

# Predictors of survival for pediatric extracorporeal cardiopulmonary resuscitation

## A systematic review and meta-analysis

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### Abstract

**Background:** The use of extracorporeal cardiopulmonary resuscitation (ECPR) has improved survival in patients with cardiac arrest; however, factors predicting survival remain poorly characterized. A systematic review and meta-analysis was conducted to examine the predictors of survival of ECPR in pediatric patients.

**Methods:** We searched EMBASE, PubMed, SCOPUS, and the Cochrane Library from 2010 to 2021 for pediatric ECPR studies comparing survivors and non-survivors. Thirty outcomes were analyzed and classified into 5 categories: demographics, pre-ECPR laboratory measurements, pre-ECPR co-morbidities, intra-ECPR characteristics, and post-ECPR complications.

**Results:** Thirty studies (n = 3794) were included. Pooled survival to hospital discharge (SHD) was 44% (95% CI: 40%–47%,  $I^2 = 67%$ ). Significant predictors of survival for pediatric ECPR include the pre-ECPR lab measurements of PaO<sub>2</sub>, pH, lactate, PaCO<sub>2</sub>, and creatinine, pre-ECPR comorbidities of single ventricle (SV) physiology, renal failure, sepsis, ECPR characteristics of extracorporeal membrane oxygenation (ECMO) duration, ECMO flow rate at 24 hours, cardiopulmonary resuscitation (CPR) duration, shockable rhythm, intra-ECPR neurological complications, and post-ECPR complications of pulmonary hemorrhage, renal failure, and sepsis.

**Conclusion:** Prior to ECPR initiation, increased CPR duration and lactate levels had among the highest associations with mortality, followed by pH. After ECPR initiation, pulmonary hemorrhage and neurological complications were most predictive for survival. Clinicians should focus on these factors to better inform potential prognosis of patients, advise appropriate patient selection, and improve ECPR program effectiveness.

**Abbreviations:** CPR = cardiopulmonary resuscitation, ECPR = extracorporeal cardiopulmonary resuscitation, ECMO = extracorporeal membrane oxygenation, ELSO = extracorporeal life support organization, RR = risk ratio, SHD = survival to hospital discharge, SMD = standardized mean differences, SV = single ventricle.

**Keywords:** cardiac arrest, extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, pediatric

## 1. Introduction

While cardiopulmonary resuscitation (CPR) has been shown to dramatically improve survival rates for pediatric in-hospital cardiac arrest patients, overall survival to hospital discharge (SHD) for these patients after prolonged CPR remains low at approximately 28%.<sup>1–3</sup> The adoption of extracorporeal membrane oxygenation (ECMO) since 1976 has greatly increased survival rates for this patient population.<sup>4–7</sup>

The use of ECMO for cardiopulmonary resuscitation (ECPR) has been increasing rapidly in pediatric and adult populations.<sup>8,9</sup>

Recent analysis of the extracorporeal life support organization database (ELSO) estimated SHD rates for pediatric ECPR patients to be 42%.<sup>10</sup> Lasa et al demonstrated not only increased survival but also increased favorable neurological outcomes in ECPR compared to conventional CPR.<sup>10</sup>

Variability in survival outcomes and limited data on associated risks including severe neurological, renal, and cardiac complications have led to a lack of consensus on implementation guidelines and patient selection.<sup>7,11–13</sup> These factors place the decision to cannulate onto the provider's clinical judgement.

NS and AS contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The data used for this meta-analysis were obtained from articles listed within the list of references corresponding to Table 1. All supplementary tables and figures are attached under the supplemental materials file, along with the PRISMA Checklist and PRISMA Flow Diagram. The corresponding author (N.S.) can be contacted for further information.

Supplemental Digital Content is available for this article.

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How to cite this article: Sood N, Sangari A, Goyal A, Conway JAS. Predictors of survival for pediatric extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis. *Medicine* 2022;101:39(e30860).

Received: 23 May 2022 / Received in final form: 30 August 2022 / Accepted: 31 August 2022

<http://dx.doi.org/10.1097/MD.0000000000030860>

**Key Points:**

- Predictors of survival in pediatric ECPR are poorly understood, and no randomized controlled trials exist on this topic.
- This meta-analysis is the largest study to date examining these factors, investigating 30 possible predictors and including 30 studies (n = 3794).
- This study found that the factors most associated with mortality prior to ECPR initiation were increased CPR duration, decreased lactate levels, and decreased pH.

This variability, coupled with rapidly improving technological developments and increased adoption of ECPR within the last 10 years, has made a meta-analysis covering the most recent literature a necessity.<sup>[14,15]</sup> This literature review and meta-analysis analyzed predictors of survival in the most recent studies on pediatric ECPR to identify risk factors for mortality, allowing providers to make more informed decisions on patient selection and improve ECPR program effectiveness.

**2. Methods****2.1. Data source and search strategy**

Database searches were performed by 2 independent researchers in EMBASE, PubMed, SCOPUS, and the Cochrane Library with individual search strategies for each database (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/H424>). Text-word searches and standardized medical subject heading were included in the search terms. References cited in eligible reviews were also examined. Studies between January 1, 2010 and February 5th, 2021 were searched without language restrictions. No methodology filters or document filters were used.

**2.2. Study eligibility**

Studies were included if humans enrolled were under 21 years of age, ECPR was performed during cardiac arrest, stratification between ECPR survivors and non survivors was present, data was present with a minimum of 2 metrics reported with measures of central tendency and variability, and the publication date was between 2010 and February 2021.

Animal trials, conference abstracts, reviews, trial protocols, simulations, editorials, letters, comments, practice guidelines, book chapters, and duplicate studies were excluded. Any studies including fewer than 10 patients who underwent ECPR, outcomes that did not include SHD, and studies with incomplete data were excluded.

**2.3. Review process and data collection**

Studies were reviewed by 2 independent authors. Abstracts agreed by both reviewers were identified for detailed review of the full manuscript. Duplicate publications were identified through comparison of reports for author names, enrollment date, setting, intervention, participant number, or baseline data. Disagreements between authors over the inclusion or exclusion of studies were resolved independently by a third author. Articles were identified and data was extracted from included studies. Methodological quality was reviewed utilizing the Newcastle–Ottawa Quality Assessment scale for case-control studies or cohort studies.<sup>[16]</sup>

All outcomes examined in this meta-analysis were documented in 2 or more studies. As such, 30 predictors of survival

were examined, classified into 5 main categories: demographics, pre-ECPR laboratory measurements, pre-ECPR co-morbidities, intra-ECPR characteristics, and post-ECPR complications. Demographic information included age, gender, race, and weight. Laboratory measurements included baseline creatinine, bicarbonate, lactate, PaCO<sub>2</sub>, PaO<sub>2</sub>, and arterial pH. Preexisting co-morbidities studied were single ventricle (SV) physiology, primary myocardial disease, pulmonary hypertension, renal failure, and sepsis. Intra-ECPR characteristics included details on the ECPR treatment itself, specifically CPR duration, ECMO duration, ECMO flow rates at 4 hours and 24 hours, cannulation sites, shockable rhythm, and neurological complications. Post-ECPR complications comprised of pulmonary hemorrhage, renal failure, and sepsis. Survival rates across studies were additionally analyzed.

**2.4. Statistical analysis**

Data was analyzed using statistical software R 4.1.3. Studies that reported median and interquartile range or median and range were converted into mean and standard deviation using the methodology in Wan et al 2014.<sup>[17]</sup> Heterogeneity of pooled data was calculated using  $I^2$ .<sup>[18,19]</sup> Random-effects models were used due to the heterogeneity of study protocols unless included studies numbered fewer than 5, as recommended in the Cochrane Handbook.<sup>[20,21]</sup> Pooled risk ratios (RR) and standardized mean differences (SMD) were calculated for binary and continuous data respectively. Publication bias was assessed for all outcomes where included studies numbered 10 or more using Egger's tests and funnel plots.<sup>[22–24]</sup> All results were considered statistically significant if  $P < .05$ .

Using the Grading of Recommendations, Assessment, Development, and Evaluation approach, we evaluated the level of certainty in the data abstracted from the included studies. All predictors of survival were evaluated on risk of bias, inconsistency, indirectness, imprecision, and publication bias, and all were found to be low quality (Table S2, Supplemental Digital Content, <http://links.lww.com/MD/H425>).

**3. Results****3.1. Study selection**

The preferred reporting items for systematic reviews and meta-analyses flow diagram & study selection for this systematic review and meta-analysis is depicted in Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/H430>. The systematic search of articles identified 12,072 results. After title and abstract screening, 124 full-text articles were identified as potentially relevant. Thirty studies were included after full-text review. No randomized controlled trial was found on the subject. Table 1 summarizes the key characteristics of each study included in the meta-analysis.

**3.2. Study characteristics**

A total number of 3794 participants from 30 studies were included for analysis in this meta-analysis. The mean age of participants was 397 days, with 42% of participants being female. All studies were published between the years 2010 and 2021.

**3.3. Risk of bias**

Of the 30 studies included, 26 were assessed to be of good quality, while 4 were assessed to be of poor quality.<sup>[16]</sup> A summary of the risk of biases in each study is provided in Table S3, Supplemental Digital Content, <http://links.lww.com/MD/H426>. Publication bias was assessed in all outcomes that included 10 or more studies using Egger's test and found to be non-significant

**Table 1**  
**Characteristics of included studies.**

Author and yr	Region	Yrs	N	Female	Survival (%)	Setting	Type
Alsoufi, B., 2014 <sup>[25]</sup>	Saudi Arabia	2007-2012	39	14	41	IHCA	R
Anton-Martin, P., 2020 <sup>[26]</sup>	USA	2000-2013	73	26	44	IHCA	R
Bembea, M., 2019 <sup>[27]</sup>	USA	2000-2014	593	242	41	IHCA	R
Beshish, A., 2018 <sup>[28]</sup>	USA	2005-2015	80	40	48	IHCA	R
Brunner, A., 2016 <sup>[29]</sup>	Switzerland	2008-2014	19	NR	16	Both	R
Chen, G., 2018 <sup>[30]</sup>	Asia Pacific	1999-2016	321	142	51	IHCA	R
Chrysostomou, C., 2013 <sup>[31]</sup>	USA	2006-2010	40	15	75	NR	R
De Mul, A., 2019 <sup>[32]</sup>	Switzerland	2008-2016	55	20	25	Both	R
Erek, E., 2017 <sup>[33]</sup>	Turkey	2010-2014	25	NR	20	IHCA	R
Guo, Z., 2019 <sup>[34]</sup>	China	2017	11	3	36	IHCA	R
Huang, S., 2012 <sup>[35]</sup>	Taiwan	1999-2009	54	17	46	IHCA	R
Jolley, M., 2014 <sup>[36]</sup>	Multi	1998-2013	293	121	36	IHCA	R
Kane, D., 2010 <sup>[37]</sup>	USA	1995-2009	172	77	51	IHCA	R
Kendrill, T., 2020 <sup>[38]</sup>	Turkey	2014-2017	15	8	33	IHCA	R
Kramer, P., 2020 <sup>[39]</sup>	Germany	2005-2016	72	34	36	Both	R
McMullan, D., 2014 <sup>[40]</sup>	Multi	1998-2010	641	257	39	NR	R
Melvan, J., 2020 <sup>[41]</sup>	USA	2002-2017	184	92	43	NR	R
Philip, J., 2014 <sup>[42]</sup>	USA	2005-2012	59	NR	46	IHCA	R
Polimenakos, A., 2017 <sup>[43]</sup>	USA	2007-2011	21	NR	62	IHCA	R
Raymond, T., 2010 <sup>[44]</sup>	USA	2000-2007	199	75	44	IHCA	R
Shakoor, A., 2019 <sup>[45]</sup>	USA	2010-2017	70	28	54	IHCA	R
Shin, H., 2016 <sup>[46]</sup>	SK	2013-2016	12	6	33	NR	R
Sivarajan, V., 2011 <sup>[47]</sup>	Australia	2002-2006	37	18	38	NR	R
Topjian, A., 2019 <sup>[48]</sup>	Multi	2009-2015	157	57	46	IHCA	R
Torres-Andres, F., 2018 <sup>[49]</sup>	USA	2007-2015	58	23	65.5	Both	R
Tsukahara, K., 2014 <sup>[50]</sup>	Japan	2003-2012	21	8	14	Both	R
Walter, E., 2011 <sup>[51]</sup>	Germany	1992-2008	42	19	40	IHCA	R
Wolf, M., 2012 <sup>[52]</sup>	USA	2002-2011	90	NR	56	IHCA	R
Yates, A., 2019 <sup>[53]</sup>	USA	2013-2016	33	14	39	NR	P
Zeybek, C., 2017 <sup>[54]</sup>	Turkey	2009-2016	34	NR	33	IHCA	R

NR = not reported, P = prospective, R = retrospective, SK = South Korea.

in all outcomes except for duration of CPR. Funnel plots are shown in Figure S2, Supplemental Digital Content, <http://links.lww.com/MD/H431>.

### 3.4. Outcomes

Pooled SHD was 44% (CI 95% = 40%–47%) (Fig. S3A, Supplemental Digital Content, <http://links.lww.com/MD/H432>). Chrysostomou et al 2013 was identified as a potential outlier using leave-one-out sensitivity analysis with the highest survival rate of 75%.<sup>[31]</sup> Studies were additionally evaluated for publication bias and visual inspection of the associated funnel plot found no clear asymmetry (Fig. S3B, Supplemental Digital Content, <http://links.lww.com/MD/H432>). Egger's test found nonsignificant heterogeneity ( $P > .11$ ). Meta-regression models did not find any statistically significant association between SHD and year of publication (Table S4, Supplemental Digital Content, <http://links.lww.com/MD/H427>). Meta-regression also found no significant association between proportion of survivors and number of patients in study, which was used as a surrogate for institutional experience.

### 3.5. Patient demographics

No significant difference was found between the 1138 survivors and the 1453 non-survivors in terms of age (SMD = 0.04 [-0.14 to 0.21],  $I^2 = 72%$ ,  $P = .66$ ) or 1018 survivors and the 1343 non-survivors in terms of weight (SMD = 0.12 [-0.06 to 0.30],  $I^2 = 74%$ ,  $P = .18$ ). Gender was additionally found to be not significantly different between the 1108 survivors than the 1406 non-survivors (RR = 0.93 [0.82–1.06],  $I^2 = 22%$ ,  $P = .28$ ). Of the 4 races analyzed (White, Black, Hispanic, or Asian), none were significantly associated with an increased risk of mortality (Table 2).

### 3.6. Patient baseline laboratory measurements

On average, patients were in a state of mixed respiratory and metabolic acidosis prior to ECPR commencement, with depressed pH, elevated PaCO<sub>2</sub>, and decreased bicarbonate levels along with elevated lactate levels with hypoxemia (Table 2).

Higher PaO<sub>2</sub> levels were predictive of survival (410 survivors & 505 non-survivors, SMD = 0.25 [0.13–0.38],  $I^2 = 8%$ ,  $P < .01$ ), as were higher pH levels (833 survivors & 1153 non-survivors, SMD = 0.21 [0.09–0.33],  $I^2 = 0%$ ,  $P < .01$ ). The 291 survivors also had significantly lower lactate levels than the 306 non-survivors (SMD = -0.36 [-0.64 to -0.07],  $I^2 = 46%$ ,  $P < .001$ ), and significantly lower PaCO<sub>2</sub> levels (SMD = -0.13 [-0.26 to 0.004],  $I^2 = 0%$ ,  $P = .045$ ). However, when leave-one-out sensitivity analysis was conducted, this effect was not robust (Table S5, Supplemental Digital Content, <http://links.lww.com/MD/H428>). Survivors (n = 90) had significantly lower creatinine levels than non-survivors (n = 103) (SMD = -0.41 [-0.70 to -0.12],  $I^2 = 21%$ ,  $P < .01$ ) (Table 2). Figure 1 displays the forest plots for pre-ECPR pH.

### 3.7. Patient significant preexisting complications

Renal failure was seen in significantly fewer of the 55 survivors than 74 non-survivors (RR = 0.47 [0.28–0.81],  $I^2 = 0%$ ,  $P = .01$ ). Pre-ECPR sepsis was also associated with reduced chances of survival (RR = 0.52 [0.28–0.97],  $I^2 = 24%$ ,  $P = .04$ ) (Table 2).

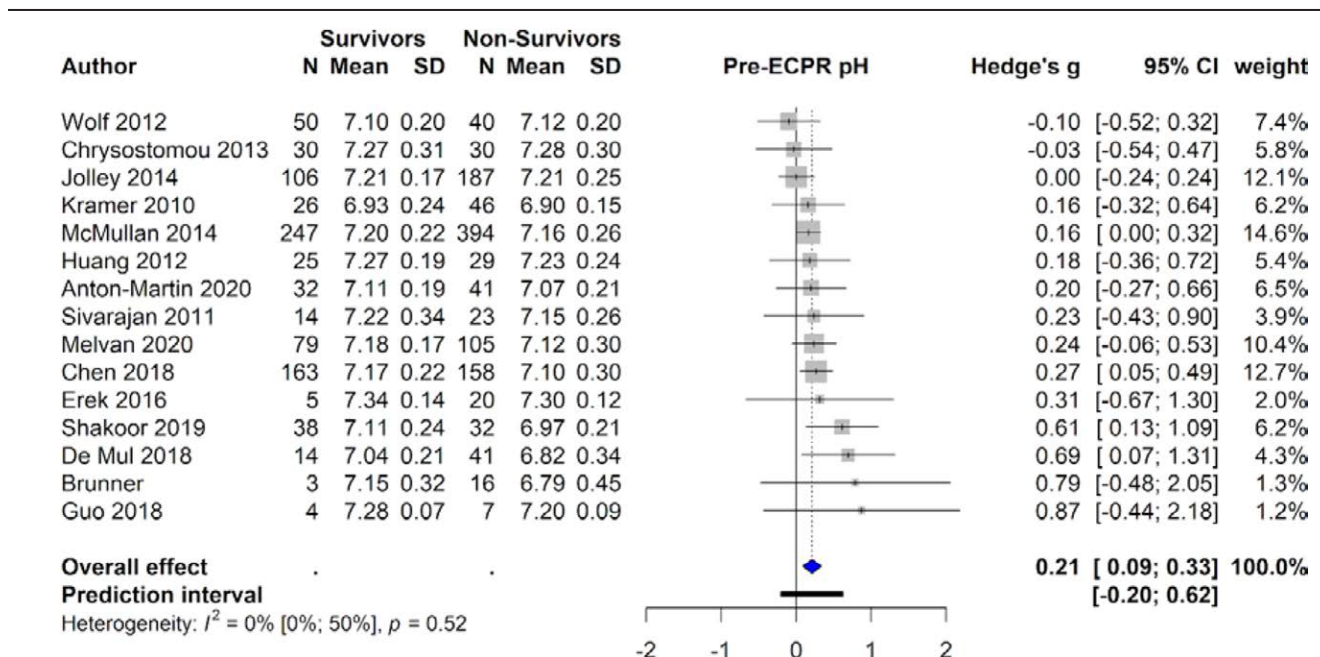
On the other hand, the odds of primary myocardial disease were not significantly different between the 403 survivors compared to the 508 non-survivors (RR = 1.14 [0.70–1.85],  $I^2 = 0%$ ,  $P = .60$ ). This pattern was also seen in pulmonary hypertension prior to ECPR (RR = 0.44 [0.12–1.61],  $I^2 = 0%$ ,  $P = .22$ ). Finally, the odds of SV physiology were not significantly different in the

**Table 2**

**Summary of metrics compared between pediatric survivors and non-survivors of ECPR.**

Metric	Studies	Population	Survivors	Non-survivors	f	P	Risk ratio [95% CI]	Hedge's g [95% CI]
<b>Demographics</b>								
Age	24	2610	343 ± 1045	440 ± 1372	72%	.66		0.04 [-0.14 - 0.21]
Gender-Male	18	2514	55%	59%	22%	.28	0.93 [0.82 - 1.06]	
Race-Asian	5	1408	11%	13%	0%	.43	0.73 [0.27 - 1.95]	
Race-Black	5	1286	15%	16%	31%	.78	1.05 [0.66 - 1.68]	
Race-Hispanic	4	1087	14%	15%	0%	.50	0.9 [0.68 - 1.21]	
Race-White	5	1286	61%	56%	14%	.54	1.05 [0.87 - 1.26]	
Weight	19	2380	6.3 ± 8.4	6.3 ± 9.8	74%	.18		0.12 [-0.06 - 0.3]
<b>Pre-ECPR lab measurements</b>								
Creatinine	4	193	0.83 ± 0.56	1.1 ± 0.7	21%	<.01		-0.41 [-0.7 - -0.12]
Bicarbonate	5	1328	19.8 ± 8.6	20 ± 9.4	18%	.68		0.03 [-0.18 - 0.25]
Lactate	11	616	6.9 ± 6.1	9.6 ± 7.6	41%	.02		-0.36 [-0.64 - -0.07]
PaCO <sub>2</sub>	5	842	55.7 ± 25.0	60.2 ± 33.0	0%	.045		-0.13 [-0.26 - 0]
PaO <sub>2</sub>	4	1061	44.1 ± 44.4	38.4 ± 37.5	8%	<.01		0.25 [0.13 - 0.38]
pH	15	2005	7.2 ± 0.2	7.1 ± 0.3	0%	<.01		0.21 [0.09 - 0.33]
<b>Pre-ecpr co-morbidities</b>								
Single ventricle physiology	12	1390	39%	45%	47%	.35	0.85 [0.58 - 1.23]	
Primary myocardial disease	12	1580	12%	7%	31%	.13	1.5 [0.87 - 2.6]	
Pulmonary hypertension	3	270	3%	5%	0%	.22	0.44 [0.12 - 1.61]	
Renal failure	3	129	24%	46%	0%	<.01	0.47 [0.28 - 0.81]	
Sepsis	3	1020	3%	6%	24%	.04	0.52 [0.28 - 0.97]	
<b>Intra-ECPR characteristics</b>								
CPR duration	17	1204	37.3 ± 25.2	47.9 ± 38.3	37%	.00		-0.36 [-0.54 - -0.18]
ECMO duration	21	2330	96.9 ± 120.3	118.9 ± 115.7	30%	.00		-0.23 [-0.36 - -0.1]
ECMO Flow Rate at 24 h	3	786	118.5 ± 49.2	130.8 ± 53.9	0%	.03		-0.15 [-0.3 - -0.01]
ECMO Flow Rate at 4 h	4	826	119.1 ± 51.1	124.3 ± 58.2	0%	.64		-0.03 [-0.17 - 0.11]
Site-femoral	2	143	11%	15%	0%	.43	0.71 [0.31 - 1.65]	
Site-neck	6	343	40%	43%	0%	.37	0.9 [0.68 - 1.19]	
Site-thorax	6	399	54%	54%	12%	.47	1.09 [0.82 - 1.45]	
Shockable rhythm	6	1205	17%	11%	0%	.01	1.51 [1.14 - 1.98]	
Neurological complications	9	2320	17%	37%	31%	<.01	0.43 [0.32 - 0.58]	
<b>Post-ECPR complications</b>								
Pulmonary hemorrhage	4	1076	2%	7%	49%	<.01	0.34 [0.17 - 0.69]	
Renal failure	4	540	22%	48%	0%	0	0.47 [0.36 - 0.61]	
Sepsis	4	243	15%	26%	0%	.033	0.57 [0.34 - 0.96]	

ECPR = extracorporeal cardiopulmonary resuscitation.



**Figure 1.** Forest plot examining pre-ECPR pH. ECPR = extracorporeal cardiopulmonary resuscitation.

613 survivors than in the 777 non-survivors (RR = 0.85 [0.58–1.23],  $I^2 = 47\%$ ,  $P = .35$ ) (Table 2).

### 3.8. Intra-ECPR characteristics

Duration of CPR was negatively associated with survival, with survivors on average receiving  $37.3 \pm 25.2$  minutes and non-survivors receiving  $47.9 \pm 38.3$  minutes of CPR (SMD = -0.36 [-0.54 to -0.18],  $I^2 = 37\%$ ,  $P < .01$ ). Duration of ECMO was also negatively associated with survival, with survivors on average receiving  $94.5 \pm 117.7$  minutes and non-survivors receiving  $116.3 \pm 115.8$  minutes of ECMO (SMD = -0.23 [-0.36 to -0.10],  $I^2 = 30\%$ ,  $P < .01$ ) (Table 2). However, publication bias was detected in the duration of CPR using Egger’s test. Leave-one-out sensitivity analysis was conducted and found the negative significant effect of CPR duration on survival was robust (Table S6, Supplemental Digital Content, <http://links.lww.com/MD/H429>). ECMO flow rate at 24 hours was also significantly reduced in survivors, with survivors receiving  $118.5 \pm 49.2$  mL/kg/min and non-survivors receiving  $130.8 \pm 53.9$  mL/kg/min (SMD = -0.15 [-0.30 to -0.01],  $I^2 = 0\%$ ,  $P = .03$ ). Patients with shockable rhythms, defined as either ventricular fibrillation or pulseless ventricular tachycardia, were more likely to survive than patients with non-shockable rhythms (RR = 1.51 [1.14–1.98],  $I^2 = 0\%$ ,  $P = .01$ ). Neurological complications during ECMO were associated with a reduced chance of survival (RR 0.43 [0.32–0.58],  $I^2 = 31\%$ ,  $P < .01$ ) (Table 2). A forest plot for CPR duration is provided in Figure 2.

### 3.9. Post-ECPR complications

Post-ECPR pulmonary hemorrhage, renal failure, and sepsis were significantly associated with decreased chance of survival. Pulmonary hemorrhage was seen 3 times as often in non-survivors than in survivors (RR = 0.34 [0.17–0.69],  $I^2 = 49\%$ ,  $P < .001$ ). Renal failure was seen twice as often in non-survivors as survivors (RR = 0.47 [0.36–0.61],  $I^2 = 0\%$ ,  $P < .01$ ). Sepsis was also associated with a reduction in survival (RR = 0.57 [0.34–0.96],  $I^2 = 0\%$ ,  $P = .03$ ) (Table 2).

## 4. Discussion

This manuscript examined the current literature regarding the use of ECPR in pediatric settings. ECPR SHD rates in pediatric populations is 44%, with an average patient age of 13 months. Meta-regression found that unadjusted survival rates have not improved over the past 10 years. This effect may be confounded by increased indications for ECPR use and expansion of ECPR use into higher-risk patient populations, including patients with non-cardiac illnesses. Meta-regression additionally found that the number of patients in a study did not correlate with survival rates, indicating that institutional experience may play less of a significant role in mortality than previously thought.<sup>[55]</sup>

We also summarized the predictors of survival to provide helpful information to clinicians responsible for patient selection at institutions with the equipment and expertise to provide ECPR. Previous systematic reviews and meta-analysis exist on the topic of pediatric ECPR; however, none quantitatively synthesize current evidence to rank predictors of survival clinicians can use to predict survival.<sup>[11,56–58]</sup> To our knowledge, this study examines the greatest breadth of predictors of survival, the most recent data, and the greatest number of patients to date in any meta-analysis of pediatric ECPR.

Prior to ECPR initiation, increased CPR duration and decreased lactate levels had among the highest associations with mortality, followed by decreased pH. After ECPR initiation, pulmonary hemorrhage and neurological complications were most predictive for survival. While the exact ranking of these variables is difficult to determine due to their overlapping confidence intervals, the evidence does suggest that clinicians should pay close attention to these variables specifically when determining patient selection for ECPR.

Thirty studies were analyzed, with survival rates ranging from 16% to 75%. This could be attributed to differing protocols, patient populations, indications and contraindications for treatment, institutional experience and equipment, and the relatively small sample sizes in each study. This wide range illustrates the need for a meta-analysis to effectively synthesize these diverging reports.

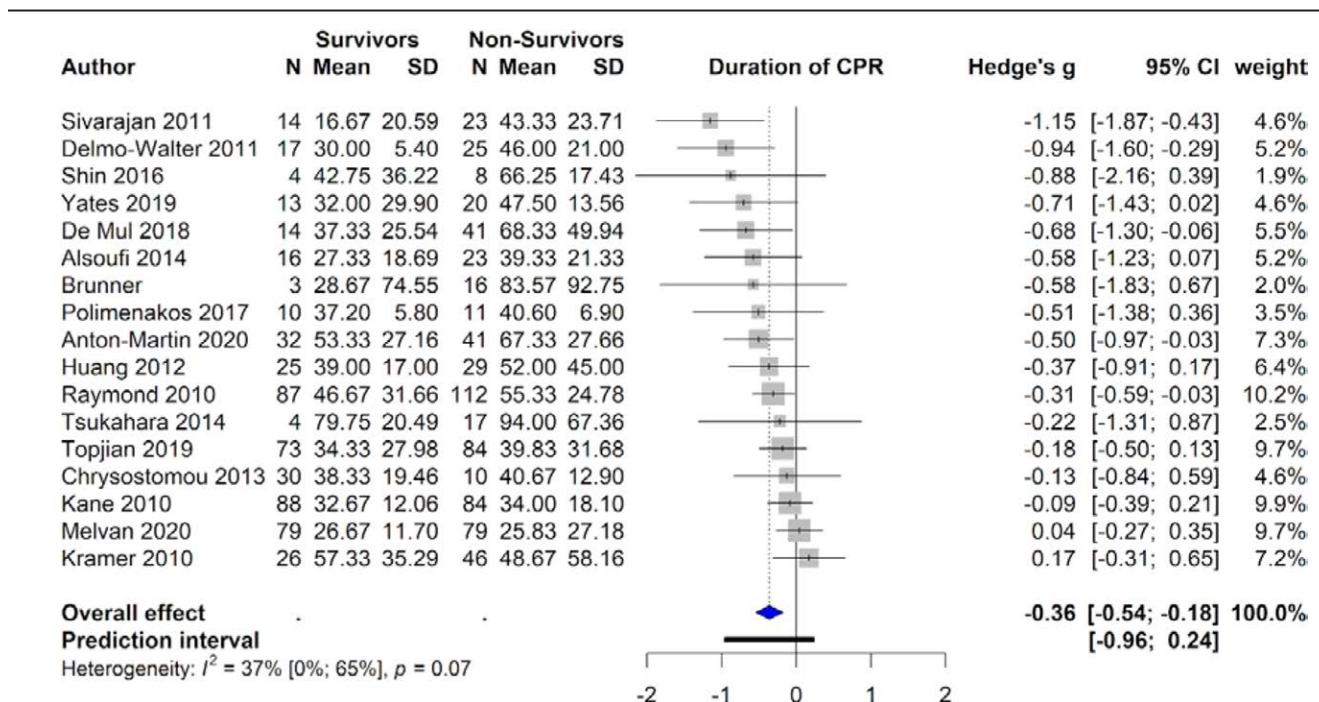


Figure 2. Forest plot for CPR duration. CPR = cardiopulmonary resuscitation.

Only one study, Chrysostomou et al 2013, demonstrated significantly higher survival rates than the pooled estimates.<sup>[131]</sup> Of note, patients in this study also had decreased acidosis, increased ECMO flow rates at 4 and 24 hours, and decreased ECMO duration times. These increased survival rates could have been due to a broader indication for ECPR. Alternatively, the preference of clinicians in the study to more quickly wean patients off ECMO may have reduced mortality, as this meta-analysis found that increased ECMO duration is negatively correlated with survival.

Age, gender, race, and weight were not found to be significantly associated with increased risk of mortality. Repeated observations have been drawn in prior literature indicating that pediatric ECPR patients have higher survival rates than adult ECPR patients.<sup>[9,59–61]</sup> In turn, many have speculated that younger pediatric patients might have higher survival rates than older pediatric patients. This meta-analysis found no evidence for such a correlation. Similar to what prior meta-analyses have found in adults, this meta-analysis found no correlation between gender or weight and mortality.<sup>[62]</sup> Prior studies have found conflicting results on whether race is associated with mortality, and this meta-analysis found that of Asian, Black, Hispanic, and White race, none were found to be significantly associated with mortality.<sup>[8,60,61,63]</sup>

Patients' baseline laboratory values at time of ECPR initiation were explored, and lower lactate levels, lower PaCO<sub>2</sub>, higher PaO<sub>2</sub>, and higher pH were found to be significant predictors of survival. Severe respiratory acidosis secondary to hypoxemia has been previously associated with decreased survival, consistent with our findings.<sup>[64,65]</sup> Elevated creatinine levels was also a significant predictor of mortality.<sup>[66,67]</sup> However, timing of creatinine measurements varied between studies, which limits the applicability of these findings.

Non-survivors were nearly twice as likely to suffer from pre-ECMO renal failure (46% vs 24%). One proposed mechanism behind this is that the existing renal failure may prevent an effective acid-base buffer response to the mixed respiratory and metabolic acidosis incurred by the cardiac arrest due to decreased bicarbonate production. This finding has not been well-examined in pediatric ECPR patients, but similar results have been shown in adult ECPR patients.<sup>[13]</sup>

In this meta-analysis, SV physiology was not significantly associated with survival. Extensive research has been done demonstrating that neonates with SV physiology are more likely to suffer from cardiac arrest.<sup>[68,69]</sup> However, conflicting evidence exists regarding the effect of SV physiology in neonates on ECMO and ECPR survival rates.<sup>[70–72]</sup> Alsoof et al 2014 found that the specific anatomic and surgical variants of SV physiology play a large role in survival rates, with patients who had aortopulmonary shunts or Norwood first-stage palliation having higher survival rates.<sup>[25,73]</sup> These confounding factors may be playing a role in the conflicting reports in the literature.

Both the pediatric and adult ECPR literature have consistently reported that patients with underlying cardiac illnesses are more likely to survive ECPR than patients with underlying non-cardiac illnesses.<sup>[74]</sup> One hypothesis is that ECMO serves as a supplement for the heart, allowing additional time for the underlying cardiac illness to resolve. Primary myocardial disease was not found to be a significant predictor of survival. This fits well with this hypothesis, as even given the additional time provided by ECMO, this specific underlying cardiac illness cannot be resolved.

One topic of key interest has been the relationship between CPR duration, time-to-ECMO initiation, and survival. This meta-analysis found that prolonged conventional CPR is associated with poor outcomes in pediatric populations.<sup>[43]</sup> Nevertheless, positive patient outcomes for ECPR have been demonstrated after 30 minutes, between 30 to 50 minutes, and even up to 90 to 220 minutes after cardiac arrest.<sup>[13]</sup> The most recent guidelines published by the International Consensus on

Cardiopulmonary Resuscitation do not indicate an optimal cutoff time after cardiac arrest beyond which return of spontaneous circulation is unlikely.<sup>[75]</sup>

Conflicting reports have also been published on the efficacy of the duration of ECMO as a predictor of survival, with several studies showing no significant difference in ECMO duration between survivors and non-survivors.<sup>[76]</sup> This meta-analysis found that ECMO duration was negatively associated with survival. As such, clinicians should continue to make efforts to reduce time spent by patients on ECMO.

ECMO flow rate at 24 hours was also shown to be a significant predictor of survival, with patients with reduced flow rates having increased chances of survival. Reduction in the rate of ECMO flow is usually initiated when the patient is considered to meet eligibility in recovery to be weaned from ECMO.<sup>[77–79]</sup> The need for a higher ECMO flow rate at the 24th hour suggests a lack of resolution of the underlying cardiac arrest or cardiac dysfunction. These patients are significantly more likely to face mortality. This is likely correlated with ECMO duration, as patients with higher flow rates at 24 hours are more likely to require ECMO for an increased duration. ECMO flow rate at 4 hours was not significantly different between survivors and non-survivors. This non-significance is likely attributable to the lack of adequate time for perfusion and resolution of the underlying cardiac arrest at the 4<sup>th</sup> hour in comparison to the 24th hour.

While most patients did not present with shockable rhythms, patients presenting with shockable rhythms were more likely to survive. These results are consistent with similar findings reported in adults.<sup>[62,80,81]</sup> Intra-ECPR neurological complications were found to be associated with a large reduction in survival, with patients presenting with neurological complications while on ECMO having a nearly 60% reduction in survival rates. Neurological complications occurred in 37% of non-survivors and should be monitored closely by clinicians as an effective prognostic factor for mortality.

Renal failure was the most common post-ECPR complication (48% of non-survivors), with sepsis (26%) more common than pulmonary hemorrhage (7%). Interestingly, pulmonary hemorrhage was the most predictive of mortality, with these complications roughly one-third as likely to occur in survivors as non-survivors. Post-ECPR renal failure and post-ECPR sepsis were roughly 50% more likely to occur in non-survivors than survivors. Renal failure, sepsis, and pulmonary hemorrhage post-ECPR have all been previously shown to be significant predictors of survival in pediatric populations.<sup>[27]</sup>

Five of the thirty included studies were studies examining data from the ELSO registry.<sup>[27,30,36,40,44]</sup> As such, the possibility of double counting patients from an institution that both published their results and reported the data to the ELSO registry exists. An additional sensitivity analysis was conducted to eliminate this possible bias by removing all ELSO registry studies and comparing these findings with the findings reported in this paper. Of the 5 most predictive variables—increased CPR duration, lactate levels, pH, pulmonary hemorrhage, and neurological complications—all remained statistically significant predictors of survival (Fig. S4, Supplemental Digital Content, <http://links.lww.com/MD/H433>).

#### 4.1. Limitations

This meta-analysis is limited by a few constraints. First, all but one study included in this meta-analysis were retrospective, and the majority were single-center reports. Chart review studies are more likely to suffer from both confounding and selection bias and cannot be conducted blinded in contrast to randomized controlled trials. However, mortality outcomes of ECPR patients are largely dependent on factors that cannot be randomly assigned, which reduces the benefit of a randomized controlled trial over retrospective observational chart reviews. Second, certain metrics contained substantial between-study

heterogeneity, and publication bias was detected for 1 metric - duration of CPR. This heterogeneity was partially accounted for by using a random-effects model whenever substantial heterogeneity was detected and by employing sensitivity analysis to validate results in which publication bias was detected. Third, certain predictor variables may be correlated, causing spurious estimates for those variables. Without access to individual patient data, these variables cannot be placed in a more comprehensive model that can control for other variables. Fourth, this meta-analysis was constrained by the data available in prior reports. Little data has been published regarding time-to-ECMO initiation, neurological outcomes, or long-term survival outcomes. Further research should examine these additional outcomes to provide a more comprehensive overview on how patients fare after ECPR.

## 5. Conclusion

This meta-analysis is the largest meta-analysis examining the greatest number of studies and greatest number of patients to date in any meta-analysis of pediatric ECPR. Thirty studies ( $n = 3794$ ) on pediatric ECPR published within the last 10 years were examined, and this analysis found the factors most associated with survival prior to ECPR initiation were increased CPR duration and lactate levels, followed by decreased pH. After ECPR initiation, pulmonary hemorrhage and neurological complications were the most associated with survival. ECPR protocols and guidelines that are adjusted to better monitor these metrics may lead to improved survival.

## Author contributions

NS and AS designed the study. AS and AG identified studies included and performed data collection. NS provided statistical analysis. JAC supervised the manuscript. All authors drafted the manuscript and have read and approved the final manuscript.

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