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Veno-Venous Extracorporeal Life Support use in Severe COVID Pneumonia

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Abstract

Objectives: Veno-venous extracorporeal life support (VV-ECLS) has been shown to improve gas exchange and survival in the setting of acute respiratory distress syndrome. Recently, VV-ECLS has been utilized as a treatment strategy for severe COVID pneumonia unresponsive to conventional treatment. The purpose of this study was to evaluate the efficacy of VV-ECLS in severe COVID pneumonia.

Methods: All patients with confirmed SARS-CoV-2 infection placed on VV-ECLS were identified from an institutional database. Clinical data were obtained from review of medical records. Patients were stratified by survival status for univariate analysis.

Results: Thirty-four patients were included in the study with a mean PaO2/FiO2 ratio of 80.71 mmHg ± 23.36 and PaCO2 value of 78.03 mmHg ± 22.93 at the time of cannulation. Median time from SARS-CoV-2 diagnosis to intubation was 10 days [IQR 4-16]. Median time from intubation to cannulation was 4 days [2-7]. Adjunctive therapies were given to 97.1% of patients, including systemic corticosteroids (97.1%), remdesivir (73.5%), tocilizumab (26.5%), and convalescent plasma (38.2%). Thromboembolic and hemorrhagic complication rates from VV-ECLS were 14.7% and 58.8%, respectively. Survivors had significantly lower hemorrhagic complication rates (31.3% vs 77.8%, p=0.006). Seventeen patients (50.0%) were successfully decannulated, and of those 94.1% (16/17) survived to hospital discharge. Overall survival to hospital discharge was 47.1% (16/34).

Conclusion: VV-ECLS serves as a rescue therapy for patients with severe SARS-CoV-2 infection failing conventional respiratory measures. Bleeding complication rates are high and associated with increased mortality.

Keywords: Quality improvement; COVID; ECMO; ECLS; Outcomes

Abbreviations: ARDS = Acute Respiratory Distress Syndrome; BMI = Body Mass Index; DVT = Deep Vein thrombosis; ECLS = Extracorporeal Life Support; ICU = Intensive Care Unit; PCR = Polymerase Chain Reaction; PE = Pulmonary Embolism; HIPAA = Health Insurance Portability and Accountability Act; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus; VV-ECLS = Veno-Venous Extracorporeal Life Support

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has led to over 925,000 deaths in the United States and over 5.8 million deaths worldwide **[1].** Despite widespread vaccine availability within the U.S., COVID-19 pneumonia Intensive Care Unit (ICU) admissions remain high **[2].** Respiratory failure requiring hospitalization is treated with supportive care and adjunct therapy (systemic corticosteroids, remdesevir, tocilizumab, and convalescent plasma) for patients as no cure has been identified for COVID-19 **[3,4].** When clinical status declines despite supportive care, escalation to Extracorporeal Life Support (ECLS) can be utilized as a treatment modality in select severe cases **[5].** Classically, VV-ECLS has been used to support patients with acute respiratory distress syndrome (ARDS) refractory to conventional critical care measures allowing for decreased ventilator requirements while the lungs recover **[6-8].** During the H1N1 influenza pandemic in 2009, ECLS was employed for severe ARDS with a 21% mortality rate **[9].** VV-ECLS use within the non-COVID-19 population carries a mortality rate of 38% with rates ranging from 35% to 52% in the COVID-19 positive population **[10-13]**. Limitations associated with ECLS include access to care as well as complications including thromboembolic and hemorrhagic incidents **[14].** More recently, studies have evaluated the use of VV-ECLS in the care of COVID-19 patients in respiratory failure with mixed results of treatment **[15-17].** With the immense death rates of COVID-19 and the potential for rapid influx of hospitalized patients due to the disease, there is a need to evaluate options for hospitalized COVID-19 patients. The purpose of this study was to evaluate the use of VV-ECLS as a rescue therapy in SARS-CoV-2 Polymerase Chain Reaction (PCR) test positive patients with severe respiratory failure. Additionally, we characterized the population in totality, and performed a subgroup analysis of survivors vs. non-survivors. We hypothesized there would be significant differences between survivors and non-survivors that can be identified and may be addressed by changes in clinical practice to improve survival.

Methods

ECLS cannulation strategy

All patients were placed on VV-ECLS. Our initial cannulation strategy was achieved by placement of a 31F Avalon Elite bicaval dual lumen cannula (MAQUET Cardiopulmonary AG, Germany) in the right internal jugular vein. We then shifted to Common Femoral Vein (CFV) cannulation with a Bio-Medicus Nextgen (Medtronic, Minneapolis, MN) 25 French drainage cannula and a 19 French return cannula in the right internal jugular vein to achieve higher flow rates. All access was obtained under ultrasound guidance and cannula position confirmed with either fluoroscopy or chest x-ray.

Anticoagulation titration and monitoring

At the time of cannulation, all patients received a bolus of unfractionated heparin. The heparin bolus dose was dependent on the patient's risk for bleeding, as determined by the cannulating surgeon, or presence of active bleeding. Those at risk for bleeding received a heparin bolus of 25 units/kg and those not at risk received a bolus

of 50 units/kg. Activated Clotting Time (ACT) monitoring was used during cannulation to monitor anticoagulant effect. Additional bolus doses were given if the ACT failed to increase > 160 sec in bleeding patients and > 200 sec in non-bleeding patients. Per institutional guidelines a continuous heparin infusion was initiated post cannulation when the ACT level was < 200 sec, there was no clinical evidence of bleeding, and deemed clinically safe by the ECLS physician. Our institution utilizes two heparin titration guidelines for ECLS, dependent on a patient's risk for bleeding. Those considered at high relative risk for bleeding or who had evidence of active bleeding were started on a low continuous infusion of heparin of 3 units/kg/h. When deemed clinically safe by the ECLS physician, the infusion was titrated per institutional guidelines to achieve a Partial Thomboplastin Time (PTT) of 40-60 seconds for patients on the bleeding protocol (evidence of active bleeding or high risk for bleeding complications) and a PTT of 60-80 seconds for patients on the non-bleeding protocol.

Patient data and variable definitions

All patients placed on VV-ECLS between March 2020 and September 2021 at the University of Virginia Health System were obtained using institutional data from individual chart reviews. The data analyzed for this study was collected with Health Insurance Portability and Accountability Act (HIPAA) patient identifiers, and performed under institutional review board #23305. All patients aged 18 years and older who were COVID positive on PCR and were placed on VV-ECLS were included in the analysis. There were no exclusions. Bleeding complications encompassed hemorrhagic stroke, severe oropharynx hemorrhage, hemothorax, severe epistaxis, retroperitoneal hemorrhage, and gross hematuria. All bleeding complications listed required transfusion. Thromboembolic complications include Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). The primary endpoint of interest was survival to discharge. Patients placed on VV-ECLS who survived to discharge were compared to those placed on VV-ECLS who did not survive to discharge.

Statistical analysis

Continuous variables are presented as either mean (standard deviation) or median (Q1-Q3). Categorical data are summarized as number (%). In the univariate analysis, the Mann-Whitney U test was used for continuous variables and the $\chi 2$ test for categorical variables. A Kaplan Meier survival analysis was performed with in-hospital mortality as the endpoint, and groups compared with the log-rank test. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, NC). Statistical significance was set at p value of less than 0.05.

Results

Study population and patient characteristics

Demographic data for the patients placed on VV-ECLS are shown in **Table 1**. A total of thirty-four patients underwent VV-ECLS with a mean age of 45.9 years ± 12.3. Race was captured as White (38.2%), Hispanic (23.5%), African American (20.6%), Asian (2.29%) and other (14.7%). Adjunctive therapies were given to 97.1% of patients, including systemic corticosteroids (97.1%), remdesivir (73.5%), tocilizumab (26.5%), and convalescent plasma (38.2%). The majority of patients were male (79.4%). The most common co-morbidity amongst the cohort was diabetes (38.2%) and patients on average were obese (body mass index 30.2 ± 6.9). Most patients were proned (85.3%) and paralyzed (95.2%) prior to VV-ECLS initiation.

Table 1: Patient Characteristics.

Variable	Statistic

	(n=34)
Female	7 (20.6%)
Race	
White	13
Hispanic	8
African	7
Asian	1
Other	5
Age, years	45.9 ±
Body Mass	30.2 ±
Diabetes	13
Hypertension	9 (26.5%)
Chronic Lung Disease	1 (2.9%)
Asthma	4
SARS-CoV-2	
Systemic	33
Tocilizumab	9
Remdesivir	25
Convalescent	13
Pronation Prior	29
Paralysis Prior to Cannulation	31 (91.2%)

Values are median (interquartile range), mean ± standard deviation, or n (%).

Extracorporeal life support and outcomes

Physiologic characteristics of patients before ECLS are shown in **Table 2.** The PaO2/FiO2 ratio was 80.71 ± 23.36 and PaCO2 was 71.14 mmHg ± 18.6 at the time of cannulation. The median time from SARS-CoV-2 diagnosis to intubation and to VV-ECLS initiation was 10 days [IQR 4-16] and 14 days [11-20] respectively. The median time from intubation to VV-ECLS initiation was 4 days [2-7.3]. Thromboembolic and hemorrhagic complication rates from VV-ECLS were 14.7% and 58.8%, respectively.

Table 2: Pre-ECLS Characteristics

Variable	**Statistic**
Days from SARS-CoV-2 Diagnosis to	10 (4 –
Days from Intubation to VV-ECLS	4 (2 –
Days from SARS-CoV-2 Diagnosis to VV-	14 (11 –
PaO2 at Time of Cannulation, mmHg	78.03 ±
PaCO2 at Time of Cannulation, mmHg	71.14 ±
PaO2/FiO2 Ratio at Time of Cannulation	80.71 ±
pH at Time of Cannulation	7.25 ±

PEEP at Time of Cannulation (mmHg)	13.71 ±
Respiratory Rate at Time of Cannulation	30.23 ±

Values are median (interquartile range), mean ± standard deviation, or n (%).

Survivors vs Non-Survivors

There were no significant differences in age, gender, comorbidities, or COVID adjunct therapy use between survivors and non-survivors **(Table 3).** Non-survivors were placed in prone positioning and paralyzed prior to cannulation more than survivors (100% vs 68.8%; p=0.01; 100% vs 81.3%; p=0.05). Survivors had significantly lower hemorrhagic complication rates (n=5 [31.3%]) compared to non-survivors (n = 14 [77.8%]) (p = 0.006) **(Table 4).**

Table 3: ECLS Characteristics and Outcomes.

Variable	Statistic
Days on ECLS	17 (10.25
Dual Site	23
Initial ECLS	4.33 ±
Initial ECLS	3.92 ±
Thrombotic	5
Bleeding	20
Continuous	13
Inhaled Nitric	12
Days from	29 (22.5
Hospital length	67 (39 –
Hospital length	24 (15 –
In-hospital	18
Discharge to	12 (75%)
Discharge with	5

Values are median (interquartile range), mean ± standard deviation, or n (%).

Table 4: Non-survivors vs. survivors

Variable	Non-Survivors	Survivors	p-value
Age	47.2 ±	44.4 ±	0.52
Gender (Female)	4 (22.2%)	3 (18.8%)	0.8
Hispanic Ethnicity	7 (38.9%)	4 (25.0%)	0.39
BMI	31.1 ±	29.1 ±	0.44
Diabetes Mellitus	7 (38.9%)	6 (37.5%)	0.93
Chronic Lung Disease	0%	1 (6.25%)	0.28
Asthma	2 (11.1%)	2 (12.5%)	0.9
Hypertension	5 (27.8%)	4 (25.0%)	0.85
Prone prior to	18	11	0.01
Paralyzed Prior to	18	13	0.05
Dual Site Cannulation	14	9 (56.3%)	0.18
Initial ECLS Flow	4.39 ±	4.22 ±	0.47
Initial ECLS Sweep	3.75 ±	4.07 ±	0.32

FiO2 at Cannulation	0.98 ±	0.97 ±	0.59
PaO2 at Cannulation	90.13 ±	85.31 ±	0.69
P:F Ratio at	74.85 ±	85.40 ±	0.2
pH at Cannulation	7.24 ±	7.28 ±	0.06
PEEP at Cannulation	15.75 ±	11.60 ±	0.54
PCO2 at Cannulation	75.46 ±	64.12 ±	0.29
Respiratory Rate at	29.1 ±	28.8 ±	0.19
Days from SARS-CoV-	8.5 (7 -	9.5 (4 -	0.66
Days from Intubation to	3 (1 -6.5)	2.5 (2 - 5)	0.09
Days from SARS-CoV-	14 (10 –	14 (7 -	0.97
Thrombotic	3 (16.7%)	2 (12.5%)	0.73
Bleeding Complications	14	5 (31.3%)	0.006
Continuous Renal	9 (50.0%)	4 (25.0%)	0.11
Inhaled Nitric Oxide	7 (38.9%)	5 (31.3%)	0.64
Systemic	17	16	0.33
Tocilizumab	7 (38.9%)	2 (12.5%)	0.08
Remdesivir	14	11	0.55
Convalescent Plasma	7 (38.9%)	6 (37.5%)	0.93

Values are median (interquartile range), mean ± standard deviation, or n (%). Groups were compared using Chi-square for categorical variables or Mann-Whitney U-tests for continuous variables. Frequency (%) for categorical variables or median (IQR) for continuous variables were shown.

Survival

Seventeen patients (50.0%) were successfully decannulated, and of those 94.1% (16/17) survived to hospital discharge. Five patients required oxygen at discharge and 75% of patients who survived were discharged to a facility. One patient did not survive after decannulation as the patient's family pursued comfort measures following tracheal obstruction and shock secondary to toxic epidermal necrolysis. The Kaplan Meier survival analysis demonstrates as hospital length of stay increases, the probability of survival decreases **(Figure 1).** Patients that survived to discharge had a 100% 6-month survival.

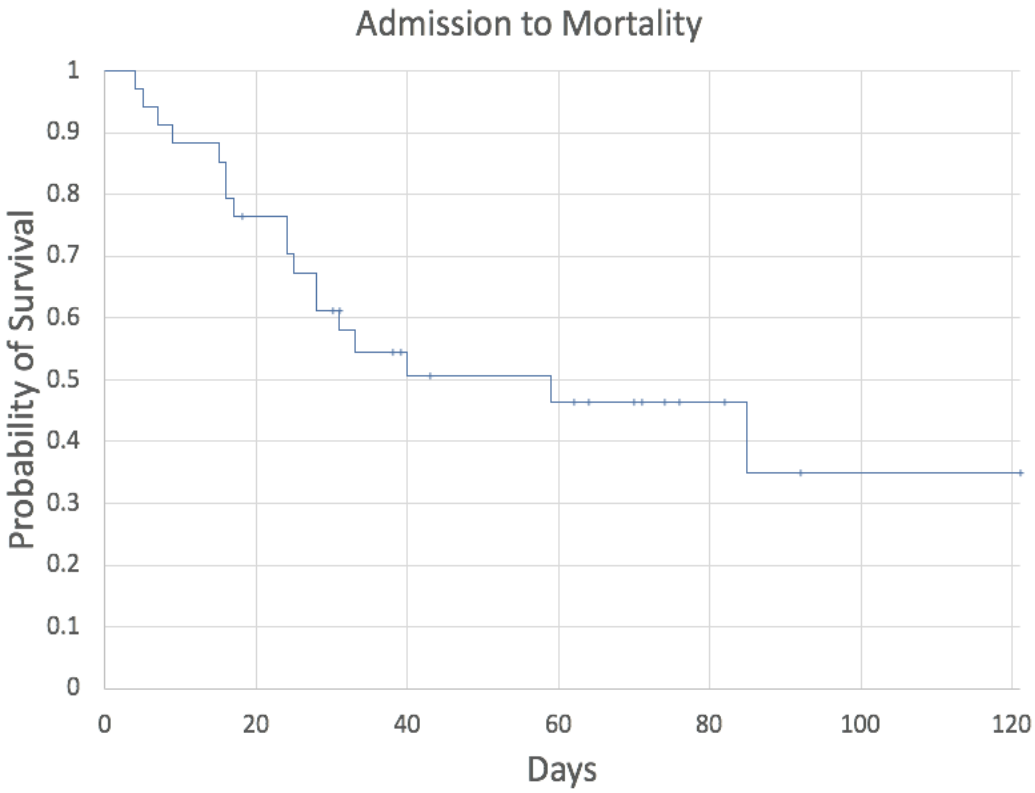

Figure 1: Kaplan Meier Curve demonstrating survival of those on ECLS for COVID Pneumonia.

Discussion

In this retrospective analysis of COVID positive patients treated with VV-ECLS, we demonstrated an overall survival to hospital discharge of 47.1%. Patients in the non-survivor group were placed in the prone position and paralyzed significantly more often than patients in the survivor group. Both groups had similar pre-ECLS physiologic data. Non-survivors had significantly increased rates of bleeding complications. There was a significant decrease in bleeding complications amongst survivors compared to non-survivors. Five (27.8%) non-survivors were found to have hemorrhagic strokes on computed tomographic imaging. In general, the amount of sedation and chemical paralysis required for this patient population makes it difficult to perform frequent assessments for stroke. It is our practice to obtain cross-sectional imaging of the head, chest, abdomen, and pelvis after initiation of ECLS support, at which point significant pathology is often identified. Unfortunately, critical illness and instability prevents these imaging studies from being able to be performed prior to cannulation in most cases. Sedation holidays are not afforded to many of these patients and we suspect more non-survivors may have had intracranial hemorrhagic complications. Initially the “coagulopathy in COVID-19” phenomenon was limited to the formation of DVTs and Pes **[18]**. Recently, this has been broadened to cover the increased risk of hemorrhagic events associated with SARS-CoV-2 infection. The increased incidence of both bleeding and thromboembolic complications associated with COVID-19 makes the anticoagulation strategy quite complex. Typically for patients on VV-ECLS, our practice is to withhold anticoagulation for any bleeding issues. However, due to the high rate of thromboembolic events in the COVID-19 patient population, we usually attempt to keep these patients on the bleeding protocol unless the bleeding complication is life-threatening. Survivors were proned and paralyzed less when compared with non-survivors. Proning awake patients has been

demonstrated to improve oxygenation in patients with ARDS and is associated with a reduced mortality **[19].** The benefit of proning patients has been reviewed and is favored in patients with severe pneumonia due to COVID however a large randomized control trial has not been perfomed **[20].** The CESAR trial demonstrated a survival benefit to transferring critically ill ARDS patients to a tertiary care ECLS center in a hub-and-spoke model **[21].** Additionally, there are limited centers proficient in the practice of ECLS with only 23 platinum level centers of excellence in the United States **[22].** Five patients presented initially to our hospital and of those five, four of them survived to discharge (80% survival). As a result, there may be a need and benefit to early identification and expedited transfer of patients eligible for VV-ECLS to a hospital with ECLS capability. Of all survivors, five (31.25%) patients required oxygen at discharge. Towards the end of the study period those admitted from February 2021 to September 2021 demonstrate a markedly increased rate of in-hospital mortality. This may in part be due to the presence of variant strains. The delta variant has been associated with greater transmissibility and virulence **[23].** The emergence of the Delta variant within the US does correlate with the observed increase in mortality **[24,25].** The worsening survival over time might also be explained by the increase in vaccination and an overall decreased severity of illness and decreased need for ELCS. With a decrease in the overall number of COVID-19 ECLS patients, those who still required ECLS due to severe ARDS skewed the results toward worse survival. Similarly, improvements in medical management of COVID-19 pneumonia meant that many patients who would have required ECLS early in the pandemic were able to be treated with conventional therapies and avoid ECLS in the later era. This study is limited by its retrospective nature which does not provide determination of causality and may be influenced by selection bias. This is a single institutional study which may not be generalizable to the population, however, does demonstrate trends which have been reproduced within the literature **[26].** Our comparison between survivors and non-survivors has a low power and would benefit from a large multi-institutional review to increase the sample size and increase generalizability of the study. VV-ECLS is a reasonable option for patients with severe COVID-19 pneumonia and failure of conventional support. However, VV-ECLS does carry a high complication rate of thromboembolic and bleeding events and high in-hospital mortality rate of 52.8%. If patients do survive to discharge, the 6-month survival of these patients is high. Early evaluation and careful patient selection should be performed prior to cannulation and consideration for lower anticoagulation parameters given high bleeding complications among non-survivors.

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