Extracorporeal membrane oxygenation support in children with severe coronavirus disease-2019: A case series

Candice Torres de Melo Bezerra Cavalcante,[a,b]* Andrea Consuelo de Oliveira Teles,[a] Isabel Cristina Leite Maia,[a] Valdester Cavalcante Pinto,[a] Jeanne Araújo Bandeira,[a] Emanoel Pimentel Cruz,[a] Raimunda Selma Antero Sousa Onofre,[a] Fabrício Barreira Pombo,[a] Marcelo Borges Cavalcante,[b,c] and Klebia Magalhães Pereira Castello Branco [a]

[a]Hospital Dr. Carlos Alberto Studart Gomes, Av. Washington Soares, 1321 - Edson Queiroz, Fortaleza, CE CEP 60811-905, Brazil
[b]Medical Course, Universidade de Fortaleza - UNIFOR, Fortaleza, CE, Brazil
[c]Postgraduate Program in Medical Sciences, Universidade de Fortaleza - UNIFOR, Fortaleza, CE, Brazil

The Lancet Regional Health - Americas 2022;11: 100260
Published online 7 May 2022
https://doi.org/10.1016/j.lana.2022.100260

Summary

Background The coronavirus disease-2019 (COVID-19) pandemic has predominantly affected the adult population, but with a significantly lower prevalence in children. Most pediatric patients with COVID-19 have mild course; however, a small number progressed to acute respiratory distress syndrome, hypoxemia, despite optimized conventional therapies. Thus, this study aimed to report a series of six cases of children with severe acute respiratory syndrome coronavirus 2 infection who were supported by extracorporeal membrane oxygenation (ECMO) due to refractory hypoxemic respiratory failure.

Methods This observational, retrospective, and descriptive study reported a series of cases. Data were retrospectively collected from the medical records of patients who were admitted to the Pediatric Cardiologic Intensive Care of Hospital Dr. Carlos Alberto Studart Gomes and Hospital Regional da Unimed, between March 1, 2020, and June 30, 2021. Sociodemographic, clinical, and laboratory data were analyzed.

Findings The median age was 1.8 years (range: 0.4–14.5 years), 66.7% were males, and weight varied from 13 to 110 kg. The mean time between the onset of symptoms and cannulation, ECMO duration, and ventilation time were 15 days (range: 6–24 days)], 11 days (range: 6–19 days), and 20.5 days (range: 14–33 days), respectively. Five (83.3%) children were successfully decannulated and four survived with hospital discharge. One child died on ECMO support due to multiple organ dysfunction syndromes after 13 days and another one died 3 days after decannulation due to extensive hemorrhagic stroke. Our case series revealed a 33.3% in-hospital mortality rate. ECMO appears as a viable intervention in selected patients who failed conventional therapies in the pediatric population.

Funding This observational study received no funding.

Keywords: Child; COVID-19; Respiratory distress syndrome; Extracorporeal membrane oxygenation

Introduction

In December 2019, the infectious respiratory disease was initially reported in Wuhan, China. Since then, an unexpected outbreak of a highly contagious novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread globally.[1–3]

The coronavirus disease-2019 (COVID-19) pandemic has predominantly affected the adult population, but with a significantly lower prevalence in children, approximately 1%–5% of children under 18 years old.[4–6] Additionally, the true number of pediatric cases is unknown since a greater proportion of children have asymptomatic disease.[7]

Most pediatric patients with COVID-19 have mild course and better overall outcomes; however, the prevalence of severe and critical cases range from 3% to approximately 11% according to age group, being higher in children under 1 year old. SARS-COV-2-related death

*Corresponding author at: Hospital Dr. Carlos Alberto Studart Gomes, Av. Washington Soares, 1321 - Edson Queiroz, Fortaleza, CE CEP 60811-905, Brazil.
E-mail address: candicebezerratm@gmail.com (C.T.d.M.B. Cavalcante).

Research in context

Evidence before this study

The estimated overall prevalence of COVID-19 in children under 18 years of age is about 1–5%. It is also likely that the true number of pediatric cases is unknown, as a greater proportion of children have asymptomatic disease. The prevalence of severe and critical cases ranges from 3% to 11% according to age group, being higher in children under one year. During the current pandemic, some international organizations including WHO and Extracorporeal Life Support Organization (ELSO) started to consider a role for Extracorporeal Membrane Oxygenation (ECMO) as supportive therapy to COVID-19-related ARDS with refractory hypoxemia despite optimized conventional therapies.

Added value of this study

In this paper, we report a series of six cases of children with severe SARS-CoV-2 infection who were supported by Extracorporeal Membrane Oxygenation (ECMO) due to refractory hypoxemic respiratory failure. Also, we compared our results with those already reported in the literature, especially in case series published in Europe and the United States. To our knowledge, this is the first study in Latin America that evaluated the use of ECMO in cases of COVID-19.

Implications of all the available evidence

The in-hospital mortality rate in our case series was 33.3%, similar to those related by Extracorporeal Life Support Organization (31%) and previous pediatric study (43%). ECMO appears as a viable intervention in selected patients who failed conventional therapies in the pediatric population

in children and adolescents is rare, and children with comorbidities are at greater risk of death.[8–12] These patients can develop acute respiratory distress syndrome (ARDS), a multisystem inflammatory syndrome in children (MIS-C), sepsis, and multiple organ dysfunction syndromes (MODS), which require intensive care unit admission in approximately one-third of cases and the use of mechanical ventilation in 5%.[8,11–15] Supportive care is the mainstay of therapy for patients with severe or critical COVID-19, with mostly good responses. However, some cases progress to respiratory failure refractory to conventional therapies.[16]

Since the novel swine-origin influenza A (H1N1) epidemic in 2009, the use of extracorporeal life support (ESLO) in ARDS has been encouraged as rescue therapy in severe H1N1-related ARDS, whereas numerous studies have shown extracorporeal membrane oxygenation (ECMO) support as an alternative to reduce intensive care unit (ICU) mortality in critical patients.[17–20] During the current pandemic, some international organizations, including the World Health Organization (WHO) and ESLO Organization (ELSO), started to consider the role of ECMO support as supportive therapy for COVID-19-related ARDS with refractory hypoxemia despite optimized conventional therapies s.[21–23] However, little experience was reported in using ECMO support in patients with SARS-CoV-2 infection, especially in children. Most published cases with the use of ECMO in children with COVID-19 were related to shock due to MIS-C.[24]

Therefore, this study aimed to report a series of six cases of children with severe SARS-CoV-2 infection with ECMO support due to refractory hypoxemic respiratory failure.

Materials and methods

This observational, retrospective, and descriptive study with a series of cases was conducted following the Consensus-based Clinical Case Reporting Guideline Development (The CARE Guidelines).

Study setting, design, participants, and data source

Data were retrospectively collected by reviewing the medical records of patients who were admitted to the Pediatric Cardiologic Intensive Care of Hospital Dr. Carlos Alberto Studart Gomes (HCASG) and Hospital Regional da Unimed, between March 1, 2020, and June 30, 2021. The same ECMO team was involved in the care of these patients in both hospitals. All patients had confirmed COVID-19 diagnosis by reverse transcription-polymerase chain reaction (RT-PCR) and presented with severe respiratory failure refractory to conventional therapies and were supported with ECMO therapy. The inclusion criteria were: age under 18 years, confirmed COVID-19 infection and for COVID-19-related ARDS with refractory hypoxemia. The exclusion criteria were death before 24 h of hospitalization, patients with MODS and no more indication for ECMO support indication and refusal to sign the informed consent form.

Treatment

Patients were placed on ECMO support at related hospitals. During which, routine exams were performed to monitor the coagulation every 4 h to adjust the heparin doses. Other laboratory tests were collected to assess other organ involvement and to screen for bacterial infections. Antibiotic regimens were targeted according to culture results. Echocardiograms were performed almost daily to assess myocardial function, as well as to exclude complications.

Measurements

A standardized data collection form was created to obtain sociodemographic data (age, gender, weight,

height, and body mass index [BMI]) and COVID-19-related clinical variables (preexisting medical conditions, onset of symptoms, main symptoms, disease progression, and associated comorbidities). The mode, parameters, and time duration of mechanical ventilation, as well as arterial blood gas control, other laboratory data, and therapies (prone position, use of neuromuscular blockade, nitric oxide, glucocorticoids, intravenous Immunoglobulin [IVIG] therapy, and use of vasoactive drugs) were also recorded. The following variables were collected for ECMO data: type of ECMO, cannulation sites, duration of ECMO runs, main clinical complications, and outcomes.

The main outcome was death. All patients were referred to the outpatient clinic for follow-up. All data were obtained by reviewing the medical records.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences statistical program (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Categorical variables were presented in frequency and percentage, and the numerical data were analyzed in their mean and standard deviation, median, and interquartile rate (IQR), with a confidence interval of 95%. Statistical methods of comparison were not applied, since then could lead to misinterpretation due to the small number of cases in this casee series.

Ethics

The study was approved by the Research Ethics Committee of the HCASG and Ethical approval was obtained from the Brazilian's National Ethics Committee (process number CAAE 56055821.4.0000.5039), with written informed consent from their parents and/or guardians.

Results

A total of six patients aged <18 years with severe COVID-19 were admitted between January 1, 2021, and June 30, 2021, for ECMO support due to COVID-19-related ARDS with refractory hypoxemia. The demographic characteristics of all patients are presented in Table 1. A summary of the evolution, main complications, and outcomes of each case are presented in Table 2.

The median age was 1.8 years (range: 5 months to 16 years) and the median weight was 65 kg (range: 13 −110 kg). All six patients have confirmed SARS-CoV-2 infection by RT-PCR, lower respiratory tract infections signs and symptoms at presentation, and radiological findings of severe ARDS. One patient had a proven associated viral coinfection (sincicial respiratory virus). Of the six patients, five had some comorbidity, of whom four were obese, one was a preterm baby (gestational age of 34 weeks) with bronchopulmonary dysplasia, and one had an abdominal sepsis coinfection following an appendectomy.

The mean time between the onset of symptoms and the start of mechanical ventilation was 10 days (range: 3 −19 days). All patients were ventilated in pressure-controlled mode with the following median parameters: peak inspiratory pressure of 27 cmH_2O (range: 18 −35 cmH_2O); positive end-expiratory pressure of 11.0 cmH_2O (range: 8−14 cmH_2O), and a fraction of inspired oxygen (FiO_2) of 100%. The partial pressure of oxygen/FiO_2 ratio was 65.0 (range: 55−86) and the partial pressure of carbon dioxide was 65 mmHg (range: 61−86 mmHg) before starting ECMO support. The median mechanical ventilation duration before the cannulation was 5 days (range: 1−8 days). Three patients (50%) were placed in a prone position and all patients were on the neuromuscular blockade and only one (16.7%) was put on inhaled nitric oxide.

Regarding COVID-19 therapies and immunomodulators, all patients received glucocorticoids, 33.3% received IVIG, and 66.7% were supported with vasoactive support after starting ECMO. The mean time between the onset of symptoms and cannulation was 14.83 ± 6.24 days (range: 9−19 days). Two (33.3%) patients were supported by venous-venous, whereas four (66.7%) were supported by venous-arterial ECMO support due to inadequately-sized venous cannulas for venous-venous ECMO support. During ECMO support, all children were managed with lung-protective ventilation application in pressure-controlled mode. Of these children, none received a tracheostomy during all hospital stays. All children were anticoagulated with unfractionated heparin according to institutional protocol and without complications of thrombosis. Adjuvant therapies, such as antiviral therapy, immunomodulation, and convalescent plasma, were not administered. Three patients (50%) progressed to acute kidney injury during the ICU stay; of them, none required renal replacement therapy. One patient had severe hepatic dysfunction as part of MODS, two (33.3%) had a hemorrhagic complication, and one (16.7%) had a neurologic complication.

The median ECMO run duration was 11 days (range: 6−19 days) and the mean ventilation time was 20.5 ± 7.2 days (range: 16.2−29.2 days). Five (83.3%) children were successfully decannulated and four survived hospital discharge. One child (16.7%) died on ECMO due to MODS after 13 days and another one died 3 days after decannulation due to extensive hemorrhagic stroke. The first patient was a 3-year-old boy, who was submitted to open appendectomy and progressed with abdominal sepsis and COVID-related ARDS on postoperative day 8. He had mild ventricular dysfunction before the ECMO run. Unfortunately, his condition progressed to an extensive hemorrhagic stroke 6 days after starting ECMO besides considerable pulmonary status

Variables	*Patient 1*	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	3 years	16 years	5 months	5 months	14 years	7 months
Gender	Male	Female	Female	Male	Male	Male
Weight (kg)	28	83	5.4	7.6	110	13
Height (cm)	118	161	70	67	170	69
Z score weight/height for age	>+ 3	>+3	-2	0	>+3	>+3
BMI (kg/m^2)	20.1	32	11	16.9	38	27.3
Pre-existing medical conditions	Obesitity Abdominal sepsis (day 8 of appendix removal)	Obesity	Prematurity (GA 34 w) BDP	CMA	Obesity	Obesity
Onset of symptoms	January 08, 2021	February 10, 2021	February 26, 2021	April 01, 2021	April 10, 2021	April 26, 2021
Pyrexia	Yes	Yes	No	Yes	Yes	Yes
Upper respiratory tract infection	No	No	Yes	Yes	Yes	Yes
Lower respiratory tract infection	Yes	Yes	Yes	Yes	Yes	Yes
Gastrointestinal symptoms	Yes	Yes	No	No	Yes	No
Radiological findings suggestive of pneumonia/ ARDS	Yes	Yes	Yes	Yes	Yes	Yes
Viral co-infection	No	No	No	No	No	Yes (RSV)
EI	January 11, 2021	March 01, 2021	March 10, 2021	April 06, 2021	April 18, 2021	May 13, 2021
Canullation	January 19, 2021	March 06, 2021	March 16, 2021	April 07, 2021	April 23, 2021	May 13, 2021
Pre-ECMO intubation (days)	8	5	6	1	5	1
Conventional ventilation						
• PIP (cmH_2O)	34	18	20	24	30	35
• PEEP (cmH2o)	14	12	10	8	14	10
• FiO2 (%)	100	100	100	100	100	100
• PaO2/FiO2	65	58.8	86.3	63	55	63
Pre-ECMO support						
• Prone position	Yes	Yes	No	No	Yes	No
• Neuromuscular blockade	Yes	Yes	Yes	Yes	Yes	Yes
• NO	No	No	No	Yes	No	No
COVID-19 therapies/immunomodulators						
-Glucocorticoids	Yes	Yes	Yes	Yes	Yes	Yes
- IVIG	No	Yes	No	Yes	No	No
- Vasoactive support	Yes	Yes	No	Yes	No	Yes
Pre-ECMO blood gas						
pH	7.3	7.2	6.9	7,0	7.2	7.3
$PaCO_2$ (mmHg)	64.1	70	65	86	61	65
PaO_2 (mmHg)	65.1	58.8	54.2	63	55	35

Table 1 *(Continued)*

Variables	*Patient 1*	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
$SatO_2$ (%)	85	89	83	77	79	63
Lactate (mmol/L)	1.1	0.9	1.7	4.2	1.2	2.5
Ventricular dysfunction	Moderate biventricular dysfunction EF: 32 %	No	No	No	No	Moderate biventricular dysfunction
Inflammatory tests						
D-dimer (µg/dL)	21.4	3.8	1.2	1.0	15.9	0.6
Fibronogen (mg/dL)	244	615	120	141	447	201
CPK (U/L)	-		-	109	755	173
CRP (mg/L)	8.6	6.4	-	4.0	18.9	10.7
Ferritina (ng/mL	727	-	-	382.3	-	190.8
Troponin (ng/mL)	-	-	-	-	< 0,1	9.1
LDH (U/L)	1192	-	-	-	822	750

***Table 1*: Demographic characteristic and clinical variables of six patients supported on ECMO.**

GA (gestational age); BMI (body mass index); RSV (respiratory sincicial virus); ECMO (extra-corporeal membrane oxygenation); CMA(cow's milk allergy); MIS-C (Multisystem inflammatory syndrome in children); ARSD (acute respiratory distress syndrome); EI (endotracheal intubation); PEEP (positive end-expiratory pressure); PIP (peak inspiratory pressure); FiO_2 (fraction of inspired oxygen); PaO_2 (partial pressure of arterial oxygen); $PaCO_2$ (partial pressure of carbone dioxide); $SatO_2$ (saturation of oxygen); IVIG (intravenous immunoglobulin therapy); D-dimer: reference value < 0.5 µg/dL; Fibrinogen: reference value: 180–350 mg/dl; CPK (creatine phosophokinase): reference values < 180 a 200 U/L); CRP (C-reactive protein): reference values < 0,1 mg/dL; Ferritin: reference values: 30–400 ng/mL; Troponin: reference value <0.4 ng/mL); LDH (lactic acid dehydrogenase): reference value < 280 U/L.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Support type	V-A	V-V	V-A	V-A	V-V	V-A
Cannulation (date)	01/19/21	03/06/21	03/16/21	04/07/21	04/23/21	05/13/21
Sites of canullation	LFV/ RCA	RJV/ RFV	RJV/RCA	RJV/RCA	RJV/ RFV	RJV/RCA
Decanullation (date)	01/25/21	03/18/21	03/23/21	04/18/21	05/12/21	05/24/21
Duration of ECMO (days)	6	13	7	11	19	11
AKI	No	Yes	Yes	No	Yes	No
Hepatic disfunction	No	Yes	No	No	Mild	No
Hemorragic complications	Hemorrhagic stroke	Yes	No	No	No	No
Neurologic complications	Hemorrhagic stroke	No	No	No	No	No
Mechanical ventilation time (days)	14	17	18	28	33	23
Outcome	Death	Death	Discharge	Discharge	Discharge	Discharge
Cause of death	BD	MODS	-	-	-	-

***Table 2*: ECMO support data, complications and outcomes.**
ECMO: extra-corporeal membrane oxigenation; V-V: venovenous ECMO; V-A: venoarterial ECMO; LFV: left femoral vein; RCA: right carotid artery; RJV: right jugular vein; RFV: right femural vein; AKI: acute kidney injury; RST: renal substituion therapy; BD: brain death; MODS: Multiple Organ Dysfunction Syndrome.

improvement. The second case was a 16-year-old girl with class 1 obesity (BMI of 32 kg/m^2), who progressed to MODS and did not show significant radiological improvement during treatment. All the remaining patients are doing well after hospital discharge and are asymptomatic on outpatient clinical follow-up.

Discussion

In the last four decades, ECMO has become a lifesaving tool to support severe forms of respiratory and cardiac failure in neonates, children, and adults. The number of its runs has had a dramatic rise over the last 25–30 years.[19,25] The latest ELSO reported >75,000 pediatric patients who received ECMO support, with survival to decannulation or transfer rates ranging from 42% to 73% depending on indications and age group.[26] Herein, we report six patients on ECMO support due to COVID-19-related ARDS with refractory hypoxemia. Ages varied and comorbidities were present in most cases. A mortality of 33% was obtained in this case series.

During the 2009 H1N1, as well as the Middle East respiratory syndrome coronavirus outbreaks, great interest was paid in the use of ECMO support as rescue therapy for patients with severe ARDS.[18–21,23] More recently, the WHO and ESLO have endorsed the use of ECMO support for adult patients with COVID-19-related refractory respiratory failure with high predicted mortality.[27,28]

SARS-CoV-2 seems to less severely affect children than adults; however, the pediatric population can progress with severe disease forms. Derespina et al. performed a retrospective observational study to describe the clinical manifestations and outcomes of critically ill children (from 1 month to 21 years) with COVID-19 in New York City, who are admitted to pediatric ICUs from March to May 2020. The median age of the 70 children was 15 (IQR: 9–19) years; 61.4% were males, and 74.3% had comorbidities. Vasopressor support was required in 20% of patients, and ARDS developed in 30%. Most of the critically ill children were adolescents, with comorbidities, requiring some form of respiratory support (70%), and one requiring ECMO support.[9]

A systematic review was performed with a total of 7480 children and newborns with SARS-COV-2 (0–18 years). Patients mainly showed mild to moderate signs of infections. Severe and critically ill children accounted for 2% and 0.6% of the total sample size, respectively. The overall estimated mortality was 0.08%, with a higher proportion of newborns with a critical illness. The underlying disease was identified in 20% of children and none showed worse outcomes compared to previously healthy patients.[29]

To our knowledge, this is the first study on pediatric COVID-19 that is supported by ECMO in Latin America, outside of North America and Europe. Our hospitals are located in the limited source Northeast region of Brazil and have become references for congenital heart disease treatment in the region. Since 2012, we have started on an ECMO program and conducted 65 ECMO runs. All patients were transferred to our service from other tertiary pediatric hospitals without an ECMO program.

ECMO applications for children with COVID-19 are scarcely reported, thus its comparison with other experiences is difficult. The largest case series of ESLO use in children with SARS-CoV-2 infection was performed by The European Chapter of the ELSO (EuroELSO). They published a prospective survey among 52 European neonatal and pediatric centers from March 15 to the end of June 2020, during the first wave of the COVID-19 pandemic. They included seven patients from four European countries aged 54 days to 16 years, of whom four patients were older than 11 years; the median age was 11.5 years (range: 54 days–16 years), 43% were males, and two (29%) had underlying comorbidities. The mean ECMO duration was 7 days (range: 7–11 days), with a median ICU stay of 16 days (range: 7–20 days). Five (71%) children were successfully decannulated and four (57%) survived hospital discharge.[30] The most severe cases seem to occur in two pediatric groups: newborns and adolescents. Herein, the age at presentation ranged from 5 months to 16 years and half of our patients were younger than 1 year.[9,29,30]

Brazil is a federative unit that comprises 26 states and 1 federal district, with approximately 212 million inhabitants. Our state, named Ceará, is located in the northeastern and has approximately 8.8 million inhabitants. A total of 601,067 cases were confirmed with COVID-19 in our state until December 8, 2021. The number of cases in patients ages <19 years were 74,128, which corresponded to 12.3% of the total cases (<1 year was 5,534 cases; 1–9 years was 20,526 cases, and 10–19 years was 48,068, which corresponds to 7.4%, 27.7%, and 64.9% of pediatric cases, respectively). To date, the overall mortality rate of patients aged <19 years old was 0.79% in 2020 and 1% in 2021.[31,32] Similar to previous publications, mortality is lower in children than adults.[33,34] The mortality in this group remained low during the first and second waves despite the slightly higher number of cases in adolescents in 2021 (0.31% in 2020 and 0.37% in 2021). All of our cases occurred in 2021, thus severe cases in children and adolescents in 2020 were possibly not appropriately and early referred to ECMO due to inadequate knowledge about disease pathophysiology and management.[31,32] Another point that should be evaluated is the role of virulence of new strains in this second wave in our country.

Until December 14, a total of 10,955 COVID-19 cases of ECMO were registered to ELSO. Few related publications are reported on the pediatric population, thus we compared our findings to the ELSO reported data (Table 3). A total of 277 patients had initiated ECMO at least 90 days ago, with a 31% related in-hospital

Number of cases	Our cohort	Total (All locations) 277 cases	ARSD cohort (All locations) 107 cases	Total (Latin America) 12 cases	ARSD cohort (Latin américa) 5 cases
Age (Years); median (IQR)	1.8 (0.4,14)	11(1,16)	13 (1,17)	11 (0,3)	5 1 (0,9)
BMI (Kg/m^2); median (IQR)	24.4 (15, 33)	27 (18,37)	33 (22,42)	15 (12,19)	19 (17,32)
Sex; male; total (%)	4 (66.6%)	51 % (142)	50 % (53)	58 % (7)	60 % (3)
Pré-ECMO comorbidities					
Diabetes	0	9 % (25)	13 % (14)	8 % (1)	20 % (1)
Hypertension	0	7 % (19)	13 % (14)	8 % (1)	20 % (1)
Obesity	0	38 % (104)	51 % (53)	25 % (3)	40 % (2)
Acute Ilness					
Acute heart failure; total (%)	2 (33.3%)	16 % (43)	5 % (5)	8 % (1)	0 % (0)
Myocarditis	0	10 % (29)	0 % (0)	0 % (0)	0 % (0)
Acute Kidney injury	0	19 % (52)	17 % (18)	8 % (1)	20 % (1)
Pre-ECMO intubations (days); median (IQR)	5 (0.75, 6.5)	0,9 (0.2,3.7)	1.3 (0.3, 3.8)	6 (2.1, 9.3)	1,7 (1.1-2.9)
Ventilatory parameters					14.5(13,15.2)
PEEP, cmH_2O; median (IQR)	11 (9.5, 14)	12 (8,15)	14 (10,17.5)	15 (12,20)	28 (28,28)
PIP, cmH_2O; median (IQR)	27 (19.5, 34.2)	32 (28,38)	36 (29.2, 38.8)	28 (28,28)	54 (44,64)
PaO_2/FiO_2; median (IQR)	63 (57.8, 70.3)	66 (53,107)	64 (54,84)	47 (42,57)	56 (49,70)
PCO_2, cmH_2O; median (IQR)	65 (63.3, 74)	52 (42,66)	59 (49,69)	50 (42,71)	
Pre-ECMO support					
Prone position; total (%)	3 (50%)	21 % (58)	39 % (41)	50 % (6)	80 % (4)
Neuromuscular blockers, total (%)	6 (100%)	69 % (191)	79 % (83)	67 % (8)	80 % (4)
Inhaled pulmonar vasodilators, total (%)	1 (16.7%)	37 % (102)	48 % (50)	17 % (2)	20 % (1)
Any vasoactive support, total (%)	4 (66.6%)	66 % (182)	61 % (64)	92 % (1)	80 % (1)
Therapies, Immunomodulators (steroids)	6 (100%)	88 % (244)	98 % (105)	67 % (8)	80 % (4)

***Table 3*: Registry dashboard of ECMO-supported COVID-19 patient data.**
BMI: Body mass index; ECMO; ECMO: extra-corporeal membrane oxigenation; IQR: interquartile range; PEEP: Positive end-expiratory pressure; PIP: Peak inspiratory pressure; FiO_2: Fraction of inpired oxygen; PaO_2: partial pressure of arterial oxygen; $PaCO_2$: Partial pressure of carbone dioxide.

mortality. An ARDS cohort with 107 patients (38.6% of the total) was separately analyzed. Pre-ECMO risk factors were evaluated; the median age was 13 years (IQR: 1.16), and males had a slightly higher prevalence (51%). Compared to the rest of the patients, this cohort had more pre-ECMO comorbidities, such as obesity, hypertension, and diabetes. Similar to our sample, most patients did not present significant cardiac involvement, thus the main indication for support was severe pulmonary condition.[26]

However, due to the limited number of centers that provide ECMO in our country, especially in our region, patient access was more difficult and the time between the start of mechanical ventilation and the start of ECMO was long, with a median of 5 days (IQR: 0.75 −6.5). Similarities were observed regarding the ventilation mode and parameters used before ECMO runs. Previous publications reported the use of high ventilatory parameters before starting ECMO.[33,34] Our experience shows the potential role of ECMO in managing ARDS due to COVID-19 and should be considered as a therapeutic option in patients who develop refractory hypoxemia despite maximal conventional mechanical ventilation during other respiratory virus outbreaks.

Finally, the median duration of ECMO support in children was lower than observed in adults, probably due to a lower number of lesions in other organs, such as impaired renal function.[33,34] The in-hospital mortality rate in our case series was 33.3%. The overall mortality reported by ESLO and Di Nardo et. Al were 31% and 43%, respectively.[26,30] An important aspect to highlight is that the mortality of patients who are supported by ECMO due to COVID-19-related ARDS with refractory hypoxemia was similar to the mortality evidenced in cases of support for other pulmonary complications in the pediatric group.[26,32]

Our study limitations include the small-volume center despite being reference centers for ECMO support in our region, and all patients were referred from other services as it is a retrospective work, and not all laboratory tests are available.

COVID-19 is generally a mild disease in children, including infants. Only a small proportion develop a severe disease that requires ICU admission and prolonged ventilation. Additionally, fatal outcomes are overall rare. The COVID-19 pandemic highlights challenges of management strategies in patients with severe ARDS, and ECMO appears as a viable intervention in

selected patients who failed conventional therapies in the pediatric group. Efforts must continue to better elucidate the pathophysiology and specific treatment options for COVID-19, as antiviral and immunomodulatory drugs and future prospective studies must be done to better determine the risk factors, indications, predictors, optimal time, procedural considerations, and post-cannulation management strategies of ECMO in this population.

Contributors

CTMBC designed the study, conducted the literature search, analyzed the data, drafted and revised the manuscript; ACOT, ICLM, VCPJ, JAB, EPC, RSASO, FBP, MBC, KMPCB analyzed the data, revised the manuscript, and provided a critical review of the manuscript; and all authors read and approved the final manuscript.

Data sharing statement

Hospital Dr. Carlos Alberto Studart Gomes does not release datasets related to patient data. Data is derived from electronic health records. Any supporting results or data, including explanations about the structure of the data or how it was obtained beyond the scope of the materials and methods section can be obtained from the corresponding author.

Declaration of interests

The authors report no conflicts of interest.

Funding

This observational study received no funding.

References

1 World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 11 March 2020. World Health Organization URL: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. Accessed 20 December 2021.
2 Di Nardo M, van Leeuwen G, Loreti A, et al. A literature review of 2019 novel coronavirus (SARS-CoV2) infection in neonates and children. *Pediatr Res*. 2021;89:1101–1108.
3 Nicola M, Alsafi Z, Sohrabi C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): a review. *Int J Surg*. 2020;78:185–193.
4 Zhang Y. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. *Chin J Epidemiol*. 2020;41:145–151.
5 Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA*. 2020;14(323):1335.
6 CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:343–346.
7 Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109:1088–1095.
8 Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145:e20200702.
9 Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;226:55–63.e2.
10 Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus infection in hospitalized infants under 1 year of age in China. *JAMA*. 2020;323:1313–1314.
11 Mustafa NM, A Selim L. Characterisation of COVID-19 pandemic in paediatric age group: a systematic review and meta-analysis. *J Clin Virol*. 2020;128: 104395.
12 Liu W, Zhang Q, Chen J, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. *N Engl J Med*. 2020;382:1370–1371.
13 Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382:1663–1665.
14 CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):422–426.
15 Tsankov BK, Allaire JM, Irvine MA, et al. Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;103:246–256.
16 Li L, Li R, Wu Z, et al. Therapeutic strategies for critically ill patients with COVID-19. *Ann Intensive Care*. 2020;10:45.
17 Sukhal S, Sethi J, Ganesh M, Villablanca PA, Malhotra AK, Ramakrishna H. Extracorporeal membrane oxygenation in severe influenza infection with respiratory failure: a systematic review and meta-analysis. *Ann Card Anaesth*. 2017;20:14–21.
18 Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care*. 2018;8:3.
19 Cho HJ, Heinsar S, Jeong IS, et al. ECMO use in COVID-19: lessons from past respiratory virus outbreaks-a narrative review. *Crit Care*. 2020;24:301.
20 Combes A, Pellegrino V. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1)-associated acute respiratory distress syndrome. *Semin Respir Crit Care Med*. 2011;32:188–194.
21 Shekar K, Badulak J, Peek G, et al. Extracorporeal life support organization coronavirus disease 2019 interim guidelines: a consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. *ASAIO J*. 2020;66:707–721.
22 Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med*. 2020;8:518–526.
23 Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med*. 2020;46:854–887.
24 Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): a systematic review of clinical features and presentation. *Paediatr Respir Rev*. 2021;38:51–57.
25 Makdisi G, Wang IW. Extra corporeal membrane oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis*. 2015;7:E166–E176.
26 The extracorporeal life support organization (ELSO) Registry. URL: https://www.elso.org/Registry.aspx. Accessed 20 December 2021.
27 World Health Organization: Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (nCoV) Infection is Suspected. World Health Organization URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance. Accessed 20 December 2021.
28 Extracorporeal Life Support Organization (ELSO). COVID-19 Interim Guidelines. A Consensus Document from an International Group of Interdisciplinary ECMO Providers. Extracorporeal Life Support Organization (ELSO) URL: https://www.elso.org/Portals/0/Files/pdf/guidelines%20elso%20covid%20for%20web_Final.pdf. Accessed 20 December 2021.

29 Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr*. 2020;179:1029–1046.

30 Di Nardo M, Hoskote A, Thiruchelvam T, et al. Extracorporeal membrane oxygenation in children with coronavirus disease 2019: preliminary report from the collaborative European chapter of the extracorporeal life support organization prospective survey. *ASAIO J*. 2021;67(2):121–124.

31 Governo do Estado do Ceará. Secretaria Estadual de Saúde. Boletim epidemiológico 2020. URL: https://www.saude.ce.gov.br/download/covid-19/. Accessed 20 December 2021.

32 Governo do Estado do Ceará. Secretaria Estadual de Saúde. Boletim epidemiológico 2021. URL: https://www.saude.ce.gov.br/download/covid-19/. Accessed 20 December 2021.

33 Ramanathan K, Shekar K, Ling RR, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Crit Care*. 2021;25(1):211. (London, England).

34 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the extracorporeal life support organization registry. *Lancet*. 2020;396:1071–1078.