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Clinical Research

Extracorporeal Cardiopulmonary Resuscitation in Infants: Outcomes and Predictors of Mortality

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Background: Extracorporeal cardiopulmonary resuscitation (E-CPR) plays an indispensable role when resuscitation fails; however, extracorporeal life support (ECLS) in infants is different from that in adults. The objective of this study was to evaluate the outcomes of E-CPR in infants.
Methods: A single-center retrospective study was conducted, analyzing 51 consecutive patients (age <1 year) who received E-CPR for in-hospital cardiac arrest between 2010 and 2021.
Results: The median age and body weight was 51 days (interquartile range [IQR], 17–111 days) and 3.4 kg (IQR, 2.9–5.1 kg), respectively. The cause of arrest was cardiogenic in 45 patients (88.2%), and 48 patients (94.1%) had congenital cardiac anomalies. The median conventional cardiopulmonary resuscitation (C-CPR) time before the initiation of ECLS was 77 minutes (IQR, 61–103 minutes) and duration of ECLS was 7 days (IQR, 3–12 days). There were 36 in-hospital deaths (70.6%), and another patient survived after heart transplantation. In the multivariate analysis, single-ventricular physiology (odds ratio [OR], 5.05; p=0.048), open sternum status (OR, 8.69; p=0.013), and C-CPR time (OR, 1.47 per 10 minutes; p=0.021) were significant predictors of in-hospital mortality. In a receiver operating characteristic curve, the optimal cut-off of C-CPR time was 70.5 minutes. The subgroup with early E-CPR (C-CPR time <70.5 minutes) showed a tendency for lower in-hospital mortality tendency (54.5% vs. 82.8%, p=0.060), albeit not statistically significant.
Conclusion: If resuscitation fails in an infant, E-CPR could be a life-saving option. It is crucial to improve C-CPR quality and shorten the time before ECLS initiation.

Keywords: Pediatric cardiopulmonary resuscitation, Conventional cardiopulmonary resuscitation, Extracorporeal cardiopulmonary resuscitation, Pediatric extracorporeal membrane oxygentation

Introduction

Extracorporeal cardiopulmonary resuscitation (E-CPR) is defined as the application of extracorporeal life support (ECLS) during ongoing conventional cardiopulmonary resuscitation (C-CPR) [1]. The use of E-CPR for the adult population was started in 1976, while its first implementation in the pediatric population was reported in 1992 [2,3]. Currently, early initiation of E-CPR is recommended in patients with theoretically reversible causes [4]. Since E-CPR has been widely applied, numerous studies have reported better survival and neurocognitive outcomes after E-CPR than after C-CPR [5-9].

In the meantime, the application of ECLS in young infants or neonates has several theoretical differences from its use in the adult population or older children. First of all, central direct cannulation into the great vessels or heart chambers is frequently required because of the inadequate size of the peripheral vessels. Secondly, the etiology of cardiac arrest, as well as its association with an underlying congenital heart defect and cardiac surgery, might differ between these populations. Therefore, this study sought to analyze the clinical outcomes of E-CPR in young infants and to identify factors associated with survival.

Methods

Patients and definitions

The Asan medical center institutional review board approved data collection and analysis, and the requirement for informed consent was waived (approval number, 2021-0660; date of approval, April 30, 2021). This study retrospectively analyzed consecutive patients who received E-CPR for in-hospital cardiac arrest between January 2010 and March 2021. Patients aged less than 1 year at the time of cardiac arrest were included in the study population. The initiation of ECLS was considered in patients who were unable to be resuscitated by prolonged C-CPR and who did not have an irreversible underlying disease. Only patients in whom ECLS was started during ongoing C-CPR without recovery of spontaneous circulation (ROSC) were included. In each patient, data from the first E-CPR were used for analysis.

All data were retrospectively collected by review of medical records. Patients' baseline profiles and underlying diagnoses were analyzed. For categorizing underlying cardiac defects, patients with 2-series circulation without significant shunt lesions were considered to have biventricular circulation. At the time of cardiac arrest, the time, the duration of the C-CPR, the location, and the initial characteristics of the patient were collected. The duration of C-CPR was defined as the interval between the initial documentation of cardiac arrest and the initiation of ECLS pump flow. The ECLS strategies, profiles, and clinical outcomes were reviewed. Outcomes of interest were ECLS weaning and decannulation, in-hospital mortality, documented end-organ damage (e.g., cerebral infarction, intra-abdominal organ dysfunction), and long-term survival.

Extracorporeal life support protocols

The decision to initiate ECLS during C-CPR was made based on the clinical situation. If a patient did not show ROSC after 3 to 5 regular cycles of C-CPR and efforts to correct the underlying etiology of cardiac arrest, ECLS implementation was considered. We did not exclude patients from the initiation of E-CPR due to an extended duration of C-CPR if the quality of C-CPR was promising (e.g., early identification of cardiac arrest, minimal interruption of C-CPR, favorable vital signs during C-CPR). However, E-CPR initiation was not considered in patients who had documented irreversible end-organ damage or whose legal guardians were unwilling to apply ECLS. All cannulations were done surgically by an experienced pediatric cardiac surgeon. The cannulation site was decided based on the patient's underlying characteristics. For example, in patients who had undergone cardiac surgery via sternotomy several days before cardiac arrest, the preferred approach was central with cannulation at the ascending aorta and right atrial appendage. The preferred vessels for peripheral cannulation were the right common carotid artery and right internal jugular vein if the sizes of these vessels were sufficient for cannulation. Routine additional cannulation for decompression of the left heart was not done; however, in patients with pulmonary congestion on a chest radiograph or who showed spontaneous echocardiographic contrast within the left heart chambers, additional cannulation was done in the left atrial appendage or individual pulmonary vein. The size of the cannula was determined by the target vessel size and the patient's body surface area.

After the cannulation of arterial and venous cannulas, the targeted flow rate was determined to provide sufficient blood flow within the range of the normal cardiac index for each patient. The targeted flow rate was upregulated in patients with systemic-pulmonary shunt lesions (e.g., Blalock-Taussig shunt) or a septic condition. Optimization of the targeted flow rate was determined by the patient's perfusion demand, cardiopulmonary status, and the size of the used cannulas. A hemostatic clip was temporarily applied to control the blood run-off in patients with severe pulmonary over-circulation because of the shunt lesions. The use of inotropes was minimized after the initiation of ECLS; however, vasopressors were used in patients with profound hypotension. Mechanical ventilation was optimized to decrease barotrauma of the lung. Hypothermia was not routinely used in all patients; however, body temperature was managed to prevent hyperthermia. Intravenous heparin was used for anticoagulation with targeted activated clotting time of 150 seconds or a targeted activated partial thromboplastin time of 60 seconds in patients without significant bleeding. When a patient showed improved ventricular function on transthoracic echocardiography, ECLS weaning was started. Intravenous inotropes, vasopressors, and ventilator supply were initiated, and ECLS support was gradually decreased by about 30% of the normal cardiac index for 1–3 days. In patients who had promising vital signs and arterial blood gas profiles, ECLS was terminated. If the patients had no sign of deterioration for about 30 minutes, decannulation was done.

Statistical methods

To assess the normality of the data distribution, the Sha-

piro-Wilk test was used. Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as means±standard deviations or medians and interquartile ranges according to the distribution of the variables. The chi-square test with the Fisher exact test was applied to compare intergroup differences of categorical variables, and the Student t-test or Mann-Whitney U test was used to compare continuous variables. Logistic regression analysis was used to identify factors associated with in-hospital adverse outcomes. Variables showing p-values less than 0.1 in the univariate analysis were used in the multivariate analysis, which was conducted to identify significant risk factors for the outcome. Significant variables were obtained by stepwise selection in a backward direction, excluding the variables showing p-values more than 0.05. The goodness of fit of the multivariate model was tested with the Nagelkerke R^2 measure. A receiver operating characteristic (ROC) curve was made to determine the optimal cut-off value (i.e., the value with the greatest Youden index). Kaplan-Meier survival curves and the log-rank test were used to analyze time-dependent events during long-term follow-up. Linear mixed models were constructed to evaluate variables that changed over time (e.g., arterial blood gas analysis [ABGA] profile changes during C-CPR). A p-value less than 0.05 was considered statistically significant. All analyses were performed using R software ver. 4.0.5 (https://www.r-project.org/).

Results

Baseline characteristics

During the study period, 51 patients had E-CPR. The median age and body weight at the time of cardiac arrest were 51 days (interquartile range [IQR], 17 to 110.5 days) and 3.4 kg (IQR, 2.9 to 5.1 kg), respectively. Congenital heart disease was diagnosed in 48 patients (94.1%), while 18 of them (18/48, 37.5%) had biventricular physiology. Before cardiac arrest, 32 patients (62.7%) had a cardiac operation within 48 hours, and 23 patients (45%) had an open sternum status at the time of the cardiac arrest. The common category of the previous operation was stage 1 palliation (21 patients; 21/32, 65.6%), followed by anatomical repair (10 patients; 10/32, 31.2%). A majority of patients had a cardiogenic etiology of cardiac arrest (45 patients, 88.2%), while bradycardia or pulseless electrical activity (46 patients, 90.2%) was the most common initial rhythm. Forty-seven cardiac arrests (92.2%) occurred in the intensive care unit, and 2 episodes started in the operating room. One of the 2 patients who had E-CPR in the operating room underwent ELCS initiation during a hybrid procedure for stent insertion in the right ventricular tract. Another patient had cardiac arrest while preparing for intensive care unit transfer after the Rastelli operation. An advanced airway was present in 49 patients (96.1%), as well as a central line in 46 patients (90.2%). Central cannulation was performed in 47 patients (92.2%), and the median C-CPR time before the initiation of ECLS was 77 minutes (IQR, 60.5 to 102.5 minutes). The baseline characteristics and features of cardiac arrest are summarized in Table 1.

Clinical outcomes

The median duration of ECLS was 7 days (IQR, 3 to 12 days). There were 36 in-hospital deaths (70.6%). Thirty patients died because of profound cardiac dysfunction and ECLS weaning failure. Initially, ECLS was able to be weaned and decannulation could be performed in 22 patients (43.1%). However, 3 patients had re-initiation of ECLS and died subsequently, while another died within less than 3 days without another ECLS run. Among the remaining patients, 4 additional patients died. The causes of death in these patients were sepsis in 1 patient (at 59 days after ECLS weaning), severe capillary leak syndrome in 1 patient (at 50 days after ECLS weaning), and untreatable intramyocardial dissecting hematoma in one patient (32 days after ECLS weaning). Another patient underwent a Norwood operation 9 days after ECLS weaning; however, this patient experienced a postoperative cardiopulmonary bypass weaning failure, which was followed by required re-initiation of ECLS and mortality (at 14 days after initial ECLS weaning).

Finally, 14 patients survived to discharge after ECLS weaning, and 1 more could survive to discharge after heart transplantation. In survivors after weaning (14 patients), the median duration of ECLS was 4 days (IQR, 3 to 6 days), while the duration was 9 days (IQR, 3 to 13 days) in patients who could not achieve ECLS weaning or survived after weaning (p=0.007). Of 15 patients who survived to discharge, brain damage was found in 8 patients (8/25, 32%). The full profile of early outcomes and the clinical flow are illustrated in Fig. 1. Only abnormal findings on post-cardiac arrest surveillance imaging studies were found in 6 patients, while 2 patients had abnormal findings with a neurologic deficit (quadriplegia in all 2 patients). One patient, who required heart transplantation, had concomitant kidney damage requiring permanent dialysis. The median follow-up duration was 0.5 months (IQR, 0.3 to 12.8 months),

Table 1. Baseline characteristics of the study population

Characteristic	Value
Baseline characteristics	
Male sex	27 (52.9)
Age (day)	51 (17–110.5)
Weight (kg)	3.42 (2.92–5.12)
Genetic abnormality	3 (5.9)
Underlying major defects	
Congenital heart disease	48 (94.1)
Biventricular physiology	18 (35.3)
Cardiomyopathy	2 (3.9)
Congenital diaphragmatic hernia	1 (2.0)
Previous cardiac operation	32 (62.7)
Stage 1 palliation	21 (41.2)
Anatomical repair	10 (19.6)
Bidirectional cavopulmonary anastomosis	1 (2.0)
Presence of systemic-pulmonary shunt	18 (35.3)
Features related to cardiac arrest	
Etiology	
Cardiogenic	45 (88.2)
Respiratory	5 (9.8)
Unknown	1 (2.0)
Initial rhythm	
Bradycardia with profound hypotension/pulseless electrical activity	46 (90.2)
Ventricular fibrillation/pulseless ventricular tachycardia	4 (7.8)
Unknown	1 (2.0)
Location	
Intensive care unit	47 (92.2)
Operating room	2 (3.9)
Emergency room	1 (2.0)
Ward	1 (2.0)
Presence of an advanced airway	49 (96.1)
Presence of a central line	46 (90.2)
Open sternum status	23 (45.1)
Conventional cardiopulmonary resuscitation time (min)	77.00 (60.50–102.50)
Approach	
Central	47 (92.2)
Peripheral	4 (7.8)

Values are presented as number (%) or median (interquartile range).

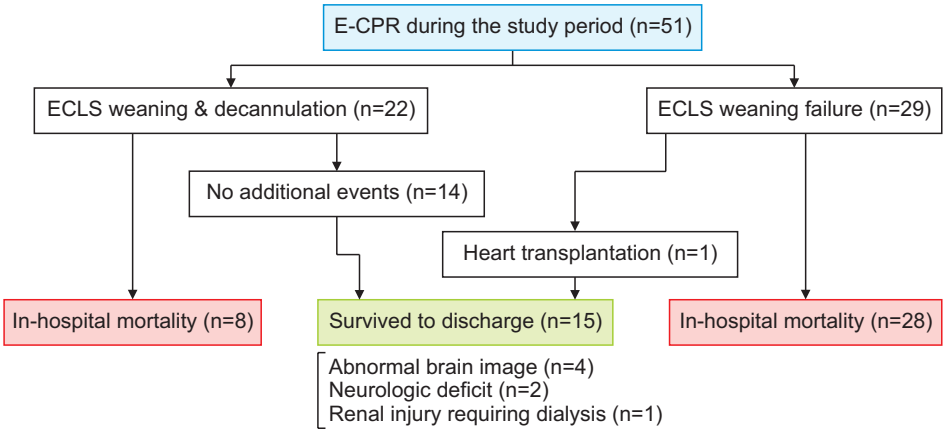

Fig. 1. The clinical flow of the study population. E-CPR, extracorporeal cardiopulmonary resuscitation; ECLS, extracorporeal life support.

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and the survival rate at 12 months was 26.6% (Fig. 2).

Predictors of in-hospital mortality

In univariate logistic regression analysis, age at cardiac arrest (odds ratio [OR], 0.99; p=0.050), single-ventricular physiology (OR, 4.50; p=0.021), presence of systemic-pulmonary shunt (OR, 5.20; p=0.047), and open sternum status (OR, 5.00; p=0.027) were associated with in-hospital mortality. In the multivariate logistic regression model (Nagelkerke R^2=0.45), single-ventricular physiology (OR, 5.05; p=0.048), open sternum status (OR, 8.69; p=0.013), and prolonged C-CPR time (OR, 1.47 per 10 minutes; p=0.021) were risk factors for in-hospital mortality (Table 2).

Duration of conventional cardiopulmonary resuscitation

Using the ROC curve (area under the curve, 0.661), the optimal cut-offs of C-CPR duration were found at 70.5 minutes (specificity, 0.67; sensitivity, 0.67), and at 103.5 minutes (specificity, 1.00; sensitivity, 0.333) (Fig. 3A). Using the optimal cut-off value of 70.5 minutes, the entire study population was stratified into 2 groups: the early E-CPR group (22 patients) and the late E-CPR group (29 patients). The late E-CPR group showed a higher tendency for in-hospital mortality (82.8% versus 54.5%, p=0.060), as well as 1-year mortality (82.8% versus 41.0%, log-rank p=0.052), although the difference was not statistically significant (Fig. 3B). A subgroup analysis was done on 43 patients who had ABGA results during C-CPR. Initial ABGA was done at a median of 10 minutes (IQR, 6.5 to 22.5 days) after cardiac arrest. In the initial ABGA, the median pH and lactate levels were 7.19 (IQR, 7.03 to 7.44) and 11.9 mmol/L (IQR, 6.8 to 14.9 mmol/L), respectively. The linear mixed model revealed that during C-CPR, pH decreased significantly (–0.03 per 10 minutes, p<0.001), and lactate increased significantly (0.62 mmol/L per 10 minutes, p<0.001) over time (Fig. 4).

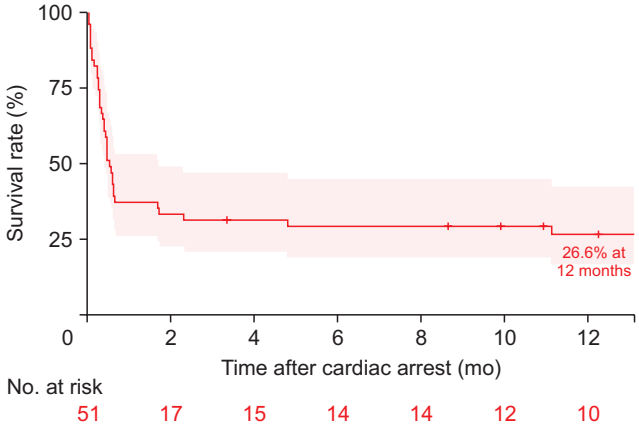

Fig. 2. Overall survival in the entire study population.

Discussion

Numerous studies have demonstrated the survival benefit and encouraging outcomes after E-CPR [5,9-12]. Although immense resources are required to enable the timely utilization of E-CPR for pediatric patients, it has been widely applied [13-15]. This study demonstrated the effectiveness of E-CPR, especially in young infants. The majority of the study population experienced cardiac arrest, especially during the postoperative period after surgery for congenital heart disease. It is noteworthy that the survival-to-discharge rate was 29.4%, which was somewhat disappointing, but a considerable proportion of patients who

Table 2. Results of logistic regression analysis for in-hospital mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (day)	0.99 (0.98–1.00)	0.050		
Weight (kg)	0.72 (0.49–1.05)	0.086		
Genetic abnormality	0.82 (0.07–9.83)	0.88		
Congenital heart disease	1.21 (0.10–14.50)	0.88		
Single-ventricular physiology	4.50 (1.25–16.17)	0.021	5.05 (1.01–25.27)	0.048
Presence of systemic-pulmonary shunt	5.20 (1.02–26.47)	0.047		
Open sternum status	5.00 (1.20–20.81)	0.027	8.69 (1.77–57.41)	0.013
Cardiogenic etiology	0.44 (0.05–4.15)	0.48		
C-CPR time (10-minute intervals)	1.22 (0.98–1.51)	0.078	1.47 (1.12–2.17)	0.021
Central cannulation	2.62 (0.33–20.55)	0.36		

OR, odds ratio; CI, confidence interval; C-CPR, conventional cardiopulmonary resuscitation.

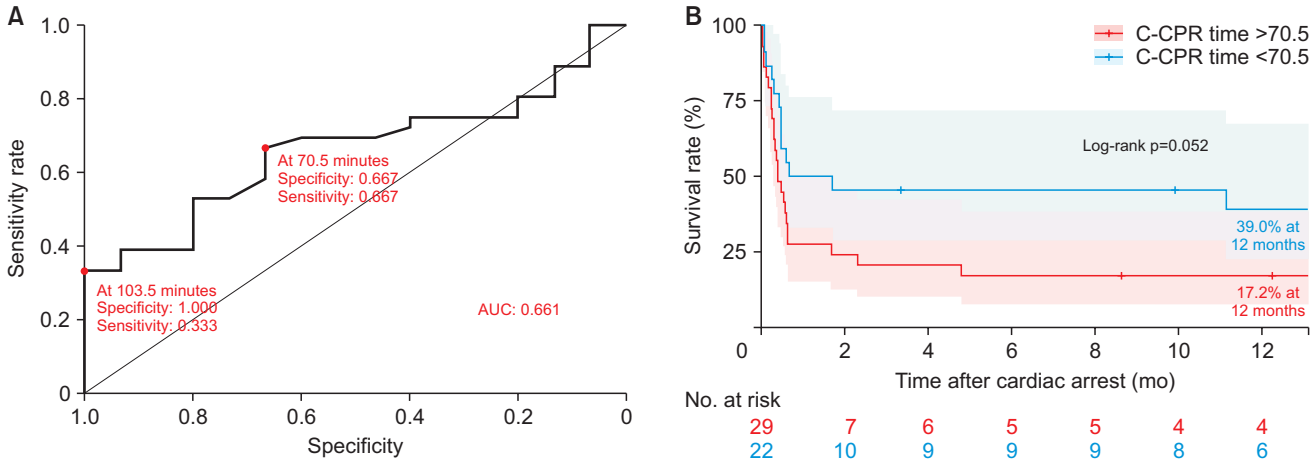

Fig. 3. (A) Receiver operating characteristic curve and optimal cut-off of conventional cardiopulmonary resuscitation time for predicting in-hospital mortality. (B) Kaplan-Meier survival curve stratified by the optimal conventional cardiopulmonary resuscitation time of 79.5 minutes. AUC, area under the curve; C-CPR, conventional cardiopulmonary resuscitation time.

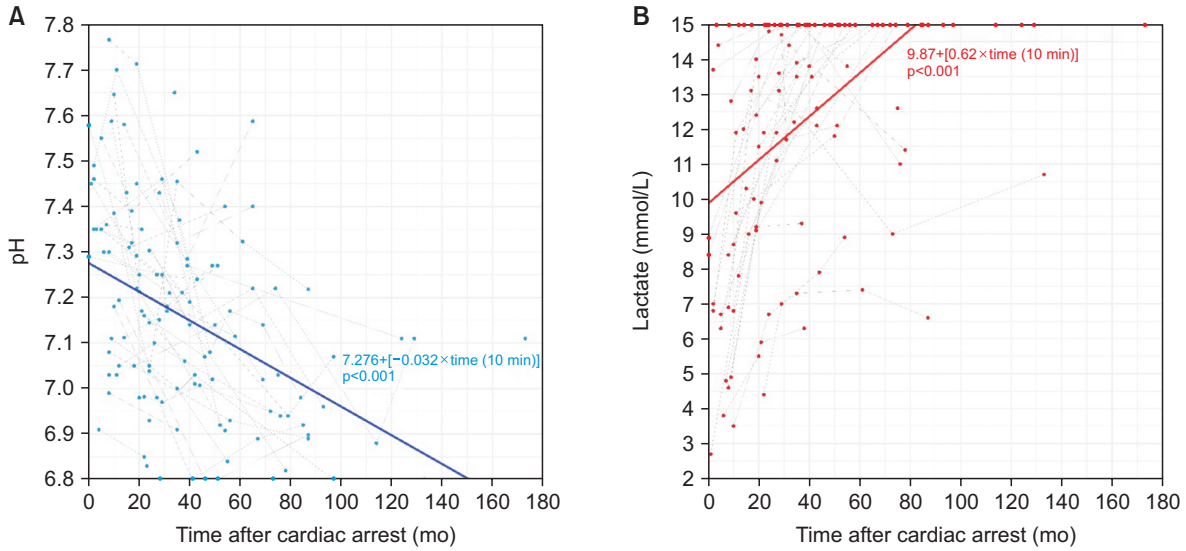

Fig. 4. (A, B) Changes in pH and lactate in arterial blood gas analysis during conventional cardiopulmonary resuscitation.

eventually died benefited from E-CPR.

Lasa et al. [7] reported improved survival and neurological outcomes in children with E-CPR than with C-CPR alone. The application of E-CPR has been recommended in pediatric patients with refractory cardiac arrest [16,17]. A programmed E-CPR protocol and preparation would benefit E-CPR survival. Kane et al. [15] reported a 51% rate of survival to discharge with the aid of a programmed E-CPR protocol, which provided a median C-CPR time of 33 minutes. Their program involved early decision-making to apply ECLS in patients who could not achieve ROSC after 2 cycles of C-CPR. They also had in-hospital physicians and pre-primed circuits. In another study by Alsoufi et al. [18], the reported survival-to-discharge rate and duration of C-CPR were 41% and 32 minutes, respectively. They suggested strategies to minimize the time for the initiation of ECLS, such as leaving the chest open after cardiac surgery and preparing snare sutures for cannulation. Although strategic preparation to reduce the time for initiation of ECLS is essential, the requirements for resources, which include readily available devices for ECLS and experts for cannulation, are substantial. By contrast, preparing these resources after the onset of cardiac arrest takes considerable time, resulting in worse outcomes.

In our study, the median duration of C-CPR was 77 minutes, which was relatively long. The main reason for the long C-CPR duration could have been a lack of in-house on-duty surgeons for ECLS cannulation and pre-primed ECLS circuit. Another problem could be late decision-making to start E-CPR. Recently, upon cardiac arrest, we intended to prepare ECLS promptly and gather surgical teams immediately to minimize the C-CPR time. As a result, the C-CPR time (69 minutes versus 88.5 minutes, p=0.06) and survival to discharge (39.1% versus 17.9%, p=0.09) rates showed improvements—albeit without reaching statistical significance—in more the recent era within the entire study period (since 2015, 23 patients). Several attempts should be made to reduce C-CPR duration and to improve clinical outcomes. First of all, it is imperative to initiate ECLS before arrest. Therefore, clinicians in intensive care teams should always consider preemptive ECLS application, as well as early contact with the cardiac surgical team, once cardiac arrest is already evident. Furthermore, a readily available prepared ECLS system is mandatory. This includes not only prepared ECLS circuits, but also blood products. Type-O blood products could be used for immediate preparation in several situations. Furthermore, a comprehensive system for surgical procedures for ECLS implementation (e.g., surgical teams and instruments) should always be prepared and utilized promptly after C-CPR has commenced.

In the meantime, several studies have reported the influence of C-CPR time. Some have demonstrated an association between prolonged C-CPR time and worse clinical outcomes [19-22], whereas others showed no associations [23-26]. We demonstrated the negative impact of prolonged C-CPR time on clinical outcomes. Our study cohort encompassed a wide range of C-CPR durations; therefore, the impact of C-CPR duration could be clearly demonstrated. Furthermore, the wide distribution of C-CPR duration could help us identify the optimal cut-off value for predicting mortality. We thought that it was reasonable for the quality of C-CPR to be directly related to clinical outcomes, and the duration of C-CPR would be a clear indicator of the overall quality of C-CPR. Therefore, it is plausible that a longer duration of C-CPR would be associated with worse outcomes. In the meantime, other parameters could also reflect the quality of C-CPR. Garcia Guerra et al. [5] demonstrated that a longer duration of lactate clearance after the initiation of E-CPR was associated with worse clinical outcomes. In addition, De Mul et al. [27] reported that the last lactate level and pH in ABGA before the initiation of E-CPR were related to clinical outcomes. In our study, we did not incorporate these values into the analysis because these values were missing in several patients, and these markers could also be a surrogate for appropriate ECLS support or the pre-arrest condition. These markers are also not within the scope of parameters that physicians can directly manipulate in clinical situations. Therefore, we focused on the impact of C-CPR duration. In the subgroup analysis, we tried to apply these values to clarify the negative effect of a long C-CPR time. The pH and lactate levels in ABGA worsened as the duration of C-CPR became longer.

From some points of view, the association between C-CPR duration and clinical outcomes was not apparent. In the univariate analysis, the association was not statistically significant. However, its significance became more evident in the multivariate analysis. A theoretical explanation of these findings could be that the quality of C-CPR might be associated with clinical outcomes. In the multivariate analysis, open sternum status and single-ventricular physiology were significant risk factors for in-hospital mortality. To leave the sternum open could be a valuable strategy to reduce the time for ECLS initiation; however, postoperative open sternum status could also have resulted from a patient's suboptimal condition. A previous report by Chan et al. [12] likewise showed that right carotid artery cannulation, which could be a result of clinical stability after cardiac surgery, was related to better survival. The association between C-CPR duration and clinical outcomes could also be influenced by the C-CPR quality. In some situations, complications (e.g., mediastinal bleeding or cardiac rupture) can develop during open cardiac massage. In addition, cardiac massage can only be performed effectively in infants by experienced physicians. These could be reasons for the negative impact of open sternum status on clinical outcomes. In the meantime, biventricular physiology was also associated with better survival to discharge. Biventricular physiology was defined in this study as not having a significant shunt lesion or cavopulmonary connection. Therefore, systemic perfusion could be achieved effectively during C-CPR or under ECLS. We managed extracardiac shunt lesions with temporary obstruction after the initiation of E-CPR; however, this maneuver could not be done easily under C-CPR. Similarly, numerous previous studies have reported single-ventricular physiology as a risk factor for adverse outcomes [12,13,23,28]. Therefore, in patients with single-ventricular physiology or suboptimal conditions, E-CPR should be initiated earlier, and C-CPR quality should be meticulously optimized.

Limitation

First of all, the initiation and termination of ECLS could be influenced by the physician's and guardian's decision, which could be affected by underlying conditions, quality of C-CPR, and demonstrated organ damage after the initiation of ECLS. Therefore, selection bias could have existed in the study cohort. Furthermore, residual cardiac lesions (e.g., significant valve regurgitation) that could not be subsequently managed because of the patient's condition or technical feasibility could have affected the clinical outcomes.

Conclusion

E-CPR could be implemented in young infants with prolonged C-CPR. The C-CPR duration should be minimized, and the quality of C-CPR should be optimized to improve survival, especially in patients with suboptimal underlying conditions.

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Conflict of interest

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