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# Epidemiology and patterns of tracheostomy practice in patients with acute respiratory distress syndrome in ICUs across 50 countries

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## Abstract

**Background:** To better understand the epidemiology and patterns of tracheostomy practice for patients with acute respiratory distress syndrome (ARDS), we investigated the current usage of tracheostomy in patients with ARDS recruited into the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) study.

**Methods:** This is a secondary analysis of LUNG-SAFE, an international, multicenter, prospective cohort study of patients receiving invasive or noninvasive ventilation in 50 countries spanning 5 continents. The study was carried out over 4 weeks consecutively in the winter of 2014, and 459 ICUs participated. We evaluated the clinical characteristics, management and outcomes of patients that received tracheostomy, in the cohort of patients that developed ARDS on day 1–2 of acute hypoxemic respiratory failure, and in a subsequent propensity-matched cohort.

**Results:** Of the 2377 patients with ARDS that fulfilled the inclusion criteria, 309 (13.0%) underwent tracheostomy during their ICU stay. Patients from high-income European countries ( $n = 198/1263$ ) more frequently underwent tracheostomy compared to patients from non-European high-income countries ( $n = 63/649$ ) or patients from middle-income countries ( $n = 48/465$ ). Only 86/309 (27.8%) underwent tracheostomy on or before day 7, while the median timing of tracheostomy was 14 (Q1–Q3, 7–21) days after onset of ARDS. In the subsample matched by propensity score, ICU and hospital stay were longer in patients with tracheostomy. While patients with tracheostomy had the highest survival probability, there was no difference in 60-day or 90-day mortality in either the patient subgroup that survived for at least 5 days in ICU, or in the propensity-matched subsample.

**Conclusions:** Most patients that receive tracheostomy do so after the first week of critical illness. Tracheostomy may prolong patient survival but does not reduce 60-day or 90-day mortality.

**Trial registration:** ClinicalTrials.gov, [NCT02010073](https://clinicaltrials.gov/ct2/show/study/NCT02010073). Registered on 12 December 2013.

**Keywords:** Tracheostomy, Acute respiratory distress syndrome (ARDS), ICU, Ventilation, Propensity-matched analysis

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## Background

Tracheostomy is a widely used intervention in patients with acute respiratory failure, especially when clinicians predict a patient's need for prolonged mechanical ventilation. This well-tolerated procedure reduces the requirement for sedation, results in better patient comfort, and facilitates earlier resumption of patient autonomy [1, 2]. On the other hand, tracheostomy carries risks of adverse events including procedure-related complications including death (albeit rare) and later cosmetic concerns [3]. The use of this procedure has increased over the last decade, in part because of the introduction of a practical bedside percutaneous tracheostomy technique.

Acute respiratory distress syndrome (ARDS) is a major cause of respiratory failure and presents significant clinical challenges. It accounts for about 10% of ICU admissions [4]. The Large observational study to understand the global impact of severe acute respiratory failure (LUNG-SAFE study) showed that this syndrome was both under-recognized and under-treated and associated with a high mortality rate [5]. In this study, tracheostomy was performed on 13% of the patients with ARDS [5]. However, few data are available on the current practice of tracheostomy in the ICU setting [6]. Studies examining tracheostomy practices have been confined to single countries [7], sometimes gathered in meta-analyses [8, 9]. There is a lack of detailed information on global patterns of the use of tracheostomy, patient characteristics, the management of patients with tracheostomy, and the outcomes of these patients [10]. The impact on clinical practice of the TracMan clinical trial [11], which showed no benefit for early compared to later tracheostomy, remains unclear. Given these issues, the aim of our study was to investigate by secondary analysis the current patterns of tracheostomy usage in patients with ARDS requiring invasive mechanical ventilation.

## Methods

### Design, setting, and participants

This is a sub-study of the LUNG-SAFE study, an international, multicenter, prospective cohort study of patients receiving invasive or noninvasive ventilation. LUNG-SAFE used a convenience sample of 459 ICUs located in 50 countries, spanning 6 continents. The study was conducted over 4 weeks consecutively in each participating ICU in the winter of 2014 [5]. This study examined current use of tracheostomy in patients with ARDS requiring mechanical ventilation in ICUs. We included adult patients ( $\geq 16$  years old) fulfilling ARDS criteria (according to the Berlin definition) who received invasive mechanical ventilation on day 1 or 2 from onset of acute hypoxemic respiratory failure (Fig. 1).

### Data collection and analysis

LUNG-SAFE is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov), number NCT02010073. Data were obtained from the LUNG-SAFE database, which was collected by the LUNG-SAFE investigators and the European Society of Intensive Care Medicine (ESICM) Trials Group [5]. Our study population was divided into two groups (tracheostomy and non-tracheostomy) according to whether tracheostomy was performed during the first 28 days in ICU after onset of acute hypoxemic respiratory failure. In each group, demographic factors, ARDS risk factors, patients' comorbidities, illness severity, management factors such as ventilation setting measured on the day of ARDS onset, and outcomes that occurred during the ICU and hospital stay (days of mechanical ventilation, ventilator free days (VFDs), length of stay, and 28-day, 60-day, and 90-day mortality) were analyzed. In order to reduce the impact of the immortal time bias (i.e. bias due to fact that the patient had to be alive and still in the ICU to receive a tracheostomy) for tracheostomized patients, length of ICU and hospital stay, and 28-day, 60-day and 90-day mortality were calculated from the first day on which the investigator reported that the patient was tracheostomized. The impact of geo-economic location was also examined, with 3 areas defined: (1) European countries with high income, (2) non-European rest of world high-income countries (rWORLD), and (3) middle-income countries [10]. VFDs were defined as the number of days a patient was breathing without a ventilator during the 28-day study period, which began at the time of enrollment. Patients who died during the study period were assigned 0 for the number of VFDs. Since the amount of missing values was low, as previously reported [1], no assumptions were made for missing data.

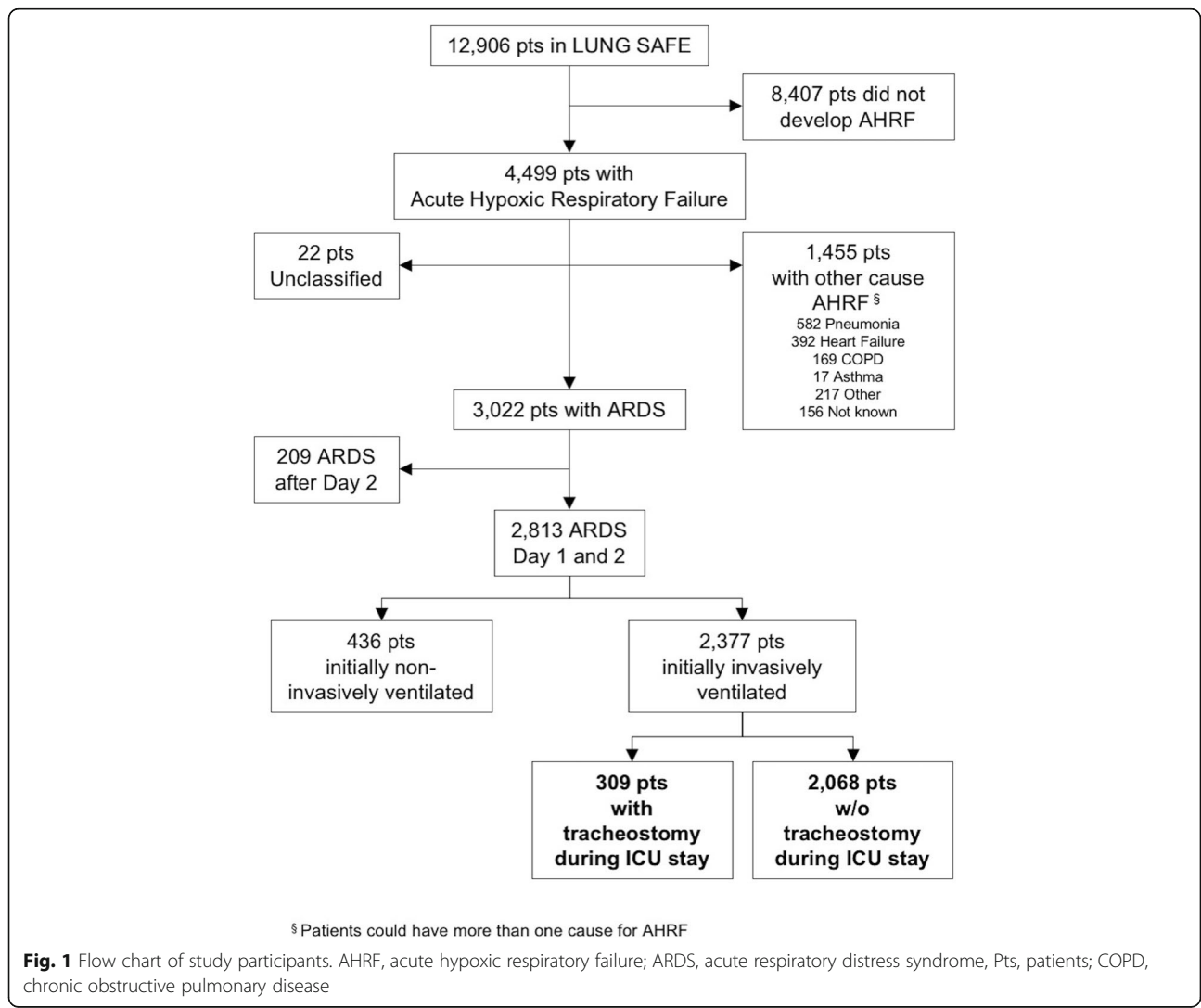
Descriptive statistics included proportions for categorical variables and mean (standard deviation) or median (interquartile range (Q1–Q3)) for continuous variables. Comparisons between groups were assessed using the chi-square or Fisher exact test for discrete variables and Student *t* test or Wilcoxon rank-sum test for continuous variables, according to the data distribution (evaluated using the Shapiro-Wilk test). ICU and hospital mortality were evaluated at ICU or hospital discharge, or at day 90, whichever occurred first [4]. Survival analysis (Kaplan-Meier (K-M) approach) was performed to investigate the time to survival in patients with or without tracheostomy. We assumed that patients discharged alive from hospital before 90 days were alive on day 90. The difference in K-M curves between the groups was assessed using the log-rank test. We further evaluated the outcomes in the subgroup of patients who had ICU stays of at least 5 days duration (from acute hypoxemic respiratory failure onset), excluding those who died

within 4 days, in order to reduce the potential for immortal time bias.

**Propensity-score matching**

To assess the effect of tracheostomy on hospital mortality and other outcomes of interest and to reduce the potential for confounding by selection, we matched patients using the propensity-score matching approach. Logistic regression was used to estimate propensity scores able to predict the probability of undergoing tracheostomy. We included predictors that would affect the indication for tracheostomy (chosen a priori as possibly influencing the choice between tracheostomy or not): age, gender, and body mass index (BMI), region of enrollment, type of admission (medical, surgical planned or not, and trauma), comorbidities, ARDS risk factors (no risk factors, only direct risk factor, only indirect risk factor, both risk factors), use of extracorporeal membrane oxygenation (ECMO), arterial gas measures (pH,

partial arterial pressure of oxygen (PaO<sub>2</sub>)/inspired fraction of oxygen (F<sub>I</sub>O<sub>2</sub>), and partial arterial pressure of carbon dioxide (PaCO<sub>2</sub>)) and non-respiratory sequential failure organ assessment (SOFA) score adjusted for missing values measured at date of ARDS onset. For tracheostomized patients, we used arterial blood gas and SOFA score measured on the last day before tracheostomy. Patients with similar propensity score in the two groups were matched (1:1 match without replacement), using a caliper of 0.2 standard deviation of the logit of the propensity score. We matched the data of the tracheostomized patient on one day before tracheostomy with those of a non-tracheostomized patient when they met the criteria for ARDS. We assessed the similarity of the matched groups through the standardized differences of each predictor. Statistical significance of the difference in means was evaluated by paired *t* test or Wilcoxon signed-rank test, while for the difference in proportions we applied McNemar's test. The primary



outcome was 90-day survival. The difference between the K-M survival curves in matched groups was assessed according to the test proposed by Klein and Moeschberger.

All *P* values were two-sided, with *P* values less than 0.05 considered as statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and R, version 3.3.3 (R Project for Statistical Computing, <http://www.R-project.org>).

## Results

Of the 2377 participants who were diagnosed with ARDS, according to the Berlin definition, on the 1st or 2nd day following development of acute hypoxemic respiratory failure and initially invasively ventilated, 309 (13.0%) underwent tracheostomy during their ICU stay (Fig. 1).

Patient demographics, including age, gender, and BMI did not differ between patients with or without tracheostomy (Table 1). There were significant variations with geo-economic region associated with the frequency of tracheostomy ( $P = 0.0002$ ). High-income European areas had a greater frequency of tracheostomy than other areas. However, there was no significant difference in the frequency of undergoing tracheostomy between rWORLD countries and middle-income countries ( $P = 0.7353$ ). Severity of ARDS at day 1 was also similar between the two groups (Table 1). Patients undergoing tracheostomy were more likely to have undergone elective surgery (Table 1), to have come from other hospital ICUs, have a lower frequency of chronic liver failure, and a higher frequency of pneumonia compared to patients that did not receive a tracheostomy (Additional file 1: Table S1). A large proportion of patients who received a tracheostomy received mechanical ventilation with spontaneous ventilator modes. Additional file 1 shows this in more detail. More patients who were on ECMO received tracheostomy compared to patients who were not on ECMO (Table 1).

The median timing of tracheostomy was 14 (Q1–Q3, 7–21) days after onset of ARDS. Only 27.8% patients received tracheostomy within 7 days (Fig. 2), whereas 74.8% received it within 14 days. There was no difference in unadjusted outcome between patients receiving early versus late tracheostomy (Additional file 2: Table S2). Additional file 2 shows this in more detail.

The duration of mechanical ventilation in patients that received tracheostomy was significantly longer than that in those that did not (median (Q1–Q3) 21.5 (13–33) days vs 7 (4–13) days,  $P < 0.0001$ ) (Table 2). Moreover, VFDs in the tracheostomy group was significantly shorter than in the non-tracheostomy group (median (Q1–Q3) 0 (0–13) days vs 15 (0–23) days,  $P < 0.0001$ ). The length of ICU and hospital stay was also longer in patients that received tracheostomy (11 (5–23) days vs 8

(4–15) days,  $P < 0.0001$  and 24 (9–44) days vs 14 (7–27) days,  $P < 0.0001$ , respectively).

The 28-day crude mortality in tracheostomized patients (23.4%) was lower than that in non-tracheostomized patients (38.1%). The 60-day and 90-day crude mortality in tracheostomized patients were both lower than that in non-tracheostomized patients (29.5% vs 41.1%,  $P = 0.0001$  and 30.8% vs 41.8%,  $P = 0.0003$ , respectively). Survival analyses showed that, at any instance during the first 90 days after enrollment, tracheostomized patients were less likely to die than those in the non-tracheostomy group (30 days,  $P < 0.0001$ ; 60 days  $P < 0.0001$ ; 90 days,  $P = 0.0001$ ; Table 2 and Fig. 3).

To reduce the impact of survivor bias, we analyzed the subgroup of patients who had been in the ICU for at least 5 days ( $n = 1670$ ). Of these patients, 17.4% were tracheostomized (290 patients). Again, we found that the duration of mechanical ventilation in the tracheostomy group was significantly longer than that in the non-tracheostomy group (median (Q1–Q3) 22 (14–34) days versus 10 (7–16) days,  $P < 0.0001$ ). Also, the length of hospital stay in the tracheostomy group was significantly longer than that in the non-tracheostomy group (25.5 (11–45) vs 20 (12–34) days,  $P = 0.0375$ ), but the length of ICU stay was similar (12 (6–24) vs 12 (8–20) days,  $P = 0.2735$ ). While 28-day mortality was significantly lower in patients that underwent tracheostomy (22.4% vs 30.3%), there was no significant difference between groups in 60-day (29.0% vs 34.6%,  $P = 0.06$ ) or 90-day (30.3% vs 35.6%,  $P = 0.09$ ) mortality.

In the propensity-matched analysis, 534 patients with and without tracheostomy were matched ( $n = 267$  per group). Table 3 lists the baseline characteristics of propensity-matched patients. There was no significant difference in the chosen covariates between matched tracheostomized patients and non-tracheostomized patients (all standardized differences  $< 0.1$ ). The histograms of the logit of propensity scores showed the good quality of the matching procedure (Fig. 4). The duration of mechanical ventilation in the tracheostomy group was significantly longer than that in the non-tracheostomy group (median (Q1–Q3) 22 (12–33.5) days vs Q1–Q3 (4–12) days,  $P < 0.0001$ ). The length of ICU and hospital stay in the tracheostomy group was significantly longer than that in the non-tracheostomy group (11 (5–24) vs Q1–Q3 (5–14) days,  $P < 0.0001$  and 24 (9–43) vs 17 (10–31) days,  $P = 0.0190$ , respectively). Survival analysis showed that patients receiving tracheostomy had higher survival probability during the follow-up time compared to those without it (Klein and Moeschberger test,  $P = 0.0379$ ) (Fig. 5). While the 28-day mortality was lower in the tracheostomy group as compared with non-tracheostomy group (22.9% vs 31.8%,  $P = 0.02$ ) (Table 4), the 60-day (29.3% vs 36.3%,  $P = 0.08$ ) or 90-day (30.5% vs 38.2%,  $P$

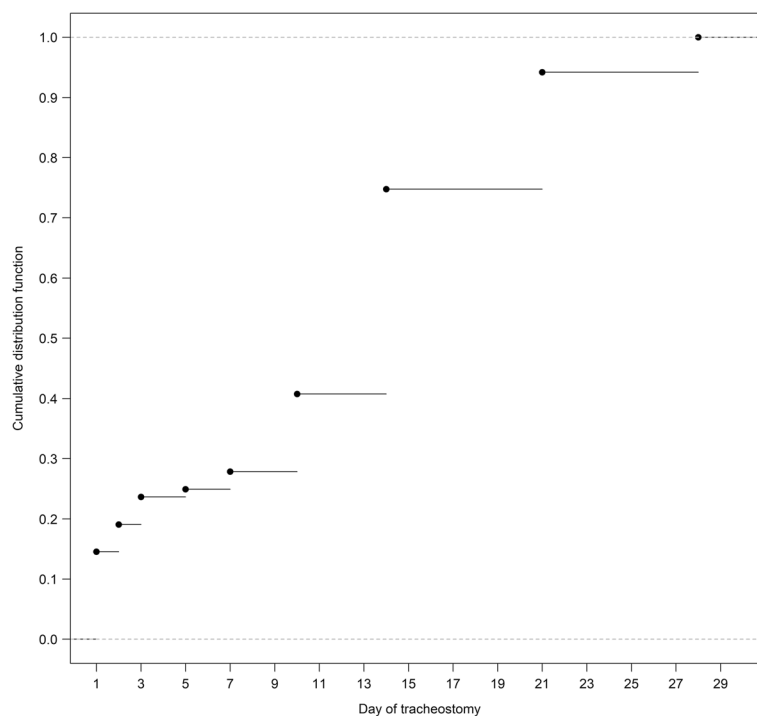
**Table 1** Baseline characteristics in patients with tracheostomy and patients with no tracheostomy. (*n* = 2377)

|  | Tracheostomy ( <i>n</i> = 309) | No tracheostomy ( <i>n</i> = 2068) | <i>P</i> value |
|--|--------------------------------|------------------------------------|----------------|
|  | Number (%) or median (Q1-Q3)   | Number (%) or median (Q1-Q3)       |                |
| Age (years)  | 63 (49–72)                     | 63 (50–74)                         | 0.1443         |
| Sex (male)   | 200 (64.7)                     | 1272 (61.5)                        | 0.2775         |
| BMI (kg/m <sup>2</sup> )   | 27.1 (23.1–30.8)               | 26.0 (22.9–30.4)                   | 0.1410         |
| Geo-economic area  |                                |                                    | 0.0002         |
| European countries with high income  | 198/1263 (15.7)                | 1065/1263 (84.3)                   |                |
| Non-European countries (rest of world) with high income                            | 63/649 (9.7)                   | 586/649 (90.3)                     |                |
| Countries with middle income   | 48/465 (10.3)                  | 417/465 (89.7)                     |                |
| Severity of ARDS at day 1  |                                |                                    | 0.9271         |
| Mild   | 95 (30.7)                      | 619 (29.9)                         |                |
| Moderate   | 144 (46.6)                     | 962 (46.5)                         |                |
| Severe   | 70 (22.7)                      | 487 (23.6)                         |                |
| Type of admission  |                                |                                    | 0.0194         |
| Medical  | 211 (68.3)                     | 1554 (75.2)                        |                |
| Surgical   | 20 (6.5)                       | 123 (6.0)                          |                |
| Postoperative (elective)   | 56 (18.1)                      | 310 (15.0)                         |                |
| Trauma   | 22 (7.1)                       | 81 (4.0)                           |                |
| Cause of AHRF  |                                |                                    |                |
| Pneumonia  | 213 (68.9)                     | 1295 (62.6)                        | 0.0317         |
| Cardiac failure  | 43 (12.9)                      | 311 (15.0)                         | 0.6051         |
| Asthma   | 4 (1.3)                        | 29 (1.4)                           | 1.0000         |
| ARDS (i.e. clinician recognized)   | 103 (33.3)                     | 684 (33.1)                         | 0.9284         |
| COPD   | 29 (9.4)                       | 205 (9.9)                          | 0.7714         |
| Unknown  | 15 (4.9)                       | 117 (5.7)                          | 0.5652         |
| Others   | 54 (17.5)                      | 418 (20.2)                         | 0.2606         |
| ARDS risk factor   |                                |                                    | 0.1675         |
| No risk factor   | 19 (6.1)                       | 157 (7.6)                          |                |
| Only indirect risk factors   | 53 (17.1)                      | 429 (20.7)                         |                |
| Only direct risk factors   | 194 (62.8)                     | 1160 (56.1)                        |                |
| Both risk factor types   | 43 (13.9)                      | 322 (15.6)                         |                |
| Illness severity at ARDS onset   |                                |                                    |                |
| pH   | 7.37 (7.29–7.43)               | 7.34 (7.26–7.41)                   | <.0001         |
| P/F ratio (mmHg)   | 156 (110–213)                  | 154 (103–215)                      | 0.6845         |
| PaCO <sub>2</sub> (mmHg)   | 42 (36–50)                     | 43 (37–51)                         | 0.2751         |
| Non-respiratory SOFA score (adjusted for missing values) (ARDS onset)              | 6 (4–9)                        | 7 (4–10)                           | 0.0010         |
| Non-respiratory SOFA score (adjusted for missing values) at day 2                  | 6 (4–9)                        | 6 (4–10)                           | 0.1333         |
| Difference in non-respiratory SOFA score (day2-day1) (adjusted for missing values) | 0 (–2–2)                       | 0 (–2–2)                           | 0.9598         |
| Mechanical ventilation settings at ARDS onset                                      |                                |                                    |                |
| Respiratory rate (set) (breaths/min)   | 18 (15–22)                     | 16 (14–20)                         | 0.0016         |
| Respiratory rate (total) (breaths/min)   | 20 (15–25)                     | 20 (16–24)                         | 0.2406         |
| Tidal volume (ml)  | 488 (400–550)                  | 457 (400–516)                      | 0.0105         |
| Tidal volume/IBW (ml/kg)   | 7.55 (6.34–8.96)               | 7.35 (6.39–8.48)                   | 0.4519         |
| PEEP (cmH <sub>2</sub> O)  | 8 (5–10)                       | 8 (5–10)                           | 0.0254         |

**Table 1** Baseline characteristics in patients with tracheostomy and patients with no tracheostomy. (n = 2377) (Continued)

|  | Tracheostomy (n = 309)       | No tracheostomy (n = 2068)   | P value |
|--|------------------------------|------------------------------|---------|
|  | Number (%) or median (Q1-Q3) | Number (%) or median (Q1-Q3) |         |
| Plateau pressure (cmH2O) (n = 79, n = 663) | 24 (20–27)                   | 23 (18–28)                   | 0.4957  |
| Peak inspiratory pressure (cmH2O)          | 27 (21–32)                   | 26 (22–32)                   | 0.6444  |
| Mean airway pressure (cmH2O)               | 14 (11–18)                   | 14 (11–18)                   | 0.4912  |
| Use of adjuncts                            |                              |                              |         |
| ECMO use                                   | 20 (6.5)                     | 35 (1.7)                     | <.0001  |
| High-dose corticosteroids                  | 36 (11.7)                    | 225 (10.9)                   | 0.6862  |
| Continuous sedation                        | 234 (75.7)                   | 1567 (75.8)                  | 0.9861  |
| Continuous neuromuscular blocking agents   | 34 (11.0)                    | 286 (13.8)                   | 0.1745  |
| Renal replacement therapy                  | 35 (11.3)                    | 169 (8.2)                    | 0.0648  |
| Inhaled vasodilators                       | 19 (6.2)                     | 84 (4.1)                     | 0.0928  |
| Neutrophil elastase therapy                | 3 (1.0)                      | 10 (0.5)                     | 0.2334  |
| Vasopressor used                           | 163 (52.8)                   | 1212 (58.6)                  | 0.0518  |

BMI body mass index, ICU intensive care unit, ER emergency room, COPD chronic obstructive pulmonary disease, NYHA New York heart association, AHRF acute hypoxemic respiratory failure, ARDS acute respiratory distress syndrome, TRALI transfusion-related acute lung injury, A/C assist control, PC pressure control, BiPAP bilevel positive airway pressure, APRV airway pressure release ventilation, SIMV synchronized intermittent mandatory ventilation, PRVC pressure-regulated volume control, PSV pressure support ventilation, HFO high-frequency oscillation, CPAP continuous positive airway pressure, IBW ideal body weight, PEEP positive end-expiratory pressure, ECMO extracorporeal membrane oxygenation, SOFA sequential organ failure assessment, PaCO2 partial arterial pressure of carbone dioxide  
 Missing data: BMI = 127; Ph = 25, PaCO2 = 25, respiratory rate (set) = 250, respiratory rate (total) = 10, tidal volume = 24, tidal volume/IBW = 122, peak inspiratory pressure = 89, mean airway pressure = 687, non-respiratory SOFA score (adjusted for missing values) = 22, non-respiratory SOFA score (adjusted for missing values) at day 2 = 379, difference in non-respiratory SOFA score (day2-day1) (adjusted for missing values) = 384



**Fig. 2** Distribution of time to tracheostomy (n = 309)

**Table 2** Outcomes in patients with tracheostomy and patients with no tracheostomy (n = 2377)

|  | Tracheostomy<br>Number (%) or median<br>(Q1-Q3) | No tracheostomy<br>Number (%) or median<br>(Q1-Q3) | P value |
|--|---|--|---------|
| Days of mechanical ventilation   |   |  |         |
| All patients   | 21.5 (13–33)                                    | 7 (4–13)   | <.0001  |
| Patient alive at hospital discharge  | 21 (14–32)                                      | 7 (4–12)   | <.0001  |
| Ventilator-free days   |   |  |         |
| All patients   | 0 (0–13)  | 15 (0–23)  | <.0001  |
| Patient alive at hospital discharge (n = 181, n = 1114)                          | 8 (0–15)  | 22 (17–25)   | <.0001  |
| Length of ICU stay (days) <sup>o</sup>   |   |  |         |
| All patients   | 11 (5–23)                                       | 8 (4–15)   | <.0001  |
| Patient alive at hospital discharge (n = 229, n = 1309)                          | 12 (6–24)                                       | 9 (5–16)   | 0.0005  |
| Length of hospital stay (days) <sup>o</sup>                                      |   |  |         |
| All patients   | 24 (9–44)                                       | 14 (7–27)  | <.0001  |
| Patient alive at hospital discharge (n = 200, n = 1165)                          | 29.5 (15–50.5)                                  | 20 (12–35)   | <.0001  |
| Hospital mortality   |   |  |         |
| 28-day* (n = 308, n = 2061)  | 72 (23.4)                                       | 786 (38.1)   | <.0001  |
| 60-day* (n = 308, n = 2061)  | 91 (29.5)                                       | 847 (41.1)   | 0.0001  |
| 90-day* (n = 308, n = 2061)  | 95 (30.8)                                       | 861 (41.8)   | 0.0003  |
| Limitation of life-sustaining therapies or measures decision (n = 308, n = 2061) | 63 (20.4)                                       | 515 (24.9)   | 0.0844  |

SD standard deviation, ICU intensive care unit, Q1–Q3 25th–75th percentile

<sup>o</sup>For tracheostomized patients, length of stay was calculated from the “approximate” date of tracheostomy

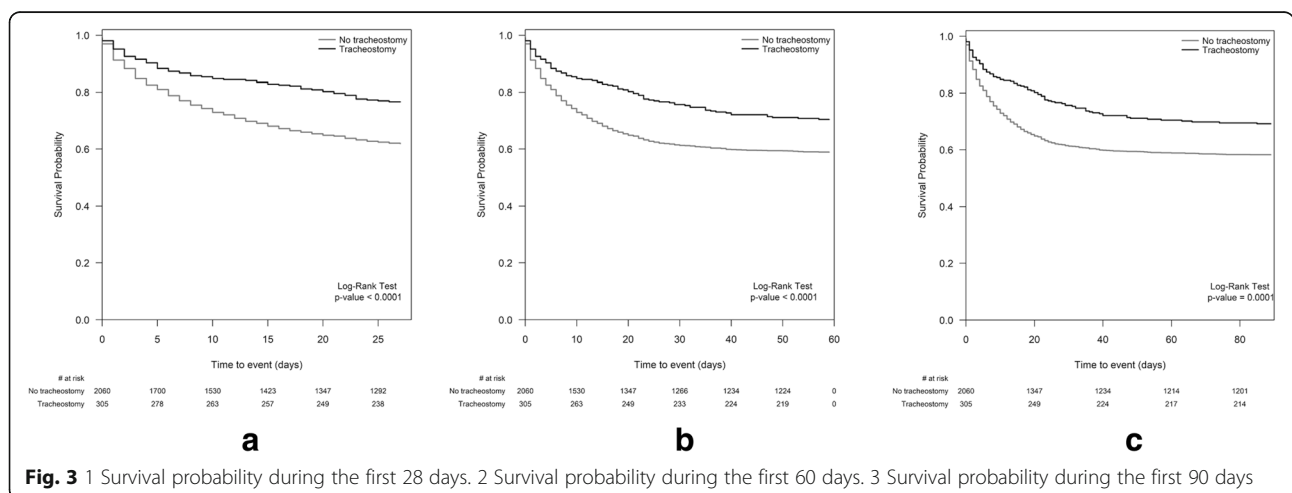
\*Mortality was evaluated according to the vital status at 28/60/90 days from acute respiratory distress syndrome onset or from the “nearest recorded” date of tracheostomy in non tracheostomized and tracheostomized patients, respectively. If the patient was discharged alive before 28/60/90 days, we considered the patient as alive

= 0.055) mortality ratio was not significantly different between tracheostomized and non-tracheostomized patients.

**Discussion**

Tracheostomy was performed in 13% of patients with ARDS that were recruited to the LUNG SAFE international, multicenter, prospective cohort study from 459 ICUs across 50 countries, predominantly (75%)

after the first week of their critical illness. Patients with tracheostomy remained longer on mechanical ventilation, and stayed longer in the ICU and in the hospital than non-tracheostomized patients. While duration of survival was increased in patients that received a tracheostomy, there was no significant increase in 60-day or 90-day survival compared to patients that did not receive a tracheostomy.



**Fig. 3** 1 Survival probability during the first 28 days. 2 Survival probability during the first 60 days. 3 Survival probability during the first 90 days

**Table 3** Description of each covariate used for the propensity-score matching in the matched sample ( $n = 534$ )

|   | Tracheostomy<br>Number (%) or mean $\pm$ sd | No tracheostomy<br>Number (%) or mean $\pm$ sd | Standardized<br>differences of mean |
|---|---|--|-------------------------------------|
| Number  | 267   | 267  |                                     |
| Age   | 58.4 $\pm$ 16.6                             | 58.9 $\pm$ 17.9                                | 0.03                                |
| Sex (male)  | 171 (64.0)                                  | 171 (64.0)                                     | 0.00                                |
| BMI   | 27.9 $\pm$ 7.8                              | 27.9 $\pm$ 15.0                                | 0.00                                |
| Geographic area   |   |  |                                     |
| European countries with high income                     | 174 (64.2)                                  | 172 (64.4)                                     | 0.02                                |
| Non-European countries with high income                 | 49 (18.4)                                   | 48 (18.0)                                      | 0.01                                |
| Countries with middle income                            | 44 (16.5)                                   | 47 (17.6)                                      | 0.03                                |
| Type of admission                                       |   |  |                                     |
| Medical   | 178 (66.7)                                  | 183 (68.5)                                     | 0.04                                |
| Surgical  | 52 (19.5)                                   | 48 (18.0)                                      | 0.04                                |
| Elective  | 19 (7.1)                                    | 21 (7.9)                                       | 0.03                                |
| Trauma  | 18 (6.7)                                    | 15 (5.6)                                       | 0.05                                |
| Comorbidities   |   |  |                                     |
| COPD or home ventilation                                | 60 (22.5)                                   | 65 (24.3)                                      | 0.04                                |
| Diabetes mellitus                                       | 64 (23.9)                                   | 64 (23.9)                                      | 0.00                                |
| Chronic renal failure                                   | 27 (10.1)                                   | 23 (8.6)                                       | 0.05                                |
| Immunosuppression or active or hematologic neoplasm     | 66 (24.7)                                   | 62 (23.3)                                      | 0.04                                |
| Heart failure (NYHA classes III-IV)                     | 19 (7.1)                                    | 22 (8.2)                                       | 0.04                                |
| Chronic liver failure (Child-Pugh Class C)              | 2 (0.7)                                     | 2 (0.7)  | 0.00                                |
| Cause of AHRF - pneumonia                               | 186 (69.7)                                  | 195 (73.0)                                     | 0.07                                |
| ARDS risk factor  |   |  |                                     |
| No risk factor  | 17 (6.4)                                    | 17 (6.4)                                       | 0.00                                |
| Only indirect risks factor                              | 45 (16.9)                                   | 39 (14.6)                                      | 0.06                                |
| Only direct risk factors                                | 168 (62.9)                                  | 173 (65.0)                                     | 0.04                                |
| Both risk factors                                       | 37 (13.9)                                   | 38 (14.2)                                      | 0.01                                |
| ECMO use  | 19 (7.1)                                    | 16 (6.0)                                       | 0.05                                |
| Arterial gas  |   |  |                                     |
| pH  | 7.4 $\pm$ 0.1                               | 7.4 $\pm$ 0.1                                  | 0.07                                |
| P/F ratio (mmHg)  | 204.1 $\pm$ 86.5                            | 199.1 $\pm$ 63.7                               | 0.07                                |
| PaCO <sub>2</sub> (mmHg)                                | 44.4 $\pm$ 13.9                             | 44.2 $\pm$ 14.1                                | 0.01                                |
| Non-respiratory SOFA score adjusted for missing values, | 5.1 $\pm$ 3.4                               | 5.1 $\pm$ 3.6                                  | 0.00                                |

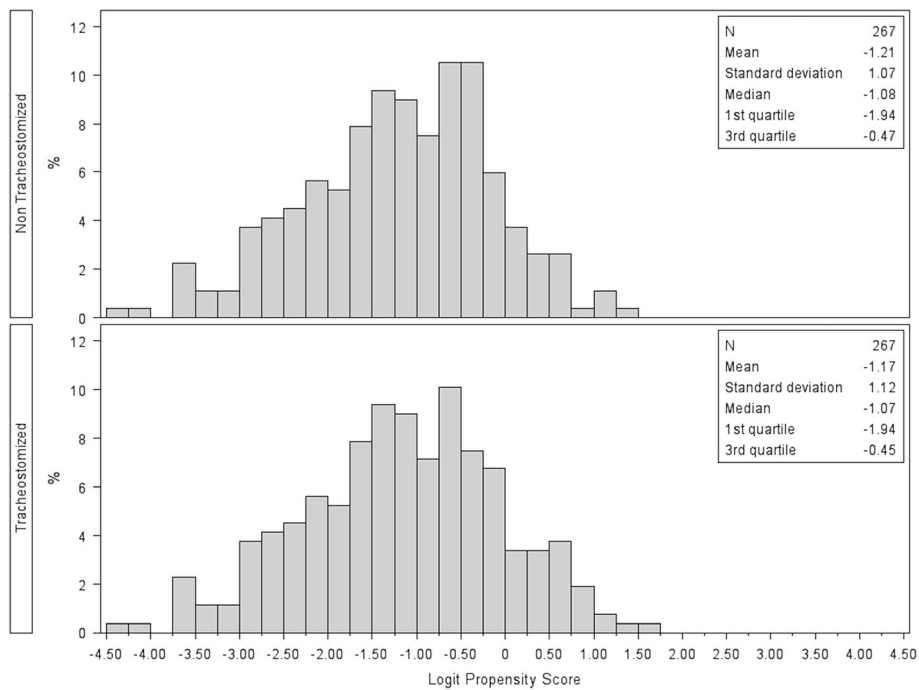
### Use of and timing of tracheostomy

The rate of tracheostomy in our cohort, 13%, is higher than that reported from a nationwide population-based study from the USA, in which 9.1% of all mechanically ventilated patients underwent tracheostomy [7]. The higher rate in our cohort could be explained by the inclusion of more patients with a severe form of respiratory failure, namely ARDS. Whether it should be performed earlier versus later is controversial [12]. While some studies reported that early tracheostomy may be related to better outcomes [3, 7], a recent large-scale randomized trial, TracMan, and a subsequent meta-analysis did not confirm

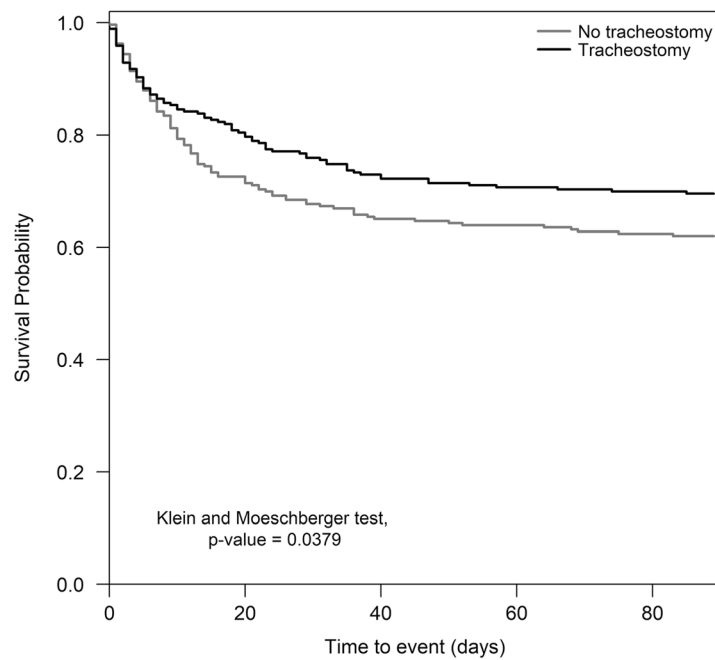
these findings [11, 13]. The TracMan study demonstrated that early tracheostomy (within 4 or 5 days of critical care admission) did not improve mortality.

In our study, the median time to tracheostomy was 14 days, similar to that reported in other recent studies [7, 14]. Only a quarter of tracheostomies were performed on or before day 7. Of the 15% of patients who received tracheostomy on day 1, a substantial proportion may have had an indication for a surgical airway (e.g. for upper airway obstruction). Excluding these patients would even strengthen the trend toward later tracheostomy. These findings on tracheostomy timing represent





**Fig. 4** Distribution of the logit of propensity scores in patients with tracheostomy ( $n = 267$ ) and without tracheostomy ( $n = 267$ ) in the matched sample



| # at risk       |     | 0   | 20  | 40  | 60  | 80 |
|-----------------|-----|-----|-----|-----|-----|----|
| No tracheostomy | 266 | 193 | 173 | 170 | 166 |    |
| Tracheostomy    | 264 | 214 | 194 | 188 | 186 |    |

**Fig. 5** Survival probability during the hospital stay in the matched sample ( $n = 534$ ). Kaplan Meier's approach, assuming as censored, those patients discharged and alive before day 90

**Table 4** Description of outcomes in the propensity-matched sample (n = 534)

|  | Tracheostomy (n = 267)       | No tracheostomy (n = 267)    | P value |
|--|------------------------------|------------------------------|---------|
|  | Number (%) or median (Q1–Q3) | Number (%) or median (Q1–Q3) |         |
| Days of mechanical ventilation                               |                              |                              |         |
| All patients   | 22 [13–33.5]                 | 8 [4–12]                     | <.0001  |
| Patient alive at hospital discharge                          | 22 [13.5–33]                 | 6 [3–11]                     | <.0001  |
| Ventilator-free days   |                              |                              |         |
| All patients   | 0 [0–11]                     | 18 [0–25]                    | <.0001  |
| Patient alive at hospital discharge                          | 7 [0–15.5]                   | 23 [18–26]                   | <.0001  |
| Length of ICU stay (days) <sup>o</sup>                       |                              |                              |         |
| All patients   | 11 [5–24]                    | 8 [5–14]                     | <.0001  |
| Patient alive at hospital discharge                          | 12 [6–25]                    | 8 [5–14]                     | 0.0002  |
| Length of hospital stay (days) <sup>o</sup>                  |                              |                              |         |
| All patients   | 24 [9–43]                    | 17 [10–31]                   | 0.0190  |
| Patient alive at hospital discharge                          | 31 [15.5–50.5]               | 23 [13–38]                   | 0.0325  |
| Hospital mortality   |                              |                              |         |
| 28-day*  | 61 (22.9)                    | 85 (31.8)                    | 0.0197  |
| 60-day*  | 78 (29.3)                    | 97 (36.3)                    | 0.0814  |
| 90-day*  | 81 (30.5)                    | 102 (38.2)                   | 0.0549  |
| Limitation of life-sustaining therapies or measures decision | 53 (19.9)                    | 59 (22.1)                    | 0.5900  |

Statistical tests accounted for the matched nature of the sample (paired *t* test or Wilcoxon signed-rank test for continuous variables, McNemar's test for dichotomous variables)

<sup>o</sup>For tracheostomized patients, length of stay was valued from the "approximate" date of tracheostomy

\*Mortality was evaluated according to the vital status at 28/60/90 days from acute respiratory distress syndrome onset or from the "nearest recorded" date of tracheostomy for non-tracheostomized and tracheostomized patients, respectively. If the patient was discharged alive before 28/60/90 days, we considered the patient as alive

a significant practice change, likely due to the findings of the TracMan study [11].

### Indications for tracheostomy

Medical indications for tracheostomy include the need for prolonged mechanical ventilation, need for airway access for secretion removal, and improvement of patient comfort [15]. A common reason for tracheostomy is the (clinician--predicted) likelihood that the patient will require prolonged mechanical ventilation. Of interest, the TracMan study demonstrated the difficulty for clinicians in predicting which patients will require prolonged ventilation support in the early phases of critical illness, given that many of their patients randomized to later tracheostomy did not receive one. In the present study, patients that received tracheostomy had fewer ventilator-free days, and required longer ICU and hospital stays. This is not to suggest that tracheostomy delayed weaning from ventilation, but is more likely a reflection of the fact that the patients that received tracheostomy were appropriately selected as being a group that would require prolonged ventilatory support.

There was considerable variation in the use of tracheostomy by geo-economic region, suggesting there are important regional and/or socio-economic differences in clinician use of tracheostomy in patients with ARDS. We used the 2016 World Bank countries socio-economic

classification, which includes data on gross national income per person, to define three major geo-economic groupings as in a previous report [10]. In high-income Europe countries, more patients underwent tracheostomy than in the other regions (non-European countries (rest of world) with high income or countries with middle income). Our findings [7] indicate that the likelihood of a patient receiving a tracheostomy appears to be influenced by factors other than those that are related to their clinical status, such as local medical practices and expertise and costs relating to the procedure and equipment.

Of interest, our study did not replicate the findings of a US study, which showed a difference in indication by patient characteristics such as gender and race/ethnicity [7]. Because our study includes data from ICUs of numerous countries and not just the USA, it might represent a more generalizable picture of worldwide patterns in the use of tracheostomy.

### Patient outcomes

Aside from emergency situations, tracheostomy is usually performed in patients who are clinically relatively stable, but likely to need prolonged ventilation. This fact means that direct comparison of patients that received a tracheostomy to those that did not may be confounded by two important sources of bias, namely bias by

indication (i.e. tracheostomy is more likely to be performed in “stable” patients) and immortal time bias (patients that die early are less likely to receive a tracheostomy). To address the latter issue, in our direct comparison of patients that received tracheostomy to those that did not, we calculated survival duration using the day of insertion of tracheostomy as “day 0”. Despite this “correction”, our data demonstrated significantly higher 28-day, 60-day and 90-day survival in patients that received tracheostomy.

Our subsequent analyses were designed to understand, and further minimize the potential for both types of bias. First, we stratified patients into subgroups to differentiate those who were in the ICU for at least 5 days, to reduce the impact of early death on outcomes. In this analysis, while 28-day mortality remained significantly lower in patients with tracheostomy, the trend to better 60-day and 90-day survival was not significant. These latter findings are confirmed in a propensity-matched analyses; patients undergoing tracheostomy had better 28-day, but not 60-day or 90-day survival. This is an important finding, as it suggests that while tracheostomy prolongs short-term survival, it may not improve longer-term outcomes.

Our finding is supported by a recent systematic review and meta-analysis that suggested there was no significant difference between early and late or no tracheostomy for length of hospital stay and long-term outcomes [8], although it was not a direct comparison between patients that received a tracheostomy and those that did not. Interestingly, another population-based US study reported conflicting results [7], in that their patients with tracheostomy had shorter lengths of stay. However, the authors raised the possibility that this finding could be due to patients being discharged to long-term care facilities because of pressures to reduce length of hospital stay. They considered that the place of death could have merely shifted from hospitals to long-term care facilities [7]. This finding underlines the need for studies that seek to determine the effect of tracheostomy on outcome to examine longer-term outcomes, including follow up of patients post hospital discharge.

### Limitations

Several limitations of this study should be acknowledged. First, our study was an observational study and as such, we cannot make causal inferences. Second, the study period was relatively short and confined to the winter season, which might have led to sampling bias. However, while winter is the epidemic season of respiratory diseases such as influenza [16], the nature of the pathophysiology of ARDS does not have a significant seasonal variation. For example, seasonal variability of ARDS prevalence was modest in the recently published APRONET study [17]. A third limitation is that the group of patients who received early tracheostomy might have included patients who did

not need tracheostomy. However, early tracheostomy was performed relatively infrequently in this study compared to previous studies [11]. Fourth, despite our efforts to address bias as discussed previously, the potential remains for bias by indication, and for immortal time bias to affect our results. Additional analyses, including confining the analyses to patients that were alive and in the ICU at 1 week, did not change the findings, confirming the robustness of the current findings. Although differences in goals of care may influence the tracheostomy decision, we did not find any difference in regard to end-of-life decision-making between the groups in our propensity-matched analysis, suggesting that this did not have an influence. Fifth, we did not have data on the methods of tracheostomy insertion, airway management methods, tracheostomy-related complications, and whether any deaths resulted from the tracheostomy itself is a limitation. Sixth, to control immortal bias, we chose the a cutoff point of early tracheostomy was day 4 from just Trach-Man study [11]. As Fig. 2 demonstrates, moving the cutoff beyond day 5 has a limited effect: only two patients would be shifted if we changed the day of tracheostomy from day 5 to day 7. Only five patients would be shifted even if we changed the day of tracheostomy from day 5 to day 10. Finally, a longer follow-up period (180 days or more) might be beneficial in helping understand the long-term outcomes in patients on prolonged mechanical ventilation.

### Conclusions

In this international, multicenter, prospective cohort study, tracheostomy was performed in 13% of patients with ARDS, and was performed predominantly (in 75%) after the first week of their critical illness. Patients with tracheostomy remained longer on mechanical ventilation, and stayed longer in the ICU, and in the hospital than non-tracheostomized patients. While duration of survival was increased in patients that received a tracheostomy, there was no significant increase in 60-day or 90-day survival, suggesting that tracheostomy may delay death but does not impact longer term survival.

### Key messages

- Tracheostomy was performed in 13% of patients with ARDS, and was performed predominantly (in 75%) after the first week of their critical illness.
- Patients with tracheostomy remained longer on mechanical ventilation, and stayed longer in the ICU, and in the hospital than non-tracheostomized patients.
- While duration of survival was increased in patients that received a tracheostomy, there was no significant increase in 60-day or 90-day survival.
- Tracheostomy might delay - rather than prevent - death in some patients with ARDS.

## Additional files

**Additional file 1: Table S1.** Additional baseline characteristics in patients with tracheostomy and no tracheostomy ( $n = 2377$ ). BMI, body mass index; ICU, intensive care unit; ER, emergency room; COPD, chronic obstructive pulmonary disease; NYHA, New York heart association; AHRF, Acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; TRALI, transfusion-related acute lung injury; A/C, assist control; PC, pressure control; BIPAP, bilevel positive airway pressure APRV, airway pressure release ventilation; SIMV, synchronized intermittent mandatory ventilation, PRVC, pressure-regulated volume control; PSV, pressure support ventilation; HFO, high-frequency oscillation; CPAP, continuous positive airway pressure IBW, ideal body weight; PEEP, positive end-expiratory pressure; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment. Missing data: source of admission to ICU = 1, Chest x-ray/CT scan number = 1. (DOCX 27 kb)

**Additional file 2: Table S2** compares outcomes between early (within 7 days of ICU admission) and late (8 days and later) thoracotomy ( $n = 280$ ). SD, standard deviation; ICU, intensive care unit; Q1–Q3; 25%–75% interquartile. Missing data: days of mechanical ventilation = 37; days of mechanical ventilation in patient alive at hospital discharge (90 days) = 139; length of ICU stay in patient alive at ICU discharge (90 days) = 58; length of hospital stay = 19; length of hospital stay in patient alive at ICU discharge (90 days) = 87; ICU, 28-day, 60-day, and 90-day mortality = 1. Participants were adult patients ( $\geq 18$  years) with severe or moderate ARDS who received mechanical ventilation and had tracheostomy. Participants were excluded if they had made the decision to withhold/withdraw treatment; if they had been transferred from another hospital with invasive mechanical ventilation; if they received tracheostomy on the first day of the study period and had been on invasive mechanical ventilation for 6 days or more; or if they had been discharged from the ICU or died in the ICU within 7 days. Length of ICU and hospital stay were calculated from their admission to discharge. Mortality was calculated from day 7 to patient discharge. Days of mechanical ventilation, length of ICU stay, and length of hospital stay were compared using linear regression models, and mortality using logistic regression models. (DOCX 17 kb)

### Abbreviations

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; ECMO: Extracorporeal membrane oxygenation; ESICM: European Society of Intensive Care Medicine; ICUs: Intensive care units; LUNG-SAFE: Large observational study to understand the global impact of severe acute respiratory failure; PaCO<sub>2</sub>: Partial arterial pressure of carbon dioxide; rWORLD: Non-European rest of world high income countries; SES: Socio-economic status; SOFA: Sequential organ failure assessment; VFDs: Ventilator-free days

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#### Availability of data and materials

Not applicable.

#### Authors' contributions

TA conceived of and designed this study, interpreted the data, drafted the manuscript, and revised the manuscript for important intellectual content. FM contributed to the acquisition of data, conducted data cleaning, analyzed the data, interpreted the data, and revised the manuscript for important intellectual content. TP interpreted the data and revised the manuscript for important intellectual content. IN jointly conceived of and designed this study and interpreted the data. UM jointly conceived of and designed this study and interpreted the data. NT jointly conceived of and designed this study and interpreted the data. KK conceived of and designed this study, interpreted the data, and revised the manuscript for important intellectual content. GB interpreted the data and revised the manuscript for important intellectual content. JL conceived of and designed this study, interpreted the data, and revised the manuscript for important intellectual content. All of the authors reviewed, discussed, and approved the final manuscript.

#### Ethics approval and consent to participate

All participating ICUs obtained ethics committee approval and obtained either patient consent or ethics committee waiver of consent in the LUNG-SAFE study. The study protocol was also reviewed and approved by the ethics committee of Mito Kyodo General Hospital, University of Tsukuba Hospital Mito Medical Center, Japan.

#### Consent for publication

Not applicable.

#### Competing interests

All authors declare that they have no competing interests.

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