

REVIEW

Extracorporeal membrane oxygenation for refractory septic shock in children

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Abstract

Children are susceptible to developing sepsis. Among its complications, septic shock is the most severe. Refractory septic shock (RSS) is defined as septic shock that is unresponsive to standard resuscitation. As the most severe complication of sepsis in children, refractory septic shock (RSS) is characterized by its rapid development and high mortality rate. In accordance with relevant guidelines and consensus, extracorporeal membrane oxygenation (ECMO) is recommended as a salvage therapy for the treatment of RSS in children. However, various controversies and difficulties still exist when ECMO is used to treat children with RSS. Thus, this review summarizes the current status, difficulties, and explorations of applying ECMO to the treatment of RSS in children.

Keywords

ECMO; RSS; Children

1. Introduction

Children are susceptible to developing sepsis. Among its complications, septic shock is the most severe. Refractory septic shock (RSS) is defined as septic shock that is unresponsive to standard resuscitation [1]. Maintaining threshold values of cardiac output (CO) and systemic vascular resistance (SVR) when used as part of the American College of Critical Care Medicine (ACCM) haemodynamic protocol improves the outcomes in pediatric septic shock [2]. Timely RSS identification and intervention are critical to improve the survival rate.

ECMO is a life-saving method used to improve the cardiopulmonary function of the patient, thereby gaining more time for other treatments to save patients' life. Before 1990, patients with ECMO treatment were prone to develop disseminated intravascular coagulation (DIC) or hemorrhage, and the poor patient prognosis issue could not be resolved properly. Therefore, ECMO was considered as relative contraindication [3] to the RSS treatment. However, advances in medical technologies, as well as strict heparin management and loop care, largely reduced the complications. In 1994, J Beca [4] recommended ECMO as a salvage therapy for the treatment of pediatric RSS in his study. In 2009 and 2017, the American College of Critical Care Medicine (ACCM) published the Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock [5, 6], which recommended ECMO for the neonatal and pediatric RSS treatment. Currently, related international guidelines on the RSS treatment (including the pediatric RSS treatment) have recommended the veno arterial extracorporeal membrane oxygenation (VA-ECMO) as the last salvage therapy for RSS, which is considered level

2C evidence [7]. Additionally, basic information such as the immune and circulatory functions, as well as the pathogen that has caused the infection, determines the survival rate of RSS patients treated with ECMO salvage therapy. Thus, the ECMO salvage therapy for children with RSS remains as an arduous task. This review will summarize the current status, difficulties, and explorations of applying ECMO to the treatment of RSS, in an effort to provide a theoretical basis for the treatment of pediatric RSS with ECMO.

2. Current status of treating RSS with ECMO

We searched the PubMed database from inception until April 2023. And the search strategy is as follows:

#1 "Extracorporeal Membrane Oxygenation" [Mesh] OR ECMO [Title/Abstract] OR "Extracorporeal Membrane Oxygenation" [Title/Abstract] OR "extracorporeal life support" [Title/Abstract] OR "extracorporeal membrane oxygenator support" [Title/Abstract]

#2 "Infant" [Title/Abstract] OR "newborn" [Title/Abstract] OR "child" [Title/Abstract] OR "pediatric" [Title/Abstract] OR "neonate" [Title/abstract] OR "Infant" [Mesh] OR "newborn" [Mesh] OR "children" [Mesh] OR "pediatric" [Mesh] OR "neonate" [Mesh]

#3 "refractory septic shock" [Mesh] OR "refractory septic shock" [Title/Abstract]

#1 and #2 and #3

And the results of the study selection process are presented in Fig. 1.

In this review, eight clinical studies of ECMO salvage ther-

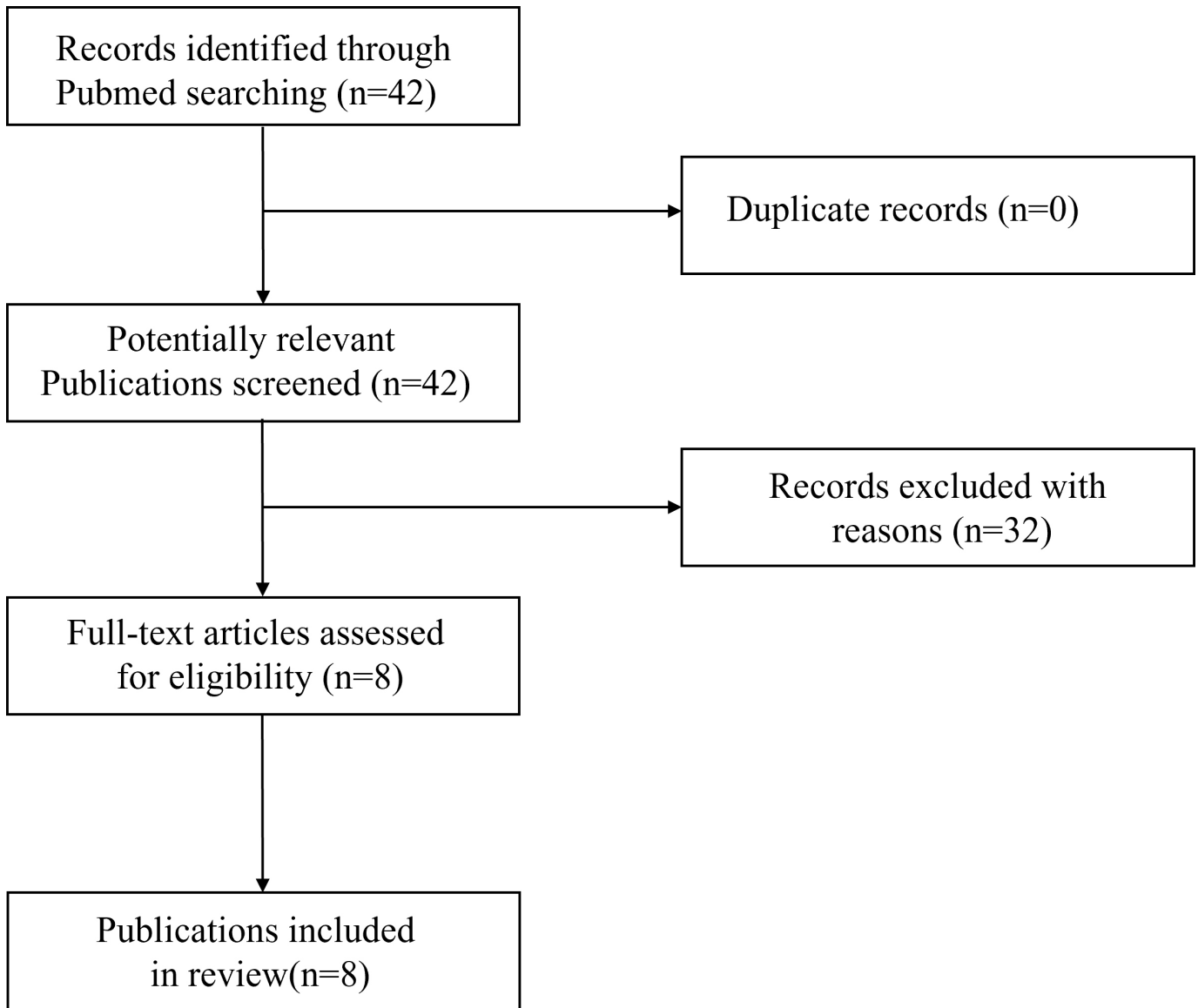


FIGURE 1. Flow chart showing the process of study selection and numbers of studies included. A total of 42 studies were found in PubMed, and there were 8 studies included in this review.

apy for pediatric RSS are analyzed in Table 1. Among them, seven [4, 8–13] are retrospective single-center studies, with a total of 144 cases analyzed; one is a prospective multicenter study, in which 70 patients (64 children and six neonates) from eight hospitals are observed. Currently, studies on ECMO for pediatric RSS treatment are mainly originated from Europe, North America, and Australia, with few covered in Asia. So, further exploration should be taken on the treatment of pediatric RSS with ECMO.

3. The difficulties of ECMO for RSS

3.1 Types of ECMO support for RSS

Peripheral VA-ECMO refers to the cannulation of the femoral artery and ipsilateral femoral vein [15–17]. And for children and neonates, the trans-cervical approach is more common than a trans-femoral approach. In 2011, MacLaren *et al.* [9] described that they placed a venous cannula in the right atrium and an arterial cannula in the ascending aorta in an open-heart

surgery, which was called “central VA-ECMO”.

Veno-venous ECMO (VV-ECMO) [15] usually refers to the cannulation of the right femoral vein and internal jugular vein. However, VV-ECMO provides no cardiopulmonary support, so blood needs to be pumped *via* the native blood pumping system. Additionally, the existing dual-lumen cannula cannot meet the requirement for high blood flow volume as it may result in hemolysis when the blood flow volume is high [15].

3.2 Survival rate of RSS patients treated with ECMO and factors affecting the survival rate

As it is shown in Table 1, it can be found that the survival rates in the studies by Beca J in 1994, Maclaren G in 2007, Rambaud J in 2015, Solé A in 2018, and Ruth A in 2021 [4, 8, 10, 11, 13] do not exceed 60%. In comparison, central VA-ECMO outperforms peripheral VA-ECMO as the survival rate of RSS patients treated with central VA-ECMO has reached 66.7% to 73.9% [8, 9, 13]. Furthermore, Bichara *et al.* [12]

TABLE 1. Status of ECMO for RSS in children.

First author	Type of the article	Country	Time of publication	Total number of cases	Children	Neonates	Type of ECMO	Centers for the study	Total survival rates
Beca J [4]	Retrospective study	Australia	1994	9	9	0	Peripheral VA-ECMO	One single center	55.6% (5/9)
Maclaren G [8]	Retrospective study	Australia	2007	45	39	6	Central VA-ECMO + peripheral VA-ECMO	One single center	46.7% (21/45)
Maclaren G [9]	Retrospective study	Australia	2011	23	23	-	Central VA-ECMO	One single center	73.9% (17/23)
Rambaud J [10]	Retrospective study	France	2015	22	8	14	Peripheral VA-ECMO	One single center	59.1% (13/22)
Solé A [11]	Retrospective study	Spain	2018	21	9	12	Peripheral VA-ECMO	One single center	42.9% (9/21)
Bichara G C V L [12]	Retrospective study	Brazil	2019	10	-	-	Peripheral veno-veno-arterial ECMO (VVA-ECMO)	One single center	70.0% (7/10)
Ruth A [13]	Retrospective study	The US	2021	14	14	0	Central VA-ECMO + peripheral VA-ECMO	One single center	57.1% (8/14)
Workman J K [14]	Prospective study	The US	2020	70	64	6	Central VA-ECMO + peripheral VA-ECMO	Multiple centers, with eight hospitals in total	45.7% (32/70)

VA-ECMO: veno arterial extracorporeal membrane oxygenation.

once applied peripheral VVA-ECMO in their study, in which ten patients were observed. When the peripheral VVA-ECMO was discontinued, the survival rate of the patients reached 70.0% (7/10). The data on the high blood flow volume during the treatment is encouraging, but the sample size is small. Therefore, more cases are needed for further exploration.

Different bacterial infections may affect the prognoses of RSS patients treated with ECMO. Chang *et al.* [18] have discovered pathogenic pathogens in 35 out of 55 RSS children treated with ECMO. Specifically, 17 children were found infected with bacteremia (with pneumococci being the most common); 16 were found infected with previous viral infections (including influenza virus, adenovirus, and respiratory syncytial virus); one was found infected with the virus-and-bacteria mixed infection; one was found infected with the invasive fungal infection. Overall, 31% of the patients survived after discharge.

In the statistics for the bacterial infections in RSS children treated with ECMO, 57% of the children were infected with *Streptococcus agalactiae*, and 36% were with *Escherichia coli* (*E. coli*) [10]. Pediatric and teenage sepsis is mainly caused by bacteria such as *Streptococcus pneumoniae*, Gram-negative bacteria, and *Staphylococcus aureus* (*S. aureus*) [11, 19], while early-onset neonatal sepsis is mainly by lactic acid-free Strep-

tococcus and late-onset one is by *Klebsiella pneumoniae* and *S. aureus* [20].

Adenovirus or influenza virus may also result in septic shock, and ECMO is the last resort to treat pediatric patients with septic shock. After the patients receive the ECMO therapy, their oxygenation index and inhaled oxygen concentration are considerably improved [20, 21]. In the study carried out by Prodhan *et al.* [22], among the 163 pediatric patients infected with adenovirus, 38% of the patients treated with ECMO survived; among the 55 neonatal patients (born in 31 days) severely infected with adenovirus, 11% of the patients treated with ECMO survived. Additionally, for critically ill patients with pH1N1 infection and severe lung injury, the ECMO therapy can improve their PaO₂/FiO₂ ratio, oxygenation index, and FiO₂. However, the influence of the pH1N1 virus on mortality rate remains uncertain [21].

It is noteworthy that the longer the ECMO treatment is, the possibilities of catheter-related infections are higher. Therefore, we should pay attention to catheter-related infections.

Some studies [23] suggested that reducing the blood lactic acid level within the first six hours of the early septic shock may improve the survival rate of pediatric patients. Scolari *et al.* [24] discovered that if the serum lactic acid levels were not decreased in the 24 hours after the shock, the mortality rate of

the patients would be approximately 100%, and that the serum lactic acid level and the clearance rate of lactic acid in 24 hours are the strongest independent predictors of short-term survival. Therefore, the ECMO therapy evaluation should be carried out as early as possible before the lactic acid level rises.

Markers for liver injury may also predict the prognosis, but currently, the mechanism of the markers for liver injury after the ECMO initiation has not been fully understood. In a study [25] taking total serum bilirubin level as a univariate factor, none of the patients with more than 30 mg/dL of total serum bilirubin level survived. Thus, bilirubin may be a marker of clinical significance for the mortality rate prediction during the treatment of RSS with ECMO.

4. Difficulties in treating RSS with ECMO

4.1 Difficulties in ECMO cannulation

The central ECMO cannulation needs to be performed by cardiac surgeons in the operating room. Open-heart surgery is invasive, which needs high requirements for the surgical environment and techniques. Additionally, patients are prone to hemorrhage during the operation, and examining patients who have experienced hemorrhage may lead to mediastinitis [9]. Overall, central ECMO cannulation is an arduous task. Therefore, peripheral ECMO is mainly used clinically as a salvage therapy for the RSS treatment.

The hemodynamics is unstable during the septic shock. VA-ECMO replaces the body's cardiac output (CO) with extracorporeal support measures. Hemorrhage during the treatment is a common complication (see Table 2). Furthermore, after surgery, the hemodynamics of the body are more unstable.

4.2 Timing of treating pediatric RSS patients with ECMO

Multiple studies [11, 26, 27] indicated that the duration of sepsis may influence the survival rate. In other words, the

shorter the interval between the RSS appearance and the use of ECMO is, the higher the survival rate of patients is after discharge. For example, in a report on treating adult patients with ECMO, Cheng *et al.* [27] discovered that the prognosis of patients would be better if they were treated with ECMO within 96 hours after developing septic shock due to Gram-positive bacteria. Additionally, when analyzing the ECMO therapy for pediatric RSS patients, Anna Solé *et al.* [11] discovered that patients who died had been treated with ECMO later than those that survived. Therefore, the ECMO therapy evaluation for pediatric RSS patients should be conducted as early as possible.

4.3 Failure to meet the circulatory needs of RSS patients with the blood flow volume provided by ECMO

Oberender *et al.* [28] argued that patients' needs for oxygen dramatically increase when developing septic shock. However, conventional peripheral ECMO fails to provide adequate blood flow volume, which cannot fully meet the body's needs for oxygen for circulation. Additionally, the mismatch between oxygen consumption and supply results in persistent hypoxia, which aggravates organ dysfunction. To resolve the mismatch in the circulation and treat hypoxia, the ECMO machine's CO, pump flow rate (PFR), and the PFR/CO ratio must be strictly controlled.

When VA-ECMO is used to restore systemic perfusion, the minimum pump flow rate should be no less than 1500 mL/min [29]. The pump flow rate depends on the rotational speed, the vascular access size, the resistance of the venous loop. However, a child's lacuna vasorum and ECMO vascular access tend to be thin, and high rotational speed and high pressure in ECMO vascular access are high-risk factors for hemolysis. Therefore, it makes it difficult to provide high blood flow volume during the treatment of pediatric RSS with ECMO.

TABLE 2. Adverse events in treating RSS with ECMO.

First author	Total number of cases	Mechanical problems in ECMO circuits	Limb ischemia	Hemorrhagic episodes	Neurological complications
Beca J [4]	9	5	-	4	4
Maclaren G [8]	45	24	6	11	4
Maclaren G [9]	23	13	-	8	-
Rambaud J [10]	22	9	-	-	2
Solé A [11]	21	10	-	1	7
Bichara G C V L [12]	10	3	-	-	7
Workman J K [14]	70	-	-	51	36
Ruth A [13]	14	-	-	11	1

ECMO mechanical problems: Including circuit clotting and hemolysis that cause circuit changes; with no oxygenator pump failure or air in the circuit.

Neurological complications: Subclinical and clinical epilepsy, cerebral ischemia, infarction or hemorrhage.

Hemorrhagic episodes: Including hemorrhage of the incised part, gastrointestinal hemorrhage, and hemorrhages other than cerebral hemorrhage.

ECMO: extracorporeal membrane oxygenation.

4.4 Hemorrhage and thrombosis during the ECMO therapy

Hemorrhage and thrombosis are common complications of ECMO therapy (see Table 2). In a study with 29 pediatric patients included, the 25 deceased (86%) were discovered to have had thrombosis or experienced hemorrhage at autopsy, nine of whom (31%) had experienced both thrombosis and hemorrhage [30]. Among the complications of hemorrhage, intracranial hemorrhage (ICH) was the most severe, with a mortality rate of 32% to 100% [31, 32]. Additionally, children and adults were different in terms of the incidence of this disease. In accordance with the data released by the ELSO Registry in 2019, the incidence of ICH among pediatric patients reaches 6% to 15%, while that among adult patients reaches 2% to 4% [33]. Moreover, the thrombosis or hemorrhage of children who still died after receiving ECMO therapy may be influenced by the prothrombin time (PT), platelet count, fibrinogen level, activated clotting time, and heparin dose. Therefore, it is a big challenge to balance the patients' anticoagulation and hemostasis during the ECMO therapy for RSS. Also, managing the coagulation system in septic children is challenging as these children often present with disseminated intravascular coagulation (DIC), but there is little data available on how to deal with this challenge.

5. Exploration researches of ECMO for RSS in children

5.1 ECMO combined with renal replacement therapy for RSS

The incidences of acute kidney injury (AKI) and fluid overload (FO) are relatively high [34] during the RSS treatment with ECMO. It is multifactorial that ECMO results in AKI. For example, excessive fluid infusion before and during the RSS treatment with ECMO has aggravated the risk of AKI.

Continuous renal replacement therapy (CRRT) can be performed independently of the ECMO circuit *via* venous access or by connecting the CRRT device to the ECMO circuit. A study [35] pointed out that “with no primary kidney diseases, none of the survivors treated with ECMO in combination with CRRT developed the end-stage renal disease (ESRD)”. Additionally, in 2019, Dado *et al.* [36] discovered that “the renal recovery rate and total survival rates of patients that need to be treated with ECMO in combination with CRRT are higher”. However, there is no long-term follow-up data for this study.

In 2019, Chen *et al.* [37] found that ECMO patients who had been undergoing AKI dialysis and AKI patients who did not dialyze a follow-up visit, with an average follow-up time of 2.4 ± 2.5 years. They discovered that the increased risks of death in the adult AKI patients treated with ECMO mainly resulted from adverse renal events and that ECMO patients who had been undergoing AKI dialysis had a worse prognosis than the AKI patients who did not dialyze.

Kuo *et al.* [38] probed into the correlation between the duration of CRRT and the long-term prognosis of adults treated with ECMO. They divided the patients into three groups of ≤ 3 days, 4–6 days, and ≥ 7 days of CRRT. ECMO patients

undergoing CRRT for ≤ 3 days recorded the highest in-hospital mortality rate, similar to the long-term survival rate of ECMO patients undergoing CRRT for ≥ 7 days. Additionally, long-term follow-up survivors featured lower rates of ESRD and ventilator dependence. The study suggested that this might be related to the fact that longer CRRT duration and later hemodynamic recovery have led to lifelong dialysis dependence.

Although CRRT provides renal support for patients when their hemodynamics is not stable, it may also exert a negative influence on prognosis. Currently, controversies arise regarding the time of the beginning of the combined renal replacement therapy, the optimal vascular access, and anticoagulation during treatment. Whether ECMO in combination with CRRT for pediatric RSS patients will exert a long-term influence on renal function still needs to be further explored and studied.

5.2 Application of ECMO to the treatment of RSS post-transplant complication

Infection is the main cause of high mortality rate after liver transplant, and severe infection makes patients susceptible to RSS. Lee *et al.* [39] collected a total of eight patients who are aged above 18 and have undergone VA-ECMO therapy after developing the RSS postoperative complication of liver transplant and found that their survival rate after discharge reaches 25% (2/8). Therefore, adult patients who have undergone liver transplants are recommended to treat RSS with VA-ECMO.

With respect to liver transplants in children, Ziogas *et al.* [40] reviewed the cases of 22 pediatric patients who had undergone ECMO therapy before liver transplant. They found that 15 of them survived (68.2%) and that their survival rate six months after undergoing treatment was $>55\%$. Additionally, Abe *et al.* [41] reported on a case of a pediatric patient whose RSS postoperative complication of the liver transplant was successfully treated with peripheral VA-ECMO. They suggested that ECMO could be a therapeutic option for the RSS postoperative complication of liver transplants in children as long as the renal function allows after the transplant.

Furthermore, in 2018, Scott *et al.* [42] also reported on a pediatric case. Specifically, after undergoing a liver transplant, the pediatric patient developed post-transplant liver dysfunction (hyperbilirubinemia and coagulation dysfunction) and RSS. Subsequently, they provided sufficient blood flow volume with central ECMO to resuscitate the pediatric patient and then performed another liver transplant. Thus, different cannulation modes have different influences on patients with circulatory failure caused by liver dysfunction and sepsis.

5.3 Application of ECMO in combination with methylene blue (MB) to RSS treatment

Some RSS cases are caused by vasoplegic syndrome (VS), especially after *Streptococcus pneumoniae* infection. VS refers to a group of syndromes still with persistent hypotension in spite of sufficient volume expansion and the application of high-dosage vasoactive drugs [43]. If the cases are treated with ECMO, the mortality rate will be up to 80% [11]. In accordance with some case reports [44], the clinically highest dosages of various vasopressor drugs and the prolonged MB infusion during the VV-ECMO treatment may reverse RSS.

However, current studies on the application of MB to sepsis are few. One related study [45] noted that MB could increase a VS patient's arterial pressure and systemic vascular resistance, but it will not influence the prognosis. Currently, there is no consensus on the optimal dosage of MB for RSS patients, and the dosage regimen is similar to that for methemoglobinemia (1–2 mg/kg) [46]. Although there is no evidence supporting the use of MB as the first-line agent for RSS treatment, MB, in combination with ECMO, can be clinically used as a remedy for the treatment of RSS caused by VS, and more experiments in the future should be performed to evaluate its efficacy.

6. Outlook

Currently, the follow-up results of the long-term prognoses of patients using ECMO are also not reported. Furthermore, there will be more in-depth studies on and analysis of ECMO technology, more proven equipment and cannulation techniques, and more new drugs and technologies available, so the chances of success in treating pediatric RSS with ECMO will be much higher. Additionally, the optimal strategy for treating RSS in children with ECMO will be well developed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YFY and XNW—wrote the manuscript, JTH, XLL and ZHX—searched references. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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