

# Association between tracheostomy and survival in patients with coronavirus disease 2019 who require prolonged mechanical ventilation for more than 14 days: A multicenter cohort study

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## ABSTRACT

**Objective:** Tracheostomy is a common procedure with potential prognostic advantages for patients who require prolonged mechanical ventilation (PMV). Early recommendations for patients with coronavirus disease 2019 (COVID-19) suggested delayed or limited tracheostomy considering the risk for viral transmission to clinicians. However, updated guidelines for tracheostomy with appropriate personal protective equipment have revised its indications. This study aimed to evaluate the association between tracheostomy and prognosis in patients with COVID-19 requiring PMV.

**Methods:** This was a multicenter, retrospective cohort study using data from the nationwide Japanese Intensive Care Patient Database. We included adult patients aged  $\geq 16$  years who were admitted to the intensive care unit (ICU) due to COVID-19 and who required PMV (for  $> 14$  days or until performance of tracheostomy). The primary outcome was hospital mortality, and the association between implementation of tracheostomy and patient prognosis was assessed using weighted Cox proportional hazards regression analysis with inverse probability of treatment weighting (IPTW) using the propensity score to address confounders.

**Results:** Between January 2020 and February 2021, 453 patients with COVID-19 were observed. Data from 109 patients who required PMV were analyzed: 66 (60.6%) underwent tracheostomy and 38 (34.9%) died. After adjusting for potential confounders using IPTW, tracheostomy implementation was found to significantly reduce hospital mortality (hazard ratio [HR]: 0.316, 95% confidence interval [CI]: 0.163–0.612). Patients who underwent tracheostomy had a similarly decreased ICU and 28-day mortality (HR: 0.269, 95% CI: 0.124–0.581; HR 0.281, 95% CI: 0.094–0.839, respectively). A sensitivity analysis using different definitions of PMV duration consistently showed reduced mortality in patients who underwent tracheostomy.

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**Conclusion:** The implementation of tracheostomy was associated with favorable patient prognosis among patients with COVID-19 requiring PMV. Our findings support proactive tracheostomy in critically ill patients with COVID-19 requiring mechanical ventilation for >14 days.

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## 1. Introduction

Tracheostomy is widely acknowledged as an essential procedure for patients undergoing mechanical ventilation (MV) due to acute respiratory failure. It is considered a safer alternative to long-term translaryngeal endotracheal intubation, which may cause subglottic and laryngeal stenosis [1,2] and spread of bacterial species from the oropharynx to the lower respiratory tract, leading to ventilator-associated pneumonia [3]. In addition, tracheostomy requires less sedative administration to improve patient comfort and reduce airway resistance [4,5]. These benefits contribute to favorable outcomes in patients who undergo early tracheostomy [6].

Patients with coronavirus disease 2019 (COVID-19) have a high rate of need for MV (range: 9.8% to 17.2% of all cases) [7–9]. Persistent viral infections tend to require prolonged MV (PMV), further underlining the importance of tracheostomy [10,11]. Therefore, the optimal clinical practice related to tracheostomy in patients with COVID-19 has been investigated. Earlier studies reported the risk for surgical providers to be directly exposed to the virus via aerosols during the procedure; therefore, international guidelines recommend delayed tracheostomy and extended MV with translaryngeal endotracheal intubation for at least 14 days or until a negative polymerase chain reaction result [12–14]. However, after a year into the COVID-19 pandemic, the risk of transmission of the virus to healthcare staff has been reported to be negligible with proper use of personal protective equipment [15–17]. Moreover, a safe tracheostomy procedure has been established [18], and proactive and aggressive implementation of tracheostomy within 14 days after COVID-19 infection is again being considered [19,20]. Therefore, using the nationwide Japanese Intensive Care Patient Database (JIPAD), we evaluated the impact of performing tracheostomy on patient outcomes among critically ill COVID-19 patients who require PMV.

## 2. Materials and methods

The Research Ethics Committee of the Osaka University in Osaka, Japan, approved this study protocol (approval number: 20531) and waived the need for informed consent.

### 2.1. Study design and population

This multicenter retrospective cohort study involved adult (aged  $\geq 16$  years) COVID-19 ICU admissions in the JIPAD. The JIPAD is a large dataset of patients who had been admitted to the ICU and established in 2014. It comprises 89 ICUs

and approximately 178,000 patients as of November 2020. Its data collection is similar to that of the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), based on a partnership agreement between the Japanese Society of Intensive Care Medicine and ANZ-ICS Center for Outcome and Resource Evaluation. A detailed description of the JIPAD has been previously published [21].

All patient records registered in the JIPAD between January 2020 and February 2021 were screened for inclusion in this study. COVID-19 diagnosis was laboratory-confirmed and was inferred from the ICU admission diagnosis related to viral pneumonia according to the APACHE III scoring system [22] or from the free text diagnosis for COVID-19. With the unanimous confirmation by three physicians from the JIPAD working group, COVID-19 diagnosis was defined as the diagnosis of COVID-19 in the ICU admission. In this study, we included adult patients who had been admitted to the ICU with a diagnosis of COVID-19 and who required PMV. Based on recent reports on the performance of a tracheostomy within 14 days, PMV was defined as MV for >14 days or tracheostomy during the ICU stay.

### 2.2. Data extraction

Detailed information on sociodemographic variables, comorbidities, severity at ICU admission, biochemical data, treatment in the ICU, and outcomes, are reported and registered for all ICU admissions in the ICUs that contribute to the JIPAD. The following data were extracted for this study: age; sex; body mass index; comorbidities (chronic heart failure, chronic respiratory failure, liver cirrhosis, liver failure, acute leukemia/multiple myeloma, lymphoma, metastatic cancer, immunosuppression, acquired immunodeficiency syndrome, and maintenance dialysis: [yes, no]); emergency admission (yes, no); admission source (emergency department, ward or other care units, or transferred from another hospital); wave; APACHE II and III scores; Sequential Organ Failure Assessment score at ICU admission; length of hospital stay before ICU admission; data within 24 h after ICU admission (heart rate, body temperature, respiratory rate, serum blood sugar, creatinine, lactate, urine output, incidence of acute kidney injury [yes, no], lowest ratio of arterial oxygen partial pressure to fractional inspired oxygen [ $\text{PaO}_2/\text{FIO}_2$ ], partial pressure of carbon dioxide, pH, and Glasgow Coma Scale); ICU treatment (venovenous extracorporeal membrane oxygenation [VV-ECMO] [yes, no], venoarterial [VA-] ECMO [yes, no], and continuous renal replacement therapy [CRRT] [yes, no]); length of ICU stay before MV commencement; duration of MV before tracheostomy; type of tracheostomy procedure (surgical, percutaneous, unknown); MV duration

in the ICU; ventilator liberation during ICU stay (yes, no); length of ICU and hospital stay; ICU, 28-day, and hospital mortality (yes, no); and hospital outcome (death, discharge, or transfer to another hospital). Liver cirrhosis or liver failure was considered chronic liver disease in this study. Comorbidities, such as acute leukemia/multiple myeloma, lymphoma, and metastatic cancer, were defined as malignancies. Patients with immunosuppression and acquired immunodeficiency syndrome were considered to have an immunodeficiency. Furthermore, according to the domestic definition, the COVID-19 waves were categorized into first (until May 2020), second (June to September 2020), and third waves (October 2020 onwards) [23].

### 2.3. Outcomes

The primary outcome of this study was in-hospital mortality. The secondary outcomes were ICU and 28-day mortality rates.

### 2.4. Statistical analyses

Continuous variables are expressed as medians and interquartile ranges (IQRs); they were compared between the groups using the Mann–Whitney U test. Categorical variables are expressed as numbers and percentages; they were compared between the groups using the chi-square test or Fisher's exact test, as appropriate. To determine the relationships between the implementation of the tracheostomy and hospitalization, ICU, and 28-day mortality rates, we constructed univariable and multivariable Cox proportional hazards regression models and calculated crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). Age (1-year increment), sex (male, female), APACHE II score (1-point increment), and the use of ECMO (VV-ECMO or VA-ECMO) during ICU stay (yes, no) were added to the multivariable model to adjust for potential confounders. Furthermore, we added weighted Cox proportional hazards regression models with inverse probability of treatment weighting (IPTW) [24] to eliminate possible erroneous effect estimates and biased CIs due to the nature of observational studies. In the IPTW method, patients were assigned weights based on the inverse of the probability of receiving treatment, as estimated by the propensity score calculated using multivariate logistic regression analysis based on potentially relevant covariates presented in Supplemental Digital Content 1. Simulated populations were formed in which patients who underwent tracheostomy were weighted by the inverse of the propensity score, and patients who required PMV without tracheostomy were weighted by the inverse of  $1 - \text{propensity score}$ . The average treatment effect estimate was then obtained by reweighting the study population to assess the effect of treatment if all patients in the population were provided with the treatment. The balance of covariates between the original cohort and cohort adjusted using IPTW was ascertained by comparing the standardized mean difference (SMD). An SMD  $<0.10$  indicated a lack of imbalance between the two groups. We also conducted a subgroup analysis stratified by severity of

illness using median APACHE II score in this cohort. The interaction effects between the implementation of tracheostomy and subgroup of mortality were assessed using a multivariable Cox proportional hazards regression model. Moreover, we conducted sensitivity analyses to further evaluate the association between tracheostomy and patient prognosis, using variations in the definition of PMV duration (7, 10, and 18 days). All statistical results were considered statistically significant at a two-sided level of 0.05. The statistical software, R (version 4.0.4;2021, R Foundation for Statistical Computing, Vienna, Austria), was used for all statistical analyses.

## 3. Results

### 3.1. Study participants

Data originating from 41 ICUs and pertaining to 453 adult ICU admissions with a diagnosis of COVID-19 were recorded in the JIPAD from January 2020 to February 2021. Among the 335 patients who required MV, 226 were liberated from MV within 14 days without them undergoing tracheostomy. We included 109 patients who required PMV; of those, 66 (60.6%) underwent tracheostomy and 43 (39.4%) received PMV for  $>14$  days without tracheostomy (Fig. 1). The median age of the patients who required PMV was 69 (IQR: 63–76) years, 76.1% were male, and the median APACHE II score was 19 (IQR: 15–24) (Table 1). The baseline characteristics at ICU admission were similar in both groups. As for the data within 24 h after ICU admission, patients who underwent tracheostomy were more likely to have lower maximum blood glucose levels and higher pH with similar PaO<sub>2</sub>/FIO<sub>2</sub> (136 [109–183] vs. 124 [86–178],  $p = 0.194$ ) than patients who received PMV without tracheostomy.

### 3.2. Processes of care during ICU stay and adjustment of patient demographics

The care process in the ICU is shown in Table 2. VV-ECMO was performed in 28.8% of patients who underwent tracheostomy, which was similar to the proportion of those who received PMV without tracheostomy (23.3%,  $p = 0.658$ ). There was also no significant difference in the proportion of patients who received VA-ECMO and CRRT between the two groups. Tracheostomy was performed at a median of 15 (IQR: 10.5–21.5) days after the commencement of MV. Thirty-five patients (53%) underwent surgical tracheostomy, and 26 (39.4%) underwent percutaneous tracheostomy. Patients who required PMV and who underwent tracheostomy were identified in 27 and 21 ICUs, respectively; the differences between these institutions were not significant (Supplemental Digital Content 1). Furthermore, the potential confounders (age, sex, APACHE II score, and the use of ECMO during ICU stay) were adjusted using IPTW, and the adjusted cohort had SMDs of  $<0.10$  for each covariate. No between-group differences were observed (Supplemental Digital Content 2).

**Table 1.** Patient characteristics and data within 24 h after intensive care unit admission.

Characteristics	All (n = 109)	PMV without tracheostomy (n = 43)	Tracheostomy (n = 66)	p value
Age, years	69 (63–76)	72 (63.5–77)	68 (63–73)	0.155
Male sex	83/109 (76.1%)	32/43 (74.4%)	51/66 (77.3%)	0.911
Body mass index, kg/m <sup>2</sup>	24.8 (22.6–27.9)	25.5 (23.0–29.0)	24.1 (22.4–26.8)	0.116
Comorbidity				
Heart failure	0/109 (0%)	0/43 (0%)	0/66 (0%)	N/A
Respiratory failure	2/109 (1.8%)	1/43 (2.3%)	1/66 (1.5%)	1.000
Chronic liver disease	0/109 (0%)	0/43 (0%)	0/66 (0%)	N/A
Malignancy	3/109 (2.8%)	0/43 (0%)	3/66 (4.5%)	0.277
Immunodeficiency	9/109 (8.3%)	3/43 (7.0%)	6/66 (9.1%)	1.000
Maintenance dialysis	6/109 (5.5%)	4/43 (9.3%)	2/66 (3.0%)	0.210
Emergency admission	106/109 (97.2%)	41/43 (95.3%)	65/66 (98.5%)	0.561
Admission source				
Emergency department	26/109 (23.9%)	11/43 (25.6%)	15/66 (22.7%)	0.746
Ward or other care units	35/109 (32.1%)	15/43 (34.9%)	20/66 (30.3%)	
Transferred from another hospital	48/109 (44.0%)	17/43 (39.5%)	31/66 (47.0%)	
Wave				
First (–May 2020)	53/109 (48.6%)	20/43 (46.5%)	33/66 (50.0%)	0.914
Second (June–September 2020)	18/109 (16.5%)	7/43 (16.3%)	11/66 (16.7%)	
Third (October 2020 onwards)	38/109 (34.9%)	16/43 (37.2%)	22/66 (33.3%)	
APACHE II score	19 (15–24)	20 (16–25)	18 (14–23)	0.106
APACHE III score	70 (56–89)	73 (63–94)	65 (54–85)	0.063
SOFA score at ICU admission	7 (5–10)	8 (6.5–10)	7 (5–9)	0.096
Length of hospital stay before ICU admission, days	0 (0–1)	0 (0–1)	0 (0–1.8)	0.997
Data within 24 h after ICU admission				
Highest heart rate, /min	102 (91–121)	102 (93–124)	101 (91–115)	0.239
Lowest heart rate, /min	63 (54–70)	63 (55–70)	62 (52–72)	0.838
Highest body temperature, °C	37.6 (37.1–38.7)	37.4 (37.1–38.7)	37.8 (37.1–38.6)	0.333
Lowest body temperature, °C	36.2 (35.7–36.8)	36 (35.4–36.6)	36.4 (35.8–36.8)	0.109
Highest respiratory rate, /min	27 (24–32)	27 (23–32)	28 (24–32)	0.723
Lowest respiratory rate, /min	14 (10–16)	14 (11–17)	14 (10–16)	0.938
Highest blood sugar level, mg/dL	218 (162–275)	252 (206–314)	200 (143–239)	<0.001
Lowest blood sugar level, mg/dL	124 (108–150)	130 (114–163)	124 (106–142)	0.110
Highest creatinine level, mg/dL	0.91 (0.69–1.27)	1.02 (0.69–1.50)	0.82 (0.68–1.12)	0.179
Lactate, mmol/L	1.5 (1.1–2.1)	1.5 (1.2–2.0)	1.5 (0.9–2.1)	0.569
Urine output, mL/day	1178 (828–1978)	1138 (820–1673)	1230 (855–2030)	0.385
Incidence of AKI	2/109 (1.8%)	2/43 (4.7%)	0/66 (0%)	0.153
Lowest PaO <sub>2</sub> /FIO <sub>2</sub> ratio	130 (98–181)	124 (86–178)	136 (109–183)	0.194
Highest PaCO <sub>2</sub> , mmHg	49.3 (44.1–58.4)	53.2 (45.3–58.6)	48.5 (43.9–56.4)	0.253
Lowest PaCO <sub>2</sub> , mmHg	36.4 (32.2–40)	35.7 (31.3–39.2)	36.7 (32.2–40.1)	0.390
Highest pH	7.44 (7.40–7.47)	7.42 (7.37–7.46)	7.45 (7.41–7.48)	0.049
Lowest pH	7.32 (7.27–7.37)	7.29 (7.24–7.34)	7.34 (7.27–7.39)	0.011
GCS	15 (13–15)	15 (14–15)	15 (13–15)	0.834

Data are presented as medians and interquartile ranges or numbers (percentages)

p values were analyzed using the Chi-square (Fisher’s exact) test or Mann-Whitney U test

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; ICU, intensive care unit; PaO<sub>2</sub>/FIO<sub>2</sub>, ratio of arterial oxygen partial pressure (PaO<sub>2</sub>) to fractional inspired oxygen (FIO<sub>2</sub>), PMV, prolonged mechanical ventilation, SOFA, Sequential Organ Failure Assessment

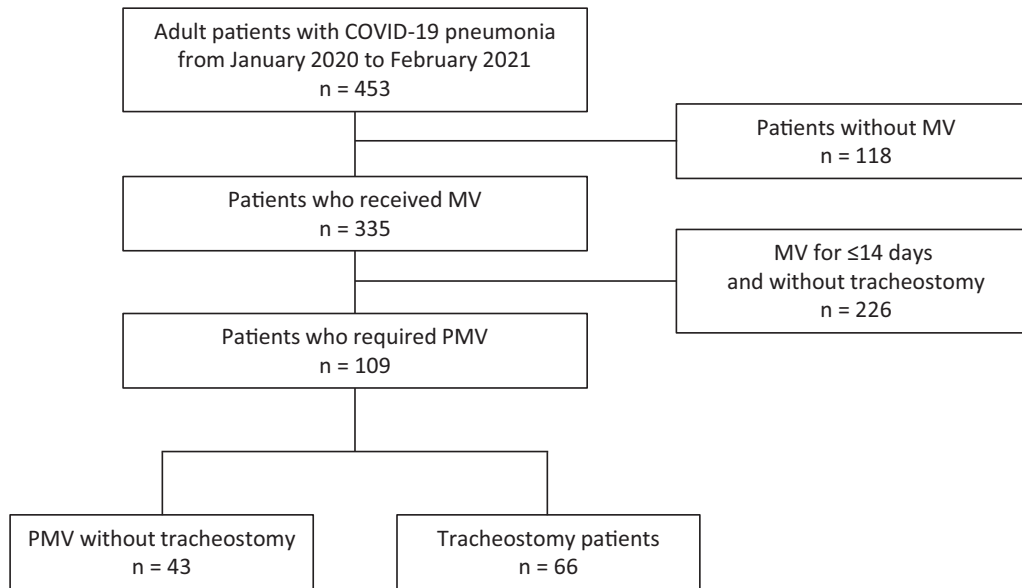
**Table 2.** Intensive care unit treatment.

Variables	All	PMV without tracheostomy	Tracheostomy	p value
VV-ECMO	29/109 (26.6%)	10/43 (23.3%)	19/66 (28.8%)	0.658
VA-ECMO	3/109 (2.8%)	1/43 (2.3%)	2/66 (3.0%)	1.000
CRRT	35/109 (32.1%)	17/43 (39.5%)	18/66 (27.3%)	0.211
Length of ICU stay before MV commencement, days	0 (0–0)	0 (0–0)	0 (0–0)	0.095
Duration of MV before tracheostomy, days	15 (10.5–21.5)	-	15 (10.5–21.5)	N/A
Procedure of tracheostomy				
Surgical tracheostomy	35/109 (32.1%)	-	35/66 (53.0%)	N/A
Percutaneous tracheostomy	26/109 (23.9%)	-	26/66 (39.4%)	
Unknown	5/109 (4.6%)	-	5/66 (7.6%)	

Data are presented as medians and interquartile ranges or numbers (percentages).

P values were analyzed using the chi-square (Fisher’s exact) test or Mann-Whitney U test.

CRRT, continuous renal replacement therapy; ICU, intensive care unit; MV, mechanical ventilation; PMV, prolonged mechanical ventilation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation



**Figure 1.** Flow chart of patient selection  
COVID-19, coronavirus disease; MV, mechanical ventilation; PMV, prolonged mechanical ventilation.

**Table 3.** Patient outcomes.

Variables	All	PMV without tracheostomy	Tracheostomy	<i>p</i> value
MV duration in ICU, days	24.6 (18.0–41.0)	20.4 (16.8–30.9)	27.0 (19.9–41.7)	0.081
ICU mortality	28/109 (25.7%)	17/43 (39.5%)	11/66 (16.7%)	0.014
Length of ICU stay, days	27.9 (20.4–44.2)	26.9 (19.2–37.0)	33.9 (21.7–48.6)	0.094
Ventilator liberation during ICU stay	59/109 (54.1%)	23/43 (53.5%)	36/66 (54.5%)	1.000
28-day mortality	15/92 (16.3%)	10/36 (27.8%)	5/56 (8.9%)	0.022
Hospital outcome				
Death	38/109 (34.9%)	21/43 (48.8%)	17/66 (25.8%)	0.046
Discharge	21/109 (19.3%)	7/43 (16.3%)	14/66 (21.2%)	
Transfer to another hospital	50/109 (45.9%)	15/43 (34.9%)	35/66 (53.0%)	
Hospital mortality	38/109 (34.9%)	21/43 (48.8%)	17/66 (25.8%)	0.023
Length of hospital stay, day	41 (23–66)	35 (23–49.5)	49.5 (31.5–77.5)	0.011

Data are presented as medians and interquartile ranges or numbers (percentages).

*P* values were analyzed using the chi-square (Fisher's exact) test or Mann-Whitney U test.

ICU, intensive care unit; MV, mechanical ventilation; PMV, prolonged mechanical ventilation.

### 3.3. Clinical outcomes

The durations of MV and ICU stay were similar between patients who underwent tracheostomy and those who received PMV without tracheostomy (Table 3). In contrast, patients who underwent tracheostomy had a longer hospital stay than those who did not undergo tracheostomy and required PMV (35 [23–49.5] vs. 49.5 [31.5–77.5] days, respectively;  $p = 0.011$ ). Of the 109 patients with COVID-19 who required PMV, 21 (19.3%) were discharged alive, 50 (45.9%) were transferred to other hospitals, and 38 (34.9%) died. Hospital mortality was significantly lower in patients who underwent tracheostomy than in those who received PMV without tracheostomy (48.8% vs. 25.8%,  $p = 0.023$ ). A similar trend was observed for ICU and 28-day mortality rates ( $p = 0.014$  and  $p = 0.022$ , respectively).

### 3.4. Impact of Tracheostomy

Tracheostomy was significantly associated with decreased hospital mortality (crude HR: 0.347, 95% CI: 0.179–0.670,

$p = 0.002$ ) (Table 4). Similar associations were observed between tracheostomy and ICU mortality (crude HR: 0.277, 95% CI: 0.126–0.611,  $p = 0.001$ ) and 28-day mortality (crude HR: 0.304, 95% CI: 0.104–0.889,  $p = 0.030$ ). Supplemental Digital Content 3 shows the association between tracheostomy and mortality in this cohort when divided into two groups based on the median APACHE II scores. Similar trends were observed regardless of severity of illness at ICU admission ( $p$  values for interaction  $\geq 0.05$ ). After adjusting for confounding factors, the multivariable analysis demonstrated a reduction in mortality with tracheostomy (adjusted HR for hospital mortality: 0.413, 95% CI: 0.210–0.814,  $p = 0.011$ ). The Cox proportional hazards regression analysis after adjustment with IPTW showed that patients who underwent tracheostomy had a lower risk for hospital mortality (HR: 0.316, 95% CI: 0.163–0.612,  $p < 0.001$ ), as well as ICU and 28-day mortality when compared with those who received PMV without tracheostomy.

The clinical outcomes of the various statistical methods are summarized in Supplemental Digital Content 4. Among the 149 patients who required MV for >10 days or who under-

**Table 4.** Association between tracheostomy and clinical outcomes: Cox regression analysis.

Outcomes	Original cohort		IPTW			
	Crude HR (95% CI)	p value	Adjusted HR (95% CI) <sup>a</sup>	p value	Crude HR (95% CI)	p value
ICU mortality	0.277 (0.126–0.611)	0.001	0.312 (0.134–0.725)	0.007	0.269 (0.124–0.581)	<0.001
28-day mortality	0.304 (0.104–0.889)	0.030	0.322 (0.108–0.958)	0.042	0.281 (0.094–0.839)	0.023
Hospital mortality	0.347 (0.179–0.670)	0.002	0.413 (0.210–0.814)	0.011	0.316 (0.163–0.612)	<0.001

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; ICU, intensive care unit; IPTW, Inverse Probability Treatment Weighting; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

<sup>a</sup> Adjusted HR for age, sex, APACHE II score, and the use of ECMO (VV-ECMO or VA-ECMO) during ICU stay.

went tracheostomy, decreased hospital mortality was significantly associated with tracheostomy (crude HR: 0.386, 95% CI: 0.205–0.727,  $p = 0.003$ ). Similar associations were observed among the 95 patients who required MV for >18 days or who underwent tracheostomy (crude HR for hospital mortality: 0.327, 95% CI: 0.164–0.653,  $p = 0.002$ ). Moreover, sensitivity analyses indicated that the prognosis was consistently favorable for patients who underwent tracheostomy, irrespective of the statistical method or PMV duration. Similar trends were observed in evaluations using the PMV definition of >7 days in addition to  $14 \pm 4$  days (among 190 patients, crude HR for hospital mortality: 0.471, 95% CI: 0.252–0.882,  $p = 0.019$ ).

## 4. Discussion

### 4.1. Key findings

Using the JIPAD registry, we conducted a multi-institutional observational study involving critically ill COVID-19 patients who required PMV. We found that approximately 60% of the patients underwent tracheostomy during their ICU stay. Our data revealed that the implementation of tracheostomy was associated with lower mortality in patients with COVID-19 who required PMV for >14 days. The clinical advantage of performing tracheostomy was reinforced with the adjustments using the IPTW method and sensitivity analyses with different PMV durations. These findings could help improve the prognosis of critically ill patients with COVID-19.

### 4.2. Relationship with previous studies

Critically ill patients who underwent MV due to COVID-19 have been reported to have high mortality rates (28–53%) in large cohorts [8,9,25,26]. These previous findings are similar to those from our ICU database, with the hospital mortality rate for patients requiring PMV for >14 days being as high as 34.9%. In a multicenter prospective cohort study using propensity score matching that was conducted using data from 50 countries, among patients with acute respiratory distress syndrome, those who underwent tracheostomy reportedly had significantly lower 28-day hospital mortality rates

than those who did not undergo tracheostomy [27]. Consequently, the potential improvement of outcomes caused by implementation of tracheostomy in COVID-19 patients has been investigated and described in several case series since the outbreak of the pandemic [16,17,28,29].

Conventional international consensus recommends MV via translaryngeal endotracheal intubation for patients with an expected MV duration <10 days and transition to tracheostomy for those with an expected MV duration of >21 days [30]. As numerous reports have shown that early tracheostomy is associated with improved patient outcomes [6,31], tracheostomy is widely considered to be performed within 1–2 weeks after MV initiation in critical care settings [32–34]. However, excessive concerns about the risk of viral transmission to clinicians have been noted, and global guidelines recommend delaying tracheostomy for at least 2–3 weeks after intubation during a pandemic [12–14,35–37]. Consequently, hesitation in performing tracheostomy reportedly resulted in the development of dysphonia, dysphagia, and airway stenosis among patients [38,39]. After approximately 1 year of experience with the COVID-19 pandemic, accumulated evidence on procedural guidelines for tracheostomy and its appropriate safety has been summarized in an updated review article [20]. In addition, a large descriptive study involving COVID-19 patients who underwent tracheostomy was recently reported in Spain [40]. A follow-up of 1 month for 1890 patients across 120 hospitals showed a low mortality rate (23.7%). Furthermore, surgeons performing tracheostomies at a median of 12 days post-intubation presented no symptoms for 2 weeks after the procedure and were proven to be antibody-negative. Based on these emerging reports, the recommendation for expeditious implementation of tracheostomy is now advocated again, regardless of whether the patient is COVID-19-positive or negative [41].

In a single-center prospective cohort study of 164 COVID-19 patients who required MV, tracheostomy was reported in 100 (61%) patients [19]. Despite similar baseline characteristics, patients who underwent tracheostomy showed a significantly higher 30-day survival rate than those who did not (85% vs. 42%, relative risk: 3.9, 95% CI: 2.3–6.4). The study also showed that aggressive tracheostomy implementation within 14 days was associated with a significantly shorter mean MV duration (21 vs. 27 days) and shorter mean ICU

stay (23 vs. 30 days). Similarly, the present study found that 60.6% of critically ill COVID-19 patients who required PMV underwent tracheostomy, providing definitive evidence of the favorable effect of tracheostomy on mortality. Hospital mortality significantly reduced in patients who underwent tracheostomy (crude HR: 0.347,  $p = 0.002$ ), and the benefit was supported by adjustments in patient characteristics and the sensitivity analysis. However, the patients in our study who underwent tracheostomy did not have a shorter duration of MV in the ICU or short ICU or hospital stays. Approximately half of the patients with COVID-19 who required PMV were transferred to other hospitals; they are more than the 23.8% of critically ill adults transferred to other hospitals in the JIPAD report before the COVID-19 pandemic [21]. Moreover, the nationwide shortage of ICU beds could have influenced the timing of discharge and transfers [42]. Hence, the impact of tracheostomy on the duration of treatment remains unclear.

#### 4.3. Implementation of tracheostomy in ICUs

In critical care settings, tracheostomy is performed to accelerate liberation from MV. Tracheostomy is recommended in patients with anticipated PMV; however, prediction of the required duration of MV has no well-defined rule [43]. Additionally, tracheostomy may also be performed due to upper airway obstruction, laryngeal edema, or viscous secretions and its indication may be a comprehensive decision by a multidisciplinary team [44,45]. These issues make it challenging to conduct appropriate investigations regarding the impact of tracheostomy. In this study, patients who underwent tracheostomy demonstrated a significantly more favorable prognosis compared to those who did not, after adjusting for potential confounders, with a median observed in-hospital survival of 28 (IQR 15.5–54.5) days after its implementation. There were no nationwide specified indications for performing tracheostomy during the study period and the individual reasons for tracheostomy were not noted in our database. However, tracheostomy in patients requiring PMV was performed with no inter-institutional differences, and tracheostomy rates for each epidemic wave were similar during the observation period. Furthermore, patients who underwent tracheostomy had similar severity of illness on admission to the ICU and treatment (ECMO or CRRT) during their stay in the ICU to those who did not. In the analysis stratified by APACHE II score, the two groups showed similar trends for either mortality rate, although the  $P$  values for Crude HR were  $\geq 0.05$  for 28-day mortality with missing data ( $n = 92/109$ ). These suggest that the decision to perform tracheostomy depended on other factors (risk of infection exposure for clinicians and availability of the procedure), rather than the patient's clinical condition. Moreover, this study was conducted as an association study of tracheostomy and patient outcomes in COVID-19 patients requiring PMV, and it did not determine the optimal timing of tracheostomy. The timing of tracheostomy has been under investigation, especially recently, and the advantages of early tracheostomy have been reported in some studies [46–48]. Therefore, the results of this na-

tionwide database-based study in Japan provides a firm basis for future investigations regarding the criteria for performing tracheostomy.

#### 4.4. Implications of study findings

Our findings imply that the implementation of tracheostomy may lead to a more favorable prognosis in critically ill patients with COVID-19 who require PMV. Tracheostomy itself is a standard procedure and should be adequately performed in ICUs in patients with COVID-19 in accordance with the relevant guidelines. Considering the significance of the present results, the indication for this appropriate procedure should be aggressively assessed by a multidisciplinary team in patients with COVID-19 who have an expected MV duration of  $>14$  days.

#### 4.5. Strengths and limitations

This study had several strengths and limitations. Having used a nationwide ICU database, the study is representative of a large number of institutions and thus has a broad generalizability. The primary limitation of this study was that it was a retrospective observational study. The study results are prone to misinterpretation and residual confounding. Second, the sample size and number of events were limited, despite the use of a registry involving numerous institutions. Third, the indications and procedures for tracheostomy were not protocolized, and the possible potential confounders precluded us from considering the detailed timing of tracheostomy. Fourth, the registry did not include information on the respiratory status or concomitant therapy at the time of tracheostomy, or detailed conditions at the varying institutions—such as medical resources.

## 5. Conclusions

According to analyses of data from the JIPAD registry, tracheostomy was significantly associated with reduced mortality in patients who required PMV due to COVID-19. Our findings provide firm evidence to endorse the proactive implementation of tracheostomy in critically ill COVID-19 patients who require PMV. These findings should be confirmed in further controlled trials.

#### Declaration of Competing Interest

The authors have reported that no support, including grants, equipment, or drugs, was received for this study.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.anl.2022.06.002.

## References

- [1] Cavaliere S, Bezzi M, Toninelli C, Foccoli P. Management of post-intubation tracheal stenoses using the endoscopic approach. *Monaldi Arch Chest Dis* 2007;67(2):73–80.
- [2] Andriolo BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev* 2015;1:CD007271.
- [3] de Carvalho Baptista IM, Martinho FC, Nascimento GG, da Rocha Santos CE, Prado RFD, Valera MC. Colonization of oropharynx and lower respiratory tract in critical patients: risk of ventilator-associated pneumonia. *Arch Oral Biol* 2018;85:64–9.
- [4] Nieszkowska A, Combes A, Luyt CE, Ksibi H, Trouillet JL, Gibert C, et al. Impact of tracheostomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients. *Crit Care Med* 2005;33(11):2527–33.
- [5] Diehl JL, El Atrous S, Touchard D, Lemaire F, Brochard L. Changes in the work of breathing induced by tracheostomy in ventilator-dependent patients. *Am J Respir Crit Care Med* 1999;159(2):383–8.
- [6] Chorath K, Hoang A, Rajasekaran K, Moreira A. Association of early vs late tracheostomy placement with pneumonia and ventilator days in critically ill patients: a meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2021.
- [7] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
- [8] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA* 2020;323(13):1239–42.
- [9] Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med* 2020;8(9):853–62.
- [10] Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581(7809):465–9.
- [11] Lamb CR, Desai NR, Angel L, Chaddha U, Sachdeva A, Sethi S, et al. Use of tracheostomy during the COVID-19 pandemic: American college of chest physicians/American association for bronchology and interventional pulmonology/Association of interventional pulmonology program directors expert panel report. *Chest* 2020;158(4):1499–514.
- [12] Sommer DD, Engels PT, Weitzel EK, Khalili S, Corsten M, Tewfik MA, et al. Recommendations from the CSO-HNS taskforce on performance of tracheostomy during the COVID-19 pandemic. *J Otolaryngol Head Neck Surg* 2020;49(1):23.
- [13] Takhar A, Walker A, Tricklebank S, Wyncoll D, Hart N, Jacob T, et al. Recommendation of a practical guideline for safe tracheostomy during the COVID-19 pandemic. *Eur Arch Otorhinolaryngol* 2020;277(8):2173–84.
- [14] Miles BA, Schiff B, Ganly I, Ow T, Cohen E, Genden E, et al. Tracheostomy during SARS-CoV-2 pandemic: recommendations from the New York head and neck society. *Head Neck* 2020;42(6):1282–90.
- [15] Thal AG, Schiff BA, Ahmed Y, Cao A, Mo A, Mehta V, et al. Tracheostomy in a high-volume center during the COVID-19 pandemic: evaluating the surgeon's risk. *Otolaryngol Head Neck Surg* 2021;164(3):522–7.
- [16] Aviles-Jurado FX, Prieto-Alhambra D, Gonzalez-Sanchez N, de Osso J, Arancibia C, Rojas-Lechuga MJ, et al. Timing, complications, and safety of tracheostomy in critically ill patients with COVID-19. *JAMA Otolaryngol Head Neck Surg* 2020;147(1):1–8.
- [17] Yokokawa T, Ariizumi Y, Hiramatsu M, Kato Y, Endo K, Obata K, et al. Management of tracheostomy in COVID-19 patients: the Japanese experience. *Auris Nasus Larynx* 2021;48(3):525–9.
- [18] Bassi M, Ruberto F, Poggi C, Diso D, Anile M, De Giacomo T, et al. Is surgical tracheostomy better than percutaneous tracheostomy in COVID-19-positive patients? *Anesth Analg* 2020;131(4):1000–5.
- [19] Queen Elizabeth Hospital Birmingham C-atSafety and 30-day outcomes of tracheostomy for COVID-19: a prospective observational cohort study. *Br J Anaesth* 2020;125(6):872–9.
- [20] Al Omari A, Al-Ashqar R, Alabd Alrhmman R, Nuseir A, Allan H, Al-zoubi F. Assessment of the harms and potential benefits of tracheostomy in COVID-19 patients: narrative review of outcomes and recommendations. *Am J Otolaryngol* 2021;42(4):102972.
- [21] Irie H, Okamoto H, Uchino S, Endo H, Uchida M, Kawasaki T, et al. The Japanese Intensive care PATient Database (JIPAD): a national intensive care unit registry in Japan. *J Crit Care* 2020;55:86–94.
- [22] Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100(6):1619–36.
- [23] Osaka prefectural government osaka prefecture new coronavirus countermeasures headquarters meeting. 2020, [http://www.pref.osaka.lg.jp/kikaku\_keikaku/sarscov2/]
- [24] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550–60.
- [25] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- [26] Zha L, Sobue T, Takeuchi T, Tanaka K, Katayama Y, Komukai S, et al. Characteristics and survival of intensive care unit patients with coronavirus disease in Osaka, Japan: a retrospective observational study. *J Clin Med* 2021;10(11).
- [27] Abe T, Madotto F, Pham T, Nagata I, Uchida M, Tamiya N, et al. Epidemiology and patterns of tracheostomy practice in patients with acute respiratory distress syndrome in ICUs across 50 countries. *Crit Care* 2018;22(1):195.
- [28] Chao TN, Harbison SP, Braslow BM, Hutchinson CT, Rajasekaran K, Go BC, et al. Outcomes after tracheostomy in COVID-19 patients. *Ann Surg* 2020;272(3):e181–e1e6.
- [29] Cardasis J.J., Rasamny J.K., Berzofsky C.E., Bello J.A., Multz A.S. Outcomes after tracheostomy for patients with respiratory failure due to COVID-19. *Ear Nose Throat J*. 2021;145561321993567.
- [30] Plummer AL, Gracey DR. Consensus conference on artificial airways in patients receiving mechanical ventilation. *Chest* 1989;96(1):178–80.
- [31] Deng H, Fang Q, Chen K, Zhang X. Early versus late tracheostomy in ICU patients: a meta-analysis of randomized controlled trials. *Medicine* 2021;100(3):e24329 (Baltimore).
- [32] McWhorter AJ. Tracheotomy: timing and techniques. *Curr Opin Otolaryngol Head Neck Surg* 2003;11(6):473–9.
- [33] Veenith T, Ganeshamoorthy S, Standley T, Carter J, Young P. Intensive care unit tracheostomy: a snapshot of UK practice. *Int Arch Med* 2008;1(1):21.
- [34] Vargas M, Sutherasan Y, Antonelli M, Brunetti I, Corcione A, Lafey JG, et al. Tracheostomy procedures in the intensive care unit: an international survey. *Crit Care* 2015;19:291.
- [35] Martín Delgado MC, Avilés-Jurado FX, Álvarez Escudero J, Aldecoa Álvarez-Santuyano C, de Haro López C, Díaz de Cerio Canduela P, et al. Consensus document of the Spanish society of intensive and critical care medicine and coronary units (SEMICYUC), the Spanish society of otorhinolaryngology and head and neck surgery (SEORL-CCC) and the Spanish society of anesthesiology and resuscitation (SEDAR) on tracheostomy in patients with COVID-19 infection. *Med. Inten.* 2020;44(8):493–9 (English Edition).
- [36] Chiang SS, Aboutanos MB, Jawa RS, Kaul SK, Houg AP, Dicker RA, et al. Controversies in tracheostomy for patients with COVID-19: the when, where, and how. *Respir Care* 2020;65(11):1767–72 .
- [37] Bier-Laning C, Cramer JD, Roy S, Palmieri PA, Amin A, Anon JM, et al. Tracheostomy during the COVID-19 pandemic: comparison of



- international perioperative care protocols and practices in 26 countries. *Otolaryngol Head Neck Surg* 2021;164(6):1136–47.
- [38] Scholfield DW, Warner E, Ahmed J, Ghufour K. Subglottic and tracheal stenosis associated with coronavirus disease 2019. *J Laryngol Otol* 2021;135(7):656–8.
- [39] Brodsky MB, Freeman-Sanderson A, Brenner MJ. Voice, swallow, and airway impairment after late tracheostomy: defining features of COVID-19 survivorship. *Laryngoscope* 2021;131(7):E2311.
- [40] Martin-Villares C, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M, Group COEC. Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. *Eur Arch Otorhinolaryngol* 2021;278(5) 1605–12.
- [41] Brenner MJ, Feller-Kopman D, De Cardenas J. POINT: tracheostomy in patients with COVID-19: should we do it before 14 days? Yes. *Chest* 2021;159(5) 1723–7.
- [42] Jen GH, Chen SY, Chang WJ, Chen CN, Yen AM, Chang RE. Evaluating medical capacity for hospitalization and intensive care unit of COVID-19: a queue model approach. *J Formos Med Assoc* 2021;120(Suppl 1):S86–94.
- [43] Raimondi N, Vial MR, Calleja J, Quintero A, Cortes A, Celis E, et al. Evidence-based guidelines for the use of tracheostomy in critically ill patients. *J Crit Care* 2017;38:304–18.
- [44] McGrath BA, Brenner MJ, Warrillow SJ, Pandian V, Arora A, Cameron TS, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Respir Med* 2020;8(7):717–25.
- [45] Sancho J, Ferrer S, Lahosa C, Posadas T, Bures E, Banuls P, et al. Tracheostomy in patients with COVID-19: predictors and clinical features. *Eur Arch Otorhinolaryngol* 2021.
- [46] Takhar A, Surda P, Ahmad I, Amin N, Arora A, Camporota L, et al. Timing of tracheostomy for prolonged respiratory wean in critically ill coronavirus disease 2019 patients: a machine learning approach. *Crit Care Explor* 2020;2(11) e0279.
- [47] Hansson A, Sunnergren O, Hammarskjöld A, Alkemark C, Taxbro K. Characteristics, complications, and a comparison between early and late tracheostomy: a retrospective observational study on tracheostomy in patients with COVID-19-related acute respiratory distress syndrome. *Health Sci Rep* 2022;5(3):e595.
- [48] Ji Y, Fang Y, Cheng B, Li L, Fang X. Tracheostomy timing and clinical outcomes in ventilated COVID-19 patients: a systematic review and meta-analysis. *Crit Care* 2022;26(1).