Original Article

Extracorporeal Cardiopulmonary Resuscitation in Children of Asia Pacific: A Retrospective Analysis of Extracorporeal Life Support Organization Registry

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Abstract

Background: Recent advances in extracorporeal membrane oxygenation (ECMO) have led to increasing interest in its use during cardiopulmonary resuscitation (CPR). However, decisions regarding extracorporeal CPR (ECPR) in children are difficult as a result of limited studies, especially in Asia Pacific. The objective of this study was to investigate trends in survival and demographic details for children with ECPR in Asia Pacific recorded in the Extracorporeal Life Support Organization (ELSO) registry from 1999 to 2016 and identify the risk factors associated with in-hospital mortality.

Methods: The data of children younger than 18 years of age who received ECPR over the past 18 years in Asia Pacific were retrospectively analyzed. The data were extracted from the ELSO registry and divided into two 9-year groups (Group 1: 1999–2007 and Group 2: 2008–2016) to assess temporal changes using univariate analysis. Then, univariate and multiple logistic regression analyses were performed between survivors and nonsurvivors to identify factors independently associated with in-hospital mortality.

Results: A total of 321 children were included in final analysis, with an overall survival rate of 50.8%. Although survival rates were similar between Group 1 and Group 2 (43.1% vs. 52.5%, $\chi^2 = 1.67$, $P = 0.196$), the median age (1.7 [0.3, 19.2] months for Group 1 vs. 5.6 [0.8, 64.9] months for Group 2, $t = -2.93$, $P = 0.003$) and weight (3.7 [3.0, 11.5] kg for Group 1 vs. 6.0 [3.4, 20.3] kg for Group 2, $t = -3.14$, $P = 0.002$) of children increased over time, while the proportion of congenital heart disease (75.9% for Group 1 vs. 57.8% for Group 2, $\chi^2 = 6.52$, $P = 0.011$) and cardiogenic shock (36.2% for Group 1 vs. 7.2% for Group 2, $\chi^2 = 36.59$, $P < 0.001$) decreased. Patient conditions before ECMO were worse, while ECMO complications decreased across time periods, especially renal complications. Multiple logistic regression analysis of ECMO complications showed that disseminated intravascular coagulation (DIC), myocardial stunning, and neurological complications were independently associated with increased odds of hospital mortality.

Conclusions: The broader indications and decreased complication rates make EPCR to be applicated more and more extensive in children in Asia Pacific region. ECMO complications such as myocardial stunning are independently associated with decreased survival.

Key words: Children; Extracorporeal Cardiopulmonary Resuscitation; Extracorporeal Life Support Organization; Extracorporeal Membrane Oxygenation

Introduction

Cardiac arrest, as a severe critical illness, is still one of the most common causes of disease-related death in children. It has poor neurological outcomes and a low survival rate, approximately 25% for in-hospital arrests and <10% for out-of-hospital arrests.[1] An observational study from Hill *et al*.[2] in 1992 reported early emergency bypass performed in children with cardiac arrest. Since then, an increasing number of studies about extracorporeal cardiopulmonary

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resuscitation (ECPR) have emerged, showing improved survival rates >30%, which might be due to the powerful mechanical pulmonary and circulatory support provided by extracorporeal membrane oxygenation (ECMO).[3-5] In 2015, the American Heart Association updated its guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care and recommended that ECPR might be considered in children suffering in-hospital cardiac arrest with cardiac diagnoses.[6] However, further recommendations and guidelines are absent because of the small number of studies with small sample sizes and narrow diagnoses. Given the rapid expansion of extracorporeal life support (ECLS) worldwide and possible survival benefits in children, more studies in this field are in demand. Moreover, no report has characterized the current situation of ECPR in Asia Pacific. The purposes of this study were to describe the demographic details, diagnosis data, information before and during ECMO support, and clinical outcomes for children with ECPR in Asia Pacific, evaluating their temporal changes and the risk factors associated with in-hospital mortality. This study retrospectively reviewed the data provided by the Extracorporeal Life Support Organization (ELSO) registry and made intensive analyses, focusing on this issue in the Asia Pacific region specifically.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Fuwai Hospital and the ELSO Steering Committee.

Data source

ELSO was founded in 1989 and has maintained the world's largest registry of ECMO use by collecting data from its active centers. In Asia Pacific, 52 centers from 12 countries and regions contribute data to the registry. After approval by the local Institutional Review Boards, centers gather information using a standardized data form voluntarily. Data use agreements between ELSO and member centers allow for the release of limited de-identified datasets for the purpose of scientific research and publication.

Study population and data categorization

ECPR, defined by the registry, means using ECLS as a part of initial resuscitation for cardiac arrest. Patients without cardiac arrest would not be considered, though ECMO is used to maintain stable hemodynamics. In this study, the data of ECPR in Asia Pacific from 1999 to 2016 were retrospectively analyzed and divided into two 9-year groups (Group 1: 1999–2007 and Group 2: 2008–2016) to assess temporal changes in demographics and outcomes. Patients should be younger than 18 years of age. Because only single-run details are recorded in the form of ELSO, patients with ECMO run number equal or larger than 2 were excluded from the study. The variables analyzed in this study included demographic data, diagnosis codes (International Classification of Diseases, 9th or 10th Revision, Clinical Modification), pre-ECMO mechanical ventilation information and arterial blood gas values, pre-ECMO support details, ECMO-related information (duration of ventilation before ECMO, hours of ECMO, pump flow at the 4th and 24th h during ECMO, ECMO complications, and others), and clinical outcomes. Two authors independently reviewed the diagnosis, pre-ECLS support, and complication codes. If there was any inconsistency, the corresponding author checked the original data and made a correction. Since some diagnostic groups were small, we defined two categories, named "congenital heart disease" (including all types of congenital anomalies of heart recorded in the registry) and "cerebrovascular disease" (including intracranial hemorrhage, occlusion and stenosis of cerebral arteries, and transient cerebral ischemia). Complications, including mechanical and physiologic ones, were categorized using unified codes determined by the ELSO registry.

Statistical analysis

The primary outcome measurement was defined as survival to hospital discharge. Demographic data and ECMO-related details were also compared between survivors and nonsurvivors. For categorical variables, data were presented by overall cases (n) and proportions (%) and compared with the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, normality of distribution was assessed by the Kolmogorov-Smirnov test. The normally distributed data were shown as the mean ± standard deviation, and the abnormally distributed data were shown as median (Q1, Q3). Student's t-test or the Mann-Whitney U-test was used to compare two groups, as appropriate. Multiple logistic regression models were established to explore risk factors associated with hospital death. The inclusion criterion of variables in regression models was a $P \leq 0.10$ in the bivariate analysis. The first model included demographic and pre-ECLS factors, the second model evaluated ECMO-related factors, and the third model analyzed ECMO complication information. All data were analyzed using SPSS version 23.0 software (IBM, Armonk, New York, USA). The statistical significance was set at a $P < 0.05$.

Results

Study population

A total of 351 patients younger than 18 years old whose data were contributed to ELSO underwent ECPR from 1999 to 2016 in Asia Pacific. Among them, thirty children whose ECMO run numbers were ≥2 were excluded from later analyses. Finally, 321 children were included in this study. The mean age of the study population was 4.1 (0.7, 58.1) months and 179 (55.8%) were males. Asian patients accounted for 42.7%. The overall survival rate was 50.8% (163/321). The number of ECPR episodes and survival rate per year are presented in Figure 1. Despite the sharp decrease in 2016 (which might be due to delayed reports), an increase in ECPR events could be found from only 1 in 1999 to 48 in 2013. The annual survival rate ranged from 0.0% to 70.4%.

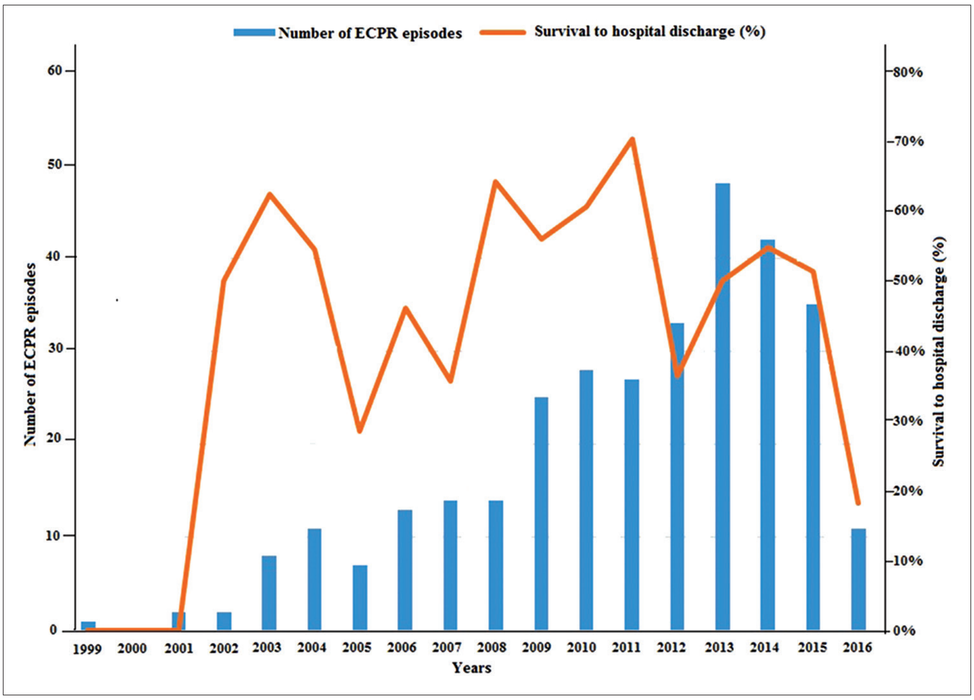

Figure 1: Annual episodes and survival rates from 1999 to 2016 in this study. ECPR: Extracorporeal cardiopulmonary resuscitation.

Period-based analysis

Table 1 shows the temporal changes in demographic and diagnostic variables between Group 1 (1999–2007; $n = 58$) and Group 2 (2008–2016; $n = 263$), as well as information before and during ECMO support. Although the survival rates were similar, the age and weight of children increased over time, accompanied by a smaller proportion of diagnoses of congenital heart disease and cardiogenic shock. Ventilator parameters and arterial blood gas values in the 6 h before ECMO support were worse in Group 2: the respiratory rate, pH, and HCO_3^- values were significantly lower in Group 2 than those in Group 1. Regarding pre-ECLS support, the use of vasopressor/inotropes, and vasodilator drugs dropped over time, while the use of steroids increased. Duration of ventilation before ECMO was significantly shorter in Group 2 than Group 1 ($P < 0.001$). The rates of ECMO complications showed an overall decrease over time periods, as expected, including oxygenator failure, surgical site hemorrhage, and dialysis use [Table 2].

Univariate and multiple logistic regression analyses of survival at hospital discharge

Comparisons of demographic features, diagnostic details, and ECMO-related information between survivors and nonsurvivors are provided in Table 3. Younger age and lower body weight were associated with survival. There was no significant difference in gender between the two groups ($P = 0.853$), while Asian race was more in nonsurvivors than survivors ($P < 0.001$). When compared with nonsurvivors, fewer patients suffered from sepsis and cerebrovascular diseases in survivors. Over 60% of survivors received anesthetic and neuromuscular blockers as pre-ECLS support, which was significantly different from nonsurvivors. Respiratory rate and peak inspiratory pressure (PIP) at the 24th h of ECMO support were lower in survivors, compared with nonsurvivors. ECMO complications, including disseminated intravascular coagulation (DIC), myocardial stunning, and neurological complications, were relatively rare in survivors (<10%). Three multiple logistic regression models of risk factors associated with mortality are shown in Table 4. Demographic and pre-ECLS factors (Model I), ECMO-related information (Model II), and ECMO complications (Model III) were evaluated to identify the risk factors associated with in-hospital mortality. Among pre-ECPR variables, Asian race was associated with increased odds of in-hospital mortality, and lower pH value before ECMO support indicated worse outcomes. In the second regression model, higher respiratory rate and PIP at the 24th h were related to lower survival. ECMO complications such as DIC and myocardial stunning confirmed by ultrasound and neurological complications were independently associated with increased odds of in-hospital mortality.

Discussion

This study retrospectively analyzed data extracted from the ELSO registry to describe changes in the clinical information of patients younger than 18 years who underwent ECPR in Asia Pacific from 1999 to 2016. A total of 321 patients were included in the study. They had an overall survival rate of 50.8%, which was slightly higher than the result of a previous international study (43%).[7] This finding might be attributed to regional disparities in economic and medical status, as well as the inclusion criteria for ECPR. With increases in age and weight and decreases in the proportions of diagnoses of congenital heart disease and cardiogenic shock, it seems that the indications for ECPR are expanding. Burke *et al*.[8] described the use of EPCR in victims of drowning, and Sawamoto *et al*.[9] showed the survival

Table 1: Comparison of demographic and clinical characteristics between two 9-year groups in this study

Characteristics	Group 1 (n = 58)	Group 2 (n = 263)	Statistical values	P
Age (months)	1.7 (0.3, 19.2)	5.6 (0.8, 64.9)	−2.93*	0.003
Weight (kg)	3.7 (3.0, 11.5)	6.0 (3.4, 20.3)	−3.14*	0.002
Male	34 (58.6)	145 (55.1)	0.21†	0.649
Race (Asian)	28 (48.3)	109 (41.4)	0.55†	0.458
Survival at hospital discharge	25 (43.1)	138 (52.5)	1.67†	0.196
Diagnosis				
Sepsis	7 (12.1)	13 (4.9)	3.00†	0.083
Arrhythmia	2 (3.4)	29 (11.0)	3.13†	0.077
Cerebrovascular disease	6 (10.3)	10 (3.8)	3.03†	0.082
Acute kidney failure	11 (19.0)	13 (4.9)	13.51†	0.001
Congenital heart disease	44 (75.9)	152 (57.8)	6.52†	0.011
Cardiogenic shock	21 (36.2)	19 (7.2)	36.59†	<0.001
Pre-ECLS information				
Ventilator parameters				
Respiratory rate (breath/min)	32 (24, 37)	26 (20, 30)	−2.25‡	0.025
FiO_2 (%)	100 (50, 100)	100 (100, 100)	−1.83‡	0.068
Arterial blood gas values				
pH	7.3 (7.0, 7.4)	7.1 (7.0, 7.3)	−1.98‡	0.048
HCO_3^- (mmol/L)	19.2 (13.0, 23.3)	16.0 (12.0, 21.0)	−2.07‡	0.039
Pre-ECLS support				
Vasopressor/inotropes	55 (94.8)	148 (56.3)	30.38†	<0.001
Vasodilator drugs	18 (31.0)	20 (7.6)	24.99†	<0.001
Bicarbonate	34 (58.6)	90 (34.2)	11.93†	0.001
Steroids	0 (0.0)	34 (12.9)	8.39†	0.004
ECMO information				
Duration of ventilation before ECMO (h)	18 (7, 59)	3 (1, 22)	−4.78‡	<0.001
Time of ECMO (h)	105 (64, 157)	94 (52, 152)	−0.74‡	0.459
Pump flow at 4th h ($ml \cdot kg^{-1} \cdot min^{-1}$)	114 (97, 138)	109 (64, 147)	−1.11‡	0.268
Pump flow at 24th h ($ml \cdot kg^{-1} \cdot min^{-1}$)	115 (95, 148)	115 (72, 141)	−0.97‡	0.334
FiO_2 at 24th h (%)	40 (21, 50)	40 (30, 50)	−1.82‡	0.068
PEEP at 24th h (cmH_2O)	8 (4, 10)	10 (6, 10)	−2.91‡	0.004
MAP at 24th h (cmH_2O)	11 (9, 12)	12 (10, 13)	−2.67‡	0.008

Data are presented as n (%) or median (Q1, Q3). *t values; †χ^2 values; ‡Z values. ECLS: Extracorporeal life support; FiO_2: Fraction of inspired oxygen; ECMO: Extracorporeal membrane oxygenation; PEEP: Positive end-expiratory pressure; MAP: Mean airway pressure; 1 cmH_2O = 0.098 kPa.

benefit of ECPR for patients of hypothermia.[8,9] Despite no apparent advance in survival rate between two groups in this study, the significantly lower pH and HCO_3^- values before ECMO support in Group 2 might indicate that more patients with complex and severe conditions received ECPR in the latter period. These results were similar to the results of a retrospective study involving 1796 adult patients.[10] Moreover, the decrease in the use of vasoactive drugs might indicate improvements in both technology and experience. It is worth noting that the use of steroids increased over time period. Although there is no consensus about steroid use during CPR, improved survival was not rare among studies worldwide, which could be explained by better hemodynamic stability and less ischemic damage induced by steroids.[11] Longer deployment times of ECMO during CPR have been associated with poor outcomes.[12-16] Medical institutions and clinical doctors have devoted themselves to developing new rapid-response systems to enhance the prognosis of those patients, some of which have shown positive effects.[17-19] It is no wonder why we saw a significant decrease in the duration of ventilation time before ECMO from the earlier period to the later one.

In accordance with expectations, the incidence of ECMO complications showed an overall decrease in this study including mechanical, hemorrhagic, neurological, renal, and infection-related complications. In 2010, Palanzo *et al.*[20] published a brief review about the evolution of ECLS, describing changes in oxygenators, pumps, anticoagulation monitoring, pressure monitoring, the newest circuits, and other factors. The polymethylpentene diffusion membranes, with all the inherent advantages of hollow-fiber membrane oxygenators, eliminated plasma leakage and extended maximum duration. Compared to roller pumps, magnetically levitated centrifugal pumps had better performance in the protection of blood elements and reduction of coagulation system activation. Moreover, advances in circuits allowed for smaller surface area, less priming, easier management, and longer duration. Fewer pediatric formulations of anticoagulation agents, lack of widespread experience, and limited expertise challenged anticoagulation and hemostasis

Table 2: Comparison of ECMO complications between two 9-year groups in this study

Items	Group 1 (*n* = 58)	Group 2 (*n* = 263)	χ^2	*P*
Mechanical complications				
Oxygenator failure	9 (15.5)	19 (7.2)	4.11	0.043
Clots in other parts	18 (31.0)	47 (17.9)	5.10	0.024
Hemorrhagic complications				
Cannulation site	12 (20.7)	56 (21.3)	0.01	0.919
Surgical site	13 (22.4)	28 (10.6)	5.91	0.015
Hemolysis (PFH >500 mg/L)	29 (50.0)	38 (14.4)	36.37	<0.001
DIC	4 (6.9)	9 (3.4)	0.72	0.397
Neurological complications				
Brain death	4 (6.9)	12 (4.6)	0.17	0.685
CNS infarction by US/CT	11 (19.0)	17 (6.5)	9.33	0.002
CNS hemorrhage by US/CT	2 (3.4)	24 (9.1)	1.37	0.243
Renal complications				
Serum creatinine 15–30 mg/L	19 (32.8)	36 (13.7)	12.17	<0.001
Dialysis use	9 (15.5)	8 (3.0)	12.36	<0.001
CAVHD use	6 (10.3)	4 (1.5)	9.51	0.002
Cardiac complications				
Arrhythmia	2 (3.4)	35 (13.3)	4.53	0.033
Hypertension requiring vasodilators	9 (15.5)	73 (27.8)	3.74	0.053
Other complications				
Culture proven infection	23 (39.7)	44 (16.7)	15.12	<0.001
Blood glucose <400 mg/L	4 (6.9)	29 (11.0)	0.88	0.349
Blood glucose >2400 mg/L	26 (44.8)	67 (25.5)	8.65	0.003
Blood pH <7.2 during ECMO	14 (24.1)	38 (14.4)	3.29	0.070
Blood pH >7.6 during ECMO	4 (6.9)	25 (9.5)	0.39	0.530

Data are presented as *n* (%). PFH: Plasma free hemoglobin; DIC: Disseminated intravascular coagulation; CNS: Central nervous system; US: Ultrasonography; CT: Computed tomography; CAVHD: Continuous arteriovenous hemodialysis; ECMO: Extracorporeal membrane oxygenation.

in children. Comparisons should be made to determine the optimal combination of coagulation monitoring parameters to achieve goal-directed anticoagulation management and better clinical outcomes.[21] In this study, we detected significant decreases in neurological and renal complications over time. A previous study reported that central nervous system (CNS) injury could occur in 22% of ECPR patients.[22] Some new therapies, such as active compression/decompression CPR with intrathoracic pressure regulation, heads-up CPR, sodium nitroprusside-enhanced CPR, and postconditioning strategies, have shown promising improvements in animal models as well as in early stages of human trials. Bundling them together could have the potential to bring better neurological survival after cardiac arrest.[23] The insufficiency of renal function might suggest worse outcomes for children receiving ECPR. A retrospective observational study performed by Smith *et al.*[24] showed that acute renal failure was associated with a significant increase in mortality. Various methods of dialysis, especially peritoneal dialysis, achieved varying degrees of success in ECMO patients.[25,26] Moreover, continuous venovenous hemofiltration could be beneficial to those patients for its tight control of fluid balance and decreased diuretic requirements, as reported by Wolf *et al.*[27] The decrease in the incidence of renal complications in this study might also be related to enhance circulatory support level and decreased use of vasoactive drugs. High blood glucose has been associated with decreased survival and poor neurological outcomes.[28,29] The improvements in hyperglycemia control during ECPR might improve CNS protection and in-hospital survival, though further study is necessary.

Comparisons were also performed between survivors and nonsurvivors. Asian patients accounted for 42.7% of subjects in this study and showed worse survival compared to other race categorizations. Mosca *et al.*[30] found that the Hispanic population had reduced survival in venovenous ECMO. Survival differences between racial subgroups and their possible factors are a worthy topic for further studies. Children with congenital heart disease were more likely to survive in this study and in Chan *et al.*'s report.[31] One possible explanation for this finding was that ECMO was often performed as a transitional method before and after operations, providing a chance of recovery for children. Anesthetic and neuromuscular blockers were more commonly used in the surviving group, which could be related to their more extensive use in children with congenital heart disease as transitional means before operations and their potential protection of the CNS and reduction of stress reactions.[23] In multiple logistic regression analysis, several factors were identified as independent risk factors of in-hospital mortality. Myocardial stunning confirmed by ultrasonography was a strong risk factor in this study (odds ratio: 10.23, 95% confidence interval: 1.20–87.41), in keeping with a previous study by Usui *et al.*[32]

Table 3: Comparison of demographic and clinical characteristics between survivors and nonsurvivors in this study

Items	Survivors (n = 163)	Nonsurvivors (n = 158)	Statistical values	P
Age (months)	2.3 (0.4, 57.2)	7.0 (0.9, 64.0)	−2.19*	0.029
Weight (kg)	4.6 (3.1, 16.1)	6.2 (3.5, 22.5)	−2.14*	0.032
Male	92 (56.4)	87 (55.4)	0.03†	0.853
Race (Asian)	54 (34.0)	83 (54.2)	13.03†	<0.001
Diagnosis				
Sepsis	5 (3.1)	15 (9.5)	5.67†	0.017
Cardiomyopathy	10 (6.1)	18 (11.4)	2.79†	0.095
Cerebrovascular disease	4 (2.5)	12 (7.6)	4.48†	0.034
Congenital heart disease	111 (68.1)	85 (53.8)	6.90†	0.009
Pre-ECLS information				
Arterial blood gas values				
pH	7.2 (7.0, 7.3)	7.1 (6.9, 7.3)	−1.91‡	0.057
HCO_3^- (mmol/L)	17.4 (12.7, 22.0)	16.0 (11.8, 21.0)	−1.54‡	0.124
Pre-ECLS support				
Anesthetic	110 (67.5)	76 (48.1)	12.37†	<0.001
Neuromuscular blockers	112 (68.7)	82 (51.9)	9.49†	0.002
Dobutamine	37 (22.7)	21 (13.3)	4.80†	0.029
ECMO information				
Duration of ventilation before ECMO (h)	5 (2, 23)	5 (2, 29)	−0.35‡	0.726
Time of ECMO (h)	95 (61, 143)	94 (31, 160)	−0.55‡	0.583
Pump flow at 4th h ($ml \cdot kg^{-1} \cdot min^{-1}$)	114 (78, 143)	108 (68, 147)	−0.32‡	0.746
Pump flow at 24th h ($ml \cdot kg^{-1} \cdot min^{-1}$)	111 (77, 136)	118 (80, 148)	−1.29‡	0.198
Respiratory rate at 24th h (breath/min)	10 (10, 18)	15 (10, 20)	−2.69‡	0.007
PIP at 24th h (cmH_2O)	20 (20, 24)	22 (20, 25)	−2.27‡	0.023
ECMO complications				
Clots in oxygenator	38 (23.3)	17 (10.8)	8.91†	0.003
Clots in other parts	45 (27.6)	20 (12.7)	11.10†	0.001
DIC	3 (1.8)	10 (6.3)	4.16†	0.041
Brain death	0 (0.0)	16 (10.1)	17.37†	<0.001
CNS infarction by US/CT	7 (4.3)	21 (13.3)	8.16†	0.004
CNS hemorrhage by US/CT	8 (4.9)	18 (11.4)	4.53†	0.033
Vasopressor/Inotropes using during ECLS	78 (47.9)	93 (58.9)	3.91†	0.048
Myocardial stunning by US	1 (0.6)	9 (5.7)	5.29†	0.021
Hypertension requiring vasodilators	53 (32.5)	29 (18.4)	8.46†	0.004

Data are presented as n (%) or median (Q1, Q3). *t values; †χ^2 values; ‡Z values. ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; PIP: Peak inspiratory pressure; DIC: Disseminated intravascular coagulation; CNS: Central nervous system; US: Ultrasonography; CT: Computed tomography; 1 cmH_2O = 0.098 kPa.

Table 4: Multiple regression models of risk factors for in-hospital mortality in children with ECPR

Factors	OR (95% CI)	P
Model I. Demographic and pre-ECLS factors		
Race (Asian)	2.98 (1.24–7.12)	0.014
pH	0.27 (0.08–0.88)	0.030
Model II. ECMO related factors		
Respiratory rate at 24th h (breath/min)	1.05 (1.01–1.09)	0.006
PIP at 24th h (cmH_2O)	1.06 (1.00–1.13)	0.050
Model III. ECMO complications		
DIC	4.51 (1.10–18.48)	0.036
Neurological complications	3.41 (1.87–6.23)	<0.001
Myocardial stunning by US	10.23 (1.20–87.41)	0.034

Model I: n = 247, Hosmer-Lemeshow test, P = 0.569; Model II: n = 274, Hosmer-Lemeshow test, P = 0.592; Model III: n = 321, Hosmer-Lemeshow test, P = 0.411. ECLS: Extracorporeal life support; ECMO: Extracorporeal membrane oxygenation; PIP: Peak inspiratory pressure; DIC: Disseminated intravascular coagulation; US: Ultrasonography; ECPR: Extracorporeal cardiopulmonary resuscitation; OR: Odds ratio; CI: Confidence interval;1 cmH_2O = 0.098 kPa.

To our knowledge, this study is the largest and, in fact, the only investigation of ECPR in children in Asia Pacific.

There some limitations in this study, which are as follows: (1) it was a retrospective study and the data included were uncontrolled; (2) there has been a sustained increase in active centers in ELSO, and not all ECPR cases in Asia Pacific were included in the registry; (3) only ECPR patients were analyzed, and this study could not assess the role of ECMO during CPR; and (4) it is unknown if the progress of technology and changes in anticoagulation strategy are directly related to the marked decline in mechanical and hemorrhagic complications. Further studies on related topics are required to benefit more patients.

In conclusion, the broader indications and decreased complication rates make EPCR to be applied more and more extensive in children in Asia Pacific region. ECMO complications such as myocardial stunning are independently associated with decreased survival.

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Conflicts of interest

There are no conflicts of interest.

References

1. Topjian AA, Berg RA, Nadkarni VM. Pediatric cardiopulmonary resuscitation: Advances in science, techniques, and outcomes. Pediatrics 2008;122:1086-98. doi: 10.1542/peds.2007-3313.
2. Hill JG, Bruhn PS, Cohen SE, Gallagher MW, Manart F, Moore CA, *et al.* Emergent applications of cardiopulmonary support: A multiinstitutional experience. Ann Thorac Surg 1992;54:699-704. doi: 10.1016/0003-4975(92)91014-Z.
3. Raymond TT, Cunnyngham CB, Thompson MT, Thomas JA, Dalton HJ, Nadkarni VM, *et al.* Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory in hospital pediatric cardiac arrest: A report from the National Registry of Cardiopulmonary Resuscitation. Pediatr Crit Care Med 2010;11:362-71. doi: 10.1097/PCC.0b013e3181c0141b.
4. Thiagarajan RR, Laussen PC, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. Circulation 2007;116:1693-700. doi: 10.1161/CIRCULATIONAHA.106.680678.
5. Naim MY, Topjian AA, Nadkarni VM. CPR and E-CPR: What is new? World J Pediatr Congenit Heart Surg 2012;3:48-53. doi: 10.1177/2150135111421353.
6. de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, *et al.* Part 12: Pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S526-42. doi: 10.1161/CIR.0000000000000266.
7. Barbaro RP, Paden ML, Guner YS, Raman L, Ryerson LM, Alexander P, *et al.* Pediatric extracorporeal life support organization registry international report 2016. ASAIO J 2017;63:456-63. doi: 10.1097/MAT.0000000000000603.
8. Burke CR, Chan T, Brogan TV, Lequier L, Thiagarajan RR, Rycus PT, *et al.* Extracorporeal life support for victims of drowning. Resuscitation 2016;104:19-23. doi: 10.1016/j.resuscitation.2016.04.005.
9. Sawamoto K, Bird SB, Katayama Y, Maekawa K, Uemura S, Tanno K, *et al.* Outcome from severe accidental hypothermia with cardiac arrest resuscitated with extracorporeal cardiopulmonary resuscitation. Am J Emerg Med 2014;32:320-4. doi: 10.1016/j.ajem.2013.12.023.
10. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV, *et al.* ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. Resuscitation 2017;112:34-40. doi: 10.1016/j.resuscitation.2016.12.009.
11. Tsai MS, Chuang PY, Yu PH, Huang CH, Tang CH, Chang WT, *et al.* Glucocorticoid use during cardiopulmonary resuscitation may be beneficial for cardiac arrest. Int J Cardiol 2016;222:629-35. doi: 10.1016/j.ijcard.2016.08.017.
12. Huang SC, Wu ET, Chen YS, Chang CI, Chiu IS, Wang SS, *et al.* Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. Crit Care Med 2008;36:1607-13. doi: 10.1097/CCM.0b013e318170b82b.
13. Tajik M, Cardarelli MG. Extracorporeal membrane oxygenation after cardiac arrest in children: What do we know? Eur J Cardiothorac Surg 2008;33:409-17. doi: 10.1016/j.ejcts.2007.12.018.
14. Sivarajan VB, Best D, Brizard CP, Shekerdemian LS, d'Udekem Y, Butt W, *et al.* Duration of resuscitation prior to rescue extracorporeal membrane oxygenation impacts outcome in children with heart disease. Intensive Care Med 2011;37:853-60. doi: 10.1007/s00134-011-2168-6.
15. Huang L, Li T, Xu L, Hu XM, Duan DW, Li ZB, *et al.* Performance of multiple risk assessment tools to predict mortality for adult respiratory distress syndrome with extracorporeal membrane oxygenation therapy: An external validation study based on Chinese single-center data. Chin Med J 2016;129:1688-95. doi: 10.4103/0366-6999.185871.
16. Wang ZY, Li T, Wang CT, Xu L, Gao XJ. Assessment of 1-year outcomes in survivors of severe acute respiratory distress syndrome receiving extracorporeal membrane oxygenation or mechanical ventilation: A Prospective observational study. Chin Med J 2017;130:1161-8. doi: 10.4103/0366-6999.205847.
17. Su L, Spaeder MC, Jones MB, Sinha P, Nath DS, Jain PN, *et al.* Implementation of an extracorporeal cardiopulmonary resuscitation simulation program reduces extracorporeal cardiopulmonary resuscitation times in real patients. Pediatr Crit Care Med 2014;15:856-60. doi: 10.1097/PCC.0000000000000234.
18. Alsoufi B, Awan A, Manlhiot C, Guechef A, Al-Halees Z, Al-Ahmadi M, *et al.* Results of rapid-response extracorporeal cardiopulmonary resuscitation in children with refractory cardiac arrest following cardiac surgery. Eur J Cardiothorac Surg 2014;45:268-75. doi: 10.1093/ejcts/ezt319.
19. Mattke AC, Stocker CF, Schibler A, Alphonso N, Johnson K, Karl TR, *et al.* A newly established extracorporeal life support assisted cardiopulmonary resuscitation (ECPR) program can achieve intact neurological outcome in 60% of children. Intensive Care Med 2015;41:2227-8. doi: 10.1007/s00134-015-4036-2.
20. Palanzo D, Qiu F, Baer L, Clark JB, Myers JL, Undar A, *et al.* Evolution of the extracorporeal life support circuitry. Artif Organs 2010;34:869-73. doi: 10.1111/j. 1525-1594.2010.01127.x.
21. Saini A, Spinella PC. Management of anticoagulation and hemostasis for pediatric extracorporeal membrane oxygenation. Clin Lab Med 2014;34:655-73. doi: 10.1016/j.cll.2014.06.014.
22. Barrett CS, Bratton SL, Salvin JW, Laussen PC, Rycus PT, Thiagarajan RR, *et al.* Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation. Pediatr Crit Care Med 2009;10:445-51. doi: 10.1097/PCC.0b013e318198bd85.
23. Moore JC, Bartos JA, Matsuura TR, Yannopoulos D. The future is now: Neuroprotection during cardiopulmonary resuscitation. Curr Opin Crit Care 2017;23:215-22. doi: 10.1097/MCC.0000000000000405.
24. Smith AH, Hardison DC, Worden CR, Fleming GM, Taylor MB. Acute renal failure during extracorporeal support in the pediatric cardiac patient. ASAIO J 2009;55:412-6. doi: 10.1097/MAT.0b013e31819ca3d0.
25. Bojan M, Gioanni S, Vouhé PR, Journois D, Pouard P. Early initiation of peritoneal dialysis in neonates and infants with acute kidney injury following cardiac surgery is associated with a significant decrease in mortality. Kidney Int 2012;82:474-81. doi: 10.1038/ki.2012.172.
26. Prodhan P, Imamura M, Garcia X, Byrnes JW, Bhutta AT, Dyamenahalli U, *et al.* Abdominal compartment syndrome

in newborns and children supported on extracorporeal membrane oxygenation. ASAIO J 2012;58:143-7. doi: 10.1097/MAT.0b013e318241ac4c.
27. Wolf MJ, Chanani NK, Heard ML, Kanter KR, Mahle WT. Early renal replacement therapy during pediatric cardiac extracorporeal support increases mortality. Ann Thorac Surg 2013;96:917-22. doi: 10.1016/j.athoracsur.2013.05.056.
28. Nurmi J, Boyd J, Anttalainen N, Westerbacka J, Kuisma M. Early increase in blood glucose in patients resuscitated from out-of-hospital ventricular fibrillation predicts poor outcome. Diabetes Care 2012;35:510-2. doi: 10.2337/dc11-1478.
29. Wang CH, Huang CH, Chang WT, Tsai MS, Yu PH, Wu YW, *et al*. Associations between blood glucose level and outcomes of adult in-hospital cardiac arrest: A retrospective cohort study. Cardiovasc Diabetol 2016;15:118. doi: 10.1186/s12933-016-0445-y.
30. Mosca MS, Narotsky DL, Liao M, Mochari-Greenberger H, Beck J, Mongero L, *et al*. Survival following veno-venous extracorporeal membrane oxygenation and mortality in a diverse patient population. J Extra Corpor Technol 2015;47:217-22.
31. Chan T, Thiagarajan RR, Frank D, Bratton SL. Survival after extracorporeal cardiopulmonary resuscitation in infants and children with heart disease. J Thorac Cardiovasc Surg 2008;136:984-92. doi: 10.1016/j.jtcvs.2008.03.007.
32. Usui Y, Chikamori T, Nakajima K, Hida S, Yamashina A, Nishimura T, *et al.* Prognostic value of post-ischemic stunning as assessed by gated myocardial perfusion single-photon emission computed tomography: A subanalysis of the J-ACCESS study. Circ J 2010;74:1591-9. doi: 10.1253/circj.CJ-10-0074.

亚太地区儿童体外心肺复苏：对体外生命支持组织登记数据的回顾性分析

摘要

背景：随着体外膜氧合技术（ECMO）的不断发展，其在心肺复苏过程中的应用正引起越来越广泛的关注。本研究的目的在于回顾性分析1999–2016年国际体外生命支持组织（ELSO）亚太地区儿童体外心肺复苏（ECPR）的登记数据，对其发展趋势进行描述并探讨影响ECPR患儿生存的独立危险因素。

方法：本研究回顾性分析了1999年1月至2016年12月期间在亚太地区接受ECPR治疗且年龄小于18岁的儿童患者的登记数据，信息来源于ELSO组织。患者首先按接受ECPR治疗的时间分成两组（第1组：1999–2007年；第2组：2008–2016年），比较两组患者的基线资料，ECMO支持前信息，ECMO支持期间信息，ECMO相关并发症等资料。随后，将患者按临床结局分为存活组及死亡组，比较其相关信息，并应用单元和多元logistic回归分析探索影响ECPR患儿生存的独立危险因素。

结果：共有321名患儿纳入本研究，总生存率为50.8%。尽管第1组及第2组患儿存活率相似（43.1% vs. 52.5%, χ^2 = 1.67, P=0.196），但第2组患儿的平均年龄 (第1组：1.7 [0.3, 19.2]月vs. 第2组：5.6 [0.8, 64.9] 月, t=−2.93, P=0.003) 及体重 (第1组：3.7 [3.0, 11.5] kg vs. 第2组：6.0 [3.4, 20.3] kg, t=−3.14, P=0.002)均高于第1组，且先天性心脏病（第1组：75.9% vs. 第2组：57.8%, χ^2 = 6.52, P=0.011）及心源性休克（第1组：36.2% vs. 第2组：7.2%, χ^2 = 36.59, P＜0.001）占比更低。相较第1组，第2组患儿ECMO支持期间并发症的发生率有所下降，尤其是肾脏相关并发症。多元logistic回归分显示ECMO相关并发症中，弥散性血管内凝血（DIC）、心肌顿抑及神经系统并发症是影响ECPR患儿生存的独立危险因素。

结论：ECPR治疗可以改善心脏骤停患儿的存活率，其适应症越来越广，并发症越来越少。ECMO相关并发症，如超声证实的心肌顿抑是影响ECPR患儿生存的独立危险因素。