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Time to Extubation Among ARDS Subjects With and Without COVID-19 Pneumonia

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BACKGROUND: Pneumonia from COVID-19 that results in ARDS may require invasive mechanical ventilation. This retrospective study assessed the characteristics and outcomes of subjects with COVID-19–associated ARDS versus ARDS (non-COVID) during the first 6 months of the COVID-19 pandemic in 2020. The primary objective was to determine whether mechanical ventilation duration differed between these cohorts and identify other potential contributory factors. METHODS: We retrospectively identified 73 subjects admitted between March 1 and August 12, 2020, with either COVID-19–associated ARDS (37) or ARDS (36) who were managed with the lung protective ventilator protocol and required >48 h of mechanical ventilation. Exclusion criteria were the following: <18 years old or the patient required tracheostomy or interfacility transfer. Demographic and baseline clinical data were collected at ARDS onset (ARDS day 0), with subsequent data collected on ARDS days 1–3, 5, 7, 10, 14, and 21. Comparisons were made by using the Wilcoxon rank-sum test (continuous variables) and chi-square test (categorical variables) stratified by COVID-19 status. A Cox proportional hazards model assessed the cause-specific hazard ratio for extubation. RESULTS: The median (interquartile range) mechanical ventilation duration among the subjects who survived to extubation was longer in those with COVID-19-ARDS versus the subjects with non-COVID ARDS: 10 (6–20) d versus 4 (2–8) d; $P < .001$. Hospital mortality was not different between the two groups (22% vs 39%; $P = .11$). The competing risks Cox proportional hazard analysis (fit among the total sample, including non-survivors) revealed that improved compliance of the respiratory system and oxygenation were associated with the probability of extubation. Oxygenation improved at a lower rate in the subjects with COVID-19–associated ARDS than in the subjects with non-COVID ARDS. CONCLUSIONS: Mechanical ventilation duration was longer in subjects with COVID-19–associated ARDS compared with the subjects with non-COVID ARDS, which may be explained by a lower rate of improvement in oxygenation status. *Key words: Extubation; weaning; Corona Virus Disease 2019; acute respiratory distress syndrome.* [Respir Care 2023;68(10):1340–1346.

Introduction

COVID-19 pneumonia can result in ARDS. Early in the pandemic, 2 distinct phenotypes of COVID-19–associated ARDS were proposed based on the unusual presentation of severe hypoxemia with only mild alterations in corresponding compliance of the respiratory system (C_{RS}).[1,2] In addition, there was a perception that COVID-19–associated ARDS resulted in a longer duration of invasive mechanical ventilation.[1] Because recovery of oxygenation determines the onset of weaning trials and low CRS largely influences the ability of the respiratory muscles to maintain unassisted breathing, we reasoned that the severity of dysfunction in both variables, along with time course of resolution, might account for the duration of ventilation. Therefore, we hypothesized that either resolution of compliance or oxygenation would likely explain any differences in the rate of successful extubation and mechanical ventilation duration between subjects with COVID-19–associated ARDS and subjects with non-COVID ARDS. Although previous studies found similar clinical outcomes and C_{RS} values between the subjects with COVID-19–associated ARDS and the subjects with non-COVID ARDS, there is limited evidence with regard to whether the probability of successful extubation differs among the subjects with COVID-19–associated ARDS.[3]

Methods

Patients with COVID-19–associated ARDS and patients with ARDS who were admitted between March 1, 2020, and August 12, 2020, were retrospectively screened, and 73 patients who met inclusion criteria were enrolled in the study (Fig. 1). Our aim was to assess whether the duration of mechanical ventilation differed between these cohorts and to identify associated factors that accounted for mechanical ventilation duration. The primary outcome was the difference in mechanical ventilation duration, defined as the duration from mechanical ventilation initiation to extubation, between the subjects with COVID-19–associated ARDS and the subjects with ARDS. Because death is a competing outcome to extubation, the primary outcome was measured in subjects who survived long enough to achieve successful extubation. Successful extubation was defined as the ability to maintain unassisted breathing without an artificial airway for >48 h. We then fitted a competing risks regression model to the total sample to account for the competing risk of death.

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Our primary intent was to examine with more clarity whether 3 aspects of mechanical ventilation duration in survivors were independently associated with the time to extubation: these being the severity of dysfunction in either (or both) oxygenation and C_{RS} as well as functional recovery time. To achieve this, we analyzed the arterial oxygen tension to inspired oxygen fraction (P_{aO_2}/F_{IO_2}), C_{RS}, and minute ventilation as time-varying characteristics. The latter was included as an indirect surrogate for the respiratory muscle power output because it reflects subjects' ventilatory total energy expenditure.[4]

In addition, we assessed other confounders that may have influenced mechanical ventilation duration. First, was mechanical ventilation duration until weaning readiness criteria were achieved. This was used as a practical signifier for both ARDS severity and critical illness severity in general. Second, was the number of days from the first successful spontaneous breathing trial (SBT) until extubation. This was done to assess clinician-related factors that may have operated as a confounding variable separate from ARDS severity. Other variables assessed that may have influenced the duration of mechanical ventilation included age, body mass index, and sex. A secondary outcome was all-cause mortality at hospital discharge.

Study inclusion criteria were the following: (1) meeting the Berlin consensus definition for ARDS,[5] (2) ARDS onset within 24 h of admission, (3) mechanical ventilation required for >48 h, (4) age ≥ 18 years, (5) ventilator management by using the National Institutes of Health ARDS Clinical Trials Network protocol.[6] Exclusion criteria were transfer to another hospital for extracorporeal membrane oxygenation and presence of a tracheostomy. However, no patients who were screened met these conditions. Institutional review board approval was granted with a waiver for consent due to the observational nature of the study (institutional review board study 16–19189).

Data were collected from the Epic (Epic Systems, Verona, Wisconsin) electronic medical record and included demographic, baseline clinical, and longitudinal data. Ventilator

QUICK LOOK

Current knowledge

Pneumonia caused by COVID-19 may result in ARDS. Prolonged invasive ventilation has been observed with COVID-19–associated ARDS. Among subjects with COVID-19, we observed the duration of mechanical ventilation frequently exceeded 7 days. These observations were appreciably different from those reported in large studies of subjects with non–COVID-19 ARDS.

What this paper contributes to our knowledge

This study compared mechanical ventilation duration in subjects with COVID-19–associated ARDS and non–COVID-19 ARDS. Mechanical ventilation duration was significantly greater in subjects with COVID-19–associated ARDS. The probability of extubation was associated with improvement in oxygenation and C_{RS}.

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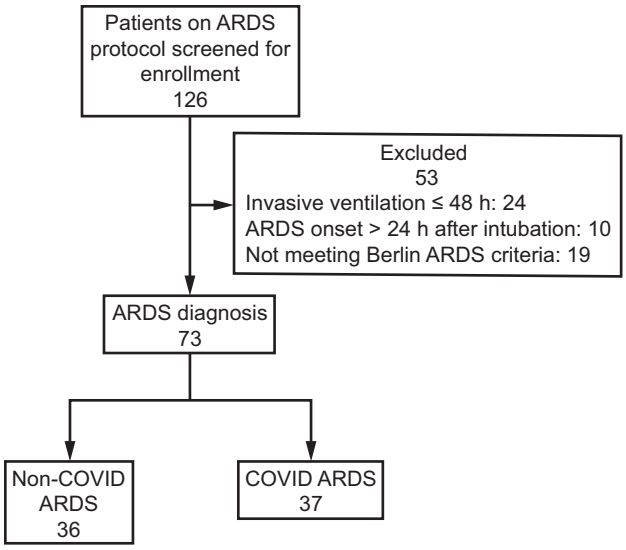


Fig. 1. Flow chart.

data were collected from the patient ventlator assessment at the time of ARDS onset (day 0) and on the patient ventlator assessment closest to 8:00 AM on subsequent calendar days (ARDS days 1, 2, 3, 5, 7, 10, 14, and 21). The ventilatory ratio was calculated by using the method of Sinha et al.[7] The driving pressure was calculated by taking the difference between plateau pressure and the measured PEEP. Weaning readiness criteria were $F_{IO_2} \leq 0.5$ and PEEP of ≤ 10 cm H_2O. The subjects were weaned by using the SBT with pressure support ventilation of ≤ 7 cm H_2O above PEEP. A successful SBT was the ability to maintain pressure support spontaneous ventilation for 2 h without signs of intolerance as defined by the National Institutes of Health ARDS Clinical Trials Network protocol.[6]

Mechanical ventilation duration was calculated as the time from initiation until successful extubation that lasted > 48 h. In those in whom a trial of extubation within 48 h failed, that period off the ventilator was considered mechanical ventilation days. The duration of mechanical ventilation until first meeting weaning readiness criteria was calculated as the number of days from mechanical ventilation initiation to the first day all criteria were achieved. We also calculated the days between the first successful SBT and the first day a trial of extubation was undertaken.

COVID-19 infection was based on laboratory confirmation by using the RNA test standard at our hospital (real-time reverse-transcriptase polymerase chain reaction). Non–COVID-19-associated ARDS etiologies were classified as due to pneumonia, aspiration, sepsis, trauma, or other etiologies (eg, pancreatitis, smoke inhalation). Trauma-associated ARDS was defined as the development of ARDS within the first 24 h of hospital admission after injury. Patient characteristics were stratified by COVID-19 infection. Continuous variables are expressed as median (interquartile range) and were compared by using the Wilcoxon rank-sum test. Categorical variables are expressed as numbers (percentages) and were compared by using the chi-square test. For the competing risks regression model, we used Cox proportional hazard models to analyze the association between predictor variables and time to extubation. This model accounts for the competing risk of death by measuring the cause-specific hazard ratio, which estimates the rate of extubation among those who are alive and ventilated.[8] Although typically used to assess the hazard of a negative event (such as an unplanned extubation), the Cox proportional hazard models were used in this context to model a positive event (planned liberation from invasive mechanical ventilation).

Predictor variables were determined a priori and included COVID-19 pneumonia, age, sex, and body mass index as fixed time covariates. The time-varying covariates included minute ventilation, C_{RS}, and P_{aO_2}/F_{IO_2}. These variables are associated with ARDS severity and may influence the probability of extubation. Linear mixed-effects models were then used to estimate the change of time-varying variables in relation to the baseline. Missing measures were carried forward from the last measured values. Differences were considered statistically significant when $P < .05$. Data were analyzed by using Stata version 16 (2019) (StataCorp, College Station, Texas). Study data were collected and managed by using REDCap electronic data capture tools hosted at the University of California San Francisco.[9,10] A sample size of 60 subjects with an equal proportion of subjects with COVID-19–associated ARDS and subjects with ARDS was determined to have 80% power to detect a 3.77-day difference in mechanical ventilation duration. The proportional hazards assumption was tested based on the Schoenfeld residuals.[11]

Results

Subjects with COVID-19–associated ARDS were distinguished from the subjects with ARDS by 3 subject characteristics: (1) primarily Hispanic-Latino descent, (2) significantly higher body mass index, and (3) a higher incidence of diabetes mellitus as a comorbidity (Table 1). There was no distinction between the study cohorts in terms of baseline illness severity or graduations of ARDS severity. The median time to meeting ARDS criteria after intubation was shorter in the subjects with COVID-19–associated ARDS compared with the subjects with ARDS, but the difference was clinically irrelevant (0 min and 200 min, respectively; $P < .001$). All the subjects were managed on volume control continuous mandatory ventilation, and there was no

Table 1. Demographics and Baseline Characteristics

Characteristic	Survivors			All Subjects		
	ARDS ($n = 22$)	COVID-19 ($n = 29$)	P	ARDS ($n = 36$)	COVID-19 ($n = 37$)	P
Age mean ± SD y	51 ± 19	55 ± 13	.39	55 ± 20	57 ± 15	.56
Men, %	82	66	.20	75	65	.35
Race/ethnicity, %			<.001			<.001
Asian descent	14	17		17	16	
African descent	23	7		22	5	
European descent	23	3		9	3	
Hispanic descent	18	72		17	76	
Other	23	0		25	0	
BMI, median (IQR) kg/m^2	26 (19–29)	29 (28–34)	<.001	25 (22–29)	29 (28–34)	<.001
Diabetes mellitus, %	9	59	<.001	19	62	<.001
Hypertension, %	32	52	.16	39	57	.13
APACHE II score, median (IQR)	12 (6–17)	10 (9–15)	.89	11 (7–18)	10 (8–15)	.90
ARDS etiology, %						<.001
Pneumonia	32	NA	NA	33	NA	
Aspiration	45	NA	NA	39	NA	
Sepsis	18	NA	NA	14	NA	
Trauma						
Thoracic	5	NA	NA	8	NA	
Non-thoracic	0	NA	NA	3	NA	
Other etiology	0	NA	NA	3	NA	
Berlin definition, %			.92			.25
Severe	27	24		42	24	
Moderate	50	59		42	59	
Mild	23	17		17	16	
Time to ARDS onset, min	205	10		200	0	<.001

BMI = body mass index
IQR = interquartile range
APACHE II = Acute Physiology and Chronic Health Evaluation II
NA = not applicable

difference in the quality of lung-protective ventilation achieved or respiratory system mechanics between the study cohorts. The subjects with COVID-19–associated ARDS required a lower minute ventilation demand at baseline, reflected in the lower base deficit and higher arterial pH (Table 2).

The mean (IQR) mechanical ventilation duration was significantly longer in the subjects with COVID-19–associated ARDS versus the subjects with ARDS (10 [6–20] d vs 4 [2–8] d; $P < .001$). This was confirmed in the unadjusted competing risks regression analysis in which the probability of extubation was lower among the subjects compared with those without COVID-19 pneumonia (cause-specific hazard ratio 0.54, 95% CI 0.30–0.96; $P = .04$). In the adjusted analysis, however, only C_{RS} and P_{aO_2}/F_{IO_2} were associated with the probability of successful extubation (Table 4). The linear mixed effects model demonstrated that the rate of P_{aO_2}/F_{IO_2} improvement was significantly slower among the subjects with COVID-19–associated ARDS compared with the subjects with ARDS (Fig. 2); yet this difference was not observed with the changes in C_{RS} .

When analyzing the different periods of mechanical ventilation, the most salient difference between the subjects with COVID-19–associated ARDS and the subjects with ARDS was the apparent prolonged duration needed to stabilize the subjects with COVID-19–associated ARDS. The subjects with COVID-19–associated ARDS required significantly more days to meet weaning readiness criteria versus the subjects with ARDS (median [IQR] 6.4 [2.6–13.3] d vs 1.4 [0.8–1.9] d; $P < .001$); however, the median [IQR] days from meeting weaning readiness criteria to the first successful SBT was not statistically different (0.73 [0.21–2.1] d vs 1.2 [0.6–1.5] d; $P = .49$). Nonetheless, the subjects with COVID-19–associated ARDS continued to receive mechanical ventilation for a longer duration versus the subjects with ARDS despite having passed an SBT (median [IQR] 2.1 [0.9 – 3.5] d vs 0.9 [0.00–2.9] d; $P = .044$). With regard to secondary outcomes, hospital mortality was not significantly different between the subjects

Table 2. Baseline Ventilation Requirements, Mechanics, Gas Exchange Characteristics

Variable	ARDS	COVID-19	*P*
Mode VC-CMV, %	100	100	
F_{IO_2}, mean ± SD	1.0 ± 0	1.0 ± 0	.003
P_{plat}, cm H_2O	23 (20–27)	25 (22–26)	.69
PEEP, cm H_2O	10 (8–12)	10 (10–14)	.049
Driving pressure, cm H_2O	13 (11–17)	13 (11–15)	.34
f, breaths/min	24 (20–30)	22 (20–26)	.09
V_T, mL/kg PBW	6 (6–7)	6 (6–6)	.76
$\dot{V}_E$, L/min	9 (7–12)	8 (7–9)	.02
C_{RS}, mL/cm H_2O	29 (21–35)	27 (23–33)	.73
Arterial pH	7.32 (7.24–7.36)	7.35 (7.30–7.39)	.032
P_{aCO_2}, mm Hg	40 (36–47)	41 (36–43)	.76
P_{aO_2}, mm Hg	84 (68–112)	104 (86–167)	.007
HCO_3^-, mEq/dL	21 (18–23)	23 (22–25)	.041
Base deficit, mEq/dL	5.8 (3.1–9.2)	3.2 (2.2–6.2)	.037
P_{aO_2}/F_{IO_2}, mm Hg	113 (87–171)	120 (101–170)	.36
Ventilatory ratio	1.57 (1.27–2.19)	1.43 (1.29–1.69)	.25

Variables are represented as median (interquartile range) unless otherwise noted.
VC-CMV = volume control ventilation
P_{plat} = plateau pressure
f = breathing frequency
V_T = tidal volume
$\dot{V}_E$ = expired minute volume
C_{RS} = compliance of the respiratory-system

with COVID-19–associated ARDS versus the subjects with ARDS (22% vs 39%; $P = .11$) (Table 3).

Table 3. Primary and Secondary Outcomes

Outcome	ARDS	COVID-19 ARDS	*P*
Mechanical ventilation days (survivors)	4 (2–8)	10 (6–20)	<.001
Days to meet weaning readiness criteria (survivors)	1.4 (0.8–1.9)	6.4 (2.6–13.3)	<.001
Days weaning readiness criteria to first successful SBT (survivors)	1.2 (0.6–1.5)	0.73 (0.21–2.1)	.49
Days from SBT pass to extubation	0.9 (0.0–2.9)	2.1 (0.9–3.5)	.044
Hospital mortality, %	39	22	.11

Variables are represented as median (interquartile range) unless otherwise noted.
WRC = weaning readiness criteria
SBT = spontaneous breathing trial

Discussion

The main finding of our study was that the subjects with COVID-19–associated ARDS required longer mechanical ventilation duration than the subjects with ARDS. The difference was related to 2 factors: first, the slower resolution in pulmonary oxygenation dysfunction that resulted in a prolonged time course until the subjects with COVID-19 met weaning readiness criteria, and second, the delay between successful SBT and a subsequent extubation trial. The longer duration between SBT passage and extubation among the subjects with COVID-19–associated ARDS may have reflected either the presence of unmeasured, non-pulmonary variables that postponed extubation (eg, neurologic impairment) or an overly cautious approach to extubation in light of the COVID-19 pandemic. With regard to the latter, it is inviting to speculate that our unfamiliarity with managing patients with novel SARS CoV-2 during the first months of the COVID-19 pandemic may have been a factor because it would instill a more cautious approach to weaning compared with ARDS. This may have been amplified by some of our early experiences when seemingly stable patients with COVID-19 suddenly developed severe cardiorespiratory instability. Although this phenomenon was a relatively common finding in subjects with COVID-19,[12] we do not have data that support this premise.

Other studies that compared subjects with COVID-19–associated ARDS with subjects with ARDS have also observed increased mechanical ventilation duration in those with COVID-19–associated ARDS.[13,14] To our knowledge, only one other study compared the probability of extubation and found no difference.[15] The investigators reported minimum clinical differences at baseline between the subjects with COVID-19–associated ARDS and the subjects with ARDS, which were consistent with our results. However, they did not compare the time course change of clinical variables. In addition, they used a different statistical method when completing their time-to-extubation analysis. Their analysis estimated the sub-distribution hazard rate, which is interpreted differently than the cause-specific hazard estimate used in our study.[8] This reflects the challenge faced when interpreting competing risk survival models, especially when death is the competing risk.

During the early months of the pandemic, much attention was paid to subjects with COVID-19–associated ARDS in whom C_{RS} remained relatively well preserved, with disproportionately more severe hypoxemia (ie, type L presentation).[2] However, at the onset of COVID-19–associated ARDS in our subjects, C_{RS} was markedly decreased and was indistinguishable from our subjects with ARDS. Moreover, the time course change in C_{RS} did not differ between the groups. In addition, our baseline C_{RS} findings among the subjects with COVID-19–associated ARDS were comparable with other studies, with the majority of baseline values ≤ 40 cm H_2O measured on similar levels of PEEP and tidal volume regardless of ARDS etiology.[15,16] Furthermore, the application and tolerance of lung-protective ventilation between our study cohorts was comparable with that reported in other studies.[13]

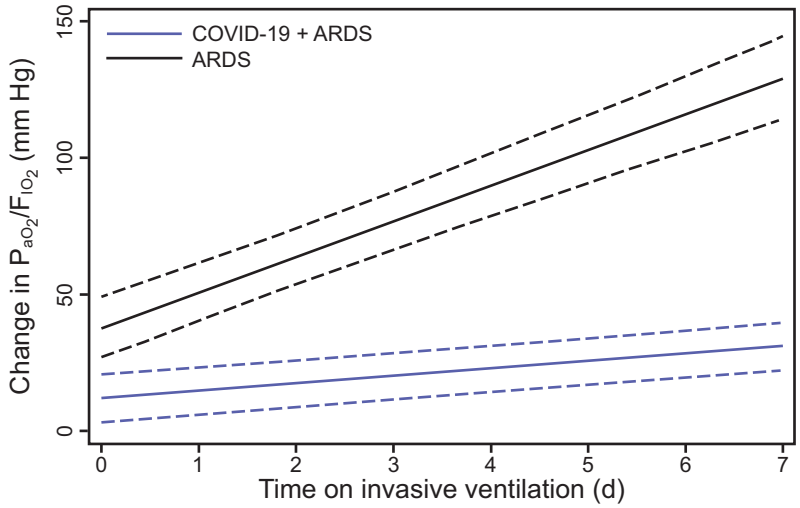
Table 4. Unadjusted and Adjusted Cox Proportional Hazards Model Evaluating Factors Associated with Extubation

Risk Factor	Cause Specific HR (95% CI)	*P*
Univariate analysis		
Baseline		
Age (per 10 y increase)	0.85 (0.7–1.02)	.08
Female gender	0.69 (0.37–1.28)	.24
COVID-19 pneumonia	0.54 (0.30–0.96)	.04
Body mass index	0.98 (0.93–1.03)	.39
Time varying		
$\dot{V}_E$*	0.89 (0.79–1.0)	.05
C_{RS}†	1.50 (1.22 to 1.86)	<.001
P_{aO_2}/F_{IO_2} (per 50 units increase)	1.52 (1.28 to 1.82)	<.001
Multivariable analysis		
Baseline		
Age (per 10 y increase)	0.98 (0.80–1.20)	.81
Women	0.83 (0.38–1.82)	.64
COVID-19 pneumonia	0.90 (0.40–2.01)	.79
Body mass index	1.01 (0.94–1.07)	.88
Time varying		
$\dot{V}_E$*	0.89 (0.79–1.01)	.08
C_{RS}†	1.35 (1.05 to 1.73)	.02
P_{aO_2}/F_{IO_2} (per 50 units increase)	1.43 (1.14 to 1.80)	.002

*Per 1-L increase in minute volume.
†Per 10-unit increase in compliance of the respiratory system.
HR = hazard ratio
$\dot{V}_E$ = expired minute volume
C_{RS} = compliance of the respiratory system

A limitation of our study was the small sample size, which may have contributed to the unusually low mechanical ventilation duration measured in our ARDS cohort and thus the external validity of these results. According to a previously published study from our institution with a sample size of 656 subjects, the median (IQR) mechanical ventilation duration in ARDS was considerably longer than that observed in our cohort: 9 (4–17) d in the previous cohort versus 4 (2–8) d in our study cohort.[17] Furthermore, 72% of our subjects with ARDS had primary lung injury from pneumonia or aspiration, and 14% had non-pulmonary ARDS. The median (IQR) mechanical ventilation duration measured in our institution's ARDS registry for these etiologic cohorts, in which lung-protective ventilation was applied, were as follows: aspiration 7 (3–14) d, pneumonia 10 (5–19) d, and sepsis 9 (4–15) d. We believe that random variation during the brief enrollment time is the most cogent explanation for our ARDS cohort's low mechanical ventilation days, which thus leads to inadvertent selection bias.

Future studies with larger sample sizes are warranted, which may address the challenge we faced with potential selection bias and might confirm our findings that the rate of oxygenation recovery is lower in the subjects with COVID-19–associated ARDS. In addition, future studies should be conducted that evaluate the statistical methods used for addressing competing risks in ARDS outcomes that precede death because the statistical techniques used



Subjects, *n*	51	51	45	41	32	26
P	.07	.008	<.001	<.001	<.001	<.001
Extubated, *n*	0	6	4	9	6	10
Deceased, *n*	2	0	3	3	2	3

Fig. 2. Mixed effects model comparing baseline and daily change in the arterial oxygen tension-to-inspired oxygen fraction between COVID-19 associated ARDS and non-COVID ARDS survivors (mean ± standard error).

for this purpose generate estimates whose interpretations are heavily nuanced and, therefore, challenging to compare directly.[18]

Conclusions

Mechanical ventilation duration in survivors was longer in subjects with COVID-19–associated ARDS compared with the subjects with ARDS. This may have been associated with the slower rate of oxygenation improvement among the subjects with COVID-19–associated ARDS, which is the primary driver of determining weaning readiness criteria. In addition, there was an apparent reluctance to proceed with a trial of extubation after the passage of an SBT.

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