MAIN TEXT

# Outcomes by cannulation methods for venovenous extracorporeal membrane oxygenation during COVID-19: A multicenter retrospective study

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## Abstract

**Purpose:** To determine if a cannulation method for venovenous extracorporeal membrane oxygenation (V-V ECMO) is related to patient outcome.

**Methods:** A retrospective, multicenter study of adult patients (≥18 years old) placed on V-V ECMO for severe respiratory failure due to COVID-19 between March 1, 2020, to April 30, 2021. Patients were divided into the following three groups based on the initial cannulation method: (1) femoral vein-femoral vein or femoral vein-internal jugular vein (dual-site, C-DS), (2) single, dual-lumen cannula in internal jugular vein with tip positioned in the pulmonary artery (C-PA), and (3) single, dual-lumen cannula in internal jugular vein with tip positioned in the inferior vena cava (C-IVC). The primary outcome was in-hospital mortality assessed by a time-to-event analysis.

**Results:** Overall, 435 patients from 17 centers comprised the study cohort. C-DS was performed in 247 (57%, age: 49, IQR:39–57 years; 30% female) cases, 99 (23%, age: 53, IQR: 42–59 years; 26% female) received C-PA, and 89 (20%) patients got C-IVC (age: 46, IQR 35–54; 33% female). At 90-days, in-hospital mortality was 60% (C-DS), 41% (C-PA), and 61% (C-IVC), $p = 0.06$. After adjustment for clinical

characteristics, the likelihood of in-hospital mortality in comparison to C-DS, was lower with C-PA (aHR: 0.52, 95%CI 0.32–0.85, $p = 0.009$) and similar with C-IVC (aHR: 0.96, 95%CI 0.63–1.47, $p = 0.86$).

**Conclusion:** Catheter-directed flow into the PA bypassing the right ventricle with a single dual-lumen cannula is associated with reduced mortality during V-V ECMO for COVID-19. These findings are limited by residual confounding and site-clustering. Further investigation is urgently warranted with randomized studies.

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) continues to threaten global health and has led to over 5 million deaths worldwide.[1] SARS-CoV-2 targets the respiratory system with subsequent development of acute respiratory distress syndrome (ARDS), severe cytokine storm, and eventual cardiopulmonary collapse.[2,3] For these critically ill patients, extracorporeal membrane oxygenation (ECMO) support has served a vital role during the pandemic. Large observational studies show that in appropriately selected patients with refractory respiratory failure, ECMO can be a potentially life-saving modality. However, there is a need to further improve outcomes as in-hospital mortality ranges from 37% to 46%.[4–9]

In patients with severe respiratory failure, venovenous (V-V) ECMO can be placed through several methods. The most utilized approach is cannulation of two separate central veins, either femoral vein-femoral vein or femoral vein-internal jugular vein. Deoxygenated blood is drained into the ECMO circuit by an inflow cannula within a central vein. After oxygenation and removal of excess carbon dioxide, blood is returned by an outflow cannula to the other central venous site. V-V ECMO can also be performed by more recently developed methods involving a single catheter with two lumens serving as inflow and outflow tracks. Two separate types of dual-lumen catheters are available with tip positioning either at the inferior vena cava (IVC) or in the pulmonary artery.[10,11] When using a dual-lumen, bicaval V-V ECMO cannula, the drainage cannula empties blood from the superior vena cava (SVC) and the IVC. Blood is returned through a second lumen with an outlet in the right atrium and a jet directed to the tricuspid valve. In both dual-site and dual-lumen, bicaval configurations blood is drained and returned proximally to the right ventricle; thus, requiring adequate right ventricular function to drive blood through the lungs to the left ventricle. A third strategy involves cannulation of the right internal jugular vein by a single, dual-lumen catheter with the placement of the distal limb in the pulmonary artery. One lumen drains blood from the right atrium and the second lumen returns blood directly to the pulmonary artery. Dual-lumen catheters obviate the need for two separate cannulation sites and distal tip positioning at the pulmonary artery allows bypass of the right ventricle. However, these catheters require additional ultrasonographic and fluoroscopic imaging to confirm appropriate device positioning which may not be readily available in some centers.

Despite the availability and utilization of the aforementioned cannulation methods, there remains a gap in knowledge as to whether a particular approach is related to outcomes. Accordingly, we conducted a multicenter study to evaluate the association between cannulation methods for V-V ECMO and in-hospital mortality in patients with COVID-19.

## 2 | METHODS

### 2.1 | Study population

A multicenter, retrospective cohort study of patients aged ≥18 years, with COVID-19 confirmed by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, who were placed on ECMO anytime between March 1, 2020, and April 30, 2021. Patients who initially received venoarterial (V-A) or veno-venoarterial (V-VA) ECMO were excluded and only those cannulated as V-V ECMO were included. The cohort was divided into the following three groups based on the initial V-V ECMO cannulation method: (1) femoral vein-femoral vein or femoral vein-internal jugular vein (Dual-Site, C-DS), (2) single, dual-lumen cannula in internal jugular vein with tip positioned in the pulmonary artery (C-PA; Protek Duo, Livanova), and (3) single, dual-lumen cannula in internal jugular vein advanced through the SVC into the right atrium with tip positioned in the IVC (C-IVC; Crescent, Medtronic, or Avalon, Avalon Laboratories).

### 2.2 | Data source and collection

Investigators at the data coordination site at Montefiore Medical Center invited centers for participation by

directly contacting surgical directors of mechanical circulatory support programs. A data use agreement was mutually agreed upon between every participating center and the data coordinating site at Montefiore Medical Center, Albert Einstein College of Medicine. The study was approved by the institutional review board (IRB) at the Albert Einstein College of Medicine and informed consent was waived (IRB protocol number: 2020-11375, approved on April 5, 2020). The study was also approved by the IRBs at all the participating centers.

A data capture tool was created using REDCap for record entry by the participating centers. All data were anonymized. Data fields included demographics, laboratory parameters, ECMO characteristics, and patient outcomes. Details of methodology to confirm data entry accuracy and site training have been previously reported.[5] Briefly, sites were individually familiarized with the data capture tool, and consistency was ensured by continuous technical support provided by the corresponding author at the data coordination center throughout the data collection period. The data capture fields contained checks for validity such as input masks and range rules for date fields and branching logic. Data consistency was maintained through built-in drop boxes with standardized responses. Records were manually inspected for data entry errors, such as those in date temporality, by the data coordination center and rectified by sites prior to analysis.

## 2.3 | Outcomes

The primary outcome was in-hospital mortality after V-V ECMO placement assessed by a time to event analysis at 90 days. Kaplan Meier curves were used to compare the probability of in-hospital mortality between groups. Follow-up began at the time of ECMO placement and was completed until the time of discharge/transfer from the ECMO center or in-hospital mortality. Patients that remained hospitalized at the ECMO center as of April 30, 2021, were censored. Cumulative incidence was administratively censored at 90 days after ECMO placement. Patients were not censored at the time of any changes in ECMO configuration and retained their initial group classification to adhere to principles of original treatment intention. Additional outcomes that were reported include the proportion of patients with complications that occurred after ECMO placement including secondary infections, deep venous thrombosis, stroke, limb ischemia, bleeding requiring transfusion, changes in ECMO configuration, and renal failure requiring dialysis. Causes of death during hospitalization were also reported.

## 2.4 | Statistical analysis

Continuous data are displayed as mean ± SD or median Q1–Q3 interquartile range (IQR) and categorical data are shown as proportions. Depending on the distribution, one-way ANOVA or Kruskal–Wallis test was used to compare continuous variables. Categorical variables were compared using chi-square test. Table S3 shows the number of observations captured for baseline characteristics. Cox-multivariable regression was used to determine the adjusted association between in-hospital mortality and cannulation methods. C-DS served as the reference group. The proportionality hazard assumption was confirmed by Schoenfeld goodness-of fit-tests. Variables included in the Cox adjustment model were those known to have an association with mortality during COVID-19 based on existing literature, captured for >90% of cases, and a univariate association with cannulation method at a $p < 0.1$. The adjustment model included the following variables: age, sex, body mass index, cardiopulmonary resuscitation prior to ECMO, transferred to ECMO hospital, prone position prior to ECMO, time from symptoms to intubation, time from intubation to ECMO, and $PCO_2$ before ECMO placement, use of intravenous steroids. We also included pre-COVID-19 center volume of ECMO cases in 2019 as a center-level adjustment variable. No data were imputed and the Cox-multivariable model contained 379 (87%) of the possible 435 cases. To assess for selection bias related to cannulation method, we conducted a falsification analysis as described previously.[12] In this falsification analysis, we compared negative control outcomes of bleeding requiring transfusion and renal failure requiring dialysis among groups with adjustment of the covariates mentioned above. As a sensitivity analysis, a separate multivariable regression model was made with the addition of established markers of disease severity including $PaO_2$:$FiO_2$ ratio, creatinine, lactic acid, and D-dimer. A $p < 0.05$ was considered statistically significant. Stata v16 (Stata Corp, LLC) and SAS software v9.4 (SAS Inc, Cary NC) were used for all statistical analysis.

## 3 | RESULTS

### 3.1 | Patient characteristics

Overall, 435 patients with COVID-19 were initially cannulated as V-V ECMO in 17 centers and comprised the study cohort. They were 49 (IQR: 38–57) years old, 128 (29%) were female and 114 (26%) were classified as Hispanic. Within the entire cohort, 261 (61%; percentages from here onwards are calculated from the available observations as noted in Table S3) had pre-existing comorbidities.

Of these patients with pre-existing conditions, 168 (64%) had hypertension and 126 (48%) had diabetes mellitus. Two-hundred thirty-four (54%) patients were transferred from another center for ECMO placement and 53 (13%) received cardiopulmonary resuscitation before ECMO placement. Patients presented 7 (IQR: 4–13) days after symptom onset and were placed on V-V ECMO 3 (IQR: 1–6) days after intubation. Inflammatory markers including ferritin (1127, IQR: 582–1981 ng/ml), C-reactive protein (20, IQR: 8–49 mg/dl), D-dimer (730, IQR: 4–4310 μg/ml) were highly elevated prior to ECMO placement.

Within the entire cohort, 247 (57%) patients were cannulated with C-DS, 99 (23%) received C-PA and 89 (20%) had C-IVC (Figure 1). Most characteristics were similar between groups with a few notable exceptions (Table 1). Patients with C-PA were older (C-PA:53, IQR 42–59; C-DS: 49, IQR 38–57; C-IVC: 46, IQR 35–54 years old, $p = 0.01$). More patients with C-DS had CPR (C-DS: 17%, C-PA: 6%, C-IVC:8%, $p = 0.01$) before ECMO cannulation in comparison to the other cannulation methods. Proportionally more patients with C-PA received steroids, but there were no significant differences in administration of other potential COVID-19 therapeutics (Table S1). The distribution of the cannulation method by the center is shown in Table S2. It is notable that the majority of the patients at every site were cannulated with the same method.

## 3.2 | Outcomes

At 90 days, 202 (46%) patients had been discharged alive, 198 (46%) had expired, 11 (3%) were still hospitalized but off ECMO, and 24 (6%) were still on ECMO support. The probability of 90 day in-hospital mortality of the entire cohort of VV-ECMO patients was 55% (95% CI: 48–61). In unadjusted analysis, the probability of 90 days in-hospital mortality in groups with each type of cannulation method was as follows: C-DS: 60%, 95% CI: 51–68, C-PA: 41%, 95% CI: 30–54, C-IVC: 61%, 95% CI: 48–75, $p = 0.06$ (Figure 2). After adjustment for clinical and center-level characteristics, the likelihood of in-hospital mortality in comparison to C-DS was lower with C-PA (aHR: 0.52, 95% CI: 0.32–0.85, $p = 0.009$) and similar with C-IVC (aHR: 0.96, 95% CI: 0.63–1.48, $p = 0.86$, Figure 3). Findings remained similar after inclusion of markers of disease severity including baseline $PaO_2:FiO_2$ ratio, creatinine, lactic acid, and D-dimer to the multivariable adjustment model (C-PA: aHR 0.52, 95% CI: 0.29–0.94, $p = 0.029$; C-IVC: aHR 1.10, 95% CI: 0.67–1.77, $p = 0.72$, Figure S1). The overall duration of ECMO was longer for patients with C-PA at 35 (IQR: 18–70) days in comparison to C-DS (19, IQR: 9–38) and C-IVC (25, IQR: 14–42) days. This may relate to a greater proportion of patients that survived in the C-PA group and did not have curtailment of device support due to expiration or withdrawal of care. In addition, patients cannulated as C-PA spent numerically less time on mechanical ventilation in comparison to the other groups. Patients supported by C-PA were more commonly discharged to home (C-PA: 57%, C-DS: 33%, C-IVC: 22%, $p = 0.02$).

## 3.3 | Complications during ECMO

In the entire cohort, complications such as bacterial pneumonia (40%), bacteremia (37%), bleeding requiring
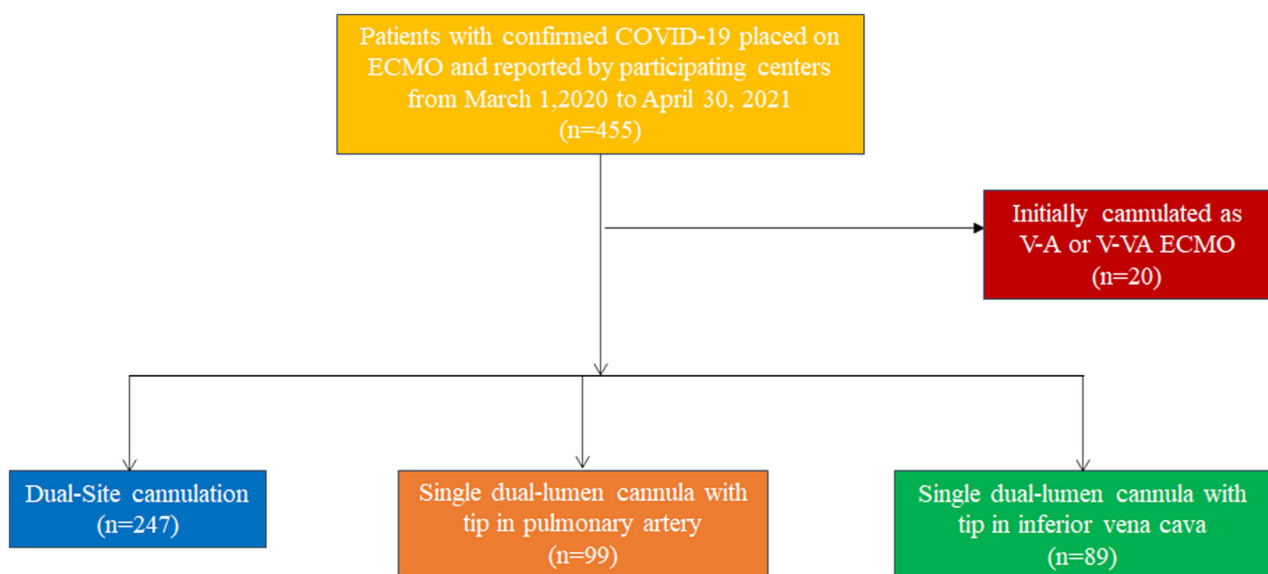


**FIGURE 1** STROBE diagram showing the formation of study groups. ECMO, extracorporeal membrane oxygenation; V-A, venoarterial; V-VA, venovenous arterial [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** Baseline characteristics prior to ECMO placement

| Clinical characteristics | All patients (n = 435) | C-DS (n = 247) | C-PA (n = 99) | C-IVC (n = 89) | p value[*] |
|---|---|---|---|---|---|
| Age (years) | 49 (38–57) | 49 (39–57) | 53 (42–59) | 46 (35–54) | 0.01 |
| Sex (n, %) | | | | | |
| Female | 128 (29) | 73 (30) | 26 (26) | 29 (33) | 0.64 |
| Male | 307 (71) | 174 (70) | 73 (74) | 60 (67) | |
| BMI (kg/m$^2$) | 33 (29–39) | 32 (29–38) | 33 (29–39) | 34 (30–40) | 0.02 |
| Race/ethnicity (n, %) | | | | | 0.35 |
| Asian | 22 (5) | 16 (6) | 3 (3) | 3 (3) | |
| Hispanic | 114 (26) | 59 (24) | 45 (45) | 10 (11) | |
| Non-Hispanic Black | 69 (16) | 32 (13) | 21 (21) | 16 (18) | |
| Non-Hispanic White | 107 (25) | 55 (22) | 29 (29) | 23 (26) | |
| Other/unknown | 123 (28) | 85 (34) | 1 (1) | 37 (42) | |
| Pre-existing comorbidities (n, %) | 261 (61) | 153 (62) | 59 (60) | 49 (58) | 0.76 |
| Hypertension (n, %) | 168 (65) | 97 (65) | 42 (72) | 29 (59) | 0.34 |
| Diabetes mellitus (n, %) | 126 (50) | 74 (51) | 31 (55) | 20 (41) | 0.31 |
| Chronic respiratory disease (n, %) | 11 (4) | 8 (5) | 0 (0) | 3 (6) | 0.18 |
| Malignant neoplasm (n, %) | 5 (2) | 3 (2) | 1 (2) | 1 (2) | 0.99 |
| Coronary artery disease (n, %) | 14 (6) | 8 (5) | 5 (9) | 1 (2) | 0.32 |
| CPR prior to ECMO (n, %) | 53 (13) | 40 (17) | 6 (6) | 7 (8) | 0.01 |
| Transferred to ECMO hospital (n, %) | 234 (54) | 121 (49) | 59 (60) | 54 (61) | 0.11 |
| Prone positioning (n, %) | 329 (77) | 206 (85) | 59 (60) | 64 (74) | <0.01 |
| Time from symptom onset to admission (days) | 7 (4–13) | 7 (4–14) | 9 (6–16) | 5 (3–9) | 0.37 |
| Time from admission to Intubation (days) | 1 (0–6) | 1 (0–5) | 0 (1–5) | 3 (0–8) | 0.06 |
| Time from intubation to ECMO (days) | 3 (1–6) | 3 (1–6) | 2 (1–5) | 3 (1–7) | 0.08 |
| Systolic blood pressure (mm Hg) | 113 (102–128) | 112 (100–125) | 115 (103–130) | 116 (108–130) | 0.02 |
| Diastolic blood pressure (mm Hg) | 64 (57–72) | 62 (55–70) | 66 (58–75) | 67 (60–75) | 0.01 |
| Vasopressors (%) | 251 (61) | 147 (64) | 57 (58) | 47 (55) | 0.34 |
| Blood gas parameters | | | | | |
| pH | 7.3 (7.2–7.4) | 7.3 (7.2–7.4) | 7.3 (7.2–7.4) | 7.3 (7.3–7.4) | 0.83 |
| PaO$_2$/FiO$_2$ | 73 (59–93) | 77 (62–98) | 69 (59–87) | 70 (55–89) | 0.57 |
| PaCO$_2$ (mm Hg) | 58 (46–72) | 60 (48–73) | 57 (46–69) | 53 (41–65) | 0.02 |
| Laboratory parameters | | | | | |
| White blood cells (×10$^3$/μl) | 14 (10–20) | 14 (9–19) | 14 (10–20) | 14 (10–20) | 0.51 |
| Platelet count (×10$^3$/μl) | 248 (188–334) | 244 (182–339) | 268 (192–370) | 242 (184–307) | 0.71 |
| Lactic acid (mmoles/L) | 1.7 (1.3–2.5) | 1.8 (1.4–2.6) | 1.7 (1.1–2.2) | 1.7 (1.2–2.4) | 0.58 |
| Creatinine (mg/dl) | 0.9 (0.6–1.4) | 0.9 (0.6–1.5) | 0.9 (0.7–1.2) | 0.8 (0.6–1.3) | 0.19 |
| International normalized ratio | 1.2 (1.1–1.3) | 1.2 (1.1–1.3) | 1.1 (1.0–1.2) | 1.2 (1.1–1.3) | 0.86 |
| Total bilirubin (mg/dl) | 0.6 (0.4–0.8) | 0.6 (0.4–0.8) | 0.6 (0.4–0.7) | 0.5 (0.4–0.8) | 0.77 |
| Ferritin (ng/ml) | 1127 (582–1981) | 1211 (650–1981) | 1029 (505–1781) | 1052 (549–2067) | 0.59 |
| C-Reactive protein (mg/dl) | 20 (8–49) | 26 (10–89) | 13 (9–27) | 23 (7–41) | 0.04 |

(Continues)

**TABLE 1** (Continued)

| Clinical characteristics | All patients (n = 435) | C-DS (n = 247) | C-PA (n = 99) | C-IVC (n = 89) | p value* |
|---|---|---|---|---|---|
| D-Dimer (μg/ml) | 730 (4–4310) | 291 (3.5–2746) | 3790 (1550–9090) | 5 (1.87–182) | 0.07 |
| Fibrinogen (mg/dl) | 602 (454–718) | 666 (487–748) | 598 (409–717) | 510 (396–670) | 0.28 |
| Lactate dehydrogenase (U/L) | 618 (456–853) | 587 (440–891) | 629 (493–808) | 642 (446–844) | 0.39 |
| Procalcitonin (ng/ml) | 0.56 (0.2–1.5) | 0.63 (0.1–1.6) | 0.49 (0.2–1.6) | 0.51 (0.2–1.1) | 0.23 |

*Note:* Number observations for each variable are listed in Table S3. Percentages represent the proportion of reported observations. Continuous variables are displayed as median (Q1–Q3).

*Unadjusted chi-square or one-way ANOVA p value comparing cannulation groups. Blood gas parameters were measured prior to ECMO placement.
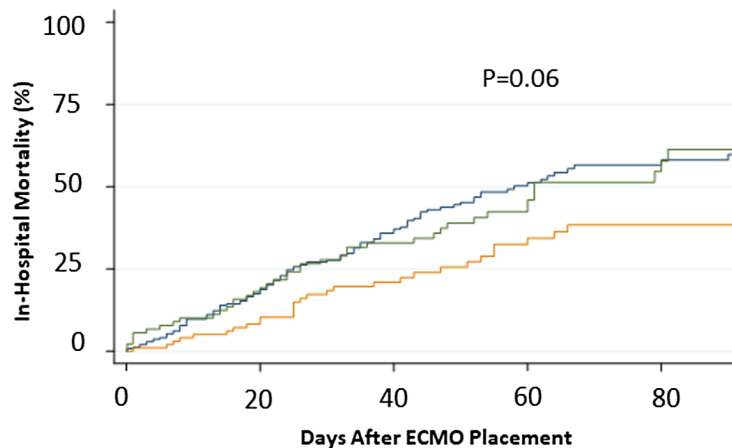


**FIGURE 2** Kaplan Meier curves comparing in-hospital mortality in patients with COVID-19 supported by venovenous extracorporeal membrane oxygenation (V-V ECMO). C-DS, dual-site cannulation; C-IVC, single dual-lumen cannula with tip positioned in the inferior vena cava; C-PA, single dual-lumen cannula with tip positioned in the pulmonary artery [Color figure can be viewed at wileyonlinelibrary.com]

transfusion (78%), and renal failure requiring replacement therapy (47%) were commonly reported (Table 2). Forty-nine patients (11%) had a stroke. Thirty-eight percent of the patients expired while on ECMO and the most common cause of death was multiorgan failure (36%). Only 26 (6%) patients had changes in ECMO circuit configuration.

## 3.4 | Falsification analysis

The proportion of patients with bleeding requiring transfusion was numerically higher in those cannulated as C-PA (88%), in comparison to C-DS (72%) and C-IVC (81%). However, after multivariable adjustment, there was no difference between groups (C-PA: aOR 1.43, 95% CI: 0.53–3.83, $p = 0.48$; C-IVC: aOR 1.47, 95% CI: 0.63–3.45, $p = 0.38$; in comparison to C-DS). Similarly, there was no difference in renal failure requiring dialysis in C-PA (aOR:0.67, 95% CI: 0.31–1.47, $p = 0.32$) and C-IVC (aOR:0.68, 95% CI: 0.34–1.35, $p = 0.27$) in comparison to C-DS. These findings suggest that the noted differences in

hospital mortality were less likely related to selection bias in cannulation strategy.

## 4 | DISCUSSION

The principal findings of this investigation comparing three separate cannulation methods of V-V ECMO during COVID-19 and outcomes are as follows: (1) a single dual-lumen catheter with tip positioned in the pulmonary artery was associated with lower in-hospital mortality in comparison to a platform with dual-site cannulation and patients supported in this manner were more frequently discharged home, (2) no difference in mortality was noted between cannulation through a single dual-lumen catheter with tip positioned in the inferior vena cava and a dual-site method, (3) bleeding, secondary infection, and renal failure requiring replacement therapy were commonly encountered adverse events, and (4) older age, cardiopulmonary resuscitation, and lower pre-COVID-19 center volume remained associated with death irrespective of
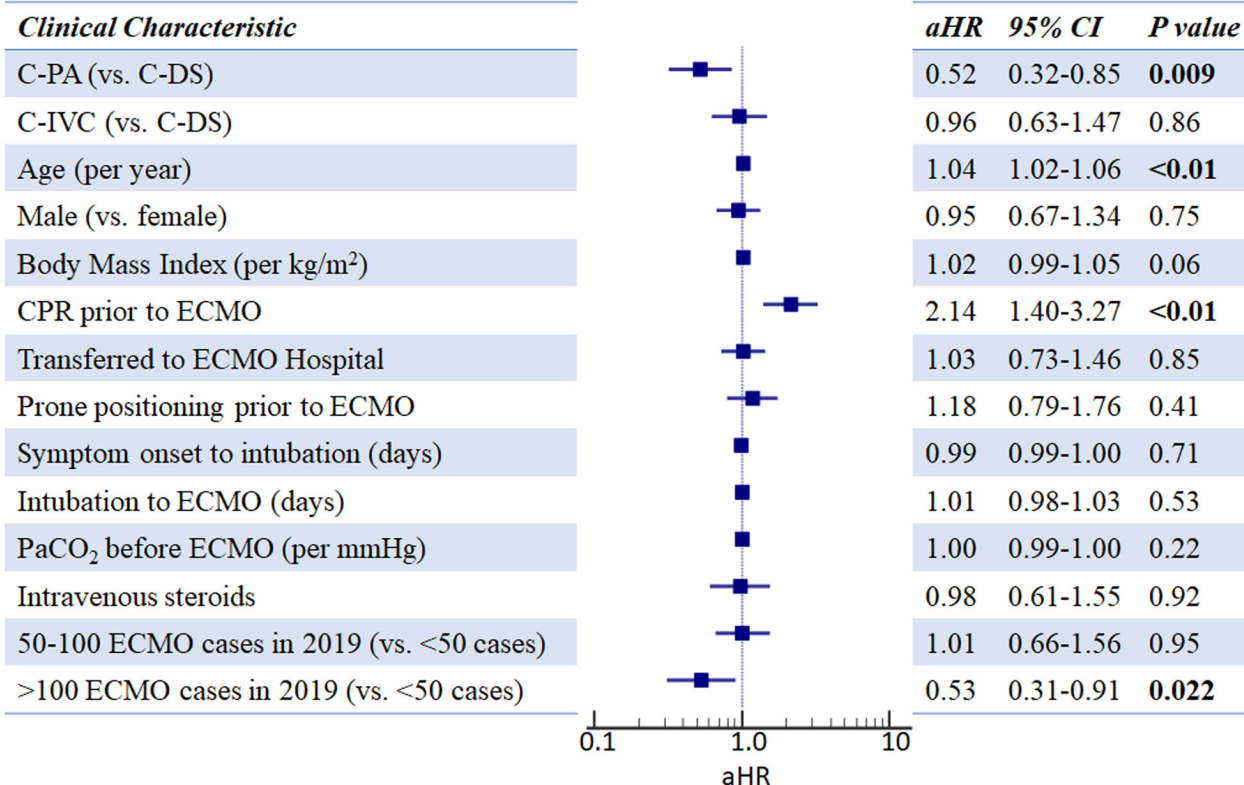
| Clinical Characteristic | | aHR | 95% CI | P value |
|---|---|---|---|---|
| C-PA (vs. C-DS) | | 0.52 | 0.32-0.85 | **0.009** |
| C-IVC (vs. C-DS) | | 0.96 | 0.63-1.47 | 0.86 |
| Age (per year) | | 1.04 | 1.02-1.06 | **<0.01** |
| Male (vs. female) | | 0.95 | 0.67-1.34 | 0.75 |
| Body Mass Index (per kg/m$^2$) | | 1.02 | 0.99-1.05 | 0.06 |
| CPR prior to ECMO | | 2.14 | 1.40-3.27 | **<0.01** |
| Transferred to ECMO Hospital | | 1.03 | 0.73-1.46 | 0.85 |
| Prone positioning prior to ECMO | | 1.18 | 0.79-1.76 | 0.41 |
| Symptom onset to intubation (days) | | 0.99 | 0.99-1.00 | 0.71 |
| Intubation to ECMO (days) | | 1.01 | 0.98-1.03 | 0.53 |
| PaCO$_2$ before ECMO (per mmHg) | | 1.00 | 0.99-1.00 | 0.22 |
| Intravenous steroids | | 0.98 | 0.61-1.55 | 0.92 |
| 50-100 ECMO cases in 2019 (vs. <50 cases) | | 1.01 | 0.66-1.56 | 0.95 |
| >100 ECMO cases in 2019 (vs. <50 cases) | | 0.53 | 0.31-0.91 | **0.022** |

0.1        1.0        10
aHR

**FIGURE 3**  Cox-multivariable model showing the association between clinical and center covariables with in-hospital mortality. aHR, adjusted hazard ratio; C-DS, dual-site cannulation; C-IVC, single dual-lumen cannula with tip positioned in the inferior vena cava; C-PA, single dual-lumen cannula with tip positioned in the pulmonary artery; CPR, cardiopulmonary resuscitation. ECMO, extracorporeal membrane oxygenation [Color figure can be viewed at wileyonlinelibrary.com]

cannulation methods. Although we observed a lower in-hospital mortality in cases with C-PA cannulation, patients in this group may have been less sick at baseline in comparison to those cannulated with other methods. This is notable as patients with C-PA were cannulated, on average, 1 day earlier following mechanical ventilation and a lower proportion of them had antecedent cardiopulmonary arrest. In addition, as most of the patients receiving C-PA were at the same center, unmeasured site-related effects such as emphasis on earlier extubation may also impact the findings. We attempted to adjust for these factors with their inclusion in the multivariable regression model. However, residual confounding and center-clustering reduce the rigor of the findings, which can only be confirmed by randomized clinical trials.

Notwithstanding unmeasured patient- and center-level differences in management, it is plausible that bypassing the right ventricle with catheter-directed flow to the pulmonary artery could be beneficial during ARDS. Pulmonary vascular resistance (PVR) can increase during ARDS by a variety of pathways including vasoconstriction by hypoxia or other mediators such as endothelins, thromboxane A2, or leukotrienes and mechanical compression by interstitial edema.[13] Moreover, thromboembolic events

and microthrombi, known to occur commonly during COVID-19,[14] cause intravascular obstruction and raise PVR. These elevations in PVR increase afterload to cause right ventricular dysfunction, which is related to poorer outcomes during ARDS.[15] Clinical right ventricular dysfunction is difficult to detect by echocardiography and without invasive hemodynamics, as the use of pulmonary artery catheters is not common during ARDS or V-V ECMO. An a priori approach utilizing a right ventricular assist device directing flow to the pulmonary artery to limit recirculation into the right ventricle may preclude overt or insidious effects of right ventricular dysfunction and could potentially lead to improved clinical outcomes.

Site-level clustering of cannulation method may impact outcomes but ultimately cannot be separated from the strategy itself. The use of specific cannulation strategies is typically dictated by numerous parameters such as availability of equipment, imaging modality, trained personnel, center experience, and preference. This was evident as the majority of the patients at every site were cannulated with the same method. Dual-site cannulation is historically a more established method of V-V ECMO support and can be implemented rapidly by most centers. Indeed, C-DS was the most performed

| Complications and outcomes | All patients (n = 435) | Dual-site (n = 247) | PA (n = 99) | IVC (n = 89) | p value* |
|---|---|---|---|---|---|
| Bacterial pneumonia | 172 (40) | 100 (41) | 33 (33) | 39 (44) | 0.31 |
| Bacteremia | 161 (37) | 78 (32) | 48 (49) | 35 (39) | 0.01 |
| Central line infection | 22 (5) | 10 (4) | 4 (4) | 8 (9) | 0.17 |
| Urinary tract infection | 54 (12) | 31 (13) | 13 (13) | 10 (11) | 0.92 |
| Deep vein thrombosis | 56 (14) | 36 (15) | 11 (12) | 9 (10) | 0.43 |
| Hemorrhagic stroke | 39 (9) | 17 (7) | 14 (14) | 7 (8) | 0.10 |
| Ischemic stroke | 10 (2) | 3 (1) | 3 (3) | 4 (5) | 0.19 |
| Limb ischemia | 23 (6) | 16 (7) | 4 (4) | 3 (3) | 0.42 |
| Bleeding requiring transfusion | 250 (78) | 117 (72) | 73 (88) | 60 (81) | 0.01 |
| Change in ECMO configuration (n, %) | 26 (6) | 16 (7) | 3 (3) | 7 (8) | 0.36 |
| Renal replacement therapy (n, %) | 151 (47) | 82 (50) | 41 (50) | 28 (28) | 0.19 |
| Expired on ECMO (n, %) | 165 (38) | 88 (35) | 38 (38) | 39 (43) | 0.30 |
| Cause of death (n, %) | | | | | <0.01 |
|   Cardiac failure | 19 (10) | 17 (15) | 0 (0) | 2 (5) | |
|   Hemorrhagic shock | 7 (4) | 4 (4) | 1 (3) | 2 (5) | |
|   Liver failure | 1 (1) | 0 (0) | 0 (0) | 1 (2) | |
|   Multi-organ failure | 69 (36) | 34 (31) | 20 (51) | 15 (37) | |
|   Respiratory failure | 23 (12) | 19 (17) | 2 (5) | 2 (5) | |
|   Septic shock | 13 (7) | 6 (5) | 6 (15) | 1 (2) | |
|   Stroke | 23 (12) | 10 (9) | 8 (21) | 5 (12) | |
|   Other | 35 (18) | 20 (18) | 2 (5) | 13 (32) | |
| Hospitalization metrics (days) | | | | | |
|   Duration of hospitalization | 42 (26–67) | 40 (25–61) | 48 (29–84) | 51 (28–78) | 0.04 |
|   Duration of mechanical ventilation | 32 (17–55) | 32 (18–53) | 28 (7–58) | 34 (18–55) | 0.10 |
|   Duration of ECMO | 23 (11–43) | 19 (9–38) | 35 (18–70) | 25 (14–42) | <0.01 |
| Discharge location (n, %) | | | | | 0.02 |
|   Home | 73 (36) | 39 (33) | 25 (57) | 9 (22) | |
|   Rehab | 82 (40) | 48 (41) | 15 (35) | 19 (44) | |
|   Facility with ventilator support | 17 (9) | 11 (10) | 1 (3) | 5 (13) | |
|   Other health care facility | 32 (15) | 20 (17) | 2 (4) | 10 (22) | |

*Note:* The number of observations reported: Deep vein thrombosis 414, hemorrhagic stroke 412, ischemic stroke 411, limb ischemia 412, bleeding requiring transfusion 320, change in ECMO configuration 413, renal replacement therapy 320, discharge location 213; Percentages represent the proportion of reported observation. Hospitalization metrics reported as median, Q1–Q3.

*Unadjusted chi-square or one-way ANOVA p value comparing cannulation groups.

approach in this analysis and in other experiences with COVID-19.[6] Superiority of neck only cannulation is conceivable as it promotes patient mobility and evades femoral cannulation. However, a lack of fluoroscopy and transesophageal echocardiography, which are needed to confirm appropriate tip positioning in the pulmonary artery[10] could limit the use of the C-PA approach. Similarly, the absence of ultrasound needed to confirm correct tip positioning limits the use of the C-IVC cannulation. Thus, any potential advantages of dual-lumen catheters with tip positioning in the pulmonary artery must be balanced by the simplicity of the two cannula, femoro-femoral, or femoro-jugular approach which can be rapidly performed at the bedside.

This study has several limitations. Given the retrospective and non-randomized study design, we cannot determine the efficacy of a particular cannulation strategy. Although a center-level adjustment for experience was made with pre-COVID-19 center volume, other unmeasured site-specific practice patterns post-ECMO placement may impact outcomes. Results from participating centers may not be reflective of those from sites with lesser experience with specific cannulation methods and differential resource availability. There were no standardized criteria for patient selection, cannulation method, or management among the participating centers. It is plausible that patients receiving C-PA were less sick so they could undergo fluoroscopic placement, but differences in outcomes persisted after adjustment for markers of disease severity including $PaO_2$:$FiO_2$ ratio, creatinine, lactic acid, and D-dimer. Moreover, falsification analyses did not indicate a selection bias in cannulation strategy, which appeared to be based on overall site preference rather than patient-level characteristics. Lastly, a deeper phenotypic characterization of the study groups with covariates such as baseline echocardiographic and invasive hemodynamic parameters was not available.

In summary, our findings indicate that in patients with refractory respiratory failure from COVID-19, V-V ECMO support through a single, dual-lumen catheter with directed outflow into the pulmonary artery was associated with reduced in-hospital mortality in comparison to dual-site cannulation. These findings remain limited by residual confounding and site-level effects and are only hypothesis generating. Further prospective and randomized studies are urgently needed to determine the optimal method of cannulation to improve outcomes of this lifesaving modality in patients with ARDS from COVID-19 and beyond.

## AUTHOR CONTRIBUTIONS
Omar Saeed, Louis H. Stein, and Scott Silvestry contributed to study conception and design, data analysis and interpretation, and drafting the manuscript. Nicolas Cavarocchi, Antone J. Tatooles, Asif Mustafa, Ulrich P. Jorde, Chikezie Alvarez, Jason Gluck, Paul Saunders, Sunil Abrol, Abe De Anda Jr., and Daniel J. Goldstein contributed to study design, data interpretation, and critical review of the manuscript.

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