DOI: 10.31276/VJSTE.2024.0009

Extracorporeal membrane oxygenation of blood in critical COVID-19 paediatric patients: 2 cases reported

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Received 11 January 2024; revised 7 February 2024; accepted 3 April 2024

Abstract:

Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in widespread global morbidity and mortality, primarily affecting adults. However, the prevalence of severe illness in children is significantly lower, with most paediatric cases presenting mild symptoms or remaining asymptomatic. A minority of cases can progress to critical illness with respiratory and circulatory failure, particularly in children with underlying medical conditions. Such cases may necessitate hospitalisation, paediatric intensive care, and ventilatory support. Severe acute respiratory distress syndrome (ARDS) may develop and, in some instances, does not improve with optimal treatment. Extracorporeal membrane oxygenation (ECMO) can be a life-saving therapy in these situations. Data were retrospectively collected from the medical records of patients admitted to the Paediatric Intensive Care Unit at Children's Hospital 2. This paper presents the successful treatment of two paediatric patients with COVID-19-related ARDS who required ECMO due to their critical condition. These cases underscore the potential of ECMO as a critical therapeutic option when conventional interventions fail in paediatric patients.

Keywords: **acute respiratory distress syndrome, children, extracorporeal membrane oxygenation, SARS-CoV-2.**

Classification number: **3.2**

1. Introduction

In late 2019, a novel coronavirus, SARS-CoV-2, emerged and caused illness in humans, eventually spreading worldwide [1, 2]. While individuals under 15 years of age account for only 8.1% of global cases, they exhibit a much lower mortality rate of 0.2%, according to a World Health Organisation (WHO) report [3]. Nevertheless, severe and fatal cases still occur, particularly in children with pre-existing conditions such as obesity, lung diseases, premature birth, weakened immune systems, diabetes mellitus, asthma, or congenital heart diseases [4-6]. In some cases, children with COVID-19 may develop respiratory failure that does not respond to standard treatments, making ECMO necessary to prevent death [7]. Although the evidence for ECMO in adults has been growing, literature concerning ECMO for children with COVID-19-related illnesses remains sparse. Here, we describe two advanced cases of COVID-19-related ARDS in children treated with ECMO, both of whom subsequently recovered without complications.

2. Case description

Patient 1: The patient, a 14-year-old girl weighing 65 kg with no pre-existing medical conditions, developed fever, cough, and breathing difficulties over four days. She was admitted to a local hospital due to severe respiratory failure, with a SpO_2 of 60%. After intubation, her SpO_2 improved to 85%. A rapid antigen test for SARS-CoV-2 returned positive, and she was transferred to the COVID-19 department at Children's Hospital 2. Upon arrival, her SpO_2 was 90%, and she was experiencing severe hypoxia, shock, and metabolic acidosis (pH of 7.19 and BE of -15). She presented with coagulopathy, diffuse lung lesions on radiography, and bronchial ARDS (as shown in Fig. 1A). The cardiac injury was indicated by an elevated troponin I level (1.69 µg/l) and reduced myocardial contractility (ejection fraction (EF) 40-45%). Polymerase chain reaction (PCR) testing for SARS-CoV-2 confirmed the diagnosis, with a Ct value of 22.37. The patient was diagnosed with sepsis, severe pneumonia, ARDS, and critical COVID-19 in a child with obesity. She was treated with high-setting mechanical ventilation,

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anti-shock infusion, vasopressors, inotropes (noradrenaline and milrinone), broad-spectrum antibiotics (meropenem, vancomycin, and colistin), dexamethasone, anticoagulants, tocilizumab, and continuous haemofiltration with an oXiris® filter to manage elevated inflammatory markers (C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin in Table 1).

Due to persistent inadequate oxygenation and a gradual increase in the blood oxygenation index (OI) despite optimal mechanical ventilation and sedation, alongside a significant rise in the vasoactive-inotropic score, veno-venous extracorporeal membrane oxygenation (V-V ECMO) was initiated 17 hours after hospital admission (Fig. 2A). The cannulation and ECMO setup were performed without complications (right internal jugular vein 19F, right femoral vein 21F). Following treatment, the patient showed stable progress, with a SpO_2 of 96-98%, heart rate of 100 bpm, mean arterial pressure of 65 mmHg, and well-controlled oxygenation and CO_2 levels. Two days after ECMO initiation, her cardiac function improved, with EF rising to 40%, and intravenous immunoglobulin (IVIG) was administered. The troponin I level decreased from 1.6 to 0.04 µg/l, and EF increased to 60% over the next few days. The patient continued to improve, tolerating minimal ventilatory settings and gradually reducing ECMO support. She was weaned off the ventilator on day 9 and ECMO on day 10. Radiography showed significant improvement (Fig. 1B), and the patient was discharged without complications.

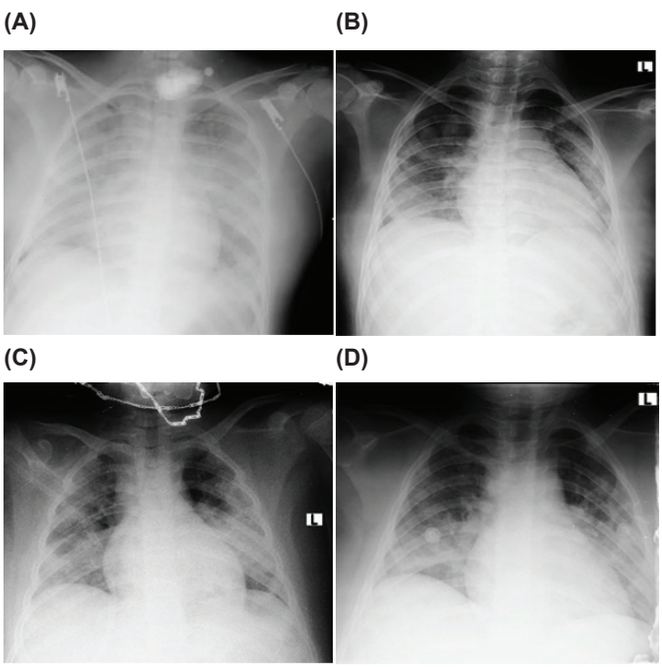


Fig. 1. (A) Radiography at admission (patient 1); (B) Radiography at ECMO withdrawal (patient 1); (C) Radiography at admission (patient 2); (D) Radiography at ECMO withdrawal (patient 2).

Patient 2: A 9-year-old boy weighing 58 kg, with no prior underlying medical conditions, presented with a 4-day illness, including low-grade fever, cough, and runny nose. He was admitted to the Emergency Department with severe shortness of breath and diffuse lung lesions were observed on radiography (Fig. 1C). SARS-CoV-2 was detected by PCR, with a Ct value of 27.02. He was initially managed with nasal continuous positive airway pressure (NCPAP) - positive end-expiratory pressure (PEEP) 10 cmH_2O, FiO_2 100%) and placed in the prone position. The patient was also treated with antibiotics (cefotaxime and vancomycin), anticoagulants, dexamethasone, and remdesivir. However, despite these interventions, his respiratory failure persisted, and his SpO_2 remained at 92-94%. Subsequently, he was placed on invasive mechanical ventilation (FiO_2: 60%, PEEP: 16 cmH_2O, PI: 10 cmH_2O) and given imipenem, colistin, tocilizumab, and extracorporeal cytokine haemadsorption therapy using the oXiris® filter due to progressive respiratory failure with elevated LDH and ferritin levels (Table 1).

Table 1. Lab test characteristics of the two patients at admission and when extracorporeal membrane oxygenation is indicated.

Characteristics	Patient 1		Patient 2	
	Admission	*ECMO indication*	*Admission*	*ECMO indication*
CRP (mg/l)	112	90	10.7	9
AST (U/l)	50	46	80	43
ALT (U/l)	23	25	43	46
Urea (mmol/l)	2.8	2.7	2.2	5.4
Creatinine (µmol/l)	65	52	45	43
Lactate (mmol/l)	7.8	2.2	0.9	1.4
LDH (U/l)	1087	1038	1686	1151
Troponin I (ug/l)	0.44	1.48	<0.01	<0.01
Ferritin (µg/l)	734	1261	591	653
PT(s)	26.9	18.9	12.2	13.5
INR	2.15	1.49	0.95	1.05
aPTT (s)	36.9	75	31.0	42.5
Fibrinogen (g/l)	5.14	5.65	4.19	3.03
D-Dimer (µg/ml)	3.62	2.35	0.78	1.97

ECMO: Extracorporeal membrane oxygenation, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactic acid dehydrogenase, PT: Prothrombin time, aPTT: Activated partial thromboplastin clotting time, INR: International normalised ratio.

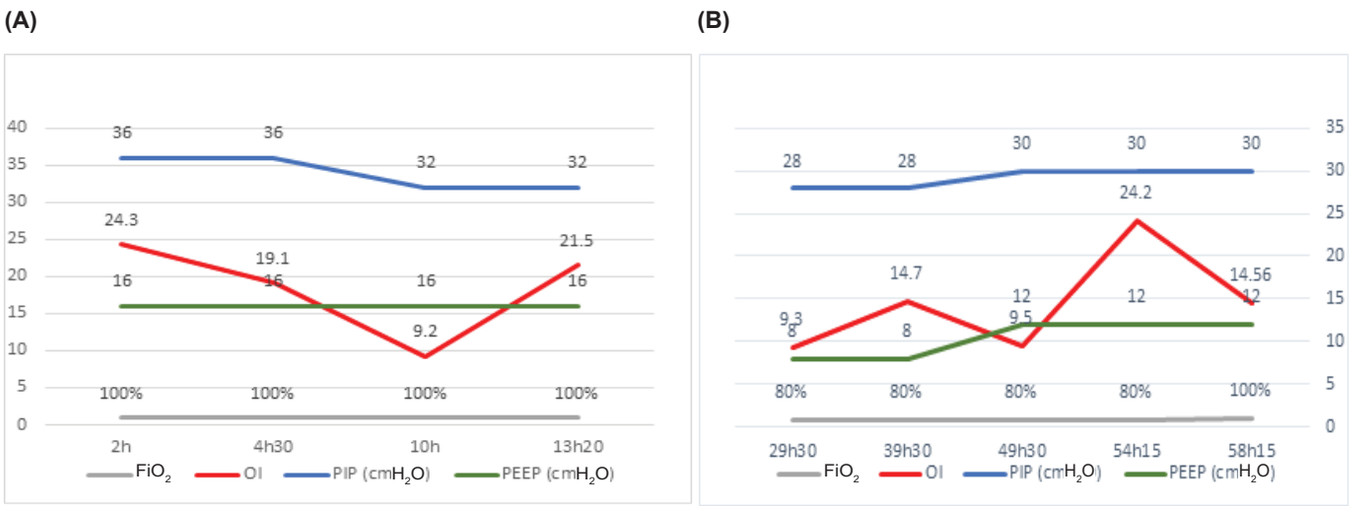
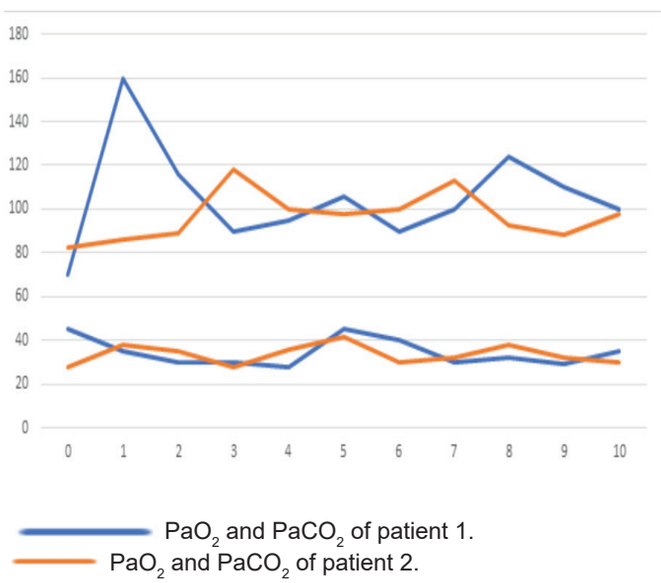


Fig. 2. (A) Blood oxygenation evolution and mechanical ventilation settings of patient 1 before ECMO, (B) Blood oxygenation evolution and mechanical ventilation settings of patient 2 before ECMO. T0: At admission, PIP: Peak inspiratory pressure, PEEP: Positive end-expiratory pressure, OI: Oxygenation index.



PaO_2: Partial pressure of oxygen; $PaCO_2$: Partial pressure of carbon dioxide.

Fig. 3. Changes in respiratory parameters of the two patients after extracorporeal membrane oxygenation.

After more than two days of hospitalisation, his blood oxygenation index deteriorated further, leading to the decision to initiate ECMO, with cannulation performed at the internal jugular vein (19F) and right femoral vein (21F) (Fig. 2B). The patient remained haemodynamically stable with good oxygenation and CO_2 levels (Fig. 3), tolerated minimal ventilator settings, and gradually reduced ECMO levels. He was successfully weaned off the ventilator on day 9 and from ECMO on day 10. His pulmonary X-ray showed significant improvement (Fig. 1D), and he was discharged without complications.

During the ECMO process (using the Maquet® RotaFlow and Maquet® Cardiopulmonary AG BE-PLS 2051), both patients received V-V ECMO with an ECMO flow of 80 ml/kg and an airflow of 4 l/min. Ventilator settings were reduced to peak inspiratory pressure/positive end-expiratory pressure (PIP/PEEP): 18/8 cmH_2O, FiO_2: 40%, and a frequency of 15 breaths per minute to minimise the risk of further lung injury. Treatments, including antibiotics, anticoagulants, sedation, and muscle relaxants, were continued. Thrombosis, bleeding, hypercoagulation, nosocomial infection/ventilator-associated pneumonia, and organ function were closely monitored. Serum albumin was maintained above 30 g/l, and haematocrit (Hct) above 35%. ECMO parameters such as transmembrane pressure, ECMO flow, and pre-and post-membrane oxygen and CO_2 concentrations were regularly checked. Lung injury was frequently assessed, and respiratory physiotherapy was coordinated to facilitate early ventilator weaning, followed by respiratory support with NCPAP. Table 2 and Fig. 3 detail the characteristics and progression of the patients' oxygenation and CO_2 levels during ECMO treatment.

Table 2. Characteristics of the two patients during extracorporeal membrane oxygenation.

Characteristics	Patient 1	Patient 2
Sex	Female	Male
Age (years)	14	9
Weight (kg)/Height (cm)/BMI	60/160/23.4	58/140/29.6
Underlying medical conditions	None	None
Onset to admission time (days)	4	4
Date of the disease when ECMO started	5	6
Pre-ECMO vasomotor	Noradrenalin, milrinone	None
PIP/PEEP (cmH_2O), FiO_2 (%) pre-ECMO	36/16, 100	30/12, 100
PIP/PEEP (cmH_2O), FiO_2 (%) post ECMO	20/10, 40	18/8, 40
Pre-ECMO ventilation time (hours)	18	50
EF pre-ECMO (%)	40	75
Initial ECMO cycle (rpm)	2800	2600
Initial ECMO flow (l/min)	4	2.7- 3
FiO_2 ECMO start	100%	100%
Heparin (min - max) UI/kg/hour	10-30	10-35
Number of used ECMO membranes	2	2
Time of ECMO (days)	10	11
Used blood products	pRBC, albumin	pRBC, platelets, albumin
Combination treatments	IVIG, tocilizumab, continuous hemofiltration adsorption	Tocilizumab, continuous hemofiltration adsorption
Length of ventilation (days)	10	10
Length of stay (days)	23	20
Outcome	Full recovery	Full recovery

pRBC: Packed red blood cells, BMI: Body mass index, PIP: Peak inspiratory pressure, PEEP: Positive end-expiratory pressure, EF: Ejection fraction, ECMO: Extracorporeal membrane oxygenation, FiO_2: Fraction of inspired oxygen, IVIG: Intravenous immunoglobulin, IU: International units.

3. Discussion

3.1. Optimisation of pre-extracorporeal membrane oxygenation treatment

The recommended lung-protective ventilatory strategy for paediatric ARDS, according to the Pediatric Acute Lung Injury Consensus Conference (PALICC) 2015 guidelines, is to maintain a plateau pressure ($P_{plateau}$) below 28 cmH_2O, which can be raised slightly to 29-32 cmH_2O in patients with reduced thoracic elasticity, aiming for a tidal volume (Vt) of 3-6 ml/kg at standard body weight. For severe paediatric ARDS (pARDS), a PEEP level of 10-15 cmH_2O is suggested, which can be increased to >15 cmH_2O in critical cases [8]. Although high PEEP levels can temporarily improve oxygenation in ARDS patients, recent evidence suggests they do not improve mortality rates. A 2021 systematic review found that while mechanical ventilation with high PEEP improved oxygenation by day 7, it did not reduce mortality [9]. Studies comparing mechanical ventilation strategies in paediatric patients with COVID-19 ARDS recommend using optimal PEEP, a driving pressure <15 cmH_2O, and assessing ARDS severity using the oxygenation index (OI) rather than the PaO_2/FiO_2 ratio [10]. High-flow nasal cannula (HFNC) ventilation, which redistributes perfusion and ventilation, can improve oxygenation in COVID-19 patients, but evidence shows it does not reduce intubation or mortality rates.

Intravenous immunoglobulin: Patient 1, who presented with acute myocarditis, elevated cardiac enzymes, and decreased EF, did not respond to continuous haemofiltration adsorption after two days. Consequently, IVIG was administered at a dose of 2 g/kg to modulate the inflammatory response and improve cardiac function. IVIG has been shown to increase survival in patients with fulminant myocarditis. A systematic analysis of 13 studies involving 1,534 adult and paediatric patients by X. Huang, et al. (2019) [11] demonstrated that IVIG significantly reduced mortality and improved EF in patients with acute myocarditis.

Cytokine storm management: Cytokine storms are common in critically ill COVID-19 patients, and their uncontrolled presence can lead to tissue damage and multi-organ failure [12-15]. A study analysed the efficacy of tocilizumab in treating COVID-19, demonstrating that its use reduced mortality and the need for mechanical ventilation in severe cases [16]. Another analysis showed that continuous haemofiltration adsorption and plasma exchange improved oxygenation in patients with severe COVID-19 respiratory failure by mitigating cytokine storms [17]. Based on this evidence, we administered continuous renal replacement therapy (CRRT) with the oXiris® filter, in combination with tocilizumab, to both patients.

3.2. Extracorporeal membrane oxygenation situation in COVID-19 patients

In September 2021, a previous study conducted a retrospective study analysing data from 4,812 adults infected with COVID-19 who received ECMO treatment at 349 centres across 41 countries, between 1 May 2020 and 31 December 2020. The mortality rate within 90 days following ECMO treatment ranged from 36.9 to 51.9%, depending on the stage of the COVID-19 outbreak. After 1 May 2021, mortality increased by 15%, with patients requiring ECMO treatment for an average of six days longer than before, and with increased corticosteroid use (43 vs 78%). Factors contributing to this increase in mortality likely included multiple underlying medical conditions and less experienced ECMO centres. The most commonly used ECMO modality was V-V ECMO (95-96%), given that severe lung damage and ARDS were the primary causes of death in adult COVID-19 patients [18].

In contrast to adults, reports of COVID-19 in children show milder illness, lower hospitalisation rates, and reduced mortality. In the US, of 3,116 children infected with COVID-19 who were hospitalised between 1 March 2020 and 19 June 2021, 827 (26.5%) were admitted to the ICU, 162 (5.2%) required HFNC, 131 (4.2%) needed NCPAP/BiPAP, 233 (7.5%) required vasopressors, 190 (6.1%) required invasive ventilation, and 21 (0.7%) died. The report also noted an increase in hospitalisations and ICU admissions with the emergence of the Delta variant, with the rate of children admitted to the Pediatric Intensive Care Unit, Children's Hospital 2 (PICU) and requiring mechanical ventilation rising to 9.8% [19]. While reports of ECMO use in children with COVID-19 are limited, there have been successful cases. As of 28 November 2021, the Extracorporeal Life Support Organization (ELSO) Registry recorded 265 children treated with ECMO for COVID-19, 41% of whom had no underlying medical conditions, and the mortality rate was 32%. The average ECMO duration was 325 hours, with V-V ECMO being the most common modality (71%), followed by veno-arterial extracorporeal membrane oxygenation (V-A ECMO) (24%) and extracorporeal cardiopulmonary resuscitation (ECPR) (5%) [20]. The two cases presented here exemplify the potential for successful ECMO outcomes, though further research is needed to better understand its use in children with COVID-19.

3.3. Extracorporeal membrane oxygenation indication

Patient 1 exhibited severe respiratory failure and hypoxia, with no elevation in CO_2 levels (as shown in Fig. 3 at time T_0). Despite high ventilator settings and 100% FiO_2, blood oxygenation did not improve, resulting in a high oxygenation index (OI) of 21.5 (as shown in Fig. 2). The patient also experienced shock with reduced myocardial contractility, necessitating the use of two vasopressors. According to the 2015 ELSO guidelines (P/F ratio <80 and MAP >20-25 cmH_2O) [21], ECMO was indicated. Although V-A ECMO would have been appropriate due to reduced heart function, the patient received V-V ECMO only, as her cardiovascular condition was not severe enough to warrant V-A ECMO. V-A ECMO carries a higher risk of complications due to arterial involvement and is more technically challenging, especially for an ECMO team with limited experience.

Although Patient 2 had a normal OI of 14.56, no vasopressor requirement, and no organ dysfunction, early ECMO initiation was necessary due to rapidly deteriorating lung function. Increasing ventilator settings did not significantly improve oxygenation, so ECMO was initiated to prevent further lung damage and complications associated with prolonged mechanical ventilation. Timely ECMO initiation is crucial, as delays in indicated cases can negatively affect survival [10]. The 2015 ELSO guidelines recommend V-V ECMO for patients with advanced respiratory failure, especially when the respiratory decline is rapid and ECMO setup may take time [21]. These were the first two ECMO cases managed by our department, and we successfully achieved ECMO initiation within approximately 120 minutes from designation.

3.4. Extracorporeal membrane oxygenation efficiency

Although severe respiratory failure is uncommon in paediatric COVID-19 cases, a recent study identified a rise in critical cases among children aged nine and older, particularly those with obesity and no other pre-existing conditions. These cases often require intensive resuscitation. Obesity has emerged as a significant risk factor for severe COVID-19 in children, highlighting the importance of early vaccination for this population [4].

While mechanical ventilation is crucial in treating severe COVID-19, pushing ventilator settings beyond optimal levels can exacerbate lung injury through barotrauma and oxygen toxicity. In such cases, ECMO serves as a life-saving bridge by supporting the failing lungs, allowing reduced ventilator settings and alleviating stress on the compromised organ [22]. ECMO successfully improved and stabilised oxygen levels in both of our patients within the following days (Fig. 3).

3.5. Early ventilator withdrawal

The strategy for early sedation and ventilator withdrawal during Awake V-V ECMO is outlined in the 2015 ELSO guidelines [23]. Patients who have progressed beyond the pulmonary and superinflammatory stages, with stable blood oxygen and CO_2 levels and gradually decreasing ECMO flow, qualify for this approach. Both patients underwent early ventilator withdrawal on day eight after ECMO support, transitioning to NCPAP for respiratory support. This approach aimed to prevent lung collapse and reduce breathing effort. Early extubation during ECMO offers several benefits, including the preservation of respiratory muscle strength, maintenance of functional residual volume, reduction of ventilation/perfusion (V/Q) mismatch, prevention of ventilator-associated pneumonia, and improved patient comfort [24]. Early physical therapy for ventilated patients is safe, and feasible, and can reduce the risk of delirium and shorten the duration of mechanical ventilation [25].

4. Conclusions

While children with COVID-19 generally experience milder symptoms compared to adults, there are cases where the disease leads to severe respiratory distress, circulatory failure, and multi-organ damage, particularly in patients with underlying conditions or obesity. A multimodal treatment approach, combining anti-inflammatory, antiviral, anticoagulant, and anti-IL6 therapies, alongside cytokine removal techniques and intravenous immunoglobulin, may improve outcomes in severe cases. For children who develop respiratory and circulatory failure and fail to respond to conventional treatments, ECMO serves as a life-saving intervention, providing temporary support for the lungs and heart, allowing time for recovery.

CRediT author statement

Thai Son Pham, Thanh Luan Vo: Methodology, Formal analysis, Original draft preparation, Visualisation; Thai Son Pham, Thanh Luan Vo, Manh Cuong Nguyen: Conceptualisation, Data curation, Investigation; Thai Son Pham, Manh Cuong Nguyen: Investigation, Visualisation, Formal analysis; Thi Ngoc Diem Dang, Duy Tan Nguyen, Chau Viet Do, Van Loc Nguyen, Huu Tung Trinh: Supervision, Validation, Writing - Reviewing and Editing.

ACKNOWLEDGEMENTS

This study was financed by Children's Hospital 2 for scientific research activities. The authors would like to express their gratitude to Huu Tung Trinh for her assistance during the experiment.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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