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# Cannulate, extubate, ambulate approach for extracorporeal membrane oxygenation for COVID-19

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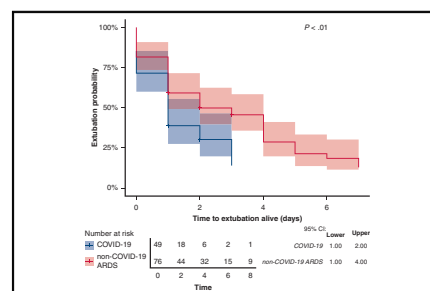
## ABSTRACT

**Objective:** We compared outcomes in patients with severe COVID-19 versus non-COVID-19-related acute respiratory distress syndrome (ARDS) managed using a dynamic, goal-driven approach to venovenous extracorporeal membrane oxygenation (ECMO).

**Methods:** We performed a retrospective, single-center analysis of our institutional ECMO registry using data from 2017 to 2021. We used Kaplan–Meier plots, Cox proportional hazard models, and propensity score analyses to evaluate the association of COVID-19 status (COVID-19-related ARDS vs non-COVID-19 ARDS) and survival to decannulation, discharge, tracheostomy, and extubation. We also conducted subgroup analyses to compare outcomes with the use of extracorporeal cytoreductive techniques (CytoSorb [CytoSorbents Corp] and plasmapheresis).

**Results:** The sample comprised 128 patients, 50 with COVID-19 and 78 with non-COVID-19 ARDS. Advancing age was associated with decreased probability of survival to decannulation ( $P = .04$ ). Compared with the non-COVID-19 ARDS group, patients with COVID-19 had a greater probability of survival to extubation ( $P < .01$ ) and comparable survival to discharge ( $P = .14$ ).

**Conclusions:** Patients with COVID-19 managed with ECMO had comparable outcomes as patients with non-COVID ARDS. A strategy of early extubation and ambulation might be a safe and effective strategy to improve outcomes and survival, even for patients with severe COVID-19. (J Thorac Cardiovasc Surg 2022; ■:1-11)



COVID-19 patients had a shorter time to extubation compared with patients with non-COVID-19 ARDS.

## CENTRAL MESSAGE

Modified EOLIA criteria, aggressive weaning strategies, early tracheostomy, and ambulation during ECMO, and a dynamic approach to candidacy during the pandemic contributed to equivalent outcomes in patients with COVID-19 compared with other causes of ARDS.

## PERSPECTIVE

Modified EOLIA criteria and a dynamic approach to candidacy for extracorporeal membrane oxygenation (ECMO) during the COVID-19 pandemic, coupled with our “cannulate, extubate, ambulate” philosophy proffered satisfactory outcomes in patients with COVID-19.

See Commentary on page XXX.

The SARS-CoV-2 COVID-19 pandemic has been the greatest health care event of this generation. It has had a broad sweeping effect on the global health and economy.<sup>1</sup> The

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intention to ambulate critically ill patients creates a “pervasive progressive culture of mobility” that influences sedation practices, pulmonary toilet practices, and drug dosing. It is potent mitigation against critical illness polyneuropathy. Indeed, as early as extracorporeal membrane oxygenation (ECMO) day 1, we seek to decrease sedation and wake the patient with a view to extubation or early



Scanning this QR code will take you to the table of contents to access supplementary information.



**Abbreviations and Acronyms**

APACHE	= Acute Physiology and Chronic Health Evaluation
ARDS	= Acute Respiratory Distress Syndrome
BMI	= body mass index
BSA	= body surface area
ECMO	= extracorporeal membrane oxygenation
EOLIA	= extracorporeal membrane oxygenation for severe acute respiratory distress syndrome
HR	= hazard ratio
ICU	= intensive care unit
PRESET-score	= Prediction of Survival on Extracorporeal Membrane Oxygenation Therapy-Score
SOFA	= Sequential Organ Failure Assessment
VV-ECMO	= venovenous extracorporeal membrane oxygenation

tracheostomy. This provides the cue to directing our rehabilitative efforts toward ambulation and perpetuates the programmatic mantra of “cannulate, extubate, ambulate.”

To further mitigate the excess mortality borne by the pandemic, we modified our approach to extracorporeal support. We adjusted our algorithms and expectations in response to dynamic, often scarce, resources, personnel, and therapeutics. Our management decisions were explicitly influenced by early experiences drawn from ECMO programs in Italy and New York at the onset of the pandemic.<sup>2-4</sup> In the face of diminishing resources, equipment shortage, supply chain interruptions, scarcity of intensive care unit (ICU) beds, declining medical workforce (physicians, nursing staff, respiratory therapists, etc), and an escalating number of cases, we restricted the use of mechanical support to carefully vetted patients who could be managed using only venovenous ECMO (VV-ECMO). After initial success in managing patients with severe acute respiratory distress syndrome (ARDS) in the pre-pandemic era, we relied on previously established early extubation and mobilization ECMO protocols, which we brought to bear in the management of patients with SARS-CoV-2. The pandemic inadvertently provided the arena in which to empirically test the safety and efficacy of our programmatic doctrine, to assess the effect on survival and potentially counter the increasingly pessimistic narrative regarding the efficacy of ECMO in patients with COVID-19.<sup>5</sup> As such, we hypothesized that the use of a modified, goal-directed algorithm, in combination with our “cannulate, extubate, ambulate”

approach to mechanical support, would yield comparable results in the management of COVID-19 and non-COVID-19 ARDS and we sought to compare outcomes in these 2 groups of patients.

**METHODS****Study Design**

We conducted a retrospective, propensity-scored, comparative analysis of survival to decannulation, discharge, extubation, and tracheostomy alive, as well as overall survival (time to death) among patients with COVID-19 versus non-COVID ARDS who required VV-ECMO. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>4</sup>

**Setting**

The institutional review board of the West Virginia University approved this study on September 9, 2020 (1903494150). We retrospectively analyzed data from the institutional ECMO registry. The details of the structure and administration of our program have been published previously.<sup>6</sup> We evaluated data from January 2017 to May 2021. During the pandemic, we adopted a conservative approach to the standard ECMO for severe ARDS (EOLIA) criteria<sup>7-13</sup> (Table 1). Additional details on the settings are available in Table E1.

**Participants**

We included patients older than 18 years of age diagnosed with COVID-19 or non-COVID-19 ARDS who required VV-ECMO. We describe detailed inclusion and exclusion criteria in Table E2.

**Outcome Variables**

The primary outcomes included time to death, decannulation, discharge, tracheostomy, and extubation alive. We computed these time-to-event variables using time in days and whether the patient was alive at the time of the event.

**Predicting Variables**

Our primary predicting variable was the diagnosis of ARDS requiring VV-ECMO. We dichotomized this into “COVID-19 related” and “non-COVID-19 related.” We evaluated additional predictors associated with time-to-event outcomes, including age, sex, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), body surface area (BSA; calculated as the square root of the height in centimeters multiplied by the weight in kilograms divided by 360), insurance (Medicare or Medicaid), the distance between patient residence and hospital, and risk scores (eg, Prediction of Survival on ECMO Therapy-Score [PRESET-Score], Acute Physiology and Chronic Health Evaluation [APACHE], Sequential Organ Failure Assessment [SOFA], and the Murray score; Table E3).<sup>14-17</sup> Finally, we compared outcomes for patients treated using cyto-reductive therapies such as CytoSorb (CytoSorbents Corp) or plasmapheresis, as well as among different ECMO systems (Cardiohelp [Maquet Cardiopulmonary], CentriMag [Abbot], and NovaLung [Fresenius Medical Care]).

**Covariates**

We selected the following covariates to balance our propensity score models: age, sex, BMI, BSA, insurance type, the distance between center and patient residence, and the duration of mechanical ventilation before ECMO ( $\leq 12$  hours, 12-24 hours, 2-7 days, and  $\geq 7$  days). We also evaluated the inclusion of severity scores as covariates, including PRESET-Score, APACHE, SOFA, and Murray scores. However, because of their high collinearity, we did not include these variables in the final model.

**TABLE 1. Modified criteria for cannulation**

Criteria for cannulation	<ul style="list-style-type: none"> <li>• Age &lt;50 y</li> <li>• PF ratio &lt;80 for 6 h</li> <li>• PF ratio &lt;50 for 3 h</li> <li>• &lt;72 h mechanical ventilation</li> <li>• BMI &lt;42</li> <li>• Attempt at proning for at least 24 h without 25% increase in PF ratio; single organ pathology (only lungs)</li> <li>• Not requiring high-dose vasoactive drugs; no requirement for VA-ECMO</li> </ul>
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PF, Fraction of inspired oxygen; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

## Statistical Methods

**Time-to-event analysis.** We evaluated the association of COVID-19 diagnosis and time-to-event outcomes using Kaplan–Meier plots. We investigated predictors contributing to each outcome using Cox proportional hazards models.<sup>18</sup> We present results for the original numeric variables and their categorized version, to improve clinical interpretation. We categorized age into younger than 24 years (young adults), between 25 and 59 years (adults), and older than 60 years (older adults).<sup>19</sup> We categorized BMI as  $\geq 30$  (obese) and  $< 30$  (nonobese).<sup>20</sup> We also split the risk scores using cutoffs associated with a poor prognosis (Table 2).<sup>15</sup> Within the Cox proportional hazards models, we considered death as a censored event, thus mitigating an immortal survival bias.<sup>21</sup> We present our results as hazard ratios (HRs) with 95% confidence intervals (CIs).

**Propensity score analysis.** We evaluated outcome differences for COVID-19 versus non–COVID-19 ARDS patients, using the data balanced through inverse probability weighting.<sup>22</sup> We evaluated balance regarding the covariates described previously.<sup>23</sup> Our propensity score analysis included missing data as a separate variable category, assigning a weight for missing variables. When we achieved covariate balance, we used Cox proportional hazards models to evaluate outcome differences among the 2 groups as described previously.

**Additional predictors.** We evaluated the effect of CytoSorb and plasma exchange therapy, as well as among different ECMO systems (Cardiohelp, CentriMag, and NovaLung). We used the same methodology described for the comparison of COVID-19 versus non–COVID-19 ARDS patients, including Kaplan–Meier plots, Cox proportional hazard models, and propensity score through inverse probability weighting. We performed all analyses using the R language (R Foundation for Statistical Computing).<sup>24</sup>

## RESULTS

Our total sample included 128 patients, 50 with COVID-19 and 78 with non–COVID-19 ARDS (Table 3). Those with COVID-19 ARDS had comparatively higher BMI ( $37.50 \pm 6.84$  vs  $32.50 \pm 11.00$ ;  $P < .01$ ). A smaller proportion of patients in the COVID-19 group had Medicare or

**TABLE 2. Risk score-based cutoffs for poor prognosis**

Factors that portend poor survival	<ul style="list-style-type: none"> <li>• APACHE &gt;23</li> <li>• SOFA &gt;10</li> <li>• Murray &gt;3</li> <li>• PRESET &gt;5</li> </ul>
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APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PRESET, Prediction of Survival on ECMO Therapy.

Medicaid insurance (8.00% vs 43.60%;  $P < .01$ ). COVID-19 patients had lower PRESET-Score ( $4.94 \pm 2.01$  vs  $7.41 \pm 2.44$ ;  $P < .01$ ), APACHE ( $18.20 \pm 8.52$  vs  $25.00 \pm 8.82$ ;  $P < .01$ ), and SOFA ( $7.03 \pm 3.14$  vs  $10.90 \pm 3.47$ ;  $P < .01$ ) scores, but higher Murray scores ( $3.27 \pm 0.64$  vs  $2.82 \pm 0.88$ ;  $P < .01$ ). Most patients lived in the state (Figure E1).

Compared with the other cohort, COVID-19 patients presented a higher probability of survival to extubation alive (HR, 2.17; 95% CI, 1.28–3.67;  $P < .01$ ), and were extubated earlier (Figures 1 and E2; Table 4). Table E4 shows the percentage of patients alive at decannulation, discharge, tracheostomy, and extubation, as well as the mean and standard deviation (SD) for the time in days to each of these events. Additional details on the time-to-event analysis are available in Table E5. Propensity score results confirmed that COVID-19 patients presented an increased probability of survival to extubation (HR, 2.07; 95% CI, 1.30–3.30;  $P < .01$ ; Table 5, Figure 1, Tables E6–E8, and Figure E3).

## Additional Predictors

Age was associated with time to decannulation and discharge alive (discharge HR, 0.97; 95% CI, 0.95–0.99;  $P < .01$ ; Table 6). Patients older than 60 years had a lower probability of survival to decannulation (HR, 0.43; 95% CI, 0.20–0.96;  $P = .04$ ) and discharge (HR, 0.23; 95% CI, 0.07–0.80;  $P = .02$ ). The PRESET-Score was also associated with the time to extubation alive (HR, 0.85; 95% CI, 0.77–0.95;  $P < .01$ ), and patients with a PRESET-Score  $> 5$  had decreased survival to extubation (they were extubated later than the patients with a lower score; HR, 0.43; 95% CI, 0.27–0.68;  $P < .01$ ). Patients with an APACHE score  $> 23$  and those with a SOFA score  $> 10$  had decreased survival to extubation alive than patients with lower APACHE and SOFA scores ( $P < .05$ ). This was also true for patients with a Murray score  $> 3$ , who had decreased survival to decannulation (HR, 0.50; 95% CI, 0.33–0.78;  $P < .01$ ) than those with lower scores. Last, patients who were transported from greater distances from the hospital had a higher probability of undergoing tracheostomy (HR, 1.00; 95% CI, 1.00–1.01;  $P < .01$ ; Table 6). Figure E4 shows Kaplan–Meier plots for the association of BMI with time-to-event outcomes. Most patients with a BMI  $> 30$  were extubated before decannulation (36.40% vs 64.80%,  $P = .13$ ).

## Adjunctive Use of Cytoreductive Techniques

A total of 25 patients in the COVID-19 group received CytoSorb therapy, whereas 25 COVID-19 patients did not (Table E9). There were no differences between the 2 groups (Table 7, Tables E10–E12, and Figures E5 and E6).

Patients who underwent plasmapheresis had a decreased probability of decannulation (HR, 0.06; 95% CI, 0.01–0.27;  $P < .01$ ), extubation (HR, 0.34; 95% CI, 0.13–0.88;  $P = .03$ ), and discharge (HR, 0.15; 95% CI, 0.03–0.85;

TABLE 3. Study sample characteristics and comparison between COVID-19 and non-COVID-19 ARDS patients undergoing VV-ECMO

Variable (Missing)	Total (n = 128)	COVID-19 (n = 50)	Non-COVID-19 ARDS (n = 78)	P value	SMD
Age (0)	46.70 ± 13.80	48.00 ± 9.36	45.80 ± 16.00	.32	0.17
Female sex (0)	53 (41.4)	21 (42.00)	32 (41.00)	1.00	0.02
BMI (0)	34.4 ± 9.88	37.50 ± 6.84	32.50 ± 11.00	<.01	0.54
BSA (7)	2.2 ± 0.326	2.26 ± 0.286	2.16 ± 0.347	.08	0.32
Medicare or Medicaid insurance (0)	38 (29.70)	4 (8.00)	34 (43.60)	<.01	0.88
Distance between patient residence and hospital (12)	124 ± 79.00	116 ± 65.10	131 ± 88.10	.30	0.19
Murray score (22)	2.97 ± 0.83	3.27 ± 0.64	2.82 ± 0.88	<.01	0.59
PRESET score (33)	6.47 ± 2.58	4.94 ± 2.01	7.41 ± 2.44	<.01	1.10
APACHE score (35)	22.70 ± 9.26	18.20 ± 8.52	25.00 ± 8.82	<.01	0.79
SOFA score (33)	9.56 ± 3.82	7.03 ± 3.14	10.90 ± 3.47	<.01	1.17
Time of mechanical ventilation before ECMO (11)				.34	0.06
≤12 h	8 (6.25)	4 (8.89)	4 (5.56)		
12-24 h	59 (46.10)	26 (57.80)	33 (45.80)		
2-7 d	36 (28.1)	12 (26.7)	24 (33.3)		
≥7 d	14 (10.90)	3 (6.67)	11 (15.30)		
Extubation timing (12)				.12	0.40
Extubated after decannulation	11 (8.59)	1 (2.50)	10 (13.20)		
Extubated before decannulation	105 (82.00)	39 (97.50)	66 (86.80)		
Cannulation strategy (0)				.05	0.42
Other	106 (82.80)	46 (92.00)	60 (76.90)		
RIJV	22 (17.20)	4 (8.00)	18 (23.10)		
Tracheostomy timing (59)				.73	0.17
Early tracheostomy (up to day 4)	48 (37.50)	15 (75.00)	33 (67.30)		
Late tracheostomy (day 5 and beyond)	21 (16.40)	5 (25.00)	16 (32.70)		
Time to decannulation, d (0)	16.90 ± 21.70	21.3 ± 27.9	14.00 ± 16.10	.10	0.31
Time to discharge, d (49)	29.40 ± 25.40	31.9 ± 29.9	26.30 ± 18.60	.31	0.23
Time to tracheostomy, d (62)	5.48 ± 6.93	5.26 ± 6.49	5.57 ± 7.17	.87	0.05
Time to extubation, d (3)	4.27 ± 16.80	1.73 ± 2.33	5.91 ± 21.40	.10	0.27
Time between cannulation and death, d (108)	32.80 ± 35.00	51 ± 44.8	17.90 ± 13.30	.06	1.00

Data are presented as mean (±SD) or n (%), except where otherwise noted. ARDS, Acute respiratory distress syndrome; VV-ECMO, venovenous extracorporeal membrane oxygenation; SMD, standardized mean difference; BMI, body mass index; BSA, body surface area; PRESET, Prediction of Survival on ECMO Therapy; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; RIJV, right internal jugular vein.

$P = .03$ ) than their non-plasmapheresis counterparts (Figure E7, Tables E13 and E14). Propensity score results confirmed that patients who received plasmapheresis had a decreased probability of decannulation (HR, 0.13; 95% CI, 0.04-0.38;  $P < .01$ ) and discharge (HR, 0.12; 95% CI, 0.02-0.77;  $P = .03$ ). Moreover, patients who received plasmapheresis had a decreased probability of tracheostomy (HR, 0.10; 95% CI, 0.03-0.36;  $P < .01$ ; Table 8, Tables E15 and E16, and Figure E8).

Finally, we compared COVID-19 versus non-COVID-19 ARDS patients within subgroups who used different ECMO systems (Cardiohelp, CentriMag, and NovaLung). The results differed very little between COVID-19 and non-COVID-19 ARDS within these subgroups (Tables E17-E32, Figures E9-E14).

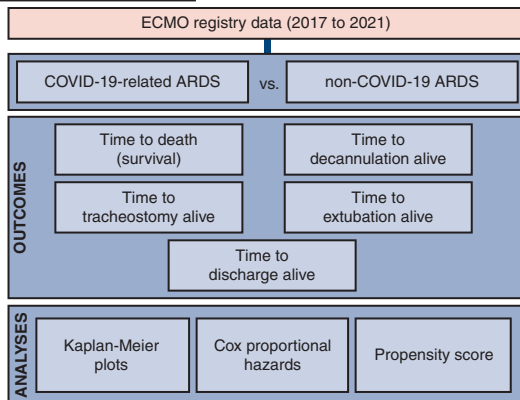
## DISCUSSION

We explored the effect of an early extubation and ambulation protocol in combination with a modified approach to candidacy. The outcomes were comparable in patients with COVID-19 and those achieved in those with non-COVID-19 ARDS. Application of this strategy in patients with COVID-19 appears to not only be safe, but our approximate survival rate of 70% is higher than the Extracorporeal Life Support Organization benchmark for COVID-19 ECMO of 52%.<sup>25</sup>

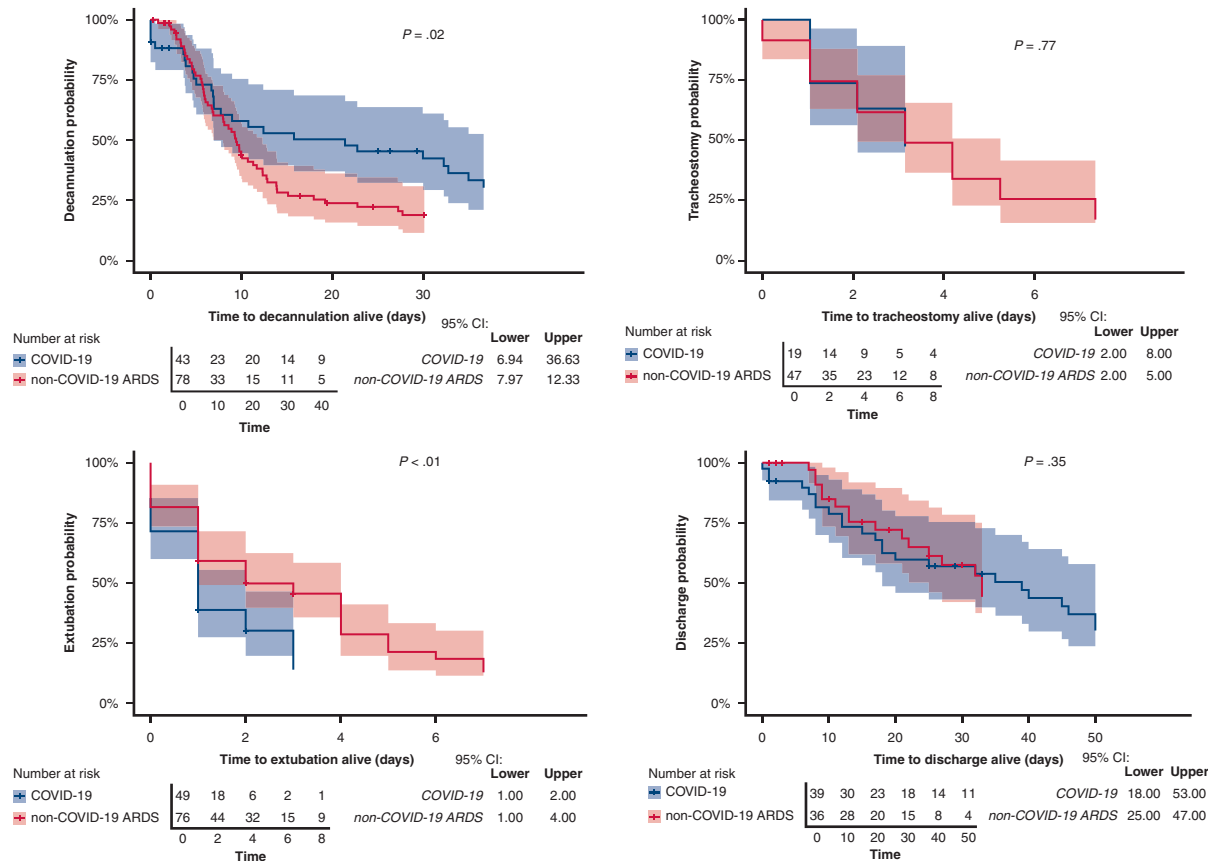
The COVID-19 pandemic has had a greater effect on health care than any other single event in several decades. The use of extracorporeal support has shown promise in the face of severe disease (World Health Organization<sup>26</sup> classification 7) refractory to conventional therapy. There

Cannulate, Extubate, Ambulate approach for Extracorporeal Membrane Oxygenation for COVID-19

Methods



Results



Outcomes	non-COVID-19 ARDS	COVID-19
Time to decannulation alive	(HR) 1 [Referent]	0.57 (0.27 – 1.19) [P = .14]
Time to tracheostomy alive	(HR) 1 [Referent]	1.63 (0.77 – 3.45) [P = .21]
Time to extubation alive	(HR) 1 [Referent]	2.07 (1.30 – 3.30) [P < .01]
Time to discharge alive	(HR) 1 [Referent]	0.92 (0.43 – 1.98) [P = .83]
Survival (time to death)	(HR) 1 [Referent]	0.40 (0.06 – 2.53) [P = .33]

Implications

Patients with COVID-19 and non-COVID ARDS managed on ECMO had comparable outcomes. A strategy of early extubation and ambulation might be safe and effective.

FIGURE 1. Study summary. Compared with non-COVID-19 acute respiratory distress syndrome (ARDS) patients, COVID-19 patients who underwent extracorporeal membrane oxygenation (ECMO) presented a higher risk of extubation alive. HR, Hazard ratio.

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**TABLE 4. Hazard ratios for survival to decannulation, discharge, tracheostomy, and extubation**

Outcome	Non-COVID-19	
	ARDS	COVID-19
Time to decannulation alive	1 (Referent)	0.67 (0.38-1.19); <i>P</i> = .17; AIC = 571; BIC = 588
Time to tracheostomy alive	1 (Referent)	1.7 (0.77-3.77); <i>P</i> = .19; AIC = 314; BIC = 327
Time to extubation alive	1 (Referent)	2.17 (1.28-3.67); <i>P</i> < .01; AIC = 664; BIC = 681
Time to discharge alive	1 (Referent)	0.88 (0.40-1.96); <i>P</i> = .76; AIC = 285; BIC = 298
Survival (time to death)	1 (Referent)	0.04 (0.00-0.48); <i>P</i> = .01; AIC = 48.80; BIC = 53.20

Data are presented as hazard ratio (95% CI), except where otherwise noted. ARDS, Acute respiratory distress syndrome; AIC, Akaike information criterion; BIC, Bayesian information criterion.

has, nevertheless, been a growing pessimism of the role of ECMO in patients with COVID-19.<sup>5</sup> Our management protocols deviated from convention in 3 ways. First, with escalating mortality with each surge, we restricted the age limit first to 60 years, then 55, and finally to 50. This decision was on the basis of escalating mortality that had been witnessed in direct proportion to each decade of life and which was confirmed by the inflection point we observed at age 48.<sup>25</sup> This was most marked in men. Beyond this age, mortality rates increase dramatically.<sup>27</sup>

Second, we modified the EOLIA criteria by limiting the period of maximal conventional therapy to 4 days or less during which the patient should have undergone a trial of proning, pulmonary vasodilator therapy (either nitric oxide or isoproterenol), and have received the gamut of conventional therapy, most important of which was intravenous

**TABLE 5. Association of COVID-19 diagnosis (COVID-19 vs non-COVID-19 ARDS) and each outcome (time to tracheostomy, extubation, decannulation, and discharge alive, as well as ECMO and total charges) through propensity score**

Outcomes	Control	COVID-19, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.57 (0.27-1.19); <i>P</i> = .14
Time to tracheostomy alive	HR, 1 (referent)	1.63 (0.77-3.45); <i>P</i> = .21
Time to extubation alive	HR, 1 (referent)	2.07 (1.30-3.30); <i>P</i> < .01
Time to discharge alive	HR, 1 (referent)	0.92 (0.43-1.98); <i>P</i> = .83
Survival (time to death)	HR, 1 (referent)	0.40 (0.06-2.53); <i>P</i> = .33

ARDS, Acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio.

steroids. If, however, there had been no improvement by day 4 despite maximal conventional therapy and the patient continued to exhibit a partial pressure of arterial oxygen/fraction of inspired oxygen ratio of <80 for >6 hours or fraction of inspired oxygen ratio <50 for >3 hours, then we pivoted to urgent cannulation, to proffer protection from the further vagaries of barotrauma that almost universally accompany high ventilatory settings and maximal driving power.

At the onset of the pandemic, our strategy of choice had been dual-site cannulation, combining right femoral venous and internal jugular venous sites. This option was predicated on the intent to limit provider exposure at a time when neither treatment nor vaccine had officially been identified. Cannulation was performed preferentially in the negative isolation environment of the ICU and only after a vaccine was ubiquitously available, did we modify our approach and venture a return to the operating room for single-site dual lumen cannulation using transesophageal and fluoroscopic guidance. Having cannulated the patient, we sought, as a matter of routine, to limit the duration of mechanical ventilation. To accomplish this, we adjusted our ventilatory strategy to accommodate patients of high BMI, a common comorbidity. Before the pandemic, we defaulted to protective settings of 4 to 6 mL/kg tidal volume, fraction of inspired oxygen 30%, positive end-expiratory pressure 10, pressure support 10, and respiratory rate of 10 with a view to limiting plateau pressure to <30 cm H<sub>2</sub>O. With growing experience, however, we concluded that this approach was not universally applicable, particularly in the context of obesity. As such, we modified the strategy and adjusted ventilatory settings on the basis of esophageal manometry and made changes in response to varying mechanics that were, in turn, influenced by body mass and variations in intrathoracic pressure secondary to the weight exerted on the chest by body fat and tissue.

Whenever possible, patients who were previously receiving high levels of sedation were weaned immediately after cannulation and it is our preference to use non-narcotic options such as dexmedetomidine and ketamine. The algorithm is substantiated further in Table E1. Throughout, we maintained a preference for early tracheostomy, typically performing this percutaneously at the bedside in the ICU within the first 4 ECMO days. The underpinnings of this decision are drawn from our intent to liberate the patient from ventilator support, sedation, and paralysis, which are insidious drivers of critical-illness polyneuropathy. Indeed, our programmatic mantra of “cannulate, extubate, ambulate” is the impetus behind mobilizing patients who are receiving ECMO to protect against extreme debilitation. Ambulation can be reliably achieved in patients with either cannulation strategy by firmly securing the cannulas and tubing using silk sutures and adhesive securement devices. Admittedly,

TABLE 6. Additional predictors for time to decannulation, discharge, tracheostomy, and extubation alive, as well as survival (time to death)

Predictors	Time to discharge alive	Time to decannulation alive	Time to tracheostomy alive	Time to extubation alive	Survival time to death
Age	0.97 (0.95-0.99); $P < .01$ ; AIC = 362; BIC = 364	0.98 (0.97-1.00); $P = .02$ ; AIC = 778; BIC = 780	1.00 (0.98-1.02); $P = .88$ ; AIC = 429; BIC = 431	1.01 (0.99-1.02); $P = .42$ ; AIC = 925; BIC = 928	0.99 (0.94-1.04); $P = .65$ ; AIC = 86.5; BIC = 87.4
Categorized age 25-59 y	0.58 (0.26-1.32); $P = .19$	0.66 (0.35-1.24); $P = .19$	0.42 (0.13-1.36); $P = .15$	1.85 (0.94-3.65); $P = .08$	1.43 (0.51-4.01); $P = .49$
Categorized age 60 y and older	0.23 (0.07-0.80); $P = .02$ ; AIC = 365; BIC = 369	0.43 (0.20-0.96); $P = .04$ ; AIC = 780; BIC = 785	0.47 (0.13-1.68); $P = .24$ ; AIC = 429; BIC = 434	1.99 (0.90-4.37); $P = .09$ ; AIC = 924; BIC = 930	
Female sex	1.28 (0.75-2.20); $P = .37$ ; AIC = 368; BIC = 370	1.24 (0.83-1.85); $P = .29$ ; AIC = 781; BIC = 784	0.72 (0.42-1.23); $P = .22$ ; AIC = 428; BIC = 430	1.25 (0.87-1.80); $P = .23$ ; AIC = 925; BIC = 927	0.59 (0.19-1.79); $P = .35$ ; AIC = 85.7; BIC = 86.7
BMI	1.01 (0.98-1.04); $P = .60$ ; AIC = 368; BIC = 370	1.00 (0.98-1.02); $P = .81$ ; AIC = 783; BIC = 785	1.02 (0.99-1.05); $P = .13$ ; AIC = 427; BIC = 429	1.01 (1.00-1.03); $P = .17$ ; AIC = 924; BIC = 927	1.00 (0.95-1.04); $P = .91$ ; AIC = 86.7; BIC = 87.7
Categorized BMI $\geq 30$	0.93 (0.48-1.82); $P = .84$ ; AIC = 369; BIC = 371	0.75 (0.50-1.12); $P = .16$ ; AIC = 781; BIC = 783	1.24 (0.755-2.03); $P = .40$ ; AIC = 428; BIC = 431	1.40 (0.96-2.04); $P = .08$ ; AIC = 923; BIC = 926	0.6 (0.21-1.76); $P = .35$ ; AIC = 85.90; BIC = 86.90
BSA	1.19 (0.48-2.94); $P = .71$ ; AIC = 369; BIC = 371	0.65 (0.33-1.30); $P = .22$ ; AIC = 715; BIC = 718	1.18 (0.51-2.75); $P = .70$ ; AIC = 387; BIC = 389	0.99 (0.55-1.75); $P = .96$ ; AIC = 860; BIC = 862	1.67 (0.43-6.59); $P = .46$ ; AIC = 86.10; BIC = 87.10
Cannulation strategy RIJV	0.75 (0.37-1.54); $P = .44$ ; AIC = 368; BIC = 370	1.01 (0.60-1.72); $P = .96$ ; AIC = 783; BIC = 785	0.94 (0.52-1.70); $P = .83$ ; AIC = 429; BIC = 431	1.30 (0.81-2.08); $P = .28$ ; AIC = 925; BIC = 928	1.07 (0.34-3.31); $P = .91$ ; AIC = 86.7; BIC = 87.7
PRESET score	1.02 (0.89-1.17); $P = .80$ ; AIC = 276; BIC = 278	1.08 (0.97-1.20); $P = .17$ ; AIC = 537; BIC = 540	1.00 (0.87-1.14); $P = .94$ ; AIC = 283; BIC = 285	0.85 (0.77-0.95); $P < .01$ ; AIC = 627; BIC = 629	1.10 (0.90-1.33); $P = .35$ ; AIC = 51.50; BIC = 52.20
PRESET score $> 5$	0.82 (0.45-1.5); $P = .53$ ; AIC = 276; BIC = 278	0.89 (0.55-1.45); $P = .64$ ; AIC = 539; BIC = 541	0.76 (0.39-1.51); $P = .44$ ; AIC = 283; BIC = 285	0.43 (0.27-0.68); $P < .01$ ; AIC = 624; BIC = 627	1.89 (0.51-7.04); $P = .34$ ; AIC = 51.4; BIC = 52
APACHE score	0.96 (0.93-1.00); $P = .07$ ; AIC = 260; BIC = 261	1.01 (0.98-1.04); $P = .46$ ; AIC = 523; BIC = 526	1.01 (0.98-1.04); $P = .38$ ; AIC = 283; BIC = 284	0.97 (0.95-1.00); $P = .02$ ; AIC = 613; BIC = 615	1.04 (0.97-1.12); $P = .24$ ; AIC = 45.70; BIC = 46.30
APACHE score $> 23$	0.73 (0.38-1.40); $P = .34$ ; AIC = 262; BIC = 264	1.09 (0.68-1.74); $P = .72$ ; AIC = 524; BIC = 526	1.12 (0.62-2.00); $P = .71$ ; AIC = 283; BIC = 285	0.65 (0.42-1.00); $P = .05$ ; AIC = 614; BIC = 617	2.05 (0.61-6.94); $P = .25$ ; AIC = 45.70; BIC = 46.20
SOFA score	0.91 (0.82-1.00); $P = .05$ ; AIC = 266; BIC = 267	1.00 (0.93-1.07); $P = .93$ ; AIC = 539; BIC = 541	1.00 (0.93-1.07); $P = .96$ ; AIC = 291; BIC = 293	0.90 (0.86-0.96); $P < .01$ ; AIC = 614; BIC = 617	1.15 (0.98-1.34); $P = .08$ ; AIC = 49.40; BIC = 50.10

(Continued)



TABLE 6. Continued

Predictors	Time to discharge alive	Time to decannulation alive	Time to tracheostomy alive	Time to extubation alive	Survival time to death
SOFA score >10	0.66 (0.33-1.32); <i>P</i> = .24; AIC = 268; BIC = 270	1.06 (0.66-1.71); <i>P</i> = .80; AIC = 539; BIC = 541	0.94 (0.52-1.69); <i>P</i> = .83; AIC = 291; BIC = 293	0.54 (0.35-0.85); <i>P</i> < .01; AIC = 620; BIC = 622	1.96 (0.61-6.30); <i>P</i> = .26; AIC = 51.10; BIC = 51.70
Murray score	0.82 (0.50-1.33); <i>P</i> = .42; AIC = 299; BIC = 301	0.55 (0.43-0.71); <i>P</i> < .01; AIC = 631; BIC = 633	0.98 (0.67-1.43); <i>P</i> = .91; AIC = 347; BIC = 349	0.93 (0.71-1.21); <i>P</i> = .57; AIC = 736; BIC = 738	0.61 (0.36-1.05); <i>P</i> = .07; AIC = 54.80; BIC = 55.50
Murray score >3	0.81 (0.46-1.44); <i>P</i> = .48; AIC = 299; BIC = 301	0.50 (0.33-0.78); <i>P</i> < .01; AIC = 637; BIC = 640	0.87 (0.51-1.48); <i>P</i> = .60; AIC = 346; BIC = 348	1.02 (0.69-1.52); <i>P</i> = .91; AIC = 736; BIC = 739	0.47 (0.15-1.44); <i>P</i> = .19; AIC = 56.10; BIC = 56.80
Medicare or Medicaid insurance	0.65 (0.30-1.37); <i>P</i> = .25; AIC = 367; BIC = 369	1.15 (0.75-1.76); <i>P</i> = .53; AIC = 782; BIC = 785	1.11 (0.67-1.82); <i>P</i> = .69; AIC = 429; BIC = 431	0.71 (0.48-1.05); <i>P</i> = .08; AIC = 923; BIC = 926	3.39 (1.15-9.99); <i>P</i> = .026; AIC = 81.80; BIC = 82.80
Distance between patient residence and hospital	1.00 (1.00-1.00); <i>P</i> = .91; AIC = 367; BIC = 369	1.00 (1.00-1.00); <i>P</i> = .43; AIC = 672; BIC = 675	1.00 (1.00-1.01); <i>P</i> < .01; AIC = 371; BIC = 373	1.00 (1.00-1.00); <i>P</i> = .35; AIC = 831; BIC = 834	1.00 (1.00-1.01); <i>P</i> = .60; AIC = 74.5; BIC = 75.4

AIC, Akaike information criterion; BIC, Bayesian information criterion; BMI, body mass index; BSA, body surface area; RIJIV, right internal jugular vein; PRESET, Prediction of Survival on ECMO Therapy; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

our approach to extubation and early ambulation is in stark contrast to the ethos in programs more accustomed to patients laying comatose for the duration of the ECMO course. Ours, however, is not a novel strategy specific to the pandemic and indeed it has been our practice cultivated over several years and which proffered the very experience that permitted extrapolation to the COVID-19 population.

We limited candidacy among the super-obese to BMI <48 in view of the difficulty in achieving adequate flows in these patients, who typically require 5 to 7 L/min. Cannulation in these patients often requires multiple people to

retract the pannus and rolls of adipose tissue that frequently obscure the cannulation sites and raise the complexity of acquiring access to deeply situated vessels. High BMI, nonetheless, is somewhat of a paradox in extracorporeal support. It has been reported to be protective in some circumstances.<sup>28-30</sup> Indeed within the calculus of mortality using the Predicting Death for Severe ARDS on VV-ECMO (PRESERVE) scoring system, a high BMI is protective, proffering a value of -2 in the scoring system in which the higher the score, the higher the risk of death.<sup>28-30</sup> As such, rigorous studies are required to better elucidate the relationship between BMI and survival in patients receiving extracorporeal support. Regarding candidacy, our results identify a dichotomy in survival in patients with age >60 years, SOFA >10, APACHE >23, PRESET-Score >5, and Murray >3. The composite use of these risk severity scores has allowed us greater insight into candidacy, selection, and might likely form the basis of an absolute contraindication after it has been tested more rigorously. In our experience, therefore, BMI alone did not constitute a contraindication.

The Food and Drug Administration emergency use authorization of CytoSorb complemented our programmatic approach to cytokine reduction in patients with virulent inflammatory illness for which we had hitherto relied only on plasma exchange techniques. As such, the third

TABLE 7. Association between CytoSorb therapy (CytoSorb vs no CytoSorb) and each outcome (time to decannulation, tracheostomy, extubation, and discharge) through propensity score

Outcome	No CytoSorb	CytoSorb, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	1.17 (0.61-2.25); <i>P</i> = .64
Time to tracheostomy alive	HR, 1 (referent)	4.41 (0.57-34.30); <i>P</i> = .16
Time to extubation alive	HR, 1 (referent)	0.79 (0.40-1.56); <i>P</i> = .50
Time to discharge alive	HR, 1 (referent)	1.21 (0.49-2.95); <i>P</i> = .68

CytoSorb is from CytoSorbents Corp. HR, Hazard ratio.

**TABLE 8.** Association between plasmapheresis therapy (plasmapheresis vs no plasmapheresis) and each outcome (time to decannulation, tracheostomy, extubation, and discharge, as well as total and ECMO charges) through propensity score

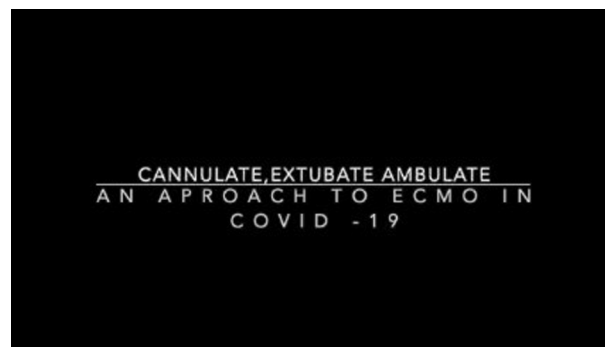
Outcomes	No plasmapheresis	Plasmapheresis, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.13 (0.04-0.38); <i>P</i> < .01
Time to tracheostomy alive	HR, 1 (referent)	0.10 (0.03-0.36); <i>P</i> < .01
Time to extubation alive	HR, 1 (referent)	0.49 (0.24-1.00); <i>P</i> = .05
Time to discharge alive	HR, 1 (referent)	0.12 (0.02-0.77); <i>P</i> = .03

ECMO, Extracorporeal membrane oxygenation; HR, hazard ratio.

deviation from the norm was our approach to the use of cytokine reduction techniques in which we adopted a threshold ferritin level of 1000 and D-dimer of 3000 as an indication for cytokine reduction therapy.<sup>31</sup> We excluded the use of interleukin 6 as a criterion for therapy because estimating this marker requires sending blood to an outside institution and precludes the timely titration of therapy. During the pandemic, we routinely incorporated the CytoSorb filter directly into the extracorporeal circuit at the outset of extracorporeal support with a view to dredging out molecules within the range of 5 and 50 kDa. In keeping with the emergency use authorization protocol, we used heparin anticoagulation during the course of the therapy before switching after 72 hours back to our programmatic bivalirudin protocol, an anticoagulation practice that has shielded us from the multiple interruptions and sequela of heparin-induced thrombocytopenia that frequently accompanies the use of heparin. The use of CytoSorb nevertheless, did not result in a difference in outcomes. Further studies will undoubtedly be necessary to more thoroughly evaluate the safety of plasmapheresis in COVID-19 patients.<sup>32</sup>

Our study has several limitations. Admittedly, our results constitute the experience of a single center in a nonrandomized retrospective analysis. As such, we do not offer this experience as an encyclopedic treatise or panacea. Instead, we acknowledge the inherent variations in circumstances, resources, and therapeutics that are characteristic in the dynamic landscape of a pandemic. For example, the 2 populations (COVID-19 and non-COVID-19-related ARDS) are fundamentally different. We attempted to address this issue using a propensity score methodology. Although the complete elimination of confounding is not entirely attainable, our goal was to minimize its effect. Because traditional regression models have a lower performance in reducing confounding compared with propensity scores,<sup>33</sup> we opted for this latter approach. Nevertheless, there were important confounding factors that we could not evaluate. These

included lag time (ie, the potential for improved institutional knowledge/program maturity over time). Indeed, it is plausible that the criteria not included in the propensity matching could represent larger outliers. Similarly, the stricter criteria for cannulation of COVID-19 patients compromises the strength of the comparison, irrespective of adjustment. Furthermore, there might have been other nuanced differences between COVID-19 and non-COVID-19 ARDS patients that we might not have been able to control in our analysis. The COVID-19 group, for instance, had a comparatively homogeneous pathophysiology (COVID-19). The non-COVID cohort, however, comprised patients with disparate etiologies, such as influenza and viral, bacterial, or fungal pneumonia, among others. This heterogeneity is also reflected in the comorbidities, the detail of which were not analyzed. Nonetheless, the non-COVID-19 ARDS group provided a suitable, albeit imperfect comparator to the study cohort and served to provide context to the use of ECMO in a novel population. Our goal therefore, was not to conduct a causative analysis, but instead to provide a frame of reference. Indeed, it was the comparison of outcomes in the use of venoarterial (VA)-ECMO in patients with non-COVID-19 ARDS, for example, that prompted the acquiescence to the prohibitive mortality in COVID-19 patients who required VA-ECMO and for how quickly the need for VA-ECMO became a contraindication to cannulation. Furthermore, the more stringent inclusion criteria for COVID-19 patients are likely part of a multipartite combination of reasons behind the increased survival observed in our cohort. Nevertheless, the risk adjudication also included PRESET-Score, Murray, and APACHE scores, each of which reflect the high acuity of patients in the COVID-19 cohort, underscoring the notion that, with conventional therapy having failed, these patients remained very sick at the time of cannulation. Therefore, in the context of the high mortality rate reported with the use of ECMO in patients with COVID-19, we share our experience in modifying the standard approach and



**VIDEO 1.** Cannulate, extubate, ambulate approach for extracorporeal membrane oxygenation for COVID-19. Video available at: [https://www.jtcvs.org/article/S0022-5223\(22\)00249-5/fulltext](https://www.jtcvs.org/article/S0022-5223(22)00249-5/fulltext).

detail our willingness to depart from the status quo in the quest to save patients in an Appalachian state with the lowest life expectancy and which was widely predicted to have the greatest mortality from SARS-CoV-2.<sup>34</sup>

## CONCLUSIONS

Our results allow the foundation for hypothesis generation in the use of cytoreductive therapies in viral illnesses, the potential for delineating an algorithm for ECMO candidacy for patients with COVID-19 on the basis of risk prediction, the effect of obesity on survival, and reexamining the optimal number of pre-cannulation days (Video 1). It might be necessary to revisit criteria for candidacy and revise the current algorithms of ECMO care. It is likely that by making changes that could bend the survival curve to a more favorable trajectory, other centers might achieve even better results than ours.

## Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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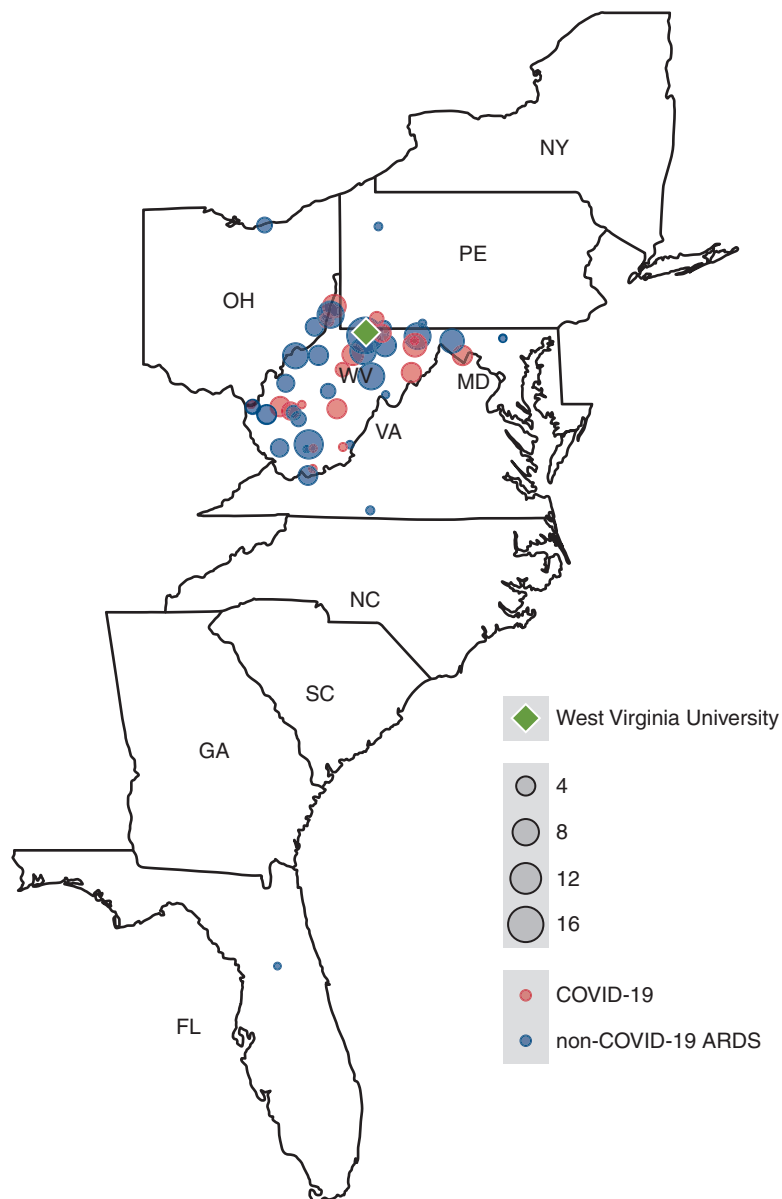
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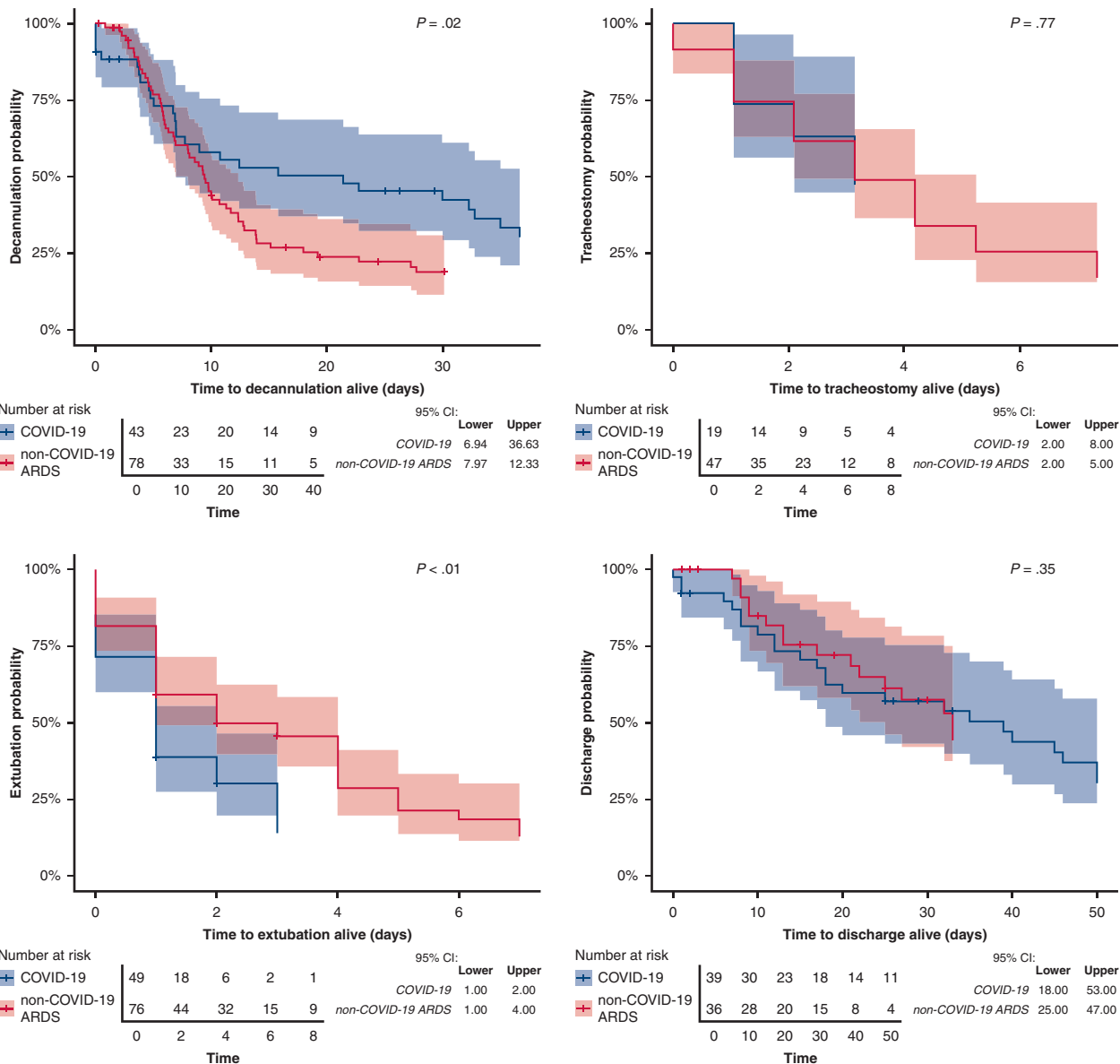
**Key Words:** COVID-19, extracorporeal membrane oxygenation, survival, decannulation, tracheostomy, extubation, discharge

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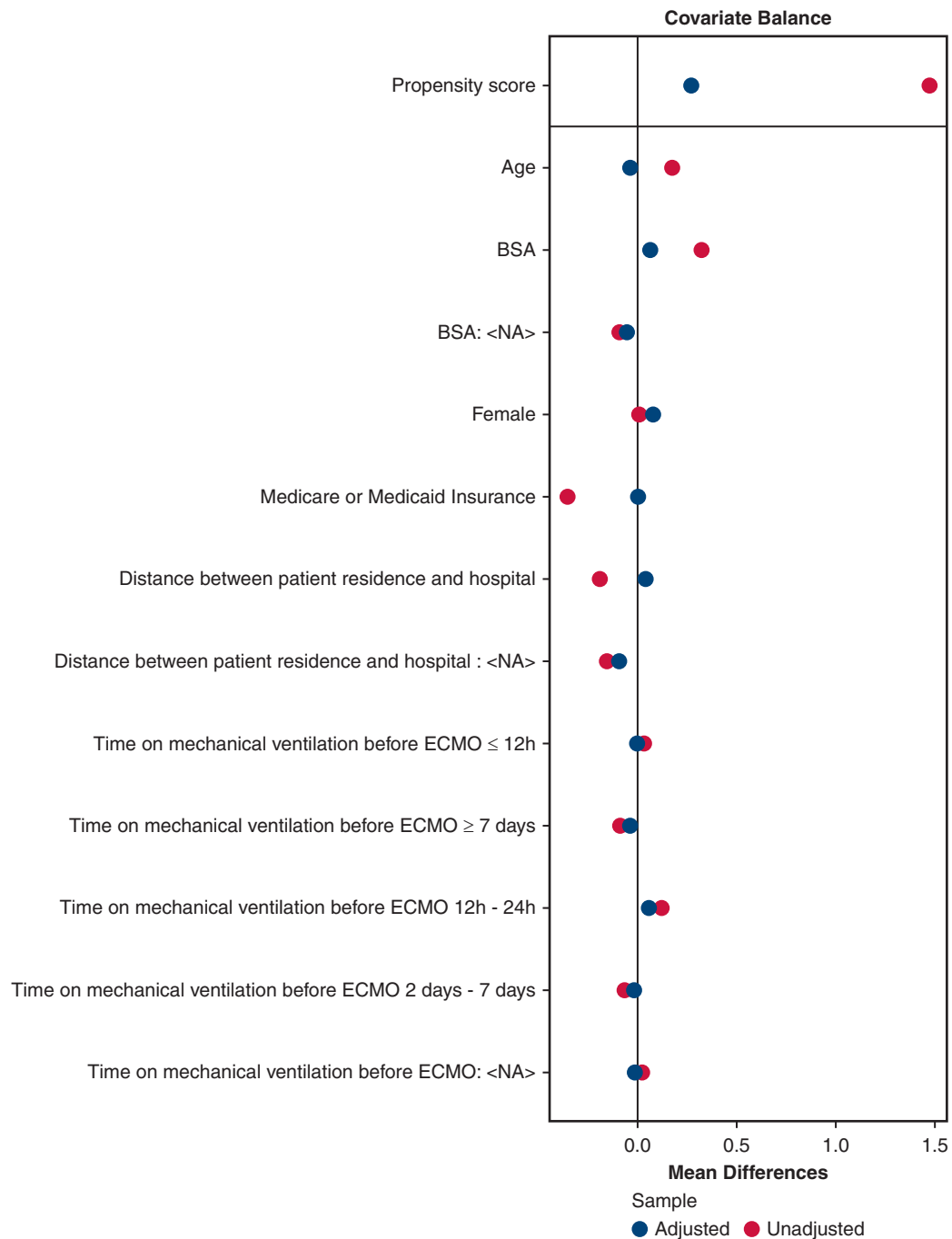


**FIGURE E1.** Regions of residence for patients in the COVID-19 (*red*) and non-COVID-19 (*blue*) acute respiratory distress syndrome (ARDS) groups. The size of each circle corresponds to the number of patients who live in that region. ARDS, Acute respiratory distress syndrome.



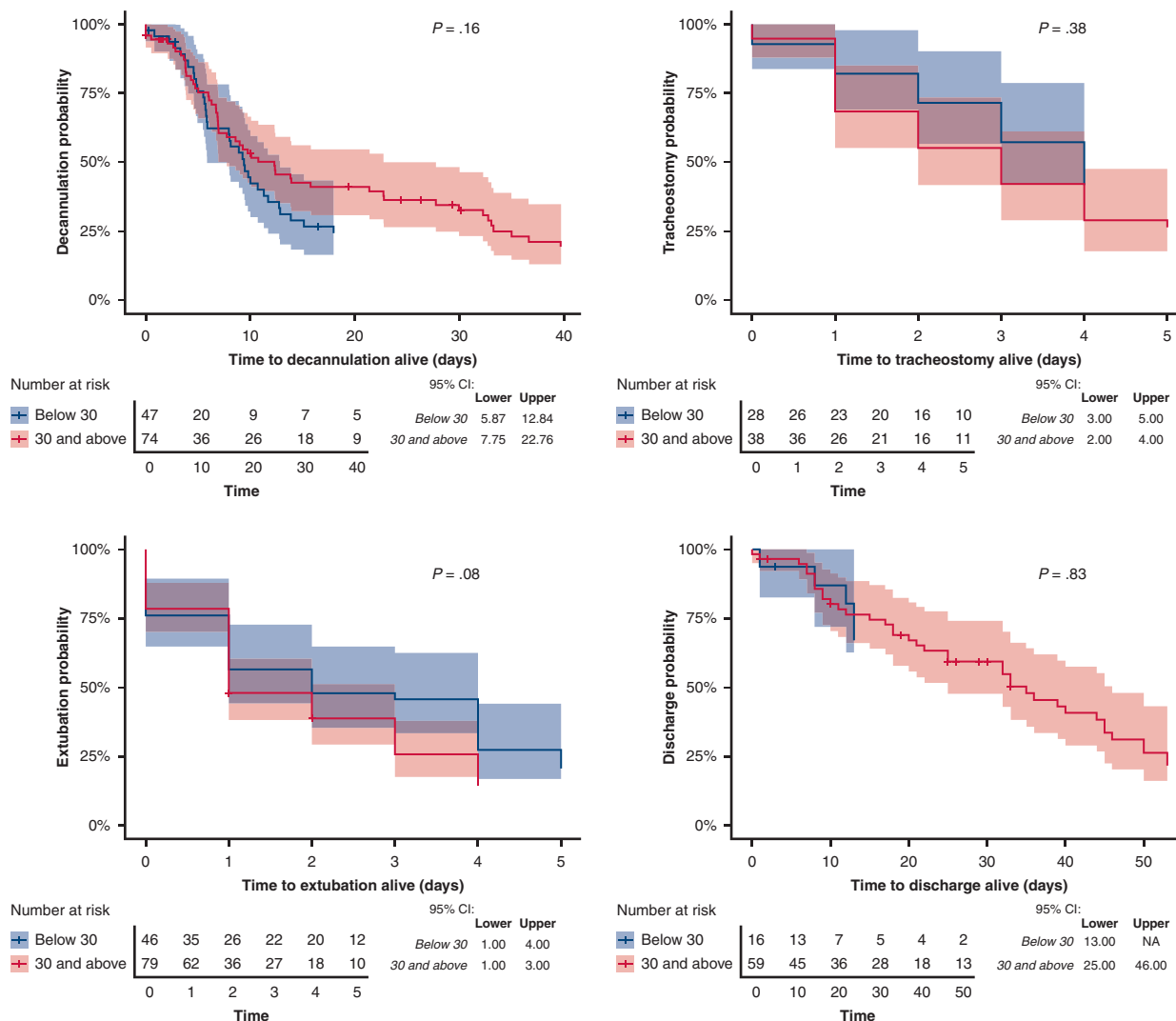
**FIGURE E2.** Kaplan–Meier plots for the unadjusted association between COVID-19 diagnosis and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation patients. The *darker lines* represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The *shaded areas* correspond to the 95% confidence intervals. ARDS, Acute respiratory distress syndrome.

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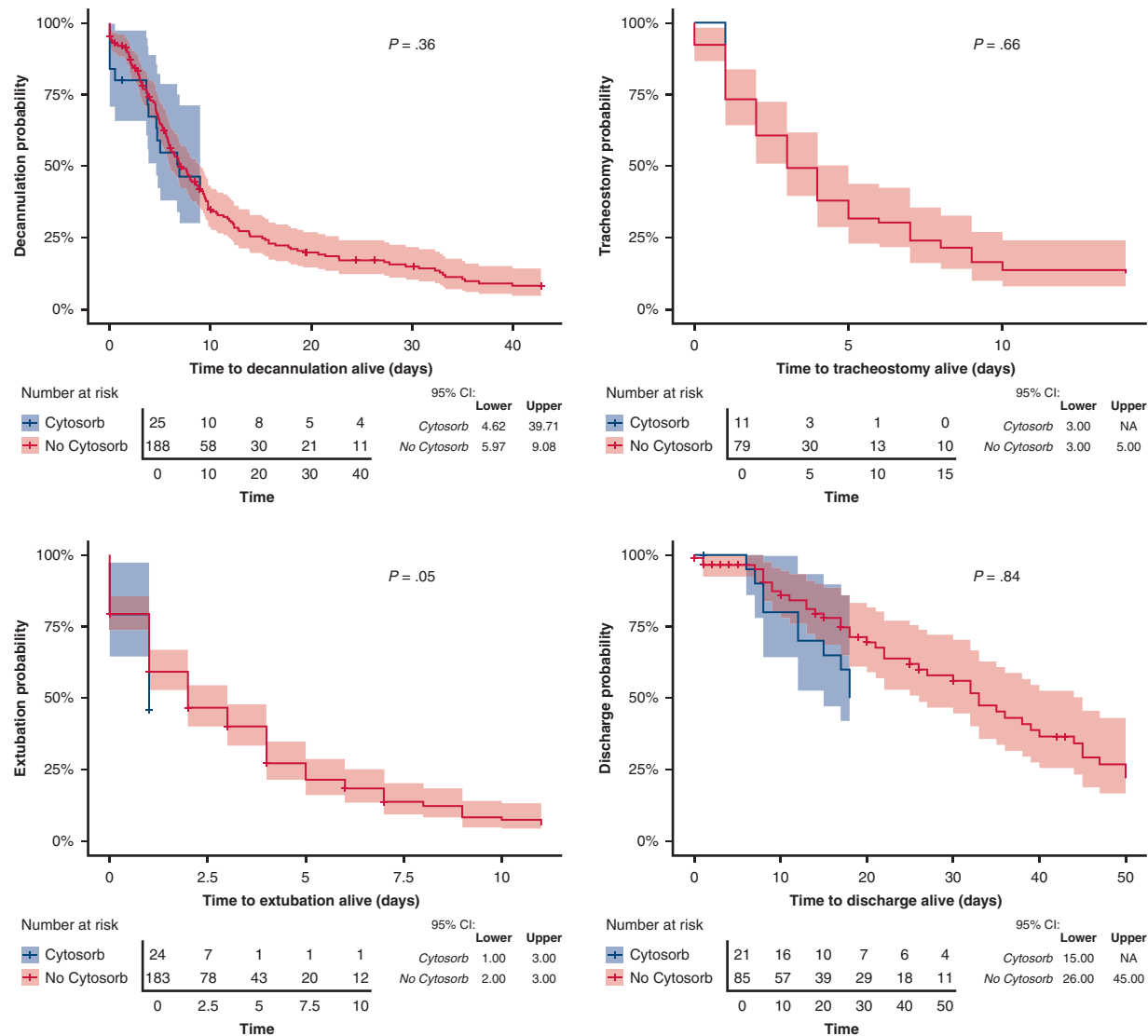
**FIGURE E3.** Covariate balance before and after adjustment for the propensity score analysis in a comparison of COVID-19 versus non-COVID-19 acute respiratory distress syndrome. *BSA*, Body surface area; *NA*, not available; *ECMO*, extracorporeal membrane oxygenation.





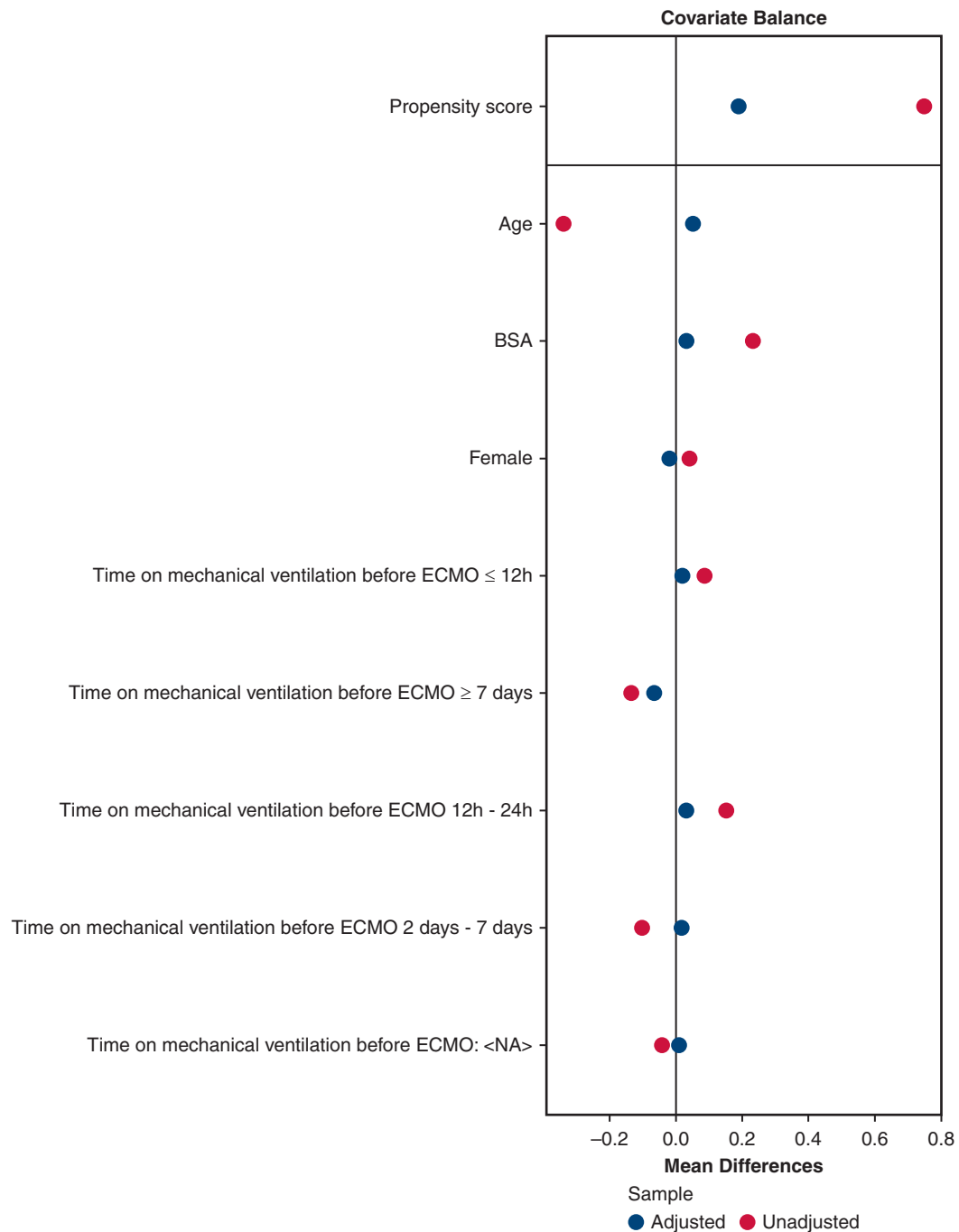
**FIGURE E4.** Kaplan–Meier plots for the unadjusted association of body mass index and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation patients. The *darker lines* represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The *shaded areas* correspond to the 95% confidence intervals. *NA*, Not reached.

MCS

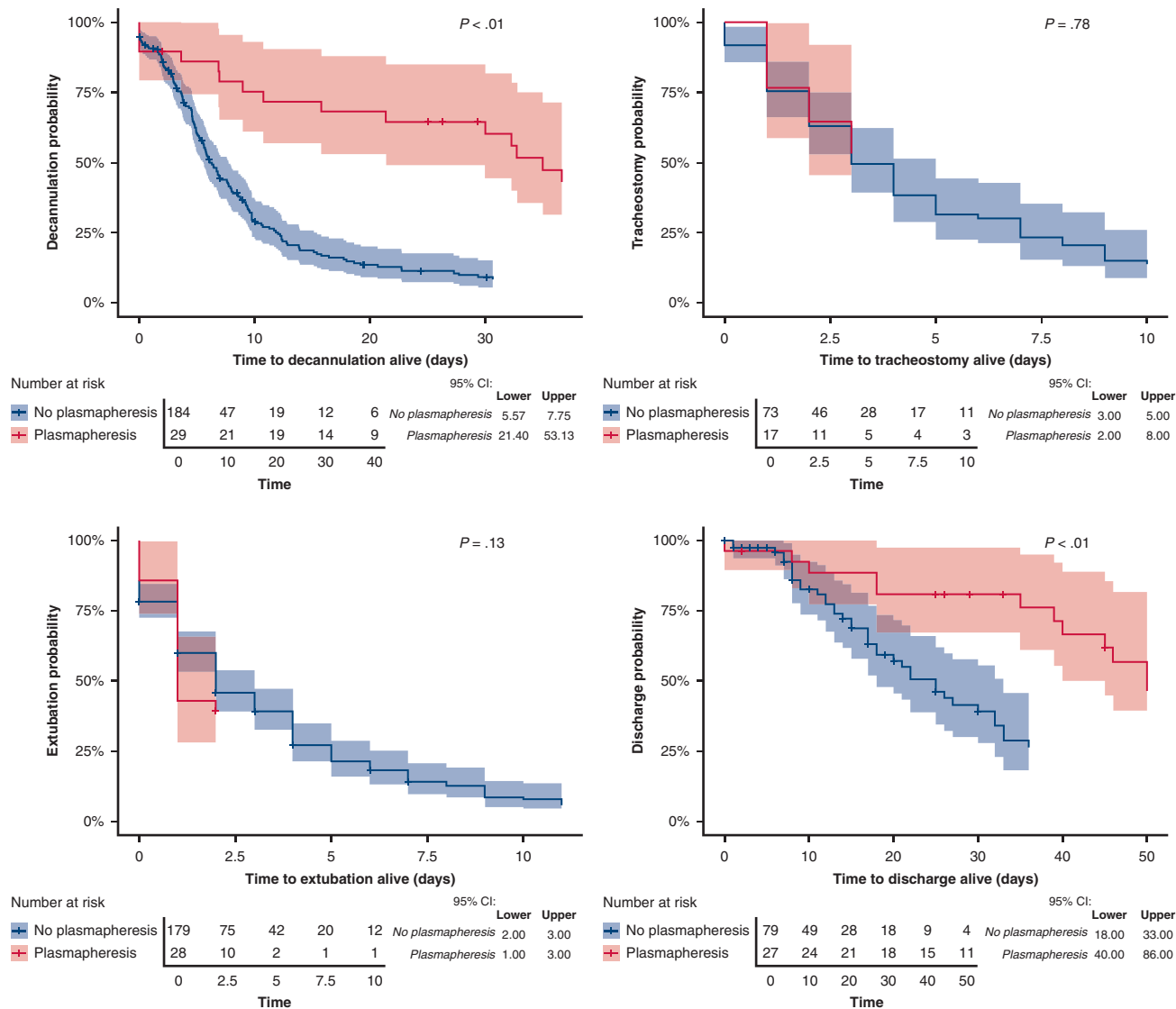


**FIGURE E5.** Kaplan–Meier plots for the association between CytoSorb (CytoSorbents Corp) therapy and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation patients. The *darker lines* represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The *shaded areas* correspond to the 95% confidence intervals. NA, Not reached.

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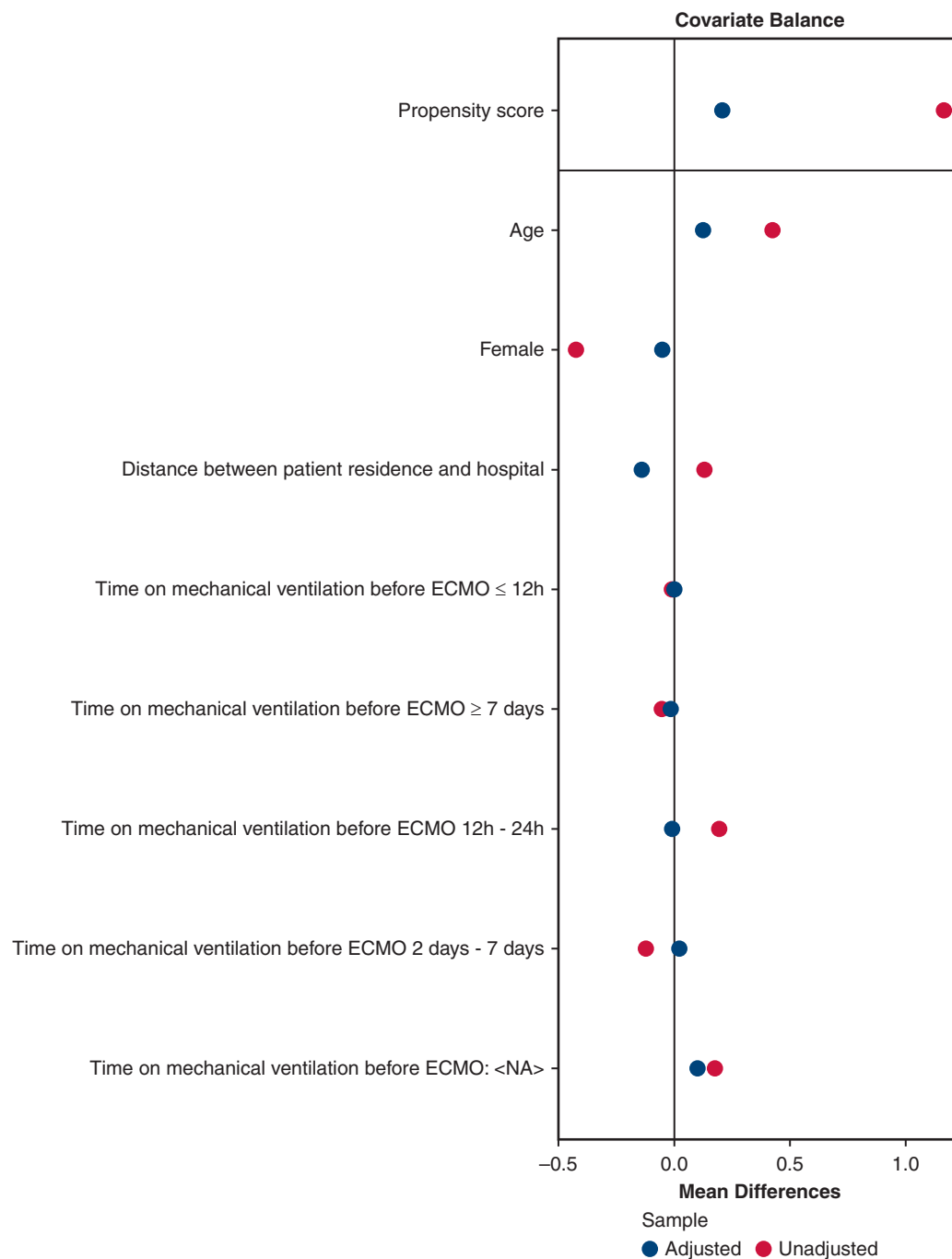


**FIGURE E6.** Covariate balance before and after adjustment for the propensity score analysis comparing extracorporeal membrane oxygenation (ECMO) patients who received CytoSorb (CytoSorbents Corp) versus those who did not receive this treatment. BSA, Body surface area; NA, not available.

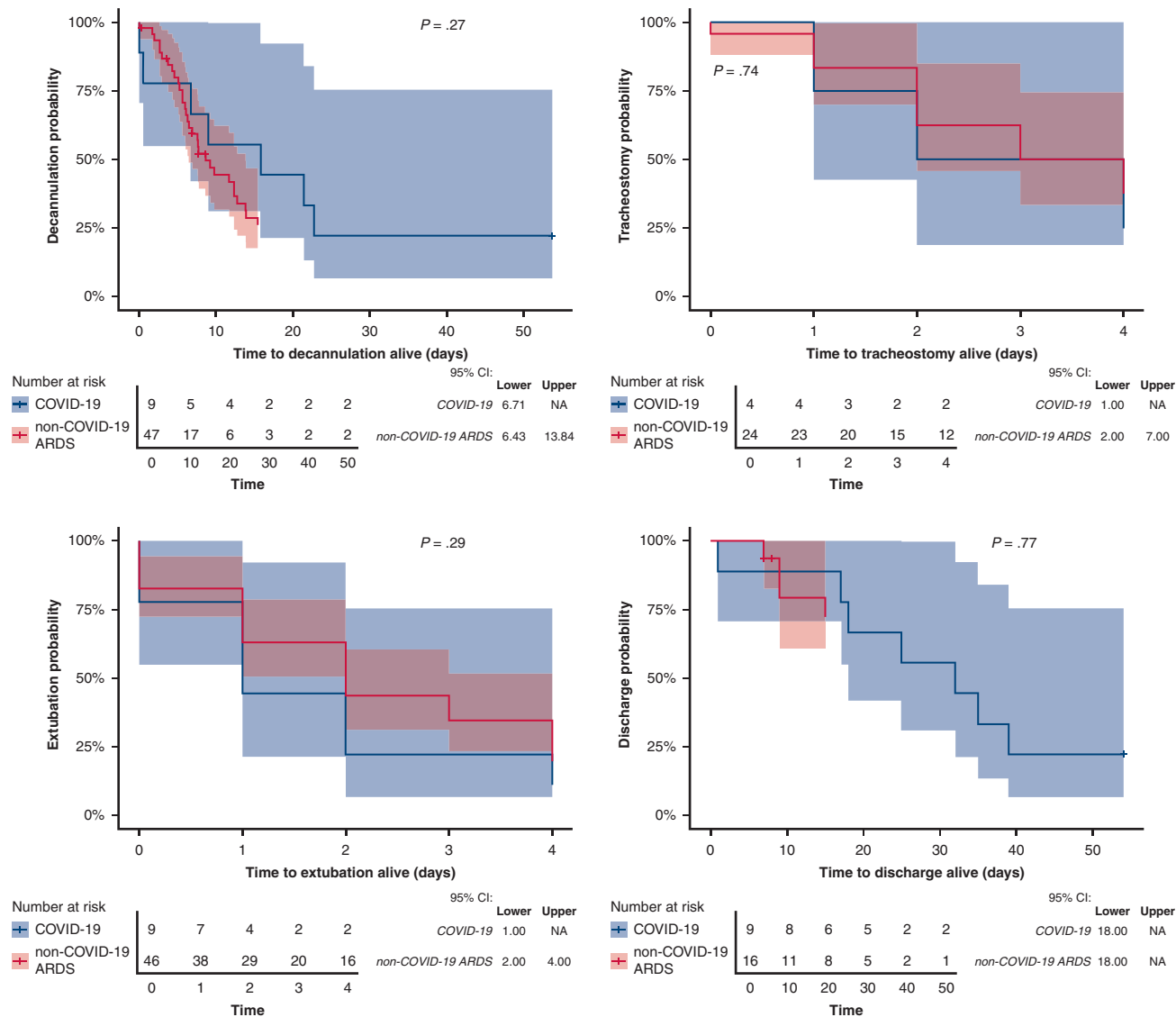


**FIGURE E7.** Kaplan–Meier plots for the association of plasmapheresis therapy and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation patients. The *darker lines* represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The *shaded areas* correspond to the 95% confidence intervals.

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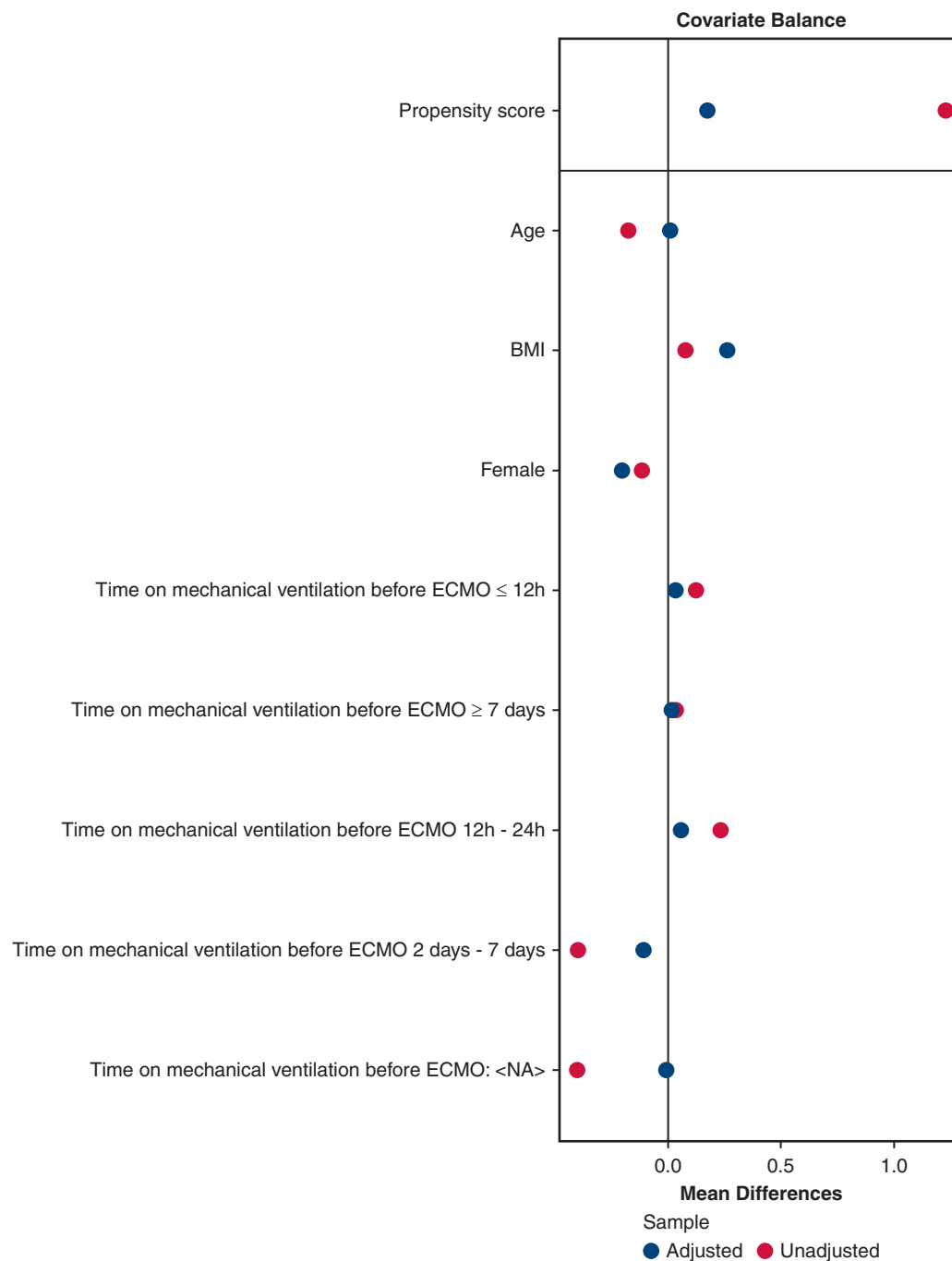


**FIGURE E8.** Covariate balance before and after adjustment for the propensity score analysis comparing extracorporeal membrane oxygenation (ECMO) patients who received plasmapheresis versus those who did not receive this treatment. NA, Not available.

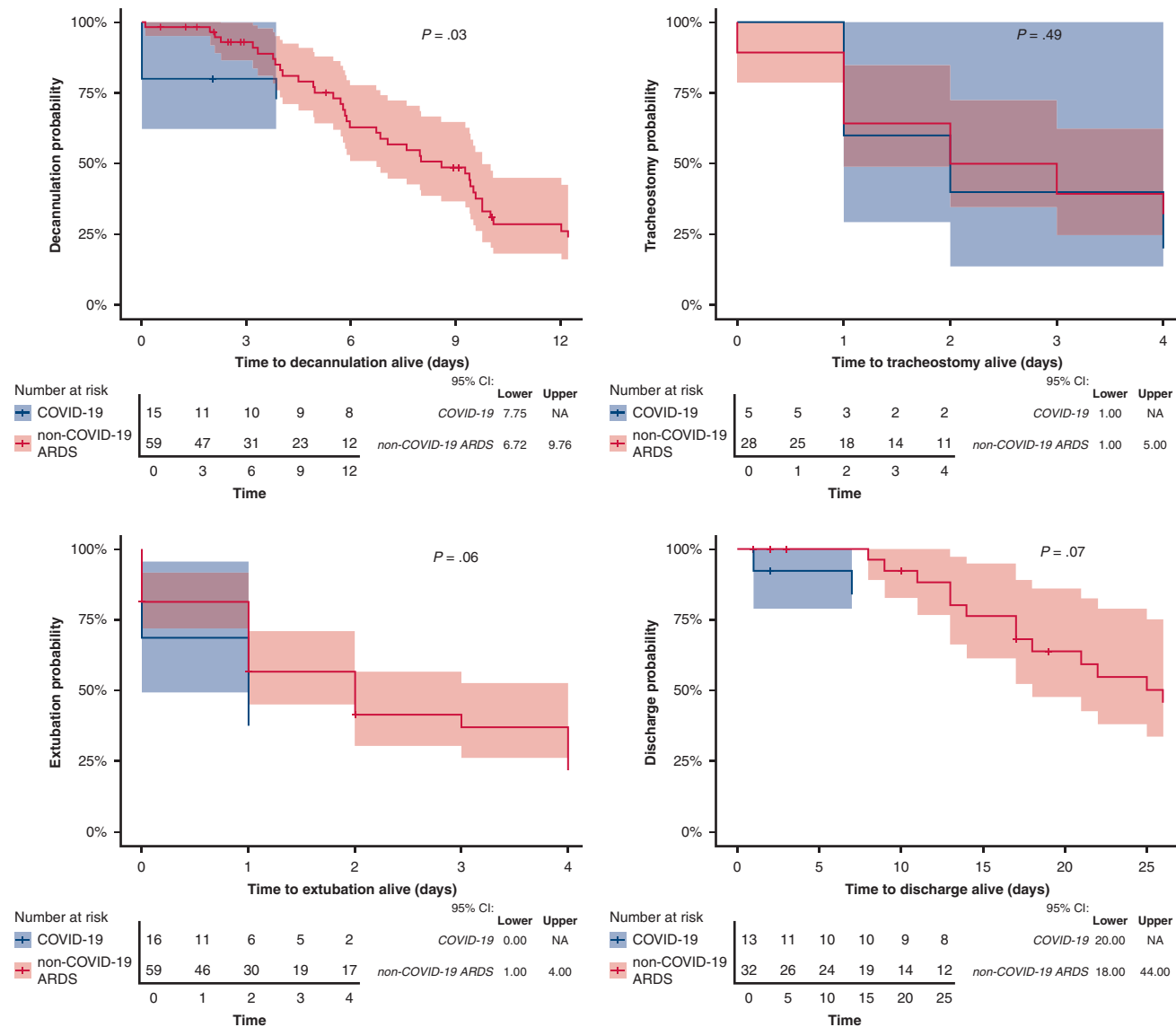


**FIGURE E9.** Kaplan–Meier plots for the association between COVID-19 diagnosis and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation (ECMO) patients who used the Cardiohelp system (Maquet Cardiopulmonary). The darker lines represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The shaded areas correspond to the 95% confidence intervals. ARDS, Acute respiratory distress syndrome; NA, not reached.

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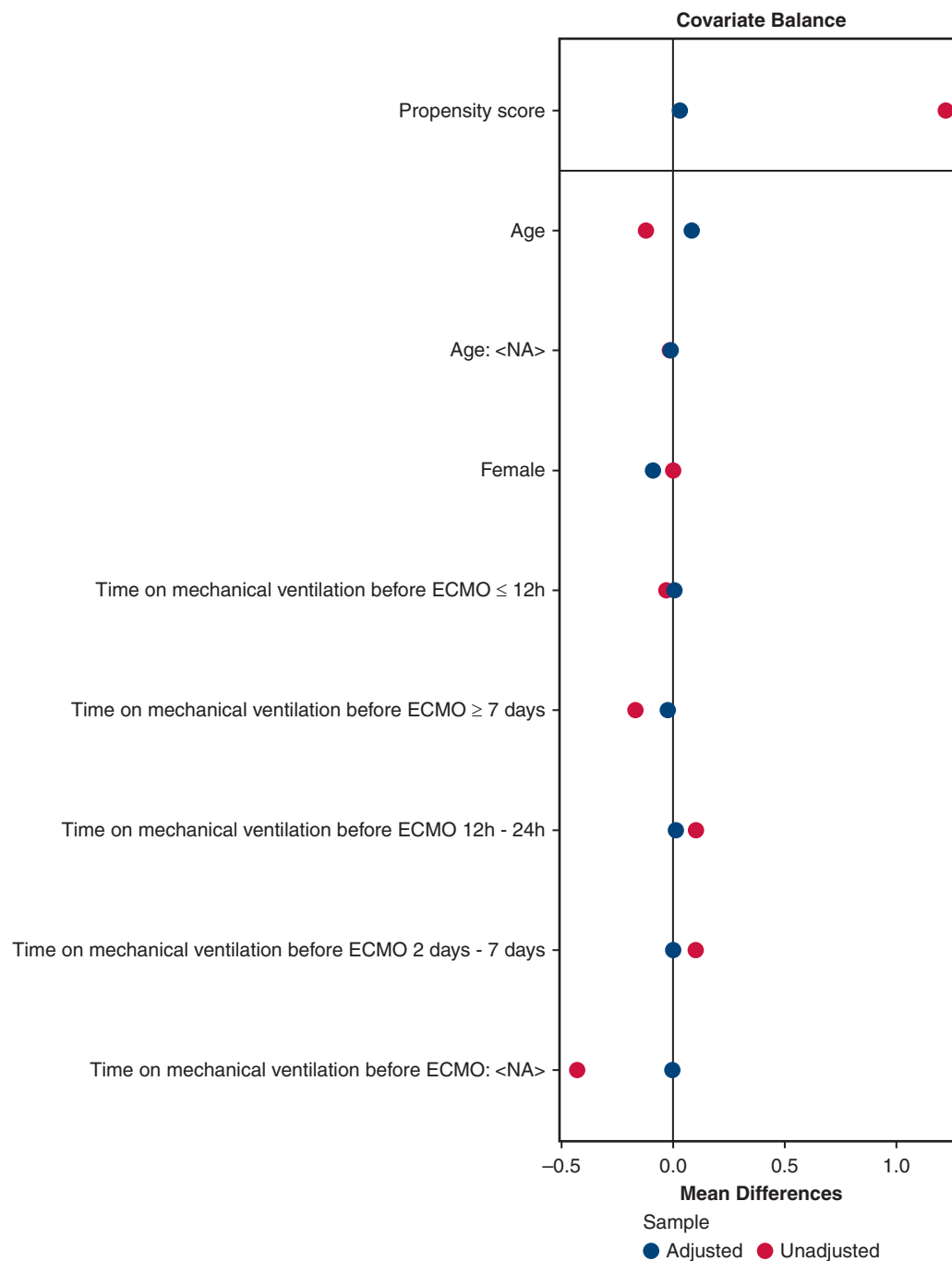
**FIGURE E10.** Covariate balance before and after adjustment for the propensity score analysis evaluating extracorporeal membrane oxygenation (ECMO) patients who used the Cardiohelp system (Maquet Cardiopulmonary). *BMI*, Body mass index; *NA*, not available.



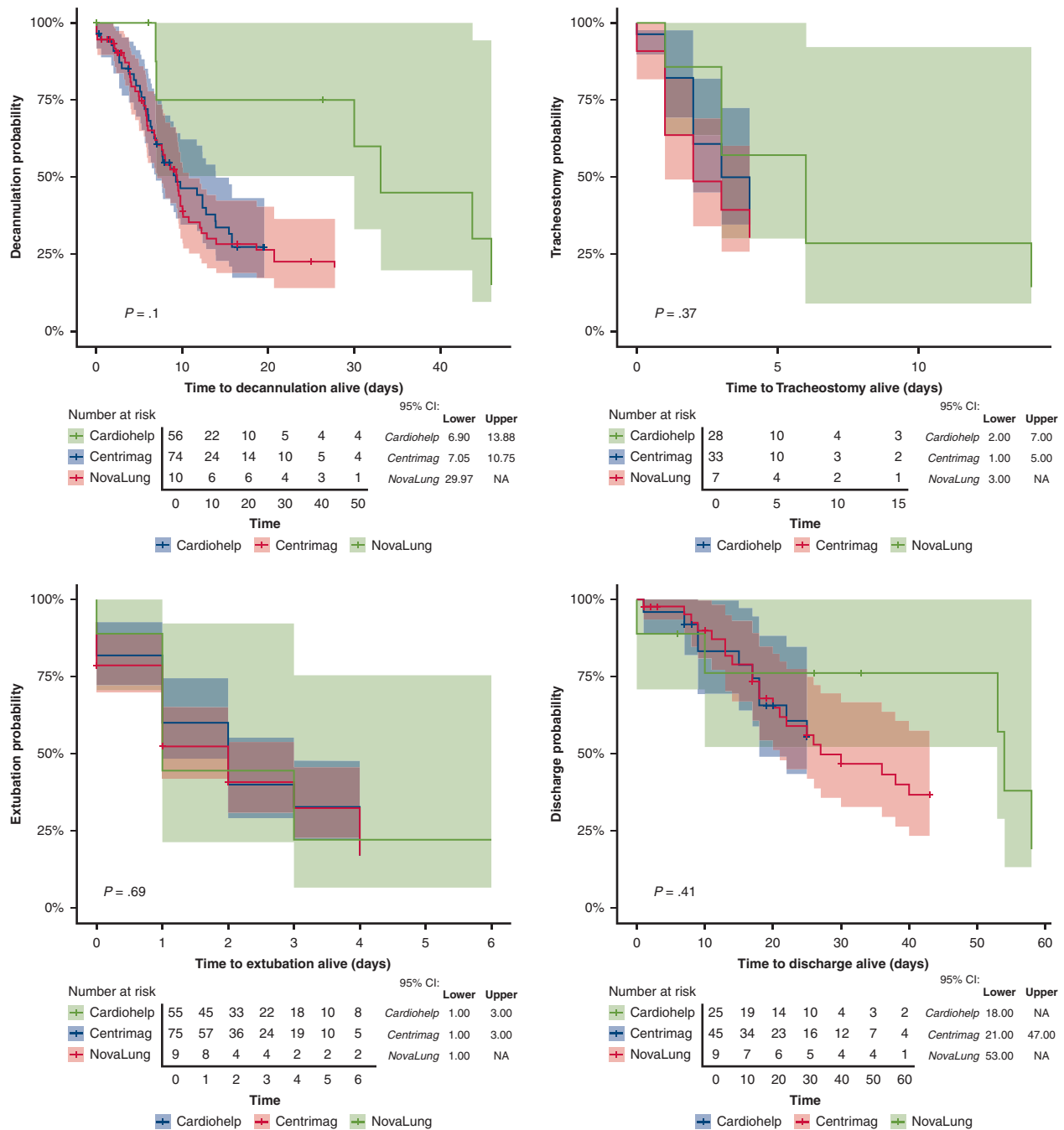
**FIGURE E11.** Kaplan–Meier plots for the association of COVID-19 diagnosis and time to decannulation, discharge, tracheostomy, and extubation alive among extracorporeal membrane oxygenation patients who used the CentriMag system (Abbot). The *darker lines* represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The *shaded areas* correspond to the 95% confidence intervals. ARDS, Acute respiratory distress syndrome; NA, not reached.

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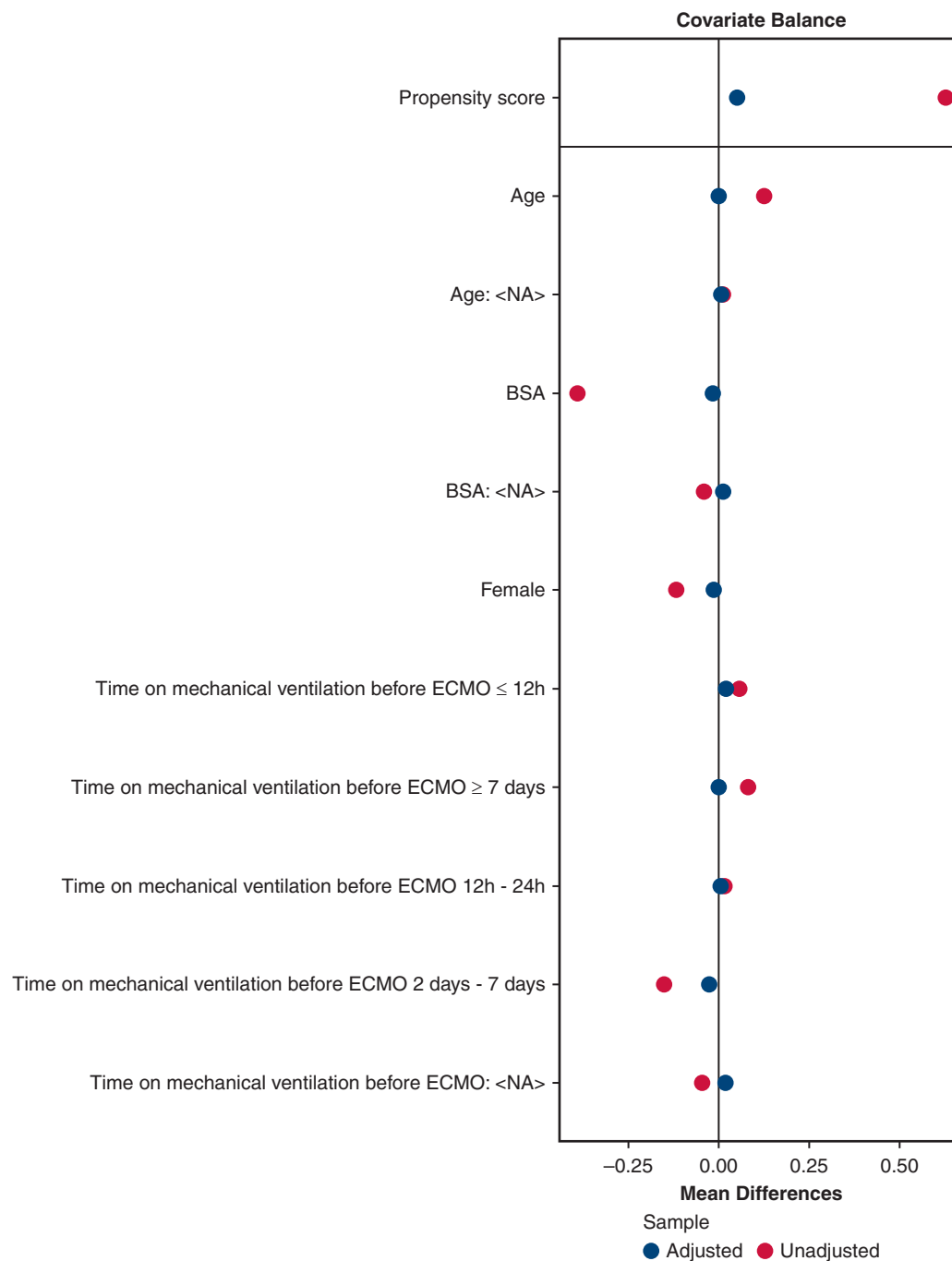


**FIGURE E12.** Covariate balance before and after adjustment for the propensity score analysis evaluating extracorporeal membrane oxygenation (ECMO) patients who used the CentriMag system (Abbot). *NA*, Not available.



**FIGURE E13.** Kaplan–Meier plots for the association among extracorporeal membrane oxygenation (ECMO) systems and time to decannulation, discharge, tracheostomy, and extubation. The darker lines represent the event probability over time (ie, the probability of decannulation, discharge, tracheostomy, and extubation alive over time). The shaded areas correspond to the 95% confidence intervals. Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot; NovaLung is from Fresenius Medical Care. NA, Not reached.

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**FIGURE E14.** Covariate balance before and after adjustment for the propensity score analysis comparing extracorporeal membrane oxygenation (ECMO) who used the Cardiohelp (Maquet Cardiopulmonary) and CentriMag (Abbot) systems. *NA*, Not available.

TABLE E1. Settings

Settings
<p>The ECMO program is administered by a working group adjourned on a monthly basis and comprising a multistakeholder alliance chaired by the Medical Director and with representation across a spectrum of clinical and administrative staff. Consensus-driven algorithms are used to guide management of anticoagulation, nutrition, antibiotic usage, ventilator weaning, extubation, tracheostomy, cannula management, ambulation, transportation, physical therapy, and hemodynamic management. A 10-bed wing of the cardiovascular intensive care unit is dedicated to ECMO patients. There is an ECMO specialist and an advanced practice provider in-house 24 h a day, as well as a designated on-call cardiothoracic surgeon for all cannulation and emergent complications.<sup>E1</sup> Two independent physicians confirmed triage and decision-making regarding candidacy for cannulation. Patients eligible for cannulation were aged between 18 and 55 y, admitted to West Virginia University Medicine, tested positive for SARS-CoV-2 using polymerase chain reaction, and fulfilled the Berlin definition for ARDS.</p> <p>Our treatment algorithm involved liberal use of adjunctive extracorporeal cyto-reduction with plasmapheresis and/or CytoSorb and the concomitant inclusion of other novel adjuncts of therapy against the virus and administered to mitigate hypoxia. These included among others, hydroxychloroquine, tocilizumab, ivermectin, remdesivir, convalescent plasma, and various monoclonal antibodies that were administered during the course of illness with varying frequency.<sup>E2-E7</sup></p> <p>Our ECMO program is the only one in the state and services 55 local counties in addition to a 4-state catchment area extending over a 250-nautical mile radius which is accessible using an EC-145 helicopter and serviced by a dedicated medical flight crew. Clinical care is largely algorithmic and follows ELSO<sup>E8</sup> policies and guidelines.</p> <p>We performed right internal jugular and ipsilateral femoral cannulation for VV-ECMO using 20-F FemFlex II femoral arterial cannulas and 25-F Bio-Medicus Multi-Stage femoral venous cannulas, respectively. We used a dual-lumen single catheter, typically the 32-F Crescent cannula placed in the right internal jugular vein with transesophageal echocardiogram and fluoroscopic guidance. Bivalirudin was the preferred anticoagulation of choice. The ECMO pump systems we most commonly used included the NovaLung oxygenator, Cardiohelp pump, and CentriMag pump. These strategies routinely proffer between 3.7 and 4.9 L/min of flow regardless of cannulation technique. The specific indications we used for plasmapheresis included hemodynamic instability, prolonged febrile state, D-dimer &gt;3000 ng/mL, and ferritin &gt;1000 ng/mL. We opted not to use interleukin 6 as a guide to bedside decisions because of the delay in retrieving the results but we used them to trend the cytokine storm longitudinally. We also removed the patient from isolation precautions on day 20, liberalizing the ability to have a visitor.</p> <p>Whenever possible, patients who were receiving high levels of sedation before cannulation (eg, paralyzed ARDS patients), were weaned immediately after cannulation. However, the time between weaning sedation and extubation varied depending on the duration of deep sedation before cannulation. In general we targeted light sedation if possible (eg, RASS of -1 to 1, CPOT &lt;3) in the absence of contraindications or concomitant illness that dictated the need for deeper sedation. For light sedation, we commonly used dexmedetomidine, ketamine, or lower-dose propofol with opioids as needed for pain management (eg, hydromorphone). For patients who required deep sedation, which varied with provider, we used higher-dose propofol, opioid infusions, benzodiazepine infusions, ketamine, or some combination thereof. Most of the intensivists avoided benzodiazepine and opioid infusions if possible. When the need for deep sedation had subsided (eg, post tracheostomy) we often attempted to wean deep sedation in lieu of light sedation as tolerated. Nearly all patients received adjunct enteral sedation depending on the clinical scenario and provider preference; there was varied use of second-generation antipsychotics (eg, quetiapine), clonidine, valproic acid, gabapentin, and phenobarbital.</p> <p>Regarding the ambulation protocol, the ECMO unit has dedicated physical therapists working in conjunction with an ECMO specialist, perfusionist, and bedside nurse, to secure the tubing and ambulate the patient using a walking aid and follow the patients around the unit with an arm chair with wheels that permits intermittent rest stops.</p>

CytoSorb is from CytoSorbents Corp; FemFlex II femoral arterial cannulas are from Edwards Lifesciences; Bio-Medicus Multi-Stage femoral venous cannulas and Crescent dual lumen cannulas are from Medtronic; the Cardiohelp pump is from Maquet Cardiopulmonary; the CentriMag pump is from Abbot. *ECMO*, Extracorporeal membrane oxygenation; *ARDS*, acute respiratory distress syndrome; *ELSO*, Extracorporeal Life Support Organization; *VV-ECMO*, venovenous extracorporeal membrane oxygenation; *F*, French; *RASS*, Richmond Agitation-Sedation Scale; *CPOT*, Critical Care Pain Observation Tool.

**TABLE E2. Inclusion and exclusion criteria**

Inclusion criteria
Inclusion criteria involved patients older than 18 y of age who were diagnosed with COVID-19 or non-COVID ARDS (on the basis of the American-European Consensus Conference definition <sup>E1</sup> ) who underwent VV-ECMO. In addition, our inclusion criteria involved patients who presented 1 of the following disease severity criteria despite optimization of MV: $FiO_2 > 80\%$ , tidal volume of 6 mL/kg, as well as predicted body weight and PEEP $> 10$ cm of water. We also only included patients who presented the following characteristics despite potential use of various usual adjunctive therapies (inhaled nitric oxide, recruitment maneuvers, prone position, high-frequency oscillation ventilation, and almitrine infusion): $PaO_2:FiO_2$ ratio $< 50$ mm Hg for $> 3$ h; or $PaO_2:FiO_2$ ratio $< 80$ mm Hg for $> 6$ h; or pH of arterial blood $> 7.25$ with a partial pressure of arterial carbon dioxide $< 60$ mm Hg for $< 6$ h, with respiratory rate increased to 35 per minute.
Exclusion criteria
Exclusion criteria involved: (A) endotracheally intubated and receiving mechanical ventilation for $< 7$ days; (B) fraction of inspired oxygen ratio of $PaO_2$ to $FiO_2$ of $< 50$ mm Hg for $> 3$ h; (C) $PaO_2:FiO_2$ ratio of $< 80$ mm Hg for $> 6$ h; and (D) arterial blood pH of $< 7.25$ with a partial pressure of arterial carbon dioxide of $\geq 60$ mm Hg for $> 6$ h with: (1) respiratory rate increased to 35 breaths per minute, (2) mechanical ventilation settings adjusted to keep a plateau pressure of $\leq 32$ cm of water; and (3) ventilator optimization (defined as an $Fio_2$ of $\geq 0.80$ , a tidal volume of 6 mL/kg of predicted body weight, and a PEEP of $\geq 10$ cm of water. Exclusionary criteria also followed Extracorporeal Life Support Organization standard as well as ECMO for Severe Acute Respiratory Distress Syndrome trial guidelines selected to mitigate confounding and bias, including: (1) age younger than 18 y or older than 65 y; (2) mechanical ventilation for $\geq 7$ days; before randomization; (3) weight of $> 1$ kg/cm of height or a body mass index of $> 45$ ; (4) long-term chronic respiratory insufficiency defined by oxygen therapy or noninvasive ventilation use; (5) cardiac failure resulting in the need for venoarterial ECMO; (6) history of heparin-induced thrombocytopenia; (7) cancer with a life expectancy of $< 5$ y; (8) moribund condition or a Simplified Acute Physiology Score value of $> 90$ (on a scale of 0-163, with higher scores indicating greater severity of illness) on the day of randomization; (9) current non-drug-induced coma after cardiac arrest; (10) evidence of irreversible neurologic injury; (11) decision to withhold or withdraw life-sustaining therapies; and (12) anticipated difficulty in obtaining vascular access for ECMO in the femoral or jugular vein.

ARDS, Acute respiratory distress syndrome; VV-ECMO, venovenous extracorporeal membrane oxygenation; MV, mechanical ventilation;  $FiO_2$ , fraction of inspired oxygen; PEEP, positive end-expiratory pressure;  $PaO_2$ , partial pressure of arterial oxygen; ECMO, extracorporeal membrane oxygenation.

TABLE E3. Scales and measures

Scale or measure	Description
SF-12	The SF-12 is a subset of the Medical Outcomes Study 36-Item Short-Form Health Survey, which is used to measure functional health and well-being from the patient's perspective. <sup>E9</sup> The SF-12 includes 12 items, with the raw scores of each item being coded, weighted, and summed into 2 summary scores: the mental component summary and the physical component summary scores. Higher scores represent a better quality of life. The SF-12 is reliable and valid in clinical and population-based applications in the United States and other countries. <sup>E9-E12</sup>
AM-PAC	The AM-PAC is a precise and comprehensive point-of-care assessment of patients' functional outcomes for acute or post acute care settings. It measures aspects such as difficulty, assistance, and limitations in activities of daily living. AM-PAC includes 3 functional areas: basic mobility, daily activity, and applied cognitive functions. The basic mobility domain evaluates the difficulty with bed mobility, sit to stand, stand to sit, supine to sit, seated transfers, ambulation, and ascending stairs. The daily activity domain assesses the assistance needed with bathing, clothing, toileting, and eating. The applied cognitive domain assesses the difficulty with understanding a presentation, understanding familiar people, remembering medications, recalling where items were placed or put away, remembering a list of items without writing them down, and managing complicated tasks. Usually, it is administered to provide health care professionals with data to assist in predicting acute care hospital discharge destinations that can be entered into the electronic medical records. <sup>E13,E14</sup>
PRESET-Score	The PRESET-Score is a tool that assists clinicians in predicting patient ECMO eligibility and the likelihood of survival. The score was developed on the basis of a univariate analysis using demographic, diagnostic, clinical, hemodynamic, and respiratory variables and associated organ dysfunction before ECMO initiation. From the univariate analysis, the authors identified 5 variables independently associated with in-hospital mortality: lactate concentration, hospital length of stay before ECMO, mean arterial pressure, platelet count, and arterial pH. These variables were converted into categorical variables using each beta parameter's relative contribution to build the PRESET-Score. <sup>E15</sup>

(Continued)

TABLE E3. Continued

Scale or measure	Description
APACHE	APACHE is a severity-of-disease classification system and 1 of several ICU scoring systems. It is applied within 24 h of admission of a patient to the ICU and helps clinicians evaluate patient disease severity. An integer score from 0 to 71 is computed from physiologic admission variables, variables, the patients' age, and chronic health status. Higher scores correspond to more severe disease and a higher risk of death. <sup>E16</sup>
SOFA	The SOFA is used to objectively and quantitatively describe the degree of organ dysfunction or failure over time. The score describes a sequence of critical illness complications and is on the basis of 6 different scores, 1 for each of the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. Each is scored from 0 to 4, with an increasing score reflecting worsening organ dysfunction. <sup>E17</sup>
Murray	The Murray score results from an equation that gives all of its variables the same linear contribution and weight, using consented cutoffs. It is calculated using the average of 4 variables (hypoxemia, compliance, alveolar consolidation in how many quadrants, and positive end-expiratory pressure) proposed for an expanded definition of the acute respiratory distress syndrome to facilitate the study and treatment of acute lung injury. Clinicians use it to decide whether a patient should be referred for conventional ventilation or ECMO. <sup>E18</sup>

*SF-12*, 12-Item Short-Form Health Survey; *AM-PAC*, Activity Measure for Post-Acute Care; *PRESET*, Prediction of Survival on ECMO Therapy-Score; *ECMO*, extracorporeal membrane oxygenation; *APACHE*, Acute Physiology and Chronic Health Evaluation; *ICU*, intensive care unit; *SOFA*, Sequential Organ Failure Assessment.

**TABLE E4. Percentage of patients alive at decannulation, discharge, tracheostomy, and extubation, as well as mean and SD for the time in day to each of these events**

Event	Alive at event (COVID-19), %	Alive at event (non-COVID-19 ARDS), %	Mean ± SD time to event (COVID-19), d	Mean ± SD time to event (non-COVID-19 ARDS), d
Decannulation	25.78	52.34	21.28 ± 27.94	14.05 ± 27.94
Discharge	22.66	41.41	31.93 ± 29.94	26.31 ± 29.94
Tracheostomy	14.84	36.72	5.26 ± 6.49	5.57 ± 6.49
Extubation	36.72	57.03	1.73 ± 2.33	5.91 ± 2.33

ARDS, Acute respiratory distress syndrome.

**TABLE E5. Time to event analysis**

Time to event analysis
First, we assessed the association among our risk factors and, because some risk scores presented a strong correlation, we selectively adjusted our analyses for the Murray score. In the time to event analysis we evaluated possible risk factors affecting time to decannulation, tracheostomy, extubation, and discharge. Our Cox proportional hazards models considered death as a censored event, thus avoiding an immortal survival bias. We evaluated the association between COVID-19 diagnosis and time to decannulation, discharge, tracheostomy, and extubation using Cox proportional hazards models adjusted for age, body mass index, and the Murray score. Hazard ratios with a value >1 indicated a faster clinical evolution to decannulation, tracheostomy, extubation, and discharge (clinically positive outcomes).

**TABLE E6. Propensity score analysis for COVID-19 versus non-COVID-19 ARDS**

Details on the propensity score analysis for COVID-19 vs non-COVID-19 ARDS
We used propensity score to ensure that our results aligned with what we could obtain with a randomized controlled trial. We compared non-COVID-19 ARDS vs COVID-19 among patients who required VV-ECMO support between January 2017 and May 2021. We evaluated time to decannulation, tracheostomy, extubation, and discharge alive using the following covariates: age, sex, BSA, insurance type, the distance between center and patient residence, and the duration of mechanical ventilation before ECMO. Our analyses indicated that age, BSA, insurance type, the distance between patient residence and hospital, and the duration of mechanical ventilation before ECMO were unbalanced in the original data (Table E7). Therefore, we adjusted all subsequent analyses for these unbalanced covariates (Table E8). Figure E3 shows the covariate balance before and after weighting adjustment. Finally, we evaluated outcome differences between COVID-19 and non-COVID-19 ARDS cases using the balanced data.

ARDS, Acute respiratory distress syndrome; VV-ECMO, venovenous extracorporeal membrane oxygenation; BSA, body surface area; ECMO, extracorporeal membrane oxygenation.

TABLE E7. Covariate balance estimation for the propensity score analysis comparison of COVID-19 versus non-COVID-19 ARDS

Covariates	Mean difference	Balance, threshold
Age	0.17	Not balanced, >0.10
BSA	0.32	Not balanced, >0.10
BSA: NA	-0.09	Balanced, <0.10
Female sex	0.01	Balanced, <0.10
Medicare or Medicaid insurance	-0.36	Not balanced, >0.10
Distance between patient residence and hospital	-0.19	Not balanced, >0.10
Distance between patient residence and hospital: NA	-0.15	Not balanced, >0.10
Duration of mechanical ventilation before ECMO ≤12 h	0.03	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≥7 d	-0.09	Balanced, <0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.12	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 2-7 d	-0.07	Balanced, <0.10
Duration of mechanical ventilation before ECMO: NA	0.023	Balanced, <0.10

ARDS, Acute respiratory distress syndrome; BSA, body surface area; NA, not available; ECMO, extracorporeal membrane oxygenation.

TABLE E8. Covariates balanced using inverse probability weights for the propensity score analysis comparison of COVID-19 versus non-COVID-19 ARDS

Covariates	Adjusted mean difference	Balance, threshold	Adjusted variability ratio
Propensity score	0.27		0.89
Age	-0.04	Balanced, <0.10	0.35
BSA	0.06	Balanced, <0.10	0.64
BSA: NA	-0.06	Balanced, <0.10	
Female sex	0.08	Balanced, <0.10	
Medicare or Medicaid insurance	0.00	Balanced, <0.10	
Distance between patient residence and hospital	0.04	Balanced, <0.10	0.63
Distance between patient residence and hospital: NA	-0.10	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≤ 12 h	-0.00	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥ 7 d	-0.04	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	0.06	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	-0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO: NA	-0.01	Balanced, <0.10	

ARDS, Acute respiratory distress syndrome; BSA, body surface area; NA, not available; ECMO, extracorporeal membrane oxygenation.



TABLE E9. Study sample characteristics and comparison of COVID-19 patients who underwent VV-ECMO and used or did not use CytoSorb

Variable (Missing)	Total (n = 50)	CytoSorb (n = 25)	No CytoSorb (n = 25)	P value	SMD
Age (0)	48.00 ± 9.36	46.40 ± 7.18	49.60 ± 11	.24	0.34
Female sex (0)	21 (42.00)	11 (44.00)	10 (40.00)	1.00	0.08
BMI (0)	37.50 ± 6.84	37.00 ± 4.81	37.90 ± 8.47	.62	0.14
BSA (0)	2.26 ± 0.29	2.29 ± 0.30	2.23 ± 0.27	.42	0.23
Medicare or Medicaid insurance (0)	2 (4.00)	2 (8.00)	0 (0.00)	.47	0.41
Distance between patient residence and hospital (0)	116 ± 65.10	106 ± 59.50	126 ± 70.00	.27	0.31
Cannulation strategy (0)				.60	0.29
Other	46 (92.00)	24 (96.00)	22 (88.00)		
RIJV	4 (8.00)	1 (4.00)	3 (12.00)		
Murray score (17)	3.25 ± 0.65	3.26 ± 0.78	3.24 ± 0.52	.91	0.04
PRESET-Score (16)	4.88 ± 2.06	4.67 ± 2.13	5.05 ± 2.04	.60	0.19
APACHE score (21)	18.20 ± 8.81	15.40 ± 7.62	21.60 ± 9.25	.07	0.73
SOFA score (19)	7.10 ± 3.23	6.12 ± 3.48	8.13 ± 2.67	.08	0.65
Duration of mechanical ventilation before ECMO (5)				.18	0.16
≤12 h	4 (8.00)	3 (13.00)	1 (4.55)		
≥7 d	3 (6.00)	0 (0.00)	3 (13.60)		
12-24 h	26 (52.00)	15 (65.20)	11 (50.00)		
2-7 d	12 (24.00)	5 (21.70)	7 (31.80)		
Extubation timing (10)				1.00	0.30
Extubated after decannulation	1 (2.00)	1 (4.55)	0 (0.00)		
Extubated before decannulation	39 (78.00)	21 (95.50)	18 (100.00)		
Tracheostomy timing (31)				1.00	0.05
Early tracheostomy (up to day 4)	14 (28.00)	8 (72.70)	6 (75.00)		
Late tracheostomy (day 5 and beyond)	5 (10.00)	3 (27.30)	2 (25.00)		
Time to decannulation (0), d	21.30 ± 27.90	17.50 ± 24.30	25.10 ± 31.20	.34	0.27
Time to discharge (7), d	31.90 ± 29.90	28.40 ± 25.10	35.30 ± 34.20	.46	0.23
Time to tracheostomy (31), d	5.26 ± 6.49	4.73 ± 3.61	6 ± 9.41	.73	0.18
Time to extubation (1), d	1.73 ± 2.33	2.04 ± 2.84	1.44 ± 1.73	.38	0.26

Data are presented as mean ± SD or n (%), except where otherwise noted. CytoSorb is from CytoSorbents Corp. VV-ECMO, Venovenous extracorporeal membrane oxygenation; SMD, standardized mean difference; BMI, body mass index; BSA, body surface area; RIJV, right internal jugular vein; PRESET-Score, Prediction of Survival on ECMO Therapy-Score; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation.

TABLE E10. Association of CytoSorb use and time to decannulation, tracheostomy, extubation, and discharge alive (hazard ratios)

Outcomes	CytoSorb	No CytoSorb, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	1.09 (0.53-2.24); P = .81; AIC = 231; BIC = 244
Time to tracheostomy alive	HR, 1 (referent)	3.84 (0.28-52.50); P = .31; AIC = 54.2; BIC = 59.2
Time to extubation alive	HR, 1 (referent)	0.65 (0.31-1.36); P = .25; AIC = 246; BIC = 260
Time to discharge alive	HR, 1 (referent)	1.31 (0.52-3.29); P = .56; AIC = 148; BIC = 158

CytoSorb is from CytoSorbents Corp. HR, Hazard ratio; AIC, Akaike information criterion; BIC, Bayesian information criterion.

**TABLE E11. Covariate balance estimation for the propensity score analysis comparing patients who received versus those who did not receive CytoSorb**

Covariates	Mean difference	Balance, threshold
Age	-0.34	Not balanced, >0.10
BSA	0.23	Not balanced, >0.10
Female sex	0.04	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≤ 12 h	0.09	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≥ 7 d	-0.14	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.15	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 2-7 d	-0.10	Not balanced, >0.10
Duration of mechanical ventilation before ECMO: NA	-0.04	Balanced, <0.10

CytoSorb is from CytoSorbents Corp. *BSA*, Body surface area; *ECMO*, extracorporeal membrane oxygenation; *NA*, not available.

**TABLE E12. Covariates balanced using inverse probability weights for the propensity score analysis comparing patients who received versus those who did not receive CytoSorb**

Covariates	Adjusted mean difference	Balance (threshold)	Adjusted variability ratio
Propensity score	0.19		0.38
Age	0.05	Balanced, <0.10	0.31
BSA	0.03	Balanced, <0.10	1.39
Female sex	-0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≤ 12 h	0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥ 7 d	-0.07	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	0.03	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO: NA	0.01	Balanced, <0.10	

CytoSorb is from CytoSorbents Corp. *BSA*, Body surface area; *ECMO*, extracorporeal membrane oxygenation; *NA*, not available.

**TABLE E13. Study sample characteristics for the comparison of COVID-19 patients who underwent VV-ECMO and used or did not receive plasmapheresis therapy**

Variable (Missing)	Total (n = 50)	No plasmapheresis (n = 21)	Plasmapheresis (n = 29)	P value	SMD
Age (0)	48.00 ± 9.36	45.70 ± 10.60	49.70 ± 8.14	.16	0.42
Female sex (0)	21 (42.00)	14 (66.70)	7 (24.10)	<.01	0.93
BMI (0)	37.50 ± 6.84	38.90 ± 8.41	36.40 ± 5.34	.24	0.356
BSA (0)	2.26 ± 0.29	2.23 ± 0.36	2.28 ± 0.23	.58	0.17
Medicare or Medicaid insurance (0)	2 (4.00)	1 (4.76)	1 (3.45)	1.00	0.07
Distance between patient residence and hospital (0)	116 ± 65.10	111 ± 67.70	120 ± 64.10	.65	0.13
Cannulation strategy (0)				1.00	0.09
Other	46 (92.00)	19 (90.50)	27 (93.10)		
RIJV	4 (8.00)	2 (9.52)	2 (6.90)		
Duration of mechanical ventilation before ECMO (5)				.60	0.06
≤12 h	4 (8.00)	2 (9.52)	2 (8.33)		
≥7 d	3 (6.00)	2 (9.52)	1 (4.17)		
12-24 h	26 (52.00)	10 (47.60)	16 (66.70)		
2-7 d	12 (24.00)	7 (33.30)	5 (20.80)		
Extubation timing (10)				.75	0.378
Extubated after decannulation	1 (2.00)	1 (7.14)	0 (0.00)		
Extubated before decannulation	39 (78.00)	13 (92.90)	26 (100.00)		
Tracheostomy timing (31)				.96	0.89
Early tracheostomy (up to day 4)	14 (28.00)	2 (100.00)	12 (70.60)		
Late tracheostomy (day 5 and beyond)	5 (10.00)	0 (0.00)	5 (29.40)		
Time to decannulation (0), d	21.30 ± 27.90	3.83 ± 5.55	33.90 ± 30.80	<.01	1.36
Time to discharge (7), d	31.90 ± 29.90	9.81 ± 9.87	45.00 ± 30.20	<.01	1.57
Time to tracheostomy (31), d	5.26 ± 6.49	2.00 ± 1.41	5.65 ± 6.76	.09	0.75
Time to extubation (1), d	1.73 ± 2.33	0.95 ± 1.12	2.32 ± 2.82	.03	0.64

Data are presented as mean ± SD or n (%), except where otherwise noted. *VV-ECMO*, Venovenous extracorporeal membrane oxygenation; *SMD*, standardized mean difference; *BMI*, body mass index; *BSA*, body surface area; *RIJV*, right internal jugular vein; *ECMO*, extracorporeal membrane oxygenation.

**TABLE E14. Association of plasmapheresis use and survival to decannulation, tracheostomy, extubation, and discharge**

Outcome	No plasmapheresis	Plasmapheresis, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	HR, 0.06 (0.01-0.27); <i>P</i> < .01; AIC = 117; BIC = 128
Time to extubation alive	HR, 1 (referent)	HR, 0.34 (0.13-0.88); <i>P</i> = .03; AIC = 155; BIC = 166
Time to discharge alive	HR, 1 (referent)	HR, 0.15 (0.03-0.85); <i>P</i> = .03; AIC = 102; BIC = 110

*HR*, Hazard ratio; *AIC*, Akaike information criterion; *BIC*, Bayesian information criterion.

**TABLE E15. Covariate balance estimation for the propensity score analysis comparing patients who received versus those who did not receive plasmapheresis**

Covariates	Mean difference	Balance, threshold
Age	0.42	Not balanced, >0.10
Female sex	-0.43	Not balanced, >0.10
Distance between patient residence and hospital	0.13	Not balanced, >0.10
Duration of mechanical ventilation before ECMO ≤12 h	-0.01	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≥7 d	-0.05	Balanced, <0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.19	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 2-7 d	-0.13	Not balanced, >0.10
Duration of mechanical ventilation before ECMO: NA	0.17	Not balanced, >0.10

ECMO, Extracorporeal membrane oxygenation; NA, not available.

**TABLE E16. Covariates balanced using inverse probability weights for the propensity score analysis comparing patients who received versus those who did not receive plasmapheresis**

Covariates	Adjusted mean difference	Balance, threshold	Adjusted variability ratio
Propensity score	0.21		1.07
Age	0.12	Not balanced, >0.10	0.84
Female sex	-0.05	Balanced, <0.10	
Distance between patient residence and hospital	-0.14	Not balanced, >0.10	0.57
Duration of mechanical ventilation before ECMO ≤12 h	0.00	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥7 d	-0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	-0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO: NA	0.10	Not balanced, >0.10	

ECMO, Extracorporeal membrane oxygenation; NA, not available.

TABLE E17. Number of patients who used each ECMO system

System	n
Cardiohelp	34
CentriMag	47
NovaLung	9
TandemHeart	1

Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot; NovaLung is from Fresenius Medical Care; and TandemHeart is from LivaNova, Inc. *ECMO*, Extracorporeal membrane oxygenation.

TABLE E18. Study sample characteristics for the Cardiohelp subgroup analysis

Variable (Missing)	Total (n = 56)	COVID-19 (n = 9)	Non-COVID-19 ARDS (n = 47)	P value	SMD
Age (0)	50.00 ± 11.40	48.40 ± 8.86	50.30 ± 11.90	.60	0.18
Female sex (0)	24 (42.90)	3 (33.30)	21 (44.70)	.79	0.23
BMI (0)	35.20 ± 10.40	35.80 ± 7.23	35.10 ± 10.90	.81	0.08
BSA (18)	2.29 ± 0.34	2.26 ± 0.32	2.29 ± 0.35	.82	0.09
Medicare or Medicaid insurance (0)	6 (10.70)	0 (0.00)	6 (12.80)	.59	0.54
Distance between patient residence and hospital (2)	156 ± 168.00	120 ± 63.10	164 ± 182.00	.20	0.33
Cannulation strategy (0)				.33	0.59
Other	24 (42.90)	8 (88.90)	16 (64.00)		
RIJV	10 (17.90)	1 (11.10)	9 (19.10)		
Duration of mechanical ventilation before ECMO (25)				.12	0.88
≤12 h	1 (1.79)	1 (12.50)	0 (0.00)		
≥7 d	3 (5.36)	1 (12.50)	2 (8.70)		
12-24 h	14 (25.00)	5 (62.50)	9 (39.10)		
2-7 d	13 (23.20)	1 (12.50)	12 (52.20)		
Extubation timing (2)				.75	0.49
Extubated after decannulation	5 (8.93)	0 (0.00)	5 (10.90)		
Extubated before decannulation	49 (87.50)	8 (100.00)	41 (89.10)		
Tracheostomy timing (28)				1.00	0.25
Early tracheostomy (up to day 4)	18 (32.10)	3 (75.00)	15 (62.50)		
Late tracheostomy (day 5 and beyond)	10 (17.90)	1 (25.00)	9 (37.50)		
Time to decannulation in d (0)	15.00 ± 21.50	27.00 ± 36.10	12.70 ± 17.00	.28	0.51
Time to discharge in d (31)	28.00 ± 23.70	37.10 ± 32.20	22.80 ± 16.20	.24	0.56
Time to tracheostomy in d (28)	5.82 ± 8.11	4.25 ± 4.03	6.08 ± 8.64	.51	0.27
Time to extubation in d (1)	2.84 ± 2.96	2.00 ± 2.24	3.00 ± 3.08	.27	0.37

Data are presented as mean ± SD or n (%), except where otherwise noted. Cardiohelp is from Maquet Cardiopulmonary. *ARDS*, Acute respiratory distress syndrome; *SMD*, standardized mean difference; *BMI*, body mass index; *BSA*, body surface area; *RIJV*, right internal jugular vein; *ECMO*, extracorporeal membrane oxygenation.

**TABLE E19.** Cox proportional hazard models for the association of COVID-19 diagnosis within the Cardiohelp subgroup and time to decannulation, discharge, tracheostomy, and extubation alive

Outcome	Non-COVID-19 ARDS	COVID-19, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.32 (0.09, 1.18); $P = .09$ ; AIC = 132; BIC = 140
Time to tracheostomy alive	HR, 1 (referent)	0.61 (0.09, 4.29); $P = .62$ ; AIC = 91.80; BIC = 97.80
Time to extubation alive	HR, 1 (referent)	1.42 (0.45, 4.44); $P = .55$ ; AIC = 165; BIC = 175
Time to discharge alive	HR, 1 (referent)	0.00 (0.00, 0.00); $P < .01$ ; AIC = 37; BIC = 40.40

Cardiohelp is from Maquet Cardiopulmonary. ARDS, Acute respiratory distress syndrome; HR, Hazard ratio; AIC, Akaike information criterion; BIC, Bayesian information criterion.

**TABLE E20.** Covariate balance estimation for the Cardiohelp subgroup analysis

Covariates	Mean difference	Balance, threshold
Age	-0.18	Not balanced, >0.10
BMI	0.08	Balanced, <0.10
Female sex	-0.11	Not balanced, >0.10
Duration of mechanical ventilation before ECMO ≤12 h	0.13	Not balanced, >0.10
Duration of mechanical ventilation before ECMO ≥7 d	0.04	Balanced, <0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.23	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 2-7 d	-0.40	Not balanced, >0.10
Duration of mechanical ventilation before ECMO: NA	-0.40	Not balanced, >0.10

Cardiohelp is from Maquet Cardiopulmonary. BMI, Body mass index; NA, not available; ECMO, extracorporeal membrane oxygenation.

TABLE E21. Covariates balanced using inverse probability weights for the Cardiohelp subgroup analysis

Covariates	Adjusted mean difference	Balance, threshold	Adjusted variability ratio
Propensity score	0.17		2.05
Age	0.01	Balanced, <0.10	0.68
BMI	0.26	Not balanced, >0.10	0.50
Female sex	-0.20	Not balanced, >0.10	
Duration of mechanical ventilation before ECMO ≤12 h	0.04	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥7 d	0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	0.06	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	-0.11	Not Balanced, >0.10	
Duration of mechanical ventilation before ECMO: NA	-0.01	Balanced, <0.10	

Cardiohelp is from Maquet Cardiopulmonary. *BMI*, Body mass index; *ECMO*, extracorporeal membrane oxygenation; *NA*, not available.

TABLE E22. Association of non-COVID-19 ARDS versus COVID-19 for patients within the Cardiohelp subgroup and each outcome (time to decannulation, tracheostomy, extubation, and discharge alive) through propensity score

Outcome	Non-COVID-19 ARDS	COVID-19, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.44 (0.06-3.08); <i>P</i> = .41
Time to tracheostomy alive	HR, 1 (referent)	2.73 (0.73-10.20); <i>P</i> = .14
Time to extubation alive	HR, 1 (referent)	2.96 (1.21-7.24); <i>P</i> = .02
Time to discharge alive	HR, 1 (referent)	0.00 (0.00-0.00); <i>P</i> < .01

Cardiohelp is from Maquet Cardiopulmonary. *ARDS*, Acute respiratory distress syndrome; *HR*, hazard ratio.

TABLE E23. Study sample characteristics for the CentriMag subgroup analysis

Variable (Missing)	Total (n = 75)	COVID-19 (n = 16)	Non-COVID-19 ARDS (n = 59)	P value	SMD
Age (1)	51.80 ± 16.20	50.40 ± 11.20	52.20 ± 17.40	.62	0.12
Female sex (1)	23 (30.70)	5 (31.20)	18 (30.50)	1.00	0.01
BMI (2)	32.90 ± 9.54	38.40 ± 8.52	31.40 ± 9.32	.01	0.78
BSA (21)	2.16 ± 0.29	2.27 ± 0.21	2.12 ± 0.31	.05	0.56
Medicare or Medicaid insurance (0)	6 (8.00)	0 (0.00)	6 (10.20)	.42	0.47
Distance between patient residence and hospital (2)	121 ± 74.60	131 ± 71.80	119 ± 75.80	.56	0.17
Duration of mechanical ventilation before ECMO (30)				.52	0.38
≤12 h	4 (5.33)	1 (6.67)	3 (10.00)		
≥7 d	8 (10.70)	1 (6.67)	7 (23.30)		
12-24 h	21 (28.00)	8 (53.30)	13 (43.30)		
2-7 d	12 (16.00)	5 (33.30)	7 (23.30)		
Extubation timing (4)				.81	0.38
Extubated after decannulation	4 (5.33)	0 (0.00)	4 (6.78)		
Extubated before decannulation	67 (89.30)	12 (100.00)	55 (93.20)		
Cannulation strategy (0)				.34	0.45
Other	40 (53.30)	15 (93.80)	25 (78.10)		
RIJV	8 (10.70)	1 (6.25)	7 (11.90)		
Tracheostomy timing (42)				.99	0.26
Early tracheostomy (up to day 4)	23 (30.70)	4 (80.00)	19 (67.90)		
Late tracheostomy (day 5 and beyond)	10 (13.30)	1 (20.00)	9 (32.10)		
Murray score (34)	2.90 ± 0.82	3.25 ± 0.52	2.74 ± 0.88	.03	0.69
PRESET score (25)	6.64 ± 2.40	4.86 ± 1.96	7.33 ± 2.20	.01	1.19
APACHE score (13)	25.90 ± 8.59	22.40 ± 8.34	26.50 ± 8.55	.18	0.49
SOFA score (11)	10.70 ± 3.64	8.25 ± 2.38	11.20 ± 3.67	.01	0.97
Time to decannulation in d (0)	12.80 ± 17.00	25.00 ± 28.50	9.44 ± 10.30	.05	0.73
Time to discharge in d (28)	25.80 ± 23.80	34.40 ± 32.70	21.80 ± 17.50	.18	0.48
Time to tracheostomy in d (42)	4.48 ± 5.80	7.20 ± 11.70	4.00 ± 4.24	.58	0.36
Time to extubation in d (0)	2.16 ± 2.25	1.50 ± 1.46	2.34 ± 2.40	.09	0.42

Data are presented as mean ± SD or n (%), except where otherwise noted. CentriMag is from Abbot. ARDS, Acute respiratory distress syndrome; SMD, standardized mean difference; BMI, body mass index; BSA, body surface area; ECMO, extracorporeal membrane oxygenation; RIJV, right internal jugular vein; PRESET, Prediction of Survival on ECMO Therapy; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.



**TABLE E24. Cox proportional hazard models for the association of COVID-19 diagnosis within the CentriMag subgroup with time to decannulation, discharge, tracheostomy, and extubation alive**

Outcomes	Non-COVID-19 ARDS	COVID-19, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.59 (0.2-1.7); $P = .32$ ; AIC = 168; BIC = 179
Time to tracheostomy alive	HR, 1 (referent)	0.71 (0.16-3.22); $P = .66$ ; AIC = 103; BIC = 112
Time to extubation alive	HR, 1 (referent)	1.22 (0.47-3.17); $P = .69$ ; AIC = 200; BIC = 212
Time to discharge alive	HR, 1 (referent)	0.35 (0.11-1.09); $P = .07$ ; AIC = 119; BIC = 129

CentriMag is from Abbot. ARDS, Acute respiratory distress syndrome HR, Hazard ratio; AIC, Akaike information criterion; BIC, Bayesian information criterion.

**TABLE E25. Covariate balance estimation for the CentriMag subgroup**

Covariates	Mean difference	Balance, threshold
Age	-0.12	Not balanced, >0.10
Age: NA	-0.02	Balanced, <0.10
Female sex	0.00	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≤12 h	-0.03	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≥7 d	-0.17	Not balanced, >0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.10	Balanced, <0.10
Duration of mechanical ventilation before ECMO 2-7 d	0.10	Balanced, <0.10
Duration of mechanical ventilation before ECMO: NA	-0.43	Not balanced, >0.10

CentriMag is from Abbot. NA, Not available; ECMO, extracorporeal membrane oxygenation.

TABLE E26. Covariates balanced using inverse probability weights for the CentriMag subgroup

Covariates	Adjusted mean difference	Balance, threshold	Adjusted variability ratio
Propensity score	0.033	Balanced, <0.10	1.13
Age	0.082	Balanced, <0.10	0.49
Age: NA	-0.01	Balanced, <0.10	
Female sex	-0.09	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≤12 h	0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥7 d	-0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	0.00	Balanced, <0.10	
Duration of mechanical ventilation before ECMO: NA	0.00	Balanced, <0.10	

CentriMag is from Abbot. NA, Not available; ECMO, extracorporeal membrane oxygenation.

TABLE E27. Association of non-COVID-19 ARDS versus COVID-19 for patients within the CentriMag subgroup and each outcome (survival to decannulation, tracheostomy, extubation, and discharge alive) through propensity score

Outcome	Non-COVID-19 ARDS	COVID-19, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.67 (0.31-1.44); <i>P</i> = .30
Time to tracheostomy alive	HR, 1 (referent)	0.76 (0.26-2.29); <i>P</i> = .63
Time to extubation alive	HR, 1 (referent)	1.36 (0.711-2.59); <i>P</i> = .35
Time to discharge alive	HR, 1 (referent)	0.50 (0.20-1.25); <i>P</i> = .14

CentriMag is from Abbot. ARDS, Acute respiratory distress syndrome; HR, hazard ratio.

TABLE E28. Study sample characteristics for the comparison among ECMO systems

Variable (Missing)	Total (141)	Cardiohelp (n = 56)	CentriMag (n = 75)	NovaLung (n = 10)	P value	SMD
Age (1)	50.90 ± 14.00	50.00 ± 11.40	51.80 ± 16.20	48.80 ± 7.77	.61	0.13
Female (1)	52 (36.90)	24 (42.90)	23 (30.70)	5 (50.00)	.27	0.24
BMI (2)	34.10 ± 9.65	35.20 ± 10.40	32.90 ± 9.54	36.60 ± 3.87	.09	0.23
BSA (39)	2.21 ± 0.31	2.29 ± 0.34	2.16 ± 0.29	2.19 ± 0.26	.21	0.39
Medicare or Medicaid insurance (0)	12 (8.51)	6 (10.70)	6 (8.00)	0 (0.00)	.52	0.09
Distance between patient residence and hospital (4)	133 ± 121.00	156 ± 168.00	121 ± 74.60	88.3 ± 58.10	.08	0.27
Duration of mechanical ventilation before ECMO (59)					.46	0.41
≤12 h	6 (4.26)	1 (3.23)	4 (8.89)	1 (16.70)		
≥7 d	11 (7.80)	3 (9.68)	8 (17.80)	0 (0.00)		
12-24 h	39 (27.70)	14 (45.20)	21 (46.70)	4 (66.70)		
2-7 d	26 (18.40)	13 (41.90)	12 (26.70)	1 (16.70)		
Extubation timing (7)					.51	0.14
Extubated after decannulation	9 (6.38)	5 (9.26)	4 (5.63)	0 (0.00)		
Extubated before decannulation	125 (88.70)	49 (90.70)	67 (94.40)	9 (100.00)		
Cannulation strategy (50)					.28	0.30
Other	72 (51.10)	24 (70.60)	40 (83.30)	8 (88.90)		
RIJV	19 (13.50)	10 (29.40)	8 (16.70)	1 (11.10)		
Tracheostomy timing (73)					.40	0.11
Early tracheostomy (up to day 4)	44 (31.20)	18 (64.30)	23 (69.70)	3 (42.90)		
Late tracheostomy (day 5 and beyond)	24 (17.00)	10 (35.70)	10 (30.30)	4 (57.10)		
Murray score (64)	2.94 ± 0.87	2.90 ± 1.00	2.90 ± 0.82	3.36 ± 0.49	.13	0.01
PRESET score (54)	6.79 ± 2.47	7.52 ± 2.46	6.64 ± 2.4	5.12 ± 2.23	.05	0.36
APACHE score (33)	24.00 ± 9.06	22.60 ± 8.77	25.90 ± 8.59	14.70 ± 9.65	.030	0.38
SOFA score (30)	10.10 ± 3.82	9.82 ± 3.86	10.70 ± 3.64	6.29 ± 3.15	.01	0.23
Time to decannulation in d (0)	14.90 ± 20.40	15.00 ± 21.50	12.80 ± 17.00	30.60 ± 31.50	.22	0.12
Time to discharge in d (59)	28.10 ± 24.90	28.00 ± 23.70	25.80 ± 23.80	39.20 ± 31.80	.47	0.09
Time to tracheostomy in d (73)	5.54 ± 7.48	5.82 ± 8.11	4.48 ± 5.80	9.43 ± 11.20	.48	0.19
Time to extubation in d (2)	2.50 ± 2.72	2.84 ± 2.96	2.16 ± 2.25	3.33 ± 4.39	.33	0.26

Data are presented as mean ± SD or n (%), except where otherwise noted. Cardiohelp is from Maquet Cardiopulmonary. ECMO, Extracorporeal membrane oxygenation; SMD, standardized mean difference; BMI, body mass index; BSA, body surface area; RIJV, right internal jugular vein; PRESET, Prediction of Survival on ECMO Therapy; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

**TABLE E29. Cox-proportional hazard models for the association among ECMO systems and time to decannulation, discharge, tracheostomy, and extubation alive**

Outcomes	Cardiohelp	CentriMag, HR (95% CI)	NovaLung, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	0.89 (0.47 = 1.70); <i>P</i> = .73	0.70 (0.21-2.29); <i>P</i> = .55; AIC = 335; BIC = 355
Time to tracheostomy alive	HR, 1 (referent)	0.85 (0.38 = 1.90); <i>P</i> = .68	0.12 (0.01-1.20); <i>P</i> = .07; AIC = 207; BIC = 224
Time to extubation alive	HR, 1 (referent)	1.49 (0.85 = 2.64); <i>P</i> = .17	1.93 (0.57-6.50); <i>P</i> = .29; AIC = 412; BIC = 433
Time to discharge alive	HR, 1 (referent)	0.91 (0.32 = 2.62); <i>P</i> = .86	1.15 (0.26-5.00); <i>P</i> = .85; AIC = 232; BIC = 249

Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot; NovaLung is from Fresenius Medical Care. *ECMO*, Extracorporeal membrane oxygenation; *HR*, hazard ratio; *AIC*, Akaike information criterion; *BIC*, Bayesian information criterion.

**TABLE E30. Covariate balance estimation for the comparison between Cardiohelp and CentriMag**

Covariates	Mean difference	Balance, threshold
Age	0.13	Not balanced, >0.10
Age: NA	0.01	Balanced, <0.10
BSA	-0.39	Not balanced, >0.10
BSA: NA	-0.04	Balanced, <0.10
Female sex	-0.12	Not balanced, >0.10
Duration of mechanical ventilation before ECMO ≤12 h	0.06	Balanced, <0.10
Duration of mechanical ventilation before ECMO ≥7 d	0.08	Balanced, <0.10
Duration of mechanical ventilation before ECMO 12-24 h	0.02	Balanced, <0.10
Duration of mechanical ventilation before ECMO 2-7 d	-0.15	Not balanced, >0.10
Duration of mechanical ventilation before ECMO: NA	-0.05	Balanced, <0.10

Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot. *NA*, Not available; *BSA*, body surface area; *ECMO*, extracorporeal membrane oxygenation.

TABLE E31. Covariates balanced using inverse probability weights for the comparison between Cardiohelp and CentriMag

Covariates	Adjusted mean difference	Balance, threshold	Adjusted variability ratio
Propensity score	0.05	Balanced, <0.10	1.06
Age	-0.00	Balanced, <0.10	2.14
Age: NA	0.01	Balanced, <0.10	
BSA	-0.02	Balanced, <0.10	0.71
BSA: NA	0.01	Balanced, <0.10	
Female sex	-0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≤12 h	0.02	Balanced, <0.10	
Duration of mechanical ventilation before ECMO ≥7 d	0.00	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 12-24 h	-0.01	Balanced, <0.10	
Duration of mechanical ventilation before ECMO 2-7 d	-0.03	Balanced, <0.10	
Duration of mechanical ventilation before ECMO: NA	0.02	Balanced, <0.10	

Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot. NA, Not available; BSA, body surface area; ECMO, extracorporeal membrane oxygenation.

TABLE E32. Association of ECMO systems and each outcome (time to decannulation, tracheostomy, extubation, and discharge alive) through propensity score

Outcome	Cardiohelp	CentriMag, HR (95% CI)
Time to decannulation alive	HR, 1 (referent)	1.05 (0.60-1.84); <i>P</i> = .86
Time to tracheostomy alive	HR, 1 (referent)	0.96 (0.53-1.76); <i>P</i> = .90
Time to extubation alive	HR, 1 (referent)	1.39 (0.84-2.28); <i>P</i> = .20
Time to discharge alive	HR, 1 (referent)	0.77 (0.27-2.19); <i>P</i> = .62

Cardiohelp is from Maquet Cardiopulmonary; CentriMag is from Abbot. HR, Hazard ratio.