Outcomes of Pediatric Extracorporeal Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis

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OBJECTIVE: The goal of this work is to provide insight into survival and neurologic outcomes of pediatric patients supported with extracorporeal cardiopulmonary resuscitation.

DATA SOURCES: A systematic search of Embase, PubMed, Cochrane, Scopus, Google Scholar, and Web of Science was performed from January 1990 to May 2020.

STUDY SELECTION: A comprehensive list of nonregistry studies with pediatric patients managed with extracorporeal cardiopulmonary resuscitation was included.

DATA EXTRACTION: Study characteristics and outcome estimates were extracted from each article.

DATA SYNTHESIS: Estimates were pooled using random-effects meta-analysis. Differences were estimated using subgroup meta-analysis and meta-regression. The Meta-analyses Of Observational Studies in Epidemiology guideline was followed and the certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation system. Twenty-eight studies (1,348 patients) were included. There was a steady increase in extracorporeal cardiopulmonary resuscitation occurrence rate from the 1990s until 2020. There were 32, 338, and 1,094 patients' articles published between 1990 and 2000, 2001 and 2010, and 2010 and 2020, respectively. More than 70% were cannulated for a primary cardiac arrest. Pediatric extracorporeal cardiopulmonary resuscitation patients had a 46% (CI 95% = 43–48%; $p < 0.01$) overall survival rate. The rate of survival with favorable neurologic outcome was 30% (CI 95% = 27–33%; $p < 0.01$).

CONCLUSIONS: The use of extracorporeal cardiopulmonary resuscitation is rapidly expanding, particularly for children with underlying cardiac disease. An overall survival of 46% and favorable neurologic outcomes add credence to this emerging therapy.

KEY WORDS: cardiac arrest; cardiopulmonary resuscitation; extracorporeal cardiopulmonary resuscitation; extracorporeal membrane oxygenation; pediatrics

The American Heart Association (AHA) estimates that the yearly prevalence of inhospital pediatric (< 18 yr old) cardiac arrests in the United States is approximately 15,200 (1). Rates of survival to hospital discharge for children with pulseless inhospital cardiac arrest (IHCA) managed with conventional cardiopulmonary resuscitation (CPR) alone is 35%, with some reports closer to 45% (2, 3). Studies report that outcomes in extracorporeal

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cardiopulmonary resuscitation (ECPR) are better than conventional CPR, with survival rates up to 50% (4–6). As efforts continue to improve outcomes after cardiac arrest, the Extracorporeal Life Support Organization (ELSO) and the AHA recommend the consideration of ECPR in the treatment of hospitalized patients with refractory cardiac arrest of potentially reversible etiology (7–9). Given the current available literature, the AHA qualifies this recommendation with "ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment".

ECPR is a rescue therapy in which an extracorporeal membrane oxygenation (ECMO) circuit is used to support patients with refractory cardiac arrest. ECPR provides support while potentially reversible causes of the arrest are identified and treated. ECPR is associated with significant morbidity and mortality, not dissimilar from those linked to ECMO (10). In a recent review of the ELSO registry, the most common patient-level complication associated with ECMO was intracranial hemorrhage at 11% (11, 12). Other complications include cerebral infarcts, seizures, and gastrointestinal hemorrhages. Selection criteria and indications for ECPR in children have not been fully established (13–15). Patient selection for ECPR continues to be a delicate balance between risk of complications and probability of survival. As a result, even with survival outcomes better than conventional CPR, the target population with maximal benefits of ECPR has not been identified (16, 17).

Data on neurologic outcomes for pediatric survivors of ECPR are sparse (18, 19). When available, these data are complicated by inconsistent reporting approaches in the literature. In contrast, reported favorable neurologic outcomes in survivors of conventional CPR are near 60% (20).

We performed an updated review and meta-analysis of ECPR studies in the pediatric literature. The primary objective was to review systematically the outcomes of ECPR in neonates and children.

MATERIALS AND METHODS

The study was conducted in adherence to the guidelines of the Declaration of Helsinki. The study was registered in the International Prospective Register of Systematic Reviews (CRD42020156920). The study was performed and analyzed following the Meta-analyses Of Observational Studies in Epidemiology statement.

Eligibility Criteria and Search Strategy

An extensive literature search was performed by the investigators and a librarian using Embase, Pubmed, Cochrane, Web of Science, Scopus, and Google Scholar. Date restrictions were set from January 1990 to May 2020. The search included all neonatal and pediatric patients from 0 to 18 years old who underwent extracorporeal life support following cardiopulmonary arrest. Hand searching through article references was used to identify any articles that may have been missed by the initial search. Studies on adults (> 18 years old), as well as studies that used ECMO for cardiac or respiratory failure after sustained spontaneous return of circulation, were excluded. Studies with animals, non-ECPR studies, conference proceedings, case reports, case series (< 10 patients), editorials, and articles not written in English were also excluded. In addition, reviews, registry reports, and secondary analyses of trials were also excluded in order to avoid patient duplication in the analysis.

Search terms included various combinations of "neonate," "infant," "infant, newborn," "child," "pediatric," "pediatrics," "adolescent," "teen," "extracorporeal membrane oxygenation," "extracorporeal life support," "ECMO," "ECMO-CPR," "ECPR," "ECMO treatment," "ECLS treatment," "extracorporeal resuscitation," "extracorporeal circulation," "extracorporeal circulations," "extracorporeal," "resuscitation," "mechanical circulatory support," "membrane oxygenator," "oxygenators, membrane," "oxygenator," "pediatric life support," "advanced life support," "basic life support," "BCLS," "mouth to mouth," "mouth-to-mouth resuscitation," "cardiopulmonary resuscitation," "cardio-pulmonary resuscitation," "cardio pulmonary resuscitation," "CPR," "heart arrest," "sinus arrest," "cardiac arrest," and "cardiopulmonary arrest".

Review Process

The entire set of records resulting from the search was screened by title and abstract by two independent investigators (R.R.L., W.H.P.). For any article for which a decision could not be reached from title or abstract, the full text was reviewed. Next, the full text of all screened articles was reviewed; any study with a sample size less than ten was excluded to eliminate positive outcome bias. Any article with conflicting data was reviewed by an independent investigator (L.R.), and any disagreements thereafter were resolved by discussion among the group. The flow diagram (**Fig. 1**) shows the study selection process and reasons for exclusion.

Data Items and Data Collection

The relevant Joanna Briggs Institute (JBI) Critical Appraisal Checklists were used to assess methodological strength (**Supplement Table 1**, http://links.lww.com/CCM/G173). The JBI Checklist assesses whether individual studies included are clear on their inclusion criteria, reliability, validity, inclusion, outcome reporting, and statistical analysis methods, leading to a systematic approach in assessing their risk of bias (21). The Grading of Recommendations Assessment, Development and Evaluations (GRADE) system was used for study appraisal (22). This system assesses risk of bias, inconsistency, indirectness, and imprecision of the results as serious or not serious. The end result is four levels of evidence, also known as quality of evidence or certainty in evidence: very low, low, moderate, and high certainties.

Data for study design, patient characteristics, interventions, and study outcomes were extracted independently. Data extracted included study period, number of patients, the age of the patients, underlying diagnoses of the population, arrest etiology, time to ECMO, site of cannulation, and outcome measures for pediatric ECPR. The primary outcome was survival to ICU discharge. Secondary outcomes analyzed survival with a favorable neurologic outcome, a definition that varied based on the tool used in each publication. These definitions were a Pediatric Cerebral Performance Category (PCPC) of 1–2 or change less than 2, Functional Status Scale (FSS) score changes less than three, normal intelligence quotient (IQ) measurements, or normal clinical exams. Other outcomes assessed included survival based on the primary indication for ECPR (cardiac vs noncardiac arrest), survival postdischarge, and adverse events.

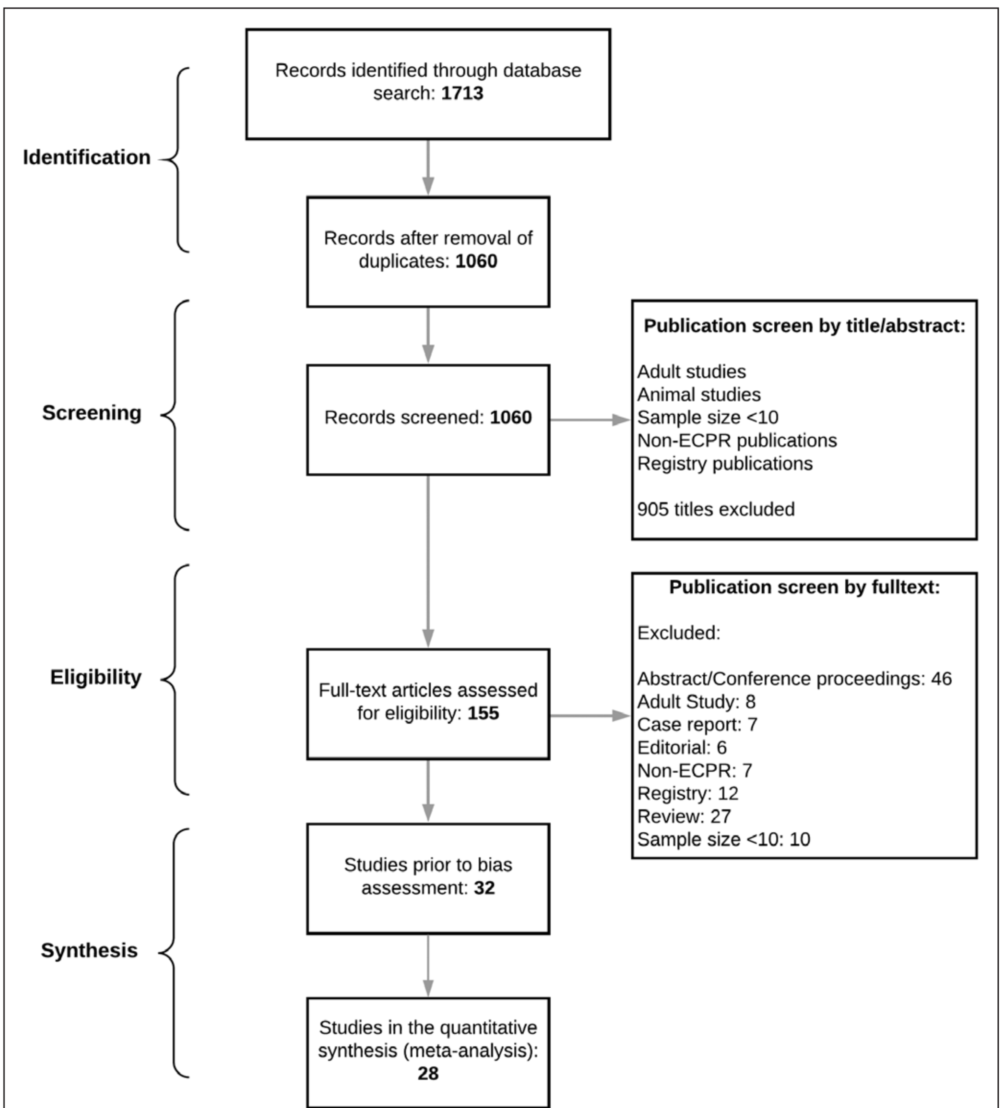

Figure 1. Flow diagram demonstrating the search strategy and selection of included studies. E-CPR = extracorporeal cardiopulmonary resuscitation.

Statistical Analysis

Descriptive statistics are reported as medians and interquartile ranges. The proportion and associated 95% CIs were used as the effect size measure for the primary (survival outcome) and secondary (neurologic outcome) outcomes. Studies were weighted with the inverse variance method and data were pooled via random-effects modeling on the basis of restricted maximum likelihood approach. We subsequently performed a leave-one-out sensitivity analysis, which iteratively removed one study at a time, to determine the influence of individual studies on the overall effect. Next, we conducted random-effects meta-regression analyses to identify potential moderators on the primary and secondary outcomes.

Clinical heterogeneity among studies was assessed qualitatively, and statistical heterogeneity was calculated with the Cochran Q and I^2 measure (23). In the forest plots, the *p* values stand for the level of statistical significance resulting when using Cochran Q, a test of statistical heterogeneity (23). Additionally, Baujat plots were used to evaluate sources of heterogeneity for all studies (24, 25). Potential publication bias was examined with a visual inspection of funnel plots and Egger' linear regression method (26). All analyses were performed using R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC). Statistical tests were two-sided with a *p* value less than 0.05 considered statistically significant.

RESULTS

Study Selection

The initial database search produced 1,713 records. Following removal of duplicates, 1,060 records were reviewed. After examination for inclusion and exclusion, a final list of 28 articles published between January 1990 and May 2020 were included in the final systematic review and meta-analysis. The majority of the included studies were observational studies or case reviews. No control groups existed in any of the studies, and no control group analysis was done. JBI checklists for the relevant study types found that all included studies were of high quality, and the risk of bias was not serious across all 28 publications.

Patients

Main features of the included studies are summarized in **Table 1**. A total of 1,348 patients were included in the final review. Among articles published between 1990 and 2000, 2001 and 2010, and 2010 and 2020, there were 32, 338, and 1,094 patients, respectively. Unadjusted survival to discharge in each decade was 56%, 44%, and 41%.

The median age of patients was 10 months, with a range of 0 days to 17 years. The predominant indication for ECPR was cardiac disease. Of the 1,348 patients, 967 required ECPR in the setting of a cardiac indication (congenital heart disease, postcardiac surgery, and heart failure). Sixty-four patients required ECPR in the setting of a primary noncardiac indication (acute respiratory distress syndrome/neonatal respiratory disease). About 317 patients had an unclear primary indication for ECPR. Time from arrest to start of ECMO was reported in18 publications; the mean time to cannulation was 43 minutes (CI 95% = 39–47 min). The mean ECMO duration for the patients was 106 hours (CI 95% = 92–120 hr), reported in 12 studies.

Outcomes

In the 28 included studies, with 1,348 patients, pooled survival at hospital discharge was 46% (CI 95% = 43–48%) (**Fig. 2**). Leave-one-out sensitivity analysis identified one potential outlier; the study by Torres-Andres et al (27) contributed the greatest heterogeneity to this outcome. Using hospital mortality as the main outcome variable, included studies were evaluated for study size effect. The generated funnel plot presented no clear asymmetry upon visual inspection. The Egger test of the intercept did not identify any significant association between study size and hospital mortality. GRADE analysis showed moderate level of certainty for the results obtained. Meta-regression models based on underlying diagnosis at time of arrest, duration of resuscitation, or age did not find any statistically significant results for association with survival (**Supplemental Table 2**, http://links.lww.com/CCM/G174).

Survival with favorable neurologic outcome was assessed as in **Figure 3**. There were 13 articles with 735 patients. Eight articles reported outcome using the PCPC. One reported using FSS, three used unspecified clinical assessments, and one used IQ testing. The 13 included studies were evaluated for study size effect. Pooled survival with favorable neurologic outcome was 30% (CI 95% = 27–33%). Limiting analysis to only survivors in the studies, hospital discharge with favorable neurologic outcome was 68% (CI 95% = 64–72%). The generated funnel plot presented some asymmetry upon visual inspection, and there was significant heterogeneity and variability in the point estimates. Leave-one-out analysis did not reveal any potential outliers. Three publications (Kane et al [28], Morris et al [29], and Prodhan et al [30]] contributed the greatest heterogeneity to this outcome. GRADE analysis showed moderate level of certainty for the evidence. Meta-regression models did not reveal any statistically significant results with respect to association between duration of arrest with neurologic outcomes (Supplemental Table 2, http://links.lww.com/CCM/G174). There was

TABLE 1.
Features of Studies Included in Final Assessment

							Neurologic Outcome	
Study	References	Study Period	Study Design	Sample Size	Median Age (mo)	% Survival	Tool	% Favorable
1	Alsoufi et al (31)	March 2000 to December 2005	Retrospective	80	35(0–26)	34		
2	Alsoufi et al (32)	2007–2012	Retrospective	39	4 (0–5)	41		
3	Anton Martin et al (33)	July 2000 to July 2013	Cohort	73	6 (0–24)	43.8	PCPC	75
4	Beshish et al (34)	2005–2015	Retrospective	80	1 (0–11)	47.5	Functional Status Scale	75
5	Burke et al (35)	December 2008 to August 2015	Retrospective	54	9 (2–37)	48.2		
6	Del Nido et al (36)	1981–1994	Retrospective	11	NA	64		
7	Delmo Walter et al (37)	January 1992 to December 2008	Retrospective	42	9 (0–207)	40.4		
8	Duncan et al (38)	1996–1998	Retrospective	11	8 (0–56)	63.6		
9	Erek et al (39)	November 2010 to June 2014	Retrospective	25	3 (0–55)	20		
10	Garcia Guerra et al (40)	January 2000 to December 2010	Prospective	55	7 (2–26)	45	Intelligence quotient	76
11	Guo et al (41)	2017	Retrospective	11	2 (0–18)	36.4	Clinical	100
12	Huang et al (42)	January 1999 to January 2006	Retrospective	26	53 (0–207)	41	PCPC	37
13	Kane et al (28)	1995–2008	Retrospective	172	6 (0–44)	51	POPC	75
							PCPC	79
14	Lowry et al (43)	2000, 2003, and 2006	Retrospective	82	NA	34		
15	Mattke et al (44)	2008–2014	Cohort	28	NA	65	PCPC	59
16	Merkle et al (45)	January 2008 to December 2016	Retrospective	39	3 (1–36)	44		
17	Morris et al (29)	1995–2002	Retrospective	66	5 (0–170)	33	PCPC/ POPC	50
18	Philip et al (46)	January 2005 to December 2012	Retrospective	59	13 (1–93)	45.7	POPC	86
19	Polimenakos et al (47)	January 2007 to December 2011	Retrospective	21	7.5 d (5–10 d)	62		

(*Continued*)

TABLE 1. (*Continued*)
Features of Studies Included in Final Assessment

Study	References	Study Period	Study Design	Sample Size	Median Age (mo)	% Survival	Neurologic Outcome	
							Tool	% Favorable
20	Prodhan et al (30)	January 2001 to March 2006	Retrospective	32	4 (0–162)	73	POPC/ PCPC	75
21	Shakoor et al (48)	January 2010 to November 2017	Retrospective	70	49	54		
22	Shin et al (49)	November 2013 to January 2016	Retrospective	12	7 (0–142)	33	Clinical	67.7
23	Sivarajan et al (50)	November 1990 to April 2006	Retrospective	61	1 (0–4)	36.1		
24	Torres-Andres et al (27)	2007–2015	Retrospective	56	3 (1–54)	65.5		
25	Turek et al (51)	April 2003 to March 2011	Retrospective	31		29	PCPC	54.5
26	von Allmen et al (52)	July 1985 to December 1988	Retrospective	10		60		
27	Wolf et al (53)	July 2002 to November 2011	Retrospective	90	25 (0–200)	55.6	Clinical	40
28	Zeybek et al (54)	2009–2016	Retrospective	12	NA	33.3		

NA = not applicable, PCPC = Pediatric Cerebral Performance Category, POPC = Pediatric Overall Performance Category.

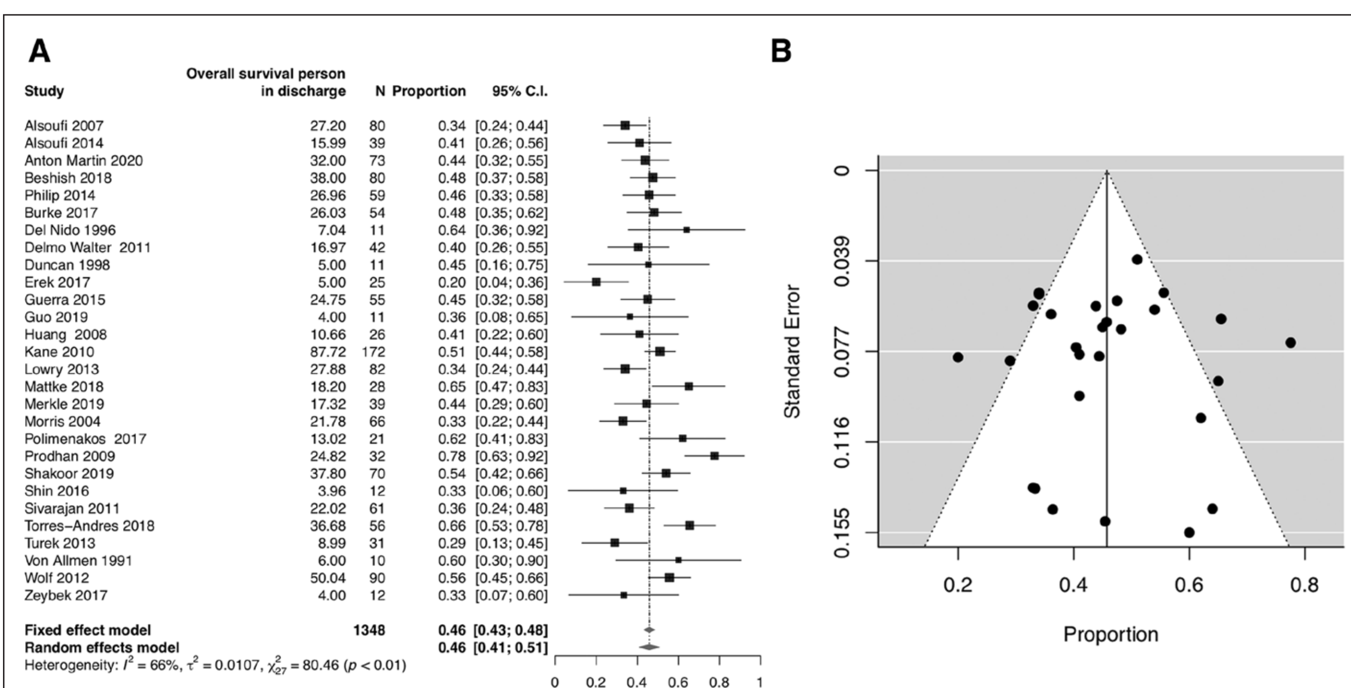

Figure 2. Overall survival. **A**, Results of the pooled survival analysis. **B**, Egger funnel plot.

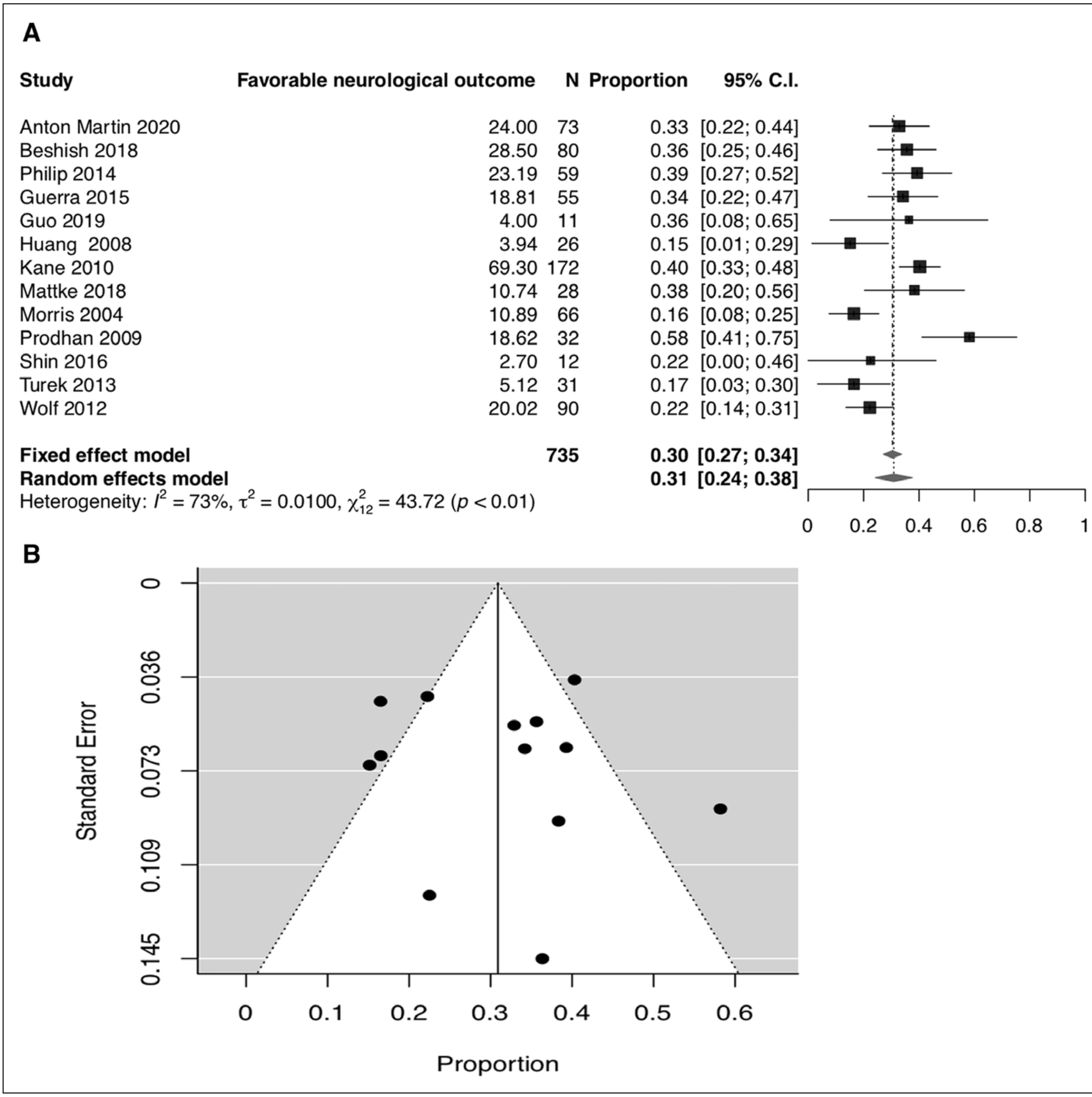

Figure 3. Survival with a favorable neurological outcome. **A**, Results of the pooled analysis of survival with a favorable neurologic outcome. **B**, Egger funnel plot.

insufficient data to analyze the factors of age, underlying diagnosis at time of arrest, duration of ECMO, and cannulation strategy for association with favorable neurologic outcome.

Nine studies with 264 survivors had long-term follow up in place, and 208 patients were alive at least 6–12 month postdischarge, a long-term survival rate of 79% (CI 95% = 76–82%). There were insufficient details available to compare long-term survival based on patient demographics, etiology of arrest, present comorbidities, laboratory/clinical parameters, or time to cannulation.

Fifteen studies, with 854 patients, reported detailed primary cannulation site information: 469 patients (55%) were cannulated through the chest, 314 (37%) were cannulated through the neck, and 71 (8%) were cannulated through the groin. About 523 of these patients, across seven studies, had survival outcomes and accompanying detailed cannulation information;

there were no significant differences between the survivors and nonsurvivors in terms of cannulation sites.

Four studies reported failure of myocardial recovery, with occurrence rates between 10% and 20%. Renal failure was reported in two studies, with an occurrence rate of 35–50%. There was no rigorous documentation of other ECPR-related complications.

Quality of Studies

A summary of our risk of bias evaluations using the JBI is in Supplemental Table 1 (http://links.lww.com/CCM/G173). Evaluation of studies by the JBI checklist for prevalence studies found that most studies were of high quality, with 28 of the 28 studies attaining a score above 7 out of 10. Most studies had low or unclear risk of bias in each domain. Egger test yielded nonsignificant results for publication bias in our primary outcomes. The GRADE assessments are presented in **Supplemental Table 3** (http://links.lww.com/CCM/G175). There was moderate certainty of evidence for mortality and neurologic outcomes for ECPR in pediatric population.

DISCUSSION

ECPR is a growing indication for ECMO use (55, 56). Our meta-analysis from 28 observational studies with a total of 1,348 patients showed a survival rate of 46%. The median age of the patients was 10 months. Mean arrest time was under 45 minutes. Pooled survival with favorable neurologic outcome was 30%. In the nine studies that reported long-term follow up, long-term survival was 79%. Our meta-analysis showed that more than 70% of the patients supported with ECPR had an underlying cardiac diagnosis, whereas less than 5% received ECPR for a respiratory indication. In our review, the use of ECPR in pediatric patients has increased over the last 3 decades; other work shows that the biggest growth and outcome improvement have been seen in adults (57, 58). We show that unadjusted survival rates have slightly decreased each decade. This is likely multifactorial; a possible etiology is the increasing adoption of the modality in increasingly complex patients (59). Additionally, an increase in the use of ECPR to support patients with noncardiac diagnoses, a population known to have worse outcomes, may explain the decrease in survival over time.

The earliest reports of successful use of ECPR were in the 1990s. Analyses of the ELSO registry identified risk factors of poor outcomes, including cardiac arrest in setting of underlying noncardiac disease (60, 61). Subsequent work from the Get with the Guidelines registry showed better survival and favorable neurologic outcomes with ECPR (ECPR: 40% and 27%, respectively, vs conventional CPR: 27% and 18%) (5). There was also a survival advantage for patients with cardiac disease who required ECPR (62). Based on these data, the AHA included ECPR as a treatment option in the cardiac arrest algorithm. Our review and meta-analysis show a slightly higher rate of survival (46%) and survival with favorable neurologic outcome (30%) in comparison with the registry data.

Thirteen studies reported neurologic complications to be a significant cause of morbidity and mortality. In the four studies that reported failure of myocardial recovery, the occurrence rate varied around 10–20%. Renal failure was reported only in two studies, with an occurrence rate of 35–50%. From the meta-regression-analysis, we were unable to derive any prearrest variables to be a predictor of mortality.

The nature of ECPR poses ethical and logistic challenges for assessing safety and efficacy of the therapy using randomized study designs. Thus, survival benefits of ECPR have been largely derived from retrospective cohort studies. There are inherent challenges with retrospective studies, as they are subject to indication bias. To address some of the challenges, we used JBI risk assessment tool for cohort studies and GRADE assessment to assess risk of bias in the outcomes published in these studies. Unlike the previous reviews on pediatric ECPR, which include patients predominantly from registry studies, we exclude registry studies to avoid duplication of patients. This allowed for accurate assessment of overall survival with a focus on neurologic outcome.

ECPR is a complex, resource intense therapy that must be deployed in a timely manner to affect meaningfully survival and neurologic outcomes. Experience and consistency have been reported to been a key component of a successful program (63, 64). Education through simulation and institution of structured ECPR programs may be a key to better outcomes, and this has been recently demonstrated in the literature (65). Our review, however, has not found enough data to formally support this conclusion and makes this field another target for future work.

The review is based on nonrandomized and nonpropensity-matched studies. Advancement in technology over the years can account for some variations between studies. Center variability, criteria for patient selection, program variation, and lack of consistency in reporting of results could add to the heterogeneity of the data. The heterogeneity was accounted for in our model by using leave-one-out sensitivity analysis. Furthermore, based on the JBI checklists, we found studies were of high quality and the risk of bias was not serious. Finally, the GRADE analysis revealed that there was moderate amount of certainty in the results provided for mortality and neurologic outcomes. The risk of bias was low in the studies reporting on ECPR, though there was serious inconsistency in reporting among the publications included. This could be mainly attributed to the nature of the therapy and the lack of a comparative arm (traditional CPR). It is important to note that most patients receiving ECPR are likely to receive care at high-resource institutions, and so outcomes outlined in this review are not to be compared with conventional CPR reports without appropriate adjustment.

In our meta-analysis, there were limited data available to understand the outcomes of ECPR based on the underlying diagnosis of cardiac disease versus pulmonary, as most studies that reported the patient outcomes did not report the outcomes by underlying diagnosis. There are limited data available from the subgroup analysis of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) study in which patients with postcardiac surgery had better outcomes (66). This is an area that requires further research.

CONCLUSIONS

The use of ECPR is growing, particularly for underlying cardiac disease, with overall survival of 46% and favorable neurologic outcomes. Children under 2 years appear to be the largest cohort in the group. Future areas of research should focus on understanding the role of ECPR in noncardiac illness and out of hospital cardiac arrest, the impact of CPR quality and ECPR program organization on survival, as well as long-term functional and quality of life in ECPR survivors.

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