



## ECMO Cannulation Criteria in COVID-19 (ECC-VID) and Obesity: A Literature Review and Retrospective Cohort Analysis

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### Abstract

Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO) continues to be used as rescue therapy for patients with Acute Respiratory Distress Syndrome (ARDS) secondary to Coronavirus Disease 2019 (COVID-19). Although there is emerging literature on the use of and mortality associated with V-V ECMO in the management of patients with COVID-19, our understanding of who may benefit from this management strategy remains limited.

Our clinicians sought to provide further insight into pre-cannulation characteristics and mortality in a cohort of patients with COVID-19 associated ARDS managed with V-V ECMO that primarily consisted of obese patients (90%, n=18) with a BMI of 30 kg/m<sup>2</sup> or greater. Our findings not only revealed high survival to hospital discharge (70%, n=14), but demonstrated non-inferior outcomes and survival in obese patients.

With an imminent next wave of rising infections, knowledge of which patients have a better chance of survival with the initiation of V-V ECMO is essential. Obese patients have been historically underrepresented in ECMO outcomes literature, but our findings suggest the utilization of ECMO for COVID-19 associated ARDS in these patient subsets should be considered and outcomes should be further explored.

**Keywords:** V-V ECMO; COVID-19; Obesity; Critical care; Acute respiratory distress syndrome

### Introduction

Despite the emergence of therapeutics such as dexamethasone and Remdesivir, it is estimated that approximately 15% of patients with Coronavirus Disease 2019 (COVID-19) will develop severe acute Respiratory Distress Syndrome (ARDS) [1]. Accordingly, international organizations and the extra corporeal life support organization recommend veno-venous extracorporeal membrane oxygenation for management of severe ARDS in COVID-19 [2,3]. Although there is emerging literature on the use of Veno-Venous Extracorporeal Membrane (V-V ECMO), the utility in patients with COVID-19 associated ARDS is currently being explored. Reported mortality has been wide ranging, with some earlier cohorts demonstrating significant mortality while others reported a lower mortality comparable to non-COVID-19 patients [4-9]. The recent publication of a large, international cohort study from the Extracorporeal Life Support Organization (ELSO) registry-citing an in-hospital mortality 90 days after ECMO initiation in patients with COVID-19 associated Acute Respiratory Failure (ARDS), consistent with previously reported survival rates in ARDS-has increased insight into ECMO mortality in the setting of COVID-19 [10].

Obese patients are at high risk of developing severe disease despite studies prior to the pandemic showing a possible decrease in mortality in critical ill obese patients [11,12]. A growing body of evidence has found an independent and strong association of adverse outcomes--including death--in the obese population with COVID-19 [13,14].

Exploration of ECMO utilization in obese patients prior to the COVID-19 pandemic dates back to the early 2000's when case reports described the feasibility of cannulating the morbidly obese

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[15,16] and subsequent reports of relatively comparable outcomes [17,18]. There have also been reports that obese patients on ECMO may have a higher rate of survival compared to non-obese patients, it is unclear if this applies to COVID-19 [19].

With the possibility of successive peaks of infection, it will become paramount to have a better understanding of which patients may potentially benefit from V-V ECMO. Prior to the pandemic, many clinicians relied on the principles established by the Extracorporeal Life Support Organization (ELSO) as well as the Extracorporeal Membrane Oxygenation for Severe ARDS (EOLIA) and Conventional Ventilatory Support vs. Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trials to guide decisions for V-V ECMO initiation [20-22]. Although ELSO has published COVID-19 specific guidelines that can help determine candidacy for V-V ECMO, these guidelines were developed with an evolving understanding of ARDS in COVID-19 [3]. Amongst relative contraindications listed in these guidelines, include conditions such as an immunocompromised state, obesity with BMI  $\geq 40$ , older adults aged 65 or older and those with advanced organ dysfunction [23].

Some have contended that prior viral respiratory outbreaks may help guide decision making regarding the initiation of V-V ECMO, however, we now understand that the pathophysiology of COVID-19 is very unique [24]. In this study, researchers sought to provide further insight into pre-cannulation characteristics and mortality in a cohort of COVID-19 associated ARDS managed with V-V ECMO that primarily consisted of extremely obese patients.

## Methods

This retrospective case review was approved by the Emory University IRB. Subjects were all critically ill, adult patients ( $\geq 18$  years of age) with laboratory-confirmed COVID-19 RNA who were admitted to a single ICU from March 29<sup>th</sup>, 2020 through August 27<sup>th</sup>, 2020 and placed on ECMO for COVID-19 associated ARDS. All diagnostic testing and therapeutic interventions-including decisions with respect to ECMO candidacy and cannulation-were performed at the discretion of the treating clinicians. At our institution, a multidisciplinary team consisting of members of diverse critical care medicine and cardiothoracic surgery backgrounds is responsible for consultation, cannulation and management of all patients on ECMO. Our research team retrospectively reviewed demographic, clinical, and diagnostic data obtained during each patient's admission.

Authors sought to evaluate factors-including those referenced by expert clinical groups such as ELSO and studies of ECMO in ARDS such as EOLIA-for ECMO cannulation consideration and contraindications, including: Age, Body Mass Index (BMI), pregnancy, ratio of arterial partial pressure to fractional inspired oxygen (P/F ratio) and duration of Mechanical Ventilation (MV) [21,25]. Primary outcome evaluated was survival to hospital discharge.

Secondary outcomes examined included: length of hospital and Intensive Care Unit (ICU) stay and duration of MV and ECMO support.

Additional clinical and diagnostic data from the 24 h prior to cannulation of subjects were also examined. Serum diagnostics reviewed and reported were peak C-Reactive Protein (CRP), d-dimer, fibrinogen and lactate. Clinical characteristics, conditions and events reported were those noted within 24 h prior to cannulation and included: Renal replacement therapy requirement, vasopressor

requirements, and occurrence of thromboembolic event and presence of concomitant infections. Acute Physiology and Chronic Health Evaluation II (APACHE 2) and Sequential Organ Failure Assessment (SOFA) were additionally examined in attempts to reflect the severity of critical illness within our cohort and attempt to capture potential mortality predictors. Results calculated from the Respiratory ECMO Survival Prediction (RESP) scoring tool--a tool validated, developed and used to predict survival after ECMO cannulation in severe ARDS--were additionally examined and reported for all subjects.

Obesity was defined and classified according to the world health organization (WHO) criteria; Class III or extreme obesity was defined as BMI greater than or equal to 40 kg/m<sup>2</sup> [26]. Vasopressor requirement was further delineated into two categories, single vasopressor requirement and a two vasopressor requirement and/or norepinephrine equivalent of greater than 0.1 mcg/kg/min. Glasgow Coma Scale (GCS) within APACHE 2 scoring was obtained based on pre-intubation documentation. Thromboembolic events were defined as Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and cardiac arrest/Pulseless Electrical Activity (PEA) due to catastrophic cardiovascular thromboembolism. All patients within this cohort received a course of corticosteroids and were on systemic anticoagulation; steroid choice was dictated by clinicians and based on availability of clinical outcomes data at time care was provided [27].

Given the small sample size descriptive statistics including median, interquartile range, and percentages were used to summarize the data. Patient characteristics are expressed as n(%) for categorical variables and mean for all continuous variables. Univariate statistics was performed using Chi-squared for all categorical variables and student's t-test for all continuous variables. All statistical calculations were performed using Microsoft Excel and SPSS Data Analysis Software.

## Results

During the described study time period, V-V ECMO was initiated on 20 critically ill patients diagnosed with ARDS in the setting of COVID-19 and admitted to our ECMO referral center. The mean age of those in the cohort was 42 years old (Standard Deviation (SD) of 15). Fifty five percent (n=11) were female, two of which were pregnant. Sixty five percent of patients (n=13) were black. The median BMI of the cohort was 45.8 (Interquartile Range (IQR) 34 to 62). Ninety percent (n=18) of patients were obese with a BMI of 30 kg/m<sup>2</sup> or greater. The majority, sixty percent (n=12) met Class III extreme obesity criteria with a BMI greater than 40 kg/m<sup>2</sup>. Thirty percent (n=6) met Class I or II obesity criteria with a BMI ranging from 30 kg/m<sup>2</sup> to 40 kg/m<sup>2</sup>. The remaining two patients (10%) were overweight.

Predominance of patients had one known pre-existing medical condition (55% (n=11)) and were in severe ARDS (75% (n=15)) at time of cannulation. The median P:F ratio at time of cannulation was 84 (IQR 84 to 103). Sixty five percent (n=13) had a vasopressor requirement at time of cannulation; amongst those with a vasopressor requirement, six subjects (46%) required two or more vasopressors or had an norepinephrine requirement of greater than or equal to 0.1 mcg/kg/min. Median duration of mechanical ventilatory support prior to ECMO cannulation was 5 days (IQR 4 to 7 days).

Within this cohort median APACHE II scores were found to be 11 (IQR 7.5 to 13). SOFA scoring demonstrated a median of 6.5 (IQR

**Table 1:** Cohort demographics and pre-cannulation characteristics.

Demographics	Full Cohort (n=20)
Age in years [mean (SD)]	42 (15)
BMI kg/m <sup>2</sup> [median (IQR)]	45.8 (34-62)
Overweight BMI 25.9 kg/m <sup>2</sup> -29.9 kg/m <sup>2</sup> [n (%)]	2 (10%)
Class I Obesity BMI 30 kg/m <sup>2</sup> -34.9 kg/m <sup>2</sup> [n (%)]	3 (15%)
Class II Obesity BMI 35 kg/m <sup>2</sup> -39.9 kg/m <sup>2</sup> [n (%)]	3 (15%)
Class III Obesity BMI >40 kg/m <sup>2</sup> [n (%)]	12 (60%)
Male Gender [n(%)]	9 (45%)
Pregnant [n(%)]	2 (10%)
Black [n(%)]	13 (65%)
Hispanic [n(%)]	4 (20%)
White [n(%)]	3 (15%)
# of Pre-existing conditions [n (%)]	
0 conditions	3 (15%)
1 condition	11 (55%)
2 conditions	2 (10%)
3 conditions	3 (15%)
4 conditions	1 (5%)
Asthma [n(%)]	7 (35%)
Hypertension [n(%)]	10 (50%)
Diabetes [n(%)]	3 (15%)
Other Pre-cannulation Factors/Characteristics	
APACHE II score [median (IQR)]	11 [IQR 7.5-13]
SOFA score [median (IQR)]	6.5 [IQR 4.5-10]
RESP score [median (IQR)]	4 [IQR 3-5]
Mechanical Ventilation in days [median (IQR)]	5 [IQR 4-7]
Vasopressor Requirement [n (%)]	13 (65%)
Norepi ≥ 0.1mcg/kg/min or need for 2 vasopressors [n (%)]	6 (46%)
RRT Requirement [n (%)]	3 (15%)
P/F ratio [median (IQR)]	84 (IQR 84-103)
ARDS [n (%)]	20 (100%)
Mild [n (%)]	1 (5%)
Moderate [n (%)]	4 (20%)
Severe [n (%)]	15 (75%)
CRP mg/L [median (IQR)]	180 [IQR 82-240]
Fibrinogen mg/dL [median (IQR)]	613 [IQR 337-783]
Lactate mmol/L [median (IQR)]	1.2 [IQR 1.0-1.3]
D-dimer ng/mL [median (IQR)]	3084 [IQR 1217-6607]

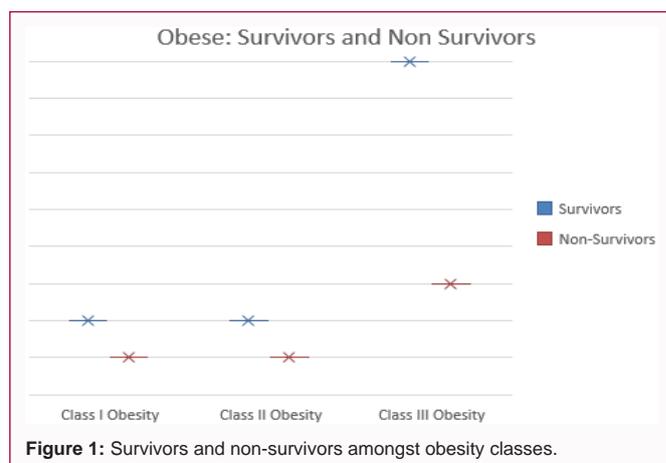
4.5 to 10). Laboratory and diagnostics of this patient cohort included a vast range of peak values amongst patients with median C-Reactive Protein (CRP) values of 180 mg/L (IQR 82 to 240) and fibrinogen 613 mg/dL (IQR 337 to 783). Additional information regarding demographics, clinical characteristics and diagnostics for the entire cohort is provided in Table 1.

### Outcomes

Amongst our cohort, seventy percent of patients (n=14) survived to hospital discharge. Hospital length of stay was a median of 29 days (IQR 20 to 40). ICU length of stay was 27 days median (IQR 15 to

**Table 2:** Demographic and pre-cannulation characteristics amongst survivors and non-Survivors.

Demographics	Survivors (n=14)	Non-Survivors (n=5)	P value
Age	42.5 ± 12.8	35 ± 5.4	0.23
BMI	46.9 ± 12.5	47.4 ± 18.4	0.95
BMI >40 (%)	64.3 (9/14)	40 (2/5)	0.36
BMI >50 (%)	35.7 (5/14)	20 (1/5)	0.52
Overweight BMI 25 kg/m <sup>2</sup> -29.9 kg/m <sup>2</sup> (%)	7.1 (1/14)	20 (1/5)	0.43
Class I Obesity BMI 30 kg/m <sup>2</sup> -34.9 kg/m <sup>2</sup> (%)	14.3 (2/14)	20 (1/5)	0.77
Class II Obesity BMI 35 kg/m <sup>2</sup> -39.9 kg/m <sup>2</sup> (%)	14.3 (2/14)	20 (1/5)	0.77
Class III Obesity BMI >40 kg/m <sup>2</sup> (%)	64.3 (9/14)	40 (2/5)	0.36
Male Gender (%)	50 (7/14)	40 (2/5)	0.71
Black (%)	71.4 (10/14)	60 (3/5)	0.65
Hispanic (%)	21.4 (3/14)	20 (1/5)	0.95
White (%)	7.1 (1/14)	20 (1/5)	0.43
Pregnant	7.1 (1/14)	20 (1/5)	0.43
# of Pre-existing conditions	1.6 ± 1	0.6 ± 0.8	0.06
Asthma (%)	42.9 (6/14)	0 (0/5)	0.08
Hypertension (%)	50 (7/14)	40 (2/5)	0.71
Diabetes (%)	28.6 (4/14)	0 (0/5)	0.19
Other Pre-cannulation Factors/Characteristics:			
APACHE II	9.5 ± 3.9	9.9 ± 1	0.83
SOFA	6.5 ± 2.7	7.76 ± 1.7	0.36
RESP	3.36 ± 1.4	4.1 ± 0.5	0.45
Vasopressor Requirement (%)	57.1 (8/14)	100 (5/5)	0.08
Norepi ≥ 0.1 mcg/kg/min or need for 2 vasopressors	28.6 (4/14)	60 (3/5)	0.22
RRT Requirement (%)	21.4 (3/14)	0 (0/5)	0.27
P/F ratio	102.6 ± 54.5	76.4 ± 14.6	0.31
CRP	167.4 ± 104	262.5 ± 144	0.13
Fibrinogen	580.6 ± 183.5	486.6 ± 92.4	0.29
Lactate	1.3 ± 0.4	1.42 ± 0.41	0.57
D-dimer	4504 ± 4280	3812 ± 1475.7	0.73



32). Duration of ECMO support requirement was a median of 12.5 days (IQR 6 to 17). Although none of the pre-cannulation criteria characteristics examined were found to be statistically significant

predictors of mortality; notably absent differences amongst survivors and non-survivors with respect to BMI ( $p=0.95$ ) was observed. Subsequent evaluation of subsets of extremely obese patients with BMI $>40$  kg/m<sup>2</sup> and BMI $>50$  kg/m<sup>2</sup> demonstrated lack of statistical significance with respect to mortality prediction ( $p=0.36$  and  $p=0.52$  respectively). A comparison between survivors and non-survivors with respect to pre-cannulation characteristics is provided in Table 2.

## Discussion

In this cohort we examined several pre-cannulation characteristics including, but not limited to age, Body Mass Index (BMI), pregnancy, (P/F ratio) and duration of MV-of our subjects. Despite the inclusion of those with a BMI greater than or equal to 40 into our cohort and a predominance of patients with severe ARDS, we found a mortality similar to those cited in the most recent ELSO reports of COVID-19 associated ARDS, and historically cited in non-COVID associated ARDS publications [10,21]. Amongst the examined pre-cannulation criteria and characteristics of this cohort, no individual variables or characteristics including obesity were found to be associated with increased mortality.

Lack of association between increased mortality with respect to gender, and race are consistent with those reported in patients suffering from COVID-19 who required ECMO [10]. The association between BMI and mortality in VV-ECMO-particularly with respect to ARDS secondary to COVID-19- has yet to be thoroughly explored in the literature. Although few publications prior to the COVID-19 pandemic have demonstrated feasibility of cannulation, suggested technical modifications to accommodate for increased flow requirements and reported favorable outcomes in obese adult patients placed on V-V-ECMO, published results of cohorts with respiratory failure secondary to COVID-19 have predominantly consisted of patients with BMI less than 40 thus limiting awareness of outcomes in this patient population [28,29]. The limitations of our series include the number of patients evaluated in a retrospective nature from a single medical center. However, our institution is a regional ECMO center that services a state and surrounding region with a diverse population of over 15 million people. The small sample size may result in a study that is underpowered [10,16,28] to show a statistical difference, however, there is no signal in the data suggesting that morbidly obese with COVID-19 have worse outcomes on VV ECMO. We were careful in drawing conclusions from this dataset to limit it to non-inferiority. Additional limitations include the lack of long term follow up data beyond survival to hospital discharge and more longitudinal complications due to the relatively recent nature of the COVID-19 pandemic. However, in the interest of time given the ongoing pandemic, we felt that it was important to share our experience in anticipation and ahead of potential subsequent peaks in cases of illness. Severity indices and morbidity predictors selected by our team were guided by current literature and selected based on limitations associated with retrospective review of an electronic medical record.

Amidst the international devastation induced by this pandemic, a substantial amount of information is yet to be understood about critically ill patients with COVID-19 requiring VV-ECMO. Our cohort not only contributes to the existing literature demonstrating a relatively low mortality in patients who receive ECMO support for COVID-19 associated ARDS, but is hypothesis generating with respect to the potential non inferiority of outcomes and survival on ECMO for those who are morbidly obese. Additionally, it raises

the question as to whether ECMO referral centers should consider modifications to cannulation consideration and expansion of inclusion criteria employed prior to the COVID-19 pandemic. Morbidly obese patients have been historically underrepresented in ECMO outcomes literature, but our findings suggest the utilization of ECMO for COVID-19 associated ARDS in these patient subsets should be considered and outcomes should be further explored.

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