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Clinical paper

Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support☆

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ABSTRACT

Aim: Cardiopulmonary resuscitation (CPR) using extracorporeal life support (ECLS) for in-hospital cardiac arrest (IHCA) patients has been assigned a low-grade recommendation in current resuscitation guidelines. This study compared the outcomes of IHCA and out-of-hospital cardiac arrest (OHCA) patients treated with ECLS.

Methods: A total of 77 patients were treated with ECLS. Baselines characteristics and outcomes were compared for 38 IHCA and 39 OCHA patients.

Results: The time interval between collapse and starting ECLS was significantly shorter after IHCA than after OHCA (25 (21–43) min versus 59 (45–65) min, $p < 0.001$). The weaning rate from ECLS (61% versus 36%, $p = 0.03$) and 30-day survival (34% versus 13%, $p = 0.03$) were higher for IHCA compared with OHCA patients. IHCA patients had a higher rate of favourable neurological outcome compared to OHCA patients, but the difference was not statistically significant (26% versus 10%, $p = 0.07$). Kaplan–Meier analysis showed improved 30-day and 1-year survival for IHCA patients treated with ECLS compared to OHCA patients who had ECLS. However, multivariate stepwise Cox regression model analysis indicated no difference in 30-day (odds ratio 0.94 (95% confidence interval 0.68–1.27), $p = 0.67$) and 1-year survival (0.99 (0.73–1.33), $p = 0.95$).

Conclusion: CPR with ECLS led to more favourable patient outcomes after IHCA compared with OHCA in our patient group. The difference in outcomes for ECLS after IHCA and OHCA disappeared after adjusting for patient factors and the time delay in starting ECLS.

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Cardiac arrest is a major cause of unexpected death in developed countries. Cardiac arrest has a poor prognosis, and despite conventional cardiopulmonary resuscitation (CPR), only a few patients can fully resume their former lifestyle.[1,2] The main reason for poor prognosis in cardiac arrests are a lack of return of spontaneous circulation (ROSC), re-arrest from haemodynamic instability after ROSC and hypoxic brain injury. In some studies, alternative CPR using extracorporeal life support (ECLS) (previously called emergency cardiopulmonary bypass, extracorporeal membrane oxygenation, percutaneous cardiopulmonary bypass or percutaneous cardiopulmonary support) was reported to be effective in patients in whom ROSC could not be achieved by conventional CPR.[3–8] CPR using ECLS has been assigned a low-grade recommendation in current resuscitation guidelines for in-hospital cardiac arrest (IHCA) patients.[9] It is thought that ECLS for out-of-hospital cardiac arrest (OHCA) has worse outcomes compared with ECLS for IHCA patients. We therefore examined the outcomes and differences between IHCA and OHCA patients treated with ECLS.

1. Methods

1.1. Study populations

We retrospectively collected data from a single-centre ECLS registry of IHCA and OHCA patients admitted to Hiroshima City Hospital between April 2006 and October 2009. The primary endpoint was 30-day survival.

1.2. Inclusion criteria of ECPR

When CPR was performed in an IHCA or OHCA patient in Hiroshima City Hospital, a brief and quick evaluation was con-

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ducted during CPR to check eligibility for ECLS and to set up the ECLS system. The main criteria for performing ECLS were an age of 18–74 years, ventricular fibrillation (VF) on electrocardiogram during CPR, an estimated interval of less than 15 min from the patient's collapse to starting resuscitation, a presumed cardiac origin or pulmonary embolism as the cause of the arrest and ROSC not achievable within 20 min of conventional CPR by medical personnel, as reported previously.[10] Patients were excluded if they met any of the following criteria: a terminal illness that preceded the arrest and acute aortic dissection with pericardial effusion observed by echocardiography. Written informed consent for ECLS was obtained from family members. In many cases, because of the urgency to establish ECLS, oral permission was obtained first, and written informed consent was obtained once ECLS was established.

1.3. ECLS system

The circuit for ECLS comprises a centrifugal pump, a membrane oxygenator, a heat exchanger and bypass cannulae. We performed ECLS using a Carmeda Bioactive Surface circuit, Maxima Plus PRF hollow membrane oxygenator and Biopump centrifugal blood pump (Medtronic Inc., Anaheim, California, USA) from 2003 to 2007, and the Capiox emergent bypass system, Capiox-SX membrane oxygenator and Terumo EBS centrifugal pump (Terumo Inc., Tokyo, Japan) from 2007 to 2009. Both circuits have a priming volume of approximately 0.5 l and were primed with normal saline solution and heparin.

1.4. CPR and ECLS management

The cardiologists from the department of cardiology managed advanced cardiac life support in 81% of OHCA patients transported to Hiroshima City Hospital after emergency room arrival. Cardiologists were trained to set up the ECLS systems within 10 min and they managed to do it in all cases. In cases of OHCA, the doctor who received the telephone call from the out-of-hospital emergency medical personnel evaluated the indication for ECLS and whether the patient was suitable for it. The cardiology team prepared for advanced cardiac life support, alerted the catheter laboratory and prepared the ECLS system before patient arrival. If an OHCA patient suitable for ECLS had not achieved ROSC on hospital arrival advanced cardiac life support was continued according to the guidelines. If ROSC could not be achieved after the second dose of epinephrine, the patient was transferred with ongoing continuous chest compressions to the catheter laboratory. The femoral vein and artery were percutaneously cannulated to achieve extracorporeal circulation, and circulatory support (ECLS) was started in the catheter laboratory. A similar system of transfer to the catheter laboratory after failed advanced life support was used to establish ECLS for IHCA patients. We defined return of cerebral circulation (ROCC) as the time when artificial blood flow was started using the centrifugal pump. The initial pump flow rate was kept at greater than 60 ml kg^{-1} min^{-1}. The pump flow was controlled to maintain a minimum flow of 2.0 l min^{-1} and a total flow of over 2.5 l min^{-1} m^{-2} according to the patient's body surface area. We also administered heparin (100 U kg^{-1}) to maintain the activated clotting time approximately 160–200 s for each patient immediately after cannulation. During the period of weaning from ECLS, the activated clotting time was adjusted to 200–250 s. Following this, emergency coronary angiography, percutaneous coronary intervention, emergency pulmonary angiography, intra-aortic balloon pumping (IABP), pulmonary angiography and/or placement of a pulmonary artery catheter were performed if necessary, and patients were transferred from the catheter laboratory to the coronary care unit to continue further intensive care. During transfer from the catheter laboratory to the coronary care unit, computed tomography was routinely performed. In haemodynamically stable comatose patients treated with ECLS, IABP and/or drugs, mild hypothermia was induced by rapid injection of cold saline, surface cooling, using a heat exchanger attached to the ECLS circuit, and/or the direct blood cooling by a coil attached to a circuit for continuous haemodiafiltration[3]. Rapid injection of cold saline was initiated during initial CPR in many cases of OHCA. Since patients who started ECLS were supported by an artificial circulation, we also recorded time to return of a spontaneous heart beat (ROSB) after ROCC compared with ROSC in conventional CPR. Left heart decompression was required to unload left ventricular end-diastolic pressure in cases of persistent lung edema with frothy sputum.

1.5. Statistical analysis

Baseline characteristics; treatment, and outcomes, including ROSB, weaning from ECLS, 30-day survival and favourable neurological outcome were compared between IHCA and OHCA patients. Continuous variables are presented as medians (with interquartile ranges), and categorical variables as numbers and percentages. Baseline data were compared by Mann–Whitney *U*-test for continuous variables and by chi-square test or Fisher's exact test for categorical variables, as appropriate. Kaplan–Meier curves, with a follow-up of up to 1 year, were plotted to show the survival trend. Log-rank test was used to compare the 30-day and 1-year survival differences between the ECPR-treated IHCA and OHCA patients. Cardiac arrest status (IHCA or OHCA) and covariates that had statistically significant differences, shown in Table 1 (age, sex, initial rhythm of VF, and collapse to ROCC), were added to stepwise Cox regression model to estimate the hazards of 30-day and 1-year survivals. Because the covariate time interval from collapse to the start of CPR was strongly associated with bystander CPR, we excluded it from the stepwise Cox regression model. The JMP statistical package (version 5.0.1 J, SAS Institute, Cary, North Carolina, USA) was used for all statistical analyses. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

2. Results

2.1. Baseline characteristics of study patients

A flow diagram of the study patients and their outcomes is shown in Fig. 1. A total of 77 ECLS-treated cardiac arrest patients were enrolled in this study. The baseline clinical characteristics, treatment and findings for the study patients are shown in Tables 1 and 2.

Thirty-eight patients were IHCA and 39 were OHCA. The OHCA patients were significantly younger than the IHCA patients (68 (58–73) years versus 56 (49–64) years, $p < 0.01$). The percentage of males (58% versus 85%, $p < 0.01$) and the rate of initial rhythm of VF (26% versus 49%, $p = 0.04$) were significantly higher in OHCA than in IHCA patients. The rate of bystander CPR administration was significantly higher in IHCA than in OHCA patients (92% versus 72%, $p = 0.02$). The time interval from collapse to start of CPR (0 (0–1) min versus 1 (1–8) min, $p < 0.001$) and the time interval from collapse to ROCC (25 (21–43) min versus 59 (45–65) min, $p < 0.001$) were significantly shorter in IHCA than in OHCA patients.

Coronary artery bypass grafting (CABG) was performed in seven IHCA patients and no OHCA patients. The use of therapeutic hypothermia was greater for OHCA (54%) than IHCA patients (11%) ($p < 0.001$). The rate of emergency coronary angiography was higher forOHCA (85%) than IHCA patients (68%); however, the difference was not statistically significant ($p = 0.09$). There was no difference in the rate of performing primary percutaneous coronary intervention

Table 1
Baseline clinical characteristics of in- and out-of-hospital cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation.

	In-hospital cardiac arrest (*n* = 38)	Out-of-hospital cardiac arrest (*n* = 39)	*p* value
Age, years (interquartile range)	68 (58–73)	56 (49–64)	<0.01
Male, *n* (%)	22 (58)	33 (85)	<0.01
Body mass index, BMI (interquartile range)	22.9 (21.3–24.9)	24.2 (22.0–26.0)	0.08
Initial rhythm			0.02
Ventricular fibrillation/pulseless ventricular tachycardia, *n* (%)	10 (26)	19 (49)	
Pulseless electrical activity, *n* (%)	26 (68)	14 (36)	
Asystole, *n* (%)	2 (5)	6 (15)	
Witnessed cardiac arrest, *n* (%)	35 (92)	32 (82)	0.31
Bystander cardiopulmonary resuscitation, *n* (%)	35 (92)	28 (72)	0.02
Time interval from emergency medical system call to arrival at hospital arrival, min (interquartile range)		30 (26–40)	
Time interval from collapse to start of cardiopulmonary resuscitation, min (interquartile range)	0 (0–1)	1 (1–8)	<0.001
Time interval from collapse to return of cerebral circulation, min (interquartile range)	25 (21–43)	59 (45–65)	<0.001
Medical history			
Hypertension, *n* (%)	21 (55)	18 (46)	0.42
Dyslipidemia, *n* (%)	8 (21)	8 (21)	0.95
Diabetes mellitus, *n* (%)	10 (26)	6 (15)	0.24
Myocardial infarction, *n* (%)	5 (13)	5 (13)	>0.99
Heart failure, *n* (%)	7 (18)	2 (5)	0.09
Cause of cardiac arrest			
Acute coronary syndrome, *n* (%)	21 (55)	22 (56)	0.92
Old myocardial infarction, *n* (%)	1 (3)	2 (5)	>0.99
Spasm of coronary artery, *n* (%)	0 (0)	1 (3)	>0.99
Pulmonary embolism, *n* (%)	6 (16)	6 (15)	0.96
Myocarditis, *n* (%)	2 (5)	1 (3)	0.62
Other, *n* (%)	8 (21)	7 (18)	0.73
Site of cardiac arrest			
Emergency room, *n* (%)	6 (16)		
Coronary care unit, *n* (%)	8 (21)		
Catheter laboratory, *n* (%)	13 (34)		
Other, *n* (%)	11 (29)		
Home, *n* (%)		8 (21)	
Public place, *n* (%)		31 (79)	
Initial arterial blood gas			
pH (interqurtile range) (*n*)	7.24 (7.09–7.39) (24)	7.02 (6.90–7.14) (25)	<0.001
Base excess (interqurtile range) (*n*)	−9.9 (−18.0 to −6.2) (24)	−15.6 (−22.0 to −8.9) (26)	0.10
Emergency coronary angiography, *n* (%)	26 (68)	33 (85)	0.09
Primary percutaneous coronary intervention, *n* (%)	14 (37)	15 (38)	0.88
Coronary artery bypass grafting, *n* (%)	7 (18)	0 (0)	<0.01
Therapeutic hypothermia, *n* (%)	4 (11)	21 (54)	<0.001
Target core temperature (interquartile range)	33 (33–33)	33 (33–34)	0.20
Time interval from collapse to target core temperature, min (interquartile range)	84 (59–180)	158 (118–182)	0.15
Cooling duration, h (interquartile range)	22 (11–42)	26 (24–48)	0.79
Rewarming duration, h (interquartile range)	42 (11–72)	42 (12–73)	0.82
Use of intra-aortic balloon pumping, *n* (%)	27 (71)	25 (64)	0.51
Use of left ventricular assist device, *n* (%)[a]	3 (8)	1 (3)	0.36
Duration of extracorporeal life support, h (interquartile range)	9 (5–62)	10 (3–40)	0.30
Duration of hospital stay, day (interquartile range)	18 (2–34)	1 (0–11)	<0.001
Complications[b]			
Malperfusion of leg, *n* (%)	7 (18)	8 (21)	0.82
Bleeding or hematoma, *n* (%)	26 (68)	23 (59)	0.39
Pneumonia, *n* (%)	9 (24)	7 (18)	0.54
Sepsis, *n* (%)	3 (8)	3 (8)	>0.99
Acute kidney injury, *n* (%)	14 (37)	9 (23)	0.19
Pressure sore, *n* (%)	2 (5)	1 (3)	0.62

[a] BVS 5000 Bi-ventricular Support System (Abiomed, Danvers, Massachusetts).
[b] Complications were assessed by two or more physicians according to physical examination, laboratory data, and/or imaging modalities.

(PCI), use of IABP, use of left ventricular assist device and successful percutaneous cannulation between IHCA and OHCA patients.

2.2. Outcomes

Outcomes of the study patients are shown in Table 2. No significant difference was observed in the rate of ROSB between IHCA and OHCA patients (89% versus 79%, $p = 0.23$). The rate of weaning from ECLS (61% versus 36%, $p = 0.03$) and 30-day survival (34% versus 13%, $p = 0.03$) were higher for IHCA than for OHCA patients. An increased rate of favourable neurological outcomes was observed for IHCA than for OHCA patients; however, the difference was not statistically significant (26% versus 10%, $p = 0.07$).

Baseline clinical characteristics, in-hospital treatment and findings of the study patients according to survival or death at 30 days are shown in Online Supplement Tables 1 and 2. The time interval from collapse to ROCC was significantly shorter for those who survived to 30 days than those who died (28 (23–48) min versus 51

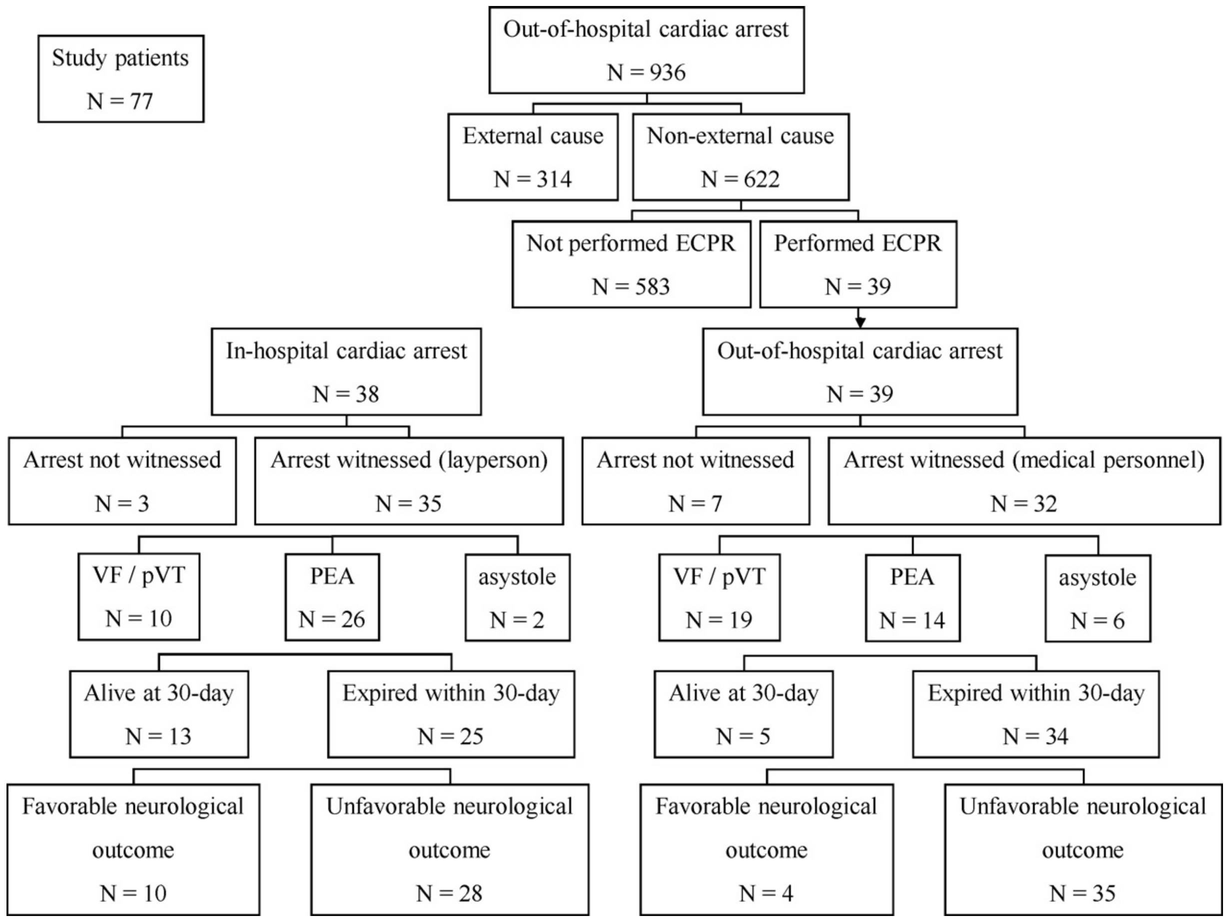

Fig. 1. Flow diagram of the study patients and outcomes.

(27–63) min, $p = 0.02$). No significant difference was observed in the rate of emergency coronary angiography between 30-day survival and death patients (78% versus 76%, $p > 0.99$). The rate of primary PCI (61% versus 31%, $p = 0.02$), CABG (28% versus 3%, $p < 0.01$) and use of IABP (89% versus 61%, $p = 0.03$) were higher for 30-day survivors patients than for 30-day death patients.

Kaplan–Meier analysis showed a survival benefit favouring the IHCA group over the OHCA group at 30 days ($p = 0.02$) as well as at 1 year ($p = 0.044$) (Fig. 2). Multivariate stepwise Cox regression model analysis indicated no difference between OHCA and IHCA for 30-day (odds ratio (OR) 0.94 (95% confidence interval (CI) 0.68–1.27), $p = 0.67$) and 1-year survival (OR 0.99 (95% CI 0.73–1.33), $p = 0.95$) (Table 3). The time interval from collapse to ROCC was negatively associated with 30-day (OR 0.98 (95% CI 0.96–0.99), $p < 0.01$) and 1-year survival (OR 0.98 (95% CI 0.96–0.99), $p < 0.01$). Initial rhythm of VF was positively associated with 30-day survival (OR 1.32 (95%

Table 2
Outcomes of in- and out-of-hospital cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation.

	In-hospital cardiac arrest (*n* = 38)	Out-of-hospital cardiac arrest (*n* = 39)	*p* value
Successful percutaneous cannulation, *n* (%)	37 (97)	38 (97)	>0.99
Return of spontaneous beating, *n* (%)	34 (89)	31 (79)	0.23
Weaned from extracorporeal life support, *n* (%)	23 (61)	14 (36)	0.03
30-day survival, *n* (%)	13 (34)	5 (13)	0.03
1-year survival, *n* (%)	10 (26)	5 (13)	0.16
Neurological findings at the time of hospital discharge			
Favourable neurological outcome, *n* (%)	10 (26)	4 (10)	0.07
Good cerebral performance, *n* (%)	10 (26)	3 (8)	
Moderate cerebral disability, *n* (%)	0 (0)	1 (3)	
Unfavourable neurological outcome, *n* (%)	28 (74)	35 (90)	
Severe cerebral disability, *n* (%)	1 (3)	0 (0)	
Coma or vegetative state, *n* (%)	0 (0)	1 (3)	
Dead, *n* (%)	27 (71)	34 (87)	
Cause of death within 30-day			
Haemodynamic instability, *n* (%)	15 (60)	26 (76)	
Multiple organ failure, *n* (%)	4 (16)	3 (9)	
Withdrawal of intensive therapy for severe neurologic damage, *n* (%)	3 (12)	4 (12)	
Pneumonia	1 (4)	0 (0)	
Others	2 (8)	1 (3)	

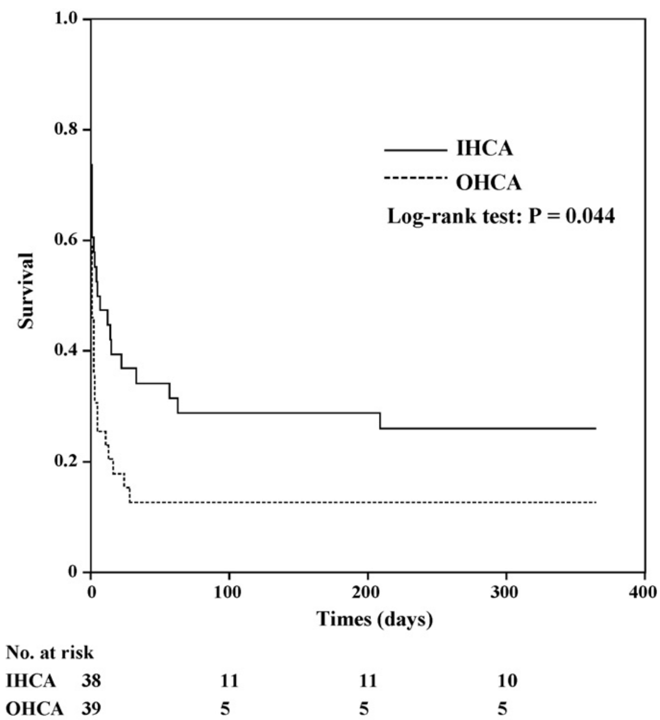

Fig. 2. Kaplan–Meier plot of the survival curves in the in- and out-of-hospital cardiac arrest patients treated with extracorporeal cardiopulmonary resuscitation. IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.

CI 1.00–1.78), $p = 0.048$) and had a tendency towards a better 1-year survival (OR 1.28 (95% CI 0.98–1.70), $p = 0.07$).

3. Discussion

Following ECLS, the survival rate at 30 days and 1 year was higher in IHCA than in OHCA patients. However, this difference in outcomes between the two sets of patients was mainly due to patient factors and a shorter interval from collapse to starting ECLS after IHCA. ECLS provides temporary total circulatory support with artificial blood flow and increased coronary perfusion. It increases the rate of successful defibrillation, prevents re-arrest from post-resuscitation myocardial dysfunction and enables subsequent therapeutic interventions.[6] In OHCA patients who were candidates for ECPR, we could start to prepare for the procedure ECPR at the time of the telephone call from the out-of-hospital emergency medical personnel. We had shorter time for preparing the ECLS system and catheter laboratory for IHCA cases than for OHCA cases. However, OHCA patients need to be transported from the scene to the hospital. In this study the median time elapsed from the emergency medical system call to hospital arrival was 30 min. As a result, the time interval from collapse to ROCC was about 30 min less for IHCA than for OHCA patients (median 25 min versus 59 min). Bystander CPR was initiated in all cases in IHCA patients, but only in 88% of OHCA patients. The quality of bystander CPR may have been better for IHCA than OHCA patients.

Cardiologists set up all the ECLS systems, performed cannulation and managed the ECLS system in this study. Since the ECLS systems used in this study were closed circuits, they were easy for us to set up rapidly in an emergency situation. Cannulation was performed in all patients using a percutaneous Seldinger technique. Compared to surgical techniques percutaneous cannulation is faster, although there is a higher incidence of local hematoma and bleeding. Bleeding or hematoma at the cannulation site makes management of patients difficult and can lead to a bad outcome.[3] The rate of successful percutaneous cannulation was 97% in this study. In cases in which cannulation was difficult, subsequent surgical cannulation can be useful. We were unable to percutaneously cannulate one patient with severe atherosclerotic peripheral vascular disease. The large ECLS cannulae of the current systems in use make rapid percutaneous cannulation of upper limb vessels difficult.

The adverse events of ECLS are increasing cardiac after load, haemorrhage, lower limb ischaemia and embolism. No significant differences were observed in the incidence of complications between IHCA and OHCA patients. In the case of IHCA patients, we had less time to set up the ECLS system; however, it was successfully implemented in all patients treated with ECLS. A longer duration of ECLS support is associated with increased complications, primarily bleeding or haematoma at the cannulation site. The duration of ECLS support was significantly longer in patients with bleeding or haematoma than in those without (39 (11 67) h versus 4 (1–6) h, $p < 0.001$). We observed that the incidence of bleeding or haematoma was higher in cardiac arrest patients undergoing ECLS than in the patients without cardiac arrest undergoing the procedure. As we cannulated using the Seldinger technique during chest compressions, the operator faced difficulty in palpating the femoral artery to correctly puncture or insert guidewires into the vessels. Multiple puncture attempts resulted in injured vessels and a higher incidence of haematoma or bleeding. In some cases, nursing changes in posture stressed the cannulation site and caused bleeding or haematoma. Because of these reasons, we speculate that weaning from ECLS should be done as early as possible.

We started extracorporeal circulation in the catheter laboratory on most of the study patients. We confirmed appropriate position of guidewires by X-rays. Confirmation can also be obtained with ultrasonography; the positioning of the venous cannula from the femoral vein into the right atrium requires an experienced operator. This method allows us to rapidly start ECLS; however, complications such as perforation and cannulation of the wrong artery or vein are likely to be more common. Since ECLS is expensive and

Table 3
Multivariate stepwise Cox regression analysis for the factors associated with the 30-day and 1-year survival.

	Odds ratio	95% confidence interval	*p* value
30-day survival			
Out-of-hospital cardiac arrest	0.94	0.68–1.27	0.67
Time interval from collapse to start of extracorporeal life support (every 1 min)	0.98	0.96–0.99	<0.01
Initial rhythm of ventricular fibrillation	1.32	1.00–1.78	0.048
1-year survival			
Out-of-hospital cardiac arrest	0.99	0.73–1.33	0.95
Time interval from collapse to start of extracorporeal life support (every 1 min)	0.98	0.96–0.99	<0.01
Initial rhythm of ventricular fibrillation	1.28	0.98–1.70	0.07

Cardiac arrest status, age, sex, initial rhythm of ventricular fibrillation, and time interval from collapse to start of extracorpoeal life suport were added to stepwise Cox regression model to estimate the hazards of 30-day and 1-year survival. Covariates shown in the table were finally included in the Cox regression model.

labour intensive, further studies are necessary to assess the benefits and cost-effectiveness.

The ECLS system with heat exchanger primed in cold saline could induce hypothermia rapidly and control temperature easily. A combination of ECLS and therapeutic hypothermia can provide more favourable neurological outcomes with rapid induction of hypothermia.[3,11–13] We performed therapeutic hypothermia in 32% of the study patients. The patients who did not achieve ROSB or haemodynamic stability, in spite of ECLS, were not treated with hypothermia and all of them died. Further studies of achieving early ROSC or ROSB and improved circulatory support devices that enable circulatory support to be rapidly established will improve outcomes of cardiac arrest patients. Early use of ECLS as described in our study should be feasible in centres with emergency cardiac catheter laboratories.[14]

4. Study limitations

This study is a non-randomised observational study which has limitations common to all retrospective investigations. However, all consecutive cardiac arrest patients treated with ECLS were prospectively included in a single-centre registry. This study was not a multi-centre study; the emergency medical systems and in-hospital emergency systems are different in various areas and hospitals.

5. Conclusions

We demonstrated that outcomes of patients treated with ECLS were better for IHCA patients than OHCA ones. The difference in outcomes for ECLS after IHCA and OHCA disappeared after adjusting for patient factors and the time delay in starting ECLS.

Conflict of interest statement

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.resuscitation.2010.03.037.

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