Combined Use of ECMO, Prone Positioning, and APRV in the Management of Severe COVID-19 Patients

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ABSTRACT

BACKGROUND: Severe COVID-19-associated Acute Respiratory Distress Syndrome (ARDS) may warrant extracorporeal membrane oxygenation (ECMO). We evaluated the safety and physiologic changes in oxygenation and hemodynamic profile during ECMO, prone positioning, and the two modalities combined in patients receiving veno-venous (VV) ECMO.

METHODS: Cohort study of consecutive adult patients with COVID-19-associated ARDS requiring VV-ECMO, classified into three groups: ECMO support only; Prone positioning only; and Prone positioning during ECMO. We collected hemodynamic, respiratory and ventilation variables as follows: pre-treatment, 1, 6, and 24 h post-treatment, and documented treatment-related complications. On-treatment variables were compared with pre-treatment using one-sample paired t-test with Bonferroni correction.

RESULTS: Fourteen patients (mean age 48.1 [SD 9.3] years, male [100%]) received VV-ECMO. Of those, 10 patients had data during prone positioning alone and seven had data while proned on ECMO. While on ECMO, patients had improvement in oxygen saturation, PaO_2/FiO_2 ratio, and minute ventilation up to 24 h post-treatment. Vasopressor requirements increased with ECMO at 1 h and 24 h post-treatment. Prone positioning was not associated with clinically significant hemodynamic or respiratory changes, either alone or during ECMO support. All patients sustained deep tissue injuries, but only those on the face or chest were related to prone positioning. Three patients required cannula replacement. In-hospital mortality was 43%.

CONCLUSIONS: VV-ECMO and prone positioning in patients with COVID-19 ARDS was overall well-tolerated; however, physiologic improvements were marginal, and patients sustained deep tissue injuries. Although this was a selected population with high mortality, our data call into question the benefits of these management modalities in this severe COVID-19 population.

KEYWORDS: SARS-CoV-2, acute respiratory distress syndrome, mechanical ventilation, extra-corporeal membrane oxygenation

Background

The ongoing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has resulted in an overwhelming number of ICU admissions, which has not only posed a significant challenge for the ICU community but has also placed a significant strain on healthcare resources. A very resource intensive intervention often used as a rescue in the escalation of Acute Respiratory Distress Syndrome (ARDS) therapy is extracorporeal membrane oxygenation (ECMO). In the context of the current pandemic, there have been varying reports regarding the role of ECMO in the management of COVID-19 associated ARDS. An early observational study conducted in China reported no mortality difference in COVID-19 patients with ARDS, comparing ECMO (57%) with mechanical ventilation (63%).[1] On the other hand, a pooled analysis reported a 94% mortality in COVID-19 patients requiring ECMO versus 71% in patients who received mechanical ventilation, while a study from the international ELSO Registry reported an estimated 90-day in-hospital mortality rate of 38% after ECMO initiation.[2,3]

During the COVID-19 pandemic, we have employed an unconventional mix of therapeutic modalities to overcome the challenges of managing COVID-19 patients with severe, refractory ARDS, where ARDS in this population of patients has been described as phenotypically different from typical ARDS.[4] Prone positioning in the setting of VV-ECMO for treatment of patients with typical ARDS has been previously studied with conflicting results, with two retrospective studies reporting improved survival in the group of patients proned and two other studies that did not report improved survival.[5–8]

With limited available reports on the use of prone positioning while on VV-ECMO in typical ARDS, a majority being retrospective studies, and even fewer reports in the setting of COVID-19 ARDS specifically, we reviewed the data of a

cohort of consecutive patients treated with ECMO, prone positioning, and airway pressure release ventilation (APRV) due to COVID-19 ARDS. Our primary goal was to take a closer look at the physiologic changes associated with the initiation of these interventions and to determine the extent of improvement in hemodynamic and oxygenation profiles associated with these advanced interventions.

Methods

We retrospectively reviewed the medical record to identify all patients with COVID-19-associated ARDS who were admitted to the ICU at Yale New Haven Hospital (YNHH) between March 01, 2020 and May 31, 2020 and managed with VV-ECMO. The Yale University Institutional Review Board reviewed and approved the study protocol for this medical record review and waived the need for informed consent.

Study Population

Eligibility criteria included patients over 18 years of age, who tested positive for COVID-19 and required VV-ECMO for severe hypoxemia.

ECMO Management

ECMO indications included: 1) Hypoxic failure necessitating Acute Respiratory Distress Syndrome network (ARDSnet) protocol[9] nearing 48 h (PaO$_2$/FiO$_2$ ratio less than 100 mm Hg); 2) Severe hypercarbia in the presence of hypoxia with pH less than 7.2 and not amenable to ventilatory adjustments or renal adjustments; and 3) Presence of the two indications above despite chemical paralysis, prone positioning, and/or ARDSnet protocol, nearing twelve hours with plateau pressure greater than 30 and respiratory rate greater than 35.

Absolute ECMO contraindications included: 1) Salvage ECMO as emergent intervention (patient not expected to survive despite ECMO); 2) Non-recoverable neurological injury; 3) Cardiac arrest lasting greater than nine minutes prior to achieving return of spontaneous circulation (see relative contraindications for more details); 4) Greater than 65 years of age; 5) Pre-existing malignancy (excluding prostate cancer or cured cancer with survival free of cancer greater than five years), currently receiving chemotherapy, immunosuppression therapy, coagulation disorder (thrombotic or blood dyscrasia); 6) Pre-existing severe advanced pulmonary disease; 7) Liver fibrosis, liver failure, portal hypertension; 8) Advanced dementia, extreme frailty, failure to thrive prior to COVID-19; 9) ongoing bloodstream infection; and 10) Multisystem organ failure involving more than two organs.

Relative ECMO contraindications included: 1) Cardiac arrest, unless patient is less than 50 years old (with no pre-existing conditions that will preclude ECMO) and return of

spontaneous circulation is achieved within nine minutes; 2) Duration of intubation greater than seven days; 3) Neurological event (stroke/intracerebral hemorrhage/subdural hematoma) except recovered prior non-disabling neurological event in a patient under 50 years old (with no pre-existing conditions that will preclude ECMO); 4) Chronic renal failure requiring hemodialysis; 5) Liver dysfunction excluding stable synthetic hepatic function; 6) Symptomatic or untreated peripheral vascular disease (PVD); and 7) Septic shock with vasoplegia resistant to high dose pressors.

Procedural contraindications included: 1) Very poor access for ECMO (including conversion to veno-arterial cannulation from VV configuration); and 2) Relative body mass index (BMI) > 40 kg/m^2 resulting in inability to meet oxygenation requirements by traditional ECMO circuit.

The VV-ECMO configuration utilized in all patients was right femoral (25-29 Fr)-right internal jugular (18-24 Fr) cannulation, placed using ultrasound guidance. The average initial flow was 5.34 L/min (n = 14) and the average final flow was 4.98 L/min (n = 12).

Prone Positioning Management

The decision to turn the patient to the prone position was determined shortly after cannulation if there was no improvement after adequate stabilization time on ECMO. Patients were not proned if they underwent a tracheotomy within the preceding four days. Other contraindications included skin pressure necrosis and lack of clinical improvement after multiple sessions. Patients were proned for a default of 16 h, and the duration was shortened if there was suspicion of a deep tissue injury or if there was a developing one present where extra padding was used to minimize the extension. Patients were placed in the prone position with the help of a dedicated prone team, which consisted of three nurses, who regularly proned patients throughout the hospital, a respiratory therapist, a perfusionist, and the patient's bedside nurse.

Data Collection

All data were collected from the YNHH EPIC electronic health record. Each patient was assigned a unique patient ID, and each patient's age, sex, race, height, weight, and BMI were recorded at hospital admission. The World Health Organization (WHO) Illness Severity Score[10] was determined upon both hospital admission and discharge.

We defined three treatment combinations: 1) ECMO only; 2) Prone only; and 3) Prone during ECMO. For each treatment combination, ventilatory and hemodynamic variables were collected at four time points: pre-intervention, 1h-post (within one hour after intervention), 6h-post (six hours after intervention), and 24h-post (24 h after intervention initiation).

Table 1. Patients' demographics and baseline characteristics at hospital admission in 14 patients with severe COVID-19 requiring ECMO.

Variable	N (%)	Mean (SD)
Age (y)		48.1 (9.3)
Gender		
Male	14 (100)	
Race		
White or Caucasian	6 (43)	
Black or African American	2 (14)	
Other / Not Listed	6 (43)	
BMI (kg/cm^2)	14 (100)	36.5 (6.2)
Comorbidities		
Hypertension	6 (43)	
Hyperlipidemia	6 (43)	
Diabetes	4 (29)	
Coronary Artery Disease	0 (0)	
Chronic Obstructive Pulmonary Disease	0 (0)	
Hypothyroidism	2 (14)	
Smoking Status		
Never Smoker	10 (71)	
Current or Former Smoker	2 (14)	
Unknown	2 (14)	
WHO Illness Severity Score		5.9 (1.4)
4 Hospitalized, O$_2$ mask or nasal cannula	4 (29)	
5 Non-invasive ventilation or high-flow O$_2$	1 (7)	
6 Intubation and mechanical ventilation	1 (7)	
7 Ventilation + additional organ support	8 (57)	
SOFA Score at admission to		
Hospital		5.9 (3.7)
Cardiothoracic ICU		8.1 (2.6)
ECMO duration (days)		22.2 (7.5)
Prone Only	10 (71)	
Sessions		2.1 (1.4)
Duration (hours)		14.6 (3.8)
Prone during ECMO	7 (50)	
Sessions		4 (3.6)
Duration (hours)		16.2 (2.9)

Abbreviations: APRV, Airway pressure release ventilation; BMI, Body mass index; ECMO, Extracorporeal membrane oxygenation; SOFA, Sequential organ failure assessment.

For the pre-intervention time point, we captured the last change in ventilation settings prior to the start of the intervention, and vitals were collected at the time point closest to that of the ventilation settings. For the 1h-post time point, we collected ventilation setting changes within one hour after the start of the intervention. If the ventilation settings did not change within that hour, they were assumed to be the same as those prior to the start of the intervention. For the 6h-post time point, ventilation settings were recorded at six hours after intervention initiation and were assumed to be the same as the last documented settings if there was no documentation at the 6h-post time point. Vitals were collected as close as possible to the 6h-post time point, but no earlier than one hour prior to the 6h-post time point. If an intervention ended prior to the 6 h-post time point, data was collected at the latest time point prior to the end of the intervention that had available data. Lastly, for the 24h-post time point, ventilation data was recorded at 24h-post intervention initiation, and vitals were recorded at the time point closest to 24h-post intervention initiation, but no earlier than 22h-post intervention. If a patient was started on ECMO within 24 h after prone initiation, the last set of vitals and ventilation settings prior to ECMO initiation was recorded. No patients were proned within 24 h after ECMO initiation.

At each time point, we recorded the patient's vital signs including temperature, heart rate, respiratory rate, blood pressure, O$_2$ saturation, PaO$_2$ (partial pressure of oxygen in arterial blood), and ECMO FiO$_2$ (FDO$_2$) and pump sweep. Ventilation settings included ventilation mode, exhaled / release volume, total respiratory rate, minute ventilation (calculated), positive end-expiratory pressure (PEEP), ventilator FiO$_2$, inspiratory time setting, inspiratory pressure, and plateau pressure; for APRV, we also recorded: pressure high, pressure low, time high, time low, and release volume. Both ECMO FiO$_2$ and ventilator FiO$_2$ were collected at the same time as the PaO$_2$ for the purpose of calculating the PaO$_2$/FiO$_2$ ratio. Patients were ventilated with either assist-control or APRV, and the appropriate ventilation settings were collected for each mode.

For medication data (neuromuscular blockers, sedation agents, and pressors) at the pre-intervention time point, the most recent medication infusion rate prior to the start of the intervention was recorded. At the 1h-post time point, the earliest change in infusion rate within 30 minutes after the start of the intervention was documented, and if there was no change, the infusion rate was assumed to be the same as that prior to the start of the intervention. At the 6h-post and 24h-post time points, the earliest change in infusion rate within 30 minutes of that time point was recorded, and if there was no change, the infusion rate was assumed to be the same as just prior to that time point.

In addition, we calculated the sequential organ failure assessment (SOFA) score (range: 0-24; higher scores indicate more

Table 2. Changes in vital signs and ventilator/ECMO settings before and after the intervention. Data are expressed as mean (SD).

Variable	Pre	1 h-post	6 h-post	24 h-post	p-values*
ECMO (n = 14)					
Temperature (°C)	37.2 (2.2)	36.9 (0.61)	36.4 (0.7)	36.6 (0.17)	0.99; 0.784; 0.99
HR (beats/min)	113.2 (13.8)	97.2 (12.6)	87.4 (20.0)	93.6 (19.9)	0.001[%]; 0.0004[%]; 0.117
RR (breaths/min)	30.9 (4.3)	17.9 (10.5)	16.7 (9.1)	11.6 (6.4)	0.230; 0.023[%]; 0.075
Systolic BP (mm Hg)	113.8 (16.6)	116.3 (19.5)	109.4 (12.0)	117.8 (21.7)	0.99; 0.837; 0.99
O_2 Saturation (%)	90 (5.3)	98.5 (2.5)	97.9 (2.2)	96.4 (2.9)	0.009[%]; 0.009[%]; 0.021[%]
ECMO Sweep (L/min)	NA	5.2 (1.9)	4.6 (1.4)	5.7 (1.4)	NA
PaO_2/FiO_2 Ratio (mm Hg)	93.4 (35.4)	213.4 (126.1)	210.4 (94.3)	222.3 (67.0)	0.027[%]; 0.039[%]; 0.002[%]
PaO_2/FDO_2 Ratio (mm Hg)	93.4 (35.4)	159.2 (56.7)	109.6 (25.7)	93.3 (20.6)	0.076; 0.899; 0.99
Tidal Volume (mL/kg)	370.7 (68.5)	329.9 (123.6)	228.1 (115.8)	181 (123.7)	0.515; 0.0002[%]; 0.001[%]
Total RR (breaths/min)	29.2 (5.1)	17.7 (10.6)	14.8 (6.8)	11.6 (5.7)	0.047[%]; 0.0004[%]; 0.0007[%]
Minute Ventilation (L/min)	10.7 (2.0)	5.7 (3.9)	3.0 (2.1)	2.1 (1.4)	0.034[%]; 0.00001[%]; 0.000002[%]
PEEP (cmH_2O)	16 (3.3)	16.3 (3.1)	15.6 (3.0)	14.5 (2.8)	0.99; 0.99; 0.99
Plateau Pressure (cmH_2O)	34.9 (5.2)	34.7 (5.0)	31.3 (4.2)	26.8 (6.1)	0.99; 0.449; 0.130
Prone Positioning while Not on ECMO (n = 10)					
Temperature (°C)	37.7 (1.5)	38.1 (1.5)	38.4 (1.1)	37.4 (1.9)	0.223; 0.532; 0.99
HR (beats/min)	98.9 (18.1)	98.5 (17.1)	107.1 (18.4)	106.2 (19.8)	0.99; 0.496; 0.99
RR (breaths/min)	27.6 (5.3)	24.6 (7.5)	28.3 (4.6)	32.5 (2.7)	0.99; 0.99; 0.99
Systolic BP (mm Hg)	119.3 (11.2)	129.2 (25.3)	113 (14.0)	120.2 (13.0)	0.844; 0.366; 0.99
O_2 Saturation (%)	91.4 (4.5)	93.5 (3.9)	94 (3.3)	92.9 (5.0)	0.361; 0.206; 0.713
PaO_2/FiO_2 Ratio (mm Hg)	98.5 (32.8)	124.3 (53.2)	123.2 (41.5)	118.2 (46.3)	0.170; 0.087; 0.396
Tidal Volume (mL/kg)	387.3 (48.7)	376.2 (33.7)	364 (42.9)	374.7 (69.7)	0.99; 0.512; 0.99
Total RR (breaths/min)	26.7 (4.5)	28.8 (3.5)	28.9 (3.8)	28.6 (3.8)	0.220; 0.080; 0.282
Minute Ventilation (L/min)	10.4 (2.3)	10.9 (1.8)	10.6 (2.1)	10.8 (2.8)	0.955; 0.99; 0.99
PEEP (cmH_2O)	15.3 (1.7)	15.8 (2.7)	15.2 (2.5)	14.8 (2.2)	1; 0.585; 0.507
Plateau Pressure (cmH_2O)	35.3 (5.2)	34.8 (4.5)	33.7 (3.3)	32.5 (2.7)	0.960; 0.740; 0.107
Prone Positioning while on ECMO (n = 7)					
Temperature (°C)	36.7 (0.36)	36.6 (0.18)	36.7 (0.15)	36.6 (0.11)	0.99; 0.99; 0.891
HR (beats/min)	102.3 (26.3)	100.6 (23.6)	91.3 (17.2)	95.9 (22.9)	0.99; 0.436; 0.99
RR (breaths/min)	9.8 (3.5)	13.2 (4.3)	11.8 (10.3)	13 (9.1)	0.187; 0.99; 0.799
Systolic BP (mm Hg)	133.3 (20.8)	131.4 (20.3)	126.1 (16.2)	109.4 (10.5)	0.99; 0.99; 0.038[%]
O_2 Saturation (%)	92.1 (3.4)	94.9 (3.6)	95.4 (3.3)	95.7 (2.9)	0.307; 0.223; 0.145
ECMO Sweep (L/min)	6.1 (2.4)	6.1 (2.4)	6.8 (1.8)	6.5 (2.1)	
PaO_2/FiO_2 Ratio (mm Hg)	76.6 (10.0)	90.5 (30.4)	94.3 (28.4)	81.7 (31.9)	0.605; 0.397; 0.99
PaO_2/FDO_2 Ratio (mm Hg)	76.6 (10.0)	90.5 (30.4)	94.3 (28.4)	81.7 (31.9)	0.605; 0.397; 0.99
Tidal Volume (mL/kg)	244.1 (148.4)	190.7 (147.0)	192.1 (145.1)	241.6 (140.0)	0.752; 0.838; 0.99
Total RR (breaths/min)	10.7 (5.9)	16.1 (13.8)	13 (10.0)	13.3 (11.6)	0.796; 0.99; 0.99

(continued)

Table 2. Continued.

Variable	Pre	1 h-post	6 h-post	24 h-post	p-values*
Minute Ventilation (L/min)	2.1 (1.2)	2.3 (1.9)	2.1 (1.8)	2.5 (1.4)	0.99; 0.99; 0.99
PEEP (cmH$_2$O)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	13.7 (3.7)	NA; NA; NA
Plateau Pressure (cmH$_2$O)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	28.9 (5.5)	NA; NA; NA

Abbreviations: BP, blood pressure; ECMO, Extracorporeal membrane oxygenation; FDO$_2$, Fraction of oxygen delivered by ECMO; FiO$_2$, Fraction of inspired oxygen; HR, Heart rate; PaO$_2$, Partial pressure of oxygen in arterial blood; PEEP, Positive end-expiratory pressure; RR, Respiratory rate.
* p-values comparing pre-intervention versus the post-intervention time points: 1 h (first p-value), 6 h (second p-value), 24h (third p-value). P-values are adjusted for multiple comparisons using Bonferroni corrections.
%p-value < .05.

severe organ failure) at two time points: admission to the hospital and admission to the cardiothoracic ICU.[11] The GCS used to calculate the SOFA score was assumed to be 15 if the patient had no evidence of altered mental status, stroke, or traumatic brain injury prior to sedation and paralysis. We also calculated the average number of days on ECMO, average number of prone sessions, average duration of prone sessions, and average total duration of prone positioning. Patient outcome parameters included: duration of ICU and hospital stay, WHO Illness Severity Score and vital status at hospital discharge. One-year vital status was collected via chart review.

Statistical Analysis

All statistical analyses were performed with the use of R software (version 4.0.0). Categorical variables were expressed as frequencies (n) with percentages (%), and continuous variables as means with standard deviations (SD). Continuous variables were compared between time points (pre-intervention vs 1h-post, pre-intervention vs 6h-post, and pre-intervention vs 24h-post) using the one-sample paired t-test. The McNemar test was used to analyze paired dichotomous variables. Bonferroni correction was applied to account for multiple comparisons. A two-tailed alpha level of 0.05 was required for statistical significance.

Results
Study Population

A total of 15 patients were admitted to the YNHH ICU and placed on ECMO for COVID-19-associated ARDS with refractory hypoxemia. Of those, 14 patients received VV-ECMO and one patient received venoarteriovenous-ECMO and was excluded. Characteristics of the study population are summarized in Table 1. Mean age of the study population was 48 years and 100% were men. The average WHO illness severity score was 5.9 (SD 1.4) upon admission. Eight patients were transferred from an outside hospital and were either placed on ECMO by the YNHH ECMO team at the outside hospital prior to transfer or after arrival at YNHH. Patients required ECMO for an average of 22.2 (SD 7.5) days. Ten patients had episodes of proning while not on ECMO (nine before and one after) for an average of 14.6

(SD 3.8) hours over 2.1 (SD 1.4) sessions. Seven patients had episodes of proning while on ECMO for an average of 16.2 (SD 2.9) hours over 4.0 (SD 3.6) sessions. Thirteen patients were ventilated using APRV while on ECMO.

ECMO

For the 14 patients, data were available for 5 to 10 patients at any given time point (Table 2). When comparing the pre-intervention and 1h-post time points for the ECMO only group, ECMO support was associated with lower heart rate ($p = .001$), total respiratory rate ($p = .047$), and minute ventilation ($p = .03$). ECMO support was also associated with increased oxygen saturation ($p = .009$) and PaO$_2$/FiO$_2$ ratio ($p = .03$), but only when the PaO$_2$/FiO$_2$ ratio was calculated with the ventilator FiO$_2$ and not ECMO FiO$_2$. At 6h-post intervention, the changes in heart rate ($p < .001$), oxygen saturation ($p = .009$), PaO$_2$/FiO$_2$ (ventilator FiO$_2$; $p = .04$), total respiratory rate ($p < .001$), and minute ventilation ($p < .001$) were improved compared with baseline, and in addition, respiratory rate ($p = .02$) and tidal/release volume ($p < .001$) were lower. At 24-h post intervention, changes in oxygen saturation ($p = .02$), total respiratory rate ($p < .001$), tidal/release volume ($p = .001$), minute ventilation ($p < .001$), and PaO$_2$/FiO$_2$ ratio (ventilator FiO$_2$; $p = .002$) were also improved compared with baseline (Table 2).

Pressor requirements were increased at 6 h and 24 h after ECMO initiation compared with baseline ($p = .03$ and $p = .008$, respectively).

Prone Only

During prone only episodes, which occurred either prior to or after ECMO, data were generally available for 9 to 10 patients at any given point (Table 2). There were no significant changes from baseline in hemodynamic profile or oxygenation (Table 2). There were also no significant changes in pressor requirements associated with prone positioning.

Prone During ECMO

All seven patients who were proned during ECMO were ventilated with APRV during at least one prone session

(Supplementary Table 1). Data were available for seven patients. There were no significant changes from baseline in hemodynamic profile or oxygenation and no changes in pressor requirements associated with prone positioning while on ECMO (Table 2).

Complications

Three patients required ECMO cannula exchange, one due to bacteremia, one due to difficulty advancing the cannula, and one for possible damage to the cannula during prone positioning. While on ECMO, six patients acquired bacteremia and five patients developed acute kidney injury that necessitated continuous renal replacement therapy. In addition, one patient experienced a decline in right ventricular systolic function. All patients sustained deep tissue pressure injuries; however, only those sustained to the face and chest were found to be related to prone positioning. The APRV ventilation mode was utilized in 13 patients, and of those 13, three patients developed a pneumothorax and one developed barotrauma with pneumomediastinum and subcutaneous emphysema while on APRV.

Patient Outcomes

The average ICU stay was 37.4 (SD 13.8) and average hospital length of stay was 41.7 (SD 18.2) days (Table 3). The average WHO illness severity score at hospital discharge was 5.6 (SD 2.3). The overall hospital mortality rate was 43% (n = 6). Of the eight surviving patients, one patient was discharged with just limitation of activity, one patient was discharged to a long-term acute care facility with no oxygen requirement, five patients were discharged either to an outside hospital or to a long-term acute care hospital on oxygen therapy via mask or nasal cannula, and one patient was discharged to an outside hospital on mechanical ventilation.

Table 3. Patients' characteristics at hospital discharge.

Variable	N (%)	Mean (SD)
ICU stay (days)	14 (100)	37.4 (13.8)
Hospital stay (days)	14 (100)	41.7 (18.2)
WHO Illness Severity Score	14 (100)	5.6 (2.3)
2 Limitation of activity	1 (7)	
3 Hospitalized, no O$_2$ therapy	1 (7)	
4 Hospitalized, O$_2$ mask or nasal cannula	5 (36)	
5 Non-invasive ventilation or high-flow O$_2$	0 (0)	
6 Intubation and mechanical ventilation	1 (7)	
7 Ventilation + additional organ support	0 (0)	
8 Death	6 (43)	

At one-year follow-up, five of the patients who were discharged to an acute care facility were eventually discharged home without any further complications. One of the patients discharged to an acute care facility required readmission at an outside hospital for acute respiratory failure with hypoxia and difficult airway requiring emergency tracheostomy. That patient subsequently returned to the same rehabilitation facility and was discharged home several weeks later. One patient who was discharged to an outside hospital for long term acute care was eventually discharged home. The other patient who was discharged to an outside hospital was discharged to a hospital outside this healthcare system and further follow-up records were unavailable for review.

Discussion

During the current pandemic, researchers have identified several differences between typical ARDS and COVID-19 associated ARDS. Due to the phenotypic differences in these two forms of ARDS, it has been unclear whether the role of ECMO and prone positioning would be the same in COVID-19-associated ARDS as that which is observed in typical ARDS. While severe hypoxemia is observed in both forms of ARDS, COVID-19 ARDS has been characterized by a relatively preserved lung compliance compared to the classically low compliance in typical ARDS.[4] In addition, the differentiating hallmarks of COVID-19 patients with severe, refractory hypoxemia are the hypercoagulable and inflammatory states.[12–20] Of note, two meta-analyses, one on the use of colchicine in COVID-19 and the other on the use of tocilizumab, have shown that these pharmacological interventions have the potential to reduce the severity of COVID-19 disease by decreasing the production of pro-inflammatory cytokines.[21,22] Our study reports a case series of patients with COVID-19-associated ARDS who received VV-ECMO support, a subset of whom was proned during ECMO. We also describe the use of prone positioning alone and APRV in this patient population, and evaluate the safety of these interventions by examining the physiologic changes and complications that arose with the intervention(s). Complications observed in this cohort while on ECMO included right ventricular systolic function decline, acute kidney injury requiring continuous renal replacement therapy, and bacteremia. Cannula complications related to prone positioning or ECMO were infrequent. Patients sustained deep tissue injuries that resolved without further complications and were not entirely related to prone positioning.

In this cohort of patients, several hemodynamic and oxygenation parameters, such as oxygen saturation, PaO$_2$/FiO$_2$ ratio, and minute ventilation improved with ECMO support for at least 24 h; however, this improvement was not clinically relevant. This is likely due to the ongoing lung injury and the dramatic reduction in mechanical ventilator support, which was implemented as a part of the lung protective strategy to prevent further lung injury. Aligning with the results of a

recently conducted retrospective review on the use of ECMO in COVID-19 patients with ARDS, we also describe an improvement in PaO_2/FiO_2 ratio after ECMO initiation.[23] However, there are conflicting reports on the impact of combined VV-ECMO and prone positioning on PaO_2/FiO_2 ratio.[7,24–26] In particular, contrary to our results, one case series conducted on 23 COVID-19 ARDS patients found an improvement in PaO_2/FiO_2 ratio in the setting of combined VV-ECMO and prone positioning.[26] Another retrospective cohort study conducted during the first year of the pandemic found that in COVID-19 patients who were proned, a greater proportion of these patients were placed on ECMO or died if they did not experience an increase in PaO_2/FiO_2 ratio after initial pronation.[27] Currently, it is unclear whether PaO_2/FiO_2 ratio is a valid predictor of clinical improvement. It is also unclear how much the ventilator and ECMO both individually contribute to oxygenation, so here we report two PaO_2/FiO_2 ratios, one calculated with the ventilator FiO_2 and the other with the ECMO FiO_2.

During their hospitalization, all patients acquired multiple deep tissue pressure injuries, and while a decent number were a direct result of prone positioning, not all of them were. Prone positioning led to frequent injuries primarily on the face, including cheek, chin, and lip, and the chest. Other causes of pressure injuries included the anchor fast and trach flange, and other sites of pressure injuries included sacral spine, buttocks, thigh, and heel. It has been previously described that male gender, age greater than or equal to 60 years, and a BMI of greater than $28 \, kg/m^2$ is associated with a greater risk of pressure ulcer development.[28] Our cohort consisted exclusively of male patients with an average BMI of 37, which may explain to a certain extent the high incidence of pressure injuries observed. Despite the frequency of these injuries and regardless of their cause, with appropriate wound care, many resolved without further sequelae. Other possible complications of prone positioning, such as unplanned extubation, displacement of the endotracheal tube, and premature removal of other devices, were not observed in our cohort.

APRV was utilized in this cohort of patients in order to maintain lung protective strategies. Muscle relaxants were used while patients were on APRV, as patients were fully supported by ECMO and the contribution of spontaneous breaths early in the disease was negligible. A known complication of APRV is barotrauma.[29] In our series, three patients sustained barotrauma with pneumothorax; however, only one patient required chest tube placement.

In this cohort of patients, all but two patients (86%) required vasopressor support while in the ICU as well as while on ECMO. The rate of vasopressor usage in this group was elevated compared to the 66% weighted average of five observational clinical studies (n = 1010) of COVID-19 patients admitted to the ICU, but falls within their range of 35-94%.[30] This high rate of vasopressor use likely suggests a high frequency of hemodynamic instability in COVID-19 patients admitted to the ICU. Furthermore, it has been previously reported that hemodynamic instability appears to be one of the main factors contributing to mortality in patients with ARDS,[31] which may partially account for the high mortality rate observed in this cohort. Norepinephrine was the most commonly used vasopressor agent, followed by vasopressin. Four patients required two vasopressor agents at the 6-h time mark after ECMO placement, and one patient required three vasopressor agents at the 24-h time mark. This aligns with the current NIH COVID-19 treatment recommendations of using norepinephrine as a first-line vasopressor and either vasopressin or epinephrine as a second-line agent.[32]

We acknowledge several limitations of our study. Our study was conducted during the early stages of the COVID-19 pandemic; and therefore, our results may have differed if obtained during the current COVID-19 circumstances due to the emergence of different COVID-19 variants and the availability of the COVID-19 vaccination. Due to the single institution setting, small sample size, and missing data in certain parameters due to some patients being transferred from an outside hospital, we are unable to draw definitive conclusions. For the prone only group, which included ten patients, the most commonly missing variables were inspiratory time setting and inspiratory pressure. For the prone during ECMO group, which included seven patients, the most commonly missing variables were respiratory rate and inspiratory time setting. In addition, for the prone during ECMO group, the duration between ECMO initiation and the first prone session varied among patients.

Another limitation is that all patients who were placed on ECMO were males, which may suggest that males suffer from more severe disease. This aligns with a recently published meta-analysis that found that although the number of COVID-19 cases does not differ significantly between sex, the risk of more severe disease and death is significantly higher in males than in females.[33] Despite these limitations, this case series is the first description of the utilization of prone positioning combined with APRV and VV-ECMO in patients with ARDS secondary to COVID-19, and to our knowledge, the first description of this combination in ARDS in general.

Literature examining the use of VV-ECMO and prone positioning in patients with severe COVID-19 ARDS is sparse. Moreover, the reports on outcomes are conflicting and not necessarily consistent with data from ARDS not related to COVID-19. Randomized controlled trials in both populations to further evaluate patient outcomes and the potential benefits of this combined therapy are ongoing (NCT04139733, NCT04607551).

Conclusion

The use of VV-ECMO, prone positioning, and APRV in a select population of patients with severe COVID-19 ARDS

was generally overall well-tolerated; however, the physiologic improvements observed were marginal. The use of these modalities results in several serious, but reversible, complications, and given the impact of these complications on patient care, it is critical for clinicians to be aware of these risks and be prepared to address them should they arise.

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Author Contribution(s)

Stephanie L Ong: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Research Ethics Approval and Patient Consent

The Yale University Institutional Review Board reviewed and approved the study protocol for this medical record review and waived the need for informed consent (IRB# 2000028433).

Trial registration

NA.

Availability of Data and Materials

Data could be made available by contacting the corresponding author.

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Supplemental Material

Supplemental material for this article is available online.

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List of Abbreviations

AKI	Acute kidney injury
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
ARDSnet	Acute respiratory distress syndrome network
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CRRT	Continuous renal replacement therapy
CTICU	Cardiothoracic intensive care unit
ECMO	Extracorporeal membrane oxygenation
FDO_2	Fraction of oxygen delivered by ECMO
FiO_2	Fraction of inspired oxygen
HR	Heart rate
ICU	Intensive care unit
IJ	Internal jugular
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MICU	Medical intensive care unit
PVD	Peripheral vascular disease
PaO_2	Partial pressure of oxygen
PDE	Prone during ECMO
PEEP	Positive end-expiratory pressure
RR	Respiratory rate
ROSC	Return of spontaneous circulation
SD	Standard deviation
SOFA	Sequential organ failure assessment
VA	Veno-arterial
VV	Venovenous
WBC	White blood cell
YNHH	Yale New Haven Hospital