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Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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ABSTRACT

objectives: Little is known about the efficacy of extracorporeal resuscitation (ECPR) for elderly patients with out-of-hospital cardiac arrest (OHCA). The aim of this study was to evaluate the efficacy of ECPR in elderly patients with OHCA.

design: Single-center retrospective cohort study.

setting: A critical care center that covers a population of approximately 1 million residents.

participants: Consecutive OHCA patients aged ≥18 years who underwent ECPR from 2005 to 2013.

primary and secondary outcome measures: Primary outcomes were one-month survival and neurologically favourable outcomes. Outcomes were compared between patients aged <75 years and those aged ≥75 years. In the sensitivity analysis, analyses were repeated with data divided by patients aged 1) >70 years and 2) ≥65 years.

Results: Overall, 139 OHCA patients who underwent ECPR were eligible for our analyses. The one-month survival rate was lower but not significantly in the age ≥75 group compared with the age <75 group (10% vs. 20%, p=0.37). In the sensitivity analysis, age ≥70 was significantly associated with poor one-month survival (8% vs. 23%, p=0.03), whereas age

≥65 was not associated (15% vs. 22%, p=0.39). These associations remained in multivariable analyses. No patient aged ≥75 years survived with neurologically favourable outcomes.

Conclusions: Advanced age was associated with lower one-month survival. Furthermore, no patient survived with neurologically favourable outcomes in patient aged ≥75 years.

Keywords: extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly

Strengths and limitations of this study

1. This study is the first study that investigate the the efficacy of extracorporeal resuscitation for elderly patients with out-of-hospital cardiac arrest, including patients aged ≥75 years.
2. Our sample consisted of retrospective data from a single canter in Japan, thereby our inferences might not be generalizable to other healthcare settings.

1. **Introduction**

Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.[1-3] In 2014, the national annual number of OHCA of cardiac origin was 70,000 in Japan,[4] with an increase in the number of elderly patients.[5] As with the burden of aging population is expected to grow further in Japan,[6] aging is also an important issue in other developed nations, resulting in an increased incidence of OHCA in elderly patients.[5] There is therefore a compelling need to develop optimal management strategies and policies to treat OHCA in elderly patients.

To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR) for patients with OHCA have been shown as a highly advanced medical treatment.[7-10] The recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science*.[1] In addition, the *European Resuscitation Council Guidelines for Resuscitation* recommends the consideration of ECPR for cases such as paediatric resuscitation and asthma-related cardiac arrest.[11] Further, subsequent observational studies have demonstrated that the utilization of ECPR was associated with improved survival compared to conventional cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable conditions.[12,13] The implementation of ECPR for OHCA might therefore be extended in future. However, the utilization of ECPR for elderly patients — a population with limited cardiovascular and pulmonary reserve — remains controversial.[14] To our knowledge, no studies have yet focused on the utilization of ECPR for elderly patients with OHCA. Although some reports suggest that an age of ≥75 years should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,[15,16] a literature using the international Extracorporeal Life Support Organization registry suggested that age should not be a bar against the consideration of the utilization of ECMO in elderly patients.[17]

To address this knowledge gap in the literature, we assessed the mortality and neurological outcomes of elderly patients with OHCA who underwent ECPR, using consecutive data from a tertiary care centre in Osaka, the second largest prefecture in Japan.

2. Material and Methods

2.1. Study design and settings

This retrospective analysis of medical records from single canter in Japan was conducted at Osaka Saiseikai Senri Hospital, a tertiary care canter approved by the Ministry of Health, Labour and Welfare and located in the northern city of Suita, Osaka, Japan. This hospital covers a population of approximately 1 million residents, of which 200 to 250 OHCA patients are treated annually. In this area, for all OHCA patients including suspected OHCA (based on the information from the emergency telephone call that contains keywords that may indicate heart attack or cardiac arrest), the Fire-Defense Headquarters requested the mobilization of a physician-staffed ambulance from our Hospital. The institutional review board of Osaka

Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

2.2. Selection of participants and data collection

We included consecutive OHCA patients aged ≥18 years old who underwent ECPR between January 2005 and September 2013. For all OHCA patients, the well-trained emergency physician assessed the implementations for ECPR during transportation and then informed the hospital medical staff in the emergency department via telephone. In the present study, approximately 80% of OHCA cases were transported by physician-staffed ambulances, and all patients were treated by emergency physicians in accordance with the Advanced Cardiac Life Support guidelines of the emergency department.[18]

Implementation criteria of ECPR for OHCA patients are shown in **Table 1**. Absolute implementation criteria for ECPR was OHCA patients with refractory ventricular fibrillation (Vf), defined as Vf sustained after three attempts of defibrillation with potentially treatable conditions. Relative implementations for ECPR were OHCA patients with presumed treatable conditions with asystole or pulseless electrical activity. Patient age was not considered when using ECPR. The patients with the following were excluded: stroke, terminal malignancy, cirrhosis, severe chronic obstructive pulmonary disease, poor daily living activities, and assessed as “inadequate implementations” for ECPR by the team leader.

2.3. ECMO management and post-resuscitation care

The final decision to initiate ECPR was dependent on the opinions of the attending physicians. To achieve successful and rapid implementation, the ECMO team was consisted of well-trained emergency physicians, cardiologists, and clinical engineers. Chest compression was continued until the start of ECMO. The percutaneous cannulation technique for venous and arterial ECMO accesses was used, with the use of 13.5 F in size cannulae for the femoral artery and 19.5 F in size cannulae for the femoral vein. Urgent coronary angiography was performed for OHCA patients with suspected cardiac origin. The patients diagnosed as acute myocardial infarction were performed primary percutaneous intervention with conventional technique for culprit lesion. All post-resuscitated patients after implementation of ECMO received the optimal medical care, regardless of age and clinical diagnosis. The patients were provided adequate oxygenation, vasopressors and fluid administration maintain systolic arterial pressure at 90 mmHg, target temperature management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage equivalent to brain death, withdrawal of ECMO was considered.

2. 4 Data collection and Quality control

The measured variables were patient demographics, prehospital characteristics (i.e., time-course, initial rhythm, presence of return of spontaneous circulation, and managements), resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic balloon pumping), and the cause of cardiac arrest. Prehospital variables were collected based on the information from paramedics and the emergency physician who treated the patient with physician-staffed ambulance. The resuscitation time-course was collected by the emergency physician who treated the patient with the physician-staffed ambulance and medical staff in the emergency department. Other measurements including post resuscitation care were recorded by the attending physician with using a standardized data collection form.

2.5. Outcomes

Outcomes of interest were one-month survival and neurologically favourable outcomes.

Neurologically favourable outcomes were defined as a Cerebral Performance Categories (CPC) score of 1 or 2.[19]

2.6. Statistical analyses

To assess the association between advanced age and outcomes, "elderly" patients were defined as those aged ≥75 years, as previously reported.[2,20,21] Patients characteristics and outcomes were compared between those aged <75 years and those aged ≥75 years. Continuous data were presented as the median (interquartile) with differences analysed using the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with differences analysed using chi-square test or Fischer's exact test as appropriate.

A multivariable logistic regression model was fitted to study the association between patient age and outcomes. Potential confounding factors based on biological plausibility and previous studies were included.[2,8,10,22] Variables included gender, shockable rhythm, CPR by bystanders, and the use of therapeutic hypothermia. Shockable rhythm was defined as Vf and ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. Odds ratios (ORs) and confidence intervals (CIs) were then calculated. In the sensitivity analysis, to assess the consistency of the association between advanced age and survival or favourable neurologic outcome at 1 month after cardiac arrest, univariable and multivariable analyses were repeated and modelled with data divided by patients aged 1) >70 years and 2) ≥65 years. Data analyses were conducted using JMP statistical software (V.10.0.2; SAS Institute, Cary, NC, USA). All statistical tests were two-tailed, and the chosen type 1 error rate was $p < 0.05$.

3. Results

During the study period, 152 consecutive OHCA patients underwent ECPR. Among them, 5 patients without follow-up due to transport to another hospital and 8 patients who did not meet the inclusion criteria (traumatic arrest [n=3], accidental hypothermia [n=3], and subarachnoid haemorrhage [n=2]) were excluded, leaving 139 patients eligible for our analysis (119 patients in the <75 years group and 20 patients in the ≥75 years group, **Figure 1**).

Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 13% of patients were women (**Table 2**). In 39% of cases, a bystander performed CPR. Shockable rhythm (i.e., Vf and VT) accounted for 88% of cases. Physician-staffed ambulances transported 83% of cases. The median time from call to arrival at a hospital was 41 min (IQR, 33-50 min), and from call to implementation of ECMO was 56 min (IQR, 49-69 min). As post-resuscitation therapy, therapeutic hypothermia was completed in 45% of patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately 70% of cardiac arrests were caused by acute myocardial infarction. There were no significant differences in prehospital characteristics, resuscitation time-course, interventions, and causes of cardiac arrest between patients aged ≥75 years and those aged <75 years.

In overall patients, one-month survival was 19% (95%CI, 13%-26%). The proportion of one-month survival was lower in patients aged ≥75 years than in those aged <75 years, but not significant (10% vs. 20%, p=0.37, **Figure 2A**). In the sensitivity analysis, the proportion of one-month survival was significantly lower in patients aged ≥70 compared to those aged <70 years (8% vs. 23%, p=0.03, **Figure 2B**). There was no significant difference in one-month survival between patients aged ≥65 years and those aged ≤65 years (15% vs. 22%, p=0.39, **Figure 2C**).

In the multivariable analyses, these associations were remained (**Table 3**). The one-month survival was lower but not significant in patients aged ≥75 years than in those aged <75 years (adjusted OR, 0.36; 95% CI 0.05-1.45). In the sensitivity analysis, one-month survival was significantly lower in patients aged ≥70 years compared to those aged <70 years (adjusted OR, 0.21; 95% CI 0.04-0.71).

The overall proportion of neurologically favourable outcomes was 6% (95% CI, 3%-12%) in elderly patients with OHCA. Among patients aged ≥75 years, no patient survived with neurologically favourable outcomes, although 8% of patients aged <75 years survived with neurologically favourable outcomes (0% vs. 8%, p=0.36). In the sensitivity analysis, the proportion of neurologically favourable outcomes was lower in patients aged ≥70 years than in those aged <70 years (3% vs. 8%, p=0.48), but not significant. Also, there were no significant differences in proportions of neurologically favourable outcomes between patients aged ≥65 years and those aged <65 years (6% vs. 7%, p=1.00). In the multivariable analyses, both age ≥70 and ≥65 were not significantly associated with poorer neurological outcomes (adjusted OR, 0.28; 95% CI, 0.01-1.63), and 0.89; 95% CI, 0.21-3.51, respectively).

4. Discussion

In this retrospective analysis from an urban tertiary care hospital, we found that advanced age was associated with miserable one-month survival and neurologically favourable outcomes in patients with OHCA who underwent ECPR. Surprisingly, no patient aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. To the best of our knowledge, this is the first study to assess the efficacy of ECPR in elderly patients with OHCA. These findings provide valuable clues for creating optimal strategy for elderly patients with OHCA in the aging era.

Our study observed that no patients aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. Moreover, ECPR did not improve outcomes in elderly patients aged ≥70 years with OHCA compared with younger patients. Although previous studies reported that ECPR was more effective in treating OHCA patients than conventional CPR, these studies did not assess the effect of advanced age – their findings were based on studies limiting to patients aged <75 years.[9,10] A multicentre prospective observational study in Japan demonstrated that the survival rate at one-month after cardiac arrest was significantly higher in the ECPR group than in the non-ECPR group (27% vs. 6%) and that the proportion of neurologically favourable outcomes was also significantly higher in the ECPR group (12.3% vs. 1.5%).[10] Our results that overall one-month survival rate of 20% and one-month survival with neurologically favourable outcomes of 7% are comparable results with these previous findings,[9,10] despite we included patients aged ≥75 years. Therefore, focusing on the elderly patients, our findings might suggest limitations in using ECPR to treat elderly patients with OHCA.

The reasons for the observed lack of efficacy of ECPR among elderly patients are likely multifactorial. First, consistent with the fact that the elderly are the population with limited cardiovascular and pulmonary reserve, the survival rate of OCHA patients was lower in older patients than in younger ones.[23] An observational study in the US demonstrated that advanced age was a factor associated with lower survival rate at discharge among OHCA patients (19.4% for ≤80 years vs. 9.4% for 80-89 years, and 4.4% for ≥90 years).[23] Second, shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an observational study in the US, shorter duration of CPR was significantly associated with neurologically favourable outcomes – 90% of patients with neurologically favourable outcomes required less than16 minutes of CPR.[24] In our findings, the median time from cardiac arrest to ROSC or implementing of ECMO was 54 min, which is considerably longer than in the previous study in the US.[24] However, patients who require ECPR are "non-responders" to conventional CPR within 20 minutes.[12] In addition, another ECPR study also showed a lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our findings.[8] Taken together, advanced age as the vulnerable population and a longer CPR duration may help explain the lack of efficacy of ECPR for elderly patients with OHCA in the present study.

Importantly, the cost burden of ECPR is also significant. In Japan, the incremental cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted life-year (QALY).[25] Considering the acceptable ICER for introducing a new treatment is approximately £20,000-30,000,[26] this financial burden is unacceptably high. Further, another Japanese study suggested that the average cost for treating an OHCA patient was approximately £1,250.[27] Aging, and its associated costs are increasing, constituting an enormous financial burden throughout the developed world. Given this significant financial burden and our present observations (i.e. miserable survival and neurologic outcomes in patients aged ≥75 and ≥70 years), implementations of ECPR in elderly patients with OHCA are extremely limited with respect to cost-efficacy. Our observations facilitate further investigations to elucidate the cost-effectiveness of ECPR for elderly patients with OHCA.

Despite the significant healthcare resource burden of ECPR, the present study did not demonstrate the efficacy of ECPR for elderly patients with OHCA. However, this does not indicate that CPR should not be utilized for elderly patients. Although advanced age was a factor associated with poor outcomes in OHCA patients in the present study, this factor alone does not appear to be a good criterion for denying patients conventional CPR based on a previous report.[23] Additionally, experts say that decisions regarding termination of resuscitation should not be based on age.[28] However, given our present findings regarding poor outcomes among elderly patients and the extremely high cost of ECPR, the implementation of ECPR for elderly patients should be carefully considered in this aging era.

Limitations

We acknowledge that the study has several potential limitations, however. First, as our sample consisted of retrospective data from a single canter in Japan, our inferences might not be generalizable to other healthcare settings. However, the observed association has plausible mechanisms and persisted across different analytical assumptions. Although formal validation of the study in other healthcare settings is warranted, our inferences are likely present in different practical settings. Second, we did not collect the complete data of daily living activities and medication use before cardiac arrest. However, an experienced emergency physician or cardiologist assessed whether or not the cause of cardiac arrest was a treatable and appropriate condition for ECPR implementation based on information gained from the patient's relatives and cardiac arrest situation. Third, because no patient survived with neurologically favourable outcomes among patients aged ≥75 years, multivariable logistic regression model did not fit to examine the association between age ≥75 and neurologically favourable outcomes. Nevertheless, the impact of our finding — no patient survived with neurologically favourable outcomes — might be supported by the underlying biological vulnerability among elderly patients. In addition, the limited statistical power might be the reason for the inconsistent association between age ≥75 years and one-month survival in the unadjusted model. Finally, although the implementation for ECPR was assessed based on the protocol and by experienced physicians, our data are subject to selection bias. In general, however, the implementation of ECPR for elderly patients was the stricter than that for younger patients, which might have biased our conclusions toward the null.

Conclusions

Our analysis of consecutive data from a tertiary care hospital in an urban area of Japan demonstrated that advanced age was a significant factor in poor one-month survival.

Furthermore, no patient survived with neurological outcomes among age ≥75 years. Our findings might help improve survival rates and neurological outcomes of OHCA elderly patients and facilitate further observation, intervention, and discussion regarding the utilization of ECPR for elderly patients with OHCA.

List of abbreviations: out-of-hospital cardiac arrest, OHCA; extracorporeal cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY; confidence interval, CI

DISCLOSURES:

Ethics approval and consent to participate and Consent for publication: The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

Availability of data and materials: The data used in this study were not publically available.

Competing interests: There are no conflict of interest.

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Authors' contributions: TG, SM, NT, HS, YH and Taka planned the study. TKit provided statistical advice on study design. TG analysed the data. TG drafted the manuscript, and all authors contributed substantially to its revision. TG takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Table 1. Implementation Criteria for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre

Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.	
Indication criteria	
Absolute indication	Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)
Relative indication	Presumed treatable conditions*
	Hypothermia
	Drug intoxication
Exclusion criteria	
Stroke	
Terminal malignancy	
Cirrhosis	
Chronic obstructive pulmonary disease	
Poor activities of daily living	
In a case who the team leader judged "inadequate indication" for ECPR	

Abbreviations: ECMO, extracorporeal membranous oxygenation; Vf, Ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation

* Judged by an emergency physician who treats the patient with physician-staffed ambulance.

1 **Table 2. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation**

	Overall (n=139)	Age 18-74 years (n=119)	Age ≥75 years (n=20)	P values
Baseline characteristics				
Age, year, median (IQR)	63 (55-71)	60 (53-67)	79 (77-83)	<0.001
Women, n (%)	18 (13%)	17 (14%)	1 (5%)	0.47
Prehospital characteristics, n (%)				
CPR by bystanders	54 (39%)	49 (41%)	5 (25%)	0.22
Shockable rhythm†	121 (88%)	103 (87%)	18 (90%)	1.00
Physician-staffed ambulance	115 (83%)	100 (84%)	15 (75%)	0.34
Re-arrest after ROSC during transportation‡	13 (9%)	12 (10%)	1 (5%)	0.69
Resuscitation time courses, median (IQR)				
Call to Hospital, min	41 (33-50)	40 (33-50)	43 (32-53)	0.77
Call to ECPR, min	56 (49-69)	56 (49-70)	56 (46-65)	0.52
Call to ROSC§ or ECPR, min	54 (46-65)	54 (45-65)	55 (46-59)	0.60
Interventions, n (%)				
Therapeutic hypothermia (completed)	62 (45%)	56 (47%)	6 (30%)	0.22
Intra-aortic balloon pumping	107 (77%)	92 (77%)	15 (75%)	0.78
Causes of cardiac arrest, n (%)				
Acute myocardial infarction	98 (71%)	83 (70%)	15 (75%)	0.79
Structural heart disease	10 (7%)	9 (8%)	1 (5%)	1.00
Aortic dissection	6 (4%)	5 (4%)	1 (5%)	1.00
Arrhythmia	6 (4%)	5 (4%)	1 (5%)	1.00
Asphyxia	3 (2%)	2 (2%)	1 (5%)	1.00

Other*	6 (4%)	6 (5%)	0 (0%)	1.00
Unknown	10 (7%)	9 (8%)	1 (5%)	1.00

Abbreviation: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Septic shock, asthma, and pulmonary hypertension.

† Ventricular fibrillation and pulseless ventricular tachycardia.

‡ Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

§ Defined as spontaneous circulation sustained for ≥20 minutes.

1 **Table 3. Univariable and Multivariable Associations Between Age categories and Outcomes in OHCA patients**

	ORs (95% CI)*					
	Primary model		Sensitivity analysis			
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
One-month survival						
≥75 years old (vs. <75 years old)	0.43 (0.10-2.03)	0.36 (0.05-1.45)	-	-	-	-
≥70 years old (vs. <70 years old)	-	-	0.27 (0.08-0.95)	0.21 (0.04-0.71)	-	-
≥65 years old (vs. <65 years old)	-	-	-	-	0.66 (0.28-1.58)	0.60 (0.23-1.51)
Neurologically favourable outcomes						
≥75 years old (vs. <75 years old)	N/A†	N/A†	-	-	-	-
≥70 years old (vs. <70 years old)	-	-	0.29 (0.04-2.41)	0.28 (0.01-1.63)	-	-
≥65 years old (vs. <65 years old)	-	-	-	-	0.90 (0.23-3.52)	0.89 (0.21-3.51)

Abbreviation: OHCA, out-of-hospital cardiac arrest; OR, odds ratio; CI, confidence interval.

*Adjusted for sex, CPR by bystanders, shockable rhythm, and therapeutic hypothermia.

†No patient aged ≥75 years survived with neurologically favourable outcomes.

2

3

1 **FIGURE LEGENDS**

2 **Figure 1.** Patients receiving extracorporeal cardiopulmonary resuscitation

3 **Figure 2.** Univariable associations between age and outcomes.

4

Figure 1

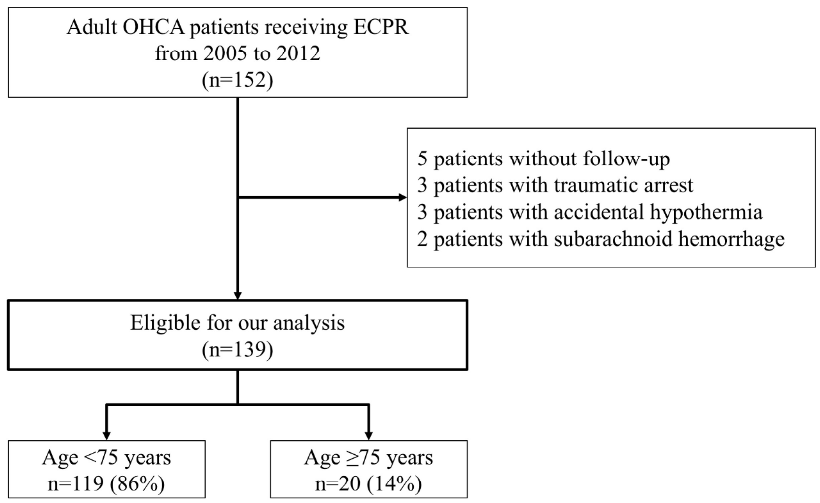

Figure 1

1057x793mm (72 x 72 DPI)

Figure 2A

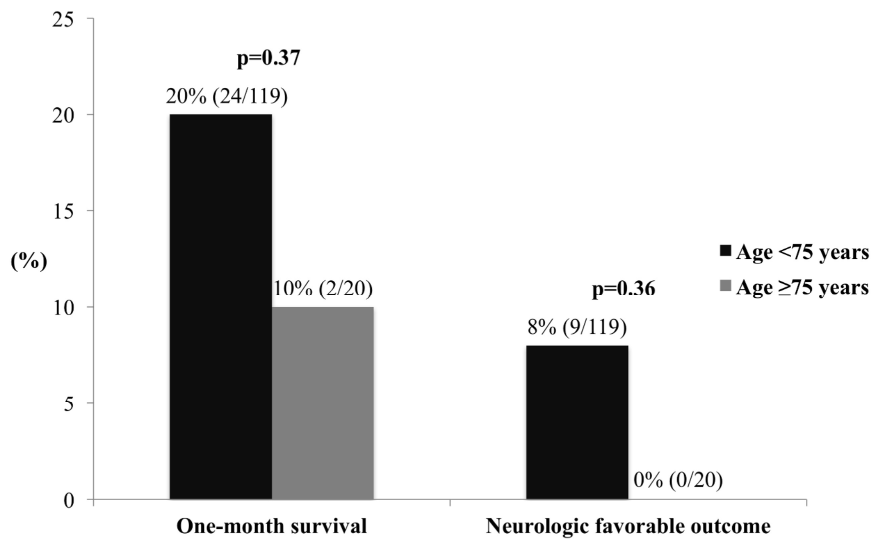

Figure 2A

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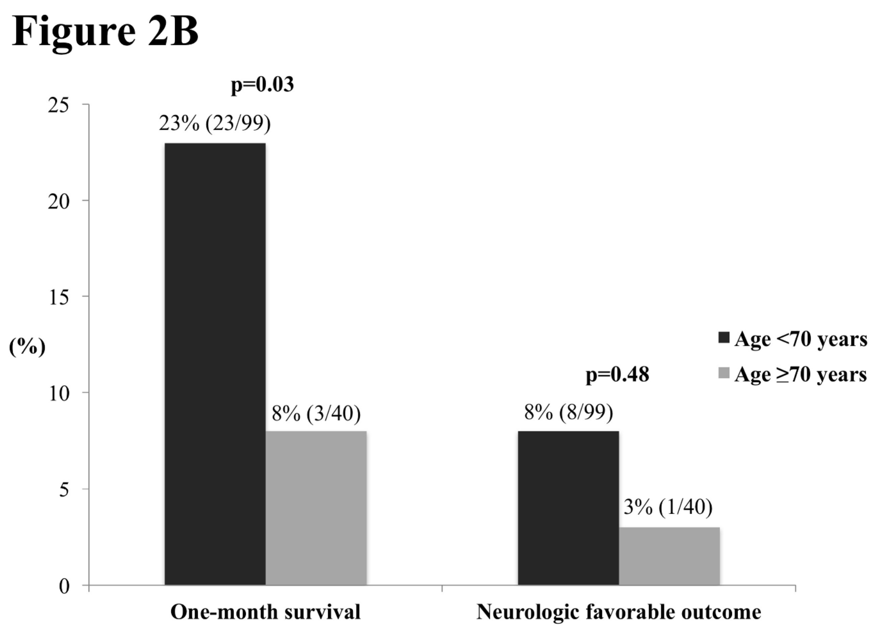

Figure 2C

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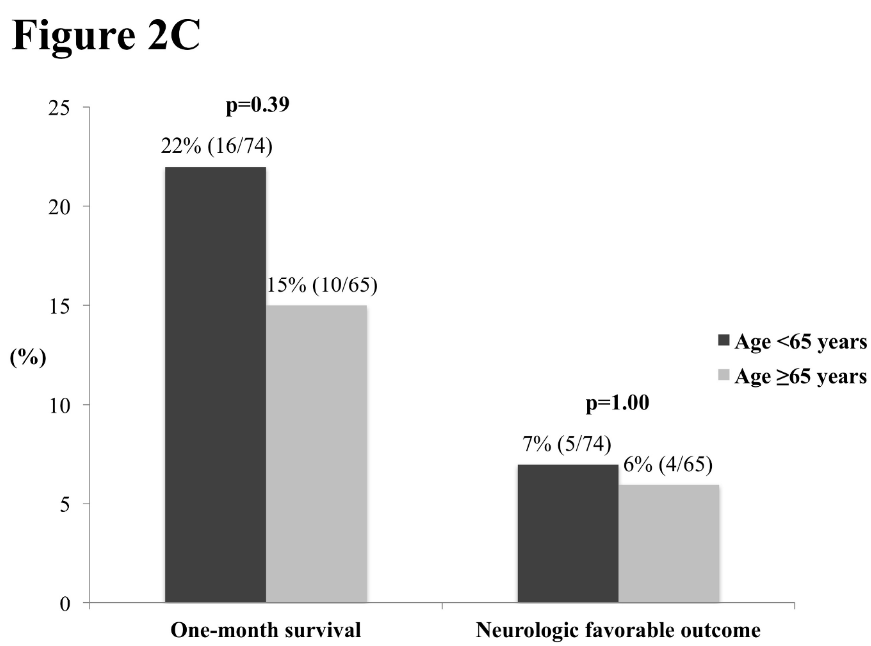

Figure 2C

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,9
		(b) Indicate number of participants with missing data for each variable of interest	8,9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8,9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8,9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	8,9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8,9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11, 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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ABSTRACT

objectives: Little is known about the effectiveness of extracorporeal resuscitation (ECPR) for elderly patients with out-of-hospital cardiac arrest (OHCA). The aim of this study was to examine the impact of age on outcomes among OHCA patients treated with ECPR.

design: Single-centre retrospective cohort study.

setting: A critical care centre that covers a population of approximately 1 million residents.

participants: Consecutive OHCA patients aged ≥18 years who underwent ECPR from 2005 to 2013.

primary and secondary outcome measures: Primary outcomes were one-month neurologically favourable outcomes and survival. Outcomes were compared between patients aged <75 years and those aged ≥75 years. In the sensitivity analysis, analyses were repeated using decade of age as a categorical variable.

Results: Overall, 144 OHCA patients who underwent ECPR were eligible for our analyses. Of these, 122 patients were aged <75 years and 22 patients were aged ≥75 years. Among OHCA patients aged ≥75 years, no patient survived with neurologically favourable outcomes, whereas 8% of patients aged <75 years survived with neurologically favourable outcomes

(0% [95CI 0%-0%] vs. 8% [95%CI 4%-15%]). Likewise, the proportion of one-month survival was lower in patients aged ≥75 years compared to those in aged <75 years (14% [4%-36%] vs. 20% [14%-29%]). These associations between advanced age and poor outcomes remained in the multivariable adjusted models, and the sensitivity analysis using decades of age as a categorical variable.

Conclusions: In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, the one-month neurological survival in 122 patients aged 75 years was 8%, whereas none of the 22 patients aged ≥75 years survived with intact neurological outcomes. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥75 years.

Keywords: extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly

Strengths and limitations of this study

1. This study is the first study investigating the impact of age on outcomes among OHCA patients treated with ECPR, including patients aged ≥75 years.
2. Our sample consisted of retrospective data from a single centre in Japan with a limited sample size; thereby our inferences might not be generalizable to other healthcare settings.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.[1-3] In 2014, the national annual number of OHCA of cardiac origin was 70,000 in Japan,[4] with an increase in the number of elderly patients.[5] As the aging population is expected to grow further in Japan[6] as well as other developed nations, the increased incidence of OHCA in elderly patients will become a further burden.[5] There is, therefore, a compelling need to develop optimal management strategies and policies to treat OHCA in elderly patients.

To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR) for patients with OHCA have been shown as a highly advanced medical treatment.[7-10] The recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science*.[1] In addition, the *European Resuscitation Council Guidelines for Resuscitation* recommends the consideration of ECPR for cases such as paediatric resuscitation and asthma-related cardiac arrest.[11] Further, subsequent observational studies have demonstrated that the utilization of ECPR was associated with improved survival compared to conventional cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable conditions.[12,13] The indication of ECPR for OHCA might, therefore, be extended in the future. However, the utilization of ECPR for elderly patients — a population with limited cardiovascular and pulmonary reserve — remains controversial.[14] Indeed, ECPR clinical protocols are likely to include an age limit as a contraindication of ECPR, whereas there is not sufficient supporting evidence.[15] Although some reports suggest that an age of ≥75 years should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,[16,17] a literature using the international Extracorporeal Life Support Organization registry suggested that age should not be a bar against the consideration of the utilization of ECMO in elderly patients.[18] Furthermore, a recent systematic review of prognostic factors for ECPR recipients following OHCA has failed to establish a link between age and poor prognosis following ECPR.[19]

To address this knowledge gap in the literature, we assessed the neurological outcomes and mortality of elderly patients with OHCA who underwent ECPR, using consecutive data from a critical care centre in Osaka, the second largest prefecture in Japan.

2. Material and Methods

2.1. Study design and settings

This retrospective analysis of medical records from a single centre in Japan was conducted at Osaka Saiseikai Senri Hospital, a critical care centre approved by the Ministry of Health, Labour and Welfare and located in the northern city of Suita, Osaka, Japan. This hospital covers a population of approximately 1 million residents, treating 200 to 250 OHCA patients annually. In this area, for all OHCA patients including suspected OHCA (based on the information provided by the emergency telephone call from the patient containing keywords that indicate heart attack or cardiac arrest), the Fire-Defense Headquarters requested the mobilization of a physician-staffed ambulance from our Hospital. All OHCA patients are transported to the hospital, regardless of whether ROSC was achieved (i.e., none are declared dead at the scene). The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

2.2. Selection of participants and data collection

We abstracted data from medical records of consecutive OHCA patients aged ≥18 years old who underwent ECPR between January 2005 and September 2013. In our centre, all OHCA patients including EMS-witnessed cases are recorded in the form of an electronical medical chart as our data resource. We abstracted necessary data from the medical chart for this study. For all OHCA patients, the emergency physician assessed the indications for ECPR during transportation and then informed the hospital medical staff in the emergency department via telephone. To confirm the eligibility of ECPR for OHCA patients, in our critical care medical centre, the on-site physicians used mobile phones to discuss the eligibility of ECPR with other in-hospital attending physicians. In the present study, approximately 80% of OHCA cases were transported by physician-staffed ambulances, and all patients were treated by emergency physicians and the Advanced Cardiac Life Support guidelines of the emergency department.[20]

Indications of ECPR for OHCA patients are shown in **Table 1**. Absolute indications for ECPR were OHCA patients with refractory ventricular fibrillation (Vf), defined as sustained Vf after three attempts of defibrillation with potentially treatable conditions. Relative indications for ECPR were OHCA patients with presumably treatable conditions with pulseless electrical activity or asystole, hypothermia, and drug intoxicatoin. Patient age was not considered when using ECPR. Patients with the following were excluded: stroke, terminal malignancy, cirrhosis, severe chronic obstructive pulmonary disease, poor daily living activities, and assessed as “inadequate indications” for ECPR by the team leader.

2.3. ECMO management and post-resuscitation care

The final decision to initiate ECPR depended on the opinions of the attending physicians. To achieve successful and rapid implementation, the ECMO team consisted of emergency physicians, cardiologists, and clinical engineers. Chest compression was continued until starting ECMO. The percutaneous cannulation technique for venous and arterial ECMO accesses was used to deliver ECMO with a 13.5 F arterial cannulae or a 19.5 F venous cannulae via femoral artery or vein. The cannulation was performed in the ED or ED adjoining cardiac catheterization room. Urgent coronary angiography was performed for OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial infarction were performed a primary percutaneous intervention with conventional technique for culprit lesions. All post-resuscitated patients after implementation of ECMO received guideline recommended care,[1] regardless of age and clinical diagnosis. The patients were provided adequate oxygenation, vasopressors and fluid administration to maintain systolic arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage equivalent to brain death, withdrawal of ECMO was considered.

2. 4 Data collection and Quality control

The measured variables were patient demographics, prehospital characteristics (i.e., time-course, initial rhythm, presence of return of spontaneous circulation, and managements), resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic balloon pumping), and the cause of cardiac arrest. The attending physician at the morning conference decided the cause of cardiac. Prehospital variables were collected by the information from paramedics and the emergency physicians who treated the patient with physician-staffed ambulance. The resuscitation time-course was collected by the emergency physician who treated the patient with the physician-staffed ambulance and medical staff in the emergency department. Other measurements including post resuscitation care were recorded by the attending physician using a standardized data collection form.

2.5. Outcomes

Outcomes of interest were one-month neurologically favourable outcomes and survival. Neurologically favourable outcomes were defined as a Cerebral Performance Categories (CPC) score of 1 or 2.[21] The attending physician in-charge of the rounds or the outpatient determined the CPC score.

2.6. Statistical analyses

To assess the association between advanced age and outcomes, "elderly" patients were defined as those aged ≥75 years, as previously reported.[2,22,23] Patients characteristics and outcomes were compared between those aged <75 years and those aged ≥75 years. Continuous data were presented as the median (interquartile) with differences analysed using the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with differences analysed using chi-square test or Fischer's exact test as appropriate. We also illustrated the associations between age and each outcome by using a LOWESS smoother with calculating 95% confidence interval using a bootstrap method.

A multivariable logistic regression model was fitted to study the association between patient age and outcomes. Potential confounding factors based on biological plausibility and previous studies were included.[2,8,10,24] Variables included gender, shockable rhythm, witnessed arrest, and CPR by bystanders. Shockable rhythm was defined as Vf and pulseless ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. Odds ratios (ORs) and confidence intervals (CIs) were then calculated. In the sensitivity analysis, to assess the consistency of the associations between advanced age and outcomes, we further repeated the analysis using age as a categorical variable: age ≤39, 40-49, 50-59, 60-69, 70-79, and >80 years. We analyzed data using STATA 15.0 (StataCorp, College Station, TX) and R statistical software (version 3.4.0).

3. Results

During the study period, 152 consecutive OHCA patients underwent ECPR. Among them we excluded five patients without follow-up as they were transported to another hospital for further advanced care (e.g., implementation of left ventricular assistive device) and another three patients with traumatic arrest, leaving 144 patients eligible for our analysis (122 patients in the <75 years group and 22 patients in the ≥75 years group; **Supplemental Figure**

1).

Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 15% of patients were women (**Table 2**). In 38% of cases, a bystander performed CPR. Shockable rhythm (i.e., Vf and pulseless VT) accounted for 61% of cases. Physician-staffed ambulances transported 81% of cases. The median time from call to arrival at the hospital was 41 min (IQR, 33-50 min), and from call to implementation of ECMO was 57 min (IQR, 49-70 min). On admission, the median pH value was 6.95 and median serum lactate level was 12.5 mmol/L. For post-resuscitation therapy, therapeutic hypothermia was completed in 44% of patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately 70% of cardiac arrests were caused by acute myocardial infarction. There were no significant differences in prehospital characteristics, resuscitation time-course, interventions, and causes of cardiac arrest between patients aged ≥75 years and those aged <75 years, while the pH value and serum lactate level were preferable (i.e., high pH value and low lactate level) in patients aged ≥75 years, compared to those aged <75 years. Detailed information on patient characteristics according to decades of age is shown in **Supplemental Table 1**.

Overall, the proportion of neurologically favourable outcomes was 7% (95% CI, 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. **Figure 1** illustrates the associations between age and each outcome. The rate of one-month neurologically favourable outcomes remained around 8% between 18 and 70 years and decreased as age increased. Likewise, the rate of one-month survival remained around 20% between 18 and 70 years and decreased as age increased as age increased, with a highest survival rate at age 60 years.

Table 3 demonstrates the associations between age and outcomes. Among patients aged ≥75 years, no patient survived with neurologically favourable outcomes, although 8% of patients aged <75 years survived with neurologically favourable outcomes (0% [95CI

0%-0%] vs. 8% [95%CI 4%-15%]). The proportion of one-month survival was lower in patients aged ≥75 years than in those aged <75 years (14% [95%CI 4%-36%] vs. 20% [95%CI 14%-29%]). These associations remained in the unadjusted and adjusted models.

In the sensitivity analysis using decades of age, although the samples size was limited, advanced age (age 70-79 years and age 80-89 years) was associated with poor one-month neurologically favourable outcomes and survival compared to age 18-39 years (**Table 3**).

4. Discussion

In this retrospective analysis from an urban critical care hospital, we found that advanced age was likely to be associated with the lower rate of one-month neurologically favourable outcomes and survival in patients with OHCA who underwent ECPR, although the limited number of cases did not detect statistical significance. The rate of neurologically favourable outcomes and one-month survival decreased after age 70 years old. Surprisingly, no patient aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. These findings provide valuable clues for creating optimal strategy for elderly patients with OHCA in the aging era.

Our study observed that no patients aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. Although previous studies reported that ECPR was more effective in treating OHCA patients than conventional CPR, these studies did not assess the effect of advanced age – their findings were based on studies limited to patients aged <75 years.[9,10] A multicentre prospective observational study in Japan demonstrated that the survival rate at one-month after cardiac arrest was significantly higher in the ECPR group than in the non-ECPR group (27% vs. 6%) and that the proportion of neurologically favourable outcomes was also significantly higher in the ECPR group (12.3% vs. 1.5%).[10] Our results that overall one-month survival rate of 20% and one-month survival with neurologically favourable outcomes of 8% are comparable results with these previous findings,[9,10] despite we included patients aged ≥75 years. Therefore, focusing on the elderly patients, our findings might suggest limitations in using ECPR to treat elderly patients with OHCA.

The reasons for the observed lack of effectiveness of ECPR among elderly patients are likely multifactorial. First, consistent with the elderly being the population with limited cardiovascular and pulmonary reserve, the survival rate of OCHA patients was lower in older patients than in younger patients.[25] An observational study in the US demonstrated that advanced age was a factor associated with lower survival rate at discharge among OHCA patients (19.4% for ≤80 years vs. 9.4% for 80-89 years, and 4.4% for ≥90 years).[25] Second, shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an observational study in the US, shorter duration of CPR was associated with neurologically favourable outcomes – 90% of patients with neurologically favourable outcomes required less than 16 minutes of CPR.[26] In our findings, the median time from cardiac arrest to ROSC or implementing of ECMO was 54 min, which is considerably longer than in the previous study in the US.[26] However, patients who require ECPR are "non-responders" to conventional CPR within 20 minutes.[12] In addition, another ECPR study also showed a lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our findings.[8] Due to the vulnerability of elderly patients, elderly patients might not withstand the prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable population and a longer CPR duration may help explain the lack of effectiveness of ECPR for elderly patients with OHCA in the present study.

Importantly, the cost burden of ECPR is also significant. In Japan, the incremental cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted life-year (QALY).[27] Considering the acceptable ICER for introducing a new treatment is approximately £20,000-30,000,[28] this financial burden is unacceptably high. Further, another Japanese study suggested that the average cost for treating an OHCA patient was approximately £1,250.[29] Aging, and its associated costs are increasing, constituting an enormous financial burden throughout the developed world. Given this significant financial burden and our present observations (i.e. the low rate of neurologic outcomes and survival in patients aged ≥75), indications of ECPR in elderly patients with OHCA might be limited with respect to cost-effectiveness. Our observations facilitate further investigations to elucidate the cost-effectiveness of ECPR for elderly patients with OHCA.

Despite the significant healthcare resource burden of ECPR, the present study did not demonstrate the effectiveness of ECPR for elderly patients with OHCA. However, this does not indicate that CPR should not be utilized for elderly patients. Although advanced age could be a factor associated with poor outcomes in OHCA patients in the present study, this factor alone does not appear to be a well established criterion to deny patients for conventional CPR based on a previous report.[25] Additionally, experts say that decisions regarding termination of resuscitation should not be based on age.[30] However, given our present findings regarding poor outcomes among elderly patients and the extremely high cost of ECPR, the indication of ECPR for elderly patients should be carefully considered in this aging era.

Limitations

We acknowledge several potential limitations to our study. First, as our sample consisted of retrospective data from a single centre in Japan, our inferences might not be generalizable to other healthcare settings. However, the observed association not only has plausible mechanisms but also persisted across different analytical assumptions. Although formal validation of the study in other healthcare settings is warranted, our inferences likely present in different practical settings. Second, there was lack of data on daily living activities, medication use, comorbidities before cardiac arrest including a poorer neurological state pre-arrest. In addition, information on whether the ECPR was implemented during active chest compressions and on the results of percutaneous coronary intervention was also not available. However, an experienced emergency physician or cardiologist assessed whether the cause of cardiac arrest was treatable and appropriate for ECPR based on information gained from the person accompanying the patient and the situation of cardiac arrest. Third, because no patient survived with neurologically favourable outcomes among patients aged ≥75 years, multivariable logistic regression model did not fit to examine the association between age ≥75 and neurologically favourable outcomes. Nevertheless, the impact of our finding — no patient survived with neurologically favourable outcomes — might be supported by the underlying biological vulnerability among elderly patients. In addition, the nonstatistical differences in the outcomes between age <75 group and age ≥75 group might be attributable to the small sample size in age ≥75 group (n=22). Finally, although the indication for ECPR was assessed based on the protocol and by experienced physicians, our data are subject to selection bias. In general, however, the indication of ECPR for elderly patients was stricter than that for younger patients, which might have biased our conclusions toward the null.

Conclusions

In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, the one-month neurological survival in 122 patients aged 75 years was 8%, whereas none of the 22 patients aged ≥75 years survived with intact neurological outcomes. The one-month survival was 20% in patients <75 years and 14% in patients aged ≥75 years.

These associations between advanced age and poor outcomes were consistent in the sensitivity analysis using decades of age as a categorical variable. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥75 years. In addition, clinicians should carefully select patients up to age 70-75. While the eligibility of ECPR should not be determined by age as a single variable, our findings might not only help improve the survival rate and neurological outcomes of elderly patients with OHCA but also facilitate further observation, intervention, and discussion regarding the utilization of ECPR for elderly patients with OHCA.

List of abbreviations: out-of-hospital cardiac arrest, OHCA; extracorporeal cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY; confidence interval, CI

DISCLOSURES:

Ethics approval and consent to participate and Consent for publication: The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

Availability of data and materials: The data used in this study were not publically available.

Competing interests: There are no conflict of interest.

Funding: None

Authors' contributions: TG, SM, NT, HS, YH and Tkai planned the study. TKit supervised and provided statistical advice on study design. TG analysed the data. TG drafted the manuscript, and all authors contributed substantially to its revision. TG takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Table 1. Indications for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre

Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.	
Indication criteria	
Absolute indication	Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)
Relative indication	Presumed treatable conditions with PEA/Asystole*
	Hypothermia
	Drug intoxication
Exclusion criteria	
Stroke	
Terminal malignancy	
Cirrhosis	
Chronic obstructive pulmonary disease	
Poor activities of daily living	
In a case who the team leader judged "inadequate indication" for ECPR	

Abbreviations: ECMO, extracorporeal membranous oxygenation; Vf, Ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; PEA, pulseless electrical activity

* Judged by an emergency physician who treats the patient with physician-staffed ambulance according to he initial rhythm.

1 **Table 2. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation**

	Overall (n=144)	Age 18-74 years (n=122)	Age ≥75 years (n=22)
Baseline characteristics			
Age, year, median (IQR)	63 (55-71)	60 (53-67)	80 (77-83)
Women, n (%)	22(15%)	19 (16%)	3 (14%)
Prehospital characteristics, n (%)			
CPR by bystanders	54 (38%)	49 (40%)	5 (23%)
Shockable rhythm*	88 (61%)	78 (64%)	10 (45%)
Physician-staffed ambulance	117 (81%)	102 (84%)	15 (68%)
Re-arrest after ROSC during transportation†	14 (10%)	12 (10%)	2 (9%)
Resuscitation time courses, median (IQR)			
Call to Hospital, min	41 (33-50)	40 (33-50)	43 (32-51)
Call to ECPR, min	57 (49-70)	57 (50-70)	57 (47-66)
Call to ROSC‡or ECPR, min	54 (46-65)	54 (46-65)	55 (46-59)
Blood test on admission			
pH, mean (IQR)	6.95 (6.80-7.10)	6.93 (6.80-7.08)	7.09 (6.93-7.16)
Serum lactate, mmol/L, mean (IQR)	12.5 (9.8-14.7)	12.8 (10.5-15.1)	10.5 (8.0-11.4)
Interventions, n (%)			
Therapeutic hypothermia (completed)	63 (44%)	57 (47%)	6 (27%)
Intra-aortic balloon pumping	111 (77%)	94 (77%)	17 (77%)
Causes of cardiac arrest, n (%)			
Acute myocardial infarction	100 (69%)	84 (69%)	16 (73%)
Structural heart disease	11 (8%)	9 (8%)	1 (5%)

Aortic dissection	6 (4%)	5 (4%)	1 (5%)
Arrhythmia	6 (4%)	5 (4%)	1 (5%)
Asphyxia	3 (2%)	2 (2%)	1 (5%)
Other§	7 (5%)	6 (5%)	1 (5%)
Unknown	12 (8%)	11 (9%)	1 (5%)

Abbreviation: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Ventricular fibrillation and pulseless ventricular tachycardia.

† Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

‡ Defined as spontaneous circulation sustained for ≥20 minutes.

§ Accidental hypothermia, asthma, pulmonary hypertension, septic shock, and subarachnoid haemorrhage.

1 **Table 3. Univariable and Multivariable Associations Between Age categories and Outcomes in OHCA patients**

	Number of cases (%)	Unadjusted odds ratios (95% CI)	Adjusted odds rations (95% CI)
Primary analysis			
Neurologically favourable outcomes			
Age 18-74 years (n=122)	10 (8%)	1 (reference)	1 (reference)
Age ≥75 years (n=22)	0 (0%)	N/A	N/A
One-month survival			
Age 18-74 years (n=122)	25 (20%)	1 (reference)	1 (reference)
Age ≥75 years (n=22)	3 (14%)	0.61 (0.17-2.24)	0.62 (0.16-2.39)
Sensitivity analysis			
Neurologically favourable outcomes			
Age 18-39 years (n=12)	2 (17%)	1 (reference)	1 (reference)
Age 40-49 years (n=11)	1 (9%)	0.50 (0.04-6.44)	0.41 (0.03-5.74)
Age 50-59 years (n=35)	1 (3%)	0.15 (0.01-1.79)	0.12 (0.01-1.61)
Age 60-69 years (n=44)	5 (11%)	0.64 (0.10-3.80)	0.57 (0.09-3.70)
Age 70-79 years (n=31)	1 (3%)	0.17 (0.01-2.04)	0.15 (0.01-1.92)
Age ≥80 years (n=11)	0 (0%)	N/A†	N/A†
One-month survival			
Age 18-39 years (n=12)	3 (25%)	1 (reference)	1 (reference)
Age 40-49 years (n=11)	2 (18%)	0.67 (0.09-4.99)	0.49 (0.06-4.04)
Age 50-59 years (n=35)	7 (20%)	0.75 (0.16-3.52)	0.58 (0.12-2.90)
Age 60-69 years (n=44)	12 (27%)	1.13 (0.26-4.87)	0.91 (0.19-4.34)
Age 70-79 years (n=31)	3 (10%)	0.32 (0.05-1.88)	0.26 (0.04-1.66)
Age ≥80 years (n=11)	1 (10%)	0.30 (0.03-3.42)	0.30 (0.02-3.64)

Abbreviation: OHCA, out-of-hospital cardiac arrest; OR, odds ratio; CI, confidence interval.

*Adjusted for sex, CPR by bystanders, shockable rhythm, and therapeutic hypothermia.

†No patient aged ≥75 years survived with neurologically favourable outcomes.

FIGURE LEGENDS

Figure 1. The associations between and one month neurologically favourable outcomes and survival.

Supplemental Figure 1. Patients receiving extracorporeal cardiopulmonary resuscitation

Figure 1

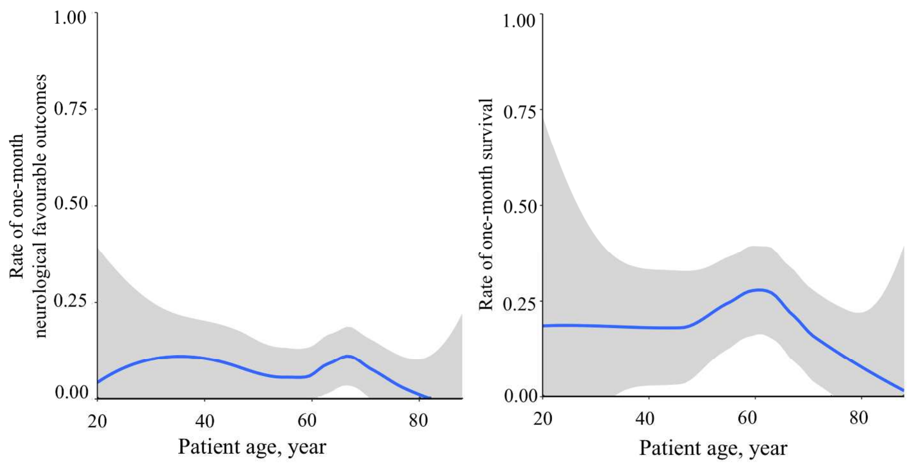

Figure 1

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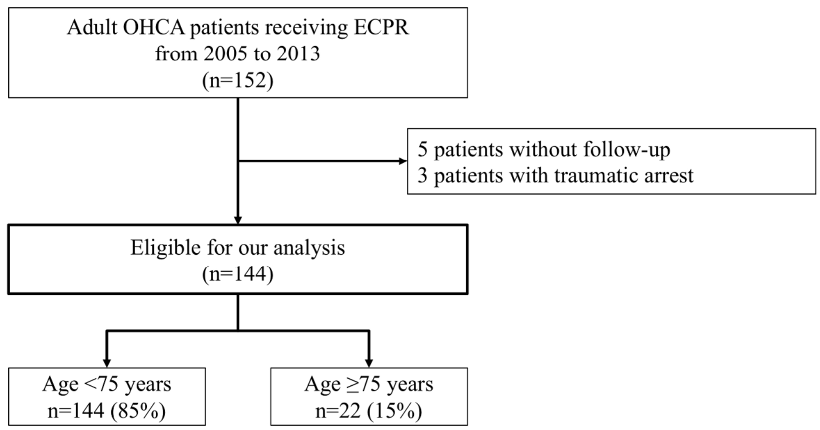
Supplemental Figure 1



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Supplemental Table 1. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation

	Age 18-39 years (n=12)	Age 40-49 years (n=11)	Age 50-59 years (n=35)	Age 60-69 years (n=44)	Age 70-79 years (n=31)	Age ≥ 80 years (n=11)
Baseline characteristics						
Women, n (%)	4 (33%)	3 (27%)	4 (11%)	4 (9%)	4 (13%)	3 (27%)
Prehospital characteristics, n (%)						
CPR by bystanders	5 (42%)	1 (9%)	16 (46%)	18 (41%)	10 (32%)	4 (36%)
Shockable rhythm*	8 (67%)	6 (55%)	27 (77%)	26 (59%)	16 (52%)	5 (45%)
Physician-staffed ambulance	11 (92%)	10 (91%)	28 (80%)	37 (84%)	25 (81%)	6 (55%)
Re-arrest after ROSC during transportation†	0 (0%)	2 (18%)	3 (9%)	6 (14%)	2 (6%)	1 (9%)
Resuscitation time courses, median (IQR)						
Call to Hospital, min	48 (32-55)	36 (33-51)	40 (30-46)	40 (32-50)	43 (33-51)	44 (32-61)
Call to ECPR, min	64 (53-76)	59 (47-78)	54 (48-67)	56 (49-66)	58 (51-68)	60 (46-74)
Call to ROSC‡ or ECPR, min	68 (58-78)	50 (42-78)	53 (38-64)	54 (46-63)	55 (46-63)	47 (43-66)
Blood test on admission						
pH, mean (IQR)	6.75 (6.64-7.01)	6.88 (6.75-7.12)	6.92 (6.72-7.03)	6.95 (6.85-7.11)	7.05 (6.84-7.18)	7.02 (6.88-7.16)
Serum lactate, mmol/L, mean (IQR)	15.1 (13.2-19.7)	13.9 (11.7-17.6)	13.3 (10.6-16.9)	12.5 (9.6-14.1)	11.1 (9.1-12.5)	9.6 (7.6-11.3)
Interventions, n (%)						
Therapeutic hypothermia (completed)	4 (33%)	7 (64%)	12 (34%)	24 (55%)	14 (45%)	2 (18%)
Intra-aortic balloon pumping	8 (67%)	11 (100%)	26 (74%)	33 (75%)	23 (74%)	10 (91%)
Causes of cardiac arrest, n (%)						
Acute myocardial infarction	4 (33%)	9 (82%)	27 (77%)	30 (68%)	22 (71%)	8 (73%)
Other cardiovascular diseases§	6 (50%)	1 (9%)	6 (17%)	5 (11%)	5 (16%)	1 (9%)

Other reasons**	2 (17%)	1 (9%)	2 (6%)	9 (20%)	4 (13%)	2 (18%)

Abbreviation: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Ventricular fibrillation and pulseless ventricular tachycardia.

† Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

‡ Defined as spontaneous circulation sustained for ≥20 minutes.

§ Aortic dissection, structural heart disease, and arrhythmia

** Accidental hypothermia, asphyxia, asthma, pulmonary hypertension, septic shock, and subarachnoid haemorrage.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	8-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Resuscitation, Emergency Medicine, cardiac arrest, elderly, Extracorporeal membrane oxygenation

Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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ABSTRACT

objectives: Little is known about the effectiveness of extracorporeal resuscitation (ECPR) for elderly patients with out-of-hospital cardiac arrest (OHCA). The aim of this study was to examine the impact of age on outcomes among OHCA patients treated with ECPR.

design: Single-centre retrospective cohort study.

setting: A critical care centre that covers a population of approximately 1 million residents.

participants: Consecutive OHCA patients aged ≥18 years who underwent ECPR from 2005 to 2013.

primary and secondary outcome measures: Primary outcomes were one-month neurologically favourable outcomes and survival. Outcomes were compared between patients aged <75 years and those aged ≥75 years. In the sensitivity analysis, analyses were repeated using decade of age as a categorical variable.

Results: Overall, 144 OHCA patients who underwent ECPR were eligible for our analyses. Of these, 122 patients were aged <75 years and 22 patients were aged ≥75 years. Among OHCA patients aged ≥75 years, no patient survived with neurologically favourable outcomes, whereas 8% of patients aged <75 years survived with neurologically favourable outcomes

(0% [95CI 0%-0%] vs. 8% [95%CI 4%-15%]). Likewise, the proportion of one-month survival was lower in patients aged ≥75 years compared to those in aged <75 years (14% [4%-36%] vs. 20% [14%-29%]). These associations between advanced age and poor outcomes remained in the multivariable adjusted models, and the sensitivity analysis using decades of age as a categorical variable.

Conclusions: In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, the one-month survival with good neurological outcome in 122 patients aged <75 years was 8%, whereas none of the 22 patients aged ≥75 years survived with intact neurological outcomes. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥75 years.

Keywords: extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly

Strengths and limitations of this study

1. This study is the first study investigating the impact of age on outcomes among OHCA patients treated with ECPR, including patients aged ≥75 years.
2. There are consistent findings in the sensitivity analyses using decade of age as a categorical variable.
3. Our sample consisted of retrospective data from a single centre in Japan with a limited sample size; thereby our inferences might not be generalizable to other healthcare settings.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.[1-3] In 2014, the national annual number of OHCA of cardiac origin was 70,000 in Japan,[4] with an increase in the number of elderly patients.[5] As the aging population is expected to grow further in Japan[6] as well as other developed nations, the increased incidence of OHCA in elderly patients will become a further burden.[5] There is, therefore, a compelling need to develop optimal management strategies and policies to treat OHCA in elderly patients.

To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR) for patients with OHCA have been shown as a highly advanced medical treatment.[7-10] The recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science*.[1] In addition, the *European Resuscitation Council Guidelines for Resuscitation* recommends the consideration of ECPR for cases such as paediatric resuscitation and asthma-related cardiac arrest.[11] Further, subsequent observational studies have demonstrated that the utilization of ECPR was associated with improved survival compared to conventional cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable conditions.[12,13] The indication of ECPR for OHCA might, therefore, be extended in the future. However, the utilization of ECPR for elderly patients — a population with limited cardiovascular and pulmonary reserve — remains controversial.[14] Indeed, ECPR clinical protocols are likely to include an age limit as a contraindication of ECPR, whereas there is not sufficient supporting evidence.[15]Although some reports suggest that an age of ≥75 years should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,[16,17] a literature using the international Extracorporeal Life Support Organization registry suggested that age should not be a bar against the consideration of the utilization of ECMO in elderly patients.[18] Furthermore, a recent systematic review of prognostic factors for ECPR recipients following OHCA has failed to establish a link between age and poor prognosis following ECPR.[19]

To address this knowledge gap in the literature, we assessed the neurological outcomes and mortality of elderly patients with OHCA who underwent ECPR, using consecutive data from a critical care centre in Osaka, the second largest prefecture in Japan.

2. Material and Methods

2.1. Study design and settings

This retrospective analysis of medical records from a single centre in Japan was conducted at Osaka Saiseikai Senri Hospital, a critical care centre approved by the Ministry of Health, Labour and Welfare and located in the northern city of Suita, Osaka, Japan. This hospital covers a population of approximately 1 million residents, treating 200 to 250 OHCA patients annually. In this area, for all OHCA patients including suspected OHCA (based on the information provided by the emergency telephone call from the patient containing keywords that indicate heart attack or cardiac arrest), the Fire-Defense Headquarters requested the mobilization of a physician-staffed ambulance from our Hospital. All OHCA patients are transported to the hospital, regardless of whether ROSC was achieved (i.e., none are declared dead at the scene). The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

2.2. Selection of participants and data collection

We abstracted data from medical records of consecutive OHCA patients aged ≥18 years old who underwent ECPR between January 2005 and September 2013. In our centre, all OHCA patients including EMS-witnessed cases are recorded in the form of an electronical medical chart as our data resource. We abstracted necessary data from the medical chart for this study. For all OHCA patients, the emergency physician assessed the indications for ECPR during transportation and then informed the hospital medical staff in the emergency department via telephone. To confirm the eligibility of ECPR for OHCA patients, in our critical care medical centre, the on-site physicians used mobile phones to discuss the eligibility of ECPR with other in-hospital attending physicians. In the present study, approximately 80% of OHCA cases were transported by physician-staffed ambulances, and all patients were treated by emergency physicians and the Advanced Cardiac Life Support guidelines of the emergency department.[20]

Indications of ECPR for OHCA patients are shown in **Table 1**. Absolute indications for ECPR were OHCA patients with refractory ventricular fibrillation (Vf), defined as sustained Vf after three attempts of defibrillation with potentially treatable conditions. Relative indications for ECPR were OHCA patients with presumably treatable conditions with pulseless electrical activity or asystole, hypothermia, and drug intoxicatoin. Patient age was not considered when using ECPR. Patients with the following were excluded: stroke, terminal malignancy, cirrhosis, severe chronic obstructive pulmonary disease, poor daily living activities, and assessed as "inadequate indications" for ECPR by the team leader.

2.3. ECMO management and post-resuscitation care

The final decision to initiate ECPR depended on the opinions of the attending physicians. To achieve successful and rapid implementation, the ECMO team consisted of emergency physicians, cardiologists, and clinical engineers. Chest compression was continued until starting ECMO. The percutaneous cannulation technique for venous and arterial ECMO accesses was used to deliver ECMO with a 13.5 F arterial cannulae or a 19.5 F venous cannulae via femoral artery or vein. The cannulation was performed in the ED or ED adjoining cardiac catheterization room. Urgent coronary angiography was performed for OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial infarction were performed a primary percutaneous intervention with conventional technique for culprit lesions. All post-resuscitated patients after implementation of ECMO received guideline recommended care,[1] regardless of age and clinical diagnosis. The patients were provided adequate oxygenation, vasopressors and fluid administration to maintain systolic arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage equivalent to brain death, withdrawal of ECMO was considered.

2. 4 Data collection and Quality control

The measured variables were patient demographics, prehospital characteristics (i.e., time-course, initial rhythm, presence of return of spontaneous circulation, and managements), resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic balloon pumping), and the cause of cardiac arrest. The attending physician at the morning conference decided the most likely cause of cardiac arrest. Prehospital variables were collected by the information from paramedics and the emergency physicians who treated the patient with physician-staffed ambulance. The resuscitation time-course was collected by the emergency physician who treated the patient with the physician-staffed ambulance and medical staff in the emergency department. Other measurements including post resuscitation care were recorded by the attending physician using a standardized data collection form.

3.5. Outcomes

Outcomes of interest were one-month neurologically favourable outcomes and survival. Neurologically favourable outcomes were defined as a Cerebral Performance Categories (CPC) score of 1 or 2.[21] The attending physician in-charge of the rounds or the outpatient determined the CPC score.

2.6. Statistical analyses

To assess the association between advanced age and outcomes, "elderly" patients were defined as those aged ≥75 years, as previously reported.[2,22,23] Patients characteristics and outcomes were compared between those aged <75 years and those aged ≥75 years. Continuous data were presented as the median (interquartile) with differences analysed using the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with differences analysed using chi-square test or Fischer's exact test as appropriate. We also illustrated the associations between age and each outcome by using a LOWESS smoother with calculating 95% confidence interval using a bootstrap method.

A multivariable logistic regression model was fitted to study the association between patient age and outcomes. Potential confounding factors based on biological plausibility and previous studies were included.[2,8,10,24] Variables included gender, shockable rhythm, witnessed arrest, and CPR by bystanders. Shockable rhythm was defined as Vf and pulseless ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. Odds ratios (ORs) and confidence intervals (CIs) were then calculated. In the sensitivity analysis, to assess the consistency of the associations between advanced age and outcomes, we further repeated the analysis using age as a categorical variable: age ≤39, 40-49, 50-59, 60-69, 70-79, and >80 years. We also analysed data with excluding patients who were implemented ECMO potentially due to persistent hypotension after ROSC (i.e., patients who had a temporal ROSC during transportation or any comments in the medical record regarding response to the resuscitation). We analyzed data using STATA 15.0 (StataCorp, College Station, TX) and R statistical software (version 3.4.0).

3. Results

During the study period, 152 consecutive OHCA patients underwent ECPR. Among them we excluded five patients without follow-up as they were transported to another hospital for further advanced care (e.g., implementation of left ventricular assistive device) and another three patients with traumatic arrest, leaving 144 patients eligible for our analysis (122 patients in the <75 years group and 22 patients in the ≥75 years group; **Supplemental Figure 1**).

Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 15% of patients were women (**Table 2**). In 38% of cases, a bystander performed CPR. Shockable rhythm (i.e., Vf and pulseless VT) accounted for 61% of cases. Physician-staffed ambulances transported 81% of cases. The median time from call to arrival at the hospital was 41 min (IQR, 33-50 min), and from call to implementation of ECMO was 57 min (IQR, 49-70 min). On admission, the median pH value was 6.95 and median serum lactate level was 12.5 mmol/L. For post-resuscitation therapy, therapeutic hypothermia was completed in 44% of patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately 70% of cardiac arrests were caused by acute myocardial infarction. There were no significant differences in prehospital characteristics, resuscitation time-course, interventions, and causes of cardiac arrest between patients aged ≥75 years and those aged <75 years, while the pH value and serum lactate level were preferable (i.e., high pH value and low lactate level) in patients aged ≥75 years, compared to those aged <75 years. Detailed information on patient characteristics according to decades of age is shown in **Supplemental Table 1**.

Overall, the proportion of neurologically favourable outcomes was 7% (95% CI, 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. **Figure 1** illustrates the associations between age and each outcome. The rate of one-month neurologically favourable outcomes remained around 8% between 18 and 70 years and decreased as age increased. Likewise, the rate of one-month survival remained around 20%

between 18 and 70 years and decreased as age increased as age increased, with a highest survival rate at age 60 years.

Table 3 demonstrates the associations between age and outcomes. Among patients aged ≥75 years, no patient survived with neurologically favourable outcomes, although 8% of patients aged <75 years survived with neurologically favourable outcomes (0% [95CI 0%-0%] vs. 8% [95%CI 4%-15%]). The proportion of one-month survival was lower in patients aged ≥75 years than in those aged <75 years (14% [95%CI 4%-36%] vs. 20% [95%CI 14%-29%]). These associations remained in the unadjusted and adjusted models.

In the sensitivity analysis using decades of age, although the samples size was limited, advanced age (age 70-79 years and age 80-89 years) was associated with poor one-month neurologically favourable outcomes and survival compared to age 18-39 years (**Table 3**). After excluding patients who were implemented ECMO potentially due to persistent hypotention after ROSC, there were 71 patients in aged <75 years and 12 patients in aged ≥75 years. The survival rate was 18% (95%CI 12%-31%) in aged <75 years, while no patient survived in patients aged ≥75 years (p=0.09). There were 5 patients (7%; 95%CI 3%-16%) with neurologically favourable outcome in aged <75 years.

4. Discussion

In this retrospective analysis from an urban critical care hospital, we found that advanced age was likely to be associated with the lower rate of one-month neurologically favourable outcomes and survival in patients with OHCA who underwent ECPR, although the limited number of cases did not detect statistical significance. The rate of neurologically favourable outcomes and one-month survival decreased after age 70 years old. Surprisingly, no patient aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. These findings provide valuable clues for creating optimal strategy for elderly patients with OHCA in the aging era.

Our study observed that no patients aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. Although previous studies reported that ECPR was more effective in treating OHCA patients than conventional CPR, these studies did not assess the effect of advanced age – their findings were based on studies limited to patients aged <75 years.[9,10] A multicentre prospective observational study in Japan demonstrated that the survival rate at one-month after cardiac arrest was significantly higher in the ECPR group than in the non-ECPR group (27% vs. 6%) and that the proportion of neurologically favourable outcomes was also significantly higher in the ECPR group (12.3% vs. 1.5%).[10] Our results that overall one-month survival rate of 20% and one-month survival with neurologically favourable outcomes of 8% are comparable results with these previous findings,[9,10] despite we included patients aged ≥75 years. Therefore, focusing on the elderly patients, our findings might suggest limitations in using ECPR to treat elderly patients with OHCA.

The reasons for the observed lack of effectiveness of ECPR among elderly patients are likely multifactorial. First, consistent with the elderly being the population with limited cardiovascular and pulmonary reserve, the survival rate of OCHA patients was lower in older patients than in younger patients.[25] An observational study in the US demonstrated that advanced age was a factor associated with lower survival rate at discharge among OHCA patients (19.4% for ≤80 years vs. 9.4% for 80-89 years, and 4.4% for ≥90 years).[25] Second, shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an observational study in the US, shorter duration of CPR was associated with neurologically favourable outcomes – 90% of patients with neurologically favourable outcomes required less than 16 minutes of CPR.[26] In our findings, the median time from cardiac arrest to ROSC or implementing of ECMO was 54 min, which is considerably longer than in the previous study in the US.[26] However, patients who require ECPR are "non-responders" to conventional CPR within 20 minutes.[12] In addition, another ECPR study also showed a lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our findings.[8] Due to the vulnerability of elderly patients, elderly patients might not withstand the prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable population and a longer CPR duration may help explain the lack of effectiveness of ECPR for elderly patients with OHCA in the present study.

Importantly, the cost burden of ECPR is also significant. In Japan, the incremental cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted life-year (QALY).[27] Considering the acceptable ICER for introducing a new treatment is approximately £20,000-30,000,[28] this financial burden is unacceptably high. Further, another Japanese study suggested that the average cost for treating an OHCA patient was approximately £1,250.[29] Aging, and its associated costs are increasing, constituting an enormous financial burden throughout the developed world. Given this significant financial burden and our present observations (i.e. the low rate of neurologic outcomes and survival in patients aged ≥75), indications of ECPR in elderly patients with OHCA might be limited with respect to cost-effectiveness. Our observations facilitate further investigations to elucidate the cost-effectiveness of ECPR for elderly patients with OHCA.

Despite the significant healthcare resource burden of ECPR, the present study did not demonstrate the effectiveness of ECPR for elderly patients with OHCA. However, this does not indicate that CPR should not be utilized for elderly patients. Although advanced age could be a factor associated with poor outcomes in OHCA patients in the present study, this factor alone does not appear to be a well established criterion to deny patients for conventional CPR based on a previous report.[25] Additionally, experts say that decisions regarding termination of resuscitation should not be based on age.[30] However, given our present findings regarding poor outcomes among elderly patients and the extremely high cost of ECPR, the indication of ECPR for elderly patients should be carefully considered in this aging era.

Limitations

We acknowledge several potential limitations to our study. First, as our sample consisted of retrospective data from a single centre in Japan, our inferences might not be generalizable to other healthcare settings. However, the observed association not only has plausible mechanisms but also persisted across different analytical assumptions. Although formal validation of the study in other healthcare settings is warranted, our inferences likely present in different practical settings. Second, there was lack of data on daily living activities, medication use, comorbidities before cardiac arrest including a poorer neurological state pre-arrest. In addition, information on whether the ECPR was implemented during active chest compressions and on the results of percutaneous coronary intervention was also not available. However, an experienced emergency physician or cardiologist assessed whether the cause of cardiac arrest was treatable and appropriate for ECPR based on information gained from the person accompanying the patient and the situation of cardiac arrest. Third, because no patient survived with neurologically favourable outcomes among patients aged ≥75 years, multivariable logistic regression model did not fit to examine the association between age ≥75 and neurologically favourable outcomes. Nevertheless, the impact of our finding — no patient survived with neurologically favourable outcomes — might be supported by the underlying biological vulnerability among elderly patients. In addition, the nonstatistical differences in the outcomes between age <75 group and age ≥75 group might be attributable to the small sample size in age ≥75 group (n=22). Fourth, our study might include ECMO cases for persistent hypotension after ROSC. However, there are consistent results after excluding patients who were implemented ECMO potentially due to persistent hypotension after ROSC in the ED. Finally, although the indication for ECPR was assessed based on the protocol and by experienced physicians, our data are subject to selection bias. In general, however, the indication of ECPR for elderly patients was stricter than that for younger patients, which might have biased our conclusions toward the null.

Conclusions

In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, the one-month survival with good neurological outcome in 122 patients aged <75 years was 8%, whereas none of the 22 patients aged ≥75 years survived with intact neurological outcomes. The one-month survival was 20% in patients <75 years and 14% in patients aged ≥75 years. These associations between advanced age and poor outcomes were consistent in the sensitivity analysis using decades of age as a categorical variable. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥75 years. In addition, clinicians should carefully select patients up to age 70-75. While the eligibility of ECPR should not be determined by age as a single variable, our findings might not only help improve the survival rate and neurological outcomes of elderly patients with OHCA but also facilitate further observation, intervention, and discussion regarding the utilization of ECPR for elderly patients with OHCA.

List of abbreviations: out-of-hospital cardiac arrest, OHCA; extracorporeal cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY; confidence interval, CI

DISCLOSURES:

Ethics approval and consent to participate and Consent for publication: The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

Availability of data and materials: The data are not allowed for public use by institutional review board.

Competing interests: There are no conflict of interest.

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Authors' contributions: TG, SM, NT, HS, YH and Tkai planned the study. TKit supervised and provided statistical advice on study design. TG analysed the data. TG drafted the manuscript, and all authors contributed substantially to its revision. TG takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Table 1. Indications for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre

Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.	
Indication criteria	
Absolute indication	Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)
Relative indication	Presumed treatable conditions with PEA/Asystole*
	Hypothermia
	Drug intoxication
Exclusion criteria	
Stroke	
Terminal malignancy	
Cirrhosis	
Chronic obstructive pulmonary disease	
Poor activities of daily living	
In a case who the team leader judged "inadequate indication" for ECPR	

Abbreviations: ECMO, extracorporeal membranous oxygenation; Vf, Ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; PEA, pulseless electrical activity

* Judged by an emergency physician who treats the patient with physician-staffed ambulance according to he initial rhythm.

1 **Table 2. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation**

	Overall (n=144)	Age 18-74 years (n=122)	Age ≥75 years (n=22)
Baseline characteristics			
Age, year, median (IQR)	63 (55-71)	60 (53-67)	80 (77-83)
Women, n (%)	22(15%)	19 (16%)	3 (14%)
Prehospital characteristics, n (%)			
Witnessed cases*	25 (18%)	22 (19%)	3 (14%)
CPR by bystanders**	54 (38%)	49 (40%)	5 (23%)
Shockable rhythm***	88 (61%)	78 (64%)	10 (45%)
Physician-staffed ambulance	117 (81%)	102 (84%)	15 (68%)
Re-arrest after ROSC during transportation†	14 (10%)	12 (10%)	2 (9%)
Resuscitation time courses, median (IQR)			
Call to Hospital, min	41 (33-50)	40 (33-50)	43 (32-51)
Call to ECPR, min	57 (49-70)	57 (50-70)	57 (47-66)
Call to ROSC‡or ECPR, min	54 (46-65)	54 (46-65)	55 (46-59)
Blood test on admission			
pH, mean (IQR)	6.95 (6.80-7.10)	6.93 (6.80-7.08)	7.09 (6.93-7.16)
Serum lactate, mmol/L, mean (IQR)	12.5 (9.8-14.7)	12.8 (10.5-15.1)	10.5 (8.0-11.4)
Interventions, n (%)			
Therapeutic hypothermia (completed)	63 (44%)	57 (47%)	6 (27%)
Intra-aortic balloon pumping	111 (77%)	94 (77%)	17 (77%)
Causes of cardiac arrest, n (%)			
Acute myocardial infarction	100 (69%)	84 (69%)	16 (73%)

Structural heart disease	11 (8%)	9 (8%)	1 (5%)
Aortic dissection	6 (4%)	5 (4%)	1 (5%)
Arrhythmia	6 (4%)	5 (4%)	1 (5%)
Asphyxia	3 (2%)	2 (2%)	1 (5%)
Other§	7 (5%)	6 (5%)	1 (5%)
Unknown	12 (8%)	11 (9%)	1 (5%)

Abbreviation: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Including witnessed by emergency medical service

** Including patients witnessed by emergency medical service (EMS) and those who had CPR by the EMS

*** Ventricular fibrillation and pulseless ventricular tachycardia.

† Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

‡ Defined as spontaneous circulation sustained for ≥20 minutes.

§ Accidental hypothermia, asthma, pulmonary hypertension, septic shock, and subarachnoid haemorrage.

1 **Table 3. Univariable and Multivariable Associations Between Age categories and Outcomes in OHCA patients**

	Number of cases (%)	Unadjusted odds ratios (95% CI)	Adjusted odds rations (95% CI)
Primary analysis			
Neurologically favourable outcomes			
Age 18-74 years (n=122)	10 (8%)	1 (reference)	1 (reference)
Age ≥75 years (n=22)	0 (0%)	N/A	N/A
One-month survival			
Age 18-74 years (n=122)	25 (20%)	1 (reference)	1 (reference)
Age ≥75 years (n=22)	3 (14%)	0.61 (0.17-2.24)	0.62 (0.16-2.39)
Sensitivity analysis			
Neurologically favourable outcomes			
Age 18-39 years (n=12)	2 (17%)	1 (reference)	1 (reference)
Age 40-49 years (n=11)	1 (9%)	0.50 (0.04-6.44)	0.41 (0.03-5.74)
Age 50-59 years (n=35)	1 (3%)	0.15 (0.01-1.79)	0.12 (0.01-1.61)
Age 60-69 years (n=44)	5 (11%)	0.64 (0.10-3.80)	0.57 (0.09-3.70)
Age 70-79 years (n=31)	1 (3%)	0.17 (0.01-2.04)	0.15 (0.01-1.92)
Age ≥80 years (n=11)	0 (0%)	N/A†	N/A†
One-month survival			
Age 18-39 years (n=12)	3 (25%)	1 (reference)	1 (reference)
Age 40-49 years (n=11)	2 (18%)	0.67 (0.09-4.99)	0.49 (0.06-4.04)
Age 50-59 years (n=35)	7 (20%)	0.75 (0.16-3.52)	0.58 (0.12-2.90)
Age 60-69 years (n=44)	12 (27%)	1.13 (0.26-4.87)	0.91 (0.19-4.34)
Age 70-79 years (n=31)	3 (10%)	0.32 (0.05-1.88)	0.26 (0.04-1.66)
Age ≥80 years (n=11)	1 (10%)	0.30 (0.03-3.42)	0.30 (0.02-3.64)

Abbreviation: OHCA, out-of-hospital cardiac arrest; OR, odds ratio; CI, confidence interval.

*Adjusted for sex, CPR by bystanders, shockable rhythm, and therapeutic hypothermia.

†No patient aged ≥75 years survived with neurologically favourable outcomes.

FIGURE LEGENDS

Figure 1. The associations between and one month neurologically favourable outcomes and survival.

Supplemental Figure 1. Patients receiving extracorporeal cardiopulmonary resuscitation

Figure 1

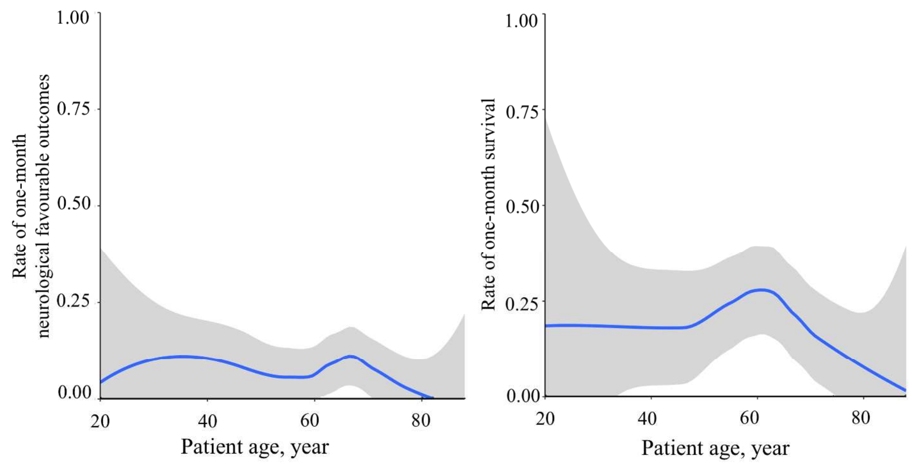

Figure 1

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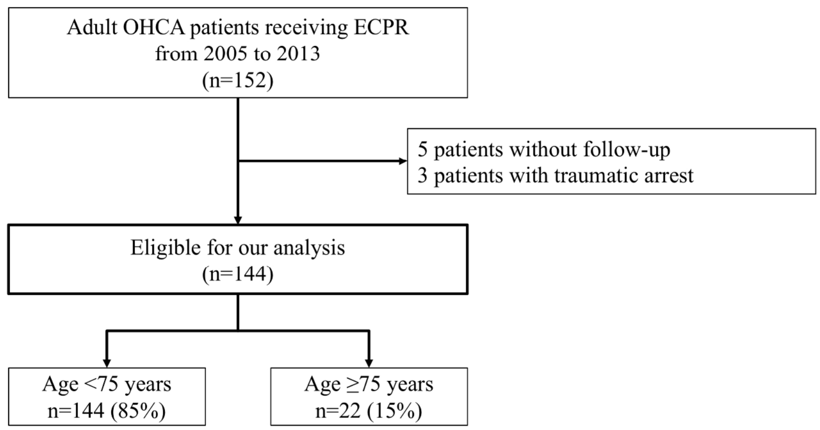
Supplemental Figure 1



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Supplemental Table 1. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation

	Age 18-39 years (n=12)	Age 40-49 years (n=11)	Age 50-59 years (n=35)	Age 60-69 years (n=44)	Age 70-79 years (n=31)	Age ≥ 80 years (n=11)
Baseline characteristics						
Women, n (%)	4 (33%)	3 (27%)	4 (11%)	4 (9%)	4 (13%)	3 (27%)
Prehospital characteristics, n (%)						
CPR by bystanders	5 (42%)	1 (9%)	16 (46%)	18 (41%)	10 (32%)	4 (36%)
Shockable rhythm*	8 (67%)	6 (55%)	27 (77%)	26 (59%)	16 (52%)	5 (45%)
Physician-staffed ambulance	11 (92%)	10 (91%)	28 (80%)	37 (84%)	25 (81%)	6 (55%)
Re-arrest after ROSC during transportation†	0 (0%)	2 (18%)	3 (9%)	6 (14%)	2 (6%)	1 (9%)
Resuscitation time courses, median (IQR)						
Call to Hospital, min	48 (32-55)	36 (33-51)	40 (30-46)	40 (32-50)	43 (33-51)	44 (32-61)
Call to ECPR, min	64 (53-76)	59 (47-78)	54 (48-67)	56 (49-66)	58 (51-68)	60 (46-74)
Call to ROSC‡ or ECPR, min	68 (58-78)	50 (42-78)	53 (38-64)	54 (46-63)	55 (46-63)	47 (43-66)
Blood test on admission						
pH, mean (IQR)	6.75 (6.64-7.01)	6.88 (6.75-7.12)	6.92 (6.72-7.03)	6.95 (6.85-7.11)	7.05 (6.84-7.18)	7.02 (6.88-7.16)
Serum lactate, mmol/L, mean (IQR)	15.1 (13.2-19.7)	13.9 (11.7-17.6)	13.3 (10.6-16.9)	12.5 (9.6-14.1)	11.1 (9.1-12.5)	9.6 (7.6-11.3)
Interventions, n (%)						
Therapeutic hypothermia (completed)	4 (33%)	7 (64%)	12 (34%)	24 (55%)	14 (45%)	2 (18%)
Intra-aortic balloon pumping	8 (67%)	11 (100%)	26 (74%)	33 (75%)	23 (74%)	10 (91%)
Causes of cardiac arrest, n (%)						
Acute myocardial infarction	4 (33%)	9 (82%)	27 (77%)	30 (68%)	22 (71%)	8 (73%)
Other cardiovascular diseases§	6 (50%)	1 (9%)	6 (17%)	5 (11%)	5 (16%)	1 (9%)

Other reasons**	2 (17%)	1 (9%)	2 (6%)	9 (20%)	4 (13%)	2 (18%)

Abbreviation: IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Ventricular fibrillation and pulseless ventricular tachycardia.

† Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

‡ Defined as spontaneous circulation sustained for ≥20 minutes.

§ Aortic dissection, structural heart disease, and arrhythmia

** Accidental hypothermia, asphyxia, asthma, pulmonary hypertension, septic shock, and subarachnoid haemorrage.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	8-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis

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ABSTRACT

objectives: Little is known about the effectiveness of extracorporeal resuscitation (ECPR) for elderly patients with out-of-hospital cardiac arrest (OHCA). The aim of this study was to examine the impact of age on outcomes among OHCA patients treated with ECPR.

design: Single-centre retrospective cohort study.

setting: A critical care centre that covers a population of approximately 1 million residents.

participants: Consecutive OHCA patients aged ≥18 years who underwent ECPR from 2005 to 2013.

primary and secondary outcome measures: Primary outcomes were one-month neurologically favourable outcomes and survival. To determine the association between advanced age and each outcome, we fitted multivariable logistic regression models using 1) age as a continuous variable and 2) age as a catgrocail variable (<50 years, 50-59 years, 60-69 years, and ≥70 years).

Results: Overall, 144 OHCA patients who underwent ECPR were eligible for our analyses. The proportion of neurologically favourable outcomes was 7% while survival was 19% in patients with OHCA. After the adjustment for potential confounders, while advanced age was non-significantly associated with neurologically favourable outcomes (adjusted OR 0.96 [95%CI 0.91-1.01]; P=0.08), the association between advanced age and the poor survival rate was significant (adjusted OR 0.96 [95%CI 0.93-0.99]; P=0.04). Additionally, compared to age <50 years, age ≥70 was non-significantly associated with poor neurological outcomes (adjusted OR 0.08 [95%CI 0.01-1.00]; P=0.051), whereas age ≥70 was significantly associated with worse survival in the adjusted model (adjusted OR 0.14 [95%CI 0.03-0.80]; P=0.03).

Conclusions: In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, we found that advanced age was associated with the lower rate of one-month survival in patients with OHCA who underwent ECPR. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥70 years.

Keywords: extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly

Strengths and limitations of this study

1. This study is the first study investigating the impact of age on outcomes among OHCA patients treated with ECPR, including patients aged ≥75 years.
2. There are consistent findings in both multivariable models using age as continuous variable and as a categorical variable.
3. Our sample consisted of retrospective data from a single centre in Japan with a limited sample size; thereby our inferences might not be generalizable to other healthcare settings.

1. **Introduction**

Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.[1-3] In 2014, the national annual number of OHCA of cardiac origin was 70,000 in Japan,[4] with an increase in the number of elderly patients.[5] As the aging population is expected to grow further in Japan[6] as well as other developed nations, the increased incidence of OHCA in elderly patients will become a further burden.[5] There is, therefore, a compelling need to develop optimal management strategies and policies to treat OHCA in elderly patients.

To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR) for patients with OHCA have been shown as a highly advanced medical treatment.[7-10] The recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science*.[1] In addition, the *European Resuscitation Council Guidelines for Resuscitation* recommends the consideration of ECPR for cases such as paediatric resuscitation and asthma-related cardiac arrest.[11] Further, subsequent observational studies have demonstrated that the utilization of ECPR was associated with improved survival compared to conventional cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable conditions.[12,13] The indication of ECPR for OHCA might, therefore, be extended in the future. However, the utilization of ECPR for elderly patients — a population with limited cardiovascular and pulmonary reserve — remains controversial.[14] Indeed, ECPR clinical protocols are likely to include an age limit as a contraindication of ECPR, whereas there is not sufficient supporting evidence.[15]Although some reports suggest that an age of ≥75 years should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,[16,17] a literature using the international Extracorporeal Life Support Organization registry suggested that age should not be a bar against the consideration of the utilization of ECMO in elderly patients.[18] Furthermore, a recent systematic review of prognostic factors for ECPR recipients following OHCA has failed to establish a link between age and poor prognosis following ECPR.[19]

To address this knowledge gap in the literature, we assessed the neurological outcomes and mortality of elderly patients with OHCA who underwent ECPR, using consecutive data from a critical care centre in Osaka, the second largest prefecture in Japan.

2. Material and Methods

2.1. Study design and settings

This retrospective analysis of medical records from a single centre in Japan was conducted at Osaka Saiseikai Senri Hospital, a critical care centre approved by the Ministry of Health, Labour and Welfare and located in the northern city of Suita, Osaka, Japan. This hospital covers a population of approximately 1 million residents, treating 200 to 250 OHCA patients annually. In this area, for all OHCA patients including suspected OHCA (based on the information provided by the emergency telephone call from the patient containing keywords that indicate heart attack or cardiac arrest), the Fire-Defense Headquarters requested the mobilization of a physician-staffed ambulance from our Hospital. All OHCA patients are transported to the hospital, regardless of whether ROSC was achieved (i.e., none are declared dead at the scene). The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

2.2. Selection of participants and data collection

We abstracted data from medical records of consecutive OHCA patients aged ≥18 years old who underwent ECPR between January 2005 and September 2013. In our centre, all OHCA patients including EMS-witnessed cases are recorded in the form of an electronical medical chart as our data resource. We abstracted necessary data from the medical chart for this study.

For all OHCA patients, the emergency physician assessed the indications for ECPR during transportation and then informed the hospital medical staff in the emergency department via telephone. To confirm the eligibility of ECPR for OHCA patients, in our critical care medical centre, the on-site physicians used mobile phones to discuss the eligibility of ECPR with other in-hospital attending physicians. In the present study, approximately 80% of OHCA cases were transported by physician-staffed ambulances, and all patients were treated by emergency physicians and the Advanced Cardiac Life Support guidelines of the emergency department.[20]

Indications of ECPR for OHCA patients are shown in **Table 1**. Absolute indications for ECPR were OHCA patients with refractory ventricular fibrillation (Vf), defined as sustained Vf after three attempts of defibrillation with potentially treatable conditions. Relative indications for ECPR were OHCA patients with presumably treatable conditions with pulseless electrical activity or asystole, hypothermia, and drug intoxicatoin. Patient age was not considered when using ECPR. Patients with the following were excluded: stroke, terminal malignancy, cirrhosis, severe chronic obstructive pulmonary disease, poor daily living activities, and assessed as "inadequate indications" for ECPR by the team leader.

2.3. ECMO management and post-resuscitation care

The final decision to initiate ECPR depended on the opinions of the attending physicians. To achieve successful and rapid implementation, the ECMO team consisted of emergency physicians, cardiologists, and clinical engineers. Chest compression was continued until starting ECMO. The percutaneous cannulation technique for venous and arterial ECMO accesses was used to deliver ECMO with a 13.5 F arterial cannulae or a 19.5 F venous cannulae via femoral artery or vein. The cannulation was performed in the ED or ED adjoining cardiac catheterization room. Urgent coronary angiography was performed for

OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial infarction were performed a primary percutaneous intervention with conventional technique for culprit lesions. All post-resuscitated patients after implementation of ECMO received guideline recommended care,[1] regardless of age and clinical diagnosis. The patients were provided adequate oxygenation, vasopressors and fluid administration to maintain systolic arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage equivalent to brain death, withdrawal of ECMO was considered.

2. 4 Data collection and Quality control

The measured variables were patient demographics, prehospital characteristics (i.e., time-course, initial rhythm, presence of return of spontaneous circulation, and managements), resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic balloon pumping), and the cause of cardiac arrest. The attending physician at the morning conference decided the most likely cause of cardiac arrest. Prehospital variables were collected by the information from paramedics and the emergency physicians who treated the patient with physician-staffed ambulance. The resuscitation time-course was collected by the emergency physician who treated the patient with the physician-staffed ambulance and medical staff in the emergency department. Other measurements including post resuscitation care were recorded by the attending physician using a standardized data collection form.

3.5. Outcomes

Outcomes of interest were one-month neurologically favourable outcomes and survival.

Neurologically favourable outcomes were defined as a Cerebral Performance Categories (CPC) score of 1 or 2.[21] The attending physician in-charge of the rounds or the outpatient determined the CPC score.

2.6. Statistical analyses

Continuous data were presented as the median (interquartile) with differences analysed using the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with differences analysed using chi-square test or Fischer's exact test as appropriate. We also illustrated the associations between age and each outcome by using a LOWESS smoother with calculating 95% confidence interval using a bootstrap method.

To determine the association between advanced age and each outcome, we fitted multivariable logistic regression models using 1) age as a continuous variable and 2) age as a catgrocail variable (<50 years, 50-59 years, 60-69 years, and ≥70 years). These age categories were determined based on the association between age and outcomes. Potential confounding factors were selected based on *a priori* knowledge[2,8,10,22] and factors that showed a significant association with the outcome in the univariate analysis. Variables included, shockable rhythm, witnessed arrest, CPR by bystanders, re-arrest after ROSC during transportation, and pH on hospital arrival. Shockable rhythm was defined as Vf and pulseless ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. While the use of therapeutic hypothermia was significantly associated with the survival outcome, we did not include this variable in multivariable models because this variable is an intermediate between ECPR implementation and outcomes. Odds ratios (ORs) and confidence intervals (CIs) were then calculated. In addition, we have summarized the results in patients aged ≥75 years (n=22), which is the suggested upper limit of age for implementation of extracorporeal membrane oxygenation support.[16,17] We analyzed data using STATA 15.0 (StataCorp, College Station, TX) and R statistical software (version 3.4.0).

2.7. Patient and Public Involvement

Patients and public were not involved in this study.

3. Results

During the study period, 152 consecutive OHCA patients underwent ECPR. Among them we excluded five patients without follow-up as they were transported to another hospital for further advanced care (e.g., implementation of left ventricular assistive device) and another three patients with traumatic arrest, leaving 144 patients eligible for our analysis. The median patient age was 63 (interquartile range [IQR], 55-71) years, and 15% of patients were women (**Table 2**). In 38% of cases, a bystander performed CPR. Shockable rhythm (i.e., Vf and pulseless VT) accounted for 61% of cases. Physician-staffed ambulances transported 81% of cases. The median time from call to arrival at the hospital was 41 min (IQR, 33-50 min), and from call to implementation of ECMO was 57 min (IQR, 49-70 min). On admission, the median pH value was 6.95 and median serum lactate level was 12.5 mmol/L. For post-resuscitation therapy, therapeutic hypothermia was completed in 44% of patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately 70% of cardiac arrests were caused by acute myocardial infarction.

Overall, the proportion of neurologically favourable outcomes was 7% (95% CI, 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. Patients with neurologically favourable outcomes were more likely to have re-arrest after ROSC during transportation compared to those without (P=0.03). For one-month survival, survived patients were more likely to have shockable rhythm, re-arrest after ROSC during transportation, and to be treated with therapeutic hypothermia compared to non-survived patients (all, P<0.05).

Figure 1A and 1B illustrate the associations between age and each outcome. The rate of one-month neurologically favourable outcomes had a biphasic association curve with a peak around age 40 years and 65 years (Figure 1A). The survival rate increased from age 50 years with a peak around age 60, and decreased thereafter (Figure 1B). The survival rate around age 70 years became similar to those of age <50 years.

Table 3 demonstrates the association between age and outcomes. Overall, in the unadjusted models using age as a continuous variable, age was non-significantly associated with the worse one-month neurological outcomes and survival. After the adjustment for potential confounders, while advanced age was non-significantly associated with worse neurological outcomes (adjusted OR 0.96 [95%CI 0.91-1.01]; P=0.08), the association between advanced age and poor survival rate was significant (adjusted OR 0.96 [95%CI 0.93-0.99]; P=0.04). Similar associations were found in the analyses using age as a categorical variable. Compared to age <50 years, age ≥70 was associated with poor neurological outcomes (adjusted OR 0.08 [95%CI 0.01-1.00]; P=0.051) and significantly associated with the worse survival in the adjusted model (adjusted OR 0.14 [95%CI 0.03-0.80]; P=0.03). Among patient aged 75 years, which is the suggested upper limitation of age for implementation of ECPR, only 3 patients survived and no patients survived with neurologically favourable outcomes.

4. Discussion

In this retrospective analysis from an urban critical care hospital, we found that advanced age was associated with the lower rate of one-month survival and neurologically favourable outcomes in patients with OHCA who underwent ECPR. The rate of neurologically favourable outcomes and one-month survival decreased after age 70 years old. In addition, no patient aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. These findings provide valuable clues for creating optimal strategy for elderly patients with OHCA in the aging era.

Our study observed that age ≥70 was associated with the lower survival rate and no patients aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. Although previous studies reported that ECPR was more effective in treating OHCA patients than conventional CPR, these studies did not assess the effect of advanced age – their findings were based on studies limited to patients aged <75 years.[9,10] A multicentre prospective observational study in Japan demonstrated that the survival rate at one-month after cardiac arrest was significantly higher in the ECPR group than in the non-ECPR group (27% vs. 6%) and that the proportion of neurologically favourable outcomes was also significantly higher in the ECPR group (12.3% vs. 1.5%).[10] Our results that overall one-month survival rate of 20% and one-month survival with neurologically favourable outcomes of 8% are comparable results with these previous findings,[9,10] despite we included patients aged ≥75 years. Therefore, focusing on the elderly patients, our findings might suggest limitations in using ECPR to treat elderly patients with OHCA.

The reasons for the observed lack of effectiveness of ECPR among elderly patients are likely multifactorial. First, consistent with the elderly being the population with limited cardiovascular and pulmonary reserve, the survival rate of OCHA patients was lower in older patients than in younger patients.[23] An observational study in the US demonstrated that advanced age was a factor associated with lower survival rate at discharge among OHCA patients (19.4% for ≤80 years vs. 9.4% for 80-89 years, and 4.4% for ≥90 years).[23] Second, shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an observational study in the US, shorter duration of CPR was associated with neurologically favourable outcomes – 90% of patients with neurologically favourable outcomes required less than 16 minutes of CPR.[24] In our findings, the median time from cardiac arrest to ROSC or implementing of ECMO was 54 min, which is considerably longer than in the previous study in the US.[24] However, patients who require ECPR are "non-responders" to conventional CPR within 20 minutes.[12] In addition, another ECPR study also showed a lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our findings.[8] Due to the vulnerability of elderly patients, elderly patients might not withstand the prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable population and a longer CPR duration may help explain the lack of effectiveness of ECPR for elderly patients with OHCA in the present study.

Importantly, the cost burden of ECPR is also significant. In Japan, the incremental cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted life-year (QALY).[25] Considering the acceptable ICER for introducing a new treatment is approximately £20,000-30,000,[26] this financial burden is unacceptably high. Further, another Japanese study suggested that the average cost for treating an OHCA patient was approximately £1,250.[27] Aging, and its associated costs are increasing, constituting an enormous financial burden throughout the developed world. Given this significant financial burden and our present observations, indications of ECPR in elderly patients with OHCA might be limited with respect to cost-effectiveness. Our observations facilitate further investigations to elucidate the cost-effectiveness of ECPR for elderly patients with OHCA.

Despite the significant healthcare resource burden of ECPR, the present study did not demonstrate the effectiveness of ECPR for elderly patients with OHCA. However, this does not indicate that CPR should not be utilized for elderly patients. Although advanced age could be a factor associated with poor outcomes in OHCA patients in the present study, this factor alone does not appear to be a well established criterion to deny patients for conventional CPR based on a previous report.[23] Additionally, experts say that decisions regarding termination of resuscitation should not be based on age.[28] However, given our present findings regarding poor outcomes among elderly patients and the extremely high cost of ECPR, the indication of ECPR for elderly patients should be carefully considered in this aging era.

Limitations

We acknowledge several potential limitations to our study. First, as our sample consisted of retrospective data from a single centre in Japan, our inferences might not be generalizable to other healthcare settings. However, the observed association not only has plausible mechanisms but also persisted across different analytical assumptions. Although formal validation of the study in other healthcare settings is warranted, our inferences likely present in different practical settings. Second, there was lack of data on daily living activities, medication use, comorbidities before cardiac arrest including a poorer neurological state pre-arrest. In addition, information on whether the ECPR was implemented during active chest compressions and on the results of percutaneous coronary intervention was also not available. However, an experienced emergency physician or cardiologist assessed whether the cause of cardiac arrest was treatable and appropriate for ECPR based on information gained from the person accompanying the patient and the situation of cardiac arrest. Third, our study might include ECMO cases for persistent hypotension after ROSC. However, the association was significant after adjusting for the potential persistent hypotension after ROSC (i.e., re-arrest after ROSC during transportation). Finally, although the indication for ECPR was assessed based on the protocol and by experienced physicians, our data are subject to selection bias. In general, however, the indication of ECPR for elderly patients was stricter than that for younger patients, which might have biased our conclusions toward the null.

Conclusions

In our analysis of consecutive OHCA data from a critical care hospital in an urban area of Japan, we found that advanced age was associated with the lower rate of one-month survival in patients with OHCA who underwent ECPR. The rate of neurologically favourable outcomes and one-month survival decreased after age 70 years old. In addition, no patient aged ≥75 years survived with neurologically favourable outcomes at one-month after cardiac arrest. Although larger studies are required to confirm these results, our findings suggest that ECPR may not be beneficial for OHCA patients aged ≥70 years. While the eligibility of ECPR should not be determined by age as a single variable, our findings might not only help improve the survival rate and neurological outcomes of elderly patients with OHCA but also facilitate further observation, intervention, and discussion regarding the utilization of ECPR for elderly patients with OHCA.

List of abbreviations: out-of-hospital cardiac arrest, OHCA; extracorporeal cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY; confidence interval, CI

DISCLOSURES:

Ethics approval and consent to participate and Consent for publication: The institutional review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of informed consent.

Availability of data and materials: The data are not allowed for public use by institutional review board.

Competing interests: There are no conflict of interest.

Funding: None

Authors' contributions: TG, SM, NT, HS, YH and Tkai planned the study. TKit supervised and provided statistical advice on study design. TG analysed the data. TG drafted the manuscript, and all authors contributed substantially to its revision. TG takes responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Table 1. Indications for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre

Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.	
Indication criteria	
Absolute indication	Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)
Relative indication	Presumed treatable conditions with PEA/Asystole*
	Hypothermia
	Drug intoxication
Exclusion criteria	
Stroke	
Terminal malignancy	
Cirrhosis	
Chronic obstructive pulmonary disease	
Poor activities of daily living	
In a case who the team leader judged "inadequate indication" for ECPR	

Abbreviations: ECMO, extracorporeal membranous oxygenation; Vf, Ventricular fibrillation; ECPR, extracorporeal cardiopulmonary resuscitation; PEA, pulseless electrical activity

* Judged by an emergency physician who treats the patient with physician-staffed ambulance according to he initial rhythm.

Table 2. Characteristics of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal Cardiopulmonary Resuscitation

	Overall	Neurologically favourable outcomes			Survival outcome		
	(n=144)	CPC 1-2 (n=10)	CPC 3-5 (n=134)	P value	Survived (n=28)	Not survived (n=116)	P value
Baseline characteristics							
Age, year, median (IQR)	63 (55-71)	62 (48-68)	64 (55-72)	0.30	61 (55-67)	64 (55-72)	0.23
Women, n (%)	22 (15%)	1 (10%)	21 (16%)	0.63	3 (11%)	19 (16%)	0.56
Prehospital characteristics, n (%)							
Witnessed cases*	25 (18%)	2 (20%)	24 (18%)	0.87	8 (29%)	17 (16%)	0.11
CPR by bystanders**	54 (38%)	3 (30%)	51 (38%)	0.61	7 (25%)	47 (41%)	0.13
Shockable rhythm***	88 (61%)	7 (70%)	81 (60%)	0.55	22 (79%)	66 (57%)	0.04
Physician-staffed ambulance	117 (81%)	6 (60%)	11 (83%)	0.07	21 (75%)	96 (83%)	0.35
Re-arrest after ROSC during transportation†	14 (10%)	3 (30%)	11 (8%)	0.03	8 (29%)	6 (5%)	<0.001
Resuscitation time courses, median (IQR)							
Call to Hospital, min	41 (33-50)	34 (32-42)	42 (33-50)	0.12	41 (32-47)	41 (34-51)	0.41
Call to ECPR, min	57 (49-70)	60 (50-90)	57 (49-67)	0.39	60 (51-78)	56 (48-68)	0.40
Call to ROSC‡or ECPR, min	54 (46-65)	53 (27-64)	54 (46-65)	0.57	52 (32-66)	54 (46-65)	0.57
Blood test on admission							
pH, mean (IQR)	6.95 (6.80-7.10)	6.82 (7.08-7.23)	6.95 (6.80-7.09)	0.23	6.99 (6.86-7.19)	6.94 (6.78-7.08)	0.12
Serum lactate, mmol/L, mean (IQR)	12.5 (9.8-14.7)	13.3 (9.6-14.6)	12.4 (9.8-14.7)	0.93	11.1 (9.2-14.8)	12.5 (10.5-14.7)	0.41
Interventions, n (%)							
Therapeutic hypothermia (completed)	63 (44%)	5 (50%)	58 (43%)	0.68	19 (68%)	44 (38%)	<0.004
Intra-aortic balloon pumping	111 (77%)	8 (80%)	103 (77%)	0.82	24 (86%)	87 (75%)	0.23

Causes of cardiac arrest, n (%)				0.68			0.59
Acute myocardial infarction	100 (69%)	7 (70%)	93 (70%)		19 (68%)	81 (70%)	
Structural heart disease	11 (8%)	0 (0%)	11 (8%)		2 (7%)	9 (8%)	
Aortic dissection	6 (4%)	0 (0%)	6 (4%)		0 (0%)	6 (5%)	
Arrhythmia	6 (4%)	2 (20%)	4 (3%)		3 (11%)	3 (3%)	
Asphyxia	3 (2%)	0 (0%)	3 (2%)		0 (0%)	3 (3%)	
Other§	7 (5%)	0 (0%)	7 (5%)		1 (4%)	6 (5%)	
Unknown	12 (8%)	1 (10%)	11 (8%)		3 (11%)	9 (8%)	
Admission year				0.32			0.20
2005	4 (3%)	1 (10%)	3 (2%)		2 (7%)	2 (2%)	
2006	18 (13%)	1 (10%)	17 (13%)		5 (18%)	13 (11%)	
2007	15 (10%)	0 (0%)	15 (11%)		2 (7%)	13 (11%)	
2008	19 (13%)	2 (20%)	17 (13%)		3 (11%)	16 (14%)	
2009	7 (5%)	0 (0%)	7 (5%)		2 (7%)	5 (4%)	
2010	19 (13%)	1 (10%)	18 (13%)		3 (11%)	16 (14%)	
2011	26 (18%)	1 (10%)	25 (19%)		3 (11%)	23 (20%)	
2012	22 (15%)	1 (10%)	21 (16%)		2 (7%)	20 (17%)	
2013	14 (10%)	3 (30%)	11 (8%)		6 (21%)	8 (7%)	

Abbreviation: CPC, Cerebral Performance Categories; IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation.

* Including witnessed by emergency medical service

** Including patients witnessed by emergency medical service (EMS) and those who had CPR by the EMS

*** Ventricular fibrillation and pulseless ventricular tachycardia.

† Defined as re-cardiac arrest after spontaneous circulation sustained for ≥20 minutes during transportation.

‡ Defined as spontaneous circulation sustained for ≥20 minutes.

§ Accidental hypothermia, asthma, pulmonary hypertension, septic shock, and subarachnoid haemorrage.

Table 3. Univariable and Multivariable Associations Between Age categories and Outcomes in OHCA patients

	Number of cases (%)	Unadjusted odds ratios (95% CI)	P value	Adjusted odds ratios (95% CI)*	P value
Primary analysis					
Age as continuous variable					
Neurologically favourable outcomes	10 (7%)	0.97 (0.93-1.02)	0.24	0.96 (0.91-1.01)	0.08
One-month survival	28 (19%)	0.98 (0.96-1.01)	0.31	0.96 (0.93-0.99)	0.04
Age as categorical variable					
Neurologically favourable outcomes					
Age 18-49 years (n=23)	3 (13%)	1 (reference)		1 (reference)	
Age 50-59 years (n=35)	1 (3%)	0.20 (0.02-2.01)	0.17	0.15 (0.01-1.87)	0.18
Age 60-69 years (n=44)	5 (11%)	0.85 (0.19-3.95)	0.84	0.56 (0.10-3.25)	0.94
Age ≥70 years (n=42)	1 (2%)	0.16 (0.02-1.66)	0.13	0.08 (0.01-1.00)	0.051
One-month survival					
Age 18-49 years (n=23)	5 (22%)	1 (reference)		1 (reference)	
Age 50-59 years (n=35)	7 (20%)	0.90 (0.25-3.27)	0.87	0.74 (0.17-3.34)	0.70
Age 60-69 years (n=44)	12 (27%)	1.35 (0.41-4.45)	0.62	0.83 (0.20-3.40)	0.80
Age ≥70 years (n=42)	4 (10%)	0.38 (0.09-1.58)	0.18	0.14 (0.03-0.80)	0.03

Abbreviation: OHCA, out-of-hospital cardiac arrest; OR, odds ratio; CI, confidence interval.

* Adjusted for witnessed arrest, bystander CPR, shockable rhythm, re-arrest after ROSC during transportation, and pH on hospital arrival.

FIGURE LEGENDS

Figure 1. The associations between and one month survival and neurologically favourable outcomes.

1

Figure 1

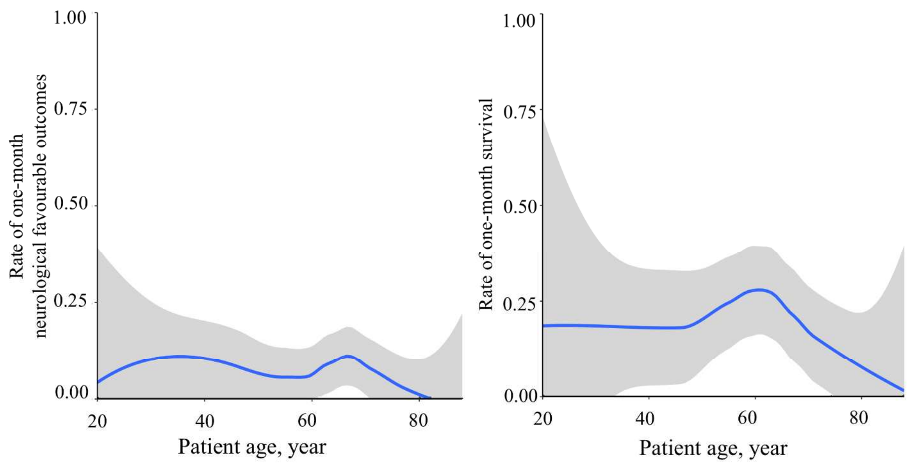

Figure 1

253x190mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	7-8

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	8-10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.