Original Article

Optimal extracorporeal cardiopulmonary resuscitation inclusion criteria for favorable neurological outcomes: a single-center retrospective analysis

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Aim: Although age ≤75 years, witnessed arrest, shockable initial cardiac rhythm, and short cardiac arrest duration are commonly cited inclusion criteria for extracorporeal cardiopulmonary resuscitation (ECPR), these criteria are not well-established, and ECPR outcomes remain poor. We aimed to evaluate whether the aforementioned inclusion criteria are appropriate for ECPR, and estimate the improvements in prognoses associated with their fulfillment.

Methods: Between October 2009 and December 2017, we retrospectively examined consecutive out-of-hospital cardiac arrest patients who were admitted to our hospital and received ECPR. We established four ECPR inclusion criteria: age ≤75 years, witnessed arrest, shockable initial cardiac rhythm, and call-to-hospital arrival time ≤45 min, and also evaluated the relationship between these criteria and patient outcomes.

Results: During the study period, 1,677 out-of-hospital cardiac arrest patients were admitted to our hospital, and 156 (9%) with ECPR were examined. The proportion of favorable neurological outcomes was 15% (24/156). However, when the study population was limited to individuals who fulfilled all four criteria, 27% (15/55) had favorable neurological outcomes; only one patient had favorable outcomes when two or more criteria were fulfilled. There was a significant positive linear correlation between the proportion of cases with favorable neurological outcomes and fulfillment of the four criteria ($P = 0.005$, $r = 0.975$).

Conclusion: Fulfillment of at least three of the aforementioned criteria could yield improved ECPR outcomes.

Key words: Extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, inclusion criteria, outcome, out-of-hospital cardiac arrest

BACKGROUND

THE SURVIVAL RATES associated with out-of-hospital cardiac arrest (OHCA) have been increasing in recent times due to an emphasis on the chain of survival and increased use of public-access defibrillators.[1] However, the outcomes of refractory cardiopulmonary arrest (CPA) patients in whom the return of spontaneous circulation (ROSC) is not achieved with conventional cardiopulmonary resuscitation (CPR) remain poor.[2] The effectiveness of extracorporeal membrane oxygenation (ECMO)-assisted resuscitation, also known as extracorporeal CPR (ECPR), has been reported on recently. However, according to a systematic review including 833 ECPR cases, only 13% of patients had favorable neurological outcomes; thus, ECPR outcomes remain poor.[3] Therefore, ECPR should be undertaken on OHCA patients with the potential to recover with favorable neurological outcomes.

Witnessed arrest and shockable initial cardiac rhythms are predictors of survival in OHCA.[2] Goto *et al*.[4] reported that three prehospital variables—absence of prehospital ROSC, unwitnessed cardiac arrest, and unshockable initial cardiac rhythm—predicted 1-month mortality after OHCA with >99% positive predictive value. Increasing age is also a predictor of poor outcomes in OHCA.[5] In ECPR patients, longer cardiac arrest durations are associated with poor outcomes.[6,7] Therefore, age ≤75 years, witnessed arrest, shockable initial cardiac rhythm, and short cardiac arrest duration are commonly cited as inclusion criteria for ECPR.[3]

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However, due to a lack of established inclusion criteria, ECPR is undertaken on refractory OHCA patients even if they do not fulfill the aforementioned criteria.[3,6]

This retrospective study aimed to estimate the improvements in ECPR-related prognoses in association with various degrees of fulfillment of the four ECPR inclusion criteria (age ≤75 years, witnessed arrest, shockable initial cardiac rhythm, and short cardiac arrest duration).

METHODS

Study design

BETWEEN OCTOBER 2009 and December 2017, we retrospectively analyzed consecutive OHCA patients aged ≥16 years who were admitted to our hospital and received ECPR. Patients received ECPR if ROSC was not achieved despite conventional CPR provision for ≥20 min. Exclusion criteria for ECPR were: presence of a "do not attempt resuscitation" order, patients' family members refused the ECPR, presence of existing terminal illness and/or severe activities-of-daily living disabilities, exogenous cause of arrest (e.g., trauma), and suspicions of acute aortic dissection being the cause of arrest. Additionally, even if patients did not fulfill the exclusion criteria, those who were evaluated as having no chance of survival by physicians (e.g., non-shockable initial cardiac rhythm and continued asystole during CPR) did not receive ECPR. All patients received out-of-hospital resuscitation from emergency medical service (EMS) teams, according to Japanese CPR guidelines.[8] Neurological outcomes were evaluated using the cerebral performance category (CPC) on the day of hospital discharge; a CPC of 1–2 indicated favorable outcomes. We evaluated the relationship between age ≤75 years, witnessed arrest, shockable initial cardiac rhythm and call-to-hospital arrival time ≤45 min, and ECPR outcomes. Call-to-hospital arrival time was defined as the time from call receipt or witnessed arrest by EMS teams to hospital arrival. Low-flow time is defined as the time from CPR initiation to ECPR; thus, it cannot be calculated at the time of hospital arrival. To determine the need for ECPR initiation at the time of hospital arrival, we adopted "call receipt (or witnessed by EMS)-to-hospital arrival time" in place of low-flow time. Written informed consent for coronary angiography and ECPR was obtained from patients' family members. The study protocol conformed to the tenets of the Declaration of Helsinki and its amendments, and was approved by the Institutional Review Board of Osaka Saiseikai Senri Hospital (Suita, Japan).

The ECMO system and ECPR management administered have been previously reported on.[7] All ECPR patients received targeted temperature management (TTM).[7]

Statistical analysis

Data are presented as median (interquartile range) for continuous variables, and number and percentage for categorical variables. Continuous variables were compared using the Mann–Whitney *U*-test, and categorical variables with the χ^2-test or Fisher's exact test. The relationships between the proportion of cases with favorable neurological outcomes and degree of fulfillment of the four ECPR criteria were analyzed using Spearman's rank correlation tests. All statistical analyses were carried out using SPSS software (version 21.0; SPSS, Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

DURING THE STUDY period, 1,677 OHCA patients were admitted to our hospital, of whom 158 (9%) received ECPR (Fig. 1). After the exclusion of two ECPR patients due to a lack of data, 156 (9%) were finally included. The participants' median age was 64 years, and 131 (84%) were aged ≤75 years. A total of 135 (87%) patients had a witnessed arrest and 103 (66%) had a shockable initial cardiac rhythm. The median call-to-hospital arrival time was 37 min, and 119 (76%) arrived at the hospital ≤45 min from the call receipt. The cause of arrest was acute coronary syndrome in 73 (47%) patients who sequentially underwent percutaneous coronary intervention. The etiologies of cardiac arrest among the "others" included: acute aortic dissection (n = 10), accidental hypothermia (n = 4), valvular disease (n = 2), subarachnoid hemorrhage (n = 2), hypoxia due to acute heart failure (n = 2), sepsis (n = 2), hypoxia due to chronic obstructive pulmonary disease (n = 1), diabetic ketoacidosis (n = 1), and unknown (n = 22). All the participants were comatose (Glasgow Coma Scale score 3) after ECMO initiation and received TTM; however, due to hemodynamic instability, 34°C TTM was carried out in only 33 (21%) patients. A total of 56 (36%) cases were successfully weaned from ECMO, 39 (25%) survived to hospital discharge, and 24 (15%) had a favorable neurological outcome (Table 1).

Comparison between favorable and unfavorable outcomes

The call-to-hospital arrival time was shorter (median, 32 versus 39 min; $P < 0.001$) and 34°C TTM was more frequently carried out (46% versus 17%; $P = 0.001$) in the favorable neurological outcome group. However, there were no

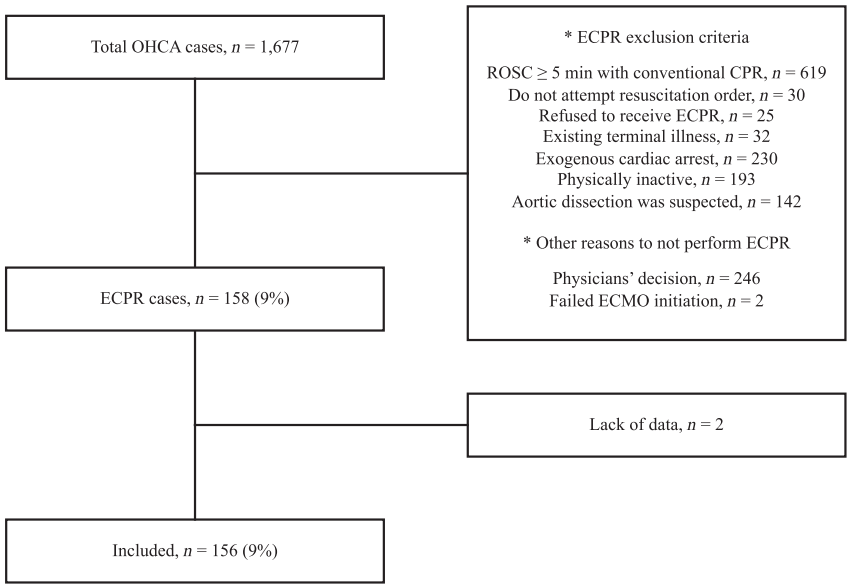

Fig. 1. Flowchart of participant inclusion in the study. CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

differences in terms of age, witnessed arrest, or shockable initial cardiac rhythm between the two groups (Table 1). On the inclusion of patients who did not receive ECPR due to the physicians' decision (n = 246), the favorable neurological outcome group was found to have a younger age (median, 55 versus 68 years; P = 0.003), a higher frequency of witnessed arrest (88% versus 53%; P = 0.001) and shockable initial cardiac rhythm (83% versus 25%; P < 0.001), and a shorter call-to-hospital arrival time (32 versus 38 min, P < 0.001) (Table 2).

Proportion of patients with favorable neurological outcomes across various degrees of inclusion criteria fulfillment

Figure 2 shows the number of patients and proportion of those with favorable neurological outcomes across the various degrees of ECPR criteria fulfillment. On limiting the population to patients who fulfilled all four criteria, 27% (15/55) had favorable neurological outcomes. The proportion of cases with favorable neurological outcomes decreased as the number of fulfilled criteria decreased (three criteria: n = 72, CPC1–2 = 8 [11%]; two criteria: n = 24, CPC1–2 = 1 [4%]; one criterion: n = 4, CPC1–2 = 0 [0%]; and no criteria: n = 1, CPC1–2 = 0 [0%]). There was a significant positive linear correlation between the proportion of cases with favorable neurological outcomes and degree of ECPR criteria fulfillment (P = 0.005, r = 0.975).

DISCUSSION

THE MAJOR findings of this study are that 27% (15/55) of patients had favorable neurological outcomes when the population was limited to those who fulfilled all four ECPR inclusion criteria, whereas only one patient had favorable neurological outcomes when the number of fulfilled criteria was two or more.

Extracorporeal cardiopulmonary resuscitation is undertaken in cases with "refractory CPA due to a reversible cause"; however, owing to a lack of other established inclusion criteria, comparing the ECPR outcomes in past reports is difficult, and ECPR outcomes remain poor.[3,6] Therefore, appropriate ECPR inclusion criteria need to be established for better outcomes.

Age ≤75 years, witnessed arrest, and shockable initial cardiac rhythm[3] are known predictors of OHCA outcomes; however, their correlation with ECPR is not well reported. In a meta-analysis by Debaty *et al*.,[6] there was no significant relationship between age and ECPR outcomes; however, 10 of the full-length articles verified in that analysis included relatively young patients, and in four of those reports, the cohort was limited to those aged ≤75 years.[6,9–18] Therefore, underlying age limitations could have affected the study results. No report to date has focused on the relationship between witnessed arrest and ECPR outcomes. Tanguay-Rioux *et al*.[19] reported that the likelihood of having an initial shockable cardiac rhythm declines with each additional

Table 1. Comparisons between favorable and unfavorable neurological outcomes among patients who underwent extracorporeal cardiopulmonary resuscitation (ECMO)

	All *n* = 156	CPC1–2 *n* = 24	CPC3–5 *n* = 132	*P*-value
Age, years	64 (50–72)	55 (41–68)	65 (51–72)	0.080
Age ≤ 75 years	131 (84)	21 (88)	110 (83)	0.770
Men	128 (82)	18 (75)	110 (83)	0.390
Witnessed arrest	135 (87)	21 (88)	114 (86)	1.000
Bystander-initiated CPR	78 (50)	14 (58)	64 (48)	0.380
Initial cardiac rhythm				
Shockable	103 (66)	20 (83)	83 (63)	0.140
Pulseless electrical activity	34 (22)	3 (13)	31 (23)	
Asystole	19 (12)	1 (4)	18 (14)	
Call to hospital arrival, min	37 (30–45)	32 (22–35)	39 (31–46)	<0.001
Call to hospital arrival ≤ 45 min	119 (76)	24 (100)	95 (72)	0.003
Hospital arrival to ECMO, min	13 (11–17)	13 (10–15)	13 (11–17)	0.470
Low-flow time, min	47 (41–57)	41 (28–46)	47 (43–58)	<0.001
Etiology of arrest				
Acute coronary syndrome	73 (47)	9 (38)	64 (48)	0.030
Ischemic cardiomyopathy	13 (8)	1 (4)	12 (9)	
Other cardiomyopathy	9 (6)	3 (13)	6 (5)	
Primary arrhythmia	8 (5)	4 (17)	4 (3)	
Pulmonary embolism	7 (4)	2 (8)	5 (4)	
Others	46 (29)	5 (21)	41 (31)	
34°C targeted temperature management	33 (21)	11 (46)	22 (17)	0.001
Successfully weaned off ECMO	56 (36)	24 (100)	32 (24)	
Survival to hospital discharge	39 (25)	24 (100)	15 (11)	

Data are presented as the number (column %) of patients or median (interquartile range).
CPC, cerebral performance category; CPR, cardiopulmonary resuscitation.

Table 2. Comparisons between the favorable and unfavorable neurological outcome groups in the extended population of patients who underwent extracorporeal cardiopulmonary resuscitation

	All *n* = 402	CPC1–2 *n* = 24	CPC3–5 *n* = 378	*P*-value
Age, years	67 (56–76)	55 (41–68)	68 (57–76)	0.003
Age ≤ 75 years	296 (74)	21 (88)	275 (73)	0.110
Witnessed arrest	222 (55)	21 (88)	201 (53)	0.001
Initial cardiac rhythm				
Shockable	115 (29)	20 (83)	95 (25)	<0.001
Pulseless electrical activity	89 (22)	3 (13)	86 (23)	
Asystole	198 (49)	1 (4)	197 (52)	
Call to hospital arrival, min	37 (32–43)	32 (22–35)	38 (32–46)	<0.001
Call to hospital arrival ≤ 45 min	304 (76)	24 (100)	280 (74)	0.004

Data are presented as the number (column %) of patients or median (interquartile range).
CPC, cerebral performance category.

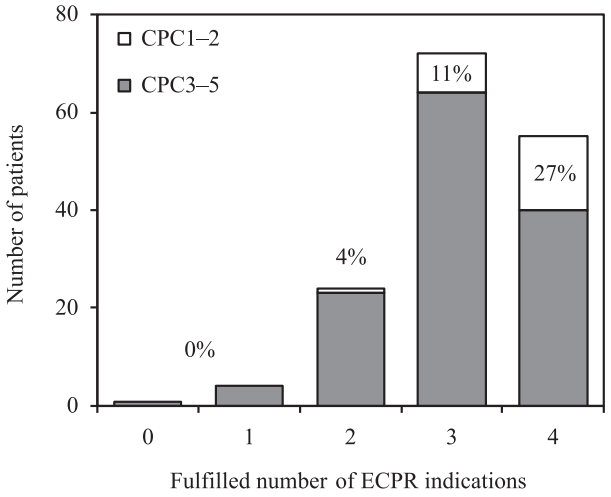

Fig. 2. Proportion of cases with favorable neurological outcomes by the degree of extracorporeal cardiopulmonary resuscitation (ECPR) criteria fulfillment. The proportions of patients with favorable neurological outcomes were 0% (0/1), 0% (0/4), 4% (1/24), 11% (8/72), and 27% (15/55) when the number of fulfilled ECPR inclusion criteria were 0, 1, 2, 3, and 4, respectively. The white box represents the number of patients with favorable neurological outcomes; the light gray box represents the number of patients with unfavorable neurological outcomes. CPC, cerebral performance category.

no-flow time minute (from the time of cardiac arrest to the commencement of chest compressions); therefore, the outcomes of unwitnessed arrest patients, whose cardiac arrest durations tend to be longer than those of witnessed arrest patients, are considered to be worse than those associated with witnessed arrest. Debaty *et al*.[6] reported that a shockable initial cardiac rhythm and shorter low-flow time are predictors of favorable outcomes in ECPR. In such settings, age ≤75 years, witnessed arrest, shockable initial rhythm, and shorter cardiac arrest duration are appropriate as ECPR inclusion criteria; accordingly, we established four inclusion criteria: age ≤75 years, witnessed arrest, shockable initial cardiac rhythm, and call-to-hospital arrival time ≤45 min. The age limit (≤75 years)—the most commonly used limit—was decided upon based on previous studies.[3,20] We previously reported that the maximum permissible low-flow time was 60 min for favorable outcome achievement; the median time from hospital arrival to ECMO use was approximately 15 min in our study (Table 1).[7] Therefore, the call-to-hospital arrival time limit was set at ≤45 min. However, as the call-to-hospital arrival time limit depends on the average time from "hospital arrival time to ECMO initiation", the appropriate limit might vary based on each institution's system.

There was no relationship between age, witnessed arrest and shockable initial cardiac rhythm, and neurological outcomes in our ECPR patients; however, on the inclusion of patients who did not receive ECPR due to the physicians' decision, those in the favorable neurological outcome group tended to be younger (median, 55 versus 68 years; $P = 0.003$), and have a higher frequency of witnessed arrest (88% versus 53%; $P = 0.001$) and shockable initial cardiac rhythm (83% versus 25%, $P < 0.001$) (Tables 1 and 2). This result suggests that the underlying selection of ECPR candidates affected our results. Older patients with non-witnessed arrest and non-shockable rhythm tended to not receive ECPR based on physicians' decisions as their outcomes are generally poor. This could explain the absence of a relationship between age, witnessed arrest and shockable initial cardiac rhythm, and neurological outcomes in the participants. The proportion of cases with favorable neurological outcomes was 15% (24/156). However, this value increased to 27% (15/55) on considering only those who fulfilled all four criteria; only one patient who fulfilled two or more criteria had a favorable outcome. Therefore, ECPR should be undertaken for patients who fulfill at least three of the four criteria for ECPR outcome improvements.

Our study did not verify each value of the four criteria, or the optimal age and cardiac arrest duration cut-off points for the achievement of favorable outcomes. Owing to the small sample size, it was difficult to evaluate each value of the four criteria in this study cohort; however, these values have frequently been adapted as ECPR inclusion criteria in previous studies.[3,6,7,9–18,20] The aim of this study, rather than to evaluate each value of the four criteria, was to evaluate whether compliance with them contributes to favorable outcomes.

All the patients in this study were comatose after ECMO initiation and received TTM; however, 34°C TTM was carried out in only 21% of the patients due to hemodynamic instability. Targeted temperature management is an established treatment strategy in comatose OHCA survivors; however, the optimal target temperature is not well established.[21] Therefore, we positively adapted 36°C TTM if the patients were hemodynamically unstable.

To the best of our knowledge, this is the first research to analyze the optimal ECPR inclusion criteria for OHCA patients, and estimate its value. We aim to undertake a multicenter and/or prospective study in the future to verify the effectiveness of our ECPR inclusion criteria and establish universal standard criteria for ECPR in the future.

This study has several limitations. First, this was a single-center retrospective study with a relatively small sample size, due to which we could not perform multiple logistic analyses. Second, not all the refractory CPA patients

received ECPR and there was a selection bias for ECPR. Third, we did not consider the influence of the arrest causes and post-resuscitation care (i.e., TTM) on patient outcomes. Finally, we evaluated the outcomes at the time of hospital discharge, and long-term outcomes were not evaluated.

CONCLUSIONS

OUR findings suggest that ECPR should be carried out on patients who fulfill at least three of our four criteria for improved ECPR outcomes.

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DISCLOSURE

Approval of the research protocol and informed consent: This study was approved by the Institutional Review Board of Osaka Saiseikai Senri Hospital. The need for informed consent was waived on account of the retrospective study design.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None declared.

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