学位論文

Shorter Interval from Witnessed Out-Of-Hospital Cardiac Arrest to Reaching the Target Temperature Could Improve Neurological Outcomes After Extracorporeal Cardiopulmonary Resuscitation with Target Temperature Management: A Retrospective Analysis of a Japanese Nationwide Multicenter Observational Registry

（目撃ある院外心停止に対する体温管理療法を併用した体外循環式心肺蘇生において、より短時間の目標体温到達は神経学的予後を改善させる：日本救急医学会院外心停止レジストリ２次解析）

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Original Article

Shorter interval from witnessed out-of-hospital cardiac arrest to reaching the target temperature could improve neurological outcomes after extracorporeal cardiopulmonary resuscitation with target temperature management: a retrospective analysis of a Japanese nationwide multicenter observational registry

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Running head: Shorter interval of ECPR OHCA improve outcomes

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Abstract

Introduction: Extracorporeal cardiopulmonary resuscitation (ECPR) with extracorporeal membrane oxygenation (ECMO) is a more promising treatment for out-of-hospital cardiac arrest (OHCA) than conventional cardiopulmonary resuscitation (CCPR). However, previous studies that compared ECPR and CCPR included mixed groups of patients with or without target temperature management (TTM). In the present study, we compared the neurological outcomes of OHCA between ECPR and CCPR with TTM in all patients.

Material and methods: We performed retrospective subanalyses of the Japanese Association for Acute Medicine OHCA registry. Witnessed adult cases of cardiogenic OHCA treated with TTM were eligible for this study. We used univariate and multivariable analyses in all eligible patients to compare the neurological outcomes after ECPR or CCPR. We also conducted propensity score analyses of all patients and according to the interval from witnessed OHCA to reaching the target temperature (IWT) of ≤600, ≤480, ≤360, ≤240, and ≤120 min.

Results: We analyzed 1146 cases. The propensity score analysis did not show a significant difference in favorable neurological outcomes (defined as a Glasgow–Pittsburgh Cerebral Performance Category of 1–2 at 1 month after collapse) between

EPCR and CCPR (odds ratio: OR 4.683 [95% confidence interval: CI 0.859–25.535], $P = 0.747$). However, ECPR was associated with more favorable neurological outcomes in patients with IWT of ≤600 min (OR 7.089 [95%CI 1.091–46.061], $P = 0.406$), ≤480 min (OR 10.492 [95%CI 1.534–71.773], $P = 0.0168$), ≤360 min (OR 17.573 [95%CI 2.486–124.233], $P = 0.0042$), ≤240 min (OR 38.908 [95%CI 5.045–300.089], $P = 0.0005$), and ≤120 min (OR 200.390 [95%CI 23.730–1692.211], $P < 0.001$).

Conclusions: The present study revealed significant differences in the neurological outcomes between ECPR and CCPR in patients with TTM whose IWT was ≤600 min.

Keywords: Cerebral Performance Category, conventional cardiopulmonary resuscitation, extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, out-of-hospital cardiac arrest, therapeutic hypothermia

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) with extracorporeal membrane oxygenation (ECMO) is a promising therapy that showed greater effectiveness than conventional cardiopulmonary resuscitation (CCPR) for out-of-hospital cardiac arrest (OHCA) (Chen 2019, Twohig 2019, Holmberg 2018, Kim 2016). Even with ECPR, it is important to shorten the no- and low-flow time (NLT) to improve the outcomes of OHCA (Wengenmayer 2017). An aggressive strategy of initiating ECPR after 20 min of advanced life support provided superior improvements in outcomes, compare to latter initiation (Lamhault 2017). Therefore, when comparing the outcomes between ECPR and CCPR, we should consider the NLT to assess the effectiveness of ECPR correctly. We previously compared the outcomes of ECPR and CCPR in cases without target temperature management (TTM) in retrospective analyses of a Japanese nationwide multicenter observational study. Although we found that ECPR had worse outcomes in all cases, ECPR may be superior to CCPR in cases with a NLT exceeding 30 min (Kitada 2020).

However, the efficacy of ECPR combined with TTM is unclear (Chen 2020, Kim 2019). When assessing the effectiveness of TTM, various factors should be considered. First, the time taken to reach the target temperature (TT) after OHCA is an important aspect of TTM (The hypothermia after cardiac arrest study group 2002, Bernard 2002, Nielsen 2013). However, it is unknown whether the interval from witnessed OHCA to reaching the target temperature (IWT) affects the neurological outcomes in cases treated with ECPR or CCPR. Therefore, we should consider the IWT and NLT when comparing ECPR and CCPR in cases with TTM. Second, the TT varies between 33 and 36 °C. Maintaining a TT below 34 °C is thought to result in better neurological outcomes, although the effectiveness of this approach is unknown (Kalra R 2018). Because a lower TT might affect the outcomes and may be related to the IWT, the TT should also be considered when comparing the effects of ECPR and CCPR.

In Japan, a nationwide observational registry of OHCA was established by the Japanese Association for Acute Medicine (JAAM-OHCA registry), with patient enrollment starting in June 2014, and now includes about 3.7% of all ECPR cases (Kitamura 2018). In this study, we retrieved clinical data for all adult cases of witnessed, cardiogenic OHCA registered between June 2014 and December 2017 to assess the effectiveness of ECPR with TTM. We performed multivariable analyses and propensity score analyses by using IWT, NLT, and lower TT as adjustment factors to investigate whether ECPR is associated with significant improvements in neurological outcomes compared with CCPR. We also investigated whether IWT and lower TT are significantly associated with the neurological outcomes.

Material and methods

Study design

We used the prospective JAAM-OHCA registry of OHCA patients treated at 288 critical care centers in Japan. The registry was approved by the ethics committees at Kyoto University, the participating institutions, and each hospital. We retrieved the clinical data for cases registered between June 2014 and December 2017 for retrospective analyses.

Patients

Between June 2014 and December 2017, a total of 34,754 cases of OHCA were registered in the JAAM-OHCA registry. We retrieved data for patients who satisfied the following criteria: (1) witnessed collapse with OHCA; (2) age >18 years; (3) cardiogenic cause of OHCA; (4) ECMO started or return of spontaneous circulation (ROSC), and hospitalization; and (5) received TTM.

Study outcomes and statistical analysis

Neurological outcomes were assessed in all patients using the Glasgow–Pittsburgh Cerebral Performance Category (CPC), which includes five categories: CPC 1 (good recovery), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (death) (Jennett 1975). We defined favorable neurological outcomes as a CPC of 1–2 at 1 month after collapse.

Among 1146 eligible patients, ECPR was performed in 268 and CCPR was performed in 878. The patients' age, sex, bystander cardiopulmonary resuscitation (BCPR), shockable rhythm (SR [ventricular fibrillation/ventricular tachycardia; VF/VT]), NLT, IWT, and lower TT (≤34 °C) were retrieved from the database as potential confounding factors for the outcomes of ECPR.

The patients were divided into those with favorable (CPC 1–2) or unfavorable (CPC 3–5) outcomes. These two groups were compared using univariate and multivariable analyses. Univariate analyses were performed with the Mann−Whitney *U* test or Fisher's exact test, as appropriate. Multivariable analyses were performed using logistic regression analysis, in which the dependent variable was favorable neurological outcomes (CPC 1–2) and the independent variables were age, sex (male), BCPR, SR (VF/VT) as the initial rhythm, NLT, IWT, lower TT (≤34 °C), and ECPR. NLT was defined as the interval from witnessed OHCA to reperfusion (start of ECMO in ECPR or ROSC in CCPR). IWT was defined as the interval from witnessed OHCA to reaching the TT. These variables were analyzed in all eligible patients.

Propensity score analysis was performed by taking into account the age, sex (male), BCPR, SR (VF/VT) as the initial rhythm, NLT, IWT, and lower TT (≤34 °C) using the inverse probability of treatment-weighting (IPTW) method, to compare the proportion of patients with favorable neurological outcomes (CPC 1–2) between cases treated by ECPR or CCPR in the overall cohort and according to IWT cutoff values (≤600, ≤480, ≤360, ≤240, and ≤120 min).

Multivariable analyses were also performed after dividing the patients according to the IWT (all patients, ≤480 min, and ≤240 min) for ECPR and CCPR cases separately. As above, we performed logistic regression analysis with favorable neurological outcomes (CPC 1–2) as the dependent variable, whereas age, sex (male), BCPR, SR (VF/VT) as the initial rhythm, NLT, IWT, and lower TT (≤34 °C) were included as independent variables.

In all analyses, a *P*-value of <0.05 was considered statistically significant. All statistical analyses, except for the propensity score analysis, were performed with SPSS version 25.0 (IBM, Armonk, NY, USA). The propensity score analysis with the IPTW method was performed with R software version 4.0.1 (GNU general public license).

Results

The registry comprised 34,754 patients. Of 3731 cases with or without TTM, ECPR was performed in 47% (268/575) and CCPR in 28% (878/3156). Overall, 1146 patients satisfied all eligibility criteria (i.e., witnessed cardiogenic OHCA, age >18 years, hospitalization, and treatment with TTM; Fig. 1).

Table 1 shows the characteristics of cases who received either ECPR (n = 268) or CCPR (n = 878). Multivariable analysis revealed significant differences in age, sex (male), SR (VF/VT), NLT, IWT, and favorable neurological outcomes (CPC 1–2) between the two groups.

Table 2 compares the patients divided according to whether their neurological outcomes were favorable (CPC 1–2) or unfavorable (CPC 3–5) in all eligible patients. The multivariable analysis revealed significant differences in age, BCPR, SR (VF/VT), NLT, and percentage of patients who received ECPR between the two groups. Although the percentage of patients who received ECPR was lower among those with favorable neurological outcomes, the multivariable analysis showed a positive effect of ECPR on favorable neurological outcomes (odds ratio [OR] 1.817; 95% confidence interval [CI] 1.048–3.149, $P < 0.001$).

Table 3 compares the favorable neurological outcomes (CPC 1–2) between the ECPR and CCPR groups by propensity score analysis with the IPTW method, in the overall cohort and according to IWT (≤600, ≤480, ≤360, ≤240, and ≤120 min). In the overall cohort, ECPR did not show a significant improvement in favorable neurological outcomes (CPC 1–2) (OR 4.683, 95% CI 0.859–25.535, P = 0.0747). However, in patients with IWT ≤600, ≤480, ≤360, ≤240, and ≤120 min, ECPR was associated with improvements in favorable neurological outcomes (CPC 1–2) with OR of 7.089, 10.492, 17.573, 38.908, and 200.390, respectively (all $P < 0.05$).

Tables 4 and 5 show the results of multivariable analyses according to IWT for all patients and in patients with an IWT ≤480 or ≤240 min for cases who received ECPR (Table 4) or CCPR (Table 5), separately. Among cases who received ECPR, favorable neurological outcomes (CPC 1–2) were achieved in 17% of all cases, 18% of cases with IWT ≤480 min, and 18% of cases with IWT ≤240 min. IWT was not significantly associated with favorable neurological outcomes (CPC 1–2). In this analysis, NLT was the only factor showing a significant association with favorable neurological outcomes (CPC 1–2). Among CCPR cases, favorable neurological outcomes (CPC 1–2) were achieved in 44% of all patients, 46% of patients with IWT ≤480 min, and 43% in patients with IWT ≤240 min. IWT was not significantly associated with favorable neurological outcomes (CPC 1–2). However, in cases who received CCPR, age, BCPR, SR, and NLT were significantly associated with favorable neurological outcomes (CPC 1–2) in the multivariable analysis in all cases and in cases with an IWT ≤480 or ≤240 min.

Discussion

In the present study, although propensity score analysis did not show significant difference between ECPR and CCPR, even though NLT was longer in ECPR cases (53 vs. 23 min), we found positive effects of ECPR on neurological outcomes in patients with an IWT of ≤600 min. Furthermore, the effectiveness of ECPR increased, as illustrated by increasing ORs, as IWT decreased.

Comparing the present data with those of our previous analyses ECPR and CCPR without TTM in patients registered in the JAAM-OHCA registry in the same period (between June 2014 and December 2017) showed that TTM may improve the neurological outcomes of OHCA (Kitada 2020). In the current analysis, among patients with TTM, neurological favorable outcomes (CPC 1–2) were achieved in 17% of cases who received ECPR and 44% of cases who received CCPR. These values in patients with TTM are greater than those in our previous analysis of patients without TTM (7%

and 17%, respectively). The results of the propensity score analyses also revealed differences in outcomes between the two studies. In our earlier study, we found that ECPR cases was associated with significantly worse neurological outcomes ($P = 0.010$), even though ECPR had significantly better neurological outcomes in patients with a NLT of >30 min). In comparison, in our present study, the propensity score analysis did not reveal a difference in the neurological outcomes between ECPR and CCPR in the overall cohort. However, ECPR was superior to CCPR in cases with a IWT of ≤600 min based on the ORs obtained by propensity score analysis.

In the present study, the propensity score analysis showed that a shorter IWT may improve the neurological outcomes. However, in multivariable analyses of the neurological outcomes in the ECPR and CCPR groups, IWT was not a significant factor, nor was TTM with a lower TT. The results of the propensity score analysis in patients divided by IWT might reflect the potential effectiveness of shortening the IWT, but we cannot exclude the possible effect of NLT and other factors, or that shortening IWT could result in worse neurological outcomes in CCPR cases without ECMO who receive artificial circulatory support. The present study did not show that a lower TT was advantageous. Lowering the TT is a common research topic for TTM. A meta-analysis by Chen et al. suggested that lower TT may be associated with improved neurological outcomes in patients who receive ECPR (Chen 2020). However, in six of 13 articles included in that meta-analysis, the control groups were compared with an ECPR group with a lower TT or were treated without TTM. Thus, the efficacy of lower TT is unclear.

The TTM trial conducted by Nielsen et al. revealed no advantage of a lower TT for treating shockable or non-shockable OHCA (Nielsen 2013, Frydland 2015). Although normothermia (36 °C) was frequently chosen as the TT, several problems were reported, including low compliance with the TT, high rate of fever, and a trend towards worsening in patient outcomes. Therefore, it is difficult to achieve the TT, even when aiming for normothermia (Bray 2017). Other aspects of TTM are also widely discussed, including how to manage induction, maintenance, rewarming, sedation, and management of post-TTM fever (Taccone 2020). ECPR with ECMO makes it easier to manage fever compared with using surface devices or even intravascular devices in CCPR. Thus, using ECMO to control body temperature may affect the outcomes of ECPR with TTM.

This study has several limitations. First, although the registry includes a nationwide cohort, the study was performed retrospectively, which may introduce some bias. Second, the neurological outcomes were assessed in terms of the CPC 1 month after resuscitation. The neurological outcomes may have changed after 6 months or 1 year. Third, although the propensity score analysis demonstrated the efficacy of ECPR in certain subgroups, other factors may confound the results and introduce some bias. Fourth, cases without TTM were excluded in the present study, but the reasons why TTM was not performed are unknown and could introduce selection bias. Forth, IWT was affected by body temperature on admission, however, only 80% (926/1146) of cases had data [median and interquartile range was 35.8 (34.9–36.3) ^{0}C, n = 926], moreover, only 29% (267/926) was measured as core temperature, therefore, body temperature on admission was not used for adjustment of propensity score analysis. Fifth, our ECPR data showed 22% (59/268) of IWT>600 min (28 cases) or unknown (31 cases), TTM with these cases were unclear and could be bias. Finally, although previous and present studies have shown superiority of ECPR than CCPR in similar setting, the effects of TTM during ECPR are still equivocal and the effectiveness of TTM and lower TT should be examined in future trials.

Conclusions

These subanalysis of a nationwide Japanese cohort study found no difference in favorable neurological outcomes between ECPR and CCPR in patients who received

TTM. However, propensity score analysis showed that the neurological outcomes were more favorable with ECPR compared with CCPR in patients with an IWT ≤600 min.

Abbreviations

ECPR: Extracorporeal cardiopulmonary resuscitation

ECMO: Extracorporeal membrane oxygenation

OHCA: Out-of-hospital cardiac arrest

CCPR: Conventional cardiopulmonary resuscitation

NLT: No- and low-flow time

TTM: Target temperature management

IWT: Interval from witnessed OHCA to reaching the target temperature

TT: Target temperature

ROSC: Return of spontaneous circulation

CPC: Glasgow–Pittsburgh Cerebral Performance Category

BCPR: Bystander cardiopulmonary resuscitation

SR: Shockable rhythm

VF: Ventricular fibrillation

VT: Ventricular tachycardia

OR: Odds ratio

CI: Confidence interval

Declarations

Ethical approval and consent to participate

The registry was approved by the ethics committees at Kyoto University, participating institutions, and each hospital.

Research statement

The datasets are only available to the study group.

Author disclosure statement

No competing financial interests exist.

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Authors' contributions

SY and TK conceived and designed the study, wrote the study protocol, contributed to the acquisition of clinical data, performed the statistical analyses and wrote the first draft of the manuscript. All authors reviewed and revised the manuscript, and approved the final version.

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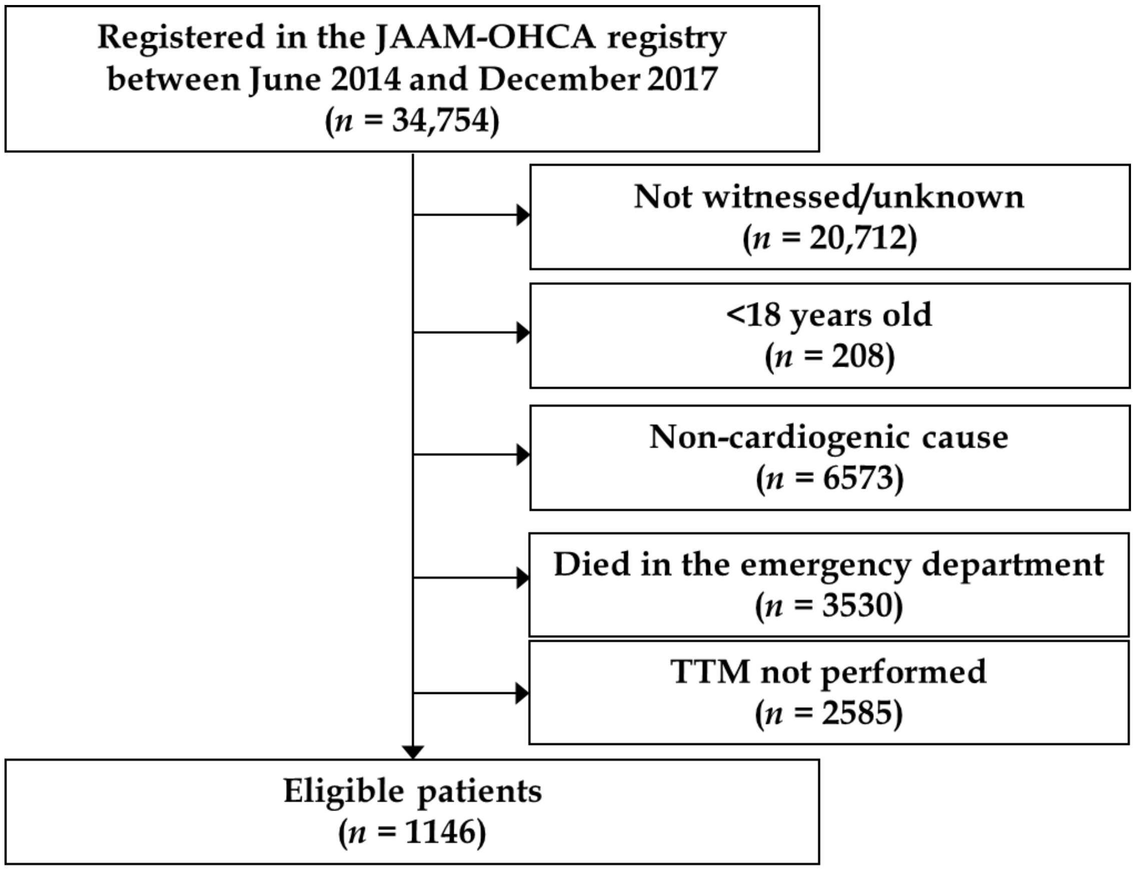

Figure legend

Fig. 1 Patient disposition

A total of 1146 patients were eligible for the study

JAAM-OHCA Japanese Association of Acute Medicine, Out-of-Hospital Cardiac Arrest,

TTM target temperature management

Table 1 Comparison of ECPR and CCPR in univariate and multivariable analyses

Variables	ECPR (*n* = 268)	CCPR (*n* = 878)	Univariate *P*-value	Multivariable *P*-value	OR (95% CI)
Age (years)	56 (46–66)	65 (52–73)	<0.001	<0.001	0.970 (0.957–0.983)
Male (%)	231 (86%)	687 (78%)	0.004	0.017	1.961 (1.131–3.402)
BCPR (%)	135 (50%)	449 (51%)	0.834	0.105	0.722 (0.487–1.070)
SR (%)	194 (72%)	498 (57%)	<0.001	0.170	1.344 (0.881–2.049)
NLT (min)[a]	53 (45–65)	23 (15–36)	<0.001	<0.001	1.093 (1.078–1.108)
IWT (min)[b]	254 (106–423)	350 (239–508)	<0.001	0.105	1.000 (0.999–1.000)
TT ≤34 °C (%)	202 (77%)	616 (72%)	0.113	0.138	1.410 (0.895–2.220)
CPC 1–2 (%)	46 (17%)	390 (44%)	<0.001	0.490	0.833 (0.497–1.398)

Values are median (interquartile range) or *n* (%)

OHCA, out-of-hospital cardiac arrest; ECPR, extracorporeal cardiopulmonary resuscitation; CCPR, conventional cardiopulmonary resuscitation; OR, odds ratio; CI, confidence interval; BCPR, bystander cardiopulmonary resuscitation; SR, shockable rhythm; NLT, no- and low-flow time; IWT, interval from witnessed OHCA to reaching the target temperature; TT, target temperature; CPC, Cerebral Performance Category

[a]Defined as the interval from witnessed OHCA to the start of reperfusion (start of extracorporeal membrane oxygenation for ECPR or return of spontaneous circulation for CCPR)

[b]Defined as the interval from witnessed OHCA to reaching the target temperature

Table 2 Comparison of favorable and unfavorable neurological outcomes in univariate and multivariable analyses

Variables	Favorable outcomes (CPC 1–2) (*n* = 436)	Unfavorable outcomes (CPC 3–5) (*n* = 710)	Univariate *P*-value	Multivariate *P*-value	OR (95% CI)
Age (years)	58 (47–70)	65 (54–73)	<0.001	<0.001	0.962 (0.951–0.974)
Male (%)	345 (79%)	573 (81%)	0.542	0.794	1.056 (0.702–1.586)
BCPR (%)	275 (63%)	309 (44%)	<0.001	<0.001	2.328 (1.672–3.240)
SR (%)	311 (71%)	381 (54%)	<0.001	<0.001	3.259 (2.285–4.650)
NLT (min)[a]	17 (12–25)	39 (27–52)	<0.001	<0.001	0.902 (0.888–0.916)
IWT (min)[b]	344 (227–481)	323 (198–496)	0.156	0.625	1.000 (0.999–1.000)
TT ≤34 °C (%)	317 (75%)	501 (72%)	0.299	0.723	1.070 (0.738–1.550)
ECPR (%)	46 (11%)	222 (31%)	<0.001	0.033	1.817 (1.048–3.149)

Values are median (interquartile range) or *n* (%)

OHCA, out-of-hospital cardiac arrest; CPC, Cerebral Performance Category; OR, odds ratio; CI, confidence interval; BCPR, bystander cardiopulmonary resuscitation; SR, shockable rhythm; NLT, no- and low-flow time; IWT, interval from witnessed OHCA to reaching the target temperature; TT, target temperature; ECPR, extracorporeal cardiopulmonary resuscitation

[a]Defined as the interval from witnessed OHCA to the start of reperfusion (start of extracorporeal membrane oxygenation for ECPR or return of spontaneous circulation for CCPR)

[b]Defined as the interval from witnessed OHCA to reaching the target temperature

Table 3 Comparisons between ECPR and CCPR by propensity score analysis with the IPTW method

Variables	Treatment	*n*	CPC 1–2	OR (95% CI)	*P* value
All patients	ECPR	268	46 (17%)	4.683 (0.859–25.535)	0.0747
	CCPR	878	390 (44%)		
IWT[a]					
≤600 min	ECPR	209	37 (18%)	7.089 (1.091–46.061)	0.0406
	CCPR	673	308 (46%)		
≤480 min	ECPR	192	35 (18%)	10.492 (1.534–71.773)	0.0168
	CCPR	596	273 (46%)		
≤360 min	ECPR	165	33 (20%)	17.573 (2.486–124.233)	0.0042
	CCPR	433	191 (44%)		
≤240 min	ECPR	111	20 (18%)	38.908 (5.045–300.089)	0.0005
	CCPR	214	92 (43%)		
≤120 min	ECPR	64	11 (17%)	200.390 (23.730–1692.211)	<0.0001
	CCPR	60	23 (38%)		

Values are median (interquartile range) or *n* (%)

OHCA, out-of-hospital cardiac arrest; IPTW, inverse probability of treatment-weighting; ECPR, extracorporeal cardiopulmonary resuscitation; CCPR, conventional cardiopulmonary resuscitation; CPC, Cerebral Performance Category; OR, odds ratio; CI, confidence interval; IWT, interval from witnessed OHCA to reaching the target temperature

[a]Defined as the interval from witnessed OHCA to reaching the target temperature.

The propensity score analysis incorporated the following variables: age, sex (male), bystander cardiopulmonary resuscitation, shockable rhythm, no- and low-flow time (interval from witnessed OHCA to reperfusion), interval from witnessed OHCA to reaching the target temperature, and target temperature ≤34 °C.

Table 4 Multivariable analysis of favorable neurological outcomes in ECPR cases

Variables	All cases (n = 268)	*P*-value	OR (95% CI)	IWT ≤480 min (n = 192)	*P*-value	OR (95% CI)	IWT ≤240 min (n = 111)	*P*-value	OR (95% CI)
Age (years)	56 (46–66)	0.046	0.975 (0.950–1.000)	56 (46–66)	0.117	0.978 (0.952–1.006)	55 (46–66)	0.182	0.976 (0.943–1.011)
Male (%)	231 (86%)	0.192	0.541 (0.215–1.362)	164 (85%)	0.157	0.480 (0.174–1.327)	95 (86%)	0.276	0.470 (0.121–1.825)
BCPR (%)	135 (50%)	0.328	1.439 (0.695–2.981)	93 (48%)	0.889	1.058 (0.476–2.353)	53 (48%)	0.048	3.250 (1.009 –10.472)
SR (%)	194 (72%)	0.292	1.567 (0.680–3.610)	137 (71%)	0.360	1.535 (0.613–3.842)	74 (67%)	0.427	1.624 (0.491–5.375)
NLT (min)[a]	53 (45–65)	0.006	0.964 (0.939–0.990)	54 (44–66)	0.010	0.964 (0.937–0.991)	54 (44–66)	0.007	0.944 (0.906–0.985)
IWT (min)[b]	254 (106–423)	0.979	1.000 (0.999–1.001)	199 (89–301)	0.777	1.000 (0.996–1.003)	99 (75–156)	0.614	1.002 (0.993–1.012)
LTT (%)	202 (77%)	0.266	1.736 (0.657–4.585)	153 (81%)	0.299	1.862 (0.576–6.025)	96 (87%)	0.634	1.526 (0.268–8.682)
CPC 1–2	46 (17%)			35 (18%)			20 (18%)		

Values are median (interquartile range) or n (%)

OHCA, out-of-hospital cardiac arrest; ECPR, extracorporeal cardiopulmonary resuscitation; OR, odds ratio; CI, confidence interval; BCPR, bystander cardiopulmonary resuscitation; SR, shockable rhythm; NLT, no- and low-flow time; IWT, interval from witnessed OHCA to reaching the target temperature; LTT, lower target temperature (≤34 °C); CPC, Cerebral Performance Category

[a]Defined as the interval from witnessed OHCA to the start of reperfusion (start of extracorporeal membrane oxygenation)

[b]Defined as the interval from witnessed OHCA to reaching the target temperature

Table 5 Multivariable analysis of favorable neurological outcomes in CCPR cases

Variables	All cases (n = 878)	P-value	OR (95% CI)	IWT ≤480 min (n = 596)	P-value	OR (95% CI)	IWT ≤240 min (n = 214)	P-value	OR (95% CI)
Age (years)	65 (52–73)	<0.001	0.958 (0.944–0.971)	65 (53–74)	<0.001	0.958 (0.942–0.973)	67 (51–74)	<0.001	0.947 (0.923–0.972)
Male (%)	687 (78%)	0.460	1.190 (0.750–1.888)	461 (77%)	0.795	0.931 (0.542–1.600)	157 (73%)	0.909	0.948 (0.379–2.371)
BCPR (%)	449 (51%)	<0.001	2.502 (1.705–3.672)	304 (51%)	<0.001	2.408 (1.534–3.780)	103 (48%)	0.019	2.614 (1.173–5.824)
SR (%)	498 (57%)	<0.001	3.805 (2.540–5.701)	332 (56%)	<0.001	3.723 (2.329–5.952)	111 (52%)	0.010	2.904 (1.296–6.506)
NLT (min)[a]	23 (15–36)	<0.001	0.884 (0.867–0.901)	23 (16–36)	<0.001	0.888 (0.869–0.908)	24 (17–37)	<0.001	0.887 (0.851–0.923)
IWT (min)[b]	350 (239–508)	0.641	1.000 (0.999–1.000)	283 (203–373)	0.046	1.002 (1.000–1.004)	162 (115–211)	0.239	1.004 (0.997–1.011)
LTT (%)	616 (72%)	0.878	0.967 (0.632–1.481)	429 (73%)	0.916	0.973 (0.585–1.618)	144 (68%)	0.375	0.689 (0.303–1.570)
CPC 1–2	390 (44%)			273 (46%)			92 (43%)		

Values are median (interquartile range) or n (%) of cases

OHCA, out-of-hospital cardiac arrest; CCPR, conventional cardiopulmonary resuscitation; OR, odds ratio; CI, confidence interval; BCPR, bystander cardiopulmonary resuscitation; SR, shockable rhythm; NLT, no- and low-flow time; IWT, interval from witnessed OHCA to reaching the target temperature; LTT, lower target temperature (≤34 °C); CPC, Cerebral Performance Category

[a]Defined as the interval from witnessed OHCA to the start of reperfusion (return of spontaneous circulation)

[b]Defined as the interval from witnessed OHCA to reaching the target temperature