

# Extracorporeal Cardiopulmonary Resuscitation: Predictors of Survival

Dong Hee Kim, M.D., Joon Bum Kim, M.D., Ph.D., Sung-Ho Jung, M.D., Ph.D.,  
Suk Jung Choo, M.D., Ph.D., Cheol Hyun Chung, M.D., Ph.D., Jae Won Lee, M.D., Ph.D.

*Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine*

**Background:** The use of extracorporeal life support (ECLS) in the setting of cardiopulmonary resuscitation (CPR) has shown improved outcomes compared with conventional CPR. The aim of this study was to determine factors predictive of survival in extracorporeal CPR (E-CPR). **Methods:** Consecutive 85 adult patients (median age, 59 years; range, 18 to 85 years; 56 males) who underwent E-CPR from May 2005 to December 2012 were evaluated. **Results:** Causes of arrest were cardiogenic in 62 patients (72.9%), septic in 18 patients (21.2%), and hypovolemic in 3 patients (3.5%), while the etiology was not specified in 2 patients (2.4%). The survival rate in patients with septic etiology was significantly poorer compared with those with another etiology (0% vs. 24.6%,  $p=0.008$ ). Septic etiology (hazard ratio [HR], 2.84; 95% confidence interval [CI], 1.49 to 5.44;  $p=0.002$ ) and the interval between arrest and ECLS initiation (HR, 1.05 by 10 minutes increment; 95% CI, 1.02 to 1.09;  $p=0.005$ ) were independent risk factors for mortality. When the predictive value of the E-CPR timing for in-hospital mortality was assessed using the receiver operating characteristic curve method, the greatest accuracy was obtained at a cutoff of 60.5 minutes (area under the curve, 0.67; 95% CI, 0.54 to 0.80;  $p=0.032$ ) with 47.8% sensitivity and 88.9% specificity. The survival rate was significantly different according to the cutoff of 60.5 minutes ( $p=0.001$ ). **Conclusion:** These results indicate that efforts should be made to minimize the time between arrest and ECLS application, optimally within 60 minutes. In addition, E-CPR in patients with septic etiology showed grave outcomes, suggesting it to be of questionable benefit in these patients.

*Key words:* 1. Cardiac arrest  
2. Cardiopulmonary resuscitation  
3. Extracorporeal circulation  
4. Sepsis

## Introduction

Despite great efforts to save arrested patients throughout the history of medicine, the proportion of patients surviving free of neurologic sequelae is still very limited, with a <8% to 29% survival rate [1,2]. Extracorporeal life support (ECLS) in the setting of

cardiopulmonary resuscitation (CPR), which was first introduced in the 1960s, has re-emerged as a promising approach drawing particular interest among medical practitioners in the past decade. Namely, extracorporeal CPR (E-CPR) has shown improved survival as well as superior neurologic outcomes in recent observational studies, which were prompted by

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*Corresponding author: Joon Bum Kim, Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea  
(Tel) 82-2-3010-5416 (Fax) 82-2-3010-6966 (E-mail) Jbkim1975@amc.seoul.kr*

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technical advances in ECLS equipment such as generalization of small portable devices with more comfortable and rapid-access availability [3-7].

In this study, we sought to evaluate the outcomes of E-CPR in a high-volume center in Korea with a particular interest on cause-specific outcomes, and to determine the independent factors associated with survival.

## Methods

### 1) Subject patients

We queried our institutional cardiac surgical database to identify consecutive adult patients ( $\geq 18$  years old) who underwent ECLS in the setting of CPR from May 2005 to December 2012. Overall, 85 patients were identified and their medical records were reviewed retrospectively. Patients were categorized into three groups based on the etiology of the arrest: cardiogenic, septic, and hypovolemic. The primary outcome of the study was 30-day or in-hospital mortality.

### 2) Extracorporeal life support setup and devices

The ECLS team consisted of certified cardiovascular surgeons, cardiothoracic surgical residents, and cardiopulmonary bypass technicians. The CPR and ECLS teams were available at all times. The decision to apply ECLS was made by the attending doctors in charge of the CPR team. The application of ECLS was more strongly considered when there were refractory cardiac arrests despite prolonged CPR ( $>15$ – $30$  minutes) or recurrent episodes of cardiac arrest within a short time period. Contraindications for ECLS included ongoing bleeding that was not surgically correctable, advanced stages of cancer with limited life expectancy, or refusal from the patients or guardians. The ECLS devices were readily available, and could be installed on-site within 20 minutes after the decision to use ECLS. After priming the ECLS circuit in the preparation room, the device was usually delivered to the CPR site within 10 minutes. Cannulation was usually achieved by blind puncture of both the femoral vein and femoral artery using the Seldinger method. In cases where such access was unavailable, such as morbid obesity or severe volume depletion status, direct femoral cannulation was performed using open methods. A distal perfusion cannula was applied whenever possible after the initiation of ECLS

using a fine additional catheter (16-gauge) placed distal to the ECLS inflow cannula. Selection of cannula was determined according to the patient's body surface area (BSA): (1) BSA  $<1.5$  m<sup>2</sup>: 15 Fr. arterial cannula and 22 Fr. venous cannula; (2) BSA, 1.5–1.7 kg/m<sup>2</sup>: 17 Fr. arterial cannula and 24 Fr. venous cannula; and (3) BSA  $>1.7$  m<sup>2</sup>: 17 Fr. arterial cannula and 25 Fr. venous cannula. We used three commercially available ECLS devices during the study period: the Capiiox emergency bypass system (Terumo, Tokyo, Japan), the Quadrox permanent life support system (Maquet, Rastatt, Germany), and the Bio-Console 560 system (Medtronic, Minneapolis, MN, USA). An albumin-heparin coated circuit was routinely used. The ECLS flow was maintained with a target cardiac index of 2.2 L/min/m<sup>2</sup> or greater. Vasopressors or inotropics were used to maintain the mean arterial blood pressure above 65 mmHg, and intravenous sedative drugs with or without a neuromuscular blocker were routinely used during the ECLS support. Anticoagulation was maintained by using IV heparin with a target activated clotting time of 180 to 200 seconds. In cases where ongoing bleeding occurred, anticoagulation was stopped or was converted to use IV nafamostat mesilate (Futhan; Torii Pharmaceutical, Tokyo, Japan). The ECLS weaning was considered based on the clinical parameters such as restoration of pulse pressure ( $>20$  mmHg), improvements in chest roentgenography findings, and normalization of blood lactate levels as well as echocardiographic improvement of biventricular functions. A detailed description about management of ECLS has been published previously [8,9].

### 3) Statistical analysis

Categorical variables are presented as frequencies and percentages and continuous variables are expressed as mean $\pm$ standard deviation. The Kaplan-Meier method was used to delineate conditional probability of survival and log-rank test was used to compare the survival rates among groups. To determine the independent predictors of mortality, logistic regression models were used. Baseline profiles listed in Table 1 were assessed in univariable logistic regression models and variables with a p-value  $<0.20$  in univariable analyses were candidates for the multivariable models. Multivariable analyses involved a stepwise-backward elimination technique and only

**Table 1.** Baseline characteristics of patients (n=85)

Characteristic	Value
Male gender	56 (65.9)
Age (yr)	56.7±16.6 (58, 18-85)
<b>Etiology of arrest</b>	
Cardiogenic	62 (72.9)
Acute coronary syndrome	21 (24.7)
Post-cardiotomy heart failure	20 (23.5)
Congestive heart failure	8 (9.4)
Arrhythmia	6 (7.1)
Pulmonary embolism	4 (3.5)
Myocarditis	3 (3.5)
Sepsis	18 (21.2)
Hypovolemic	3 (3.5)
Unknown	2 (2.4)
<b>Initial rhythm</b>	
Ventricular tachycardia/fibrillation	35 (41.2)
Pulseless electrical activity	28 (32.9)
Asystole	9 (10.6)
Others	13 (15.3)
<b>Location of starting ECLS</b>	
Intensive care unit	55 (64.7)
General ward	10 (11.8)
Emergency room	7 (8.2)
Operating room	6 (7.1)
Catheterization room	5 (5.9)
Others	2 (2.4)
<b>Time interval between arrest and initiation of ECLS (min)</b>	
0-29	25 (29.4)
30-59	23 (27.1)
60-120	25 (29.4)
>120	12 (14.1)

Values are presented as mean±standard deviation (median, range) or number (%), unless otherwise stated. ECLS, extracorporeal life support.

variables with a p-value <0.10 remained in the final model. Results were expressed as an odds ratio with 95% confidence intervals (CIs). The predictive value of the time interval between cardiac arrest and the initiation of ECLS on mortality was analyzed using the receiver operating characteristic (ROC) curves, in which the optimal cutoff value corresponded to the value with the greatest accuracy (sensitivity+specificity).

All reported p-values are 2-sided. Statistical analyses were performed with IBM SPSS Statistics for Windows ver. 21.0 software (IBM Co., Armonk, NY, USA).

## Results

### 1) Baseline characteristics

Among the 85 subject patients, 45 patients had undergone surgical procedures before E-CPR during the index hospitalization. Of these cases, 26 were major cardiovascular operations while the remaining 19 cases were non-cardiac operations, which included liver transplantation in 6 cases, gastro-intestinal operations in 4 cases, lung resection in 3 cases, gynecologic procedures in 2 cases, a hepatobiliary procedure in 1 case, a renal resection in 1 case, a peripheral vascular surgery in 1 case, and a brain tumor resection in 1 case. The 26 cardiovascular operations were as follows: coronary bypass grafting in 8 cases, valve replacement surgery with or without maze operation in 5 cases (including 1 case of transfemoral aortic valve implantation), aortic surgery in 4 cases, combined valve and coronary procedures in 4 cases, heart transplantation in 2 cases, resection of a cardiac tumor in 1 case, pericardiectomy in 1 case, and closure of atrial septal defect combined with tricuspid annuloplasty in 1 case.

Overall, the causes of arrest were cardiogenic in 62 patients (72.9%), septic in 18 patients (21.2%), and hypovolemic in 3 patients (3.5%), while the etiology was not specified in 2 patients (2.4%). Details on the cardiogenic arrests are summarized in Table 1. Underlying medical conditions constituting the septic arrest were pneumonia in 8 patients (9.4%), abdominal infection in 4 patients (4.7%), and infection of other sites in 6 patients (7.1%).

The most common initial rhythm at the time of arrest was ventricular arrhythmia (41.2%), followed by pulseless electrical activity (32.9%), and asystole (10.6%) in descending order (Table 1). The majority of patients received E-CPR in the intensive care unit (n=55, 64.7%), followed by general wards, and the emergency room. The median time interval between time of arrest and the initiation of ECLS was 49 minutes (quartile 1-3, 24 to 82 minutes).

### 2) Outcomes

In order to treat the underlying acute coronary syndrome, 7 patients (8.2%) underwent percutaneous coronary angiography and subsequent additional coronary intervention including 1 case of coronary artery bypass grafting. Major complications related with

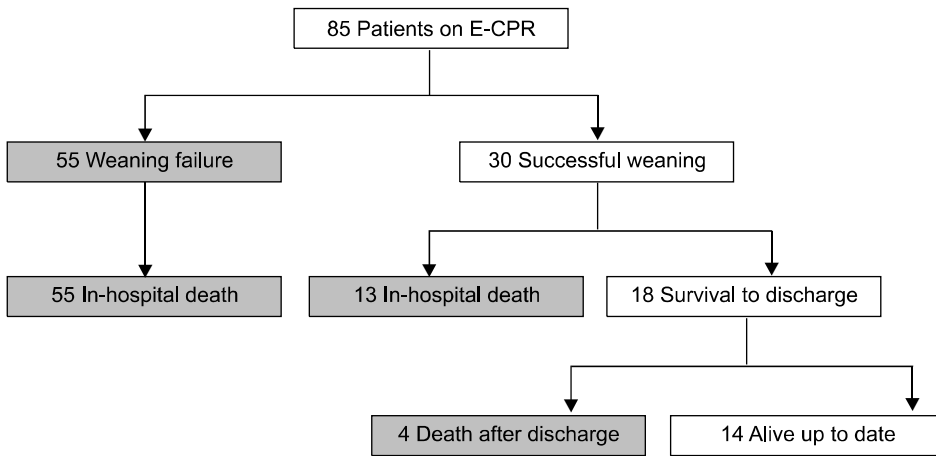


Fig. 1. Flowchart of the outcomes in patients receiving E-CPR. E-CPR, extracorporeal cardiopulmonary resuscitation.

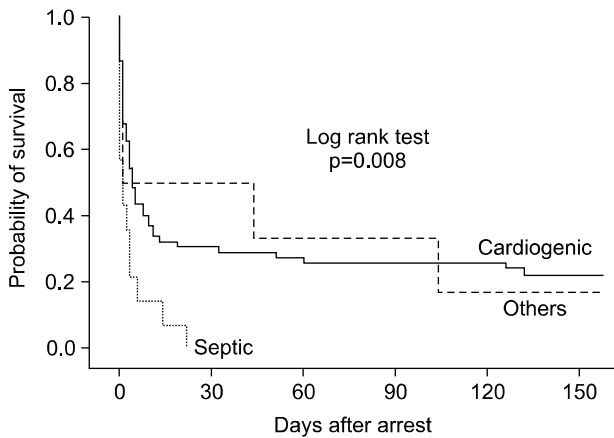


Fig. 2. Probability of survival according to the etiology of arrest.

ECLS included mediastinal bleeding in 10 cases, limb ischemia in 6 cases, bowel ischemia in 1 case, and cannulation related complications in 4 cases. The overall survival outcomes of E-CPR are summarized in Fig. 1. Among the subject patients, 30 patients (35.3%) were successfully weaned off from ECLS while 55 patients (64.7%) died on ECLS during the index hospitalization. An additional 12 out of the 30 patients who were successfully weaned off from ECLS died in-hospital after the ECLS weaning resulting in an overall 21.2% hospital survival rate (n=18). During the follow-up period, there were 4 more cases of mortality after hospital discharge. All of the patients with septic etiology died before discharge, while those with another etiology had a hospital survival rate of 24.6% (p=0.008) (Fig. 2).

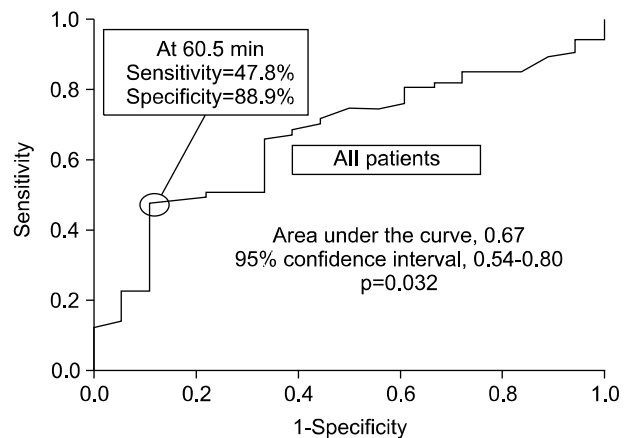
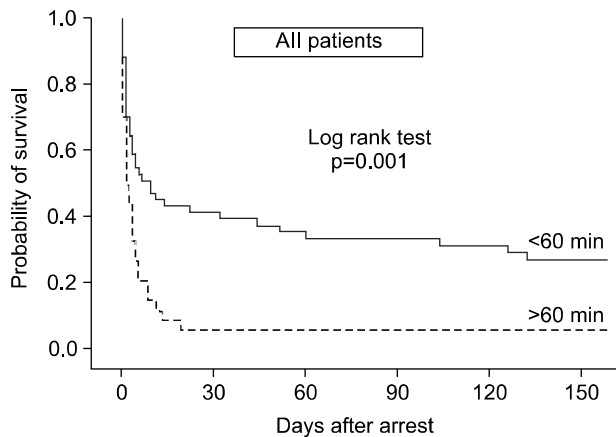


Fig. 3. The predictive timing of initiation of extracorporeal cardiopulmonary resuscitation using a receiver operating curve.

### 3) Predictors of survival

In multivariable analysis, septic etiology (hazard ratio [HR], 2.84; 95% CI, 1.49 to 5.44; p=0.002) and the time interval between arrest and ECLS initiation (HR, 1.05; 95% CI, 1.02 to 1.09 by 10 minutes increment; p=0.005) emerged as significant and independent predictors of mortality.

When the predictive value of E-CPR timing was determined using the ROC curve, the area under the curve was 0.67 (95% CI, 0.54 to 0.80; p=0.032) and the greatest accuracy in the differentiation of mortality outcome was obtained at a cutoff of 60.5 minutes (47.8% sensitivity and 88.9% specificity) (Fig. 3). The survival rate was significantly different on each side of this cutoff of 60.5 minutes (rate of survival to discharge: 31.4% vs. 5.9%, p=0.005) (Fig. 4).



**Fig. 4.** Probability of survival according to the time between arrest and initiation of extracorporeal cardiopulmonary resuscitation.

## Discussion

Mortality and morbidity of sudden cardiac arrest is still high: survival rates vary from 1% to 5% for the out-of-hospital cardiac arrests and from 17% to 25% for the in-hospital arrests [10,11]. Moreover, prolonged duration of CPR has been recognized as the strongest predictor of poor outcomes. In the 1960s, E-CPR was first introduced for patients refractory to conventional CPR [12]. Shin et al. [13] revealed that the use of ECLS in the setting of CPR showed improved survival and neurologic outcomes especially for in-hospital cardiac arrests. Maekawa et al. [14] also reported similar improvements in clinical outcomes for cases with out-of-hospital cardiac arrests. By providing as much systemic perfusion as the body requires even during cardiac arrest, ECLS may also contribute to the recovery of damaged myocardium by restoring the coronary perfusion. In addition, definite treatment for the causative disease of cardiac arrest such as acute myocardial infarction can be undertaken under stable body perfusion with the aid of ECLS [15]. Specific indications for E-CPR, however, have not been established yet. In the 2010 the American Heart Association Guidelines recommended E-CPR as a class IIb procedure when the E-CPR can be initiated in a short time inpatients with reversible etiology of arrest [3].

Previous studies have shown that a higher survival rate is achieved by a more prompt response time between arrest and initiation of E-CPR [16,17]. In the present study, we also demonstrated that longer du-

ration between time of arrest and initiation of E-CPR was an independent risk factor for mortality. Every 10-minute increment in the time interval translated to a 5% increment of mortality risk (HR of 1.05). This finding suggests that the mobile ECLS systems should be readily available at all times and experienced teams have to reside in-hospital to initiate the ECLS as soon as possible. The decision on whether to apply ECLS should also be made as soon as possible whenever conventional CPR does not effectively restore patients' CPR promptly. Chen et al. [18] revealed that a target response time below 60 minutes is an important factor to improve outcomes. In this study, the greatest accuracy in differentiating mortality outcomes was obtained at 60.5 minutes, which correlates very well with prior studies. Given that the time requirement for preparing the ECLS and cannulation is about 20 minutes by experienced teams, the decision to perform E-CPR has to be made within 30 to 40 minutes during conventional CPR.

Prior studies have demonstrated that an age greater than 60 years, underlying primary disease, initial rhythm as pulseless electrical activity or asystole, location of arrest, arrest during working hours, and quality of CPR were all associated with increased mortality after conventional CPR [13,19,20]. There have been only a few studies that have sought to evaluate the impact of etiologic factors for cardiac arrest on the outcomes in the setting of CPR. Of note, no patients with septic etiology survived at discharge in the present study.

In theory, septic shock primarily involves vasodilatory mechanisms in addition to myocardial dysfunction, which is only seen in a far advanced disease process. For this reason, ECLS perhaps does not offer benefits for patients with septic shock. In addition, septic shock resulting in completely circulatory collapse is usually compromised by multi-organ failure, which cannot be treated by circulatory support alone. Finally, ECLS in the setting of sepsis can aggravate a systemic inflammatory response, potentially resulting in a more profound systemic vasoplegic reaction and blood loss. As shown from the results of this study, cardiac arrests of septic origin may not be an optimal candidates for E-CPR. These need to be addressed by further studies on the treatment of sepsis.

### 1) Limitations

The retrospective design is the major limitation of this study. Further, it only included a relatively small number of patients for drawing robust statistical conclusions. There is an entry bias in the decision to undertake ECLS in the setting of CPR, and there might have been a number of other patients who did not undergo E-CPR during the study period even with similar baseline conditions to the study subjects. Finally, the results shown in this study are representations from a unique practice in a large-volume tertiary center in Korea; therefore they may not be generalizable to other settings.

### 2) Conclusions

In the situation of cardiac arrest, E-CPR is alternative option, especially refractory arrest under prolonged CPR or recurrent arrest. An effort must be made to minimize the time between arrest and ECLS initiation, optimally within 60 minutes; therefore, the ECLS team and machine must be prepared. In the event of arrest with septic etiology, the usage of ECLS must be considered carefully, and its effects need to be evaluated through further studies.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

### Acknowledgments

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