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***Original Article** / Özgün Makale*

Efficacy of extracorporeal membrane oxygenation in pediatric COVID-19 and MIS-C cases: A single-center experience

Pediatrik COVID-19 ve MIS-C olgularında ekstrakorporeal membran oksijenizasyonunun etkinliği: Tek merkez deneyimi

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ABSTRACT

Background: This study aimed to evaluate the need and the indication of extracorporeal membrane oxygenation (ECMO) in patients diagnosed with coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C) followed up in the pediatric intensive care unit by the demographic, clinical, and laboratory data and treatment response.

Methods: A total of 79 patients (43 males, 36 females; median age: 138 months; range, 6 to 210 months) with COVID-19 and MIS-C followed up between September 2020 - September 2021 were included in this retrospective study. Demographic and clinical data were retrospectively collected from patient files, and clinical data, laboratory findings, chest X-rays, and echocardiography results of six patients (1 male and 5 female, median age: 159 months, range, 13 to 210 months) who needed ECMO due to poor response to medical treatment were recorded before and after the ECMO therapy.

Results: Extracorporeal membrane oxygenation therapy was performed on one patient with a positive COVID-19 polymerase chain reaction test and five patients with MIS-C in our unit. Five patients were supported with venoarterial (v-a) ECMO, and one patient was supported with venovenous ECMO. Median hospitalization time was 29 (range, 24 to 50) days, median Pediatric Risk of Mortality score was 19.5 (range, 11 to 36), and median length of mechanical ventilation was 23.5 (range, 10 to 45) days. The median vasoactive inotropic score was 55.5 (range, 18 to 110) before ECMO, while the median vasoactive inotropic score was 11 (range, 0 to 34) after ECMO. Four patients were successfully weaned off ECMO, and one of these patients was lost due to brain death 15 days after the weaning. One patient infected with the delta variant of COVID-19, which remained positive during the clinical course, and one patient diagnosed with MIS-C was lost despite the v-a ECMO support. Three of the patients were discharged. Thrombosis developed in the superficial femoral artery of one patient on the cannulated side during v-a ECMO. No death due to complications of ECMO was recorded.

Conclusion: In our study, although the majority of our patients followed up with the diagnosis of COVID-19 and MIS-C showed a mild or moderate clinical course, it was observed that a severe clinical course could develop in a small number of patients and that ECMO treatment may be needed in these patients. In agreement with the ECMO studies with different indications in the literature, we conclude that ECMO therapy may markedly contribute to the prognosis in COVID-19 and MIS-C patients when the initiation and termination timing of therapy is correct.

Keywords: Coronavirus disease 2019, extracorporeal membrane oxygenation, multisystem inflammatory syndrome in children.

ÖZ

Amaç: Çalışmamızda koronavirüs hastalığı 2019 (COVID-19) ve çocuklarda multisistem enflamatuar sendrom (MIS-C) tanısıyla çocuk yoğun bakım ünitemizde izlenen hastaların demografik, klinik ve laboratuvar verileri ve tedavi yanıtları ile ekstrakorporeal membran oksijenizasyonu (ECMO) tedavi gereksinimi ve endikasyonu araştırıldı.

Çalışma planı: Bu retrospektif çalışmaya Eylül 2020 - Eylül 2021 tarihleri arasında COVID-19 ve MIS-C tanısı ile takip edilen 79 hasta (43 erkek, 36 kadın; medyan yaş 138 ay; dağılım, 6-210 ay) dahil edildi. Hastaların demografik ve klinik verileri geriye dönük olarak hasta dosyalarından kaydedilmiş olup, bu hastaların içinde medikal tedaviye yetersiz yanıt nedeniyle ECMO desteğine ihtiyaç duyan altı hastanın (1 erkek, 5 kadın, medyan yaş: 159 ay; dağılım, 13-210 ay) ECMO tedavisi öncesi ve sonrası klinik verileri, laboratuvar bulguları, akciğer grafileri ve ekokardiyografi sonuçları kaydedildi.

Bulgular: Ünitemizde COVID-19 polimeraz zincir reaksiyon testi pozitif olan bir hastaya ve MIS-C tanısı olan beş hastaya ECMO tedavisi uygulandı. Beş hasta venoarteriyel (v-a) ECMO, bir hasta ise venovenöz ECMO desteği aldı. Medyan yatış süresi 29 (dağılım, 24-50) gün, medyan Pediatrik Mortalite Riski skoru 19.5 (dağılım, 11-36) ve medyan mekanik ventilatörde kalış süresi 23.5 (dağılım, 10-45) gün idi. Ekstrakorporeal membran oksijenizasyonu öncesi hastaların medyan vazoaktif inotropik skoru 55.5 (dağılım, 18-110) iken ECMO sonrası medyan vazoaktif inotropik skoru 11 (dağılım, 0-34) idi. Dört hasta ECMO'dan başarılı şekilde uzaklaştırılırken, bu hastalardan biri ECMO'dan ayrıldıktan 15 gün sonra beyin ölümü nedeniyle kaybedildi. COVID-19 delta varyantı ile enfekte olup yatışından itibaren PCR testi pozitif olan bir hasta ve MIS-C tanısı olan bir hasta v-a ECMO desteğine rağmen kaybedildi. Hastalardan üçü taburcu edildi. Bir hastanın yüzeyel femoral arterinde v-a ECMO sırasında arteriyel kanül tarafında trombüs oluştu. Ekstrakorporeal membran oksijenizasyonu komplikasyonuna bağlı ölüm izlenmedi.

Sonuç: Çalışmamızda COVID-19 ve MIS-C tanısı ile takip edilen hastaların çoğunluğunun hafif ya da orta klinik seyir göstermesine rağmen, az sayıda hastada ağır klinik seyir gelişebileceği ve bu hastalarda ECMO tedavisine ihtiyaç duyulabileceği gözlendi. Literatürdeki diğer nedenler ile uygulanan ECMO çalışmalarıyla benzer şekilde, tedaviye başlama ve tedaviyi sonlandırma kararı doğru zamanlama ile yapıldığında COVID-19 ve MIS-C hastalarında ECMO uygulamasının prognoza önemli katkısının olabileceğini düşünmekteyiz.

Anahtar sözcükler: Koronavirüs hastalığı 2019, ekstrakorporeal membran oksijenizasyonu, çocuklarda multisistem enflamatuar sendrom.

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The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was declared by the World Health Organization (WHO) as a global pandemic on March 11, 2020. Although mild or moderate symptoms are more frequently observed in children compared to adult patients, severely affected patients develop difficulty in breathing and hypoxia, and critical patients may develop rapid progression into acute respiratory distress syndrome (ARDS), sepsis, and multiple organ failure.[1] Additionally, multisystem inflammatory syndrome in children (MIS-C) was first reported by the National Health Service (NHS) in the United Kingdom on April 27, 2020. Multisystem inflammatory syndrome in children is a condition characterized by multisystemic organ involvement, including skin, cardiovascular, gastrointestinal, and respiratory systems, in which clinical findings can overlap with Kawasaki disease.[2] Although MIS-C is generally observed with a mild clinical course, patients may need inotropic support in the pediatric intensive care unit (PICU) due to cardiac dysfunction and hypotension, noninvasive or invasive mechanical ventilation support due to respiratory failure, and extracorporeal membrane oxygenation (ECMO) support.[3]

Extracorporeal membrane oxygenation is an alternative and life-saving treatment for cases of cardiopulmonary insufficiency that do not respond to medical treatment. There is a limited number of studies in the literature regarding the use of ECMO in pediatric patients diagnosed with COVID-19 and MIS-C. There are only a few studies and case presentations regarding the use of ECMO in certain patient groups: those with myocardial failure due to post-COVID-19 (primary inflammation) and post-MIS-C (secondary inflammation) related pathologies and those with ARDS-related respiratory failure that is unresponsive to conventional medical treatment modalities.[4,5]

Given these points, there are still many questions and assignments to complete in terms of treatment methods and life-saving modalities in patients with COVID-19 and MIS-C. In this study, we retrospectively analyzed the clinical features, laboratory findings, and the response to the treatment of children diagnosed with COVID-19 and MIS-C who underwent ECMO in our PICU.

PATIENTS AND METHODS

A total of 79 patients who were followed up in the PICU of Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital with the diagnosis of MIS-C and positive PCR test results between September 2020 and September 2021 were included in this retrospective study. Among them, 37 patients were followed up with MIS-C (19 males, 18 females, median age: 146 months, range, 9 to 210 months) and 42 patients were followed up with a positive PCR test (24 males, 18 females, median age: 123 months, range, 6 to 196 months). Six of them (1 male and 5 female, median age: 159 months, range, 13 to 210 months) required ECMO support for SARS-CoV-2 infection due to inadequate response to medical treatment. A confirmed case of COVID-19 was defined as a child with exposure history, signs, and symptoms suggestive of COVID-19, together with an abnormal chest computed tomography (CT) scan and a positive polymerase-chain-reaction (PCR) test. They were tested, treated, and followed up by the same pediatric COVID-19 team throughout their hospital stay. Additionally, the other possible respiratory viruses and pathogens were screened in all cases. Swab tests for respiratory tract bacterial and viral infections were performed. Blood investigations, including blood culture and procalcitonin levels, were used in the differential diagnosis of secondary bacterial infections. A real-time reverse-transcriptase-PCR assay was performed for the detection of SARS-CoV-2 according to the guidelines established by the WHO. Nasal and pharyngeal swabs were used to collect samples for this test. The Canadian Paediatric Surveillance Program, Royal College of Paediatrics and Child Health in the United Kingdom, Centers for Disease Control and Prevention in the United States, and WHO have each determined a case definition for MIS-C, with commonalities being fever, clinical evidence of inflammation, and single or multiple organ involvement. We diagnosed our patients according to these MIS-C guidelines.[6,7] The demographic data (age and sex), laboratory findings (levels of creatinine, lactate, albumin, lactate dehydrogenase, international normalized ratio, troponin I, and ferritin), echocardiography measurements, pre-and post-ECMO vasoactive inotropic score (VIS), Pediatric Risk of Mortality (PRISM), Pediatric Logistic Organ Dysfunction, and organ failure index (OFI) scores,[8-10] and ventilation parameters were recorded from our electronic hospital information system records, and patients' forms were filled upon admission.

Clinical and laboratory findings before treatment were recorded as pre-ECMO, and the findings at the 24 h of treatment were recorded as post-ECMO). All patients were followed with invasive arterial catheterization to monitor arterial blood pressure and arterial blood gas analyses.

Heparin was given to all patients before and during ECMO. Loading dose of heparin was calculated as 50 U/kg to be administered prior to cannulation. Then heparin infusion continued at 10-30 U/kg/h during ECMO; activated clotting time was monitored throughout this infusion. Targeted intervals for several parameters were as follows: activated clotting time between 170-220 sec, hemoglobin levels >10 g/dL, and thrombocyte count >100,000/m^3. Adjunct flow volume was kept between 100-150 mL/kg/min to keep venous oxygen saturation above 70%; adjustments were made depending on the hemodynamic features of each patient. The fraction of inspired oxygen (FiO_2) was kept between 40-60%, as the target arterial oxygen saturation was 94% or above. Throughout the ECMO treatment, all patients were monitored via daily chest X-rays and echocardiography, and they were put in pressure-controlled synchronized intermittent mechanical ventilation. Targeted intervals for the ventilator parameters during ECMO were as follows: a FiO_2 between 30-45%, respiratory rate of 10-18/min, and positive end-expiratory pressure between 8-12 cmH_2O. Cannulation was done by pediatric cardiovascular surgeons. In one patient, central venoarterial (v-a) ECMO cannulas were placed by surgical sternotomy. Conventional two-site (v-a and venovenous [v-v]) cannulation strategies were applied for peripheral ECMO in the remaining patients. Median sizes of infusion and drainage cannula used in peripheral ECMO were 15 (15-18) and 19 (19-21) Fr, respectively. During femoral artery cannulation, a 5 Fr reperfusion cannula was placed in the superficial femoral artery for anterograde extremity perfusion by ultrasonography. Sweep gas on ECMO was set at 0.5-4 L/min to keep the target pCO_2 level in the range of 35-45 mmHg in blood gas analysis. Therapeutic plasma exchange (TPE) was performed with Prismaflex® TPE 1000 and TPE 2000 sets (Baxter International Inc. Deerfield, Illinois, USA) due to multiorgan failure (American Society for Apheresis category III), and continuous renal replacement therapy (CRRT) was performed with Prismaflex® Oxiris and HF-20 sets (Baxter International Inc. Deerfield, Illinois, USA) due to the fluid load, acute kidney injury, and metabolic status. Continuous renal replacement therapy and TPE were continued via a separate hemodialysis catheter during ECMO treatment in all patients. Charcoal hemoperfusion therapy was applied in all patients during ECMO due to unresponsiveness to other treatments. Charcoal hemoperfusion therapy was performed with an Adsorba® filter (Baxter International Inc. Deerfield, Illinois, USA) through the ECMO system or a separate hemodialysis catheter in two and four patients, respectively. Based on the transthoracic echocardiography examinations, ECMO flow rates were reduced when adequate improvement of cardiac functions was achieved. Doses of vasoactive inotropic agents and heparin were adjusted when necessary. Extracorporeal membrane oxygenation was terminated upon sufficient cardiac function. Extracorporeal membrane oxygenation flow rates were reduced by 50%, and the patients were decannulated.

Statistical analysis

Statistical analysis was performed using the PASW version 17.0 software (SPSS Inc., Chicago, IL, USA) In the study, median, minimum and maximum values and numbers (n) and percentages (%) were used for descriptive data. Chi-square (or Fisher exact test, where appropriate) test was used for comparison of classified data. Conformity of continuous variables to normal distribution was examined by visual (histogram and graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). The Mann-Whitney U test was used to compare continuous variables that did not fit the normal distribution. Statistical significance level was determined as <0.05.

RESULTS

The median duration of hospitalization was 7.0 (range, 3.0 to 34.0) and 6.0 (range, 2.0 to 38.0) days in MIS-C and positive PCR groups, respectively. When we compared MIS-C, positive PCR, and ECMO patients in three groups, duration of hospitalization, duration of mechanical ventilation, mortality, VIS, PRISM/OFI scores, and need for CRRT/TPE and mechanical ventilation were significantly higher in ECMO patients. There was no statistically significant difference in the duration of noninvasive mechanical ventilation between the three groups (Table 1).

Of six patients who required ECMO support, five were female, and one was male. The median age of the patients was 159 (range, 13 to 210) months. The median length of hospital stay was 29 (range, 24 to 50) days. One of these patients (case 6) had a positive PCR test for COVID-19 and the others were followed as MIS-C patients. Four of our patients did not have any preexisting medical condition, whereas one had ulcerative colitis and one had asthma (Table 2). All of these patients had at least two organ failures prior to ECMO. Case 4, who had a history of asthma, was supported with v-v ECMO using the right jugular vein and right femoral vein. The remaining patients were connected to v-a ECMO. In our only patient positive for COVID-19 with PCR (case 6), v-a ECMO cannulation was centrally placed by surgical sternotomy. Considering the side of arterial

Table 1. Clinical features of patients

	ECMO patients				MIS-C patients				COVID PCR+ patients					
	n	%	Median	Min-Max	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*1	*p*2
Hospitalization (day)			29.0	24.0-50.0			7.0	3.0-34.0			6.0	2.0-38.0	<0.001	<0.001
Vasoactive inotropic score			55.5	18.0-110.0			0	0-40.0			0	0-35.0	<0.001	<0.001
Mechanical ventilation													0.001	0.007
Yes	6	100			8	25			17	39.5				
No	0	0			24	75			26	60.5				
Mechanical ventilation time (day)			21.5	8.0-45.0			0.5	0-12.0			4.0	0-35.0	<0.001	<0.001
NIMV time (day)			2.5	1.0-4.0			0	0-12.0			3.0	0-10.0	0.147	0.561
PRISM			19.5	11.0-36.0			2.5	0-24.0			2.0	0-24.0	<0.001	<0.001
Organ failure index			3.5	2.0-6.0			1.0	0-4.0			0	0-6.0	0.001	<0.001
CRRT													<0.001	<0.001
Yes	6	100			4	12.5			7	16.3				
No	0	0			28	87.5			36	83.7				
TPE													0.024	0.004
Yes	6	100			15	46.9			15	34.9				
No	0	0			17	53.1			28	57.1				
Mortality													0.002	0.031
Yes	3	50			0	0			4	9.3				
No	3	50			32	100			39	90.7				

ECMO: Extracorporeal membrane oxygenation; MIS-C: Multisystem inflammatory syndrome in children; COVID-19: Coronavirus disease 2019; PCR: Polymerase-chain-reaction; NIMV: Noninvasive mechanical ventilation; PRISM: Pediatric risk of mortality; CRRT: Continuous renal replacement therapy; TPE: Therapeutic plasma exchange; p1: P value between ECMO and MIS-C patients; p2: P value between ECMO and COVID-19 PCR positive patients; Case 1-5 were followed up with MIS-C and case 6 were followed up with positive PCR test result.

Table 2. Clinical features of patients

Case	Age (month)	Known diseases	PRISM	PELOD	OFI	PICU duration	ECMO duration	ECMO initiation day*	Cannula location
1	210	UC	36	22	6	25	5	3	Right FA-Right JV
2	120		14	13	3	29	6	4	Left FA-Right FV
3	180		33	22	4	29	9	9	Right FA-Right FV
4	171	Asthma	11	10	2	24	4	3	Right JV-Right FV
5	147		16	9	4	50	12	10	Left FA-Left FV
6	13		23	9	3	40	18	12	Right CCA-JV

PRISM: Pediatric risk of mortality; PELOD: Pediatric logistic organ dysfunction; OFI: Organ failure index; PICU: Pediatric intensive care unit; ECMO: Extracorporeal membrane oxygenation; UC: Ulcerative colitis; FA: Femoral artery; JV: Jugular vein; FV: Femoral vein; CCA: Common carotid artery; * ECMO initiation day refers to follow-up time in the pediatric intensive care unit before the initiation of ECMO.

cannulation, the right femoral artery was preferred in two patients (cases 1 and case 3), and the left femoral artery was preferred in two patients (cases 2 and 5) during peripheral v-a ECMO cannulation. Similarly, considering the presence of central vein cannulation or hemodialysis catheter placement, ipsilateral femoral vein, contralateral femoral vein, and ipsilateral jugular vein were used as the vascular access in two (cases 3 and 5), one (case 2), and one (case 1) patient, respectively. Cardiopulmonary resuscitation was applied to one patient (case 2) for 5 min before ECMO due to cardiopulmonary arrest. All patients received CRRT and TPE once a day before ECMO. Hemoperfusion therapy procedure was applied, and TPE treatment was initiated every 12 h in all patients during ECMO.

Table 3. Laboratory findings before and after ECMO

	Case					
Laboratory	1	2	3	4	5	6
Lactate (pre)	5.6	2.4	7.4	1.0	1.2	2.1
Lactate (post)	1.5	1.2	1.5	0.5	0.9	4.0
Albumin (pre)	1.11	2.85	3.45	3.53	3.63	2.70
Albumin (post)	3.48	3.20	3.34	3.04	3.85	3.80
Lactate/albumin ratio (pre)	3.73	0.84	2.10	0.28	0.33	0.77
Lactate/albumin ratio (post)	0.43	0.375	0.44	0.16	0.23	1.05
Creatinine (pre)	2.73	0.91	0.95	0.66	3.93	0.41
Creatinine (post)	1.25	0.36	0.53	0.35	0.96	0.21
LDH (pre)	3273	244	1233	403	5869	383
LDH (post)	945	213	596	342	201	875
INR (pre)	1.67	1.82	1.67	1.25	1,44	1.41
INR (post)	1.39	1.33	1.34	1.14	1.23	1.22
Troponin (pre)	1.000	0.028	0.430	0.003	0.030	0.080
Troponin (post)	0.900	0.066	0.310	0.010	0.060	0.050
Ferritin (pre)	5461	304	3381	18	918	212
Ferritin (post)	697	131	1293	22	298	1698

ECMO: Extracorporeal membrane oxygenation; LDH: Lactate dehydrogenase; INR: International normalized ratio; Post: Values after 24 h of ECMO therapy, Pre: Values just before the ECMO.

Table 4. Hemodynamic and ventilation parameters

	Case					
Parameters	1	2	3	4	5	6
EF (pre)	23	38	35	75	34	46
EF (post)	50	78	45	88	22	60
MAP (pre)	48	50	45	67	50	50
MAP (post)	90	110	70	83	70	68
HR (pre)	165	144	180	140	80	170
HR (post)	72	82	80	86	70	120
VIS (pre)	177	110	183	18	184	143
VIS (post)	34	32	18	0	84	34
PEEP (pre)	9	8	15	10	7	10
PEEP (post)	6	5	5	8	7	9
Ppeak (pre)	34	31	35	35	38	25
Ppeak (post)	28	22	25	20	16	25
PaO_2/FiO_2 (pre)	260	220	120	130	180	180
PaO_2/FiO_2 (post)	430	350	280	290	250	392

EF: Ejection fraction; Pre: Values just before the ECMO; Post: Values after 24 h of ECMO therapy; MAP: Mean arterial pressure; HR: Heart rate; VIS: Vasoactive inotrope score; PEEP: Positive end-expiratory pressure; Ppeak: Peak inspiratory pressure; PaO2: Partial arterial oxygen pressure; FiO_2: Fraction of inspired oxygen.

Following the ECMO therapy, rapid and significant improvements were observed in laboratory findings related to organ failure (including the levels of lactate, creatinine, lactate dehydrogenase, international normalized ratio, troponin, and lactate/albumin ratio) and ferritin levels, which is an important inflammatory marker (Table 3).

Circulatory failure parameters (heart rate, mean arterial blood pressure, and VIS) and respiratory failure parameters that are predictive of the need for mechanical ventilation support (ratio of partial pressure of arterial oxygen to FiO_2, positive end-expiratory pressure, peak inspiratory pressure) were recorded as pre-ECMO and post-ECMO and compared. These parameters also improved significantly in all patients 24 h after the initiation of ECMO support (Table 4). Prior to ECMO, transthoracic echocardiography was applied to all patients and the median left ventricular ejection fraction was 65% (range, 23 to 78%). The median VIS was 55.5 (range, 18 to 110) before ECMO. When necessary, patients were given high doses of vasoactive medications (milrinone 0.75 mcg/kg/min, noradrenaline 0.3-1.2 mcg/kg/min, adrenaline 0.6-1 mcg/kg/min, dobutamine 10-20 mcg/kg/min, and dopamine 10-15 mcg/kg/min) before ECMO. The median VIS was 11 (range, 0 to 34), and the median ejection fraction was 66% (range, 45 to 88%) after ECMO therapy.

Four patients were successfully weaned off ECMO, and three of the decannulated patients were discharged without any neurologic sequelae. Case 3, who had been transferred to our unit from another hospital with the diagnosis of MIS-C, was successfully weaned off ECMO upon improvements of multiorgan failure signs. However, the patient was diagnosed with brain death 15 days after ECMO termination. Despite all efforts, case 6, who had a positive PCR test for COVID-19 at admission, and case 5, who was diagnosed with MIS-C, died due to multiorgan failure resistant to circulatory and respiratory supports.

Regarding complications, one patient (case 5) developed superficial femoral artery thrombosis in cannulated site despite the heparin anticoagulation and placement of a reperfusion cannula. Extremity circulation was recovered with thromboembolectomy and reperfusion cannula replacement. None of the patients had hemorrhagic complications.

DISCUSSION

Although pediatric COVID-19 patients generally have a milder clinical course during COVID-19 compared to adults, there are some studies and case

reports in the literature mentioning the critical illness in pediatric patients. In a multicenter study with the contribution of 25 European countries, the need for intensive care, mechanical ventilation, vasoactive inotropic agents, and ECMO therapy in pediatric COVID-19 patients were reported as 8%, 4%, 3%, and 1%, respectively.[11] Although it is known that extracorporeal treatment can be a life-saving option in many instances, there are some debates that it can trigger hypercoagulopathy, acute renal failure, inflammation cascade, and increase the risk of secondary bacterial infection.[12] Among 79 patients who were followed up with the diagnosis of SARS-CoV2 infection and MIS-C since the beginning of the COVID-19 pandemic, only six patients needed ECMO therapy due to circulatory and respiratory failure. We think that parameters such as PRISM score, OFI score, VIS, and need for mechanical ventilation may be used as important predictive factors for the clinical course of the disease due to significantly higher values in ECMO patients when compared to the COVID-19 and MIS-C patients. All ECMO patients received CRRT and TPE therapies before the ECMO, with statistically significantly higher frequency compared to the other patients, due to severe multiorgan failure and cytokine storm. As a difference from other patients, charcoal hemoperfusion, which is thought to be useful in cytokine storm, was added to treatment during ECMO and TPE therapy was applied twice a day.[13] These changes in treatment strategies might have contributed to the rapid recovery of clinical and laboratory parameters in the post-ECMO evaluation.

In the study of Cura Yayla et al.,[14] it is mentioned that the development of critical illness due to COVID-19 is higher in pediatric patients under the age of 1 and between the ages of 6 and 10. However, in another study presenting the data of 27 critically ill COVID-19 pediatric patients, the median age was reported as six years (range, 0.2 to 17.8 years).[15] In our article, we attribute the reason for the higher average age of our ECMO patients compared to the literature to the fact that the majority of our ECMO patients (n=5) were diagnosed with MIS-C. In our opinion, our study will contribute to the literature on this subject.

More data is available regarding the prognosis of the disease in adult patients with COVID-19. In a recently published study, among the COVID-19 patients who received ECMO therapy, overall mortality was found to be 37.1%, and this rate was 35.7% in those who received v-v ECMO therapy.[16] There are limited publications in the literature regarding the use of v-a and v-v ECMO in pediatric COVID-19 patients.[17-20] There is also a case report presenting the application of extracorporeal cardiopulmonary resuscitation with a positive outcome[5] and a report that involves the use of ECMO in two patients with congenital cardiac diseases.[21] There are various cases of MIS-C in the literature that are treated with v-a ECMO, successfully weaned off, and discharged without any sequela, including a case with thrombophilia, a case with lymphohistiocytic myocarditis, and a case with positive PCR test and positive antibody test for COVID-19.[4,22,23] Our ECMO weaning rate was 66%, and our mortality rate during discharge was 50%. In our opinion, our ECMO survival rates will also contribute to the limited data in the literature regarding the ECMO experience in pediatric COVID-19 patients.

In the past studies, ECMO-related bleeding incidence was reported as 70%, and ECMO-related thrombosis incidence was reported as 37%.[24] In a case report that is related to a patient who was diagnosed with brain death during ECMO therapy, the authors concluded that the anticoagulation strategies used to prevent thrombolytic and hemorrhagic complications of ECMO therapy should be revised for COVID-19 patients.[3] In another case report including a patient who developed carotid artery dissection during v-a ECMO cannulation, the patient was successfully weaned off ECMO, while he had left hemiparesis on discharge.[25] However, the Extracorporeal Life Support Organization (ELSO) reported that there is no evidence to recommend changes in anticoagulation, sedation, or other protocols for patients with COVID-19.[26] In our study, four patients were successfully weaned off ECMO, and three were discharged with no sequelae. None of our patients had a complication of bleeding, contrary to the current literature. In case 5, which was followed up with the diagnosis of MIS-C and developed superficial femoral artery thrombosis, we also observed frequent blockage of TPE and CRRT filters before and after ECMO despite high-dose heparin anticoagulation. In our opinion, thrombosis developed due to an underlying disease. One patient (case 3) was successfully weaned off ECMO upon the improvement of multiorgan failure signs. However, the patient was diagnosed with brain death in post-ECMO evaluation. This patient had transferred to our unit from another hospital with the diagnosis of MIS-C and had a history of visual impairment and change in consciousness before intubation. Cranial magnetic resonance imaging could not be performed before ECMO therapy due to the poor clinical condition. With these data,

we could not fully differentiate whether the brain death was a complication of ECMO or neurological involvement of the disease. We thought that brain death most probably occurred due to persistent hypotension and deep hypoxia during the transportation period. This matter is still debatable if the patient had already developed multiorgan failure during transfer, resulting in delayed ECMO, or if an ECMO-related thrombolytic complication was the cause of death.

The median duration of ECMO (>90% v-v) in COVID-19 patients from three large observational studies was 13.9 (interquartile range, 7.8 to 23.3) days, 20 (interquartile range, 10 to 40) days, and 18 days.[27] Ronco et al.[12] reported that the ECMO therapy duration is correlated with increased mortality rates in COVID-19 patients using regression analysis. The importance of v-a ECMO timing is emphasized in the ELSO COVID-19 Interim Guidelines, stating that the v-a ECMO decision should be made before multiorgan failure in COVID-19 patients due to increased risk of thromboembolism and cardiovascular complications.[26] The ELSO reported that while ECMO duration may be longer in COVID-19 patients than in non-COVID-19 ECMO patients, published mortality appears to be similar between these two groups. Additionally, it is mentioned that data collection is ongoing, and there is a signal that overall mortality may be increasing in COVID-19 patients.[26] It is reported that outcomes of delayed ECMO initiation may be worse, and the duration of ECMO may be extended.[28,29] In our study, the median duration of ECMO was 7.5 (range, 4 to 18) days and the median time of ECMO initiation was 6.5 (range, 3 to 12) days. Due to the small number of our patients, statistical data could not be given in our study. However, it is seen that the initiation time of ECMO and the duration of ECMO are longer in our patients with unfavorable outcomes. In our opinion, the most important prognostic parameters regarding the efficacy of ECMO therapy in our pediatric COVID-19 and MIS-C patients are the right timing of ECMO initiation and the duration of ECMO, which should be kept as short as possible.

In conclusion, larger studies are needed to have a better understanding of ECMO therapy in COVID-19 patients in terms of complications of ECMO and its effect on the prognosis of the disease. While there are many studies in the literature regarding the ECMO success in non-COVID 19 patients, we declare that the ECMO treatment can significantly contribute to prognosis in patients with COVID-19 and MIS-C. In our opinion, the most important point affecting the success of ECMO treatment is the right timing of ECMO initiation and the duration of ECMO, which should be kept as short as possible. Due to the limited data in the literature regarding ECMO experience in pediatric COVID-19 patients, our data will contribute to the literature.

Ethics Committee Approval: The study protocol was approved by the Non–invasive Clinical Research Ethics Committee of the Hospital of Health Science University (date/no: 08.12.2021/2021-242). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Written informed consent was obtained from each parent of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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