

## Original Research



## OPEN ACCESS

**Received:** Nov 20, 2020

**Revised:** Feb 12, 2021

**Accepted:** Mar 10, 2021

### Correspondence to

**Youngkeun Ahn, MD, PhD**

Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42, Jebong-ro, Dong-gu, Gwangju 61469, Korea.

E-mail: cecilyk@hanmail.net

Copyright © 2021. The Korean Society of Cardiology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

### ORCID iDs

Min Chul Kim

<https://orcid.org/0000-0001-6026-1702>

Youngkeun Ahn

<https://orcid.org/0000-0003-2022-9366>

Kyung Hoo Cho

<https://orcid.org/0000-0002-0377-6352>

Doo Sun Sim

<https://orcid.org/0000-0003-4162-7902>

Young Joon Hong

<https://orcid.org/0000-0003-0192-8161>

Ju Han Kim

<https://orcid.org/0000-0002-3186-0770>

Myung Ho Jeong

<https://orcid.org/0000-0003-2424-810X>

Jeong Gwan Cho

<https://orcid.org/0000-0001-7855-4490>

# Benefit of Extracorporeal Membrane Oxygenation before Revascularization in Patients with Acute Myocardial Infarction Complicated by Profound Cardiogenic Shock after Resuscitated Cardiac Arrest

Min Chul Kim , MD, PhD<sup>1</sup>, Youngkeun Ahn , MD, PhD<sup>1</sup>, Kyung Hoo Cho , MD, PhD<sup>1</sup>, Doo Sun Sim , MD, PhD<sup>1</sup>, Young Joon Hong , MD, PhD<sup>1</sup>, Ju Han Kim , MD, PhD<sup>1</sup>, Myung Ho Jeong , MD, PhD<sup>1</sup>, Jeong Gwan Cho , MD, PhD<sup>1</sup>, Dowan Kim , MD<sup>2</sup>, Kyoseon Lee , MD<sup>2</sup>, Inseok Jeong , MD, PhD<sup>2</sup>, Yong Soo Cho , MD, PhD<sup>3</sup>, Yong Hun Jung , MD, PhD<sup>3</sup>, and Kyung Woon Jeung , MD, PhD<sup>3</sup>

<sup>1</sup>Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea

<sup>2</sup>Department of Thoracic and Cardiovascular Surgery, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea

<sup>3</sup>Department of Emergency Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea




## AUTHOR'S SUMMARY

Few studies have focused on acute myocardial infarction (AMI) with cardiogenic shock after resuscitated out-of-hospital cardiac arrest (OHCA). Only a small number of studies have reported the timing of extracorporeal membrane oxygenation (ECMO) in patients with AMI with cardiogenic shock. The current study, which used the large nationwide OHCA registry, shows that ECMO treatment before revascularization can decrease 30-day mortality, compared to ECMO after revascularization, in patients with AMI complicated by profound cardiogenic shock after resuscitated cardiac arrest. The current study emphasized the importance of early ECMO therapy before revascularization in circumstance which is difficult to determine optimal revascularization timing.

## ABSTRACT

**Background and Objectives:** The study sought to investigate the impact of early extracorporeal membrane oxygenation (ECMO) support before revascularization in patients with acute myocardial infarction (AMI) complicated by profound cardiogenic shock after resuscitated cardiac arrest. It is difficult to determine optimal timing of ECMO in patients with AMI complicated by profound cardiogenic shock after resuscitated cardiac arrest.

**Methods:** Among 116,374 patients experiencing out-of-hospital cardiac arrest in South Korea, a total of 184 resuscitated patients with AMI complicated by profound cardiogenic shock, and who were treated successfully with percutaneous coronary intervention (PCI) and ECMO, were

Dowan Kim <https://orcid.org/0000-0003-2262-2882>Kyoseon Lee <https://orcid.org/0000-0001-7397-4680>Inseok Jeong <https://orcid.org/0000-0002-2249-0667>Yong Soo Cho <https://orcid.org/0000-0001-8306-2298>Yong Hun Jung <https://orcid.org/0000-0001-6005-9432>Kyung Woon Jeung <https://orcid.org/0000-0002-3478-6967>**Funding**

This study was supported by a grant of the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (2017M3A9E8023020). Data source of the current study is the Out-Of-Hospital Cardiac Arrest Surveillance, 2012, Korea Centers for Disease Control and Prevention.

**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Kim MC, Ahn Y; Data curation: Kim MC, Ahn Y; Formal analysis: Kim MC, Ahn Y; Funding acquisition: Kim MC; Investigation: Kim MC, Ahn Y; Methodology: Kim MC, Jeong I, Jung YH; Supervision: Cho KH, Sim DS, Hong YJ, Kim JH, Ahn Y, Jeong MH, Cho JG, Kim D, Lee K, Jeong I, Cho YS, Jung YH, Jeung KW; Validation: Kim MC; Visualization: Kim MC, Ahn Y; Writing - original draft: Kim MC, Ahn Y; Writing - review & editing: Kim MC, Ahn Y.

enrolled. Patients were divided into 2 groups according to the timing of ECMO: pre-PCI ECMO (n=117) and post-PCI ECMO (n=67). We compared 30-day mortality between the 2 groups.

**Results:** In-hospital mortality was 78.8% in the entire study population and significantly lower in the pre-PCI ECMO group (73.5% vs. 88.1%,  $p=0.020$ ). Thirty-day mortality was also lower in the pre-PCI ECMO group compared to the post-PCI ECMO group (74.4% vs. 91.0%; adjusted hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.47–0.93;  $p=0.017$ ). Shockable rhythm at the emergency room (HR, 0.57; 95% CI, 0.36–0.91;  $p=0.019$ ) and successful therapeutic hypothermia (HR, 0.40; 95% CI, 0.23–0.69;  $p=0.001$ ) were also associated with improved 30-day survival.

**Conclusions:** ECMO support before revascularization was associated with an improved short-term survival rate compared to ECMO after revascularization in patients with AMI complicated by profound cardiogenic shock after resuscitated cardiac arrest.

**Keywords:** Myocardial infarction; Extracorporeal membrane oxygenation; Cardiogenic shock; Out-of-hospital cardiac arrest

**INTRODUCTION**

Mortality rates for patients with acute myocardial infarction (AMI) decreased dramatically from the 1980s to the 2000s, due to the widespread use of reperfusion strategies and adjuvant pharmacological therapies.<sup>1,2</sup> However, cardiogenic shock develops in approximately 7% of patients with AMI, and is a leading cause of death.<sup>3</sup> The mortality rate for AMI complicated by cardiogenic shock still remains high, at over 40%.<sup>4–6</sup> Therefore, current guidelines for AMI recommend early revascularization in both ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) complicated by cardiogenic shock.<sup>7,8</sup>

Unfortunately, approximately 4–7% of patients with AMI experience out-of-hospital cardiac arrest (OHCA), and many patients with OHCA and AMI also present with cardiogenic shock.<sup>9–11</sup> Although immediate revascularization should be performed in patients with AMI and OHCA after successful resuscitation, many patients die without return of spontaneous circulation (ROSC). Furthermore, it is too difficult to perform coronary angiography on resuscitated patients with profound cardiogenic shock, because of the risk of cardiac death during coronary intervention. Venoarterial extracorporeal membrane oxygenation (ECMO) provides both cardiac and respiratory life support in patients with cardiogenic shock.<sup>12–14</sup> ECMO has a relatively rapid cannulation time; therefore, it can be used in the AMI setting, which requires immediate reperfusion for life saving. Several studies have shown the benefit of ECMO support in patients with AMI complicated by cardiogenic shock. However, few studies have focused on AMI with cardiogenic shock after resuscitated OHCA,<sup>15–18</sup> and only a small number of studies have reported the timing of ECMO support in patients with AMI with cardiogenic shock, who require rapid revascularization.

In the present study, we investigated whether ECMO support before revascularisation is beneficial in patients with AMI complicated by profound cardiogenic shock after resuscitated OHCA using the Korean nationwide registry.

## METHODS

### Ethical statement

The study protocols were approved by the Ethics Committee of Chonnam National University Hospital Institutional Review Board (CNUH IRB No. CNUH-2018-261) and we have complied with the latest version of the Declaration of Helsinki (2013). A waiver for informed consent was obtained from the IRB.

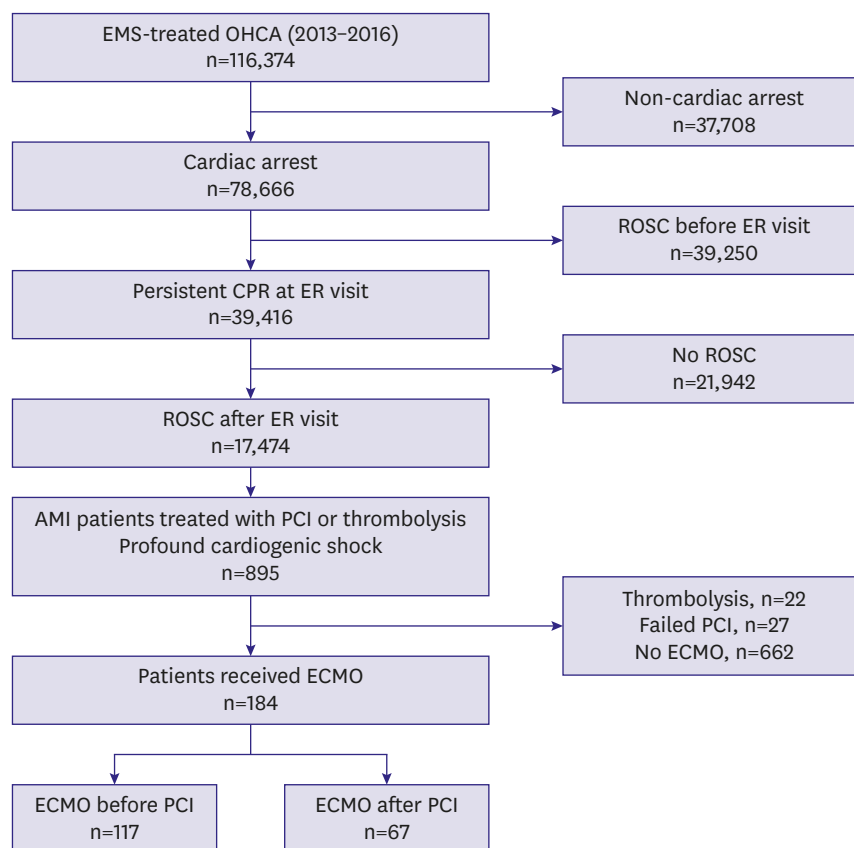
### Study setting and data sources

The Korean emergency medical services (EMS) system is a single-tiered, government-backed system that provides basic-to-intermediate level ambulance services. Emergency medical technicians are able to provide cardiopulmonary resuscitation (CPR) with an automated external defibrillator, evaluate cardiac rhythms, manage advanced airway, and inject intravenous or intraosseous fluids. The current EMS CPR protocol calls for emergency medical technicians to perform on-scene CPR using an automated external defibrillator every 2 minutes for at least 5 minutes. Advanced cardiac life support is not available at the scene, and emergency medical technicians are not permitted to declare death at the scene unless there are signs of irreversible death. EMS providers cannot stop CPR during transport to an emergency department. Consequently, all EMS-assessed patients are transported to a hospital.<sup>19)20)</sup>

Data were collected from EMS run sheets and hospital medical records using the Utstein-style reporting templates, and these data were extracted by medical record reviewers of the Korea Centers for Disease Control and Prevention.<sup>21)</sup> EMS run sheets are completed by EMS personnel and include patient information, ambulance operation information, clinical information, and treatment and transport information. The Korea Centers for Disease Control and Prevention visited all hospitals to evaluate medical records and document hospital outcomes electronically. A quality management committee composed of emergency physicians, epidemiologists, statistical experts, representatives from the fire department, and medical record review experts ensured the quality of the medical record review process. The quality management committee educated all medical record reviewers prior to joining the project, provided a standard manual for data abstraction, monthly feedback to the reviewers, and consultation on equivocal cases as needed.<sup>22)</sup>

### Study population

This study used a cross-sectional design based on a nationwide, prospective registry involving all patients who experienced OHCA and were transported to a hospital by EMS, with resuscitation efforts performed in South Korea from 2013 to 2016. A study flow chart is presented in **Figure 1**. Briefly, a total of 116,374 patients experiencing OHCA in all EMS of South Korea between January 2013 and December 2016 were enrolled. Among these, 37,708 patients with obvious non-cardiac causes, 39,250 with ROSC before the emergency room (ER) visit, and 21,942 who died without ROSC were excluded. Among the remaining 17,474 patients with ROSC after the ER visit, 895 with AMI complicated by profound cardiogenic shock after ROSC, and treated with percutaneous coronary intervention (PCI) or thrombolysis, were selected for this study. After the exclusion of 22 patients who received thrombolysis, 27 who did not receive successful PCI and 662 who were not treated with ECMO, a total of 184 patients who received ECMO therapy before (n=117) or after PCI (n=67) were analyzed.



**Figure 1.** Study flowchart.

AMI = acute myocardial infarction; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; EMS = emergency medical services; ER = emergency room; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation.

### Study definitions and endpoints

The diagnosis of AMI was based on the criteria for a third universal definition of myocardial infarction.<sup>23)</sup> Cardiogenic shock was defined as hypotension (<90/60 mmHg) for >30 minutes or a need for vasopressors or inotropes to maintain systolic blood pressure >90 mmHg, pulmonary congestion or elevated left-ventricular filling pressure, and evidence of end organ hypoperfusion (cool extremities, oliguria, lactic acidosis).<sup>12)</sup> The decision to apply ECMO was made at the physicians' discretion. The ECMO device was implanted by percutaneous or surgical cannulation, using a 14–17 Fr cannula for the femoral artery and a 21–24 Fr cannula for the femoral vein, in the ER, catheterisation room or coronary care unit. Successful PCI was defined when thrombolysis in myocardial infarction flow grade 3, with a minimum stenosis diameter <20%, was achieved, with or without coronary stenting in the culprit artery. Patients received 300 mg aspirin and 300 or 600 mg clopidogrel, 60 mg prasugrel, or 180 mg ticagrelor as a loading dose prior to PCI. After PCI, 100–300 mg aspirin and 75 mg clopidogrel daily, 5 or 10 mg prasugrel once daily, or 90 mg ticagrelor twice daily was prescribed as the maintenance dose. Therapeutic hypothermia was defined as a case receiving hypothermia treatment using external, internal or mixed cooling, with target temperature between 32 and 34°C and a target duration of 12–24 hours.<sup>22)</sup> Anticoagulation strategy and target for therapeutic hypothermia in patients underwent ECMO were deponed on each institution protocol. The definition of successful hypothermia was a recovery to alert mental status after finish of target temperature management.

The primary endpoint was 30-day mortality. We also analysed the incidence rates of in-hospital mortality and good neurologic function at discharge, with the latter defined as a score of 1 (no neurologic disability) or 2 (moderate disability; able to perform daily activities independently) on the Cerebral Performance Category scale, which is a 5-point scale used to evaluate neurologic functioning.

### Statistical analysis

Continuous variables are presented as means±standard deviation and were compared using the unpaired t-test or the Mann–Whitney rank-sum test. Discrete variables are expressed as counts with percentages and were analysed by Pearson's  $\chi^2$  test or Fisher's exact test. Kaplan–Meier curves were constructed to compare primary endpoints between the ECMO before and after PCI groups; differences were assessed using the log-rank test. Cox's proportional hazards regression model (with adjustment for covariates) was used to assess clinical outcomes. Variables that were significant in the univariate analysis ( $p < 0.1$ ) were included in the multivariate analysis.

All analyses were 2-tailed, and a  $p$  value  $< 0.05$  was considered to reflect statistical significance. All statistical analyses were performed using SPSS for Windows (ver. 21.0; SPSS Inc., Chicago, IL, USA).

## RESULTS

### Baseline characteristics and in-hospital care according to the timing of extracorporeal membrane oxygenation

**Table 1** shows the baseline characteristics and in-hospital care data according to the timing of ECMO. The mean age was similar between the 2 groups, and the rate of male patients was also comparable. In total, 76.1% of patients suffered sudden cardiac death, as observed by a witness, and only 28.8% of patients received bystander CPR. There was no significant difference in the rate of bystander CPR between groups (29.1% vs. 28.4%,  $p = 0.919$ ). Initial shockable rhythm at the scene was seen in 53.8% of patients, with almost all receiving ventricular fibrillation (50.0% of patients). At the ER visit, shockable rhythm was observed in 27.7% of patients, and ventricular fibrillation was documented in 25.5%. The rate of shockable rhythm at the scene or ER was comparable between the 2 groups. Although the total duration of CPR was similar between the 2 groups, door-to-balloon time was significantly longer in the pre-PCI ECMO group (128.5±57.3 vs. 105.5±39.1,  $p = 0.002$ ). Therapeutic hypothermia was attempted with similar frequency between the 2 groups and the success rate was also comparable. Approximately half of patients in the pre-PCI ECMO group received ECMO in the ER; however, 71.6% of patients in the post-PCI ECMO group received ECMO in the catheterization room.

### Baseline characteristics and in-hospital care according to survival or death at 30 days

Thirty-day mortality was 80.4% (148 patients). **Table 2** shows the baseline characteristics and in-hospital care data according to survival or death at 30 days. Surviving patients were younger and mostly male. Although the rate of witness CPR was similar between the 2 groups, bystander CPR was performed more often in survived patients (47.2% vs. 24.3%,  $p = 0.007$ ). Shockable rhythm, both at the scene and in the ER, was observed more often in survived patients, most of whom received ventricular fibrillation. The total duration of CPR

**Table 1.** Baseline characteristics and in-hospital care of overall population and according to timing of ECMO

Variables	All population (n=184)	ECMO before PCI (n=117)	ECMO after PCI (n=67)	p value
Age (years)	60.5±12.2	59.9±12.4	61.5±11.8	0.393
>65	76 (41.3)	44 (37.6)	32 (47.8)	0.178
Male (sex)	162 (88.0)	103 (88.0)	69 (88.1)	0.996
Year of arrest				0.600
2013	41 (22.3)	23 (19.7)	18 (26.9)	
2014	50 (27.2)	33 (28.2)	17 (25.4)	
2015	53 (28.8)	33 (28.2)	20 (29.9)	
2016	40 (21.7)	28 (23.9)	12 (17.9)	
Metropolis city	125 (67.9)	78 (66.7)	47 (70.1)	0.626
Public area	65 (35.3)	39 (33.3)	26 (38.8)	0.455
Witness of CPR	140 (76.1)	93 (79.5)	47 (70.1)	0.153
Bystander CPR	53 (28.8)	34 (29.1)	19 (28.4)	0.919
Initial ECG rhythm				
Shockable rhythm	99 (53.8)	60 (51.3)	39 (58.2)	0.364
Ventricular fibrillation	92 (50.0)	57 (48.7)	35 (52.2)	0.646
Pulseless ventricular tachycardia	3 (1.6)	0	3 (4.5)	0.021
Undetermined shockable rhythm	4 (2.2)	3 (2.6)	1 (1.5)	0.632
Pre-hospital defibrillation	97 (52.7)	63 (53.8)	34 (50.7)	0.685
Initial ECG rhythm at ER				
Shockable rhythm	51 (27.7)	32 (27.4)	19 (28.4)	0.883
Ventricular fibrillation	47 (25.5)	29 (24.8)	18 (26.9)	0.756
Pulseless ventricular tachycardia	4 (2.2)	3 (2.6)	1 (1.5)	0.632
Defibrillation at ER	120 (65.2)	76 (65.0)	44 (65.7)	0.922
Duration of CPR (minutes)	58.7±29.0	60.1±27.4	56.1±32.2	0.399
Door-to-balloon time (minutes)	120.7±52.9	128.5±57.3	105.5±39.1	0.002
Therapeutic hypothermia	38 (20.7)	23 (19.7)	15 (22.4)	0.660
Success of therapeutic hypothermia	26 (14.1)	15 (12.8)	11 (16.4)	0.500
Site of ECMO cannulation				
ER	63 (34.2)	59 (50.4)	4 (6.0)	<0.001
Catheterization room	101 (54.9)	53 (45.3)	48 (71.6)	0.001
Coronary care unit	20 (10.9)	5 (4.3)	15 (22.4)	<0.001
Duration of ECMO (day)	2.8±3.6	2.9±3.6	2.6±3.6	0.575
Failed ECMO weaning	124 (67.4)	73 (62.4)	51 (76.1)	0.056
Duration of hospitalization (day)	10.6±24.7	11.8±28.6	8.5±15.7	0.326

Values are expressed as mean±standard deviation or number (%).

CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ER = emergency room; PCI = percutaneous coronary intervention.

tended to be longer in the death group and door-to-balloon time was comparable between the 2 groups. Therapeutic hypothermia was tried with similar frequency in both groups; however, the success rate was higher in surviving patients. Surviving patients received more pre-PCI ECMO therapy compared to the death group (83.3% vs. 58.8%,  $p=0.006$ ). In total, 58.3% of surviving patients received ECMO in the ER and 60.1% of expired patients received ECMO in the catheterization room. Although 16.2% (24 patients) of the deceased patients were successfully weaned from ECMO, they eventually died of cardiac or non-cardiac problems after ECMO weaning. The total durations of ECMO and hospitalization were much longer in survived patients.

### Clinical outcomes

**Figure 2A** shows the incidence of study endpoints. In-hospital mortality was 78.8% (145 patients) in the entire study population and was significantly lower in the pre-PCI ECMO group (73.5% vs. 88.1%,  $p=0.020$ ). Thirty-day mortality was also lower in the pre-PCI ECMO group compared to the post-PCI ECMO group (74.4% vs. 91.0%,  $p=0.006$ ), and the result was similar on Kaplan-Meier survival analysis (**Figure 2B**, log-rank  $p=0.017$ ). The proportion

**Table 2.** Baseline characteristics and in-hospital care of study patients according to survival or death at 30 days

Variables	Survival (n=36)	Death (n=148)	p value
Age (years)	53.2±11.2	62.3±11.7	<0.001
> 65	7 (19.4)	69 (46.6)	0.003
Male (sex)	36 (100.0)	126 (85.1)	0.014
Year of arrest			0.165
2013	7 (19.4)	34 (23.0)	
2014	15 (41.7)	35 (23.6)	
2015	7 (19.4)	46 (31.1)	
2016	7 (19.4)	33 (22.3)	
Metropolis city	24 (66.7)	101 (68.2)	0.856
Public area	16 (44.4)	49 (33.1)	0.202
Witness of CPR	30 (83.3)	110 (74.3)	0.256
Bystander CPR	17 (47.2)	36 (24.3)	0.007
Initial ECG rhythm			
Shockable rhythm	27 (75.0)	72 (48.6)	0.004
Ventricular fibrillation	26 (72.2)	66 (44.6)	0.003
Pulseless ventricular tachycardia	0 (0.0)	3 (2.0)	0.389
Undetermined shockable rhythm	1 (2.8)	3 (2.0)	0.782
Pre-hospital defibrillation	26 (72.2)	71 (48.0)	0.009
Initial ECG rhythm at ER			
Shockable rhythm	19 (52.8)	32 (21.6)	<0.001
Ventricular fibrillation	18 (50.0)	29 (19.6)	<0.001
Pulseless ventricular tachycardia	1 (2.8)	3 (2.0)	0.782
Defibrillation at ER	29 (80.6)	91 (61.5)	0.031
Duration of CPR (minutes)	50.6±21.2	60.9±30.5	0.061
Door-to-balloon time (minutes)	116.7±55.2	121.7±52.4	0.631
Therapeutic hypothermia	10 (27.8)	28 (18.9)	0.239
Success of therapeutic hypothermia	10 (27.8)	16 (10.8)	0.009
ECMO before PCI	30 (83.3)	87 (58.8)	0.006
Site of ECMO cannulation			
ER	21 (58.3)	42 (28.4)	0.001
Catheterization room	12 (33.3)	89 (60.1)	0.004
Coronary care unit	3 (8.3)	17 (11.5)	0.586
Duration of ECMO (day)	4.0±2.7	2.5±3.7	0.008
Failed ECMO weaning	0	124 (83.8)	<0.001
Duration of hospitalization (day)	38.0±45.9	3.9±5.5	<0.001

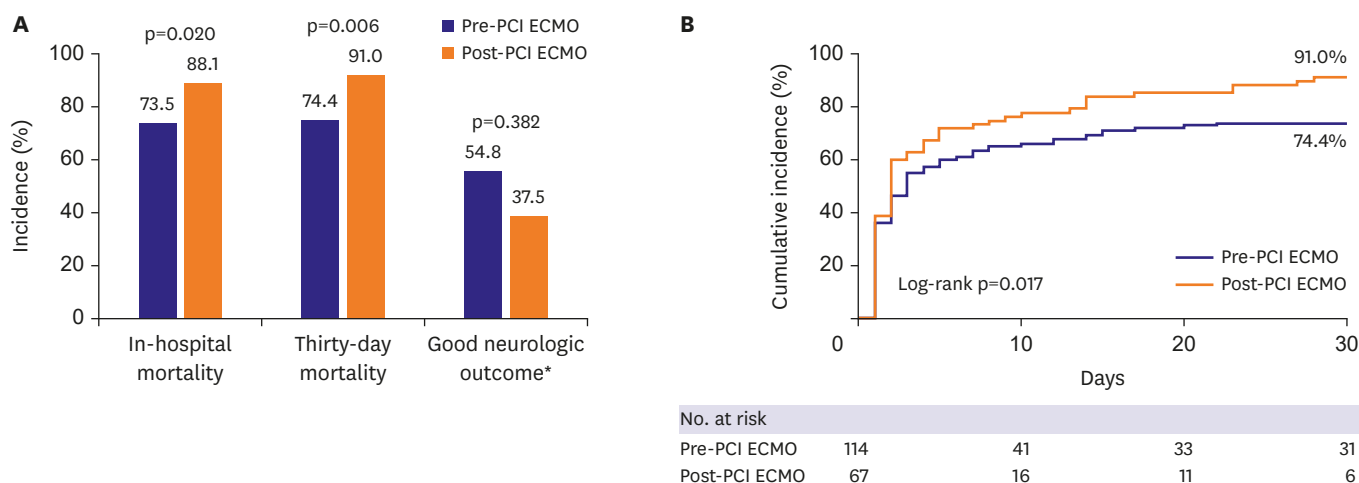
Values are expressed as mean±standard deviation or number (%).

CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ER = emergency room; PCI = percutaneous coronary intervention.

of patients with better neurologic function at discharge, defined as a Cerebral Performance Category score of 1 or 2, did not differ significantly between groups (54.8% vs. 37.5%,  $p=0.382$ ). In multivariate Cox-regression analysis, pre-PCI ECMO significantly lowered 30-day mortality compared to post-PCI ECMO (**Table 3**, adjusted hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.47–0.93;  $p=0.017$ ).

### Predictors of 30-day mortality

To investigate the independent predictors of 30-day mortality, Cox's proportional hazards regression analysis was performed (**Table 3**). Continuous variables, such as the duration of CPR and door-to-balloon time, were converted to dichotomous variables using the median value. Shockable rhythm at the ER (HR, 0.57; 95% CI, 0.36–0.91;  $p=0.019$ ) and successful therapeutic hypothermia (HR, 0.40; 95% CI, 0.23–0.69;  $p=0.001$ ) were also associated with improved 30-day survival. However, prolonged CPR significantly predicted 30-day death (HR, 1.62; 95% CI, 1.14–2.31;  $p=0.007$ ).



**Figure 2.** Incidences of study endpoints (A), and Kaplan-Meier estimates of cumulative probabilities of 30-day death for patients according to ECMO timing (B). ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention. \*Defined as scoring 1 or 2 on the cerebral performance category score.

**Table 3.** Predictors of death at 30-days

Variables	HR (95% CI)	p value
<b>Univariate analysis</b>		
Pre-PCI ECMO	0.71 (0.51-0.98)	0.039
Female (sex)	2.28 (1.42-3.64)	0.001
Age >65 years	1.50 (1.09-2.08)	0.014
Bystander CPR	0.69 (0.47-1.00)	0.051
Initial shockable rhythm	0.59 (0.42-0.81)	0.001
Duration of CPR ≥53 minutes (median)	1.47 (1.06-2.04)	0.023
Shockable rhythm at ER	0.49 (0.33-0.73)	<0.001
Door-to-balloon time ≥113 minutes (median)	1.15 (0.83-1.59)	0.390
Successful therapeutic hypothermia	0.44 (0.26-0.74)	0.002
<b>Multivariate analysis</b>		
Pre-PCI ECMO	0.66 (0.47-0.93)	0.017
Female (sex)	1.50 (0.90-2.49)	0.120
Age >65 years	1.20 (0.85-1.69)	0.313
Bystander CPR	0.71 (0.48-1.06)	0.091
Initial shockable rhythm	0.86 (0.58-1.29)	0.468
Duration of CPR ≥53 minutes (median)	1.62 (1.14-2.31)	0.007
Shockable rhythm at ER	0.57 (0.36-0.91)	0.019
Successful therapeutic hypothermia	0.40 (0.23-0.69)	0.001

CI = confidence interval; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; ER = emergency room; HR = hazard ratio; PCI = percutaneous coronary intervention.

## DISCUSSION

In the present study, we compared 30-day mortality between ECMO before PCI and ECMO after PCI in patients with AMI complicated by profound cardiogenic shock after resuscitated cardiac arrest, using data from a nationwide prospective OHCA registry. The principal findings were as follows: 1) in-hospital and 30-day mortality were unacceptably high despite successful PCI in patients with AMI complicated by cardiogenic shock after resuscitated cardiac arrest; 2) early ECMO before PCI significantly reduced both in-hospital and 30-day mortality compared to ECMO after PCI; and 3) there was a tendency toward more favourable neurologic outcomes at discharge in patients who received ECMO before PCI than those who received ECMO after PCI.



As far as we know, there are no randomized controlled trials regarding the benefit of early ECMO therapy before PCI in patients with AMI complicated by cardiogenic shock.<sup>15-18)</sup> Recently, one retrospective study compared short-term survival between ECMO before PCI and ECMO after PCI in 46 STEMI patients, and showed that ECMO before PCI improved the chance of survival in patients with STEMI with complicated refractory cardiogenic shock.<sup>24)</sup> However, there was limited evidence of the benefit of early ECMO therapy in patients with AMI after resuscitated cardiac arrest. Despite a lack of randomized controlled trials, a large meta-analysis showed the usefulness of early ECMO therapy for increasing survival and favourable neurologic outcomes in patients after resuscitated cardiac arrest.<sup>18)</sup> CPR presentation in the AMI setting is associated with high short-term mortality in cases of AMI with cardiogenic shock treated by ECMO<sup>25)</sup>; however, no study has entirely enrolled AMI patients after resuscitated OHCA. Retrospective data from 253 patients who underwent ECMO indicated that a composite endpoint of in-hospital mortality, left ventricular assist device implantation, and heart transplantation was significantly lower in ECMO before PCI than in ECMO after revascularization (32.0% vs. 49.5%; odds ratio, 0.48; 95% CI, 0.24–0.98;  $p=0.045$ ).<sup>26)</sup> In the current study, all patients were survivors after OHCA in the Korean nationwide registry contrary to above-mentioned study. Although the population recruited to this study included survivors after OHCA, in-hospital and 30-day mortality were unacceptably high, which could be due to the prolonged duration of CPR in the study population compared to other studies.<sup>17)</sup> Consequently, the early ECMO before PCI can be useful in both AMI patients complicated by shock with or without CPR. The nationwide OHCA registry used herein did not have detailed information about procedural data and initial diagnosis, such as STEMI or NSTEMI. However, patients enrolled in the current study had thrombolysis in myocardial infarction flow grade 3 after PCI, which is associated with improved mortality after ECMO.<sup>27)</sup> Furthermore, NSTEMI patients complicated by cardiogenic shock seem to have similar or worse clinical outcomes compared to STEMI patients with shock.<sup>28)</sup> Therefore, the initial diagnosis may not have impacted clinical outcomes. Early ECMO may improve the chance of favourable neurologic outcomes<sup>18)</sup>; however, there was no significant difference in the frequency of good neurologic outcomes at discharge. Because of the high in-hospital mortality in the current study, the sample size was not sufficient (the total number of survivors was 39) to assess the effect of early ECMO on neurologic outcomes. Nevertheless, there was a higher tendency toward favourable neurologic outcomes at discharge in patients who received ECMO before PCI than those who received ECMO after PCI (54.8% vs. 37.5%). However, the reduced mortality with similar neurologic outcomes suggests the potential for generating survivors with poor outcomes.

Cannulation site between early and late ECMO group was significantly different in our study. Early ECMO group more received ECMO at ER (50.4% vs. 6.0%), and late group more received it at catheterization room (45.3% vs. 71.6%) or coronary care unit (4.3% vs. 22.4%). However, the detailed baseline or angiographic characteristics, and the data about reason for late ECMO insertion after successful PCI were not available in the current registry. Although there was no definite reason for late ECMO in the current study, there was a possibility that many patients in late group received ECMO due to CPR or profound cardiogenic shock even after successful PCI. This difference rather strengthens our conclusion that early ECMO before PCI can be useful compared to ECMO after PCI in AMI patients with profound cardiogenic shock after ROSC.

In the current study, successful therapeutic hypothermia and shockable rhythm were preventive factors of 30-day mortality. Patients with poor neurologic outcomes may be prone

to severe infections, such as pneumonia, urinary tract infection or pressure sore infection, which could lead to septic shock or multi-organ failure. Shockable rhythm was also related to favourable clinical outcomes in patients treated with ECMO for refractory cardiogenic shock post-cardiac arrest.<sup>29)</sup>

The current study had several limitations. First, it used a non-randomised, observational design despite being based on a large, prospective, nationwide OHCA registry. Although we performed multivariate analysis, other variables not included in our registry may have influenced the study outcomes. Second, baseline characteristics, comorbidities and laboratory findings associated with clinical outcomes, such as serum lactate and prothrombin activity, were not considered. Third, the nationwide data we used did not include echocardiographic or renal replacement therapy data, nor detailed data of ECMO, such as pump flow. Fourth, data on in-hospital complications, such as limb ischemia, bleeding, stroke, and sepsis, which could impact mortality, were not available. Finally, the rate of ECMO implantation in the ER was high in the current study. Because all study population in the current study underwent CPR on arrival, and there might be a high probability of ECMO implantation in ER. Because non-fluoroscopy guided ECMO implantation was associated with higher complication rate, such as insertion site bleeding or catheter mal-apposition,<sup>30)</sup> this high rate of ECMO insertion at ER could impact clinical outcomes.

In conclusion, ECMO support before revascularisation was associated with improved short-term survival compared to ECMO after revascularisation in patients with AMI complicated by profound cardiogenic shock after resuscitated cardiac arrest. In the absence of randomised controlled trials, this study provides valuable information on the optimal management of these high-risk patients.

## REFERENCES

1. Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 2013;369:901-9.  
[PUBMED](#) | [CROSSREF](#)
2. Eapen ZJ, Tang WH, Felker GM, et al. Defining heart failure end points in ST-segment elevation myocardial infarction trials: integrating past experiences to chart a path forward. *Circ Cardiovasc Qual Outcomes* 2012;5:594-600.  
[PUBMED](#) | [CROSSREF](#)
3. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. *Circulation* 2009;119:1211-9.  
[PUBMED](#) | [CROSSREF](#)
4. Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes* 2016;9:117-25.  
[PUBMED](#) | [CROSSREF](#)
5. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999;341:625-34.  
[PUBMED](#) | [CROSSREF](#)
6. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 2006;295:2511-5.  
[PUBMED](#) | [CROSSREF](#)
7. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute

- myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119-77.  
[PUBMED](#) | [CROSSREF](#)
8. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.  
[PUBMED](#) | [CROSSREF](#)
  9. Kontos MC, Scirica BM, Chen AY, et al. Cardiac arrest and clinical characteristics, treatments and outcomes among patients hospitalized with ST-elevation myocardial infarction in contemporary practice: a report from the National Cardiovascular Data Registry. *Am Heart J* 2015;169:515-522.e1.  
[PUBMED](#) | [CROSSREF](#)
  10. Kvakkestad KM, Sandvik L, Andersen GØ, Sunde K, Halvorsen S. Long-term survival in patients with acute myocardial infarction and out-of-hospital cardiac arrest: a prospective cohort study. *Resuscitation* 2018;122:41-7.  
[PUBMED](#) | [CROSSREF](#)
  11. Ostenfeld S, Lindholm MG, Kjaergaard J, et al. Prognostic implication of out-of-hospital cardiac arrest in patients with cardiogenic shock and acute myocardial infarction. *Resuscitation* 2015;87:57-62.  
[PUBMED](#) | [CROSSREF](#)
  12. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J* 2015;36:1223-30.  
[PUBMED](#) | [CROSSREF](#)
  13. Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. *J Am Coll Cardiol* 2014;63:2769-78.  
[PUBMED](#) | [CROSSREF](#)
  14. Cove ME, MacLaren G. Clinical review: mechanical circulatory support for cardiogenic shock complicating acute myocardial infarction. *Crit Care* 2010;14:235.  
[PUBMED](#) | [CROSSREF](#)
  15. Kim H, Lim SH, Hong J, et al. Efficacy of veno-arterial extracorporeal membrane oxygenation in acute myocardial infarction with cardiogenic shock. *Resuscitation* 2012;83:971-5.  
[PUBMED](#) | [CROSSREF](#)
  16. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med* 2010;38:1810-7.  
[PUBMED](#) | [CROSSREF](#)
  17. Kagawa E, Dote K, Kato M, et al. Should we emergently revascularize occluded coronaries for cardiac arrest?: rapid-response extracorporeal membrane oxygenation and intra-arrest percutaneous coronary intervention. *Circulation* 2012;126:1605-13.  
[PUBMED](#) | [CROSSREF](#)
  18. Ouweneel DM, Schotborgh JV, Limpens J, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:1922-34.  
[PUBMED](#) | [CROSSREF](#)
  19. Jung E, Park JH, Kong SY, et al. Cardiac arrest while exercising on mountains in national or provincial parks: a national observational study from 2012 to 2015. *Am J Emerg Med* 2018;36:1350-5.  
[PUBMED](#) | [CROSSREF](#)
  20. Ro YS, Shin SD, Song KJ, et al. Effects of dispatcher-assisted cardiopulmonary resuscitation on survival outcomes in infants, children, and adolescents with out-of-hospital cardiac arrests. *Resuscitation* 2016;108:20-6.  
[PUBMED](#) | [CROSSREF](#)
  21. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation* 2015;132:1286-300.  
[PUBMED](#) | [CROSSREF](#)

22. Choi SW, Shin SD, Ro YS, Song KJ, Lee EJ, Ahn KO. Effect of therapeutic hypothermia on the outcomes after out-of-hospital cardiac arrest according to initial ECG rhythm and witnessed status: a nationwide observational interaction analysis. *Resuscitation* 2016;100:51-9.  
[PUBMED](#) | [CROSSREF](#)
23. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551-67.  
[PUBMED](#) | [CROSSREF](#)
24. Huang CC, Hsu JC, Wu YW, et al. Implementation of extracorporeal membrane oxygenation before primary percutaneous coronary intervention may improve the survival of patients with ST-segment elevation myocardial infarction and refractory cardiogenic shock. *Int J Cardiol* 2018;269:45-50.  
[PUBMED](#) | [CROSSREF](#)
25. Demondion P, Fournel L, Golmard JL, Niculescu M, Pavie A, Leprince P. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *Eur J Cardiothorac Surg* 2014;45:47-54.  
[PUBMED](#) | [CROSSREF](#)
26. Choi KH, Yang JH, Hong D, et al. Optimal timing of venoarterial-extracorporeal membrane oxygenation in acute myocardial infarction patients suffering from refractory cardiogenic shock. *Circ J* 2020;84:1502-10.  
[PUBMED](#) | [CROSSREF](#)
27. Chung SY, Tong MS, Sheu JJ, et al. Short-term and long-term prognostic outcomes of patients with ST-segment elevation myocardial infarction complicated by profound cardiogenic shock undergoing early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention. *Int J Cardiol* 2016;223:412-7.  
[PUBMED](#) | [CROSSREF](#)
28. Anderson ML, Peterson ED, Peng SA, et al. Differences in the profile, treatment, and prognosis of patients with cardiogenic shock by myocardial infarction classification: a report from NCDR. *Circ Cardiovasc Qual Outcomes* 2013;6:708-15.  
[PUBMED](#) | [CROSSREF](#)
29. Pineton de Chambrun M, Bréchet N, Lebreton G, et al. Venoarterial extracorporeal membrane oxygenation for refractory cardiogenic shock post-cardiac arrest. *Intensive Care Med* 2016;42:1999-2007.  
[PUBMED](#) | [CROSSREF](#)
30. Goslar T, Knafelj R, Radsel P, et al. Emergency percutaneous implantation of veno-arterial extracorporeal membrane oxygenation in the catheterisation laboratory. *EuroIntervention* 2016;12:1465-72.  
[PUBMED](#) | [CROSSREF](#)