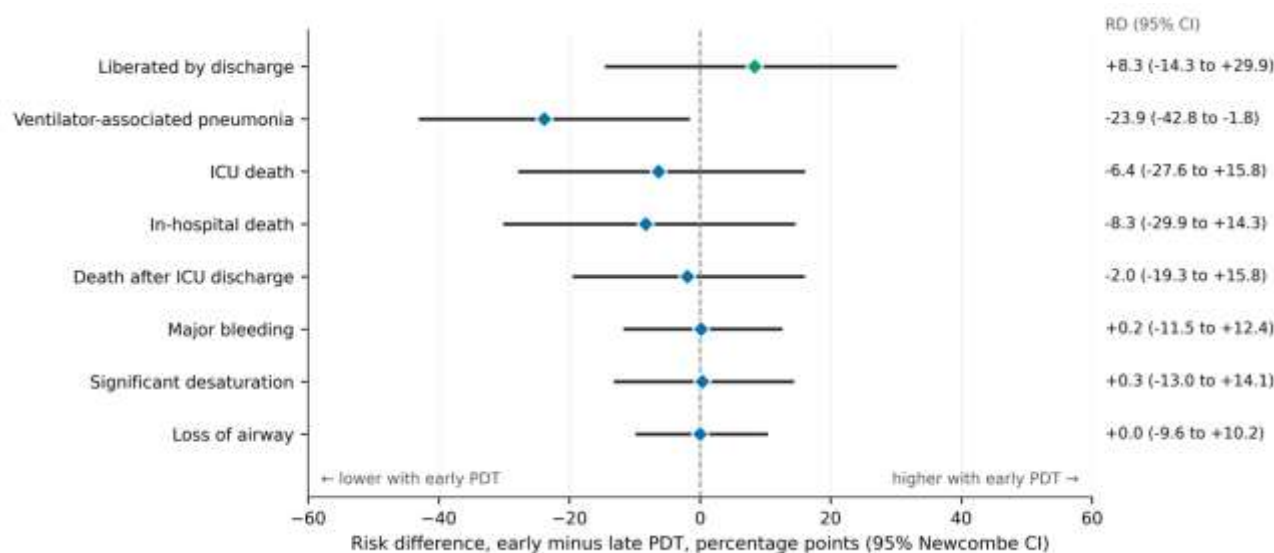


Figure 3. Risk differences between early and late tracheostomy. Diamonds show the difference in percentage points (early minus late) and lines the 95% Newcombe confidence intervals; values left of zero favor early PDT for adverse outcomes, and the green diamond marks the favorable outcome (liberation).

Thirty-two patients (45.7%; 95% CI 34.6–57.3) were liberated from ventilation by hospital discharge: 17 of 34 (50.0%; 34.1–65.9) after early and 15 of 36 (41.7%; 27.1–57.8) after late PDT (risk difference 8.3 percentage points, -14.3 to 29.9; risk ratio 1.20, 0.72–2.00; $p=0.632$). Every survivor was liberated, and no liberated patient died in hospital. ICU death occurred in 12 of 34 (35.3%) and 15 of 36 (41.7%) patients (risk difference -6.4 percentage points, -27.6 to 15.8; $p=0.630$), and in-hospital death in 17 of 34 (50.0%) and 21 of 36 (58.3%) (-8.3 percentage points, -29.9 to 14.3; risk ratio 0.86, 0.55–1.32; $p=0.632$). Overall in-hospital mortality was 54.3% (38/70; 95% CI 42.7–65.4). Eleven patients (5 early, 6 late) died in hospital after discharge from the ICU ($p=1.000$); none of them had been liberated.

Procedure-related complications were infrequent and identical in the two groups: major bleeding in one patient in each group (2.9% overall; 95% CI 0.8–9.8), significant desaturation in two patients in each group (5.7%; 2.2–

13.8) and no loss of airway (0%; 0.0–5.2). After Holm adjustment across the five testable secondary outcomes, no contrast remained significant (VAP adjusted $p=0.217$).

3.3. Time to liberation, ventilation after tracheostomy and length of stay

Because patients were classified by the day of PDT, every late-PDT patient had remained alive and ventilated for more than 7 days after intubation, a period during which liberation was impossible by definition. Measured from ICU admission, time to liberation therefore includes guaranteed ventilator time in the late group, and measured from the procedure it discards that group's pre-procedure ventilator days; both favor early PDT irrespective of any causal effect (Figure 4). As every survivor was liberated and no liberated patient died, cumulative liberation by discharge equaled survival in each group (50.0% and 41.7%), and the difference in liberation mirrored the non-significant difference in survival.

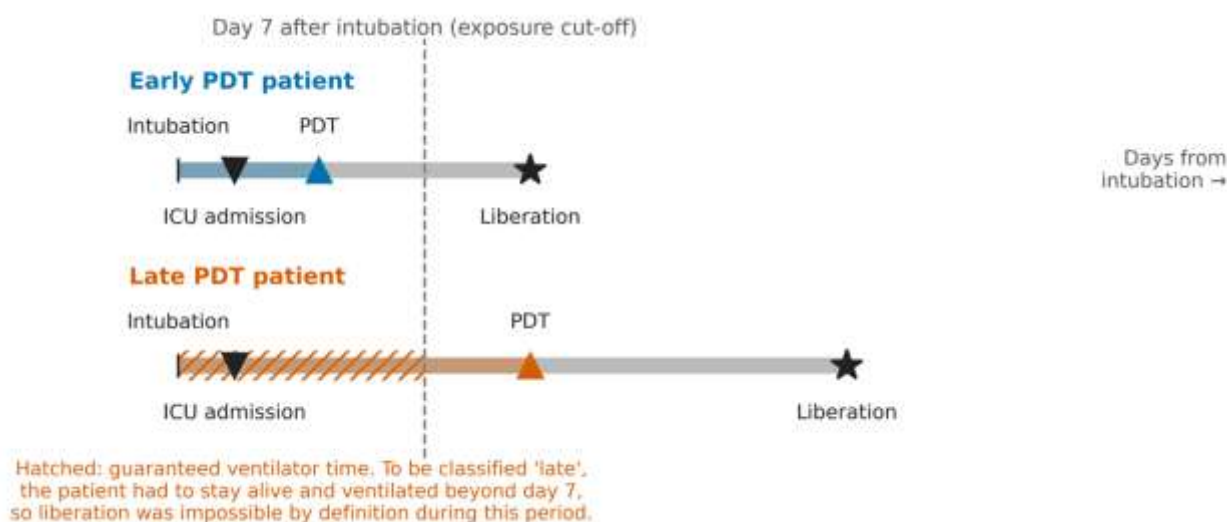


Figure 4. Why time-to-liberation comparisons by tracheostomy timing are biased. Two schematic patients illustrate how classifying patients by the day of tracheostomy creates guaranteed ventilator time (hatched) in the late group; measuring time from ICU admission or from PDT both favor early PDT. A common time-zero at intubation with landmark or clone-censor-weight analysis is required.

Among liberated patients, the median time from PDT to liberation was 6.0 days [IQR 4–8] after early and 9.0 days [7–12] after late PDT (Table 2). Across all integer datasets compatible with these medians and IQRs, the probability that an early-PDT value exceeded a late-PDT value ranged from 0.08 to 0.42 (Figure 5), so shorter post-procedure ventilation in the early group held in every compatible dataset; the corresponding *p* value, however, ranged from <0.001 to 0.436 and was not identifiable. With the alternative quartile definition the range was 0.10 to 0.45 (*p* up to 0.634), and with all 34 and 36 patients as

denominators 0.08 to 0.48 (*p* up to 0.757), so the direction, but not the significance, was robust to these assumptions. Median ICU stay was 15.0 days [11–22] after early and 19.5 days [14–27] after late PDT, and median hospital stay 24.0 [17–35] and 28.5 [20–41] days. The attainable probabilities of superiority ranged from 0.20 to 0.59 and from 0.21 to 0.59, respectively; both ranges contain 0.50, so neither the direction nor the significance of the length-of-stay differences was identifiable from the summary statistics.

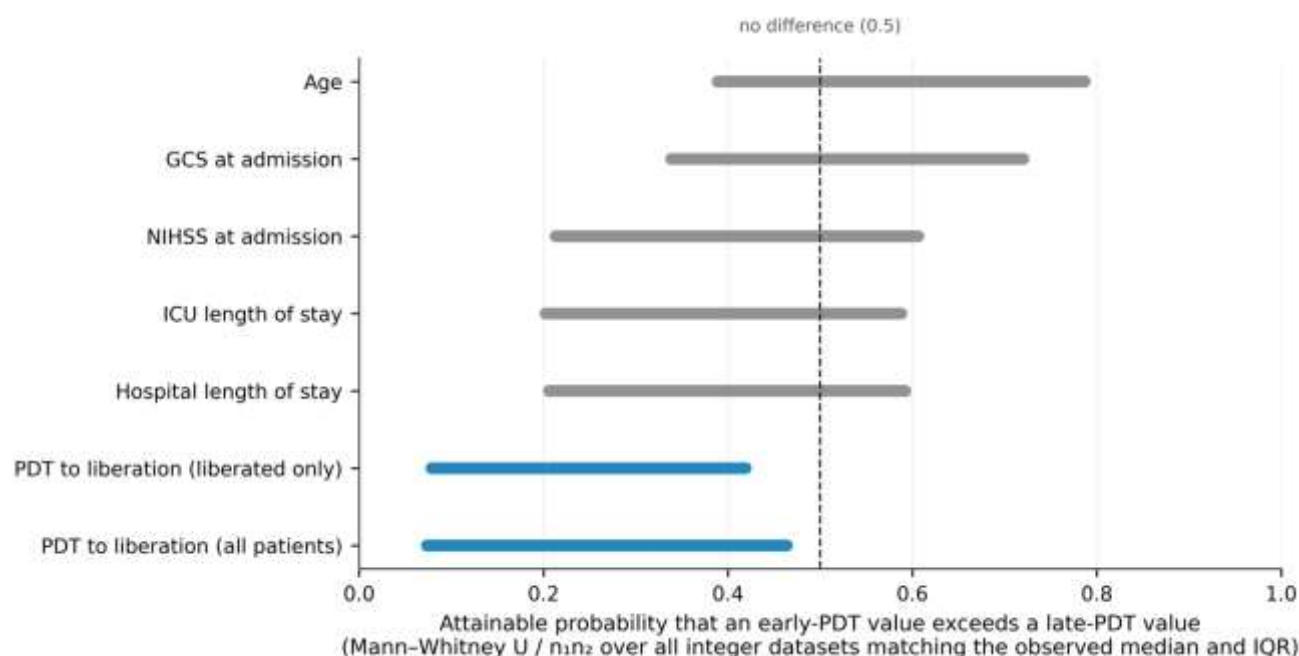


Figure 5. What the medians and interquartile ranges can and cannot establish. Bars show the attainable probability that an early-PDT value exceeds a late-PDT value across all integer datasets reproducing each observed median and IQR; bars crossing 0.50 (grey) cannot identify a difference, and bars wholly below 0.50 (blue) establish its direction but not its significance.

3.4. Sensitivity analysis over datasets consistent with the observed margins

The results of the bounds analysis are given in Table 3 and Figure 6. For VAP, the unadjusted Firth OR for early PDT was 0.34 (*p*=0.043). Adjusted for stroke type, sex, hypertension, diabetes and heart failure, the median OR across 4,000 admissible datasets was 0.34 (2.5th–97.5th percentile 0.28–0.37), and *p*<0.05 in 48.4% of them. Hill-climbing reached adjusted ORs between <0.001 and 0.68, but the upper value was found in only 1 of 40 restarts, and climbs from constructed starting configurations reached an adjusted OR of 33.2 (*p*=0.041) in a dataset that preserves every observed count. In that dataset the covariates relate to VAP in opposite directions in the two

groups; it is implausible clinically but compatible with the data. The adjusted VAP association therefore spans 1 and is not identifiable from the observed margins: the unadjusted difference would survive adjustment only under the assumption that the covariates relate to VAP similarly in the two groups, as in the random admissible datasets. Of 34,992 fits in the random-sampling and hill-climbing runs, 11 were discarded by the convergence filters. For in-hospital death, the unadjusted Firth OR was 0.72 (*p*=0.497), the median adjusted OR 0.72 (0.65–0.77) with *p*<0.05 in none of the random datasets, and the most extreme values found 0.024 and 6.02, which span 1: the data cannot identify an effect of timing on mortality after adjustment.

Table 3. Sensitivity analysis over the space of datasets consistent with the observed margins.

Association	Unadjusted OR (p)	Median OR [2.5th–97.5th percentile]*	Most extreme ORs found†	Admissible datasets with $p < 0.05$, %‡	Interpretation
A. Multivariable (Firth) models over sampled admissible datasets					
Ventilator-associated pneumonia: early PDT OR adjusted for stroke type, sex, hypertension, diabetes, heart failure	0.34 (0.043)	0.34 [0.28–0.37]	<0.001 to 33.2	48.4	Not identifiable (range spans 1)
In-hospital death: early PDT OR adjusted for stroke type, sex, hypertension, diabetes, heart failure	0.72 (0.497)	0.72 [0.65–0.77]	0.024 to 6.02	0.0	Not identifiable (range spans 1)
B. Pairwise associations by complete enumeration of admissible tables					
VAP × in-hospital death (128 admissible tables; Cramér's V 0.03–0.70)	—	—	0.012 to 98.5	50.0	Not identifiable (range spans 1)
VAP × ICU death (128 admissible tables; Cramér's V 0.01–0.82)	—	—	0.016 to 184.8	52.3	Not identifiable (range spans 1)
Haemorrhagic stroke × VAP (128 admissible tables; Cramér's V 0.01–0.79)	—	—	0.007 to 68.7	50.8	Not identifiable (range spans 1)
Haemorrhagic stroke × in-hospital death (224 admissible tables; Cramér's V 0.01–0.89)	—	—	0.006 to 487.7	49.6	Not identifiable (range spans 1)
Diabetes × VAP (120 admissible tables; Cramér's V 0.03–0.78)	—	—	0.017 to 88.2	49.2	Not identifiable (range spans 1)
Heart failure × in-hospital death (56 admissible tables; Cramér's V 0.00–0.52)	—	—	0.019 to 34.4	28.6	Not identifiable (range spans 1)

OR, odds ratio; VAP, ventilator-associated pneumonia. No patient-level cross-classification of covariates with outcomes was available; no dataset in this table is treated as observed. Block A: Firth-penalised logistic regression fitted to 4,000 datasets generated by permuting each variable's labels within each exposure group, which preserves every observed exposure-by-variable count. *Distribution across these random admissible datasets. †Most extreme values found by directed search (hill-climbing, 40 restarts × 400 label swaps per direction, plus climbs from 20,000 constructed starting configurations); in the random-sampling and hill-climbing runs, 11 of 34,992 fits were discarded by the convergence filters. These are lower bounds on the true attainable range, which may be wider. Age, GCS and NIHSS could not be included because only medians and IQRs were available. ‡Share of the sampled admissible space under within-group independent permutation (block A) or of all enumerated admissible tables (block B) with two-sided $p < 0.05$; not a probability that the association is real. Block B: complete enumeration of every within-group 2×2 table compatible with the observed margins, pooled over exposure groups.

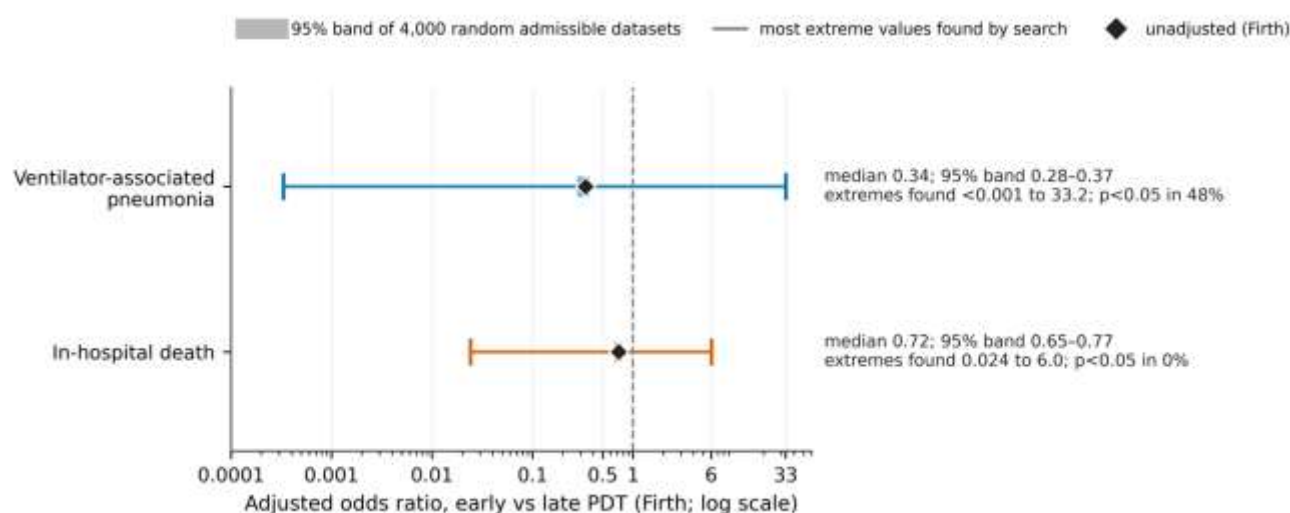


Figure 6. Covariate-adjusted odds ratios for early PDT across datasets consistent with the observed margins. Thick bars show the 2.5th–97.5th percentiles over 4,000 random admissible datasets, thin lines the most extreme values found by directed search (a lower bound on the attainable range), and diamonds the unadjusted Firth estimates; models adjust for stroke type, sex, hypertension, diabetes and heart failure. Both ranges span an odds ratio of 1.

None of the associations between pairs of outcomes or between covariates and outcomes could be identified (Table 3). For VAP and in-hospital death, 128 admissible tables gave pooled ORs from 0.012 to 98.5, and 50.0% reached $p < 0.05$; for VAP and ICU death the range was 0.016 to 184.8 (52.3% significant). Haemorrhagic stroke and VAP (0.007 to 68.7), hemorrhagic stroke and in-hospital death (0.006 to 487.7), diabetes and VAP (0.017 to 88.2) and heart failure and in-hospital death (0.019 to 34.4) were equally undetermined.

3.5. Robustness of the pneumonia difference

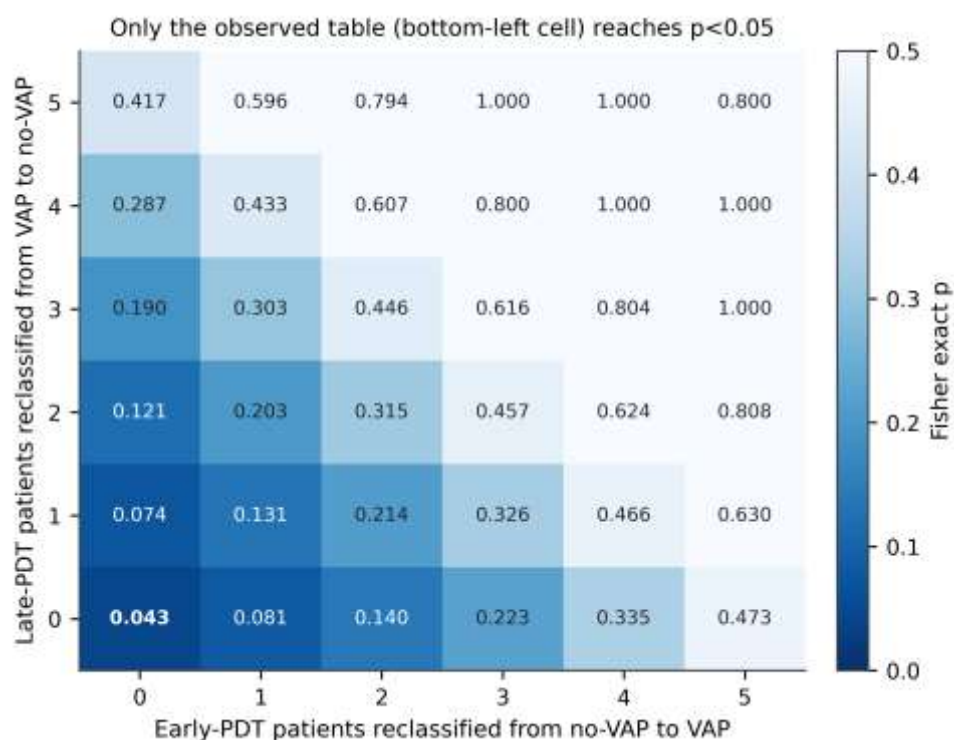
The VAP comparison was significant with the Pearson χ^2 test ($p = 0.034$), the Fisher mid- p ($p = 0.038$) and the Barnard and Boschloo tests ($p = 0.037$ and $p = 0.036$) but not with the Yates-corrected χ^2 test ($p = 0.062$), and its exact OR interval (0.10–1.04) included 1 (Table 4). The fragility index was 1, and the tipping-point analysis in Figure 7 shows that reclassifying a single early-PDT patient as having VAP ($p = 0.081$) or a single late-PDT patient as not having VAP

($p = 0.074$) would remove significance. The number needed to treat was 4.2 (95% CI 2.3 to 55.6), the E-value 3.74 (1.14 for the confidence limit) and the power to detect the observed difference 0.58. The disagreement between the Fisher p value and the exact OR interval arises because the two-sided Fisher test sums the probabilities of all tables at least as unlikely as the observed one, whereas the exact interval inverts two one-sided tests; the two can fall on opposite sides of 0.05 when, as here, the result is borderline. Under non-differential misclassification of VAP, the bias-corrected risk ratio had a median of 0.35 (95% simulation interval 0.03–0.91), and only 1.4% of draws gave a risk ratio of 1 or more; under differential misclassification with more sensitive surveillance in the late group, the median was 0.47 (0.05–1.26), with 7.0% of draws at 1 or more. If a single late-PDT VAP episode had preceded the procedure and were excluded, p would be 0.070, and with three such episodes 0.114.

Table 4. Robustness of the difference in ventilator-associated pneumonia (7/34 vs 16/36).

Analysis	Result	Interpretation
Pearson χ^2 test	p=0.034	Significant
χ^2 with Yates continuity correction	p=0.062	Not significant
Fisher exact test	p=0.043	Significant
Fisher mid-p	p=0.038	Significant
Barnard / Boschloo unconditional exact tests	p=0.037 / 0.036	Significant
Conditional exact OR	0.33 [0.10–1.04]	Interval includes 1
Risk ratio / risk difference	0.46 [0.22–0.99] / –23.9 pp [–42.8 to –1.8]	Upper limits close to null
Number needed to treat	4.2 [2.3 to 55.6]	Imprecise
Fragility index	1	One reclassified patient removes significance
Misclassification tipping point	1 early non-VAP → VAP: p=0.081; 1 late VAP → no VAP: p=0.074	Not robust to a single diagnostic error
Holm adjustment across five testable secondary outcomes	p=0.217	Not significant
Probabilistic bias analysis, non-differential misclassification (Se 0.70–0.95, Sp 0.85–0.98)	Corrected RR 0.35 [0.03–0.91]; RR ≥1 in 1.4%	Direction preserved if error is non-differential
Probabilistic bias analysis, differential (Se early 0.60–0.80, late 0.85–0.98)	Corrected RR 0.47 [0.05–1.26]; RR ≥1 in 7.0%	Interval includes 1
Reverse causation: late-PDT VAP episodes assumed to precede PDT and excluded	1 episode: p=0.070; 3 episodes: p=0.114	One prevalent case removes significance
E-value (risk ratio scale)	3.74 (confidence limit 1.14)	Weak confounding could explain the interval
Post hoc power at observed effect ($\alpha=0.05$)	0.58	Underpowered
Adjusted for five binary covariates (Table 3)	Median OR 0.34; extremes found <0.001 to 33.2	Not identifiable

OR, odds ratio; pp, percentage points. The fragility index is the smallest number of early-PDT patients whose status would have to change from no-VAP to VAP for the Fisher p value to exceed 0.05. The E-value is the minimum strength of association, on the risk-ratio scale, that an unmeasured confounder would need with both PDT timing and VAP to explain away the observed risk ratio (0.46) or its confidence limit (0.99). Barnard and Boschloo tests were computed with SciPy defaults (32-point nuisance-parameter grid). The Fisher test is a minimum-likelihood two-sided test, whereas the exact OR interval inverts two one-sided tests, so the two can disagree near $\alpha=0.05$. Bias analyses used 100,000 draws of sensitivity (Se) and specificity (Sp) from uniform distributions combined with binomial resampling of the observed counts; draws giving impossible corrected counts were discarded (5.7%).

**Figure 7.** Tipping-point analysis for ventilator-associated pneumonia. Each cell gives the Fisher exact p value after reclassifying the stated number of early-PDT patients from no-VAP to VAP (columns) and late-PDT patients from VAP to no-VAP (rows); only the observed table (bottom left) is below 0.05.

3.6. Comparison with external cohorts and trials

The cohort outcome proportions and verified external benchmarks are shown descriptively in Table 5 and Figure 8. Overall VAP was 32.9%, compared with 39.5% among 1,285 brain-injured patients in ENIO.¹¹ In propensity-matched intracerebral hemorrhage cohorts, pneumonia occurred in 54.95% of 1,210 early-tracheostomy and 59.91% of 1,210 late-tracheostomy patients; this endpoint was not restricted to VAP.²³ A randomized Indian stroke trial reported VAP in 43.3% and 50.0% of its early and late groups.²⁸ In-hospital mortality in the present cohort was

54.3%, compared with 49.4% in a Nepalese PDT cohort,²⁹ approximately 32% mortality at 6 months in SETPOINT2,¹² and 50.0% mortality at 30 days in the Indian trial.²⁸ TRACHUS reported procedure failure in 2 of 118 patients, a composite that differs from this cohort's six recorded procedural events.³⁰ No directly comparable major-bleeding benchmark was selected from the procedural review.³¹ Liberation by discharge was 45.7%, whereas WEAN SAFE reported 65.0% weaning by day 90 in a general ICU population.⁹ These descriptive contrasts do not establish between-study differences.

Table 5. Comparison of the cohort's outcome proportions with external trials and cohorts.

Outcome (group)	This cohort, n/N (%) [95% CI]	Benchmark, %	Benchmark n	Benchmark source	p	Adjusted p	Effect
VAP, whole cohort	23/70 (32.9) [23.0–44.5]	39.5	1,285	ENIO, brain-injured, ventilated ≥48 h ¹¹	—	—	—
VAP, early PDT	7/34 (20.6) [10.3–36.8]	54.95	1,210	Hallan 2022; pneumonia, early ≤7 d ²³	—	—	—
VAP, late PDT	16/36 (44.4) [29.5–60.4]	59.91	1,210	Hallan 2022; pneumonia, late >7 d ²³	—	—	—
VAP, early PDT	7/34 (20.6) [10.3–36.8]	43.3	n/r	Indian RCT, early (day 4) arm ²⁸	—	—	—
VAP, late PDT	16/36 (44.4) [29.5–60.4]	50.0	n/r	Indian RCT, late (day 10) arm ²⁸	—	—	—
In-hospital death, whole cohort	38/70 (54.3) [42.7–65.4]	49.4	83	Nepalese PDT cohort, 64% neurological ²⁹	—	—	—
In-hospital death, whole cohort	38/70 (54.3) [42.7–65.4]	32.2	366	SETPOINT2; 6-month death ¹²	—	—	—
In-hospital death, whole cohort	38/70 (54.3) [42.7–65.4]	50.0	n/r	Indian RCT, death by 30 days ²⁸	—	—	—
Procedure-related events, whole cohort	6/70 (8.6) [4.0–17.5]	1.7	118	TRACHUS; composite procedure failure ³⁰	—	—	—
Major bleeding, whole cohort	2/70 (2.9) [0.8–9.8]	n/a	n/a	Procedural review; no equivalent benchmark ³¹	—	—	—
Liberated by discharge, whole cohort	32/70 (45.7) [34.6–57.3]	65.0	5,869	WEAN SAFE, weaned by day 90, general ICU ⁹	—	—	—

Benchmarks are descriptive context, not external controls. No external-comparison hypothesis tests or standardized between-study effects are retained because case mix, endpoint definitions and follow-up differ. Hallan et al. report pneumonia, not specifically VAP; TRACHUS reports a composite procedure-failure endpoint. n/r, arm denominator not reported in the cited abstract. Procedure-related events here count six events in four to six patients; this is not a unique-patient complication proportion.

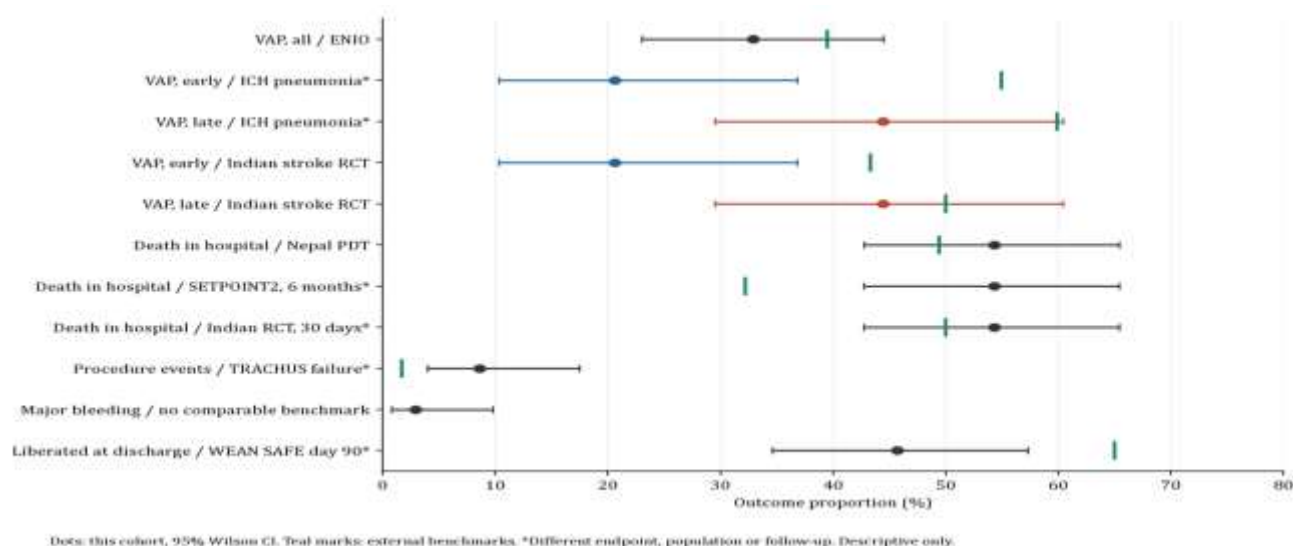


Figure 8. Descriptive external benchmarks published no later than 2025. Cohort points show observed proportions and 95% Wilson confidence intervals; vertical marks show external percentages. Pneumonia, procedure failure, mortality follow-up and weaning definitions differ where indicated. No between-study significance tests are shown; these sources are not external controls.

3.7. Precision and sample size for future studies

The precision of the whole-cohort estimates and the sample sizes required for future studies are summarized in Tables 6 and 7 and in Figure 9. The 95% CIs had half-widths of 10.8 percentage points for VAP and 11.4 for in-hospital death and liberation; estimating these proportions to within ± 5 percentage points would require 340 to 382 patients. Detecting the observed VAP risk ratio of 0.46 with 80% power would require 59 patients per group, and detecting the descriptive CENTER-TBI VAP contrast

(39.7% vs 27.2%) would require 222 per group; this traumatic brain injury scenario is not a stroke effect estimate, whereas the stroke meta-analytic OR of 0.80 would require 1,298 per group and the observed 8.3-percentage-point difference in in-hospital mortality 560 per group. For the time-to-event design recommended below, detecting a cause-specific hazard ratio of 1.5 for liberation with 80% power would require 191 liberation events, or about 209 patients per group if 45.7% are liberated.

Table 6. Precision of the present estimates and sample sizes required for future studies.

Whole-cohort proportion	Estimate, % [95% CI]	Half-width, pp	n for ± 10 pp	n for ± 5 pp
Ventilator-associated pneumonia	32.9 [23.0–44.5]	± 10.8	85	340
In-hospital death	54.3 [42.7–65.4]	± 11.4	96	382
Liberated by discharge	45.7 [34.6–57.3]	± 11.4	96	382
Procedure-related events	8.6 [4.0–17.5]	± 6.8	31	121

Required n for a two-sided 95% confidence interval of the stated half-width at the observed proportion.

Table 7. Patients per group required to detect plausible effects of early tracheostomy (two-sided $\alpha=0.05$).

Anticipated effect (source)	Control → early, %	n per group, 80% power	n per group, 90% power
VAP: risk ratio 0.46 (this cohort)	44.4 → 20.6	59	79
VAP: CENTER-TBI observational contrast ³²	39.7 → 27.2	222	297
VAP: OR 0.80 (stroke meta-analysis)	44.4 → 39.0	1,298	1,738
In-hospital death: -8.3 pp (this cohort)	58.3 → 50.0	560	750
Liberation by discharge: +8.3 pp (this cohort)	41.7 → 50.0	560	750
Liberation, cause-specific HR 1.5 (event-driven)*	191 / 256 events	209	280
Liberation, cause-specific HR 1.3 (event-driven)*	457 / 611 events	500	669
Liberation, cause-specific HR 2.0 (event-driven)*	66 / 88 events	72	96

Binary endpoints: arcsine (Cohen'sh) approximation for two independent proportions with equal allocation. *Time-to-event: Schoenfeld formula for a two-sided log-rank-type test of the cause-specific hazard of liberation with 1:1 allocation (events for 80% / 90% power); patients per group assume that 45.7% of patients are liberated, as in this cohort, with death as a competing event that removes patients from the risk set.

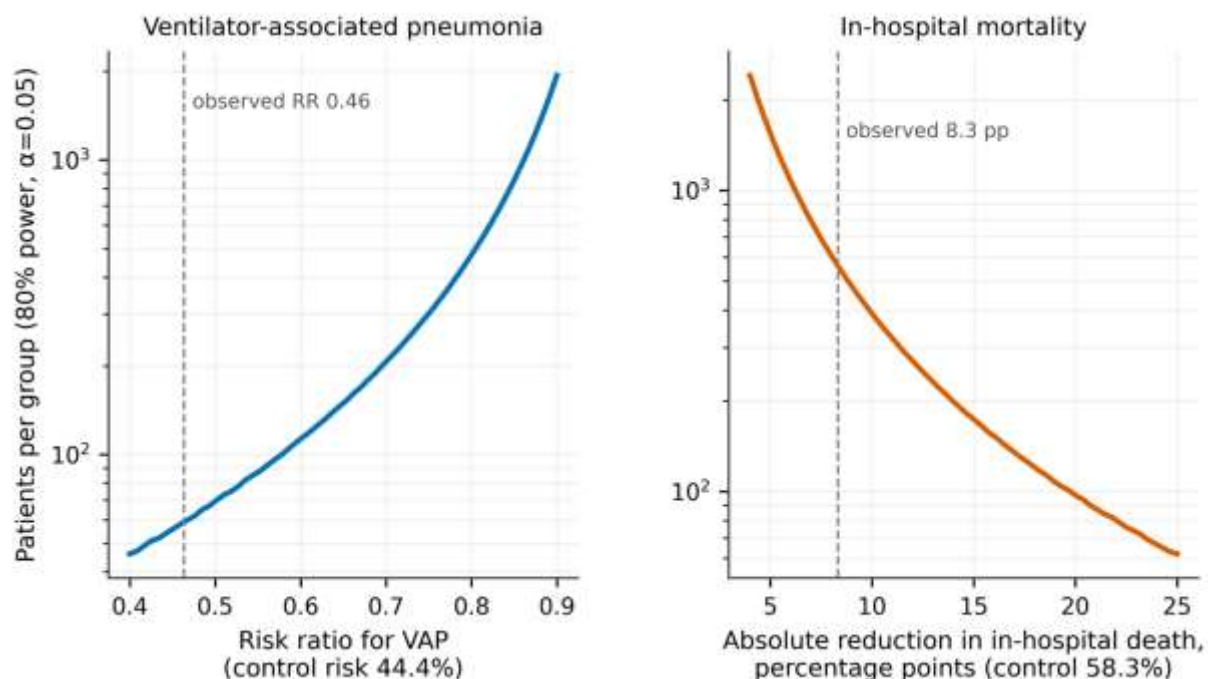


Figure 9. Sample sizes for future studies. Patients per group required for 80% power at two-sided $\alpha=0.05$ to detect a given relative reduction in ventilator-associated pneumonia (left; control risk 44.4%) or absolute reduction in in-hospital mortality (right; control 58.3%); dashed lines mark the effects observed in this cohort.

4. Discussion

In this cohort of 70 ventilated stroke patients treated with bedside PDT at a tertiary hospital in Malang, Indonesia, early PDT was associated with less VAP, but the association rested on a single patient's classification and did not survive adjustment for multiple outcomes. Liberation by discharge, ICU and in-hospital mortality, and procedural complications did not differ detectably between early and late PDT, and no time-to-liberation effect of timing can be identified from data in which the exposure is defined by the day of the procedure. The VAP association should therefore be regarded as hypothesis-generating.

These findings answer a narrower question than the randomized evidence. Every patient in this cohort

eventually received a tracheostomy, so the comparison is between early and late timing among patients who were tracheostomized, not between a strategy of early tracheostomy and a strategy of waiting among all ventilated stroke patients. In SETPOINT2, one-third of the standard-care group never needed a tracheostomy,¹² and in the target-trial emulation of tracheostomy timing in brain injury only 40% of the delayed group ever received one.²⁵ Patients who are extubated or die before day 7 without a tracheostomy, who would count as successes or failures of a 'wait' strategy, are absent from both groups here. Conditioning on a procedure that depends on the patient's course after baseline makes the late group a selected subset of patients who were still ventilated, and usually still sick, after a week; this bias favors early PDT on

every outcome that tracks illness severity, including VAP and duration of ventilation.

The direction and size of the VAP difference agree with most of the stroke literature. Meta-analysis of nine stroke studies with the same 7-day cut-off found an OR of 0.80 (95% CI 0.68–0.93) for VAP,¹⁴ a pooled analysis of stroke studies an OR of 0.75 (0.64–0.87),³³ and the Bayesian synthesis of randomized trials a 94% probability of any VAP reduction.¹⁵ In matched intracerebral hemorrhage cohorts, early tracheostomy was associated with less pneumonia (54.95% vs 59.91%), although this was not a VAP-specific endpoint.²³ CENTER-TBI reported VAP in 27.2% after early and 39.7% after late tracheostomy, in a traumatic brain injury population rather than a stroke cohort.³² National inpatient data also associated early tracheostomy after thrombectomy with less pneumonia (OR 0.449).³⁴ Randomized data are less consistent: a randomized study of 80 brain-injured patients in India found less VAP with tracheostomy within 3 days,³⁵ whereas a 64-patient Indian trial in severe stroke found VAP in 43.3% and 50.0% and identical 30-day mortality.²⁸ The risk ratio in the present cohort (0.46) is larger than the meta-analytic estimates, as expected from a small study selected for a significant result; a reasonable expectation for a future trial is closer to the meta-analytic OR of 0.80, which would require more than 1,000 patients per group.

Several features of VAP make the observed difference less secure than its *p* value suggests. The diagnosis was clinical. Across 119 VAP trials, diagnostic criteria were reported in only half and were combined in 38 different ways;³⁶ formal definitions agreed with intensivists in at most 57% of cases;³⁷ and the clinical pulmonary infection score had a sensitivity of 0.45 to 0.51.³⁸ In stroke patients, fever, leukocytosis and new infiltrates have frequent non-infectious causes, including central fever, aspiration pneumonitis and atelectasis. Because the fragility index was 1, misclassification of a single patient in either direction would change the conclusion, and differential ascertainment, such as more chest radiographs in patients who stayed intubated longer, could create a difference of this size. The timing of VAP relative to PDT was not recorded. Pneumonia acquired during the first week may itself have delayed weaning and therefore the decision to perform a tracheostomy, so that part of the association could reflect reverse causation rather than prevention. The data show how little is needed: if a single late-PDT VAP episode had preceded the procedure, *p* would be 0.070. Finally, early antibiotic prophylaxis halves early VAP in

comatose brain-injured patients (14% vs 32%),³⁹ so differences in prophylaxis between the groups, which were not recorded, could confound the comparison. The bias analyses frame these concerns quantitatively. Non-differential misclassification would, if anything, have hidden part of a true effect, but more sensitive surveillance in the late group could explain the difference, and allowing the recorded covariates to relate to VAP differently in the two groups moved the adjusted OR across 1.

A lower VAP rate could matter even without a survival benefit. In ENIO, VAP was not independently associated with ICU mortality (hazard ratio 0.71, 95% CI 0.43–1.16) but was associated with a longer ICU stay (OR 2.55).¹¹ ENIO reported VAP in 39.5% of patients, compared with 32.9% here; this is descriptive because populations and ascertainment differed. VAP definitions vary substantially across studies.^{36,37} A difference between timing strategies is therefore interpretable only when both groups are assessed with the same explicit criteria and surveillance intensity, which a retrospective comparison cannot guarantee.

The absence of a detectable mortality difference should be interpreted alongside heterogeneous evidence. SETPOINT2 found no improvement in 6-month functional outcome with early tracheostomy (modified Rankin Scale 0–4 in 43.5% vs 47.1%; adjusted OR 0.93, 95% CI 0.60–1.42).¹² Meta-analysis of 17,346 stroke patients found no association between timing and mortality.¹³ In matched intracerebral hemorrhage cohorts, 90-day and 365-day mortality did not differ, although early tracheostomy was associated with worse 30-day survival.²³ Observational CENTER-TBI findings arose in a different population and cannot establish a causal benefit for stroke.³² A traumatic brain injury registry analysis accounting for immortal time and a target-trial emulation also illustrate the importance of design; the latter reported poor 6-month outcome in 68.0% vs 72.0%.^{24,25} A severe ischemic stroke cohort found no association with 6-month severe disability (adjusted OR 1.09, 95% CI 0.35–3.45).⁴⁰ In the present cohort, even the direction of an adjusted mortality effect was unidentified. Admission GCS below 8 and hemorrhagic stroke predicted poor 1-year outcome in SPICE,⁶ while an Indonesian surgical hemorrhage cohort identified low GCS and hematoma volume as prognostic factors.²¹ With median GCS 7 and NIHSS 22–24, the present patients had severe neurological injury. Hypothesized pathways are summarized in Figure 10.

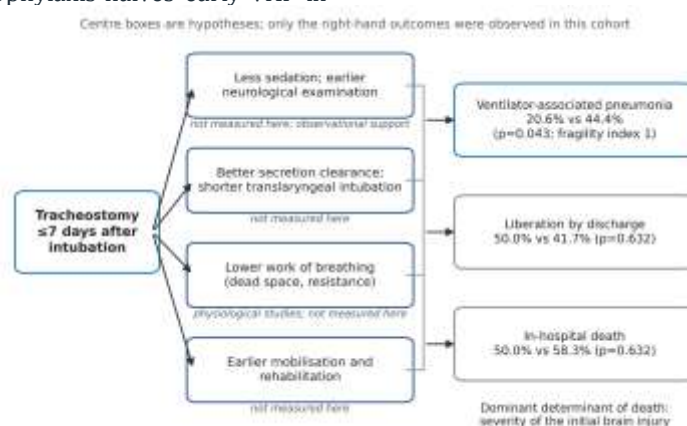


Figure 10. Hypothesised pathways linking early tracheostomy to outcomes. The four central mechanisms were not measured in this cohort and are shown as hypotheses; the right-hand boxes give the observed outcomes, of which only the difference in ventilator-associated pneumonia reached nominal significance.

The apparent acceleration of liberation after early PDT deserves particular caution, because it is precisely the type of effect that guarantee-time bias manufactures. Meta-analyses of stroke studies report 4.65 fewer ventilator days with early tracheostomy,¹⁴ and other stroke syntheses also report shorter ventilation.³³ Most of these comparisons share the structure of the present cohort: patients are grouped by when they received the procedure, so the late group is guaranteed a longer ventilation period before the procedure and is enriched for patients whose earlier weaning attempts failed. In the ENIO cohort, extubation failure was associated with 14 rather than 6 days of ventilation,¹⁰ and late tracheostomy in stroke has been associated with a 2.7-fold higher risk of reintubation,⁴¹ which is as consistent with late tracheostomy following failed weaning as with failed weaning following late tracheostomy. When exposures with this structure were modeled as time-varying, hazard ratios moved from 0.21 to 1.02 and from 0.50 to 1.00,^{16,17} and the only target-trial emulation of tracheostomy timing found no difference in outcome.²⁵ In the present data, post-procedure ventilation was shorter after early PDT in every compatible dataset, but this comparison begins at the procedure and is not an estimate of the effect of choosing early PDT on total ventilator time.

Competing risks shape the interpretation of liberation. When death competes with liberation, the cumulative incidence of liberation is bounded by survival, and in this cohort cumulative liberation by discharge equaled hospital survival exactly. A difference in cumulative incidence therefore combined a difference in speed with a non-significant difference in survival. Subdistribution hazard ratios do not describe rates among patients still at risk and are difficult to interpret when subdistribution hazards are not proportional. Competing-risk methods distinguish cause-specific hazards from cumulative incidence,⁴² and analyzing length of stay without accounting for death can produce contradictory conclusions in trauma care.⁴³ In a systematic review, 96% of trials that used ventilator-free days did not account for death as a competing event.⁴⁴ Future analyses of tracheostomy timing should report cause-specific hazards and cumulative incidences from a common time-zero and present death and liberation together.

Procedural complications were uncommon, with no detectable difference by timing. Major bleeding occurred in 2.9% and significant desaturation in 5.7%, without airway loss. Comparisons across studies require caution because complications and observation windows differ.³¹ In TRACHUS, ultrasound-guided and bronchoscopy-guided PDT each had one procedure failure (1/60 and 1/58); its composite failure endpoint is not equivalent to this cohort's event count.³⁰ A Nepalese series reported a 14.5% immediate-complication rate.²⁹ A SETPOINT2 post hoc analysis associated dilatational rather than surgical tracheostomy with fewer in-hospital infections (1.2% vs 14.6%) and shorter ventilation (14 vs 19 days), but technique selection was not randomized.⁴⁵ Another stroke neuro-ICU cohort reported more tracheostomy-related complications after early than late procedures (22.1% vs 7.3%).⁴¹ The present small cohort cannot exclude clinically important differences.

The mechanisms through which an earlier tracheostomy could act were not measured in this cohort. Sedation and analgesia fall within 24 h of tracheostomy in trauma patients,⁷ coma and delirium days decline after tracheostomy in acute respiratory distress syndrome,⁸ and

sedation depth predicts delayed weaning.⁹ Delirium affects 44% of critically ill stroke patients and adds 2.6 ventilator days,⁴⁶ and midazolam, which is used more often in middle-income countries, adds 2.8 ICU days compared with propofol in brain-injured patients.⁴⁷ An observational critical care cohort associated earlier tracheostomy with earlier sedation cessation and shorter ICU stay, without establishing causality,⁴⁸ and higher mechanical power, a marker of more severe respiratory failure, is itself associated with tracheostomy in brain injury.⁴⁹ Each of these pathways is plausible, but none can be attributed to the timing of tracheostomy without measuring it.

The Indonesian and regional context shapes both the interpretation and the stakes of these findings. Stroke burden is rising fastest in Southeast Asia,^{1,2,3} and Indonesia needs a larger and more equitably distributed stroke workforce.¹⁸ Critical care capacity in lower-middle-income Asian economies was 2.3 beds per 100,000 population in 2017¹⁹ and, despite growth during the COVID-19 pandemic, remained heterogeneous in 2022.²⁰ In-hospital mortality of 54.3% in this cohort is higher than the approximately 32% 6-month mortality in SETPOINT2 but similar to the 49.4% and 50.0% reported in Nepal and India,^{28,29} and an Indonesian surgical hemorrhage cohort reported 31.2% in-hospital mortality.²¹ Inflammatory markers such as the neutrophil-to-lymphocyte ratio have been studied for stroke-associated pneumonia risk outside Indonesia,⁵⁰ while an Indonesian VAP series reported 59.7% mortality with high cephalosporin resistance.²² In this cohort, 11 of the 38 deaths (28.9%) occurred after ICU discharge. None of these patients had been liberated, which implies that they left the ICU while still dependent on the ventilator, for example to a high-care unit; this pattern is consistent with the bed constraints described above and means that ICU mortality alone understates the risk faced by these patients. In such settings, each day of ICU occupancy has a high opportunity cost, and a strategy that shortened ventilation would be valuable even without a mortality benefit; a randomized trial in India found ICU stays of 12.1 and 18.4 days with early and late tracheostomy.²⁸ The present data cannot show that early PDT achieves this. Regional VAP surveillance with modified definitions adapted to low-resource settings⁵¹ and data on the microbiology and predictors of stroke-associated pneumonia in comparable settings⁵² offer a more reliable basis for local quality improvement than single-center comparisons of timing.

For clinical practice, these findings do not support a policy of routine early PDT in ventilated stroke patients to improve survival or speed of liberation, and they provide only fragile support for a benefit on VAP. The decision should remain individual: it should be based on the expected duration of ventilation, for which the SETscore provides a published clinical framework,⁵³ on the patient's neurological trajectory and on the family's goals of care, including patient-centered outcomes following tracheostomy.⁴⁸ In both Indian trials, patients were selected with the stroke-related early tracheostomy (SET) score, at cut-offs of 8 and 10.^{28,35} A pragmatic local rule would offer early PDT to patients who have a high SET score or a predicted need for ventilation beyond 10 to 14 days, no improvement in consciousness or airway reflexes by days 3 to 5 and no realistic prospect of extubation, provided that the family agrees; this rule should itself be evaluated in the registry proposed below rather than adopted as policy. At the institutional level, the most useful steps are prospective recording of intubation,

tracheostomy, liberation and VAP dates, a written VAP definition applied uniformly, and audit of sedation and VAP-prevention practices, which together would allow the questions left open by this study to be answered.

A specific research agenda follows. First, a multicenter Indonesian registry of ventilated stroke patients, including those never tracheostomized, should record intubation, tracheostomy, liberation, VAP-onset, death and discharge dates, with functional outcome at 6 months. Second, the effect of timing should be estimated with a target-trial emulation that compares the strategies 'tracheostomy by day 7' and 'no tracheostomy before day 10' from a common

time-zero, using cloning, censoring and inverse probability weighting, with death treated as a competing event and functional outcome as a key endpoint;²⁵ the elements of such a protocol are specified in Table 8. Third, VAP should be adjudicated by assessors unaware of tracheostomy timing, with prespecified criteria and microbiological confirmation. With the event rates observed here, 59 patients per group would detect the observed VAP contrast with 80% power, whereas a 1,000-patient-per-group design would be needed for a modest effect and more than 500 per group for a mortality difference of 8 percentage points (Table 7); about 209 patients per group would detect a cause-specific hazard ratio of 1.5 for liberation.

Table 8. Specification of a target trial and its emulation for a future multicenter registry analysis of tracheostomy timing.

Protocol element	Specification
Eligibility	Adults with acute ischaemic or haemorrhagic stroke, invasively ventilated, alive and ventilated on day 3 after intubation, no contraindication to PDT, no condition mandating tracheostomy
Treatment strategies	(1) PDT by day 7 after intubation; (2) no PDT before day 10, PDT thereafter only if still ventilated (mirroring SETPOINT2)
Assignment	Emulated: each eligible patient cloned into both strategies; clones censored when their observed care deviates from the assigned strategy
Time-zero	Day 3 after intubation (eligibility met), identical for both strategies
Outcomes	Liberation (≥ 48 h off ventilation) with death as competing event; VAP by adjudicated criteria with onset date; in-hospital death; modified Rankin Scale and decannulation at 6 months
Follow-up	From time-zero to liberation, death, hospital discharge or day 90, with 6-month telephone follow-up
Causal contrast	Per-protocol effect of the strategies
Analysis	Inverse-probability-of-censoring weights from daily GCS, NIHSS, sedation, oxygenation and extubation attempts; Aalen–Johansen cumulative incidence and cause-specific hazards; risk differences at days 28 and 90
Minimal dataset	Dates/times of intubation, PDT, extubation attempts, liberation, VAP onset, ICU discharge, death and hospital discharge; daily severity and sedation; baseline covariates; 6-month function
Sample size	≈ 209 patients per strategy for a cause-specific HR of 1.5 for liberation (80% power); 59 per strategy for the observed VAP contrast (Table 7)

The target trial is the randomized trial that the registry analysis would emulate; cloning, censoring and weighting remove guarantee-time bias by aligning eligibility, assignment and time-zero.

The study has several strengths. It reports every eligible patient treated over a full year in a setting that is under-represented in the literature. All analyses are reproducible from the group-level counts, every test was recomputed with exact methods, and the effects that the data cannot identify are stated as results rather than hidden in the limitations. The bounds analyses show which conclusions hold for every dataset compatible with the observations and which depend on unmeasured joint distributions.

The study also has important limitations. Patient-level linked records were not available, so no covariate adjustment could be performed directly, age, GCS and NIHSS could not be included in the bounds analysis, and the extremes reported for the adjusted ORs are those found by search, which may understate the attainable range. The number of patients screened and excluded is unknown, and the cohort includes only patients who received a tracheostomy, which conditions on a post-baseline event and excludes those liberated or dead before a tracheostomy was considered. The procedure day, the duration of ventilation before PDT and the timing of VAP were not recorded, so the analysis cannot distinguish prevention from reverse causation. VAP was diagnosed clinically without blinded adjudication. Finally, the study

was conducted at a single center with 70 patients and had a power of 0.58 for the observed VAP difference and about 0.1 for the observed mortality difference.

5. Conclusion

In ventilated stroke patients treated at a tertiary hospital in Malang, Indonesia, early PDT (≤ 7 days from intubation) was associated with less VAP than late PDT (20.6% vs 44.4%; risk difference -23.9 percentage points, 95% CI -42.8 to -1.8), but the association depended on a single patient's classification, did not survive multiplicity adjustment, was not identifiable after allowing for confounding by the recorded covariates and may reflect reverse causation. Liberation by discharge, ICU and in-hospital mortality and procedural complications did not differ detectably, and no effect of timing on the speed of liberation could be identified. Early PDT should therefore remain an individual decision based on the expected duration of ventilation rather than a routine policy to improve survival or weaning. Indonesian hospitals should record intubation, tracheostomy, liberation and VAP dates prospectively, so that a multicenter target-trial emulation with death as a competing event and 6-month functional

outcome can estimate the effect of tracheostomy timing reliably.

6. Declarations

Ethics approval and consent to participate. The study was approved by the CMHC Research Center Ethics Committee, Indonesia (Approval No. IRB/2024/8243). The requirement for individual informed consent was waived because only anonymized routine medical record data were used. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable.

Data availability. Requests for patient-level data should be addressed to the corresponding author and are subject to institutional and ethics approval.

Use of generative AI and AI-assisted tools. The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

Author contributions. W: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review and editing. AAA: Supervision, Validation, Writing – review and editing. AZF: Methodology, Validation, Writing – review and editing. BHL: Supervision, Resources, Writing – review and editing.

Funding. This study received no specific funding.

Competing interests. The authors declare no competing interests.

Acknowledgements. The authors thank the nursing and medical staff of the intensive care unit for their care of the patients.

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