Journal of Cardiothoracic Surgery

RESEARCH

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International treatment outcomes of neonates on extracorporeal membrane oxygenation (ECMO) with persistent pulmonary hypertension of the newborn (PPHN): a systematic review

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Abstract

Background PPHN is a common cause of neonatal respiratory failure and is still a serious condition and associated with high mortality.

Objectives To compare the demographic variables, clinical characteristics, and treatment outcomes in neonates with PHHN who underwent ECMO and survived compared to neonates with PHHN who underwent ECMO and died.

Methods We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and searched ProQuest, Medline, Embase, PubMed, CINAHL, Wiley online library, Scopus and Nature for studies on the development of PPHN in neonates who underwent ECMO, published from January 1, 2010 to May 31, 2023, with English language restriction.

Results Of the 5689 papers that were identified, 134 articles were included in the systematic review. Studies involving 1814 neonates with PPHN who were placed on ECMO were analyzed (1218 survived and 594 died). Neonates in the PPHN group who died had lower proportion of normal spontaneous vaginal delivery (6.4% vs 1.8%; *p* value > 0.05) and lower Apgar scores at 1 min and 5 min [i.e., low Apgar score: 1.5% vs 0.5%, moderately abnormal Apgar score: 10.3% vs 1.2% and reassuring Apgar score: 4% vs 2.3%; *p* value = 0.039] compared to those who survived. Neonates who had PPHN and died had higher proportion of medical comorbidities such as omphalocele (0.7%

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vs 4.7%), systemic hypotension (1% vs 2.5%), infection with *Herpes simplex virus* (0.4% vs 2.2%) or *Bordetella pertussis* (0.7% vs 2%); $p=0.042$. Neonates with PPHN in the death group were more likely to present due to congenital diaphragmatic hernia (25.5% vs 47.3%), neonatal respiratory distress syndrome (4.2% vs 13.5%), meconium aspiration syndrome (8% vs 12.1%), pneumonia (1.6% vs 8.4%), sepsis (1.5% vs 8.2%) and alveolar capillary dysplasia with misalignment of pulmonary veins (0.1% vs 4.4%); $p=0.019$. Neonates with PPHN who died needed a longer median time of mechanical ventilation (15 days, IQR 10 to 27 vs. 10 days, IQR 7 to 28; $p=0.024$) and ECMO use (9.2 days, IQR 3.9 to 13.5 vs. 6 days, IQR 3 to 12.5; $p=0.033$), and a shorter median duration of hospital stay (23 days, IQR 12.5 to 46 vs. 58.5 days, IQR 28.2 to 60.7; $p=0.000$) compared to the neonates with PPHN who survived. ECMO-related complications such as chylothorax (1% vs 2.7%), intracranial bleeding (1.2% vs 1.7%) and catheter-related infections (0% vs 0.3%) were more frequent in the group of neonates with PPHN who died ($p=0.031$).

Conclusion ECMO in the neonates with PPHN who failed supportive cardiorespiratory care and conventional therapies has been successfully utilized with a neonatal survival rate of 67.1%. Mortality in neonates with PPHN who underwent ECMO was highest in cases born via the caesarean delivery mode or neonates who had lower Apgar scores at birth. Fatality rate in neonates with PPHN who underwent ECMO was the highest in patients with higher rate of specific medical comorbidities (omphalocele, systemic hypotension and infection with *Herpes simplex virus* or *Bordetella pertussis*) or cases who had PPHN due to higher rate of specific etiologies (congenital diaphragmatic hernia, neonatal respiratory distress syndrome and meconium aspiration syndrome). Neonates with PPHN who died may need a longer time of mechanical ventilation and ECMO use and a shorter duration of hospital stay; and may experience higher frequency of ECMO-related complications (chylothorax, intracranial bleeding and catheter-related infections) in comparison with the neonates with PPHN who survived.

Keywords Extracorporeal life support, ECLS, ECMO, Extracorporeal membrane oxygenation, Neonates, Newborn, Patent ductus arteriosus, Persistent fetal circulation, Pulmonary hypertension, Systematic review

Background

Persistent pulmonary hypertension of the newborn (PPHN) is a common cause of neonatal respiratory failure and occurs in term and late preterm neonates affecting about 2 cases per 1000 live births [1, 2]. PPHN is a neonatal emergency that requires timely and accurate medical intervention to prevent severe hypoxemia, short- and long-term morbidities and mortality. Despite advances in neonatal cardiorespiratory care, PPHN is still a serious condition and associated with high mortality, ranging between 7 and 35.7% [2–5]. Intensive care units with experienced healthcare providers are required to look after neonates with PPHN and where multiple therapeutic choices such as respiratory support, rescue therapies, and pulmonary vasodilator therapy (usually with inhaled nitric oxide) are available. Neonates with refractory PPHN who fail these typical management approaches and remain persistently severely hypoxemic qualify for extracorporeal membrane oxygenation (ECMO) [6]. ECMO is a life support device that serves as a modified form of cardiopulmonary bypass and supports the newborns to maintain adequate oxygen delivery without causing ongoing lung injury from mechanical ventilation while the underlying disease process and associated PPHN resolve.

To date, some systematic reviews have been performed to evaluate the role and therapeutic benefits of ECMO use among neonates with either respiratory failure, congenital diaphragmatic hernia or sepsis [7–10]. The findings varied widely and individual studies examined various medical comorbidities and use of different classes of medications [7–10]. Moreover, none of the reviews performed sub-group analysis for patients with PPHN who underwent ECMO. Due to the lack of comprehensive and updated systematic reviews focusing on use of ECMO in neonates with PPHN, we aim in this systematic review to compare the demographic variables, clinical characteristics, and treatment outcomes in neonates with PHHN who underwent ECMO and survived compared to neonates with PHHN who underwent ECMO and died. Since newborns with PPHN often have life-threatening illness, it would be advantageous to identify the highest-risk neonates so that transfer to ECMO centres can be facilitated.

Methods

Design

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11] and was registered with PROSPERO (ID: CRD42024533967). Published articles from 1 January 2010 to 31 May 2023, with English language restriction, were selected for review from eight electronic databases (PubMed, CINAHL, Embase, Scopus, ProQuest, Wiley online library, Medline, and Nature). The search phrases included Boolean terms

'AND' and 'OR' with the following keywords in various possible combinations: "extracorporeal membrane oxygenation", "ECMO", "extracorporeal life support", "ECLS", "extracorporeal cardiopulmonary resuscitation", "ECPR", "pulmonary hypertension", "patent ductus arteriosus", "patent foramen ovale", "PPHN", "persistent fetal circulation", "persistent fetus circulation" and "persistent foetal circulation" (see Additional file 1: Supplementary Table 1 for database-specific search syntax). Articles discussing and reporting the development of PPHN in neonates who underwent ECMO were selected based on the title and abstract. Because ECMO has been increasingly used in the last years to provide hemodynamic and respiratory support in neonates with PPHN and new treatment modalities like inhaled nitric oxide and high-frequency oscillatory ventilation became available, we had to exclude studies from our review that met the inclusion criteria but were published before 2010.

Inclusion–exclusion criteria

Readily accessible peer-reviewed full articles, observational cohort studies, clinical trials, case reports, case series, and not peer-reviewed preprints that focused on development of PPHN in neonates (≤28 days old) who underwent ECMO were included. Exclusion criteria were editorials, commentaries, reviews and meta-analyses; studies with ECMO used in non-neonatal patients; studies with no ECMO performed or ECMO used in neonates without PPHN; studies with no ECMO outcomes reported; in vitro, in silico, or in vivo studies; non-human studies or studies available in other languages other than English.

Definition of PPHN

PPHN, also called persistent fetal circulation, was defined as the failure of the normal circulatory transition that occurs after birth [12]. It is a syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus [12].

Data extraction

The screening of the papers was performed independently by six reviewers (Saad Alhumaid, Abdulrahman A. Alnaim, Mohammed A. Al Ghamdi, Abdulaziz A. Alahmari, Muneera Alabdulqader and Sarah Mahmoud Al HajjiMohammed) by screening the titles with abstracts using the selection criteria. Disagreements in the study selection after the full-text screening were discussed; if agreement could not be reached, a seventh reviewer (HSA) was involved. We categorized articles as case report, case-series, cohort or controlled trial studies. The following data were extracted from the selected studies: authors; publication year; study location; study design and setting; age; proportion of male patients; patient ethnicity; delivery mode and birth weight; gestational age and Apgar score; comorbidities; etiology of PPHN and severity of hypoxia; initial ECMO mode and location of cannulation; other co-interventions used to treat PPHN; ECMO complications; duration of use of supplemental oxygen, inhaled nitric oxide, mechanical ventilation and ECMO, and duration of hospital stay; assessment of study risk of bias; and final treatment outcomes (survived or died); and they are noted in Additional file 2 (see Supplementary Table 2 for summary of the characteristics of the included studies with evidence on neonates on ECMO with PPHN (n = 134 studies), 2010–2023).

Quality assessment

Three tools were used appropriately to assess the quality of the studies included in this review: (1) Modified Newcastle–Ottawa Scale (NOS) to evaluate case report and case-series studies (scoring criteria: 5 criteria fulfilled = good, 4 criteria fulfilled = moderate, and 3 criteria fulfilled = low) [13]; (2) NOS to evaluate cohort studies (scoring criteria: > 7 scores = high quality, 5–7 scores = moderate quality, and < 5 scores = low quality) [14]; and (3) Revised Cochrane risk-of-bias tool (RoB 2.0) to evaluate randomized controlled trials (bias is assessed in five distinct domains and answers lead to judgments of "low risk of bias," "some concerns," or "high risk of bias") [15]. Quality assessment was conducted by six co-authors (Qasim M. Alalwan, Nourah Al Dossary, Header A Alghazal, Mohammed H Al Hassan, Khadeeja Mirza Almaani and Fatimah Hejji Alhassan) who separately evaluated the possibility of bias using these three tools.

Data analysis

Descriptive statistics were used to describe the data. For continuous variables, mean and standard deviation were used to summarize the data; and for categorical variables, frequencies and percentages were reported. Data were presented as either a percentage of all subjects or subjects in that group (n = cases, % of all or group) or as the number and percent in available studies reporting on that data (n = case/total available data, %). Differences between the PPHN in neonates who were placed on ECMO and survived group and PPHN in neonates who were placed on ECMO and died group were analyzed using the Chi-square (χ^2) tests (or Fisher's exact tests for expected cell count < 5 in more than 20% of the cells). The unpaired t-test was used to compare the mean duration of use of supplemental oxygen, inhaled nitric oxide, mechanical ventilation and ECMO, and duration of hospital stay in the two ECMO groups with survival and death. All p values were based on two-sided tests and

significance was set at a p value less than 0.05. Microsoft Excel 2019 (Microsoft Corp., Redmond, USA) and IBM SPSS Statistics software, version 26.0 (IBM Corp., Armonk, NY, USA) were used for all statistical analyses.

Results

Study characteristics and quality

A total of 5689 publications were identified (Fig. 1). After exclusion of duplicates and articles that did not fulfil the study inclusion criteria, one hundred and thirty-four articles were included in the qualitative synthesis of this systematic review [16–149]. Detailed characteristics of the included studies are shown in Additional file 2: Supplementary Table 2. There were 59 case report, 62 cohort, 9 case-series and 4 controlled trial studies. These studies were conducted in United States (n = 75), The Netherlands (n = 11), Japan (n = 7), China (n = 6), Germany (n = 5), United Kingdom (n = 5), South Korea (n = 3), Italy (n = 3), Spain (n = 2), France (n = 2), Australia (n = 2), Israel (n = 2), India (n = 1), Qatar (n = 1), Poland (n = 1), Taiwan (n = 1), Argentina (n = 1), Indonesia (n = 1), Singapore (n = 1), Portugal (n = 1), Thailand (n = 1), and Czech Republic (n = 1). Only one study was made within multi-countries (n = 1) [46]. The majority of the studies

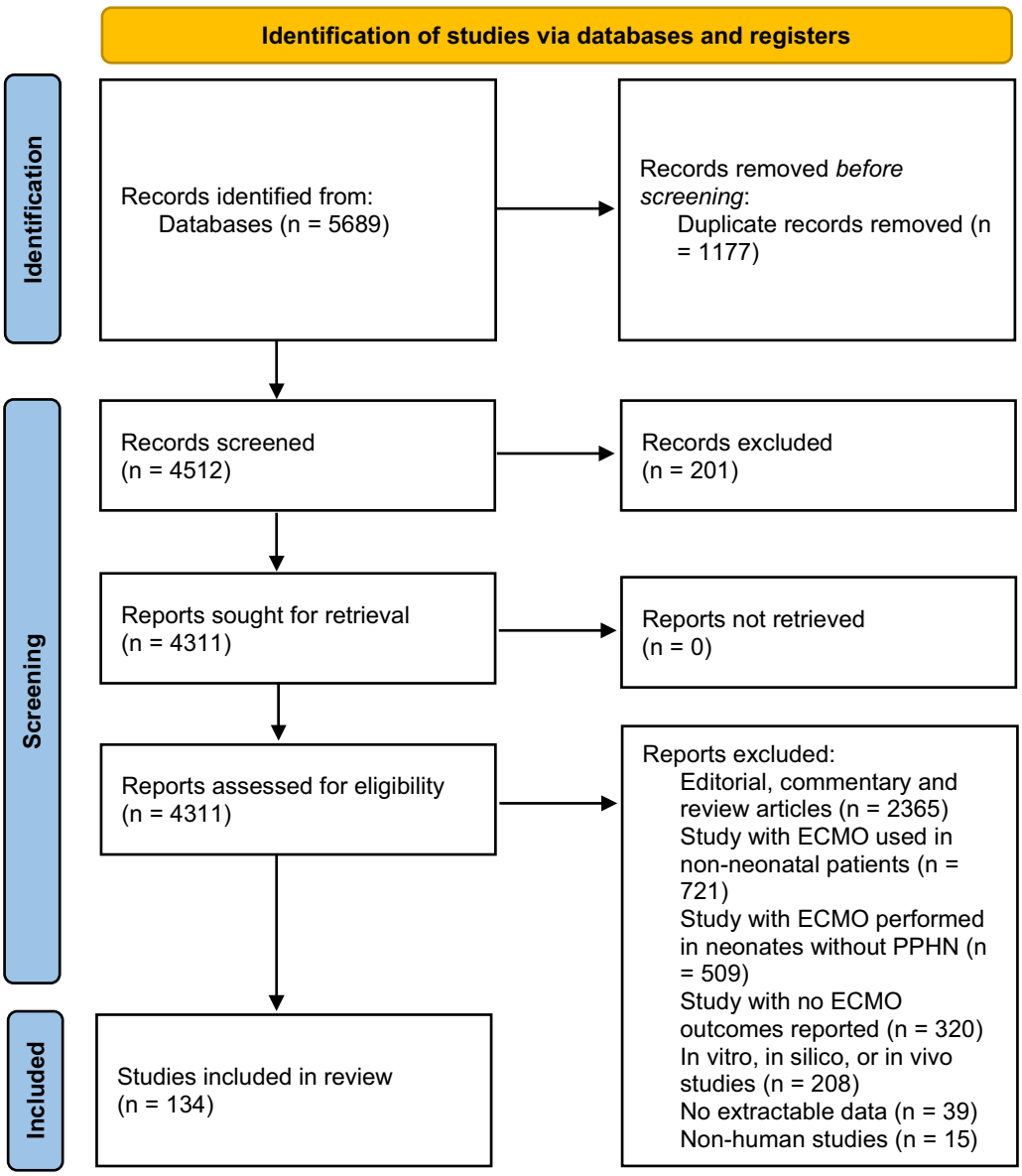

Fig. 1 Flow diagram of studies included in the systematic review

were single centre and only 16 studies were multi-centre. Almost all studies included in this review were retrospective in design except few studies were prospective (n = 5) [19, 45, 59, 61, 65]. Fifty-six studies were deemed to have high methodological quality, 8 moderate methodological quality, and 3 low methodological quality. Among the 62 included cohort studies, 39 cohort studies were found to be moderate-quality studies (i.e., NOS scores between 5 and 7) and 23 study demonstrated a relatively high quality (i.e., NOS scores > 7). The four trials had a low risk of bias based on RoB 2 (Supplementary Table 2).

Demographics and clinical characteristics of neonates with PPHN who were placed on ECMO

The included studies had a total of 1814 neonatal cases with PPHN who were placed on ECMO as detailed in Table 1. The median interquartile range (IQR) age of hospitalized neonates was 1.2 days (0.7 to 5), with an increased male predominance in neonates diagnosed with PPHN and placed ECMO in most of the studies (505/825 = 61.2%), and majority of the neonates belonged to White (Caucasian) (n = 214/393, 54.4%) and black (n = 138/393, 35.1%) ethnicity. Some neonates were born via the normal spontaneous vaginal delivery (n = 89/232, 38.4%), however, a higher proportion of these neonates were born via the caesarean delivery mode (n = 142/232, 61.2%). Around (122/142, 85.9%) of neonates were born with a normal birthweight (≥ 2500 g) but some neonates were delivered with low birthweight (≥ 1500 g to < 2500 g) (19/142, 13.4%). Most neonates were born with a normal gestational age (term: ≥ 37 weeks) (n = 143/176, 81.2%), but few neonates were born with a pregnancy range from 32 to < 37 weeks (moderate to late preterm) (n = 32/176, 18.2%). One neonate was delivered by induction of labour (n = 1); and one patient had a very low birthweight (< 1000 g) and a very preterm gestational age (28 to < 32 weeks) (n = 1) (Table 1).

Apgar score at 1 min and 5 min for these neonates were in the range of (0 to 3) (n = 21/216, 9.7%), (4 to 6) (n = 133/216, 61.6%) and (7 to 10) (n = 62/216, 28.7%). Most common medical comorbidities in neonates who suffered PPHN and underwent ECMO were omphalocele (n = 37), thrombocytopenia (n = 30), systemic hypotension (n = 26), respiratory failure (n = 23), infection with *Bordetella pertussis* (n = 21), pneumothorax (n = 19), transposition of the great arteries (n = 19), infection with *Herpes simplex virus* (n = 18) and cardiogenic shock (n = 16). The causes of PPHN were congenital diaphragmatic hernia (n = 592/1814, 32.6%), meconium aspiration syndrome (n = 170/1814, 9.4%), neonatal respiratory distress syndrome (n = 131/1814, 7.2%), pneumonia (n = 70/1814, 3.8%), sepsis (n = 67/1814, 3.7%), hypoxic ischemic encephalopathy (n = 57/1814, 3.1%), alveolar capillary dysplasia with misalignment of pulmonary veins (n = 27/1814, 1.5%), birth asphyxia (n = 26/1814, 1.4%), lung hypoplasia (n = 19/1814, 1%), idiopathic (n = 15/1814, 0.8%) and preterm premature rupture of the membranes (n = 13/1814, 0.7%) (Table 1).

Oxygen saturation index in these neonates was severe (≥ 25 and < 40) (n = 55/97, 56.7%), very severe (≥ 40) (n = 41/97, 42.3%) or moderate (≥ 15 and < 25) (n = 1/97, 1%). Neonates were initially placed on two basic modes of ECMO: venoarterial (n = 310/439, 70.6%) or venovenous (n = 122/439, 27.8%). Conversion from venovenous to venoarterial ECMO in neonates with PPHN was performed (n = 6/439, 1.4%). Only one neonate with PPHN was converted from venoarterial to venovenous ECMO (n = 1). Location of cannulation was either peripheral (internal jugular vein and femoral vein) (n = 34/57, 59.6%) or central (arterial and venous) (n = 23/57, 40.3%). One PPHN case was cannulated via the scalp vein (n = 1) (Table 1).

As expected, most common PPHN co-interventions used with ECMO were inhaled nitric oxide (n = 447/1814, 24.6%), inotropes (n = 262/1814, 14.4%), high-frequency oscillatory ventilation (n = 166/1814, 9.1%), prostacyclin (n = 122/1814, 6.7%), vasopressors (n = 96/1814, 5.3%), surfactant (n = 73/1814, 4%), hydrocortisone (n = 57/1814, 3.1%), sildenafil (n = 54/1814, 3%), vasodilators (n = 50/1814, 2.7%), therapeutic hypothermia (n = 28/1814, 1.5%), continuous positive airway pressure (CPAP) (n = 23/1814, 1.3%), sedation (n = 17/1814, 0.9%) and sodium bicarbonate (n = 13/1814, 0.7%). In addition, several blood products were used for the treatment of bleeding: packed red blood cells (n = 56), fresh frozen plasma (n = 54), platelets (n = 52) and cryoprecipitate (n = 25). The most frequent complications associated with ECMO use in neonates treated for PPHN were excess bleeding (n = 53/1814, 2.9%), thrombosis: circuit component (n = 32/1814, 1.8%), chylothorax (n = 28/1814, 1.5%), intracranial bleeding (n = 25/1814, 1.4%) and developmental delay (n = 12/1814, 0.7%) (Table 1).

The median duration of supplemental oxygen use was 24.5 days (IQR, 8 to 43.5), inhaled nitric oxide use was 14 days (IQR, 5 to 25), mechanical ventilation use was 13.5 days (IQR, 8 to 27.2) and ECMO use was 6.9 days (IQR, 3.5 to 13), while the median time of hospital stay was 30.5 days (IQR, 15 to 60). Of the 1814 neonatal cases with PPHN who were placed on ECMO, final treatment outcome of the neonates who died were documented in five hundred ninety-four cases (32.7%), while 1218 (67.1%) of the PPHN cases recovered (Table 1).

Table 1 Demographics and clinical presentation of PPHN cases placed on ECMO, stratified by treatment outcomes (n = 134 studies), 2010–2023

Variable	All (n = 1814)[a]	Survived (n = 1218)[a]	Died (n = 594)[a]	*p* value[b]
Age (days)				
< 10	118 (6.5)	77 (6.3)	41 (6.9)	0.612
10–20	9 (0.5)	2 (0.2)	7 (1.2)	
> 20	11 (0.6)	2 (0.2)	9 (1.5)	
Gender				
Female	320 (17.6)	296 (24.3)	24 (4)	0.031*
Male	505 (27.8)	446 (36.6)	59 (10)	
Ethnicity				
White (Caucasian)	214 (11.8)	185 (15.2)	29 (4.9)	0.017*
Black[c]	138 (7.6)	116 (9.5)	22 (3.7)	
Hispanic	24 (1.3)	19 (1.5)	5 (0.8)	
Asian	14 (0.8)	10 (0.8)	4 (0.7)	
Arab	3 (0.2)	1 (0.1)	2 (0.3)	
Delivery mode				
Caesarean	142 (7.8)	99 (8.1)	43 (7.2)	0.361
NSVD	89 (4.9)	78 (6.4)	11 (1.8)	
Induced labour	1 (0.05)	1 (0.1)	0	
Weight (grams)				
Normal: ≥ 2500	122 (6.7)	78 (6.4)	44 (7.4)	0.506
Low: ≥ 1500–2499	19 (1)	10 (0.8)	9 (1.5)	
Very low: < 1000	1 (0.05)	0	1 (0.2)	
Gestational age (weeks)				
Term (≥ 37 weeks)	143 (7.9)	85 (7)	58 (9.8)	0.046*
Moderate to late preterm (32 to < 37 weeks)	32 (1.8)	13 (1.1)	19 (3.2)	
Very preterm (28 to < 32 weeks)	1 (0.05)	0	1 (0.2)	
Apgar score at 1 min and 5 min				
Low: 0–3	21 (1.1)	18 (1.5)	3 (0.5)	0.039*
Moderately abnormal: 4–6	133 (7.3)	126 (10.3)	7 (1.2)	
Reassuring: 7–10	62 (3.4)	48 (4)	14 (2.3)	
Comorbidities				
Omphalocele	37 (2)	9 (0.7)	28 (4.7)	0.042*
Thrombocytopenia	30 (1.6)	20 (1.6)	10 (1.7)	
Systemic hypotension	26 (1.4)	11 (1)	15 (2.5)	
Respiratory failure	23 (1.3)	11 (1)	12 (2)	
Infection with *Bordetella pertussis*	21 (1.1)	9 (0.7)	12 (2)	
Pneumothorax	19 (1)	10 (0.8)	9 (1.5)	
Transposition of the great arteries	19 (1)	14 (1.1)	5 (0.8)	
Infection with *Herpes simplex virus*	18 (1)	5 (0.4)	13 (2.2)	
Cardiogenic shock	16 (0.9)	7 (0.6)	9 (1.5)	
Seizures	14 (0.8)	6 (0.5)	8 (1.3)	
Lung disease	13 (0.7)	2 (0.2)	11 (1.8)	
Multiorgan failure	10 (0.5)	1 (0.1)	9 (1.5)	
Metabolic acidosis	10 (0.5)	6 (0.5)	4 (0.7)	
ASD	10 (0.5)	6 (0.5)	4 (0.7)	
Pulmonary bleeding	9 (0.5)	3 (0.2)	6 (1)	
Cardiorespiratory failure	5 (0.3)	2 (0.2)	3 (0.5)	
PPHN etiology				
CDH	592 (32.6)	311 (25.5)	281 (47.3)	0.019*

Table 1 (continued)

Variable	All (n = 1814)[a]	Survived (n = 1218)[a]	Died (n = 594)[a]	*p* value[b]
MAS	170 (9.4)	98 (8)	72 (12.1)	
NRDS	131 (7.2)	51 (4.2)	80 (13.5)	
Pneumonia	70 (3.8)	20 (1.6)	50 (8.4)	
Sepsis	67 (3.7)	18 (1.5)	49 (8.2)	
HIE	57 (3.1)	45 (3.7)	12 (2)	
ACD/MPV	27 (1.5)	1 (0.1)	26 (4.4)	
Birth asphyxia	26 (1.4)	13 (1.1)	13 (2.2)	
Lung hypoplasia	19 (1)	10 (0.8)	9 (1.5)	
Idiopathic	15 (0.8)	7 (0.6)	8 (1.3)	
PPROM	13 (0.7)	7 (0.6)	6 (1)	
Severity of hypoxemia				
OI ≥ 15 and < 25: Moderate	1 (0.05)	1 (0.1)	0	0.368
OI ≥ 25 and < 40: Severe	55 (3)	52 (4.3)	3 (0.5)	
OI ≥ 40: Very severe	41 (2.3)	20 (1.6)	21 (3.5)	
Initial ECMO mode				
VA	310 (17.1)	212 (17.4)	98 (16.5)	0.061
VV	122 (6.7)	105 (8.6)	17 (2.9)	
VV to VA	6 (0.3)	6 (0.5)	0	
VA to VV	1 (0.05)	1 (0.1)	0	
Location of cannulation				
Peripheral	34 (1.9)	24 (2)	10 (1.7)	0.046*
Central	23 (1.3)	15 (1.2)	8 (1.3)	
Other PPHN treatments (co-interventions)				
iNO	447 (24.6)	301 (24.7)	146 (24.6)	0.024*
Inotropes	262 (14.4)	178 (14.6)	84 (14.1)	
HFOV	166 (9.1)	100 (8.2)	66 (11.1)	
Prostacyclin	122 (6.7)	81 (6.6)	41 (7)	
Vasopressors	96 (5.3)	57 (4.7)	39 (6.6)	
Surfactant	73 (4)	56 (4.6)	17 (2.9)	
Hydrocortisone	57 (3.1)	45 (3.7)	12 (2)	
Packed RBCs	56 (3.1)	42 (3.4)	14 (2.3)	
Sildenafil	54 (3)	42 (3.4)	12 (2)	
Fresh frozen plasma	54 (3)	43 (3.5)	11 (1.8)	
Platelets	52 (2.9)	43 (3.5)	9 (1.5)	
Vasodilators	50 (2.7)	26 (2.1)	24 (4)	
Therapeutic hypothermia	28 (1.5)	20 (1.6)	8 (1.3)	
Cryoprecipitate	25 (1.4)	20 (1.6)	5 (0.8)	
CPAP	23 (1.3)	16 (1.3)	7 (1.2)	
Sedation	17 (0.9)	14 (1.1)	3 (0.5)	
Sodium bicarbonate	13 (0.7)	12 (1)	1 (0.2)	
Nasal canula	10 (0.5)	8 (0.6)	2 (0.3)	
NMBAs	9 (0.5)	7 (0.6)	2 (0.3)	
Endothelin receptor antagonists	8 (0.4)	8 (0.6)	0	
ECMO complications				
Excess bleeding	53 (2.9)	41 (3.4)	12 (2)	0.031*
Thrombosis: circuit component	32 (1.8)	28 (2.3)	4 (0.7)	
Chylothorax	28 (1.5)	12 (1)	16 (2.7)	
ICB	25 (1.4)	15 (1.2)	10 (1.7)	
Developmental delay	12 (0.7)	9 (0.7)	3 (0.5)	

Table 1 (continued)

Variable	All (n = 1814)[a]	Survived (n = 1218)[a]	Died (n = 594)[a]	*p* value[b]
Catheter-related infection	2 (0.1)	0	2 (0.3)	
Duration on supplemental oxygen (days)				
< 7	3 (0.2)	1 (0.1)	2 (0.3)	0.495
7 to < 14	3 (0.2)	0	3 (0.5)	
≥ 14	8 (0.4)	5 (0.4)	3 (0.5)	
Duration on iNO use (days)				
< 7	3 (0.2)	2 (0.2)	1 (0.2)	0.248
7 to < 14	2 (0.1)	0	2 (0.3)	
≥ 14	6 (0.3)	4 (0.3)	2 (0.3)	
Duration of MV (days)				
< 7	7 (0.4)	4 (0.3)	3 (0.5)	0.680
7 to < 14	14 (0.8)	7 (0.6)	7 (1.2)	
≥ 14	21 (1.1)	9 (0.7)	12 (2)	
Duration of ECMO (days)				
< 7	83 (4.6)	36 (3)	47 (8)	0.563
7 to < 14	43 (2.4)	16 (1.3)	27 (4.5)	
≥ 14	35 (1.9)	15 (1.2)	20 (3.4)	
Duration of hospital stay (days)				
< 7	4 (0.2)	2 (0.2)	2 (0.3)	0.371
7 to < 14	8 (0.4)	1 (0.1)	7 (1.2)	
≥ 14	44 (2.4)	17 (1.4)	27 (4.5)	

ACD/MPV, Alveolar capillary dysplasia with misalignment of pulmonary veins; ASD, atrial septal defect; CDH, congenital diaphragmatic hernia; CPAP, continuous positive airway pressure; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; HIE, hypoxic ischemic encephalopathy; ICB, intracranial bleeding; iNO, inhaled nitric oxide; MAS, meconium aspiration syndrome; MV, mechanical ventilation; NMBAs, neuromuscular blocking agents; NRDS, neonatal respiratory distress syndrome; NSVD, normal spontaneous vaginal delivery; OI, oxygenation index; PPHN, persistent pulmonary hypertension of the newborn; PPROM, preterm premature rupture of the membranes; RBCs, red blood cells; VA, venoarterial; VV, venovenous

[a] Data are presented as number (%). Data was calculated on patients for whom the information was available

[b] Chi-square (χ^2) test was used to compare between persistent and non-persistent groups

[c] Patients with black ethnicity include African-American, Black African, African and Afro-Caribbean patients

Percentages do not total 100% owing to missing data

Treatment outcomes and predictors of mortality in neonates with PPHN who were placed on ECMO

Neonates placed on ECMO to treat PPHN were stratified based on the treatment outcomes (if survived or died). A summary of the demographic variables and clinical characteristics with regards to treatment outcomes in 1814 neonates who either had survived (n = 1218) or died (n = 594) is shown in Table 1. In both groups, many neonates had an age of < 10 days (6.3% vs 6.9%) and were delivered via caesarean operations (8.1% vs 7.2%); *p* values were > 0.05. Moreover, PPHN in neonates who were placed on ECMO and died group had lower rates of normal spontaneous vaginal delivery (1.8% vs 6.4%) but slightly higher proportion of normal birthweight (≥ 2500 g) (6.4% vs 7.4%) compared to the PPHN in neonates who were placed on ECMO and survived group (*p* values > 0.05). Those neonates with PPHN who underwent ECMO were more likely to be boys in both groups [survival: 36.6% (males) vs 24.3% (females) AND death: 10% (males) vs 4% (females); $p = 0.031$]. Most PPHN cases had a White (Caucasian) (survival: 15.2% vs death: 4.9%) or Black (survival: 9.5% vs death: 3.7%) ethnicity; $p = 0.017$ (Table 1).

Neonates in the PPHN group who were placed on ECMO and died had higher rates of normal gestational age (≥ 37 weeks) (7% vs 9.8%) but lower Apgar scores at 1 min and 5 min [i.e., low Apgar score (0–3): 1.5% vs 0.5%, moderately abnormal Apgar score (4–6): 10.3% vs 1.2% and reassuring Apgar score (7–10): 4% vs 2.3%] compared to the neonates in the PPHN group who were placed on ECMO and survived (*p* values = 0.039). Neonatal cases in the PPHN group who were placed on ECMO and died had higher proportion of medical comorbidities such as omphalocele (0.7% vs 4.7%), systemic hypotension (1% vs 2.5%), infection with *Herpes simplex virus* (0.4% vs 2.2%) or *Bordetella pertussis* (0.7% vs 2%), respiratory failure (1% vs 2%), lung disease (0.2% vs 1.8%), pneumothorax (0.8% vs 1.5%), cardiogenic shock (0.6% vs 1.5%), multi-organ failure (0.1% vs 1.5%), seizures (0.5% vs 1.3%) and pulmonary bleeding (0.2% vs 1%); $p = 0.042$. Neonates

with PPHN who were placed on ECMO and died were more likely to present due to congenital diaphragmatic hernia (25.5% vs 47.3%), neonatal respiratory distress syndrome (4.2% vs 13.5%), meconium aspiration syndrome (8% vs 12.1%), pneumonia (1.6% vs 8.4%), sepsis (1.5% vs 8.2%), alveolar capillary dysplasia with misalignment of pulmonary veins (0.1% vs 4.4%), birth asphyxia (1.1% vs 2.2%) and lung hypoplasia (0.8% vs 1.5%), however, neonates in the PPHN group who were placed on ECMO and died presented less with hypoxic ischemic encephalopathy (3.7% vs 2%); $p=0.019$ (Table 1).

Neonates with PPHN who were placed on ECMO and died were more likely to have higher severity of hypoxemia compared to the neonates with PPHN who were placed on ECMO and survived: very severe oxygenation index (≥40) (1.6% vs 3.5%); p value > 0.05. Initial ECMO modes of venoarterial (17.4% vs 16.5%) and venovenous (8.6% vs 2.9%), in addition to the conversion from venovenous to venoarterial (0.5% vs 0%) or venoarterial to venovenous (0.1% vs 0%) were higher in the group of neonates with PPHN who were placed on ECMO and survived; p value > 0.05. Neonates with PPHN who were placed on ECMO and survived had a slightly higher proportion of peripheral cannulation (2% vs 1.7%) and almost similar proportion of central ECMO cannulation (1.2% vs 1.3%); $p=0.046$. ECMO-related complications including chylothorax (1% vs 2.7%), intracranial bleeding (1.2% vs 1.7%) and catheter-related infections (0% vs 0.3%) were more frequent in the group of neonates with PPHN who were placed on ECMO and died ($p=0.031$). The use of blood transfusion and blood products such as packed red blood cells (3.4% vs 2.3%), fresh frozen plasma (3.5% vs 1.8%), platelets (3.5% vs 1.5%) and cryoprecipitate (1.6% vs 0.8%) to prevent bleeding and compensate for lost blood was reported to be higher in neonates with PPHN who were placed on ECMO and survived ($p=0.024$) (Table 1).

Neonates with PPHN who were placed on ECMO and died had a longer median time of mechanical ventilation use (15 days, IQR 10 to 27 vs. 10 days, IQR 7 to 28; $p=0.024$) and ECMO use (9.2 days, IQR 3.9 to 13.5 vs. 6 days, IQR 3 to 12.5; $p=0.033$), and a shorter median duration of hospital stay (23 days, IQR 12.5 to 46 vs. 58.5 days, IQR 28.2 to 60.7; $p=0.000$) compared to the neonates with PPHN who were placed on ECMO and survived (Table 1).

Discussion

This systematic review included 1814 neonates who suffered PPHN due to various risk factors and etiologies and were placed on ECMO from 134 observational studies to provide an insight into the clinical progression and management outcomes. To the best of our knowledge, this is the largest review to report on the development of PPHN in neonates who failed supportive cardiorespiratory care and conventional therapeutic choices and were candidates for ECMO. We found the leading causes of PPHN in neonates were congenital diaphragmatic hernia (32.6%), meconium aspiration syndrome (9.4%), neonatal respiratory distress syndrome (7.2%), pneumonia (3.8%) and sepsis (3.7%). Many of the neonates diagnosed with PPHN were < 10 days old (6.5%), male (27.8%), White (Caucasian) (11.8%) or Black (7.6%) ethnicity and delivered via caesarean section (7.8%). PPHN commonly occurred in term newborns (gestational age ≥ 37 weeks) (7.9%) and neonates delivered with a normal birthweight (≥2500 g) (6.7%). These findings are consistent with previous observations that male sex is associated with an increased risk of PPHN [150, 151], estimated rates of PPHN among White (Caucasian) and Black neonates are higher than among Hispanics and Asians [2, 152, 153], and usually occurs in a significant number of term neonates (≥37 weeks) [151, 154] or after a caesarean-section delivery [150, 151]. Male predominance in neonates with PPHN may reflect findings of sexual dimorphism in neonatal lung development favouring structural and functional lung maturation in the female gender [155], higher incidence of pulmonary disorders [156, 157] or increased risk for respiratory complications in male neonates [158]. Surfactant production has been shown to appear earlier in female lung development than in males and this earlier presence of surfactant seems to explain a higher incidence of respiratory complications such as neonatal respiratory distress syndrome (NRDS) in male than in female infants [159]. Faster alveolarization was also reported in females and higher flow rate per lung volume that may explain better response to surfactant therapy in female newborns than males [160]. Airway malacia has been frequently noticed in male infants and considered as a major cause for repeated or persistent gasping, chronic cough, and repeated respiratory tract infection in neonates [161]. Increased risk of PPHN among White (Caucasian) and Black neonates may at least be partly justified by the high occurrence of congenital diaphragmatic hernia in these two races [152, 162], a highly reported condition in PPHN patients and associated with a very high neonatal mortality (37.7%) [162–164]. Absence of endogenous prostaglandins and catecholamines release during the caesarean section in addition to the lack of physical compression from birth canal have been hypothesized to decrease removal of lung fluids responsible to raise PPHN in comparison to a normal neonatal spontaneous vaginal delivery [150]. Our results align with some prior research that reported that PPHN is rare in the very preterm newborns (< 32 weeks) [165, 166] or those delivered with low birthweight (< 1500 g) [165, 167]. On the

contrary, few studies reported PPHN to be not uncommon and increasingly diagnosed in the very preterm or low birthweight neonates [168–170]. Low incidence of PPHN in this very selected neonatal population may be explained by the large use of inhaled nitric oxide, sildenafil and steroids [171–173], in addition to the low rate of refractory pulmonary hypertension to supportive cardiorespiratory care and conventional therapies in the very preterm newborns [174–176]. It should be noted that various medical institutions adapt different ECMO criteria for neonates with PPHN who fail conventional therapies in order to avoid starting ECMO unnecessarily and exposing patients to harmful procedures, such as major canulation and systemic anticoagulation [134, 177]. Across many healthcare centres, two common ECMO selection criteria in neonates with PPHN include a birthweight > 1800 g and a gestational age > 34 weeks which may basically explain the very low incidence of PPHN in neonates with a very preterm age (< 32 weeks) or low birthweight (< 1500 g) included in our review [178, 179]. Nevertheless, various reported prevalence rates of PPHN may be explained by the differences in the sampling bias, inadequate sample size and populations studied, timing of diagnosis and variability in the echocardiographic criteria used to diagnose PPHN.

PPHN is a serious and often fatal condition, associated with a high mortality. We report a lower pooled proportion of survival in PPHN cases who underwent ECMO (n = 1218/1814, 67.1%) compared to the rates in three large reports published from the United States using data collected via the Extracorporeal Life Support Organization (ELSO) registry that included neonates with PPHN who underwent ECMO from 1986 to 2006 (n = 2432/3045, 80%) [180], 1989 to 2016 (n = 3906/5077, 77%) [181] or 2000 to 2010 (n = 1218/1504, 81%) [182], and a report published from the United Kingdom that compared national neonatal ECMO data between the United States and United Kingdom in patients diagnosed with PPHN and underwent ECMO from 1999 to 2005 (n = 796/1024, 77.7%) [183]. But these results should be interpreted with caution owing to the small number of studies and substantial heterogeneity and indicate a need for future research in this area. This variation in mortality is likely multifactorial and might be related to the differences in the assessment of ECMO outcomes in patients with PPHN, study design to a large extent, as well as selection bias, setting and population characteristics. Mortality due to ECMO use in neonates with PPHN is unlikely and may be attributable to the underlying pulmonary vascular disease instead of ECMO use or the level of health care infrastructure and various general care-seeking practices in different countries. Another important factor is the center experience and volume of cases; this could have contributed to the variability in mortality rates for neonates with PPHN who underwent ECMO. ECMO is a resource-intensive therapy requiring a multidisciplinary team of experienced medical professionals with training and expertise in initiation, maintenance, and discontinuation of ECMO in severely ill PPHN patients due to different etiologies with various medical comorbidities [184, 185]. Adequate planning, thoughtful resource allocation, and training of personnel to provide complex therapeutic interventions while adhering to strict infection control measures are all essential components of an ECMO action plan. Otherwise, our current and comprehensive review included a total of 134 studies that contributed to the refinement of evidence on the demographics and clinical characteristics and final treatment outcomes in neonates with PPHN and were placed on ECMO. Moreover, the median duration of ECMO use for all PPHN cases in the survival and death groups in our review was 7 days (IQR: 3.8 to 13), comparable to the duration ECMO support for neonates with PPHN in a report that utilized the ELSO registry and included data on > 5000 ECMO runs (6.5 days) [181].

Over the past decades since the first successful reports of ECMO use, there is a growing interest in developing tools to guide clinical decision making, to help aid in patient selection and prognostication [186–188]. This has led to the development of several prognostication tools aimed at identifying risk factors associated with poor outcomes [189, 190]. The majority of these scores have focused on mortality as an objective poor outcome and the investigators have mainly relied on registry style data with limited granularity [187–190]. While such scores can be useful in both prognostication and as risk stratification and quality assessment tools, they all lack practicality on an individual patient level with regards to decision making, as these scores have all been developed on data from patients already supported on ECMO without a comparable control cohort [186]. Unfortunately, in our review, we found there is a lot of missing data for many variables from the various studies that we included into our systematic analysis that suggests that many centres performing ECMO are not aligning their data collection to report similar levels of data and makes it challenging to assess the actual global ECMO capacity and capability for PPHN. Since the role of ECMO in the management of PPHN is unclear, all ECMO centres around the world that apply this costly intervention are highly encouraged to register with the ELSO, adapt to facilitate the systematic collection of consistent and accurate new data in order to address lack of evidence on the benefit of ECMO intervention in PPHN treatment [191]. Real-time data collection and sharing, establishing global biobanks, and nurturing an international collaborative

research culture is crucial to rapidly identify PPHN populations at risk, the neonates that stand to benefit from therapies such as ECMO [192].

The role of ECMO in the management of refractory PPHN is based by virtue of its ability to maintain adequate tissue oxygenation until pulmonary vascular resistance falls even in refractory cardiopulmonary failure. Although we accounted for the full range of clinical variables (e.g., birth weight, gestational age, comorbidities, cause of PPHN, severity of hypoxemia and treatment) known to affect survival outcomes in neonates, the specific threshold as to when pulmonary hypertension should be considered "persistent", remains poorly defined. Almost all studies we included in our review reported the abnormal echocardiographic findings and use of echocardiography to identify PPHN. Echocardiography is the most accurate diagnostic tool used to detect PPHN in any neonate with unremitting cyanosis that is unexplained by parenchymal lung disease [193, 194]. However, using *International Classification of Diseases, Ninth or Tenth Revision, Clinical Modification* (ICD-9-CM or ICD-10-CM) codes to identify PPHN and underlying etiology in many of the studies we included carries a risk of misclassification bias and might affected our final conclusions drawn [195]. Moreover, we were only able to include small number of neonates in our review who were predominantly White (Caucasian) or Black patients with congenital diaphragmatic hernia. Therefore, our analysis was not adequately powered to examine survival disparities in individual subtypes. Otherwise, mortality due to PPHN has been demonstrated to correlate with its pathophysiology, etiology, subtype and severity [2, 196, 197].

Despite its ease of implantation, management and decannulation, ECMO displays various complications. We found neonates with PPHN who died needed longer ECMO use than the neonates with PPHN who survived (9.2 days vs 6 days; $p=0.033$), a finding which may partly contradict the low incidence of excess bleeding in the neonates with PPHN who were placed on ECMO for longer time and died who also had lower requirements for blood transfusion and blood products transfusion during the treatment period ($p=0.024$). Nevertheless, the prolonged ECMO use has been reported to be independently associated with a higher incidence of bleeding as longer ECMO support means longer exposure to anticoagulant medications which may increase risk of exposure to supratherapeutic levels of anticoagulants [198, 199]. Causes of bleeding in neonates with PPHN placed on ECMO are often multifactorial and may be related to thrombocytopenia and platelets dysfunction, systemic anticoagulation, circuit-induced coagulopathy, invasive procedures, cannulation locations or underlying disease processes such as multisystem organ failure or sepsis [200, 201]. Prevention and management of bleeding and thrombosis in neonates with PPHN placed on ECMO requires a fine balance between the complications of bleeding and thrombosis and remains a difficult aspect of ECMO care [48, 202]. Although ECMO is a recent life-saving development in critical care, ECMO complications may result in mortality or permanent injury [52]. Therefore, successful neonatal ECMO requires appropriate patient selection, skilled ECMO management with trained healthcare providers and infrastructure that can help prevent or manage complications and hence requires considerable resources and manpower and is expensive [52, 203].

Limitations

Our study has several important limitations to consider. First, all of the evidence discussed in this review is based on many case reports and cohorts, and a small number of case-series and controlled trial studies each with small patient numbers and performed in single centres and not necessarily generalizable to the current ECMO outcomes in neonates with PPHN. Second, we had to compare clinical characteristic and treatment outcomes of PPHN in neonates who were placed on ECMO due to differing nature of etiologies being studied, varying complexity of the medical and surgical interventions, associated comorbidities and physiological patient differences. Third, potential limitation is the exclusion of non-English articles. As a result, important findings for ECMO outcomes in PPHN neonatal cases may have been missed. Fourth, direct comparison between studies was limited and meta-analysis was not performed due to clinical and methodological heterogeneity. Fifth, almost all studies included in this review were retrospective in design, which could have introduced potential reporting bias due to reliance on clinical case records. Finally, there were missing data for a good number of the neonates included in our review which might have reduced the statistical power and produced biased estimates, leading to invalid conclusions.

Conclusion

ECMO in the neonates with PPHN who failed supportive cardiorespiratory care and conventional therapies has been successfully utilized with a neonatal survival rate of 67.1%. Mortality in neonates with PPHN who underwent ECMO was highest in cases born via the caesarean delivery mode or neonates who had lower Apgar scores at birth. Fatality rate in neonates with PPHN who underwent ECMO was the highest in patients with higher rate of specific medical comorbidities (omphalocele, systemic hypotension and infection

with *Herpes simplex virus* or *Bordetella pertussis*) or cases who had PPHN due to higher rate of specific etiologies (congenital diaphragmatic hernia, neonatal respiratory distress syndrome and meconium aspiration syndrome). Neonates with PPHN who died may need a longer time of mechanical ventilation and ECMO use and a shorter duration of hospital stay; and may experience higher frequency of ECMO-related complications (chylothorax, intracranial bleeding and catheter-related infections) in comparison with the neonates with PPHN who survived. There is a need for more prospective multi-institutional studies that expand the currently available registry data to better correlate the ECMO treatment outcomes with patient trajectories and allow the comparison with a cohort of non-ECMO critically ill patients to mirror the influence of decision and timing of provision of ECMO support.

Abbreviations

ACD/MPV	Alveolar capillary dysplasia with misalignment of pulmonary veins
BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation
HIE	Hypoxic ischemic encephalopathy
MAS	Meconium aspiration syndrome
NRDS	Neonatal respiratory distress syndrome
PPHN	Persistent pulmonary hypertension of the newborn
VA	Venoarterial
VV	Venovenous

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03011-3.

Additional file 1.

Additional file 2.

Acknowledgements
We would like to thank authors and their colleagues who contributed to the availability of evidence needed to compile this article. We would also like to thank the reviewers for their very helpful and valuable comments and suggestions for improving the paper.

Author contributions
SA, AA.A (Abdulrahman A. Alnaim), MA.A, AA.A (Abdulaziz A. Alahmari), MA and ZAA contributed equally to the systematic review. SA, AA.A (Abdulrahman A. Alnaim), MA.A, AA.A (Abdulaziz A. Alahmari), MA, NAD and ZAA were the core team leading the systematic review. SA, AA.A (Abdulrahman A. Alnaim), MA.A, AA.A (Abdulaziz A. Alahmari), MA, HSA and SMAHM identified and selected the studies. QM.A, NAD, HAA, MHAH, KMA and FHA did the quality assessment of the studies. SA, AA.A (Abdulrahman A. Alnaim), MA.A, AA.A (Abdulaziz A. Alahmari), MSA, ASA (Aqeel S Alshakhes), ASB, AS.Al-A, FMA, JSB, AHA, AAAlM, IAAl, ASA (Ahmed Saeed Alzuwaid), MAA and YAA collected the data. SA, AA.A (Abdulrahman A. Alnaim), MA.A, AA.A (Abdulaziz A. Alahmari), HSA, SMAm, FAA, AHA, MAAlB, RHA and NA drafted the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors approved the final version of the manuscript.

Funding
None.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 7 April 2024 Accepted: 13 August 2024
Published online: 24 August 2024

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