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# Neurologic Outcomes After Extracorporeal Membrane Oxygenation – a Systematic Review

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## Abstract

**Objective—**The goal of this systematic review of the literature was to summarize neurologic outcomes following neonatal and pediatric extracorporeal membrane oxygenation (ECMO).

**Data Sources—**We conducted electronic searches of PubMed, Scopus, Web of Science, CINAHL, Cochrane, and EMBASE.

**Study Selection—**Inclusion criteria included publication dates 2000–2016, patient ages 0–18 years, and use of standardized measures to evaluate outcomes after ECMO.

**Data Extraction—**We identified 3497 unique citations; 60 full-text articles were included in the final review.

**Data Synthesis—**Studies evaluated patients with congenital diaphragmatic hernia (7), cardiac disease (8), cardiac arrest (13), and mixed populations (32). Follow-up was conducted at hospital discharge in 10 (17%) studies, and at a median of 26 (IQR, 8-61) months after ECMO in 50 (83%) studies. We found 55 outcome measures that assessed: overall health and function (4), global cognitive ability (7), development (4), motor function (5), adaptive function (2), behavior/mood (6), hearing (2), quality of life (2), school achievement (5), speech and language (6), learning and memory (4), and attention and executive function (8). Overall, 10% to as many as 50% of children scored more than 2 SD below the population mean on cognitive testing. Behavior problems were identified in 16% to 46% of children tested, and severe motor impairment was reported in 12% of children. Quality of life of former ECMO patients evaluated at school age or adolescence ranged

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from similar to healthy peers, to 31%-53% having scores more than 1 SD below the population mean.

**Conclusions—**This systematic review of the literature suggests that children who have undergone ECMO suffer from a wide range of disabilities. A meta-analysis was not feasible due to heterogeneity in pathologies, outcome measures and age at follow-up, underscoring the importance of developing and employing a core set of outcomes measures in future ECMO studies.

### Keywords

Extracorporeal membrane oxygenation; neurodevelopmental outcomes; neurocognitive outcomes; PICU; pediatrics; intensive care unit

## INTRODUCTION

The number of pediatric patients who receive extracorporeal membrane oxygenation (ECMO) support each year has been growing, with the Extracorporeal Life Support Organization (ELSO) reporting ECMO use in 3,249 infants and children in 2015 (1, 2). In the early 1990s, the vast majority of ECMO patients were neonates undergoing ECMO for respiratory indications (3). By comparison, in 2016, over half of pediatric ECMO patients were over 28 days of age, and the number of respiratory (1,331), cardiac (1,135) and extracorporeal cardiopulmonary resuscitation (ECPR) (579) cases were more evenly divided (3). Though the characteristics of patients on ECMO have changed during this time, mortality has remained stable (1–3). Among ECMO survivors, neurologic injury is a significant cause of morbidity (4–6). Between 10% and 62% of survivors have been found to have evidence of injury on neuroimaging studies (7–9), but imaging alone is not a good predictor of cognitive and functional abnormalities (7, 10, 11). An estimated 10% to 60% of ECMO survivors have neurologic disability long-term (12–14), including motor deficits (6), behavior problems (11), attention deficits and slow processing speeds (15).

The goals of this systematic review of the literature were to summarize neurologic outcomes following neonatal and pediatric ECMO and to determine the most widely used outcome measures such studies.

## MATERIALS AND METHODS

### Data Sources and Study Selection

We conducted electronic searches of PubMed, Scopus, Web of Science, CINAHL, Cochrane and EMBASE, using a combination of medical subject headings and text words to capture concepts of extracorporeal life support and neurologic outcomes as detailed in Supplemental Digital Content 1. Eligible studies included those published between January 1, 2000 and November 30, 2016, with enrollment of children from birth to 18 years, during or after ECMO support, who were evaluated for neurofunctional outcomes with a standardized measure at or after hospital discharge. We excluded case reports and case series of fewer than 10 patients, studies for which we could not separate ECMO from other populations, or children from adults, as well as reviews, editorials, and commentaries. Two investigators

(K.B. and M.B.) reviewed citations independently, and disagreement regarding eligibility was resolved by consensus.

### Data Synthesis

We constructed evidence tables by primary ECMO indication and summarized the data using descriptive statistics.

## RESULTS

We identified 3497 unique citations, of which 182 were included for full text review, and 54 met our eligibility criteria. We also identified 6 citations from hand searching review references. Ultimately, 60 studies were included in the study (Figure 1).

Thirty-four of the 60 studies (57%) were from North America, 17 (28%) were from Europe, 6 (10%) were from Asia, and 3 (5%) were from Australia. Forty-five (75%) were single center and 15 (25%) were multicenter studies. Several articles presented data from the same cohort followed over time, and were included as separate studies. Thirty studies (50%) were published between 2000 and 2010 (5, 6, 13, 16, 18–42), and 30 studies (50%) were published between 2011 and 2016 (7, 11, 15, 17, 43–68).

The median sample size was 80 (interquartile range [IQR], 36-154), and the median number of children evaluated at follow-up was 36 (IQR, 18-76). Neurologic evaluations were conducted only at hospital discharge in 10 (17%) studies and at a median of 26 (IQR, 8-61) months after ECMO in 50 (83%) studies. Twenty-nine studies (48%) enrolled newborns exclusively and were all long-term outcome studies (5–7, 15, 18–21, 23–30, 32, 34–36, 43, 44, 54–56, 60). Supplemental Digital Content 2, Supplemental Table 1 presents the types and frequencies of the 55 distinct measures used to evaluate neurodevelopmental outcomes in ECMO survivors, organized by domains evaluated (e.g., overall health and function, global cognitive ability, adaptive behavior, etc). The most commonly used outcome measures were the Pediatric Cerebral Performance Category (PCPC; 30% of studies), the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; 18%) and the Bayley Scales of Infant Development (BSID; 17%).

### ECMO Populations

Study type, years of study, country, patient age, numbers of patients enrolled, of survivors to discharge, and of patients seen in follow-up, age at follow-up, time to follow-up, outcome measures used, and main study results, are presented in Supplemental Digital Content 3, Supplemental Table 2, organized by the main diagnostic categories as presented below.

**Congenital Diaphragmatic Hernia—**There were 7 studies that evaluated CDH patients (7, 15, 19–21, 43, 44). Unfavorable neurodevelopmental outcomes defined as Mental Development Index (MDI) <70 using BSID-II (general population mean 100, SD 15), were found in 17% (3/18) and 100% (4/4) of children evaluated at a mean of 2 years, and median of 4.9 years, respectively (21, 43). Rasheed et al (20) showed that 3 of 15 survivors evaluated at a median of 7 years after neonatal ECMO had at least one IQ measure more than 2 SD below the mean, using the Wechsler Intelligence Scale for Children (WISC-III).

The mean Developmental Quotient (DQ) using the Brunet-Lezine test in 18 toddlers evaluated at 2 years was 96 (range, 77-113), and the IQ using the WISC or Revised Amsterdam Intelligence Test (RAKIT) tests in 16 children evaluated at 8 years was 91.7 (SD 19.5) (population mean, 100, SD, 15) (15, 19).

The quality of life in children who underwent ECMO for CDH as newborns was evaluated in 2 studies (15, 44). In a 1999-2003 Dutch cohort of 35 patients with CDH who required ECMO as newborns, 12 had lower quality of life in multiple domains at the age of 8 years, compared to children who had CDH managed without ECMO, using PedsQL (mean difference in total functioning score, −13.43, p=0.024) (15). In 10 children evaluated at a mean age of 5.5 years who underwent neonatal ECMO for CDH between 2002-2014, the mean score for physical functioning was 91 and for psychosocial functioning was 82, which was not significantly different from a non-ECMO CDH control group (44).

**Cardiac Disease—**In the 8 studies that evaluated patients who required ECMO support for acquired or congenital heart disease, patients were diverse in age and disease presentations (i.e., cyanotic and non-cyanotic congenital heart disease or acquired heart disease from myocarditis or cardiomyopathy) (22, 45–48, 50, 51). Three studies used the PCPC and Pediatric Overall Performance Category (POPC) to determine outcomes either at discharge or within 3 years of discharge and showed that 81%-91% were favorable, based on PCPC/POPC <3 or <4 or no change from baseline (46, 47, 50). More detailed evaluations that included neuropsychological testing revealed that, at 1 to 5 years after discharge, 25% to 50% of those seen in follow-up tested in the severely disabled range, defined as more than 2 SD below the mean for the population on the given test (i.e., WPPSI, WISC, BSID) (16, 22, 51). Studies that evaluated quality of life showed that 34% to 53% of cardiac ECMO survivors reported significantly diminished quality of life compared to age-matched, healthy peers (45, 48). One of two studies showed that quality of life was also significantly diminished compared to that of peers with cardiac disease but no history of ECMO (48).

**Cardiac Arrest—**Ten of the 13 studies that evaluated outcomes of infants and children who suffered cardiac arrest prior to ECMO enrolled only patients who underwent ECPR (37–39, 42, 49, 61–67, 69), and 3 studies included patients who achieved return of spontaneous circulation prior to cannulation for ECMO. Twelve of the 13 studies used PCPC and POPC. Favorable outcomes were defined as a PCPC/POPC < 3 or < 4, and were found in 14% to 89% of survivors to follow-up, where time to follow-up ranged from hospital discharge to 2.5 years (37–39, 61–67, 69). In a study that evaluated 17 survivors at a median of 52 months post-ECPR, over 23% of survivors were 2 or more SD below the population mean for full scale IQ measured by WPPSI-III (49). None of these 13 studies evaluated HRQOL in survivors.

**Mixed ECMO Populations—**Thirty-two studies included mixed patient populations. The outcome measures used and individual study results are presented below and in Supplemental Digital Content 3, Supplemental Table 2.

**Overall Cognition/Development/Adaptive Skills—**Most studies concluded that global ability of former ECMO patients was not severely affected, with mean scores for the

ECMO patients falling within 1 SD of the population mean (5, 6, 11, 15, 17, 19, 24, 26, 27, 29, 34–36, 55, 58). Four studies demonstrated mean scores for cognitive ability <80 (population mean, 100, SD, 15) (13, 16, 49, 51).

Five studies combined results for cognitive skills tested by WPPSI, WISC or BSID as appropriate for age (13, 15, 16, 20, 36). Among 672 cumulative individuals with IQ or MDI scores reported, the mean of the mean IQ or MDI scores was 87 (SD 10.3), at a median of 60 (IQR, 9-84) months after ECMO. An additional five Dutch studies used the RAKIT to evaluate cognitive outcomes of ECMO patients. Reporting of results was not uniform. In 3 of these studies, the mean IQ was 99.7 (SD 17.7) (n=125), 100.5 (SD 19.7) (n=79), and 99.7 (SD 18.1) (n=131), at mean follow-up times of 96, 62, and 62 months, respectively (6, 11, 34). The median IQ was 104 in a study of 99 children seen at 60 months following neonatal ECMO (58). Lastly, in a study of 102 children evaluated at 60 months following neonatal ECMO, 10% had IQ scores more than 2 SD below the mean (56).

**Behavior—**Estimates of the prevalence of any behavioral problems were significantly higher than in the general population and ranged from 10% to 50% of former ECMO patients (5, 34). “Clinically significant behavior problems” were reported in 16% to 46% of former ECMO patients. Of note, “clinically significant behavior problems” definitions were different in these studies, with cutoff scores of 60, 70 and 74 on the Achenbach Child Behavior Checklist (CBCL) (11, 24, 27, 34, 56).

**Quality of Life—**Eight studies evaluated quality of life for a total of 315 former ECMO patients using the PedsQL (13, 15, 17, 44, 48, 56, 59, 60). The PedsQL questionnaire evaluates functional categories including physical, social, emotional and school (if age appropriate). Between 31% and 53% of former ECMO patients had mean scores more than 1 SD below the population mean (13, 48, 56, 59, 60). PedsQL in these studies was conducted between 5 and 8 years of age, with 31 patients evaluated at 17 years of age. The single study which evaluated former ECMO patients at 17 years of age reported that quality of life for this cohort did not differ from healthy peers (17).

**Motor Skills—**Reported rates of motor disability ranged between 16% and 33%, and from mild (e.g., delayed in reaching motor milestones, weakness without impaired activity) to severe (e.g., quadriparesis, wheelchair dependence) (5, 6, 13, 16, 27, 30, 34, 56, 60). Almost all cohort studies reported several severely impaired survivors who were unable to engage in testing. Of a cumulative total of 532 who had undergone ECMO as newborns and were evaluated by the Motor Assessment Battery for Children (MABC) in 6 studies, 64 (12%) scored below the 5$^{th}$ percentile, indicating severe motor impairment at mean follow-up ages that ranged between 5 to 8 years (5, 6, 15, 34, 56, 60).

**School Performance—**In informal evaluations, more ECMO survivors than their healthy peers had additional help in school or were enrolled in special courses (11, 31, 42). Formal evaluations of school performance and school readiness were conducted in 5 studies (5, 24, 26, 29, 36). Three studies evaluated former neonatal ECMO patients at 5 to 8 years age using the Wide Range Achievement Test (WRAT) (24, 26, 29). The mean reading score and mean arithmetic score in these three studies (cumulative n=173) fell within 1 SD below the

mean (24, 26, 29). Patients who had seizures while on ECMO had significantly lower mean scores on the WRAT and on the Bracken Basic Concept Scale of School Readiness than survivors in the same cohort who did not have seizures (29). One study evaluated 56 former neonatal ECMO patients at 7 years of age; these children were found to have deficits in reading comprehension on the Wechsler Objective Reading Dimensions (WORD) (5). Lastly, one study evaluated 11 patients 7 years after neonatal ECMO using the Kaufman Test of Educational Achievement. Mean, reading and arithmetic scores were within 1 SD below the population mean and were not significantly different from a group who received inhaled nitric oxide and mechanical ventilation as neonates but not ECMO (36).

**Hearing and Vision—**Hearing loss was identified in 5% to 28% of ECMO survivors during follow-up testing (5, 6, 16, 18–20, 22, 30, 32, 54–56, 58). Severe visual impairment, defined as blindness or abnormal vision after correction, was reported in 0% to 5% of ECMO survivors who underwent vision evaluations (5, 6, 16, 18, 22, 31, 35, 55).

**Speech and Language—**Ten studies reported that mean expressive and receptive language scores or composite verbal scores fell between 90 and 100, and within 1 SD of the population mean (5, 20, 24, 26, 27, 35, 36, 43, 55, 58). In two studies from a Canadian cohort, one reporting solely on ECPR survivors (49), 4-5 year old ECMO survivors had a mean verbal IQ on the WPPSI-III more than 1 SD below the mean for age (51). Parish et al reported that patients with a history of seizures scored below expected for age on their verbal index with a mean of 85.4 (SD 17) at preschool age and 84.8 (SD 19.3) at school age (29). ECMO survivors who did not have seizures had a mean score of 96.9 (SD 12) at preschool age and 93.7 (SD 12) at school age (29).

**Higher Level Cognitive Skills—**Seven studies reported results of executive function, attention and memory testing (5, 11, 15, 17, 26, 29, 36). Two studies that employed the Bourdon-Vos test reported that up to 70% of 8 year old ECMO survivors who underwent testing (n=10, n=123) had slow to very slow working memory processing speed (11, 15). Using the Rey Complex Figure Test (RCFT) and the Rey Auditory Verbal Learning Test (RAVLT), Madderom et al found that deficits in memory remained substantial after controlling for the mean IQ of 28 children who underwent neonatal ECMO and were evaluated at 17 years of age (17). In contrast, Goodman et al found normal mean scores for 66 neonatal ECMO survivors with mean age of 8 years at follow-up, using the Wide Range Assessment of Memory and Learning (WRAML) (26).

**General Outcomes—**In total, 754 survivors of neonatal and pediatric ECMO were evaluated by PCPC at hospital discharge (742 individuals from 16 studies) and/or at follow up appointments (76 individuals from 4 studies). Results were available for all but one of these studies (n=69) (46). Cumulatively, at hospital discharge, 321/673 (48%) had PCPC <3 or unchanged from baseline, and 471/673 (70%) had PCPC<4 (33, 37–39, 41, 50, 52, 53, 57, 62, 63, 65–67, 69). At post-discharge follow–up, 44/76 (58%) had PCPC <3 or unchanged from baseline (33, 38, 41, 61).

## DISCUSSION

This systematic review of the literature on outcomes for critically ill infants and children supported with ECMO showed a wide range of deficits described in survivors, as well as variability in the types of outcome measures used and in the timing of follow-up evaluations, even among children with similar pathologies and ages.

Studies that concluded at time of discharge included more patients but less detailed neuropsychological evaluations, relying on the PCPC and POPC to evaluate outcomes. These scales are both 6-point scales that provide information on overall neurologic functioning and health, respectively, but do not allow for an understanding of more subtle cognitive and developmental ability. Their advantage is that they can be easily assessed, often with review of medical records, and they correlate with more thorough measures such as VABS (70). However, especially at young ages, emerging neurologic deficits may first manifest long after brain injury (71).

Follow-up studies in this review showed variable outcomes for ECMO survivors, but the data point to a risk for ongoing neurologic deficits and cognitive delays no matter the initial reason for ECMO cannulation. Owing to study heterogeneity and the large number of outcomes measures used, we were unable to conduct a meta-analysis. Several themes emerged from our review of the literature, however. The majority of studies reported IQ in the normal range in ECMO survivors, although 10% to as many as 50% of children, in selected cohorts, had scores that were more than 2 SD below the population mean. Behavior problems were identified in 16% to 46% of children tested, and severe motor impairment was reported in 12% of children. Quality of life of former ECMO patients evaluated at school age or adolescence ranged from similar to healthy peers, to 31%-53% having scores more than 1 SD below the population mean. Generally, functional outcomes reported for CDH, cardiac disease, and cardiac arrest populations appeared worse when compared to mixed ECMO populations.

To gain a full understanding of ECMO patient outcomes, it will be necessary for study teams and research networks to collaborate and develop outcome measure guidelines, which could be modeled on existing similar initiatives (e.g., for pediatric traumatic brain injury) (72). Outcome measures would need to be easy to implement and validated in several languages. Timing of follow-up could be harmonized with existing recommendations for populations at high risk for critical illness requiring ECMO (e.g., CHD) (73), with serial evaluations at toddler, preschool and school age. Based on the results of this systematic review, a combination of measures to evaluate cognition and development (e.g., BSID, WPPSI, WISC), behavior (e.g., CBCL) and motor (e.g., MABC) skills, school achievement (e.g., WRAML, WRAT) and hearing would constitute a sensible starting point for a core set of ECMO outcomes measures.

Our study has several limitations. The number of participants in each study included in the systematic literature review was low, making it difficult to draw robust conclusions from any one study. The studies included in the review used a variety of outcome measures conducted at varied time points, and thus could not be combined in a meta-analysis; many measures

were used in only a single study. Studies that used the same tests reported results differently and with various levels of detail (e.g., as mean [SD] vs percent patients with scores more than −1 SD or −2 SD below the mean, etc), which made comparison and aggregation of results difficult.

## CONCLUSION

This systematic review of the literature suggests that children who have undergone ECMO suffer from a wide range of disabilities. A meta-analysis was not feasible due to heterogeneity in pathologies, outcome measures and age at follow-up, underscoring the importance of developing and employing a core set of outcomes measures in future ECMO studies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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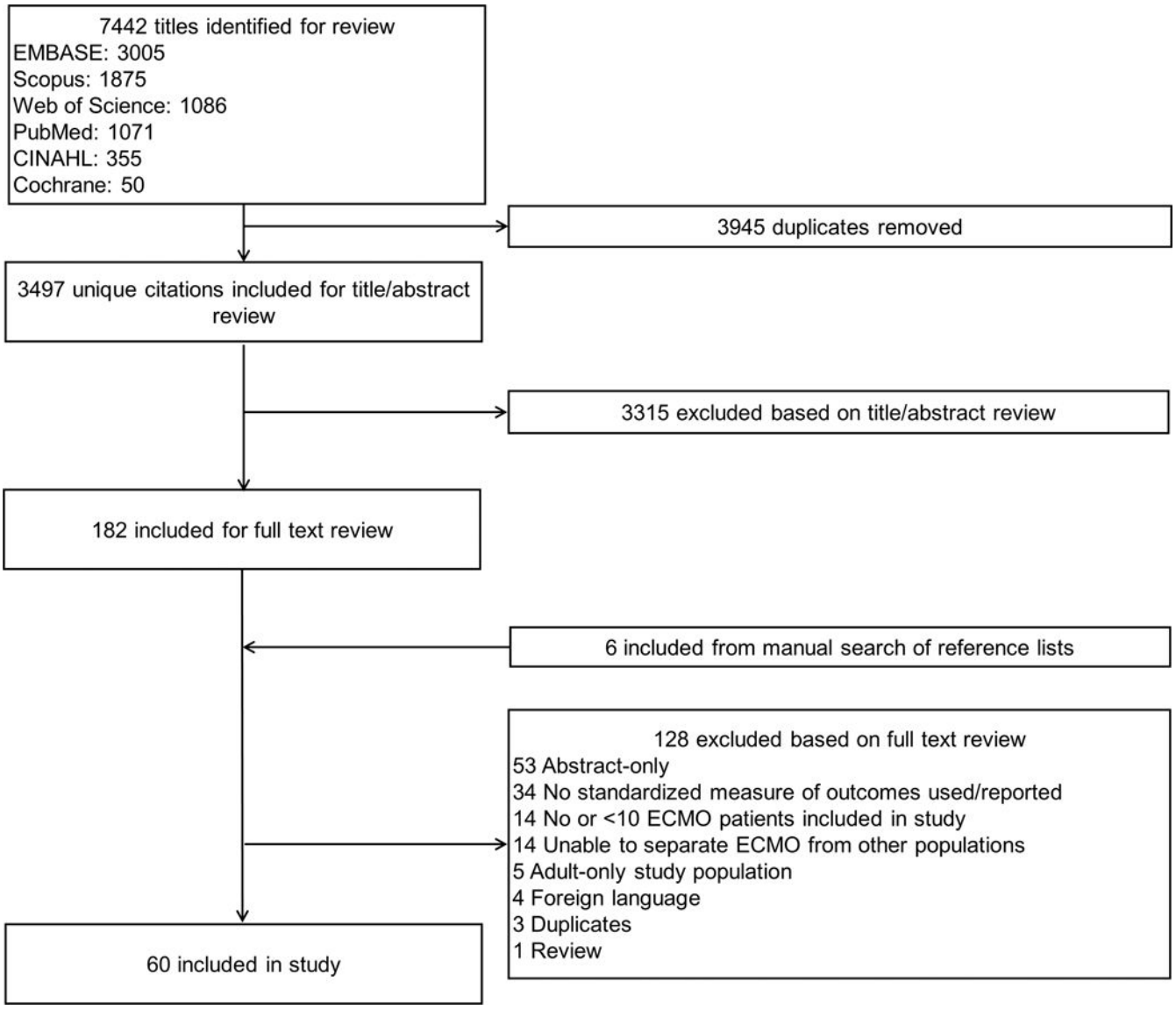


**Figure 1.**
Systematic Review Flowsheet