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Veno-venous extracorporeal membrane oxygenation in patients with SARS-CoV-2 pneumonia in Brazil: a case series

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ABSTRACT

Objective: The world has been suffering from the COVID-19 pandemic. Some COVID-19 patients develop severe viral pneumonia, requiring mechanical ventilation and measures to treat refractory hypoxemia, such as a protective ventilation strategy, prone positioning, and the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO). We describe a case series of 30 COVID-19 patients who needed VV-ECMO at the *Hospital Alemão Oswaldo Cruz*, located in the city of São Paulo, Brazil. **Methods:** We included all patients who required VV-ECMO due to COVID-19 pneumonia between March of 2020 and June of 2021. **Results:** Prior to VV-ECMO, patients presented with the following median scores: SOFA score, 11; APPS score, 7; Respiratory ECMO Survival Prediction score, 2; and Murray score, 3.3. The 60-day-in-hospital mortality was 33.3% (n = 10). **Conclusions:** Although our patients had a highly severe profile, our results were similar to those of other cohort studies in the literature. This demonstrates that VV-ECMO can be a good tool even in a pandemic situation when it is managed in an experienced center.

Keywords: Extracorporeal membrane oxygenation; COVID-19; SARS-CoV-2; Respiratory distress syndrome.

INTRODUCTION

ARDS is a challenging condition in intensive care, and if it is left untreated, it can lead to multiple organ failure and death. It can be defined as an acute condition of hypoxemia, whose pathophysiology is defined by immune-mediated disruption of the alveolar-capillary interface and noncardiogenic edema formation.[1] Since December of 2019, the world has been suffering from COVID-19, caused by the new SARS-CoV-2 virus. Most patients have mild to moderate symptoms; however, some develop severe viral pneumonia, requiring mechanical ventilation and measures to treat refractory hypoxemia, such as a protective ventilation strategies and prone positioning. However, mortality can be as high as 60%, which makes extracorporeal membrane oxygenation (ECMO) a therapeutic option in some cases.[2,3]

Our goal was to present a case series of patients with ARDS caused by COVID-19 treated at the *Hospital Alemão Oswaldo Cruz* (HAOC), a private hospital in the city of São Paulo, Brazil, who needed veno-venous ECMO (VV-ECMO).

METHODS

We included all patients admitted to the HAOC who required VV-ECMO due to COVID-19 pneumonia, confirmed by nasal swab PCR testing, and were cannulated by the hospital ECMO team between March of 2020 and June of 2021.

The HAOC is a private hospital located in the city of São Paulo and is an accredited ECMO center by the Extracorporeal Life Support Organization (ELSO). Patients were cannulated when ECMO material was available and there was an indication for VV-ECMO in accordance with the ELSO guidelines,[4] as follows: hypoxemia, defined as a Pao_2/Fio_2 ratio lower than 80 for at least 6 h or lower than 50 for at least 3 h after using a neuromuscular blocker and prone positioning; and/or hypercapnia, defined as a pH lower than 7.25 associated with a pCo_2 above 60 mmHg for at least 6 h. Patients could have already been admitted to our service or been cannulated by the ECMO Travel Team and transferred to our institution.

Patients were managed in accordance with our institutional protocol, using volume-controlled ventilation in the initial phase of ventilation, aiming at obtaining protective ventilation, defined by V_T less than or equal to 6 mL/kg of the predicted weight and plateau pressure below 30 cmH_2O. PEEP was defined in accordance with the lower-PEEP table provided in a clinical trial.[5] Other ventilation modes such as pressure-regulated volume control or other PEEP definition methods, such as PEEP titration, were used as an exception when protective

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ventilation was not achieved by means of the standard protocol. During the ventilatory weaning phase, pressure-controlled ventilation and pressure support ventilation were used. Regarding sedation, given the prolonged ventilation and sedation time, midazolam and fentanyl were the standard medications, propofol being used in cases with more difficult sedation. Other sedatives could be used as a strategy for weaning from sedation, such as ketamine and dexmedetomidine. Patients received neuromuscular blockers when they had a Pao_2/Fio_2 ratio below 150 or asynchrony unresolved with ventilatory adjustment. The selection of the neuromuscular blocker varied based on its availability. At the beginning of the study, four intensive care physicians formed the ECMO team, which had had four years of experience. They were also assisted by trained ECMO management nurses even when cannulation was performed in another site by the ECMO travel team. Cannulation was usually performed by two physicians and a nurse, preferably through the right jugular vein and the right femoral vein using an ultrasound-guided puncture when available. Contraindications of ECMO and indications of decannulation were guided in accordance with the ELSO guidelines.[4]

Data were collected retrospectively using the electronic medical record system, including laboratory tests from admission until discharge, death, transfer, or 60 days after ECMO, whichever came first. Categorical data are displayed as absolute and relative frequencies, whereas discrete and continuous data are displayed as medians and interquartile ranges considering a non-normal distribution.

RESULTS

Thirty patients who underwent VV-ECMO were included in this case series. The demographic characteristics of the patients are summarized in Table 1. Male and female patients were 16 (53.3%) and 14 (46.7%), respectively. Most patients were cannulated at our hospital, and only 2 patients were cannulated at another site by our ECMO travel team and then transferred to our hospital. The median age of the sample was 53 years (41-60 years), ranging from 26 to 73 years. Obesity was the most prevalent comorbidity, in 20 patients (66.7%), followed by hypertension, in 9 (30.0%), and hypothyroidism, in 6 (20.0%). There were at least two comorbidities in 15 (50.0%) of the cases. Only 1 patient had a previous COVID-19 vaccination record. However, the use of any medication under study for COVID-19 at the time was high, azithromycin being the most common, in 13 patients (43.3%), followed by colchicine, in 6 (20.0%), and hydroxychloroquine, in 4 (13.3%). There was also a high prevalence of antibiotic use. Only 2 patients had not used them before ECMO.

The median ventilation days before ECMO was 4 (1-10), whereas the median duration of symptoms was 19 days (13-24 days), and the length of hospital stay was 11 days (5-15 days). The clinical characteristics of the patients before ECMO are summarized in Table 2, including rescue therapy used before cannulation. As for severity, patients had a median SOFA score of 11 (8-12); a median APPS (acronym for Age, Pao_2/Fio_2 ratio, and Plateau pressure measured at 24 h after diagnosis of ARDS Score) of 7 (7-8); a median Respiratory ECMO Survival Prediction (RESP) score of 2 (2-5); and a median Murray score of 3.3 (3.3-3.0). As for ventilatory characteristics, patients had a median pulmonary compliance of 20 cmH_2O (14-24 cmH_2O) and required a median plateau pressure of 28.5 cmH_2O (25-32 cmH_2O). All patients were treated with a neuromuscular blocker (median duration = 48 h [5-144 h]), 23 patients also used the prone position maneuver, and only 1 patient used inhaled nitric oxide. Regarding laboratory characteristics, the median Pao_2/Fio_2 ratio was 66 (54-75), and there was a high prevalence of lymphopenia with a median lymphocyte count of 680 cells/mm^3 (550-990 cells/mm^3). The median pH was 7.31 (7.23–7.40).

The main indication for ECMO was hypoxemia, in 25 patients (83.3%), and hypercapnia was the sole indication in only 1 (3.3%), whereas both were present in 4 (13.3%). The characteristics of ECMO are summarized in Table 3. The median diameter of the inflow cannula was 25 Fr (23-29 Fr), whereas that of the outflow cannula was 19 Fr (19-21 Fr).

Table 1. Characteristics of the sample (N = 30).[a]

Characteristic	Result
Sex	
Male	16 (53.3)
Female	14 (46.7)
Location	
In site	28 (93.3)
ECMO travel team	02 (06.7)
Age, years	53 [41-60]
Comorbidities	
Hypertension	09 (30.0)
Diabetes	05 (16.7)
Asthma	04 (13.3)
Hypothyroidism	06 (20.0)
Obesity	20 (66.7)
BMI, kg/m^2	
< 25.0	05 (16.7)
25.0-29,9	05 (16.7)
30.0-34,9	12 (40.0)
35.0-39,9	07 (23.3)
> 40.0	01 (03.3)
Vaccinated for COVID-19	01 (03.3)
Prior drug use	
Any antibiotic	28 (93.3)
Tocilizumab	01 (03.3)
Hydroxychloroquine	04 (13.3)
Azithromycin	13 (43.3)
Remdesivir	01 (03.3)
Colchicine	06 (20.0)

ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n (%) or median [IQR].

Table 2. Clinical characteristics of the patients before the use of extracorporeal membrane oxygenation (N = 30).[a]

Characteristic	Result
Time to ECMO, days	
First symptoms to ECMO	19 [13-24]
Hospital admission to ECMO	11 [5-15]
Intubation to ECMO	4 [1-10]
Total SOFA score[b]	11 [8-12]
Vasoactive-inotropic score[b]	6 [0-25]
APPS[b]	7 [7-8]
RESP score[b]	2 [2-5]
Murray score	3.3 [3.3-3.5]
Ventilation parameters	
FIO_2, %[b]	100 [100-100]
PEEP, cmH_2O[b]	10 [10-10]
RR, breaths/min	34 [30-36]
Plateau pressure, cmH_2O[c]	28.5 [25-32]
Driving pressure, cmH_2O[c]	17 [13-24]
Pulmonary compliance, cmH_2O[c]	20 [15-24]
Laboratory analysis	
pH[b]	7.31 [7.23-7.40]
PaO_2/FIO_2[b]	66 [54-75]
pCO_2, mmHg[b]	55 [47-68]
Plasma bicarbonate, mmol/L[e]	27 [22-32]
Arterial lactate, mg/dL	14 [11-20]
White cell count, cells/mm^3[c]	12.920 [9.510-15.300]
Lymphocytes, cells/mm^3[c]	680 [550-990]
Serum creatinine, mg/dL[c]	0.90 [0.57-1.36]
Rescue therapy before ECMO	
Neuromuscular blockade, h[d,f]	48 [5-144]
Prone positioning	23 (76.7)
Inhaled nitric oxide	01 (3.3)

ECMO: extracorporeal membrane oxygenation; APPS: acronym for Age, PaO_2/FIO_2 ratio, and Plateau pressure measured at 24 h after diagnosis of ARDS Score; and RESP: Respiratory ECMO Survival Prediction score. [a]Values expressed as n (%) or median [IQR]. [b]n = 29. n = 28. [d]n = 27. [e]n = 24. [f]All patients used neuromuscular blockers, but only 27 patients had the total number of hours of treatment recorded.

Table 3. Characteristics of extracorporeal membrane oxygenation use (N = 30).[a]

Characteristic	Result
ECMO indication criteria	
Hypoxemia	25 (83.3)
Hypercapnia	01 (03.3)
Both	04 (13.3)
Diameter of inflow cannula. Fr	25 [23-29][b]
Diameter of outflow cannula. Fr	19 [19-21][b]
ECMO parameters on ECMO Day 1	
ECMO blood flow. L/min	4.5 [4.2-5.0]
Sweep gas flow. L/min	5 [4-6][c]
FmO_2. %	100 [100-100]
Ventilation parameters on ECMO Day 1	
FIO_2. %	30 [30-40]
PEEP. cmH_2O	10 [8-10]
RR. breaths/min	10 [10-12]
Plateau pressure. cmH_2O	23 [21-26][d]
Driving pressure. cmH_2O	14 [12-15][d]
Drug use	
Antibiotics for any reason	29 (96.7)
Corticosteroids	30 (100.0)
Anticoagulation drugs	29 (96.7)
Vasoactive drugs	24 (80.0)
Tracheostomy during ECMO	14 (46.7)
Renal replacement therapy during ECMO	11 (36.7)

ECMO: extracorporeal membrane oxygenation; and FmO_2: membrane fraction of oxygen. [a]Values expressed as n (%) of patients or median [IQR]. [b]n = 28. [c]n = 29. [d]n = 21.

Regarding ventilatory characteristics, there was a reduction in plateau pressure, with the median value of 23 cmH_2O (21-26 cmH_2O). However, these data were missing in 9 patients (30%). Antibiotic use remained high, in 29 (96.7%) of the patients. All of the patients used corticosteroids, and only 1 patient received no anticoagulation therapy. Dialysis during ECMO was required in 11 patients (36.7%), and so was tracheostomy, in 14 (46.7%).

The 60-day-in-hospital mortality was 33.3% (n = 10). Among the survivors, 13 (43.3%) were discharged, 5 (16.7%) were still hospitalized off of ECMO, 1 (3.3%) was still hospitalized on ECMO, and 1 (3.3%) was transferred to another hospital for lung transplantation (still on ECMO). The main cause of death was septic shock, in 7 patients (23.3%), and hemorrhagic stroke, in 3 (10.0%). Outcomes and complications are summarized in Table 4. The median duration of ECMO was 12 days (8-22 days). The most common complications were microbiologically confirmed infection, in 23 patients (76.7%); major bleeding, in 10 (33.3%); severe thrombocytopenia, in 7 (23.3%); and tachyarrhythmia requiring electrical cardioversion, in 4 (13.3%). Anticoagulation was discontinued in 16 patients (53.3%). Regarding infections, 17 patients (56.6%) had ventilator-associated pneumonia; 6 (20.0%) had bloodstream infection, and 3 (10.0%) had urinary tract infection. There was a necessity to change the ECMO circuit in only 5 patients (16.6%), adding a second inflow cannula in 3 patients (10%), adding a second membrane in 1 (3.3%), and replacing the pump and membrane due to clotting, in 1 (3.3%).

DISCUSSION

In this case series, we describe the cases of 30 patients with COVID-19 pneumonia who required VV-ECMO support due to hypoxemia and/or hypercapnia, representing the experience in our center during the pandemic. The 60-day mortality rate in this sample was 33.3%. Mortality in VV-ECMO cohorts due to COVID-19 has great variability in the literature. The first annual report of the cases found in the ELSO registry comprised a sample of 1,035 patients in early 2020 and demonstrated a 90-day mortality rate of 37%,[6] which is close to what was found in our series.

Table 4. Outcomes and complications (N = 30).[a]

Variable	Result
Outcome in 60 days	
Death	10 (33.3)
Hospital discharge	13 (43.3)
Still hospitalized off of ECMO	05 (16.7)
Still hospitalized on ECMO	01 (3.3)
Transfer for transplant	01 (3.3)
Cause of death	
Septic shock	07 (23.3)
Hemorrhagic stroke	03 (10.0)
Days on ECMO	12 [8-22]
Complications	
Major bleeding	10 (33.3)
Severe thrombocytopenia	07 (23.3)
Tachyarrhythmia	04 (13.3)
Microbiologically confirmed infections[b]	23 (76.7)
Ventilator-associated pneumonia	17 (56.7)
Bloodstream Infection	06 (20.0)
Urinary tract infection	03 (10.0)
Circuit changes	05 (16.7)
Second inflow cannula	03 (10.0)
Second membrane	01 (3.3)
Membrane change	01 (3.3)
Pump change	01 (3.3)

ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n (%) of patients or median [IQR]. [b]It refers to the number of patients who had some clinically overt infection with the infectious agent identified in a culture compatible with the focus of the infection. Even when the patient had more than one type of infection, he/she was counted only once.

Also, an American cohort study involving 130 patients reported a similar 60-day mortality rate of 34.6%,[7] as did a British cohort study involving 43 patients (32.6%),[8] and a cohort of 76 patients in Marseille, France (38%).[9] However, the second annual ELSO registry report showed that, among the 3,777 new cases reported, the 90-day mortality rate rose up to 51.9% in centers that had already participated in the first report and to 58.9% in new centers,[10] which is considerably higher than the rate found in our series. Similarly to these data, a cohort study in Warsaw involving 75 patients reported a 30-day mortality rate of 61.3%,[11] and a cohort study with 302 patients in Paris showed a 90-day mortality rate of 54%.[12] Pre-COVID mortality rates in patients undergoing VV-ECMO also showed high variability. Combes et al.[3] reported a 60-day mortality rate of 35%. However, a large German cohort study that collected data between 2010 and 2016 showed, in a sample of 12,572 patients on VV-ECMO, much higher mortality rates, varying each year from 53% to 66%.[13]

Some factors may explain this difference. In a systematic review and meta-analysis on the use of ECMO in COVID-19 involving 16 cohorts and 706 patients, Chong et al.[14] reported that survivors were younger, had fewer comorbidities, had higher pH, and used renal replacement therapy or vasoactive drugs less frequently. In that study, survivors had a mean age of 51.28 years vs. 55.15 years in nonsurvivors.[14] Our series had a mean age of 51 years and a median age of 53 years. Chong et al.[14] reported that patients with less than two comorbidities and those with two or more comorbidities presented with mortality rates of 23% and 31%, respectively. In our sample, 50% of cases had two or more comorbidities. The mean pH of survivors and nonsurvivors was 7.33 and 7.26, respectively, in that review,[14] whereas the mean and median of pH in our series were 7.3 and 7.31, respectively. In that study, renal replacement therapy was necessary in 21% and 39% of survivors and nonsurvivors, respectively,[14] whereas our patients required renal replacement therapy in 36.7% of the cases (considering the whole sample, regardless of their being survivors or nonsurvivors). Finally, vasoactive drug use was required in 76% of the survivors and in 92% of nonsurvivors in that study,[14] while vasoactive drugs were used in 80% of our cases. Table 5 compares our results with those of other four cohort studies regarding the use of ECMO in COVID-19 patients and demonstrates that our case series presented with either similar or worse risk factors than did those studies with similar mortality rates, and sometimes they were comparable to cohorts with higher mortality rates.

In addition to these factors, when analyzing the pre-ECMO data from our case series, we realized that the sample represents a group of patients who, despite having been cannulated relatively early, presented with high clinical severity and severe ARDS in a very advanced state. Our patients presented with median values as follows: SOFA score, 12; RESP score, 2; APPS score, 7; Murray score, 3.3; ventilation days before ECMO, 4 days; compliance, 20 cmH_2O; and Pao_2/FIO_2 ratio, 66. These data demonstrate a more severe patient profile than do other cohorts with similar mortality rates, which is comparable to the severity found in cohorts with higher mortality rates. This comparison is also shown in Table 5.

Another important aspect of our series was anticoagulation. All of the patients were maintained on or started anticoagulation during cannulation. However, 33.3% of them had major bleeding (defined as clinically overt bleeding which was fatal, or associated with a reduction in hemoglobin level of 2 g/dL, or transfusion of at least two units of packed red blood cells), including 3 cases of lethal hemorrhagic stroke (representing 10% of the sample and 30% of the deaths), and 23.3% had severe thrombocytopenia, causing anticoagulation to be suspended in 53.3% of the cases. However, only 1 patient had circuit clotting that required circuit replacement, and there was no diagnosis of clinical thrombosis such as deep vein thrombosis or pulmonary thromboembolism after cannulation. These data greatly diverge from those in the literature. Ripoll et al.[15] found in their observational study the occurrence of thrombosis in 66.7% of 30 patients with COVID-19 on VV-ECMO even without circuit clotting. It is noted, however, that this difference may be due

Table 5. Comparison among studies on the topic.[a]

Characteristic	Study				
	Shaefi et al.[7]	Zhang et al.[8]	Daviet et al.[9]	Lebreton et al.[12]	Present study
Participants, N	130	43	76	302	30
Country	USA	UK	France	France	Brazil
Mortality rate	34.6%	32.6%	38%	54%	33.3%
Age, years	45	49	61	52	53
More than two comorbidities	31.6%	N/A	N/A	N/A	50%
pH	N/A	N/A	7.30	7.31	7.31
Renal replacement therapy	21.8%	37.9%	33%	43%	36.7%
Use of vasoactive drugs	N/A	79.3%	N/A	N/A	80%
SOFA score	N/A	6	7	12	11
RESP score	3	4	1	N/A	2
Ventilation use before ECMO, days	2	5	6	5	4
Pao_2/Fio_2	85	67.5	71.5	61	66
Pulmonary compliance, cmH_2O	28	N/A	23	N/A	20
Thrombosis	22.6%	N/A	N/A	N/A	0
Circuit coagulation	N/A	N/A	15%	10%	3.3%
Major bleeding	24.7%	18.6%	57%	43%	33.3%
Hemorrhagic stroke	4.2%	N/A	N/A	12%	10%
Severe thrombocytopenia	N/A	N/A	N/A	18%	23.3%

ECMO: extracorporeal membrane oxygenation; and RESP: Respiratory ECMO Survival Prediction. [a]Values expressed as median, except where otherwise indicated.

to their active diagnosis,[15] something that was not performed in our series. Specifically, the occurrence of hemorrhagic stroke in the ELSO report varied from 5% to 7% between the groups.[6] Table 5 also shows the comparison of the occurrence of coagulation and anticoagulation complications between our study and four other cohorts.[7-9,12] Although the ELSO guidelines still indicate the use of anticoagulation in VV-ECMO,[5,16] there is a current tendency to use less anticoagulation even though there is no formal contraindication for it.[17] The results of our series corroborate this trend.

Because the present study is a case series, the main limitations are related to the design of the study itself. Series of cases, since they are observational studies, but mostly because they have no comparison groups, are especially subject to bias, selection bias being the most relevant one. Our study is also retrospective, which ends up contributing to this limitation. Another important factor to be mentioned was the atypical situation imposed by the pandemic that generated a lack of resources; therefore, the availability of ECMO machines, membranes, and circuits were limited, which demanded an extremely criterial decision-making prior to cannulating a patient.

In conclusion, we herein present our experience of 30 cases of patients with COVID-19 who underwent VV-ECMO. Although our patients had a highly severe profile, we obtained similar results than those in other cohort studies in the literature. This demonstrates that VV-ECMO can be a good tool even in a pandemic situation when it is managed in an experienced center.

AUTHOR CONTRIBUTIONS

FAD and FLF co-supervised the study. LMCRB and GNA: data collection and drafting the manuscript. GBFD: data collection. DI and LMCRB: data analysis. All of the authors actively participated in study conception and review of the manuscript, as well as approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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