Early Tracheostomy for ARDS Patients Supported by Venovenous Extracorporeal Membrane Oxygenation Is Associated With A Decreased Incidence of Ventilator-Associated Pneumonia, Duration of Extracorporeal Membrane Oxygenation and Mechanical Ventilation: Experience From A Single-Center Retrospective Cohort.

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Research

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Abstract

Background: Venovenous extracorporeal membrane oxygenation (ECMO) has become the ultimate supporting technique for the rescue of severe acute respiratory distress syndrome (ARDS) patients. Although tracheostomy during ECMO has proven to be beneficial, the proper time point for performing the tracheostomy remains unclear. The purpose of our study was to demonstrate whether early tracheostomy (ET; within 7 days of ECMO initiation) outweighs delayed tracheostomy (DT; 8 days of more after ECMO initiation).

Methods: A retrospective cohort study was established. All ARDS patients who underwent tracheostomy during V-V ECMO support in the intensive care unit (ICU) of a tertiary hospital from December 2013 to November 2020 were reviewed.

Results: Of the 187 ARDS patients who received V-V ECMO support, 30 (16%) underwent tracheostomy—18 (60%) during ECMO support and the other 12 after ECMO decannulation. Among the 18 patients who underwent tracheostomy while receiving ECMO, 11 (61.1%) received ET, and 7 received DT. No significant difference was found between the ET and DT groups in terms of demographic data, medical history, disease severity (estimated based on the RESP, PRESERVE, APACHE Ⅱ, SOFA and Murray scores), ARDS risk factors or mechanical ventilation duration before ECMO. The ET group showed a decreased incidence of ventilator-associated pneumonia (VAP) during ECMO support (45.5% vs. 100%; *P*= 0.038) and shortened durations of ECMO (9.0 vs. 27.0 days; *P*= 0.011) and mechanical ventilation (16.0 vs. 56.0 days; *P*= 0.027). ET did not significantly alter the all-cause ICU mortality rate (54.5% vs. 28.6%; *P*= 0.367), all-cause hospital mortality rate (which was the same as the ICU mortality rate), length of ICU stay (336 vs. 627 hours; *P*= 0.085), or length of hospital stay (26 vs. 37 days; *P*= 0.285). Local bleeding at the tracheostomy wound did not differ between the two groups (27.3% vs. 42.9%, *P*= 0.627) .

Conclusion: Compared with delayed tracheostomy, ET performed within 7 days of ECMO cannulation for severe ARDS patients could decrease the VAP incidence during ECMO support and shorten the durations of ECMO and mechanical ventilation; However, it may not improve the outcome. Prospective and multicenter studies are needed for further research.

Background

Venovenous extracorporeal membrane oxygenation (ECMO) has become the ultimate supporting technique for the rescue of severe acute respiratory distress syndrome (ARDS) patients in recent years. The EOLIA study(1, 2) and a subsequent meta-analysis(3) have proven the efficacy of ECMO, compared to conventional mechanical ventilation alone, for improving the outcomes of ARDS patients. However, due to the severity of the disease, a long duration of mechanical ventilation is likely needed for these patients to recover. Tracheostomy is commonly used for critically ill patients who require prolonged mechanical ventilation. A secondary analysis of the LUNG-SAFE study indicated that tracheostomy could increase the possibility of survival of ARDS patients in the intensive care unit (ICU) and in the hospital(4).

In addition, although there is no consensus on the impact of early tracheostomy (ET) on the mortality rate and long-term outcomes, three meta-analyses revealed that ET (performed within 7 to 10 days from intubation) for critically ill patients was associated with a lower rate of ventilator-associated pneumonia (VAP), more ventilator-free days, shorter ICU stays, and less sedation than delayed tracheotomy (DT)(5–7).

According to a cross-sectional, multicenter international survey of 173 adult respiratory ECMO centers, tracheostomy was widely performed in approximately 70% of the centers. The timing of the procedure varies greatly among different centers, and the optimal timing of the procedure is still unclear. Less than 15% of the centers reported that they would perform a tracheostomy within one week after the onset of ECMO support(8). Although several single-center studies reported potential complications of tracheostomy during ECMO support, such as minor bleeding (with an incidence rate of approximately 10–30%), major bleeding (2–11%), pneumothorax (approximately 1.5%), ECMO circuit dysfunction (0 to 3.1%), and analgosedation-related hypotension (less than 1%)(9–11), a recent international multicenter retrospective study conducted over a 9-year period and including 1,168 severe ARDS patients treated with ECMO reported that major complications were uncommon and that the rate of minor complications was acceptable(12).

Taking into account the above benefits of ET for ARDS patients, the increased use of VV-ECMO for patients with ARDS, and the acceptable safety of tracheostomy during ECMO support, it is important to determine whether ET (perfomed within 7 days of the initiation of ECMO) would also provide benefits for ARDS patients receiving ECMO support. To date, limited evidence has shown that ET is associated with a decreased duration of ECMO support and reduced ECMO–related costs(13). The aim of this study was to determine the impact of ET on severe ARDS patients who require V-V ECMO support in terms of all-cause mortality, the VAP incidence rate, the durations of mechanical ventilation and ECMO support, as well as the ICU and hospital length of stay.

Methods

Study design

This study included all consecutive severe ARDS patients receiving V-V ECMO support who underwent tracheostomy at our department, a medical ICU in a tertiary hospital with a majority of patients with respiratory diseases, from December 2013 to November 2020. Exclusion criteria included V-A ECMO support, ECMO support for surgery (such as lung transplantation) or an internal interventional procedure (such as complicated endobronchial treatment for main bronchus obstruction using a rigid bronchoscope), age younger than fourteen years and tracheostomy performed after ECMO withdrawal. This study was approved by the ethics committee of our center.

Data collection

Age, sex, body mass index (BMI), medical history, smoking history, ARDS risk factors, PaO2/FiO2 upon the initiation of ECMO and mechanical ventilation duration before ECMO were collected. Immunodeficiency was defined as an active solid tumor, hematological malignancy, HIV/AIDS or use of corticosteroids or immunosuppressants for at least the previous month. The RESP, PRESERVE, Murray, SOFA and APACHE Ⅱ scores on ECMO initiation were reviewed to estimate disease severity(14–18). Patients were stratified into an ET group (within 7 days) and a DT group (8 days or more), according to the timing of tracheostomy relative to ECMO initiation.

Tracheostomy was performed at bedside by an experienced team in accordance with the Ciaglia Blue Rhino percutaneous dilator algorithm(19). The team comprised two ICU physicians, one respiratory therapist and one ICU nurse. Heparin was suspended four hours before the procedure and was usually restarted approximately two hours after the procedure in the absence of significant local bleeding. Tracheostomy-related complications were defined as any side effects that occurred within 24 hours after the procedure, including tracheal rupture, local bleeding, pneumothorax, subcutaneous emphysema and periprocedural clotting events. Major bleeding was defined as bleeding that required the transfusion of more than two units of packed red blood cells or a surgical or interventional procedure or caused a fatal outcome(20, 21).

Ventilator-associated pneumonia (VAP) referred to pneumonia that occured more than 48 hours after endotracheal intubation(22) and was diagnosed using a combination of clinical criteria and qualitative cultures according to the algorithm recommended by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS)(23–25). The clinical criteria included the presence of new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38 ℃, leukocytosis or leukopenia, and purulent secretions). Quantitative cultures of bronchoalveolar lavage fluid (BALF) were obtained for all patients with suspected VAP in our department.

The primary outcomes were all-cause ICU mortality and hospital mortality. Secondary outcomes included the incidence rate of VAP during ECMO support, complications related to tracheostomy, duration of mechanical ventilation, duration of ECMO support, ICU length of stay and hospital length of stay.

Statistical analysis

Statistical analyses were conducted using SPSS v26.0. Differences with a *P*-value less than 0.05 were considered statistically significant. For continuous variables, the Shapiro–Wilk test was used for normal distribution testing. Data were presented as the mean ± standard deviation or median (25th, 75th percentile) and were compared with Student's t-test or Mann-Whitney's U-test according to the result of the normal distribution test. Fisher's exact test was used for categorical variables.

Results

From December 2013 to November 2020, 211 patients received ECMO support at our ICU. Twenty-four patients were excluded from this study because they received V-A ECMO or ECMO support for surgery or

internal interventional procedures. Among the 187 ARDS patients who received V-V ECMO support, 30 (16%) underwent tracheostomy. Eighteen of these tracheostomies (60%) were performed while the patient was receiving ECMO support, and the other 12 were performed after ECMO decannulation. The flow chart is shown in Fig. 1.

Among the 18 patients who underwent tracheostomy while receiving ECMO support, the average age was 50.6 years; 15 patients (83.3%) were male, and 5 patients had immunodeficiency (27.8%). The median PaO_2/FiO_2 was 62.7mmHg, and the median RESP, PRESERVE, APACHE Ⅱ, SOFA, and Murray scores were 2.2, 3.9, 14.7, 7.9, and 3.3, respectively. The risk factors for ARDS were severe pneumonia (13 patients) and interstitial lung disease (5 patients). The pathogens of the 13 patients with severe pneumonia were influenza virus in 8, *Pneumocystis jirovecii* in 2, adenovirus in 1, aspergillus in 1 and *Mycobacterium tuberculosis* in 1. The 5 patients with interstitial lung disease included 1 with acute interstitial pneumonitis, 1 with acute exacerbation of idiopathic pulmonary fibrosis, 1 with secondary organizing pneumonia and 2 with interstitial lung disease associated with anti-synthase syndrome and dermatomyositis with MDA5 antibody positivity.

Tracheostomy was performed between 0 and 31 days after the establishment of ECMO. The median interval from ECMO cannulation to tracheostomy was 5 days, with 25th and 75th percentiles of 0 days and 9.5 days, respectively. Eleven patients (61.1%) received ET, and 7 received DT. In the ET group, the median interval from ECMO cannulation to tracheostomy was 1 day, and the 25th and 75th percentiles were 0 days and 5 days, respectively. The median interval from ECMO cannulation to tracheostomy in the DT group was 11 days, and the 25th and 75th percentiles were 9 days and 16 days, respectively. Figure 2 shows the distribution of the intervals between ECMO cannulation and tracheostomy. No significant difference was found between the ET and DT groups in terms of demographic data, medical history, disease severity (estimated using the RESP, PRESERVE, APACHE Ⅱ, SOFA and Murray scores), ARDS risk factors or duration of mechanical ventilation before ECMO. Table 1 shows the baseline characteristics of the two groups.

The overall incidence rate of VAP during ECMO support was 66.7% in this retrospective cohort. In the ET group, 5 patients acquired VAP; 7 patients in the DT group acquired VAP. The ET group showed a more than 50% decrease in the incidence of VAP during ECMO support (45.5% vs. 100%; $P = 0.038$). Figure 3 shows the accumulated 28-day VAP rates of the two groups; there was a departure of the two curves, but the difference did not reach significance (chi square = 1.572, $P = 0.21$; HR 0.484, 95% CI: 0.145–1.676).The median interval from ECMO cannulation to the occurance of VAP was 2 days (from 1 day to 21 days) and 8 days (from 4 to 32 days) in the ET and DT groups, respectively, with no signifiant difference ($P = 0.149$). Shorter durations of ECMO (9.0 vs. 27.0 days; $P = 0.011$) and mechanical ventilation (16.0 vs. 56.0 days; $P = 0.027$) were observed in the ET group.However, ET did not significantly alter the all-cause mortality rate in the ICU (54.5% vs. 28.6%; $P = 0.367$), the all-cause mortality rate in the hospital (which was the same as the ICU mortality rate), the length of ICU stay (336 vs. 627 hours; $P = 0.085$) or the length of hospital stay (26 vs. 37 days; $P = 0.285$). The incidence of tracheostomy complications did not differ between the two groups (local bleeding: 27.3% vs. 42.9%, $P = 0.627$). No

procedure-related tracheal rupture, pneumothorax, subcutaneous emphysema or periprocedural clotting events were reported. No major bleeding occured. Table 2 shows the outcomes of the two groups.

We also compared the outcomes of patients with or without tracheostomy-related local bleeding (Table 3). There was no significant difference between the two groups in the all-cause mortality rates in the ICU or in the hospital, VAP incidence, duration of mechanical ventilation, duration of ECMO support, length of ICU stay or length of hospital stay (P□0.05).

Table 1
Baseline characteristics according to tracheostomy timing

	All patients (n = 18)	Early tracheostomy (n = 11)	Delayed tracheostomy (n = 7)	*P*
Age, years	50.6 ± 20.3	53.5 ± 19.9	46.1 ± 21.8	0.474
Male sex	15 (83.3)	9 (81.8)	6 (85.7)	1.000
Body mass index, kg/m^2	23.5 ± 3.9	23.7 ± 4.5	23.2 ± 3.1	0.799
Comorbidity				
Idiopathic pulmonary fibrosis	1 (5.6)	1 (9.1)	0	1.000
Hypertension	5 (27.8)	4 (36.4)	1 (14.3)	0.596
Diabetes mellitus	2 (11.1)	1 (9.1)	1 (14.3)	1.000
Coronary heart disease	3 (16.7)	3 (27.3)	0	0.245
Chronic heart dysfunction	1 (5.6)	1 (9.1)	0	1.000
Chronic kidney disease	2 (11.1)	2 (18.2)	0	0.497
Pregnancy	1 (5.6)	0	1 (14.3)	0.389
Active malignancy	1 (5.6)	1 (9.1)	0	1.000
Immunodeficiency	5 (27.8)	4 (36.4)	1 (14.3)	0.596
Smoking	10 (55.6)	6 (54.5)	4 (57.1)	1.000
RESP score	2.2 ± 2.9	2.2 ± 3.1	2.1 ± 2.9	0.979
PRESERVE score	3.9 ± 2.0	4.4 ± 1.6	3.1 ± 2.3	0.204
Murray score	3.3 ± 0.6	3.4 ± 0.5	3.1 ± 0.6	0.287
SOFA score	7.9 ± 3.5	8.4 ± 4.1	7.0 ± 1.9	0.491
APACHE Ⅱ score	14.7 ± 6.4	13.8 ± 6.1	16.2 ± 7.3	0.519
ARDS risk factor				
Pneumonia	13 (72.2)	7 (63.6)	6 (85.7)	0.596

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PRESERVE, PRedicting dEath for SEvere ARDS on VV-ECMO; RESP, Respiratory ECMO Survival Prediction; SOFA, Sequential Organ Failure Assessment.

	All patients (n = 18)	Early tracheostomy (n = 11)	Delayed tracheostomy (n = 7)	*P*
Idiopathic or secondary interstitial lung disease	5 (27.8)	4 (36.4)	1 (14.3)	0.596
PaO_2/FiO_2 on ECMO initiation, mmHg	62.7 (56.5, 75.2)	64.0 (57.0, 82.3)	61.5 (54.0, 70.2)	0.350
MV time before ECMO, hours	44.5 (5.0, 149.8)	96.0 (2.0, 224.0)	8.0 (6.0, 96.0)	0.659

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PRESERVE, PRedicting dEath for SEvere ARDS on VV-ECMO; RESP, Respiratory ECMO Survival Prediction; SOFA, Sequential Organ Failure Assessment.

Data are shown as n (%), mean ± standard deviation, or median (25th, 75th percentiles).

Table 2
Outcomes for different tracheostomy times

	All patients (n = 18)	Early tracheostomy (n = 11)	Delayed tracheostomy (n = 7)	*P*
Primary outcomes				
ICU death	8 (44.4)	6 (54.5)	2 (28.6)	0.367
Hospital death	8 (44.4)	6 (54.5)	2 (28.6)	0.367
Secondary outcomes				
VAP during ECMO	12 (66.7)	5 (45.5)	7 (100.0)	0.038
Tracheostomy complications				
Bleeding	6 (33.3)	3 (27.3)	3 (42.9)	0.627
Wound bleeding	4 (22.2)	2 (18.2)	2 (28.6)	1.000
Intratracheal bleeding	3 (16.7)	2 (18.2)	1 (14.3)	1.000
Mechanical ventilation duration, days	20.0 (12.0, 57.0)	16.0 (10.0, 33.0)	56.0 (19.0, 73.0)	0.027
ECMO duration, days	14.0 (7.5, 29.0)	9.0 (6.0, 19.0)	27.0 (17.0, 38.0)	0.011
ICU LOS, hours	613.0 (330.0, 1008.0)	336.0 (260.0, 850.0)	672.0 (459.0, 2208.0)	0.085
Hospital LOS, days	27.0 (16.25, 76.25)	26.0 (11.0, 37.0)	37.0 (19.0, 92.0)	0.285

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; VAP, ventilator-associated pneumonia.

Data are shown as n (%), mean ± standard deviation, or median (25th, 75th percentiles).

Table 3
Outcomes of patients with or without tracheostomy-related local bleeding

	All patients (n = 18)	With bleeding (n = 6)	Without bleeding (n = 12)	*P*
ICU death	8 (44.4)	3 (50.0)	5 (41.7)	1.000
Hospital death	8 (44.4)	3 (50.0)	5 (41.7)	1.000
VAP during ECMO	12 (66.7)	4 (66.7)	8 (66.7)	1.000
Mechanical ventilation duration, days	20.0 (12.0, 57.0)	23.5 (15.8, 72.3)	19.0 (12.0, 53.0)	0.616
ECMO duration, days	14.0 (7.5, 29.0)	14.5 (8.8, 23.5)	14.0 (6.0, 29.0)	0.892
ICU LOS, hours	613.0 (330.0, 1008.0)	624.0 (426.0, 2010.0)	554.0 (273.0, 860.0)	0.437
Hospital LOS, days	27.0 (16.3, 76.3)	26.0 (17.8, 83.0)	27.5 (12.5, 65.5)	0.892

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; VAP, ventilator-associated pneumonia.

Data are shown as n (%) or median (25th, 75th percentiles).

Discussion

Alhough researchers have long been interested in the safety and benefits of tracheostomy for severe ARDS patients who require V-V ECMO support, evidence of the optimal timing of this procedure is scarce. Limited data from a single-center retrospective study showed that ET within 7 days of ECMO initiation could reduce the duration of ECMO support as well as ECMO-related costs(13). To the best of our knowledge, this study was the first to show the impact of ET on the incidence of VAP during ECMO support in severe ARDS patients. The main findings of this study were that compared to delayed tracheostomy, ET could 1) decrease the incidence of VAP during ECMO support and 2) shorten the duration of both ECMO support and mechanical ventilation.

Due to the larger amount of analgesics and sedatives needed after ECMO cannulation for safety reasons, these patients theoretically seemed more likely to benefit from a reduction in VAP incidence with ET, since the procedure can decrease sedative and analgesic dosages, improve oral hygiene and reduce airway resistance(26, 27). In this study, ET reduced the VAP incidence by over 50% compared to DT, which verified our hypothesis. In addition, as a result of the reduced VAP incidence, the duration of ECMO support and mechanical ventilation time dropped significantly in the ET group compared with the DT group (by 18 days and 40 days, respectively) in this study. These results are easy to understand since high-quality evidence shows that VAP is associated with a prolonged duration of mechanical ventilation and ECMO support(28–30). The decrease in ICU length of stay in the ET group represented an absolute

reduction of 336 hours, but did not meet the criteria for statistical significance ($P = 0.085 > 0.05$). We hypothesize that future studies with larger sample sizes may reach a statistical significance.

A recent international multicenter study demonstrated that longer intervals between intubation and the initiation of ECMO, immunocompromised status and the use of corticosteroids before ECMO were strong driving factors in clinicians' decision to perform tracheostomy during ECMO rather than after ECMO decannulation and found high heterogeneity among high-volume ECMO centers (12). However, the driving factors for the decision to perform ET during ECMO seemed unclear. Considering the basic reasons for performing a tracheostomy in ECMO patients (to improve oral hygiene, phlegm drainage, and patient comfort and decrease the incidence of VAP and the dosages of analgesics and sedatives), patients with a large amount of sputum (such as those with combined bacterial infection and influenza virus infection), patients with immunodeficiency (who are susceptible and vulnerable to VAP) and patients whose lungs need a long time to recover (such as those with idiopathic or secondary interstitial lung disease) are candidates for ET according to the experience of our department. Future studies with larger sample sizes should identify the proper patients for ET and confirm the ability of ET to improve their short-term and long-term outcomes.

The safety of tracheostomy during ECMO support is another important issue. This study showed that the rate of tracheostomy-related local bleeding was approximately 30%, which is similar to previous reports(9, 10, 12). In addition, there was no significant difference in bleeding between the ET and DT groups. Since no procedure-related major bleeding, tracheal rupture, pneumothorax, subcutaneous emphysema or periprocedural clotting events occurred, and the outcomes did not differ significantly between the patients with and without local bleeding, we believe that the safety of tracheostomy performed during ECMO support in our department was acceptable under certain algorithms.

This study had several limitations. First, it was based on data from a single ECMO center, which limits the application of its conclusions to other centers. Second, the sample size was small in this study, and the findings should be confirmed with future studies. Frankly, since it is rather difficult for any single center to recruit a large number of ARDS patients who have undergone tracheostomy during ECMO support, a multicenter study could be an option in the future. However, the high heterogeneity in terms of patient types, ARDS risk factors and patient management protocols among ECMO centers should be carefully considered. Third, due to the retrospective nature of the study, recall bias was impossible to avoid. To minimize the influence of recall bias, we used objective variables as often as possible. For example, we chose to consult the temperature records on the nursing care list, the chest X ray or CT scan images and white blood cell counts to determine the exact date of VAP instead of using the date written in electronic medical records as a rough estimate. Studies with prospective designs are needed to address this limitation.

Conclusion

Compared with delayed tracheostomy, ET performed within 7 days of ECMO cannulation for severe ARDS patients could decrease the VAP incidence rate during ECMO support and shorten the durations of ECMO and mechanical ventilation, but it may not improve the outcome. Prospective and multicenter studies are needed for further research.

Abbreviations

APACHE
Acute Physiology and Chronic Health Evaluation;
ARDS
acute respiratory distress syndrome;
BALF
bronchoalveolar lavage fluid;
BMI
body mass index;
DT
delayed tracheostomy;
ECMO
extracorporeal membrane oxygenation;
ET
early tracheostomy;
ICU
intensive care unit;
MV
mechanical ventilation;
PaO_2/FiO_2
ratio of partial pressure of arterial oxygen to fraction of inspired oxygen;
PRESERVE
PRedicting dEath for SEvere ARDS on VV-ECMO;
RESP
Respiratory ECMO Survival Prediction;
SOFA
Sequential Organ Failure Assessment;
VAP
ventilator-associated pneumonia.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of China-Japan Friendship Hospital (201511). Written informed consent was provided from each patient's next of kin as the patient was unable to make decisions because of a critically ill status and consciousness disturbance.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

ZZ, SG, ML, and QZ contributed to the design and conception of the study, data analysis and interpretation, statistical analysis, and drafted the manuscript; XH, JX, FL, YZ, YF, YT, XW, XY, CL, LH, YC, TZ, and XC contributed to data collection and interpretation, and revised the manuscript. All authors read and approved the final version of the manuscript.

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Figures

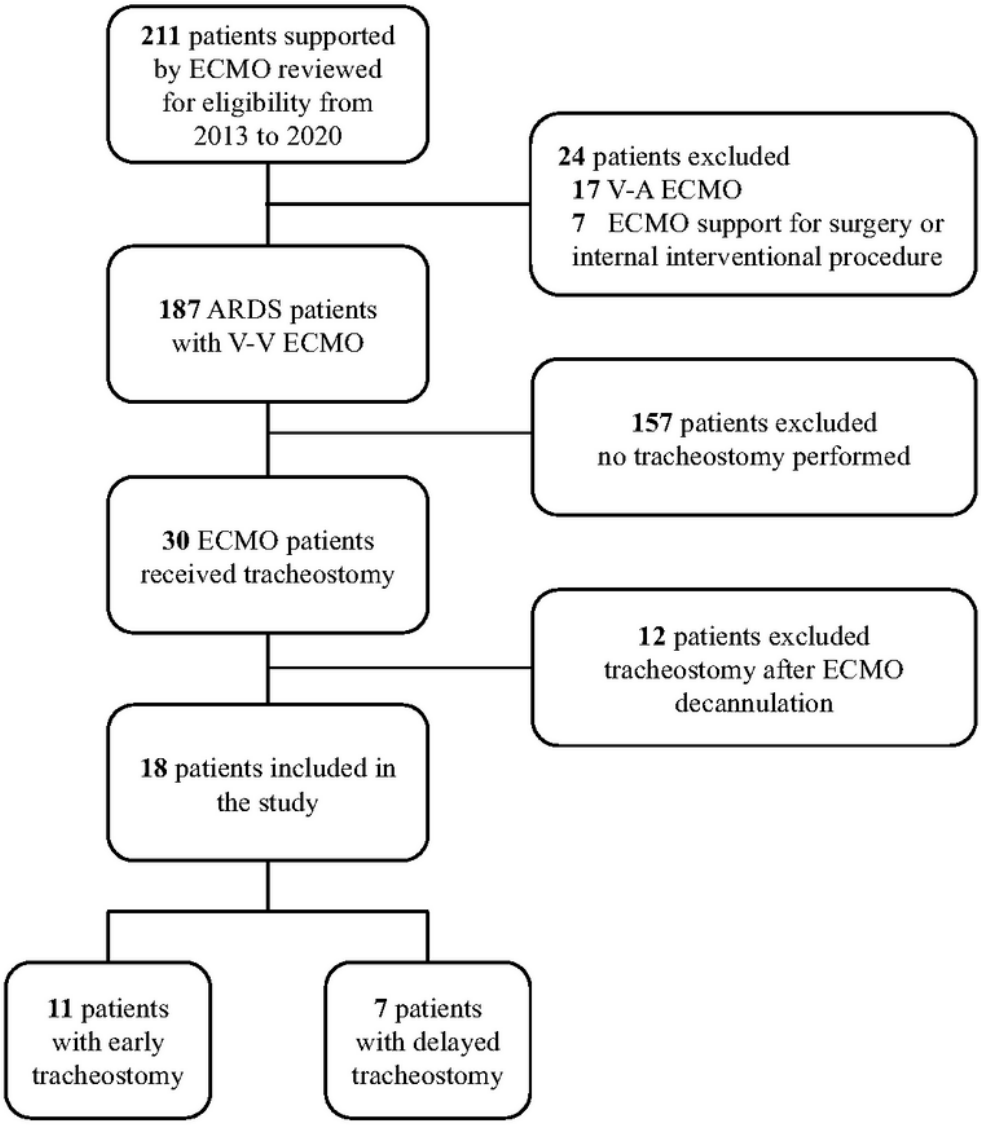

Figure 1

Flow chart of the study. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

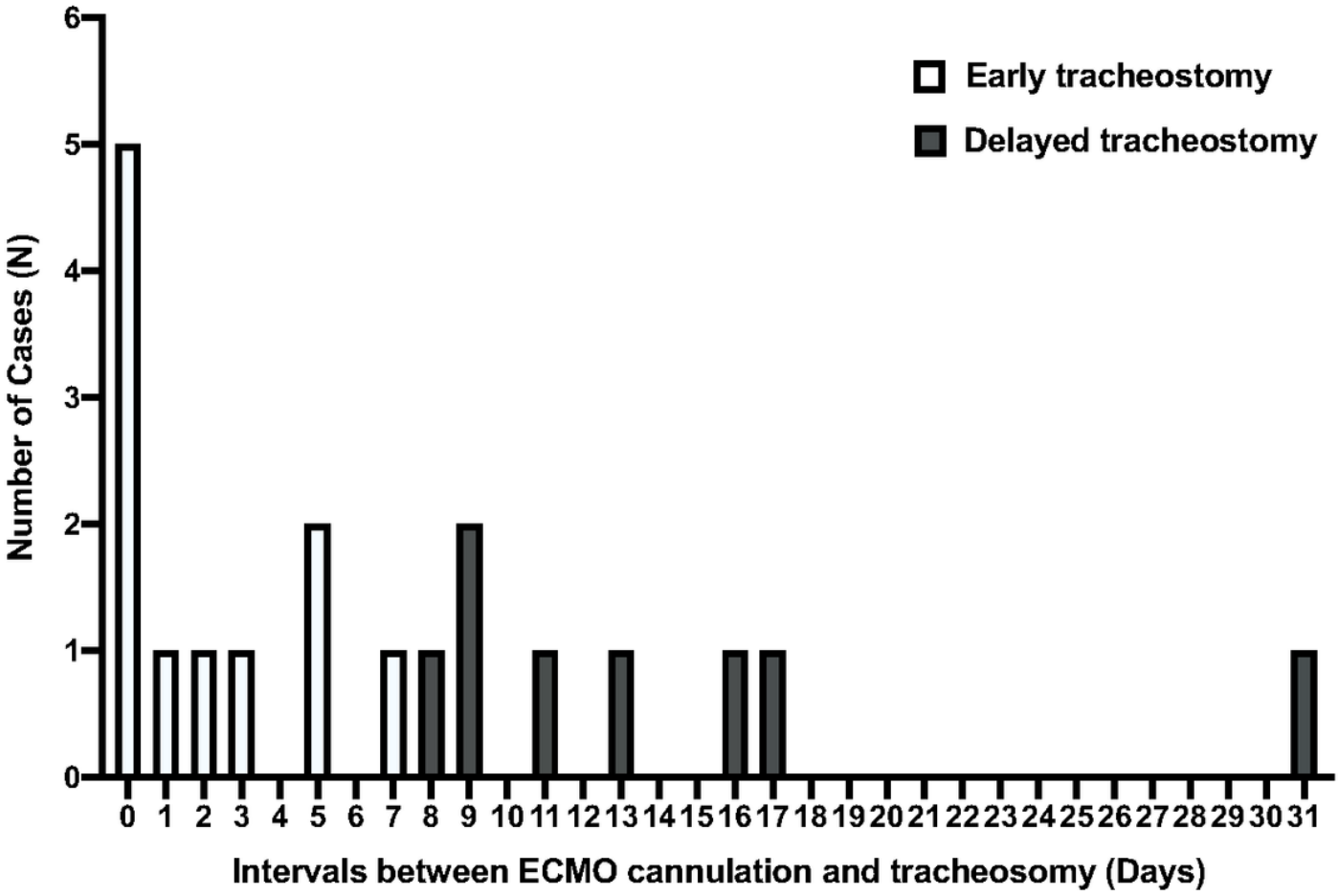

Figure 2

Distribution of the intervals between ECMO cannulation and tracheostomy.

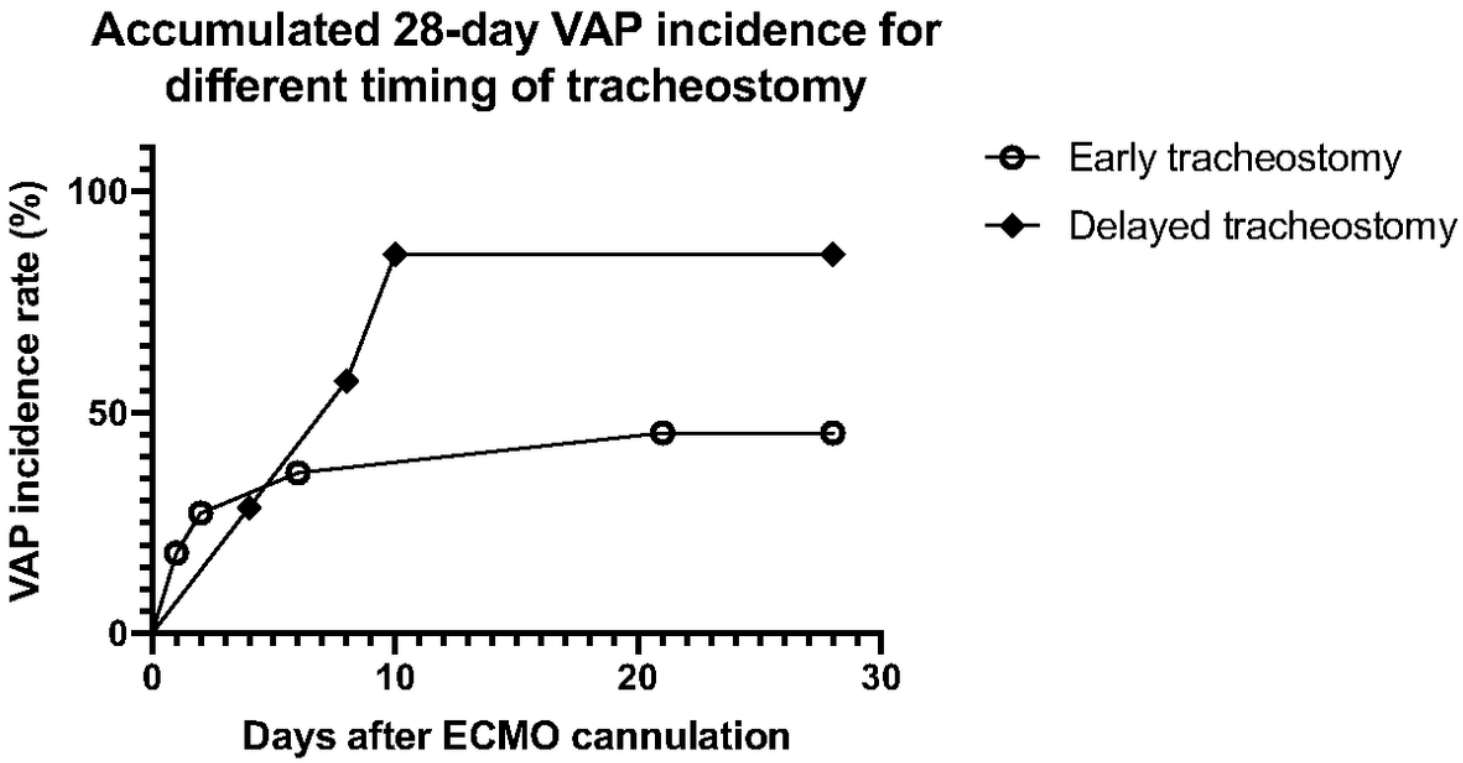

Figure 3

Accumulated 28-day VAP rates of the early tracheostomy group and the delayed tracheostomy group.