



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Extracorporeal membrane oxygenation in COVID-19 compared to other etiologies of acute respiratory failure: A single-center experience

Hamid Yaqoob<sup>a,\*</sup>, Daniel Greenberg<sup>b</sup>, Lawrence Huang<sup>b</sup>, Theresa Henson<sup>a</sup>, Aren Pitaktong<sup>b</sup>, Daniel Peneyra<sup>b</sup>, Philip J. Spencer<sup>c</sup>, Ramin Malekan<sup>d</sup>, Joshua B Goldberg<sup>d</sup>, Masashi Kai<sup>d</sup>, Suguru Ohira<sup>d</sup>, Zhen Wang<sup>e</sup>, M. Hassan Murad<sup>e</sup>, Dipak Chandy<sup>a</sup>, Oleg Epelbaum<sup>a</sup>

<sup>a</sup> Division of Pulmonary, Critical Care, and Sleep Medicine, Westchester Medical Center, 100 Woods Road Macy Pavilion, Valhalla, NY 10595, USA

<sup>b</sup> Department of Medicine, Westchester Medical Center, Valhalla, NY, USA

<sup>c</sup> Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, USA

<sup>d</sup> Division of Cardiothoracic Surgery, Westchester Medical Center, Valhalla, NY, USA

<sup>e</sup> Evidence-Based Practice Center, Mayo Clinic, Rochester, MN, USA

### ARTICLE INFO

#### Article History:

Received 30 June 2022

Revised 3 September 2022

Accepted 6 October 2022

Available online 20 October 2022

#### Keywords:

COVID-19

SARS-CoV-2

Extracorporeal membrane oxygenation

Acute respiratory distress syndrome

### ABSTRACT

**Background:** The COVID-19 pandemic has led to a boom in the use of V-V ECMO for ARDS secondary to COVID. Comparisons of outcomes of ECMO for COVID to ECMO for influenza have emerged. Very few comparisons of ECMO for COVID to ECMO for ARDS of all etiologies are available.

**Objectives:** To compare clinically important outcome measures in recipients of ECMO for COVID to those observed in recipients of ECMO for ARDS of other etiologies.

**Methods:** V-V ECMO recipients between March 2020 and March 2022 consisted exclusively of COVID patients and formed the COVID ECMO group. All patients who underwent V-V ECMO for ARDS between January 2014 and March 2020 were eligible for analysis as the non-COVID ECMO comparator group. The primary outcome was survival to hospital discharge. Secondary outcomes included ECMO decannulation, ECMO duration >30 days, and serious complications.

**Results:** Thirty-six patients comprised the COVID ECMO group and were compared to 18 non-COVID ECMO patients. Survival to hospital discharge was not significantly different between the two groups (33% in COVID vs. 50% in non-COVID;  $p = 0.255$ ) nor was there a significant difference in the rate of non-palliative ECMO decannulation. The proportion of patients connected to ECMO for >30 days was significantly higher in the COVID ECMO group: 69% vs. 17%;  $p = 0.001$ . There was no significant difference in serious complications.

**Conclusion:** This study could not identify a statistically significant difference in hospital survival and rate of successful ECMO decannulation between COVID ECMO and non-COVID ECMO patients. Prolonged ECMO may be more common in COVID. Complications were not significantly different.

© 2022 Published by Elsevier Inc.

### Introduction

In the decades following the description of the acute respiratory distress syndrome (ARDS) by Ashbaugh and colleagues<sup>1</sup> in 1967, veno-venous extracorporeal membrane oxygenation (V-V ECMO) remained a rarely used and controversial intervention for severe ARDS. Despite rising to greater prominence during the H1N1 influenza pandemic in 2009 and despite the outcome benefit of ECMO referral observed in the CESAR trial,<sup>2</sup> in 2014 global ECMO use stood

at under 7% of severe ARDS cases.<sup>3</sup> Not long prior to the catastrophic SARS-CoV-2 pandemic, ECMO skepticism was tempered by the numerically favorable findings of the EOLIA trial<sup>4</sup> and the subsequent Bayesian analysis of its results.<sup>5</sup> With the arrival of COVID-19 in 2020, the world experienced an unprecedented onslaught of acute respiratory failure and had to pragmatically resolve the question of whether V-V ECMO would be elevated to routine use. By the end of 2020, nearly 5000 patients had received ECMO across centers in the Extracorporeal Life Support Organization (ELSO),<sup>6</sup> and pooled results from studies published during that time period suggested comparable survival to that of non-COVID patients from the EOLIA trial.<sup>7</sup> Since then, the literature on COVID-19 ECMO has grown to include direct historical comparisons with ECMO for ARDS secondary to influenza, a logical viral pneumonia comparator. Much less common have been comparisons between COVID-19 ECMO and ECMO for etiologies of

*Abbreviations:* ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IJ, internal jugular; LOS, length of stay; MV, mechanical ventilation; SC, subclavian; V-V, veno-venous; WMC, Westchester Medical Center

\* Corresponding author.

E-mail address: [hamidyaqoobmd@gmail.com](mailto:hamidyaqoobmd@gmail.com) (H. Yaqoob).

ARDS not limited to influenza. In fact, to our knowledge, only one such published comparison exists, and it presents European data.<sup>8</sup> We undertook a retrospective comparison study of COVID-19 ECMO versus non-COVID-19 ECMO based on the experience of our quaternary referral center in the United States.

## Methods

This study was approved by the Institutional Review Board of New York Medical College (protocol# 14318). The requirement for informed consent was waived. All adult patients managed for ARDS with V-V ECMO at Westchester Medical Center (WMC) between January 1 2014 and March 31, 2022 were eligible for inclusion. WMC is an academic quaternary referral center in New York State. The group that received V-V ECMO between March 1, 2020 and March 31, 2022 consisted exclusively of those with ARDS due to COVID-19 (COVID ECMO). The group that received V-V ECMO prior to March 1, 2020 consisted of those with ARDS secondary to other etiologies (non-COVID ECMO). Demographical, historical, clinical, laboratory, and outcome data for the COVID ECMO group were retrospectively extracted from a database that was created upon the cannulation of the first COVID ECMO patient. The same data for the non-COVID ECMO group was retrospectively obtained from the institutional electronic medical record after identification of such patients from the administrative records of the medical center's Division of Cardiothoracic Surgery. The presence of ARDS as the proximate indication for V-V ECMO cannulation was adjudicated by two experienced pulmonary and critical care medicine experts (HY and OE). In some patients transferred from outlying hospitals, certain chronological variables requiring information about the outside clinical course could not be ascertained.

All V-V ECMO cannula insertions at WMC are performed by cardiothoracic surgeons at the bedside under ultrasound guidance and with real-time chest x-ray confirmation. There is no mobile ECMO team, so transferred patients typically arrive to WMC for onsite cannulation. At WMC, criteria for V-V ECMO initiation in ARDS have not been strictly protocolized before or during the SARS-CoV-2 pandemic, so patient eligibility throughout the study period was a matter of consensus between the clinical intensive care unit (ICU) team and the consulting cardiothoracic surgeon. During the SARS-CoV-2 pandemic, absolute and relative contraindications to V-V ECMO support have been concordant with those proposed by the ELSO guideline working group.<sup>9</sup> Selection of cannulation strategy is at the discretion of the proceduralist with possible configurations being: (1) one dual-lumen cannula (Crescent™ Medtronic, Minneapolis, MN, USA) in the right internal jugular (IJ) or left subclavian (SC) vein (2) two single-lumen cannulas in either (a) femoral/IJ or (b) femoral/femoral veins. Prone positioning while connected to ECMO is not practiced. Systemic anticoagulation with intravenous heparin targeting a partial thromboplastin time of 1.5–2 times the normal value is routinely initiated at time of circuit connection and continued in the absence of contraindications. In the event of suspected or confirmed heparin-induced thrombocytopenia, argatroban infusion is substituted for heparin. Timing of tracheostomy is left to the discretion of the clinical ICU team as is the decision of whether a patient receiving ECMO is to remain connected to the ventilator following the creation of a tracheostomy: i.e., whether ventilator discontinuation should precede ECMO discontinuation or vice versa. ECMO decannulation timing is determined by the ICU team and requires demonstration of tolerance of discontinuation of sweep gas flow for at least 12 hours. Decannulation was performed by placing a skin suture at bedside. Comorbidity burden was summarized using the Charlson Comorbidity Index.<sup>10</sup> Severity of critical illness was represented using the APACHE IV score,<sup>11</sup> whereas the RESP score<sup>12</sup> was used to quantify the anticipated ECMO prognosis. RESP is a clinical prediction rule consisting of 12 pre-ECMO variables; the range of aggregate scores is -22 to +15

with higher scores indicating better survival. For example, a score between -1 and +2 is associated with a survival of 57% while a score between -5 and -2 is associated with a survival of 33%.

The primary outcome of interest in this study was survival to hospital discharge. Secondary outcome measures included survival to (non-palliative) ECMO decannulation and rate of ECMO lasting >30 days (prolonged ECMO). Additional secondary outcome measures were the various time segments in the disease course of the two groups [e.g., time from initiation of mechanical ventilation (MV) to ECMO cannulation, duration of the ECMO run for survivors to non-palliative decannulation, ICU length of stay (LOS), and hospital LOS] and the rates of serious ECMO complications. The definitions of some of the analyzed complications are as follows:

- 1 Hemorrhage: clinically detectable bleeding resulting in red blood cell transfusion
- 2 Proven non-respiratory infection: positivity of cultures of normally sterile sites (e.g., blood, pleural fluid)
- 3 Cardiac dysfunction: new left ventricular ejection fraction <30% during ECMO
- 4 Acute kidney injury: requirement for initiation of new renal replacement therapy during ECMO

## Statistical analysis

Categorical variables are expressed as frequency (percentage) and were compared using Fisher's exact test. The Shapiro–Wilk test was used to assess normality of continuous variables. Continuous variables that are normally distributed are expressed as mean ± standard deviation (SD) and were compared using the two-tailed t-test. Continuous variables violating normality are expressed as median (interquartile range [IQR], 25–75th percentile), and statistical significance was assessed by the Kruskal–Wallis nonparametric test. The primary outcome, survival to hospital discharge, was plotted using the Kaplan–Meier curve and compared between the COVID and non-COVID groups using the unadjusted Cox proportional hazard regression model due to the small number of patients. The proportional hazards assumption was validated using the Schoenfeld residuals test. A two-tailed p value ≤0.05 was considered statistically significant. Statistical analyses were conducted using Stata version 14.1 (StataCorp LLP, College Station, TX).

## Results

A total of 36 patients comprised the COVID ECMO group while a total of 18 patients comprised the comparison group consisting of non-COVID ECMO recipients. Table 1 summarizes and compares the demographical and clinical characteristics of the two groups. Those in the COVID ECMO group were significantly older than those in the non-COVID ECMO group (median age 48 vs. 33 years;  $p = 0.029$ ). Prone positioning pre-ECMO and neuromuscular blocking agent use was more common in the COVID ECMO group compared to the non-COVID ECMO group: 39% vs. 0%;  $p = 0.002$  and 81% vs. 44%;  $p = 0.012$ , respectively. At ECMO initiation, the COVID ECMO group had higher level of mean positive end-expiratory pressure applied (14 cmH<sub>2</sub>O vs. 9 cmH<sub>2</sub>O;  $p < 0.001$ ) and was ventilated with lower absolute tidal volumes (381 ml vs. 445 ml;  $p = 0.012$ ). Also, ECMO was initiated at a lower mean PaO<sub>2</sub> level and at a correspondingly lower mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio in COVID ECMO patients than non-COVID ECMO patients: 60 mmHg vs. 91 mmHg;  $p = 0.024$  and 63 vs. 101;  $p = 0.010$ , respectively. Finally, there was a significant difference between the two groups with respect to ECMO cannulation strategies ( $p = 0.024$ ), mainly owing to a lower rate of femoral-femoral vein cannulation in the COVID group in favor of dual lumen cannula insertion into the right IJ or left SC vein. Table 2 lists the etiological categories of ARDS

**Table 1**  
Background and clinical characteristics of the two study groups.

Demographics	Non-COVID (N = 18)	COVID (N = 36)	p-value
Age, years, Median (IQR)	33 (29–42)	48 (36–59)	<b>0.029</b>
Sex, Female, n (%)	6 (33)	13 (36)	>0.99
BMI, Mean (+/- SD)	33 (10)	36 (12)	0.300
<b>Comorbidities, n (%)</b>			
Chronic Kidney Disease	2 (11)	2 (6)	0.594
Chronic Pulmonary Disease	4 (22)	2 (6)	0.087
Coronary Artery Disease	0 (0)	3 (9)	0.542
Congestive Heart Failure	2 (11)	0 (0)	0.106
History of Stroke	2 (11)	0 (0)	0.106
Diabetes Mellitus	3 (17)	10 (28)	0.506
Hypertension	8 (44)	10 (28)	0.239
History of Malignancy	1 (6)	1 (3)	>0.99
Solid Organ Transplant	1 (6)	1 (3)	>0.99
Stem Cell Transplant	1 (6)	0 (0)	0.330
Connective Tissue Disease	1 (6)	1 (3)	>0.99
<b>Charlson Comorbidity Index, Median (IQR)</b>	0 (0–2.5)	1 (0–2)	0.693
<b>Admission Source, n (%)</b>			0.365
Emergency Department	4 (22)	13 (34)	
Outside Transfer	14 (78)	23 (66)	
<b>APACHE IV Score, Median (IQR)</b>	64 (46–67)	60 (51–72)	0.633
<b>RESP Score, Mean (+/- SD)</b>	0.29 (4.44)	2.1 (3.28)	0.099
<b>Prone Positioning, n (%)</b>	0 (0)	14 (39)	<b>0.002</b>
<b>NMBA, n (%)</b>	8 (44)	29 (81)	<b>0.012</b>
<b>Ventilator Settings<sup>a</sup> Mean (+/- SD)</b>			
FiO <sub>2</sub>	93 (15)	97 (8)	0.170
PEEP, cmH <sub>2</sub> O <sup>b</sup>	9 (4)	14 (5)	< <b>0.001</b>
Tidal Volume, ml <sup>c</sup>	445 (98)	381 (66)	<b>0.012</b>
Respiratory Rate, breaths/min	22 (8)	25 (6)	0.061
Peak Pressure, cmH <sub>2</sub> O	37 (11)	32 (8)	0.146
Plateau Pressure, cmH <sub>2</sub> O <sup>d</sup>	25 (13)	31 (8)	0.172
<b>Arterial Blood Gas<sup>a</sup> Mean (+/- SD)</b>			
pH	7.31 (0.12)	7.3 (0.10)	0.769
PaCO <sub>2</sub> , mmHg	54 (21)	57 (18)	0.599
PaO <sub>2</sub> , mmHg	91 (77)	60 (14)	<b>0.024</b>
PaO <sub>2</sub> /FiO <sub>2</sub>	101 (83)	63 (17)	<b>0.010</b>
<b>ECMO Cannulation Site n (%)</b>			<b>0.024</b>
RIJV/LSCV	9 (50)	26 (72)	
FV-RIJV	4 (22)	9 (25)	
FV-FV	5 (28)	1 (3)	
<b>Tracheostomy</b>	7 (39)	21 (58)	0.250

BMI=body mass index, FV=femoral vein, LSCV=left subclavian vein, NMBA=neuromuscular blocking agent, PEEP=positive end-expiratory pressure, RIJV=right internal jugular vein

<sup>a</sup> At time of ECMO initiation

<sup>b</sup> Based on n = 18 in non-COVID group, n = 34 in COVID group

<sup>c</sup> Based on n = 16 in non-COVID group, n = 31 in COVID group

<sup>d</sup> Based on n = 9 in non-COVID group, n = 12 in COVID group

in the non-COVID ECMO group. The most frequent categories were viral pneumonia (28%) and bacterial pneumonia (22%). **Table 3** presents the primary and main secondary outcomes of this study. Survival to hospital discharge favored the non-COVID ECMO group but did not reach statistical significance: 50% vs. 33%;  $p = 0.255$ . The

**Table 2**  
Distribution of etiologies of ARDS in the non-COVID ECMO group.

Etiology	n (%)
Viral Pneumonia	5 (28)
Bacterial Pneumonia	4 (22)
Aspiration Pneumonitis	4 (22)
Trauma	2 (11)
Other	3 (17)

**Table 3**  
Primary and secondary outcomes of the study.

	Non-COVID (N = 18)	COVID (N = 36)	p-value
<b>Survival to hospital discharge, n (%)</b>	9 (50)	12 (33)	0.255
<b>Non-palliative ECMO decannulation n (%)</b>	10 (56)	13 (35)	0.245
<b>ECMO lasting &gt;30 days, n (%)</b>	3 (17)	24 (69)	<b>0.001</b>
<b>Complications, n (%)</b>			
Hemorrhage	14 (78)	34 (94)	0.087
Cardiac dysfunction	2 (11)	2 (6)	0.594
Limb ischemia	0 (0)	1 (3)	>0.99
Pneumothorax	8 (44)	12 (33)	0.551
Proven infection	7 (39)	19 (51)	0.565
Hemorrhagic CVA	2 (11)	3 (8)	>0.99
Ischemic CVA	1 (0)	1 (3)	>0.99
AKI requiring RRT <sup>a</sup>	10 (63)	24 (67)	0.764

AKI=acute kidney injury, CVA=cerebrovascular accident, RRT=renal replacement therapy

<sup>a</sup> Excluding two end-stage renal disease patients in the non-COVID group for  $n = 16$

lack of a significant survival difference was confirmed by Kaplan-Meier analysis (**Fig. 1**). Survival to non-palliative decannulation of ECMO was likewise similar between the groups. The proportion of patients connected to ECMO for >30 days was significantly higher in the COVID ECMO group: 69% vs. 17%;  $p = 0.001$ . There was no significant difference in any of the analyzed ECMO complications. Various segments of the pre-hospital and hospital disease course of the patients in the two groups are compared in **Table 4**. Median hospital days preceding intubation were significantly greater in the COVID ECMO group: 6 days vs. 0.5 days;  $p = 0.002$ . Notably, there was no significant difference in pre-ECMO duration of MV nor in the duration of the ECMO run in survivors to non-palliative decannulation between the two groups. Median ICU, but not hospital, LOS was significantly greater in the COVID ECMO group: 43.0 days vs. 20.5 days ( $p = 0.023$ ). **Table 5** depicts the frequencies of each of the possible clinical trajectories experienced by patients in the two study groups. The main outcomes and their rates in each group are illustrated in the form of a flow chart in **Fig. 2**.

## Discussion

The present study represents one of the most comprehensive comparisons available to date between patients subjected to V-V ECMO for COVID ARDS and those subjected to it for all other causes of ARDS. Special attention was paid to a comparison of the different disease course time segments in the two groups. We found no significant difference in length of pre-ECMO MV, duration of ECMO support among survivors to non-palliative decannulation, survival to hospital discharge, or serious ECMO complications. We did find a longer hospital stay preceding MV and a longer ICU LOS in the COVID ECMO group. There were also more instances of ECMO lasting >30 days among the COVID patients. The hospital survival rate of 33% in our COVID ECMO sample covering two years of the SARS-CoV-2 pandemic, although seemingly low, closely mirrors the nationwide survival figure from Germany (32%)<sup>13</sup> and results from a broad 61-hospital cohort in the United States (39%).<sup>14</sup>

A systematic literature search of MEDLINE via PubMed<sup>®</sup> using the terms “COVID” AND “ECMO” identified only two English-language studies that juxtaposed COVID ECMO patients with non-COVID ECMO patients regardless of etiology. One is a series by Pieri et al. describing the Milan experience with V-V ECMO between the years of 2009 and 2020, a time period that overlapped with the SARS-CoV-2 pandemic.<sup>15</sup> Of the 142 patients, 36% had ARDS secondary to H1N1 influenza, 9% had COVID ARDS, with the remainder consisting of a miscellany of other causes (e.g., 16% bacterial pneumonia). No direct comparison was performed between COVID ECMO and non-COVID ECMO patients in this study. Thus, the only available direct

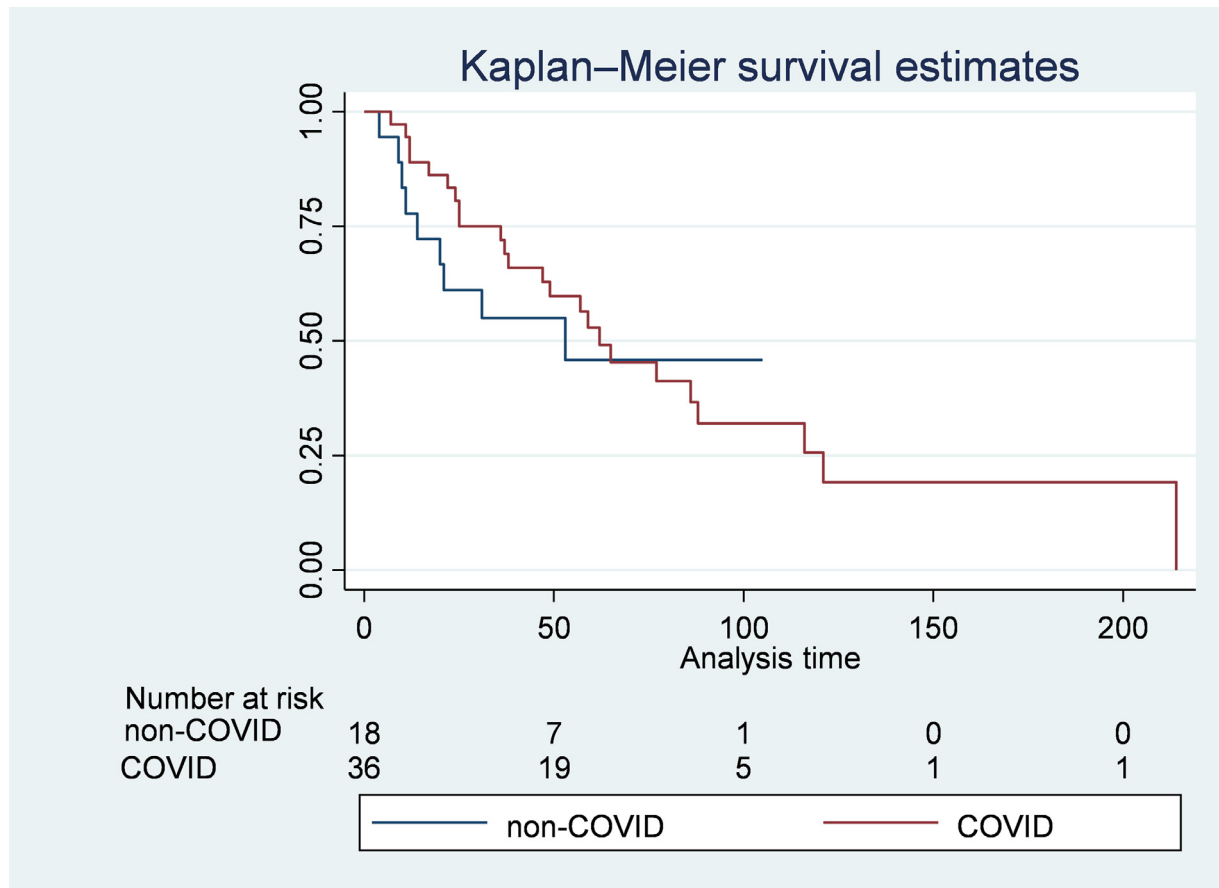


Fig. 1. Kaplan-Meier plot depicting the primary outcome of survival to hospital discharge in the two study groups.

comparison comes from the aforementioned multi-site European study by Raasveld et al.<sup>8</sup> in which 71 COVID ECMO patients were compared to 48 non-COVID ECMO patients. With the exception of gender distribution, no significant differences emerged between the two categories of ECMO recipients, including ECMO duration (13 days for COVID vs. 9 days for non-COVID;  $p = 0.16$ ) and 28-day survival (63% for COVID vs. 73% for non-COVID;  $p = 0.49$ ). There was likewise no significant difference in reported ECMO complications.

**Table 4**

List of all possible clinical trajectories and their frequencies observed in the two groups.

Trajectory	Non-COVID n (%)	COVID n (%)
MV → ECMO → TR → Off ventilator → Decannulation → Discharge	1 (6)	3 (8)
MV → ECMO → TR → Decannulation → Off ventilator → Discharge	1 (6)	4 (11)
MV → ECMO → TR → Decannulation → Discharge on ventilator	1 (6)	2 (6)
MV → ECMO → TR → Decannulation → Death	0 (0)	1 (3)
MV → ECMO → TR → Off ventilator → Comfort Care	0 (0)	3 (8)
MV → ECMO → TR → Death	0 (0)	8 (22)
MV → ECMO → TR → Comfort Care	1 (6)	1 (3)
MV → ECMO → Comfort Care	3 (7)	2 (6)
MV → ECMO → Death	4 (22)	9 (25)
MV → ECMO → Decannulation → Extubation → Discharge	3 (17)	3 (8)
MV → ECMO → Decannulation → TR → Off ventilator → Discharge	3 (17)	0 (0)
MV → ECMO → Decannulation → Death	1 (6)	0 (0)

ECMO=extracorporeal membrane oxygenation, MV=mechanical ventilation, TR=tracheostomy

The same search identified seven previously published studies comparing general hospital outcomes in COVID ECMO vs. influenza ECMO.<sup>16–22</sup> In a study from Germany, Jäckel et al.<sup>16</sup> compared 15 COVID ECMO patients against 47 influenza ECMO patients and found a numerically, but not statistically significantly, higher hospital

**Table 5**

Comparison of disease course time segments between the two groups.

	Non-COVID Median Days (IQR)	COVID Median Days (IQR)	p-value
Symptom duration before admission <sup>a</sup>	2.5 (0–5.5)	4 (2.0–7.0)	0.257
Hospitalization duration before MV <sup>b</sup>	0.5 (0–5.0)	6 (2.0–11)	<b>0.002</b>
MV duration before ECMO <sup>c</sup>	2 (1.0–7.0)	3 (1.0–8.0)	0.978
MV duration before tracheostomy <sup>d</sup>	25 (17.5–36.5)	23 (18.0–30.0)	0.750
Total MV duration <sup>e</sup>	35 (18.0–59.0)	36 (28.0–49.5)	0.691
Total ECMO duration before decannulation <sup>f</sup>	12 (8.5–33.0)	34.5 (21.5–42.5)	0.105
ICU LOS	20.5 (11.8–39.8)	43 (22.5–60.5)	<b>0.023</b>
Hospital LOS	36 (15.5–66.5)	57 (29.5–83.0)	0.083

ECMO=extracorporeal membrane oxygenation, ICU=intensive care unit, LOS=length of stay, MV=mechanical ventilation

<sup>a</sup> Based on  $n = 14$  in non-COVID group,  $n = 36$  in COVID group

<sup>b</sup> Based on  $n = 14$  in non-COVID group,  $n = 31$  in COVID group

<sup>c</sup> Based on  $n = 13$  in non-COVID group,  $n = 36$  in COVID group

<sup>d</sup> Based on  $n = 7$  (39%) in non-COVID group,  $n = 21$  (58%) in COVID group

<sup>e</sup> Based on  $n = 9$  (50%) in non-COVID group,  $n = 16$  (40%) in COVID group (limited to patients liberated from ventilator)

<sup>f</sup> Based on  $n = 10$  (56%) in non-COVID group,  $n = 13$  (35%) in COVID group (survivors to non-palliative decannulation)

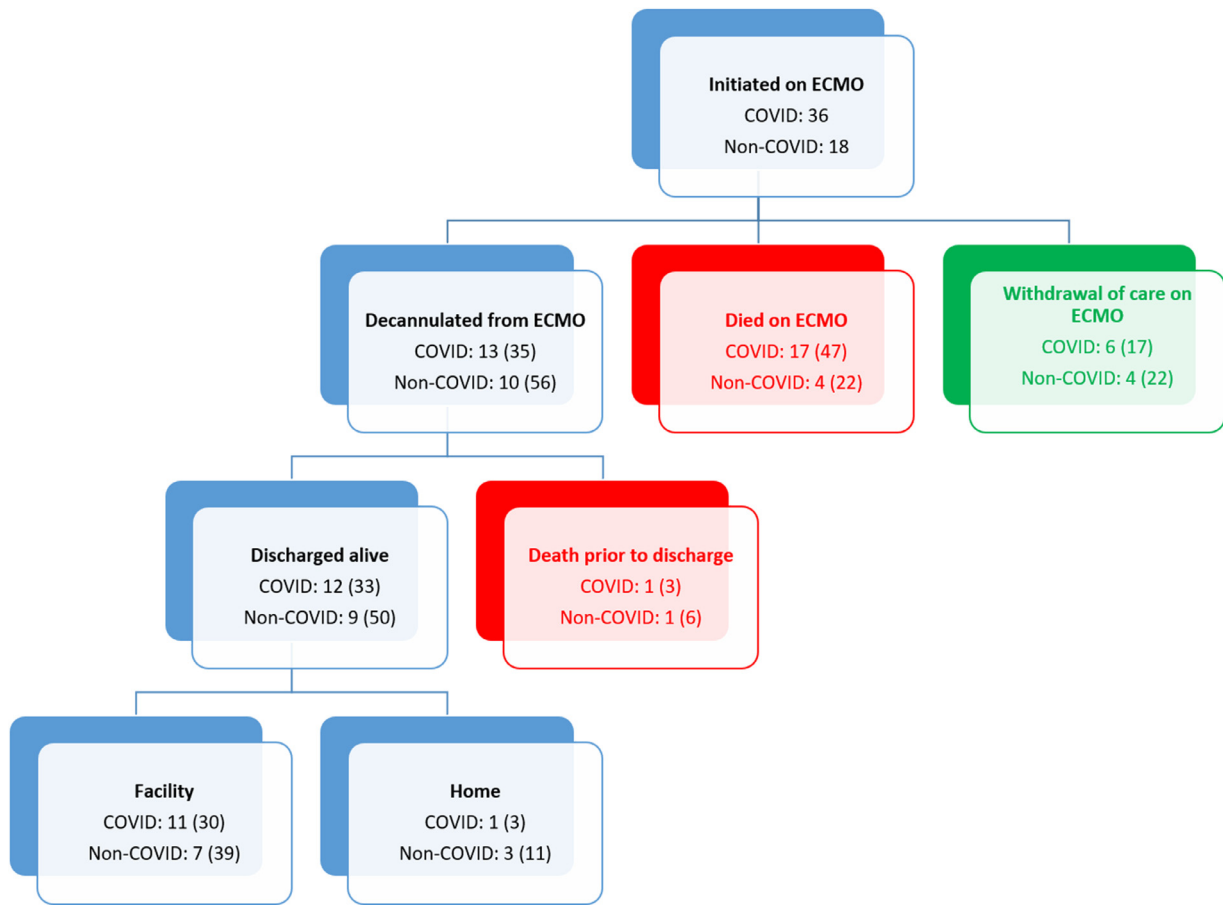


Fig. 2. Diagram summarizing the outcomes of the two study groups. Figures in parentheses denote percentages relative to the total sample size in the respective group.

survival in the influenza group versus the COVID group: 57.4% vs. 40.0%;  $p = 0.238$ . Pre-ECMO duration of MV was significantly longer in the COVID group versus the influenza group (4.6 days vs. 1.1 days;  $p < 0.001$ ); the duration of the ECMO run was also longer in the COVID group but not significantly so (11.3 days vs. 8.9 days;  $p = 0.247$ ). In a French study, Cousin et al.<sup>17</sup> compared 30 COVID ECMO patients to 22 influenza ECMO patients. Once again, duration of MV prior to ECMO was significantly longer in the COVID group versus the influenza group (6 days vs. 3 days;  $p = 0.004$ ) and, like in Jäckel et al., hospital survival numerically favored the influenza group, again failing to reach statistical significance however: 54.5% vs. 46.7%;  $p = 0.570$ ). ECMO duration was identical in both groups at 11 days. An analogous pattern to Jäckel et al. also emerged from a United Kingdom comparison between 34 COVID ECMO patients and 26 H1N1 influenza patients reported by Charlton et al.<sup>18</sup>: significantly shorter pre-ECMO MV in influenza vs. COVID (2.4 days vs. 4.9 days;  $p < 0.001$ ) with numerically, but not statistically significantly, greater

survival in the influenza group (69% vs. 53%;  $p = 0.288$ ) and longer ECMO duration in the COVID group (13.2 days vs. 12.3 days;  $p = 0.601$ ). The largest of these studies was conducted by Fanelli et al.,<sup>19</sup> analyzing a multicenter Italian cohort of 146 COVID ECMO patients and 162 H1N1 influenza ECMO patients. Survival favored the influenza group (73% vs. 46%, significant only in the unadjusted analysis) with significantly longer median pre-ECMO MV (7 days vs. 0 days;  $p = 0.0001$ ) and ECMO duration (22 days vs. 13 days;  $p = 0.0001$ ) seen in the COVID ECMO group.

The remaining three studies were conducted in the United States. Raff et al.<sup>20</sup> compared 32 COVID ECMO patients to 28 influenza ECMO patients. Once again, influenza patients spent significantly less time on mechanical ventilation before ECMO (1.5 days vs. 4.5 days;  $p < 0.001$ ), but in contrast to the aforementioned studies, hospital survival was statistically significantly better in the influenza group (63.7% vs. 34.4%;  $p = 0.041$ ). Length of time on ECMO was again greater in the COVID group, this time reaching statistical significance:

Table 6

Summary of the published studies comparing V-V ECMO initiated for COVID ARDS with that initiated for ARDS secondary to influenza. Results in bold denote a statistically significant difference for that parameter in a given study as defined by its authors.

Study	COVID ECMO N=	Flu ECMO N=	Pre-ECMO MV COVID (days)	Pre-ECMO MV Flu (days)	ECMO Duration COVID (days)	ECMO Duration Flu (days)	Survival COVID	Survival Flu
Jäckel <sup>16</sup> (Ger)	15	47	<b>4.6</b>	<b>1.1</b>	11.3	8.90	40.0%	57.4%
Cousin <sup>17</sup> (Fr)	30	22	<b>6.0</b>	<b>3.0</b>	11.0	11.0	46.7%	54.5%
Charlton <sup>18</sup> (UK)	34	26	<b>4.9</b>	<b>2.4</b>	13.2	12.3	53.0%	69.0%
Fanelli <sup>19</sup> (Italy)	146	162	<b>5.0</b>	<b>2.0</b>	<b>22.0</b>	<b>13.0</b>	54.0%	73.0%
Raff <sup>20</sup> (US)	32	28	<b>4.5</b>	<b>1.5</b>	<b>12.4</b>	<b>7.70</b>	<b>34.4%</b>	<b>63.7%</b>
Shih <sup>21</sup> (US)	53	67	NR	NR	<b>14.0</b>	<b>10.5</b>	62.3%	64.2%
Blazoski <sup>22</sup> (US)	28	17	NR	NR	<b>21.4</b>	<b>12.2</b>	<b>68.0%</b>	<b>94.0%</b>

ECMO=Extracorporeal Membrane Oxygenation, MV=Mechanical Ventilation, NR=Not Reported

12.4 days vs. 7.7 days;  $p = 0.002$ . Shih et al.<sup>21</sup> compared 53 COVID ECMO patients to 67 influenza ECMO patients. Duration of mechanical ventilation prior to ECMO was not compared directly, but length of time from admission to both intubation and ECMO cannulation was shorter in the influenza group. In this study, unlike in the others, hospital survival was quite similar between influenza ECMO patients and COVID ECMO patients: 64.2% vs. 62.3%;  $p = 0.800$ . ECMO duration was significantly longer in the COVID group: 14 days vs. 10.5 days;  $p = 0.0038$ . Finally, Blazoski et al.<sup>22</sup> compared 28 COVID ECMO cases to 17 influenza ECMO cases. A comparison of duration of pre-ECMO mechanical ventilation was not performed. ECMO survival was significantly higher in the influenza group (94% vs. 68%;  $p = 0.040$ ) as was 30-day survival (76% vs. 54%), though the latter did not reach statistical significance ( $p = 0.130$ ). Length of the ECMO run was once again greater in the ECMO group versus the influenza group: 21.4 days vs. 12.2 days;  $p = 0.025$ . The findings of these seven studies are summarized in Table 6.

A consistent pattern that has emerged from prior COVID ECMO studies and corroborated by our findings is the longer duration of one or more disease course time segments in patients with COVID compared to those with ARDS due to influenza or other etiologies (see Tables 5 and 6). One non-ECMO study of critically ill patients from the US<sup>23</sup> has reported significantly longer evolution of symptoms before hospitalization in COVID compared to influenza (7 days vs. 3.5 days;  $p < 0.001$ ), but a study from China restricted to ARDS patients found no difference in the time interval from illness onset to diagnosis of ARDS between COVID and influenza: 8 days in both groups.<sup>24</sup> The picture offered by autopsy data regarding evolution of diffuse alveolar damage (DAD), the most common histological substrate of ARDS, in COVID is potentially instructive. DAD is described as progressing over a traditionally defined timeframe across three successive phases of presumably decreasing reversibility: exudative (first 7 days from onset), organizing (7–21 days), and fibrotic (beyond 21 days).<sup>25</sup> Autopsy studies of H1N1 influenza in the US suggest rapid progression to fatal DAD with antemortem duration of illness centered on 7–8 days<sup>26,27</sup> with phases of DAD observed at their expected time points: average time in hospital for deaths with exudative DAD was only 3.4 days, for deaths with progression to organizing DAD average time in hospital was 11.7 days, and for deaths with development of fibrosing DAD average time in hospital was 31.5 days. The microscopic chronology in COVID may be very different as indicated by at least one lung autopsy study performed in China.<sup>28</sup> Median antemortem duration of illness was over 30 days in cases still showing a predominance of exudative DAD and rose to over 40 days in cases of predominantly organizing or fibrotic DAD. Median time in hospital was 20 days in cases with predominantly acute DAD and over 30 days in those with predominantly organizing or fibrotic DAD. These numbers suggest a strikingly more indolent evolution through the phases of DAD and progression to fatal DAD in COVID as compared to influenza ARDS. They also may provide the histopathological context for the longer duration of pre-ECMO MV and the longer duration of ECMO prior to death or decannulation frequently observed in comparison studies between COVID and non-COVID ARDS. The aforementioned autopsy study by Li et al. is also of interest vis-à-vis ECMO candidate selection in COVID, which usually regards increasing duration of mechanical ventilation as at least a relative contraindication to ECMO.<sup>9</sup> The median duration of mechanical ventilation in cases with predominantly exudative and organizing DAD—substrates that are viewed as reversible—was 20 days and only slightly higher in cases with predominantly fibrotic DAD at 28 days with day ranges for all three phases showing considerable overlap. These results suggest that just like the onset and progression of DAD appears to be more indolent in COVID ARDS compared to influenza and other etiologies, the degree of reversibility of DAD in COVID ARDS may be more difficult to infer from time spent on mechanical ventilation before ECMO and also from time spent on ECMO. In support of this concept are

emerging data about so-called COVID ECMO “long haulers,” which one study defined as ECMO support for >30 days and reported survival of 7 out of 10 such patients without lung transplantation.<sup>29</sup> The median duration of ECMO support in these 10 patients was 85 days. ECMO runs of this length among survivors of non-COVID ECMO are typically not seen as shown in a recent small study demonstrating significantly longer ECMO runs in COVID ECMO survivors compared to non-COVID ECMO survivors despite near-universal presence of chest computed tomography features traditionally associated with fibrosis.<sup>30</sup> Our findings regarding ECMO “long haulers” in COVID ARDS compared to non-COVID ARDS echo this emerging literature.

Our study suffers from a number of important limitations, primary among which is its retrospective, single-center design. It includes a relatively small number of ECMO patients, particularly in the non-COVID group. The non-COVID group includes two patients with ARDS due to trauma, an etiology that some may view as unsuitable for comparison to COVID ARDS. Since they were treated during non-overlapping time periods, patients in the two groups were managed differently prior to ECMO cannulation, most strikingly with respect to prone positioning, which was not employed at all in non-COVID patients but was used in over one-third of COVID patients. Ours is an ECMO center without strict protocols, so ECMO practices at our institution would be difficult to compare to those of other institutions. The vast majority of the ECMO patients in the study were transferred from outlying hospitals, so data on the clinical course at the referring hospital (e.g., duration of symptoms prior to admission) could not be ascertained for some of these transfers. There was no practice at our institution to systematically screen ECMO recipients for thromboembolism, such as with CT angiography of the chest or doppler ultrasonography, leading to a very small denominator of tested patients, so we did not report the rate of this complication.

## Conclusion

To our knowledge, the present study is only the second to present a detailed analysis of outcomes of V-V ECMO initiated for ARDS secondary to COVID compared to V-V ECMO initiated for a mix of non-COVID etiologies of ARDS. Consistent with the other published study, we found no significant difference in survival to hospital discharge, duration of ECMO in survivors to decannulation, or serious complications. Recipients of ECMO for COVID had a significantly longer hospitalization prior to the need for MV. Prolonged ECMO was more common in the COVID ECMO group. Our findings suggest that COVID ARDS tends to evolve more slowly than non-COVID ARDS, leading to initiation of ECMO later in the hospital course and to unusually long ECMO runs in many patients.

## Declaration of Competing Interest

None of the authors has any relevant competing interest to disclose.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Acknowledgements

None.

## References

- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319–323.

2. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. [published correction appears in *Lancet*. 2009 Oct 17;374(9698):1330] *Lancet*. 2009;374:1351–1363.
3. Bellani G, Laffey JG, Pham T, et al. epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. [published correction appears in *JAMA*. 2016 Jul 19;316(3):350] [published correction appears in *JAMA*. 2016 Jul 19;316(3):350] *JAMA*. 2016;315:788–800.
4. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378:1965–1975.
5. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. [published correction appears in *JAMA*. 2019 Jun 11;321(22):2245] *JAMA*. 2018;320:2251–2259.
6. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international extracorporeal life support organization registry. *Lancet*. 2021;398:1230–1238.
7. Ramanathan K, Shekar K, Ling RR, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. [published correction appears in *Crit Care*. 2021 Oct 27;25(1):375] *Crit Care*. 2021;25:211.
8. Raasveld SJ, Delnoij TSR, Broman LM, et al. Extracorporeal membrane oxygenation in patients with COVID-19: an international multicenter cohort study. *J Intensive Care Med*. 2021;36:910–917.
9. Badulak J, Antonini MV, Stead CM, et al. Extracorporeal membrane oxygenation for COVID-19: updated 2021 guidelines from the extracorporeal life support organization. *ASAIO J*. 2021;67:485–495.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
11. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med*. 2006;34:1297–1310.
12. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189:1374–1382.
13. Karagiannidis C, Slutsky AS, Bein T, Windisch W, Weber-Carstens S, Brodie D. Complete countrywide mortality in COVID patients receiving ECMO in Germany throughout the first three waves of the pandemic. *Crit Care*. 2021;25:413.
14. Hall CA, Jacobs JP, Stammers AH, et al. Multi-institutional analysis of 505 COVID-19 patients supported with ECMO: predictors of survival. [published online ahead of print, 2022 Feb 18] *Ann Thorac Surg*. 2022;S0003.. -4975:00198-9.
15. Pieri M, Donatelli V, Calabrò MC, Scandroglio AM, Pappalardo F, Zangrillo A. Eleven years of venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: from H1N1 to SARS-CoV-2. Experience and perspectives of a national referral center. [published online ahead of print, 2021 Sep 24] *J Cardiothorac Vasc Anesth*. 2021;S1053.. -0770:00842-9.
16. Jäckel M, Rilinger J, Lang CN, et al. Outcome of acute respiratory distress syndrome requiring extracorporeal membrane oxygenation in COVID-19 or influenza: a single-center registry study. *Artif Organs*. 2021;45:593–601.
17. Cousin N, Bourel C, Carpentier D, et al. SARS-CoV-2 versus influenza-associated acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation support. *ASAIO J*. 2021;67:125–131.
18. Charlton M, Dashey S, Stubbs A, et al. Comparing SARS-CoV-2 and influenza A (H1N1)pdm09-infected patients requiring ECMO - a single-centre, retrospective observational cohort experience. *J Infect*. 2021;82:84–123.
19. Fanelli V, Giani M, Grasselli G, et al. Extracorporeal membrane oxygenation for COVID-19 and influenza H1N1 associated acute respiratory distress syndrome: a multicenter retrospective cohort study. *Crit Care*. 2022;26:34.
20. Raff LA, Reid TD, Johnson D, et al. Comparative outcomes between COVID-19 and influenza patients placed on veno-venous extracorporeal membrane oxygenation for severe ARDS. *Am J Surg*. 2022;223:388–394.
21. Shih E, Squiers JJ, DiMaio JM, et al. Outcomes of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome caused by COVID-19 versus influenza. [published online ahead of print, 2021 Jun 15]. *Ann Thorac Surg*. 2021;S0003.. -4975:01033-X.
22. Blazoski CM, Baram M, Yang Q, Hirose H. Outcomes of extracorporeal membrane oxygenation in influenza versus COVID-19 during the first wave of COVID-19. *J Card Surg*. 2021;36:3740–3746.
23. Cobb NL, Sathe NA, Duan KI, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus Influenza. *Ann Am Thorac Soc*. 2021;18:632–640.
24. Tang X, Du RH, Wang R, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. *Chest*. 2020;158:195–205.
25. Beasley MB. Acute lung injury-from cannabis to COVID. *Mod Pathol*. 2022;35:1–7.
26. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol*. 2010;177:166–175.
27. Gill JR, Sheng ZM, Ely SF, et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. *Arch Pathol Lab Med*. 2010;134:235–243.
28. Li Y, Wu J, Wang S, et al. Progression to fibrosing diffuse alveolar damage in a series of 30 minimally invasive autopsies with COVID-19 pneumonia in Wuhan, China. *Histopathology*. 2021;78:542–555.
29. Mohanka MR, Joerns J, Lawrence A, et al. ECMO long haulers: a distinct phenotype of COVID-19-associated ARDS with implications for lung transplant candidacy. *Transplantation*. 2022;106:e202–e211.
30. Russ M, Menk M, Graw JA, et al. COVID-19 patients require prolonged extracorporeal membrane oxygenation support for survival compared with non-COVID-19 patients. *Crit Care Explor*. 2022;4:e0671.