Impact of Noninvasive Respiratory Support in Patients With COVID-19 Requiring V-V ECMO

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The impact of the duration of noninvasive respiratory support (RS) including high-flow nasal cannula and noninvasive ventilation before the initiation of extracorporeal membrane oxygenation (ECMO) is unknown. We reviewed data of patients with coronavirus disease 2019 (COVID-19) treated with V-V ECMO at two high-volume tertiary care centers. Survival analysis was used to compare the effect of duration of RS on liberation from ECMO. A total of 78 patients required ECMO and the median duration of RS and invasive mechanical ventilation (IMV) before ECMO was 2 days (interquartile range [IQR]: 0, 6) and 2.5 days (IQR: 1, 5), respectively. The median duration of ECMO support was 24 days (IQR: 11, 73) and 59.0% (N = 46) remained alive at the time of censure. Patients that received RS for ≥3 days were significantly less likely to be liberated from ECMO (HR: 0.46; 95% CI: 0.26–0.83), IMV (HR: 0.42; 95% CI: 0.20–0.89) or be discharged from the hospital (HR: 0.52; 95% CI: 0.27–0.99) compared to patients that received RS for <3 days. There was no difference in hospital mortality between the groups (HR: 1.12; 95% CI: 0.56–2.26). These relationships persisted after adjustment for age, gender, and duration of IMV. Prolonged duration of RS before ECMO may result in lung injury and worse subsequent outcomes. *ASAIO Journal* 2022; 68;171–177

Key Words: V-V ECMO, COVID-19, noninvasive respiratory support, HFNC, duration, outcomes, nasal cannula, ARDS, length of respiratory support, morbidity, mortality, SILI

Acute respiratory distress syndrome (ARDS) remains the leading cause of death in coronavirus disease 2019 (COVID-19) with mortality estimated to range between 34% and 39%.[1,2] Veno-venous extracorporeal membrane oxygenation (V-V ECMO) has been increasingly used in the treatment of refractory ARDS.[3–5] It has been recommended as a potential treatment for refractory hypoxemia in COVID-19 by the Extracorporeal Life Support Organization (ELSO) and the World Health Organization.[6,7]

Barbaro et al.[8] reported a mortality of 38% in patients with COVID treated with V-V ECMO in the largest pooled cohort from the ELSO registry which is comparable to outcomes in non-COVID patients. The outcomes of ECMO are highly dependent on appropriate patient selection and multiple tools have been developed to guide risk stratification. Among risk factors for poor outcomes, prolonged invasive mechanical ventilation (IMV) before V-V ECMO initiation has been associated with increased mortality.[6,9] It remains unknown if the duration of noninvasive respiratory support (RS) including high-flow nasal oxygen (HFNC) and noninvasive ventilation (NIV) affects clinical outcomes in patients undergoing V-V ECMO.

Several clinical practices related to the management of COVID-19 have evolved over the duration of the current global pandemic. Early on, many experts and centers advocated early intubation and thus, the duration of RS was short.[10–14] However, over time, many have switched to a strategy delayed intubation which requires prolonged RS.[15] Despite this trend, prolonged RS has the potential to cause additional lung injury caused by self-induced lung injury (P-SILI).[14] P-SILI has been described in animal models as well as humans and it is thought to result from high swings in transpulmonary pressures associated with vigorous inspiratory effort. Historically, the duration of IMV has been considered as a determinant of ECMO candidacy. The impact of duration of RS on ECMO outcomes has not been well assessed.

The objective of this study was to analyze the impact of the duration of RS in patients with COVID-19-related ARDS that ultimately require V-V ECMO for COVID-19-related ARDS. We hypothesize that prolonged RS is associated with worse clinical outcomes in such patients.

Materials and Methods

This study was conducted at two large tertiary care centers in Virginia and New Jersey. Data were collected for patients diagnosed with COVID-19 managed with V-V ECMO between February 01, 2020 and March 01, 2021. Adult (18 years and above) patients with SARS-CoV-2 infection diagnosed by nasal PCR were included. Patients that required veno-arterial ECMO support were excluded. The data were manually extracted using the electronic medical record system. The study was approved by the Institutional Review Board at INOVA (18-3317) and Cooper University (21-073). The requirement for informed consent was waived.

Data Collection

Baseline characteristics, comorbidities, duration of various interventions, therapies received, and transfer status were

collected. Time was defined in "days" with the day of admission as day 1 and subclassified into durations of RS, IMV, and V-V ECMO, respectively. RS was defined as the sum of the durations on HFNC and NIV. We also recorded the lowest PaO_2/FiO_2 (PF) ratio before intubation.

Outcomes

The primary outcome of interest was liberation from extracorporeal life support. Secondary outcomes included overall in-hospital mortality, liberation from mechanical ventilation, and hospital discharge.

Statistical Analysis

The distribution of all continuous data was examined for normality using visual inspection and the Shapiro-Wilk test. Characteristics of the groups are presented as the median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Categorical data are presented as counts with proportions and compared using Fisher's exact test. Survival analysis was performed using the Kaplan-Meier method and the log-rank test was used to compare groups. Time to outcome was calculated from the time of initiation of extracorporeal life support to in-hospital death, discharge, or relevant clinical outcome. Patients discharged alive were considered event-free and those that remained in the hospital on March 10, 2021, were considered censored. The Cox proportional hazards model was used to calculate hazard ratios (HRs) with their 95% CI to analyze parameter association with outcomes. Adjustments to the model were made for potential confounding variables (age, gender, and the number of ventilator days before ECMO initiation) selected *a priori* based on known associations with worse clinical outcomes.[16,17] The proportional hazard assumption was tested using Schoenfeld residuals and was found to be valid. Sensitivity analysis using Fine and Gray competing-risk regression was performed to assess for potential immortal time bias related to the competing risk of death for the outcomes of ECMO liberation, mechanical ventilation liberation, and hospital discharge. All relevant statistical tests were two-tailed and a $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA version 14 (StataCorp LP; College Station, TX).

Results

A total of 84 patients with COVID-19 required ECMO support during the study period. Six patients were excluded as support was provided *via* veno-arterial ECMO (Figure 1). The characteristics of the 78 patients with COVID-19 that required V-V ECMO support during the study period are presented (Table 1). The median age was 48 years, and the majority were male (82.0%) and non-white (80.8%).

Most patients were transferred from an outside facility (56.4%) and most received a trial of HFNC before ECMO initiation (68.0%). Use of prone positioning (88.5%) and systemic steroids (82.1%) were common while the administration of tocilizumab before ECMO initiation was more infrequent (34.6%). The median duration of RS and IMV before ECMO was 2 days (IQR: 0, 6) and 2.5 days (IQR: 1, 5), respectively. The median duration of ECMO support was 24 days (IQR: 11, 73) and 57.1% (N = 44) remained alive at the time of censure.
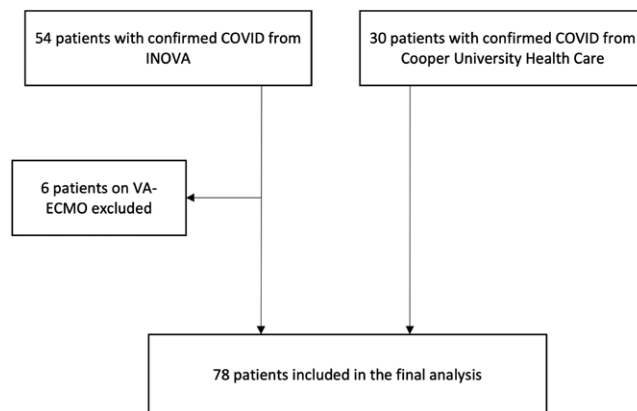

Figure 1. Flowchart of patients with COVID-19 managed with extracorporeal life support at Cooper University Hospital and INOVA Fairfax Hospital. COVID; coronavirus disease 2019. [full color online]

Patients were stratified by the median duration of RS in the cohort. Most clinical characteristics were similar between groups; however, patients that received RS ≥ 3 days were more likely to have been trialed on HFNC and were more likely to have received systemic corticosteroids before ECMO initiation. Further, patients with prolonged RS were noted to have a lower PF ratio before endotracheal intubation. Among patients that received RS for <3 days, median ECMO decannulation, ventilator liberation, and hospital discharge occurred after 16 days (IQR: 9, 35), 34 days, and 40 days (IQR: 28, 70), respectively. Although among those that received RS for ≥3 days, median ECMO decannulation, ventilator liberation, and hospital discharge occurred after 42 days (IQR: 23, 73), 59 days, and 66 days (IQR: 52, 79), respectively. Median estimated survival time was 66 days (IQR: 43, 95) for those that received RS for <3 days and 58 days (IQR: 34, 95) for those that received RS ≥3 days.

RS for ≥3 days was associated with a reduced rate of subsequent ECMO liberation (log-rank test, $p = 0.008$). ECMO liberation from the time of ECMO cannulation based on the duration of RS is displayed in Figure 2. After adjustment for age, gender, and IMV duration, RS remained associated with a reduced rate of ECMO liberation (HR: 0.357; 95% CI: 0.19–0.67). Moreover, RS for ≥3 days was associated with a significant reduction in the rate of IMV liberation (log-rank test, $p = 0.018$) and discharge from the hospital (log-rank test, $p = 0.040$) (Figures 3 and 4). This attenuated rate again persisted after multivariable adjustment, HR: 0.33; 95% CI: 0.15–0.72 and HR: 0.46; 95% CI: 0.23–0.92, respectively. There was no difference in in-hospital mortality between the groups (log-rank test, $p = 0.741$) (Figure 5). These relationships remained when death was treated as a competing risk (Table 3).

Discussion

Patients that received noninvasive RS for more than 3 days before mechanical ventilation and subsequent ECMO were approximately 50% less likely to be liberated from extracorporeal life support, mechanical ventilation, or be discharged from the hospital. There was no relationship to mortality which may be because of the limited power of the study. These relationships were independent of risk related to age, gender, and the duration of IMV and persisted when the outcomes were analyzed with consideration for the competing risk of death.

Table 1. Baseline characteristics of patients stratified by duration of respiratory support before mechanical ventilation

	All Patients	RS < 3 days	RS ≥ 3 days	
	N = 78	N = 45	N = 33	p
Demographic data				
Age (years)	48 (40, 54)	47 (40, 54)	49 (43, 55)	0.507
Gender, women	14 (18.0)	7 (15.6)	7 (21.2)	0.561
Race (non-white)	63 (80.8)	37 (82.2)	26 (78.8)	0.775
BMI	31.7 (27.5, 39.0)	32.7 (28.0, 39.0)	29.9 (26.3, 39.3)	0.448
Comorbidities				
Diabetes mellitus	30 (38.5)	17 (37.8)	13 (39.4)	0.999
Coronary artery disease	3 (3.8)	0 (0)	3 (9.1)	0.072
Hypertension	28 (35.9)	20 (44.4)	8 (24.2)	0.095
Chronic kidney disease	2 (2.6)	2 (4.4)	0 (0)	0.505
COPD	1 (1.3)	1 (2.2)	0 (0)	0.999
Clinical data before ECMO initiation				
Acute kidney injury	28 (35.9)	19 (42.2)	9 (27.3)	0.234
Renal replacement therapy	5 (6.4)	5 (11.1)	0 (0)	0.069
Transfer from outside hospital	44 (56.4)	23 (51.1)	21 (63.6)	0.356
PaO$_2$/FiO$_2$ before intubation	66.5 (55.0, 88.3)	85.0 (60.0, 146.0)	57.6 (54.0, 67.0)	0.015
Trial of HFNC	53 (68.0)	24 (53.3)	29 (87.9)	0.001
Days on HFNC before ECMO	1 (0, 4)	0 (0, 1)	5 (3, 7)	<0.001
Trial of NIVPPV	31 (39.7)	15 (33.3)	16 (48.5)	0.242
Days on NIVPPV before ECMO	0 (0, 1)	0 (0, 0)	0 (0, 4)	0.002
Days on ventilator before ECMO	2.5 (1, 5)	4 (1, 6)	2 (1, 4.5)	0.135
Days from admission to ECMO initiation	8 (5, 12)	7 (3, 9)	11 (9, 14)	<0.001
Adjunctive treatment measures				
Prone positioning	69 (88.5)	37 (82.2)	32 (97.0)	0.071
Remdesivir	46 (59.0)	28 (62.2)	18 (54.5)	0.642
Systemic steroids	64 (82.1)	33 (73.3)	31 (93.9)	0.034
Tocilizumab	27 (34.6)	19 (42.2)	8 (24.2)	0.148

Data presented as median (25th percentile, 75th percentile) or n (%) unless otherwise indicated RS, respiratory support; HFNC, High-flow nasal cannula; NIVPPV, Noninvasive positive pressure ventilation; ECMO, Extracorporeal membrane oxygenation.

Patients that received longer durations of RS before mechanical ventilation and subsequent ECMO had a lower PF ratio (57 *vs.* 85) before initiation of IMV which indicates worsening lung injury and ventilation-perfusion mismatch. It is uncertain if the difference in PF ratio between these two groups reflects the inevitable lung damage related to progressive COVID-19 infection, damage related to prolonged RS in spontaneously breathing patients, a delay before intubation due to changes in clinical practice over the course of the pandemic or a difference in the severity of illness between the two groups. However, one notable explanation for the results may be related to the added delay in the initiation of V-V ECMO caused by prolonged RS in patients eligible for ECMO support. In their seminal paper on The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction Score (RESP score), Schmidt et al.[18,19] demonstrated mortality benefit from early (<48 hours of IMV) initiation of ECMO. In the same study, peak inspiratory pressure was found to be an independent risk factor, which has been shown

to be responsible for ventilator-induced lung injury (VILI).[20–22] Thus, it can be inferred that prolonged RS might also predispose to lung injury through P-SILI.

The interest in P-SILI peaked during the pandemic following the controversial concept of various phenotypes of ARDS in COVID.[14,23] High swings in transpulmonary pressure which accompany hyperventilation can lead to pulmonary edema in animal models.[24] Spontaneously breathing patients with severe ARDS have a high ventilatory drive and increased tidal volumes, which is postulated to cause acute lung injury similar to VILI.[25] However, experimental and pathologic data are lacking and hence P-SILI remains highly debated.[26,27] More recently, Ziehr et al.[28] demonstrated in their study that respiratory failure caused by COVID behaves like traditional ARDS.

Another way to conceptualize the results is to broadly divide the patients into two sets. One set of patients have a more indolent course and are maintained on RS for prolonged time before intubation and eventual ECMO. These patients may not

Table 2. Analysis of outcomes of patients stratified by duration of respiratory support before extracorporeal life support (respiratory support <3 days as reference) with adjustment for confounders

	Unadjusted Hazard Ratio (95% CI)	p	Adjusted Hazard Ratio (95% CI)[a]	p	Adjusted Hazard Ratio (95% CI)[b]	p
Primary outcome						
ECMO liberation	0.46 (0.26–0.83)	0.011	0.43 (0.23–0.80)	0.008	0.357 (0.19–0.67)	0.002
Secondary outcomes						
Overall in-hospital mortality	1.12 (0.56–2.26)	0.747	1.19 (0.58–2.45)	0.642	1.13 (0.53–2.42)	0.757
Mechanical ventilation liberation	0.42 (0.20–0.89)	0.023	0.37 (0.17–0.82)	0.014	0.33 (0.15–0.72)	0.006
Hospital discharge	0.52 (0.27–0.99)	0.046	0.49 (0.25–0.95)	0.035	0.46 (0.23–0.92)	0.028

ECMO, extracorporeal membrane oxygenation.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender, and number of ventilator days before ECMO initiation.
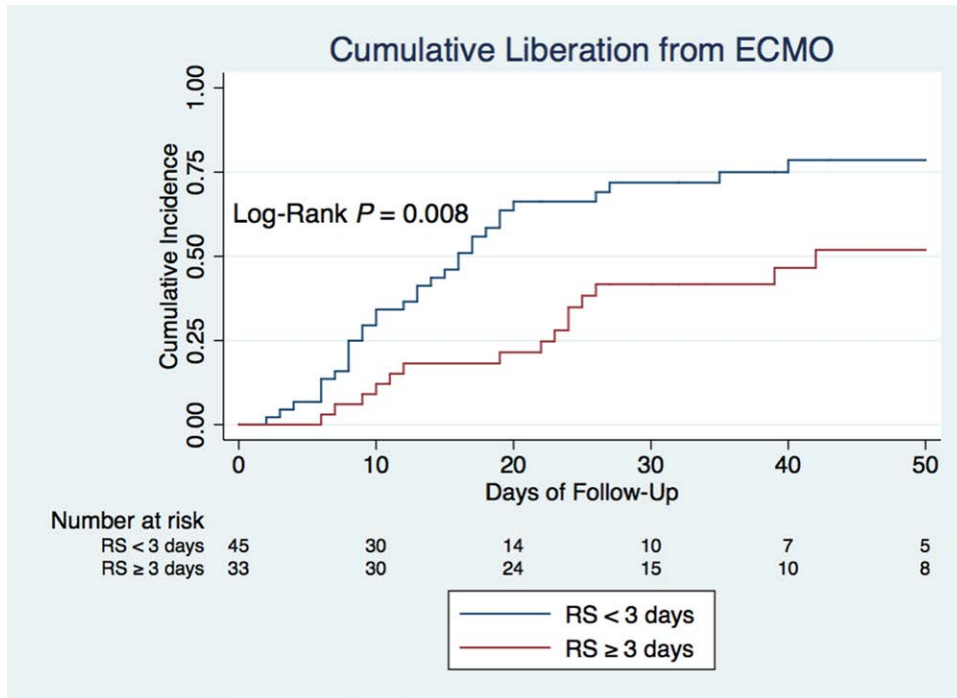
Figure 2. Kaplan-Meier cumulative incidence curve for extracorporeal membrane oxygenation (ECMO) liberation from time of initiation of extracorporeal life support based on duration of prior respiratory support (RS).

derive the full benefit of ECMO support and lung rest as compared to the more acute phenotype with less time on RS before IMV and ECMO support. These patients with more fulminant disease may derive the most benefit from ECMO, lung rest, and experience the most rapid recovery from the underlying process.

Our study has a few limitations. Despite the high volume of ECMO usage at these two centers, the sample size observed was small and limits the statistical power to detect a difference in mortality based on duration of RS and to adjust for confounding factors such as illness severity, BMI, and comorbid illnesses. However, of note, baseline characteristics were similar
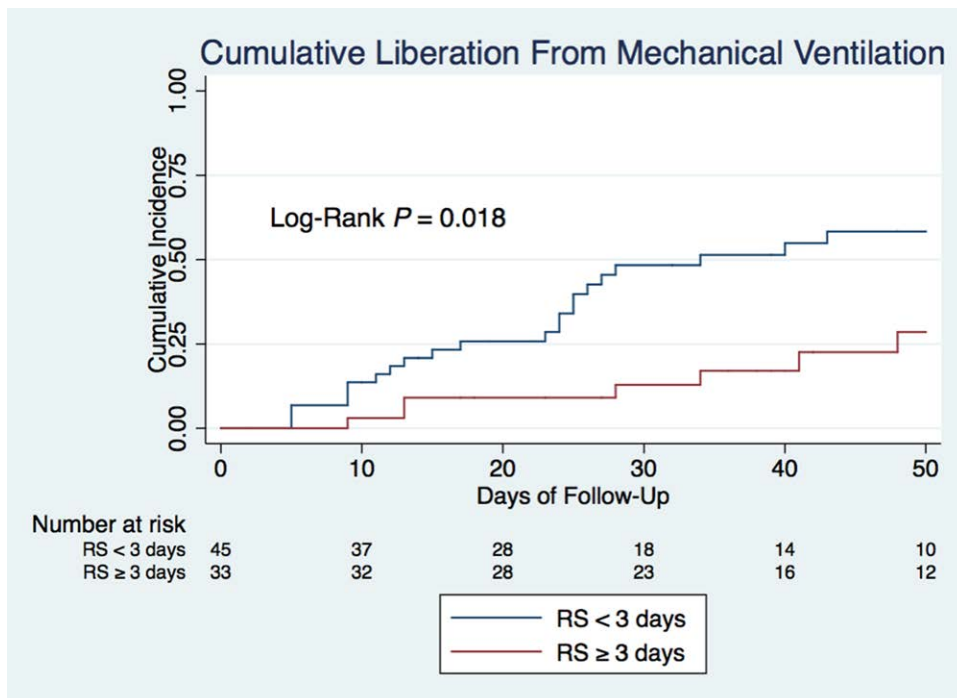

Figure 3. Kaplan-Meier cumulative incidence curve for mechanical ventilation liberation from time of initiation of extracorporeal life support based on duration of prior respiratory support (RS). full color online
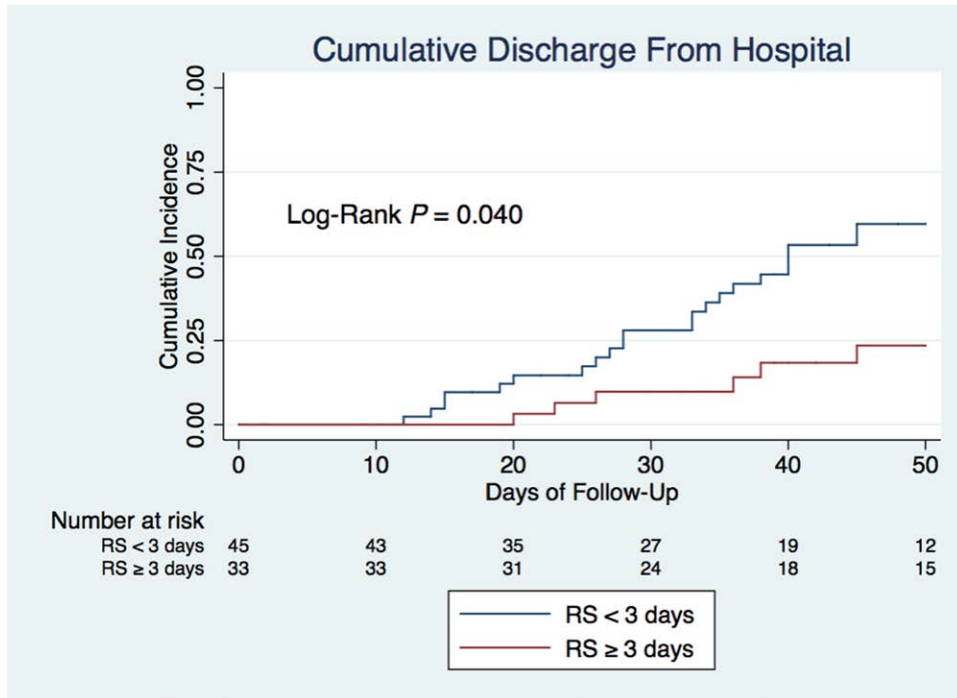
Figure 4. Kaplan-Meier cumulative incidence curve for hospital discharge from time of initiation of extracorporeal life support based on duration of prior respiratory support (RS). [full color online]

between the two groups that were compared. In addition, pre-hospital clinical characteristics such as days since symptom onset were not collected and could also represent a source of potential bias. Further, although care of severely ill patients with COVID-19 was generally standardized and similar at the two institutions involved in this study, strict adherence to a

treatment protocol could not be ensured given the retrospective nature of this analysis. Given these considerations, prospective evaluation in this population is critical to confirm our findings. For simplicity, we grouped patients receiving HFNC and NIV together. Although this grouping eased data analysis, it is possible clinical outcomes related to RS delivered by these
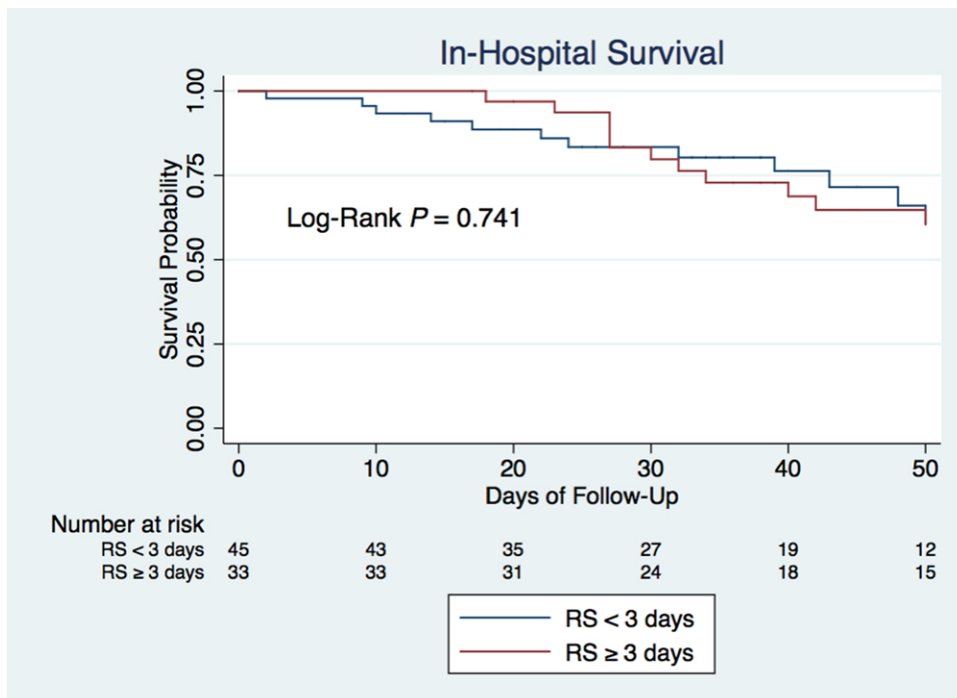

Figure 5. Kaplan-Meier survivor curve of overall in-hospital survivor from time of initiation of extracorporeal life support based on duration of prior respiratory support (RS). [full color online]

Table 3. Sensitivity analysis of outcomes controlling for the competing risk of death of patients stratified by duration of respiratory support before extracorporeal life support (respiratory support <3 days as reference) with adjustment for confounders

	Unadjusted SHR (95% CI)	p	Adjusted SHR (95% CI)[a]	p	Adjusted SHR (95% CI)[b]	p
Primary outcome						
ECMO liberation	0.53 (0.30–0.93)	0.027	0.51 (0.28–0.93)	0.028	0.46 (0.25–0.85)	0.013
Secondary outcomes						
Mechanical ventilation liberation	0.47 (0.23–0.96)	0.039	0.44 (0.20–0.96)	0.038	0.39 (0.18–0.83)	0.015
Hospital discharge	0.53 (0.29–0.97)	0.040	0.51 (0.27–0.95)	0.033	0.53 (0.28–0.99)	0.049

ECMO, extracorporeal membrane oxygenation; SHR, subdistribution hazard ratio.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender, and number of ventilator days before ECMO initiation.

two modalities differ and this too deserves specific attention in future study. For example, a patient requiring NIV support but experiencing minimal work of breathing and maintaining tidal volumes 6–8 cc/kg is likely not equivalent to a tachypneic patient with excessive tidal volumes. In addition, our population was predominantly men and non-white which may limit external generalizability. Given resource limitations during the COVID-19 pandemic, strict institutional criteria for ECMO usage were enforced. The implications of our findings in relation to more relaxed ECMO usage criteria also require further evaluation.

In conclusion, among severely ill patients with COVID-19 that required ECMO support, ≥3 days of RS before mechanical ventilation and ECMO initiation was associated with approximately 50% reduction in the rate of liberation from ECMO, IMV, and subsequent hospital discharge. Prolonged duration of RS before mechanical ventilation and ECMO may result in lung injury and worse subsequent outcomes and therefore is an important consideration when evaluating patients for consideration of ECMO support. In addition, in patients that are otherwise appropriate ECMO candidates, clinicians may consider earlier intubation and initiation on extracorporeal support rather than prolonged RS to limit the propagation of further lung injury. Prospective study would be helpful to confirm our findings and to explore if the duration of a specific type of RS such as HFNC or NIV is related to worse subsequent ECMO outcomes.

Qamar Ahmad, MD, takes responsibility for the content of the manuscript, including the data and analysis.

Q.A., A.C., A.G., and C.K. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design: C.K., Q.A., A.C., A.G., N.P., M.D., E.O., and G.C. Acquisition, analysis, or interpretation of data: A.C., Q.A., C.K. and A.G. Drafting of the article: Q.A., A.C., and C.K. Critical revision of the article: all authors.

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