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# 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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3 **1 Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly**  
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5 **2 Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis**  
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7  
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9  
10 **ABSTRACT**

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

14 **design:** Single-center retrospective cohort study.

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

16 **participants:** Consecutive OHCA patients aged  $\geq 18$  years who underwent ECPR from 2005  
17 to 2013.

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

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

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3 1  $\geq 65$  was not associated (15% vs. 22%,  $p=0.39$ ). These associations remained in multivariable  
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5 2 analyses. No patient aged  $\geq 75$  years survived with neurologically favourable outcomes.

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7 3 **Conclusions:** Advanced age was associated with lower one-month survival. Furthermore, no  
8  
9 4 patient survived with neurologically favourable outcomes in patient aged  $\geq 75$  years.

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11 5  
12  
13 6 **Keywords:** extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly  
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### 16 17 8 **Strengths and limitations of this study**

- 18  
19 9 1. This study is the first study that investigate the the efficacy of extracorporeal resuscitation  
20  
21 10 for elderly patients with out-of-hospital cardiac arrest, including patients aged  $\geq 75$  years.  
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23 11 2. Our sample consisted of retrospective data from a single canter in Japan, thereby our  
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25 12 inferences might not be generalizable to other healthcare settings.  
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### 28 29 14 **1. Introduction**

30  
31 15 Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.<sup>1-3</sup> In 2014,  
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33 16 the national annual number of OHCA of cardiac origin was 70,000 in Japan,<sup>4</sup> with an increase  
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35 17 in the number of elderly patients.<sup>5</sup> As with the burden of aging population is expected to  
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37 18 grow further in Japan,<sup>6</sup> aging is also an important issue in other developed nations, resulting  
38  
39 19 in an increased incidence of OHCA in elderly patients.<sup>5</sup> There is therefore a compelling need  
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41 20 to develop optimal management strategies and policies to treat OHCA in elderly patients.  
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45 21 To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR)  
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47 22 for patients with OHCA have been shown as a highly advanced medical treatment.<sup>7-10</sup> The  
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49 23 recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart*  
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51 24 *Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular*  
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53 25 *Care Science*.<sup>1</sup> In addition, the *European Resuscitation Council Guidelines for Resuscitation*  
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55 26 recommends the consideration of ECPR for cases such as paediatric resuscitation and  
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3 1 asthma-related cardiac arrest.<sup>11</sup> Further, subsequent observational studies have demonstrated  
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5 2 that the utilization of ECPR was associated with improved survival compared to conventional  
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7 3 cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable  
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9 4 conditions.<sup>12,13</sup> The implementation of ECPR for OHCA might therefore be extended in  
10  
11 5 future. However, the utilization of ECPR for elderly patients — a population with limited  
12  
13 6 cardiovascular and pulmonary reserve — remains controversial.<sup>14</sup> To our knowledge, no  
14  
15 7 studies have yet focused on the utilization of ECPR for elderly patients with OHCA.  
16  
17 8 Although some reports suggest that an age of  $\geq 75$  years should be a contraindication for  
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19 9 extracorporeal membrane oxygenation (ECMO) support,<sup>15,16</sup> a literature using the  
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21 10 international Extracorporeal Life Support Organization registry suggested that age should not  
22  
23 11 be a bar against the consideration of the utilization of ECMO in elderly patients.<sup>17</sup>  
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27 12 To address this knowledge gap in the literature, we assessed the mortality and  
28  
29 13 neurological outcomes of elderly patients with OHCA who underwent ECPR, using  
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31 14 consecutive data from a tertiary care centre in Osaka, the second largest prefecture in Japan.  
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## 35 16 **2. Material and Methods**

### 36 37 17 *2.1. Study design and settings*

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39 18 This retrospective analysis of medical records from single center in Japan was conducted at  
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41 19 Osaka Saiseikai Senri Hospital, a tertiary care center approved by the Ministry of Health,  
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43 20 Labour and Welfare and located in the northern city of Suita, Osaka, Japan. This hospital  
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45 21 covers a population of approximately 1 million residents, of which 200 to 250 OHCA patients  
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47 22 are treated annually. In this area, for all OHCA patients including suspected OHCA (based on  
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49 23 the information from the emergency telephone call that contains keywords that may indicate  
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51 24 heart attack or cardiac arrest), the Fire-Defense Headquarters requested the mobilization of a  
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53 25 physician-staffed ambulance from our Hospital. The institutional review board of Osaka  
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1 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  $\geq 18$  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.<sup>18</sup>

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

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3 1 the femoral artery and 19.5 F in size cannulae for the femoral vein. Urgent coronary  
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5 2 angiography was performed for OHCA patients with suspected cardiac origin. The patients  
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7 3 diagnosed as acute myocardial infarction were performed primary percutaneous intervention  
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9 4 with conventional technique for culprit lesion. All post-resuscitated patients after  
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11 5 implementation of ECMO received the optimal medical care, regardless of age and clinical  
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13 6 diagnosis. The patients were provided adequate oxygenation, vasopressors and fluid  
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15 7 administration maintain systolic arterial pressure at 90 mmHg, target temperature  
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17 8 management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the  
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19 9 patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of  
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21 10 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage  
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23 11 equivalent to brain death, withdrawal of ECMO was considered.  
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#### 29 13 *2.4 Data collection and Quality control*

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31 14 The measured variables were patient demographics, prehospital characteristics (i.e.,  
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33 15 time-course, initial rhythm, presence of return of spontaneous circulation, and managements),  
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35 16 resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic  
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37 17 balloon pumping), and the cause of cardiac arrest. Prehospital variables were collected based  
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39 18 on the information from paramedics and the emergency physician who treated the patient  
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41 19 with physician-staffed ambulance. The resuscitation time-course was collected by the  
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43 20 emergency physician who treated the patient with the physician-staffed ambulance and  
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45 21 medical staff in the emergency department. Other measurements including post resuscitation  
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47 22 care were recorded by the attending physician with using a standardized data collection form.  
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#### 53 24 *2.5. Outcomes*

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55 25 Outcomes of interest were one-month survival and neurologically favourable outcomes.  
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1 Neurologically favourable outcomes were defined as a Cerebral Performance Categories  
2 (CPC) score of 1 or 2.<sup>19</sup>

### 4 *2.6. Statistical analyses*

5 To assess the association between advanced age and outcomes, “elderly” patients were  
6 defined as those aged  $\geq 75$  years, as previously reported.<sup>2,20,21</sup> Patients characteristics and  
7 outcomes were compared between those aged  $< 75$  years and those aged  $\geq 75$  years.  
8 Continuous data were presented as the median (interquartile) with differences analysed using  
9 the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with  
10 differences analysed using chi-square test or Fischer’s exact test as appropriate.

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

### 23 **3. Results**

24 During the study period, 152 consecutive OHCA patients underwent ECPR. Among them, 5  
25 patients without follow-up due to transport to another hospital and 8 patients who did not

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3 1 meet the inclusion criteria (traumatic arrest [n=3], accidental hypothermia [n=3], and  
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5 2 subarachnoid haemorrhage [n=2]) were excluded, leaving 139 patients eligible for our  
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7 3 analysis (119 patients in the <75 years group and 20 patients in the ≥75 years group, **Figure**  
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9 4 **1**).

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11 5 Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 13%  
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13 6 of patients were women (**Table 2**). In 39% of cases, a bystander performed CPR. Shockable  
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15 7 rhythm (i.e., Vf and VT) accounted for 88% of cases. Physician-staffed ambulances  
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17 8 transported 83% of cases. The median time from call to arrival at a hospital was 41 min (IQR,  
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19 9 33-50 min), and from call to implementation of ECMO was 56 min (IQR, 49-69 min). As  
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21 10 post-resuscitation therapy, therapeutic hypothermia was completed in 45% of patients, and an  
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23 11 intra-aortic balloon pumping was used for 77% of patients. Approximately 70% of cardiac  
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25 12 arrests were caused by acute myocardial infarction. There were no significant differences in  
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27 13 prehospital characteristics, resuscitation time-course, interventions, and causes of cardiac  
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29 14 arrest between patients aged ≥75 years and those aged <75 years.

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33 15 In overall patients, one-month survival was 19% (95%CI, 13%-26%). The proportion  
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35 16 of one-month survival was lower in patients aged ≥75 years than in those aged <75 years, but  
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37 17 not significant (10% vs. 20%, p=0.37, **Figure 2A**). In the sensitivity analysis, the proportion  
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39 18 of one-month survival was significantly lower in patients aged ≥70 compared to those aged  
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41 19 <70 years (8% vs. 23%, p=0.03, **Figure 2B**). There was no significant difference in  
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43 20 one-month survival between patients aged ≥65 years and those aged ≤65 years (15% vs. 22%,  
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45 21 p=0.39, **Figure 2C**).

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48 22 In the multivariable analyses, these associations were remained (**Table 3**). The  
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50 23 one-month survival was lower but not significant in patients aged ≥75 years than in those  
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52 24 aged <75 years (adjusted OR, 0.36; 95% CI 0.05-1.45). In the sensitivity analysis, one-month  
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54 25 survival was significantly lower in patients aged ≥70 years compared to those aged <70 years

1 (adjusted OR, 0.21; 95% CI 0.04-0.71).

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

#### 14 **4. Discussion**

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

22       Our study observed that no patients aged  $\geq 75$  years survived with neurologically  
23 favourable outcomes at one-month after cardiac arrest. Moreover, ECPR did not improve  
24 outcomes in elderly patients aged  $\geq 70$  years with OHCA compared with younger patients.  
25 Although previous studies reported that ECPR was more effective in treating OHCA patients

1 than conventional CPR, these studies did not assess the effect of advanced age – their  
2 findings were based on studies limiting to patients aged <75 years.<sup>9,10</sup> A multicentre  
3 prospective observational study in Japan demonstrated that the survival rate at one-month  
4 after cardiac arrest was significantly higher in the ECPR group than in the non-ECPR group  
5 (27% vs. 6%) and that the proportion of neurologically favourable outcomes was also  
6 significantly higher in the ECPR group (12.3% vs. 1.5%).<sup>10</sup> Our results that overall  
7 one-month survival rate of 20% and one-month survival with neurologically favourable  
8 outcomes of 7% are comparable results with these previous findings,<sup>9,10</sup> despite we included  
9 patients aged  $\geq 75$  years. Therefore, focusing on the elderly patients, our findings might  
10 suggest limitations in using ECPR to treat elderly patients with OHCA.

11 The reasons for the observed lack of efficacy of ECPR among elderly patients are  
12 likely multifactorial. First, consistent with the fact that the elderly are the population with  
13 limited cardiovascular and pulmonary reserve, the survival rate of OHCA patients was lower  
14 in older patients than in younger ones.<sup>23</sup> An observational study in the US demonstrated that  
15 advanced age was a factor associated with lower survival rate at discharge among OHCA  
16 patients (19.4% for  $\leq 80$  years vs. 9.4% for 80-89 years, and 4.4% for  $\geq 90$  years).<sup>23</sup> Second,  
17 shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a  
18 critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an  
19 observational study in the US, shorter duration of CPR was significantly associated with  
20 neurologically favourable outcomes – 90% of patients with neurologically favourable  
21 outcomes required less than 16 minutes of CPR.<sup>24</sup> In our findings, the median time from  
22 cardiac arrest to ROSC or implementing of ECMO was 54 min, which is considerably longer  
23 than in the previous study in the US.<sup>24</sup> However, patients who require ECPR are  
24 “non-responders” to conventional CPR within 20 minutes.<sup>12</sup> In addition, another ECPR study  
25 also showed a lengthy median time from arrest to ROSC of 50 min in OHCA patients,

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3 1 consistent with our findings.<sup>8</sup> Taken together, advanced age as the vulnerable population and  
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5 2 a longer CPR duration may help explain the lack of efficacy of ECPR for elderly patients  
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7 3 with OHCA in the present study.

9 4 Importantly, the cost burden of ECPR is also significant. In Japan, the incremental  
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11 5 cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted  
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13 6 life-year (QALY).<sup>25</sup> Considering the acceptable ICER for introducing a new treatment is  
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15 7 approximately £20,000-30,000,<sup>26</sup> this financial burden is unacceptably high. Further, another  
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17 8 Japanese study suggested that the average cost for treating an OHCA patient was  
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19 9 approximately £1,250.<sup>27</sup> Aging, and its associated costs are increasing, constituting an  
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21 10 enormous financial burden throughout the developed world. Given this significant financial  
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23 11 burden and our present observations (i.e. miserable survival and neurologic outcomes in  
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25 12 patients aged  $\geq 75$  and  $\geq 70$  years), implementations of ECPR in elderly patients with OHCA  
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27 13 are extremely limited with respect to cost-efficacy. Our observations facilitate further  
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29 14 investigations to elucidate the cost-effectiveness of ECPR for elderly patients with OHCA.

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33 15 Despite the significant healthcare resource burden of ECPR, the present study did not  
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35 16 demonstrate the efficacy of ECPR for elderly patients with OHCA. However, this does not  
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37 17 indicate that CPR should not be utilized for elderly patients. Although advanced age was a  
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39 18 factor associated with poor outcomes in OHCA patients in the present study, this factor alone  
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41 19 does not appear to be a good criterion for denying patients conventional CPR based on a  
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43 20 previous report.<sup>23</sup> Additionally, experts say that decisions regarding termination of  
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45 21 resuscitation should not be based on age.<sup>28</sup> However, given our present findings regarding  
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47 22 poor outcomes among elderly patients and the extremely high cost of ECPR, the  
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49 23 implementation of ECPR for elderly patients should be carefully considered in this aging era.

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## 54 25 **Limitations**

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

## 23 **Conclusions**

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

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3 1 Furthermore, no patient survived with neurological outcomes among age  $\geq 75$  years. Our  
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5 2 findings might help improve survival rates and neurological outcomes of OHCA elderly  
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7 3 patients and facilitate further observation, intervention, and discussion regarding the  
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9 4 utilization of ECPR for elderly patients with OHCA.  
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12 5

13 6 **List of abbreviations:** out-of-hospital cardiac arrest, OHCA; extracorporeal  
14  
15 7 cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal  
16  
17 8 membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation  
18  
19 9 ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY;  
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21 10 confidence interval, CI  
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29 12 **DISCLOSURES:**

30 13 **Ethics approval and consent to participate and Consent for publication:** The institutional  
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32 14 review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of  
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39 18 **Competing interests:** There are no conflict of interest.

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46 21 statistical advice on study design. TG analysed the data. TG drafted the manuscript, and all  
47  
48 22 authors contributed substantially to its revision. TG takes responsibility for the paper as a  
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2 **REFERENCES**

- 3 1. 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency  
4 Cardiovascular Care Science With Treatment Recommendations. *Circulation* 2015 Oct  
5 20;132:S84-14.
- 6 2. 2015 American Heart Association guidelines for cardiopulmonary resuscitation and  
7 emergency cardiovascular care. *Circulation* 2015;132:S315-67.
- 8 3. European Resuscitation Council Guidelines for Resuscitation 2015. *Resuscitation*  
9 2015;95:1-80..
- 10 4. Ambulance Service Planning Office of Fire and Disaster Management Agency of  
11 Japan. Effect of first aid for cardiopulmonary arrest. . Ambulance Service Planning Office of  
12 Fire and Disaster Management Agency of Japan; 2014 (in Japanese). (Accessed March 03,  
13 2015, at  
14 [http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218\\_1houdou/01\\_houdoushiryou.  
15 pdf](http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218_1houdou/01_houdoushiryou.pdf) )
- 16 5. Kitamura T, Morita S, Kiyohara K, et al. Trends in survival among elderly patients  
17 with out-of-hospital cardiac arrest: a prospective, population-based observation from 1999 to  
18 2011 in Osaka. *Resuscitation* 2014;85:1432-1438.
- 19 6. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future.  
20 *Gerontologist* 2011;51:425-432.
- 21 7. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences  
22 between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary  
23 resuscitation using extracorporeal life support. *Resuscitation* 2010;81:968-973.
- 24 8. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary  
25 resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a



- 1 propensity-matched study and predictor analysis. *Crit Care Med* 2013;41:1186-1196.
- 2
- 3 9. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy
- 4 for out-of-hospital and emergency department cardiac arrest. *Resuscitation*
- 5 2014;85:1527-1532.
- 6
- 7 10. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary
- 8 resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital
- 9 cardiac arrest: a prospective observational study. *Resuscitation* 2014;85:762-768.
- 10
- 11 11. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for
- 12 Resuscitation 2010 Section 1. Executive summary. *Resuscitation* 2010;81:1219-1276.
- 13
- 14 12. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to
- 15 extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in
- 16 patients with out-of-hospital cardiac arrest: a propensity-matched study. *Crit Care*
- 17 2014;18:535.
- 18
- 19 13. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal
- 20 cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with that for
- 21 extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation* 2014;85:1219-1224.
- 22
- 23 14. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal
- 24 cardiopulmonary resuscitation in adults. *Resuscitation* 2015;91:73-75.
- 25
- 26 15. Kolla S, Lee WA, Hirschl RB, Bartlett RH. Extracorporeal life support for
- 27 cardiovascular support in adults. *ASAIO J* 1996;42:M809-819.
- 28
- 29 16. Masetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life
- 30 support for prolonged cardiac arrest. *Ann Thorac Surg* 2005;79:178-183; discussion 183-174.
- 31
- 32 17. Mendiratta P, Wei JY, Gomez A, et al. Cardiopulmonary resuscitation requiring
- 33 extracorporeal membrane oxygenation in the elderly: a review of the Extracorporeal Life
- 34 Support Organization registry. *ASAIO J* 2013;59:211-215.
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3 1 18. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life  
4  
5 2 support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation  
6  
7 3 and Emergency Cardiovascular Care. *Circulation* 2010;122:S729-767.  
8  
9 4 19. Prohl J, Rother J, Kluge S, et al. Prediction of short-term and long-term outcomes  
10  
11 5 after cardiac arrest: a prospective multivariate approach combining biochemical, clinical,  
12  
13 6 electrophysiological, and neuropsychological investigations. *Crit Care Med*  
14  
15 7 2007;35:1230-1237.  
16  
17 8 20. Chen YS, Yu HY, Huang SC, et al. Extracorporeal membrane oxygenation support can  
18  
19 9 extend the duration of cardiopulmonary resuscitation. *Crit Care Med* 2008;36:2529-2535.  
20  
21 10 21. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during  
22  
23 11 cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest  
24  
25 12 who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention.  
26  
27 13 *Circ J* 2010;74:77-85.  
28  
29 14 22. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated  
30  
31 15 cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation*  
32  
33 16 2007;116:2900-2907.  
34  
35 17 23. Kim C, Becker L, Eisenberg MS. Out-of-hospital cardiac arrest in octogenarians and  
36  
37 18 nonagenarians. *Arch Intern Med* 2000;160:3439-3443.  
38  
39 19 24. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation  
40  
41 20 efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to  
42  
43 21 novel therapies? *Circulation* 2013;128:2488-2494.  
44  
45 22 25. Asaka; Noriaki Aoki. ECPR Indication Criteria -From the Cost Effective Analysis in  
46  
47 23 SAVE-J Study- [Abstract]. *Circulation* 2013;128:A305.  
48  
49 24 26. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other  
50  
51 25 factors influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437-452.  
52  
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3 1 27. Fukuda T, Yasunaga H, Horiguchi H, et al. Health care costs related to out-of-hospital  
4  
5 2 cardiopulmonary arrest in Japan. Resuscitation 2013;84:964-969.  
6  
7 3 28. Wuerz RC, Holliman CJ, Meador SA, Swope GE, Balogh R. Effect of age on  
8  
9 4 prehospital cardiac resuscitation outcome. Am J Emerg Med 1995;13:389-391.  
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Tadahiro Goto

ECPR for elderly OHCA

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

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Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.

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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

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In a case who the team leader judged "inadequate indication" for ECPR

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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.

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ECPR for elderly OHCA

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

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ECPR for elderly OHCA

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  $\geq 20$  minutes during transportation.

§ Defined as spontaneous circulation sustained for  $\geq 20$  minutes.

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ECPR for elderly OHCA

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.

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ECPR for elderly OHCA

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5 **1 FIGURE LEGENDS**

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7 **2 Figure 1.** Patients receiving extracorporeal cardiopulmonary resuscitation

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9 **3 Figure 2.** Univariable associations between age and outcomes.

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**Figure 1**

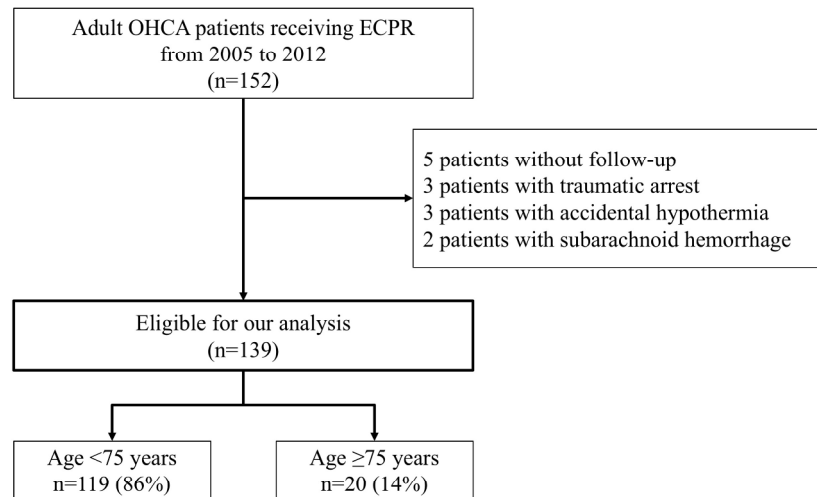


Figure 1

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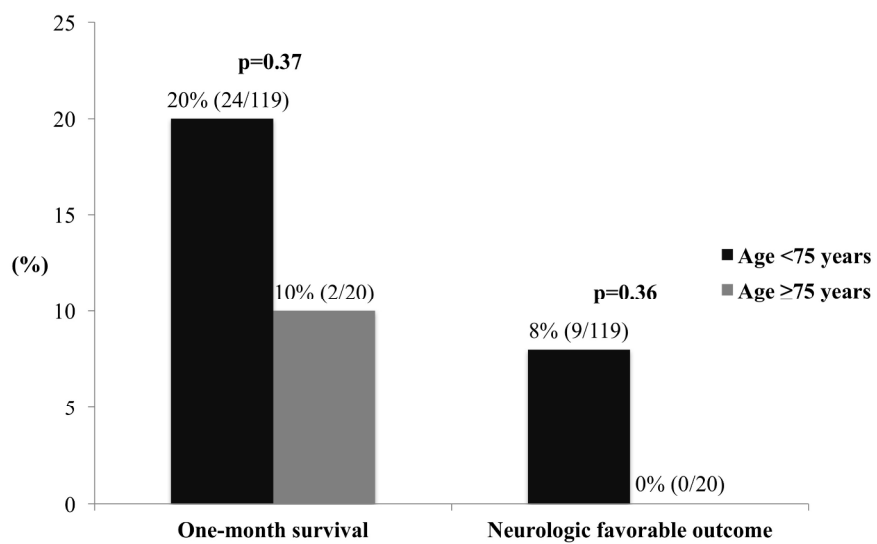
**Figure 2A**

Figure 2A

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**Figure 2B**

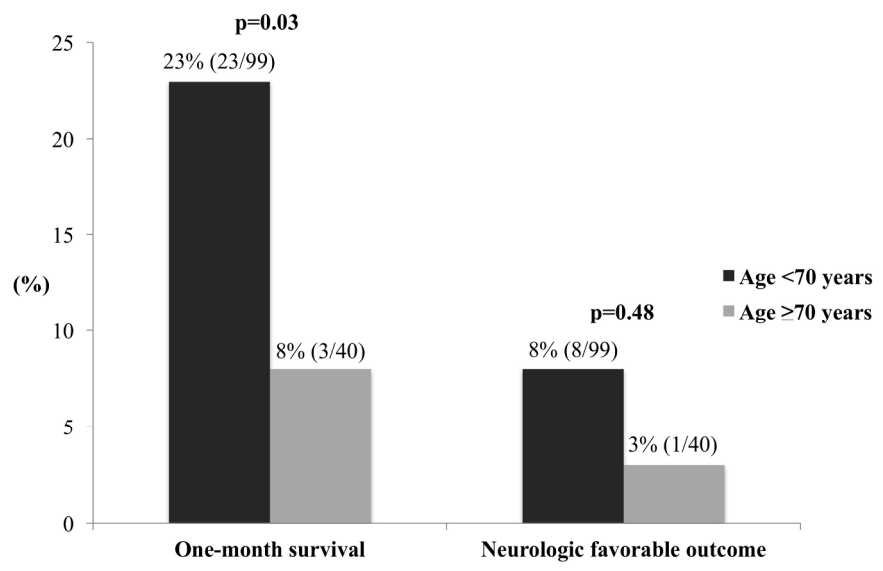


Figure 2C

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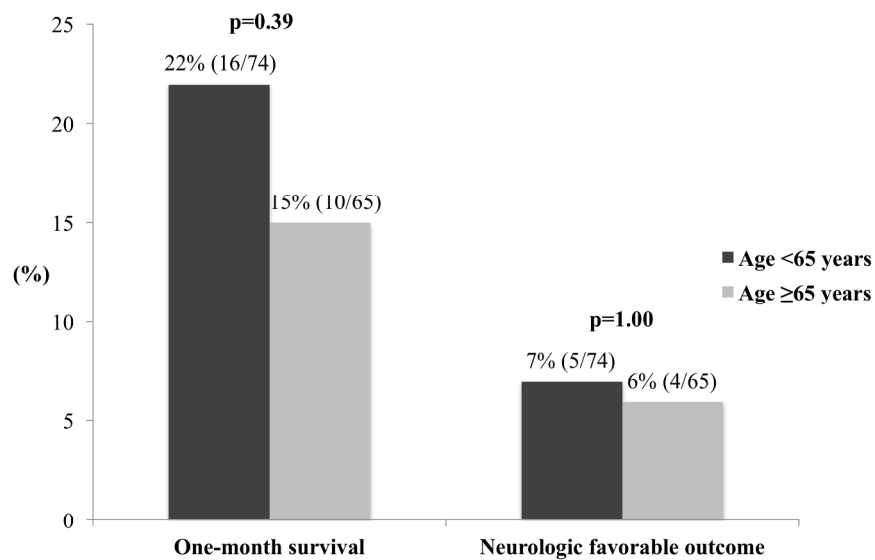
**Figure 2C**

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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8,9
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Resuscitation, Emergency Medicine, cardiac arrest, elderly, Extracorporeal membrane oxygenation

SCHOLARONE™  
Manuscripts

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3 **1 Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly**  
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5 **2 Patients with Out-of-Hospital Cardiac Arrests: a single-centre retrospective analysis**  
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ECPR for elderly OHCA

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**WORD COUNT:** 3,005 words (main text). **Abstract:** 289 words

**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  $\geq 18$  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  $\geq 75$  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  $\geq 75$  years. Among OHCA patients aged  $\geq 75$  years, no patient survived with neurologically favourable outcomes, whereas 8% of patients aged  $< 75$  years survived with neurologically favourable outcomes

1 (0% [95%CI 0%-0%] vs. 8% [95%CI 4%-15%]). Likewise, the proportion of one-month  
2 survival was lower in patients aged  $\geq 75$  years compared to those in aged  $< 75$  years (14%  
3 [4%-36%] vs. 20% [14%-29%]). These associations between advanced age and poor  
4 outcomes remained in the multivariable adjusted models, and the sensitivity analysis using  
5 decades of age as a categorical variable.

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

11  
12 **Keywords:** extracorporeal resuscitation; out-of-hospital cardiac arrest; elderly

### 13 14 **Strengths and limitations of this study**

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

### 20 21 **1. Introduction**

22 Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.<sup>1-3</sup> In 2014,  
23 the national annual number of OHCA of cardiac origin was 70,000 in Japan,<sup>4</sup> with an increase  
24 in the number of elderly patients.<sup>5</sup> As the aging population is expected to grow further in  
25 Japan<sup>6</sup> as well as other developed nations, the increased incidence of OHCA in elderly

1 patients will become a further burden.<sup>5</sup> There is, therefore, a compelling need to develop  
2 optimal management strategies and policies to treat OHCA in elderly patients.

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

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

1

## 2 **2. Material and Methods**

### 3 *2.1. Study design and settings*

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

### 16 *2.2. Selection of participants and data collection*

17 We abstracted data from medical records of consecutive OHCA patients aged  $\geq 18$  years old  
18 who underwent ECPR between January 2005 and September 2013. In our centre, all OHCA  
19 patients including EMS-witnessed cases are recorded in the form of an electronic medical  
20 chart as our data resource. We abstracted necessary data from the medical chart for this study.  
21 For all OHCA patients, the emergency physician assessed the indications for ECPR during  
22 transportation and then informed the hospital medical staff in the emergency department via  
23 telephone. To confirm the eligibility of ECPR for OHCA patients, in our critical care medical  
24 centre, the on-site physicians used mobile phones to discuss the eligibility of ECPR with  
25 other in-hospital attending physicians. In the present study, approximately 80% of OHCA

1 cases were transported by physician-staffed ambulances, and all patients were treated by  
2 emergency physicians and the Advanced Cardiac Life Support guidelines of the emergency  
3 department.<sup>20</sup>

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

### 12 13 *2.3. ECMO management and post-resuscitation care*

14 The final decision to initiate ECPR depended on the opinions of the attending physicians.  
15 To achieve successful and rapid implementation, the ECMO team consisted of emergency  
16 physicians, cardiologists, and clinical engineers. Chest compression was continued until  
17 starting ECMO. The percutaneous cannulation technique for venous and arterial ECMO  
18 accesses was used to deliver ECMO with a 13.5 F arterial cannulae or a 19.5 F venous  
19 cannulae via femoral artery or vein. The cannulation was performed in the ED or ED  
20 adjoining cardiac catheterization room. Urgent coronary angiography was performed for  
21 OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial  
22 infarction were performed a primary percutaneous intervention with conventional technique  
23 for culprit lesions. All post-resuscitated patients after implementation of ECMO received  
24 guideline recommended care,<sup>1</sup> regardless of age and clinical diagnosis. The patients were  
25 provided adequate oxygenation, vasopressors and fluid administration to maintain systolic

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3 1 arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature  
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5 2 management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the  
6  
7 3 patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of  
8  
9 4 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage  
10  
11 5 equivalent to brain death, withdrawal of ECMO was considered.  
12  
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#### 15 16 7 *2.4 Data collection and Quality control*

17  
18 8 The measured variables were patient demographics, prehospital characteristics (i.e.,  
19  
20 9 time-course, initial rhythm, presence of return of spontaneous circulation, and managements),  
21  
22 10 resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic  
23  
24 11 balloon pumping), and the cause of cardiac arrest. The attending physician at the morning  
25  
26 12 conference decided the cause of cardiac. Prehospital variables were collected by the  
27  
28 13 information from paramedics and the emergency physicians who treated the patient with  
29  
30 14 physician-staffed ambulance. The resuscitation time-course was collected by the emergency  
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32 15 physician who treated the patient with the physician-staffed ambulance and medical staff in  
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34 16 the emergency department. Other measurements including post resuscitation care were  
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36 17 recorded by the attending physician using a standardized data collection form.  
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#### 44 19 *2.5. Outcomes*

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46 20 Outcomes of interest were one-month neurologically favourable outcomes and survival.  
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48 21 Neurologically favourable outcomes were defined as a Cerebral Performance Categories  
49  
50 22 (CPC) score of 1 or 2.<sup>21</sup> The attending physician in-charge of the rounds or the outpatient  
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52 23 determined the CPC score.  
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#### 55 25 *2.6. Statistical analyses*

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3 1 To assess the association between advanced age and outcomes, “elderly” patients were  
4  
5 2 defined as those aged  $\geq 75$  years, as previously reported.<sup>2,22,23</sup> Patients characteristics and  
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7 3 outcomes were compared between those aged  $< 75$  years and those aged  $\geq 75$  years.  
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9 4 Continuous data were presented as the median (interquartile) with differences analysed using  
10  
11 5 the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with  
12  
13 6 differences analysed using chi-square test or Fischer’s exact test as appropriate. We also  
14  
15 7 illustrated the associations between age and each outcome by using a LOWESS smoother  
16  
17 8 with calculating 95% confidence interval using a bootstrap method.

19  
20 9 A multivariable logistic regression model was fitted to study the association between  
21  
22 10 patient age and outcomes. Potential confounding factors based on biological plausibility and  
23  
24 11 previous studies were included.<sup>2,8,10,24</sup> Variables included gender, shockable rhythm,  
25  
26 12 witnessed arrest, and CPR by bystanders. Shockable rhythm was defined as Vf and pulseless  
27  
28 13 ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. Odds  
29  
30 14 ratios (ORs) and confidence intervals (CIs) were then calculated. In the sensitivity analysis,  
31  
32 15 to assess the consistency of the associations between advanced age and outcomes, we further  
33  
34 16 repeated the analysis using age as a categorical variable: age  $\leq 39$ , 40-49, 50-59, 60-69, 70-79,  
35  
36 17 and  $> 80$  years. We analyzed data using STATA 15.0 (StataCorp, College Station, TX) and R  
37  
38 18 statistical software (version 3.4.0).

### 19 20 **3. Results**

21 During the study period, 152 consecutive OHCA patients underwent ECPR. Among them we  
22  
23 22 excluded five patients without follow-up as they were transported to another hospital for  
24  
25 23 further advanced care (e.g., implementation of left ventricular assistive device) and another  
26  
27 24 three patients with traumatic arrest, leaving 144 patients eligible for our analysis (122  
28  
29 25 patients in the  $< 75$  years group and 22 patients in the  $\geq 75$  years group; **Supplemental Figure**

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3 1) 1).

4  
5 2 Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 15%  
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7 3 of patients were women (**Table 2**). In 38% of cases, a bystander performed CPR. Shockable  
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9 4 rhythm (i.e., Vf and pulseless VT) accounted for 61% of cases. Physician-staffed ambulances  
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11 5 transported 81% of cases. The median time from call to arrival at the hospital was 41 min  
12  
13 6 (IQR, 33-50 min), and from call to implementation of ECMO was 57 min (IQR, 49-70 min).  
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15 7 On admission, the median pH value was 6.95 and median serum lactate level was 12.5  
16  
17 8 mmol/L. For post-resuscitation therapy, therapeutic hypothermia was completed in 44% of  
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19 9 patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately  
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21 10 70% of cardiac arrests were caused by acute myocardial infarction. There were no significant  
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23 11 differences in prehospital characteristics, resuscitation time-course, interventions, and causes  
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25 12 of cardiac arrest between patients aged  $\geq 75$  years and those aged  $< 75$  years, while the pH  
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27 13 value and serum lactate level were preferable (i.e., high pH value and low lactate level) in  
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29 14 patients aged  $\geq 75$  years, compared to those aged  $< 75$  years. Detailed information on patient  
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31 15 characteristics according to decades of age is shown in **Supplemental Table 1**.

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35 16 Overall, the proportion of neurologically favourable outcomes was 7% (95% CI,  
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37 17 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. **Figure 1**  
38  
39 18 illustrates the associations between age and each outcome. The rate of one-month  
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41 19 neurologically favourable outcomes remained around 8% between 18 and 70 years and  
42  
43 20 decreased as age increased. Likewise, the rate of one-month survival remained around 20%  
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45 21 between 18 and 70 years and decreased as age increased as age increased, with a highest  
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47 22 survival rate at age 60 years.

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49  
50 23 **Table 3** demonstrates the associations between age and outcomes. Among patients  
51  
52 24 aged  $\geq 75$  years, no patient survived with neurologically favourable outcomes, although 8% of  
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54 25 patients aged  $< 75$  years survived with neurologically favourable outcomes (0% [95CI



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3 1 0%-0%] vs. 8% [95%CI 4%-15%]). The proportion of one-month survival was lower in  
4  
5 2 patients aged  $\geq 75$  years than in those aged  $< 75$  years (14% [95%CI 4%-36%] vs. 20%  
6  
7 3 [95%CI 14%-29%]). These associations remained in the unadjusted and adjusted models.  
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9  
10 4 In the sensitivity analysis using decades of age, although the samples size was limited,  
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12 5 advanced age (age 70-79 years and age 80-89 years) was associated with poor one-month  
13  
14 6 neurologically favourable outcomes and survival compared to age 18-39 years (**Table 3**).  
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#### 18 8 **4. Discussion**

19  
20 9 In this retrospective analysis from an urban critical care hospital, we found that  
21  
22 10 advanced age was likely to be associated with the lower rate of one-month neurologically  
23  
24 11 favourable outcomes and survival in patients with OHCA who underwent ECPR, although  
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26 12 the limited number of cases did not detect statistical significance. The rate of neurologically  
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28 13 favourable outcomes and one-month survival decreased after age 70 years old. Surprisingly,  
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30 14 no patient aged  $\geq 75$  years survived with neurologically favourable outcomes at one-month  
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32 15 after cardiac arrest. These findings provide valuable clues for creating optimal strategy for  
33  
34 16 elderly patients with OHCA in the aging era.  
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36  
37 17 Our study observed that no patients aged  $\geq 75$  years survived with neurologically  
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39 18 favourable outcomes at one-month after cardiac arrest. Although previous studies reported  
40  
41 19 that ECPR was more effective in treating OHCA patients than conventional CPR, these  
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43 20 studies did not assess the effect of advanced age – their findings were based on studies  
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45 21 limited to patients aged  $< 75$  years.<sup>9,10</sup> A multicentre prospective observational study in Japan  
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47 22 demonstrated that the survival rate at one-month after cardiac arrest was significantly higher  
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49 23 in the ECPR group than in the non-ECPR group (27% vs. 6%) and that the proportion of  
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51 24 neurologically favourable outcomes was also significantly higher in the ECPR group (12.3%  
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53 25 vs. 1.5%).<sup>10</sup> Our results that overall one-month survival rate of 20% and one-month survival  
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3 1 with neurologically favourable outcomes of 8% are comparable results with these previous  
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5 2 findings,<sup>9,10</sup> despite we included patients aged  $\geq 75$  years. Therefore, focusing on the elderly  
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7 3 patients, our findings might suggest limitations in using ECPR to treat elderly patients with  
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9 4 OHCA.

10  
11 5 The reasons for the observed lack of effectiveness of ECPR among elderly patients  
12  
13 6 are likely multifactorial. First, consistent with the elderly being the population with limited  
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15 7 cardiovascular and pulmonary reserve, the survival rate of OHCA patients was lower in older  
16  
17 8 patients than in younger patients.<sup>25</sup> An observational study in the US demonstrated that  
18  
19 9 advanced age was a factor associated with lower survival rate at discharge among OHCA  
20  
21 10 patients (19.4% for  $\leq 80$  years vs. 9.4% for 80-89 years, and 4.4% for  $\geq 90$  years).<sup>25</sup> Second,  
22  
23 11 shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a  
24  
25 12 critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an  
26  
27 13 observational study in the US, shorter duration of CPR was associated with neurologically  
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29 14 favourable outcomes – 90% of patients with neurologically favourable outcomes required  
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31 15 less than 16 minutes of CPR.<sup>26</sup> In our findings, the median time from cardiac arrest to ROSC  
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33 16 or implementing of ECMO was 54 min, which is considerably longer than in the previous  
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35 17 study in the US.<sup>26</sup> However, patients who require ECPR are “non-responders” to  
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37 18 conventional CPR within 20 minutes.<sup>12</sup> In addition, another ECPR study also showed a  
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39 19 lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our  
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41 20 findings.<sup>8</sup> Due to the vulnerability of elderly patients, elderly patients might not withstand the  
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43 21 prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable  
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45 22 population and a longer CPR duration may help explain the lack of effectiveness of ECPR for  
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47 23 elderly patients with OHCA in the present study.

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49 24 Importantly, the cost burden of ECPR is also significant. In Japan, the incremental  
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51 25 cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted  
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1 life-year (QALY).<sup>27</sup> Considering the acceptable ICER for introducing a new treatment is  
2 approximately £20,000-30,000,<sup>28</sup> this financial burden is unacceptably high. Further, another  
3 Japanese study suggested that the average cost for treating an OHCA patient was  
4 approximately £1,250.<sup>29</sup> Aging, and its associated costs are increasing, constituting an  
5 enormous financial burden throughout the developed world. Given this significant financial  
6 burden and our present observations (i.e. the low rate of neurologic outcomes and survival in  
7 patients aged  $\geq 75$ ), indications of ECPR in elderly patients with OHCA might be limited with  
8 respect to cost-effectiveness. Our observations facilitate further investigations to elucidate the  
9 cost-effectiveness of ECPR for elderly patients with OHCA.

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

## 21 **Limitations**

22 We acknowledge several potential limitations to our study. First, as our sample consisted of  
23 retrospective data from a single centre in Japan, our inferences might not be generalizable to  
24 other healthcare settings. However, the observed association not only has plausible  
25 mechanisms but also persisted across different analytical assumptions. Although formal

1 validation of the study in other healthcare settings is warranted, our inferences likely present  
2 in different practical settings. Second, there was lack of data on daily living activities,  
3 medication use, comorbidities before cardiac arrest including a poorer neurological state  
4 pre-arrest. In addition, information on whether the ECPR was implemented during active  
5 chest compressions and on the results of percutaneous coronary intervention was also not  
6 available. However, an experienced emergency physician or cardiologist assessed whether  
7 the cause of cardiac arrest was treatable and appropriate for ECPR based on information  
8 gained from the person accompanying the patient and the situation of cardiac arrest. Third,  
9 because no patient survived with neurologically favourable outcomes among patients aged  
10  $\geq 75$  years, multivariable logistic regression model did not fit to examine the association  
11 between age  $\geq 75$  and neurologically favourable outcomes. Nevertheless, the impact of our  
12 finding — no patient survived with neurologically favourable outcomes — might be  
13 supported by the underlying biological vulnerability among elderly patients. In addition, the  
14 nonstatistical differences in the outcomes between age  $< 75$  group and age  $\geq 75$  group might  
15 be attributable to the small sample size in age  $\geq 75$  group ( $n=22$ ). Finally, although the  
16 indication for ECPR was assessed based on the protocol and by experienced physicians, our  
17 data are subject to selection bias. In general, however, the indication of ECPR for elderly  
18 patients was stricter than that for younger patients, which might have biased our conclusions  
19 toward the null.

20

## 21 **Conclusions**

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

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3 1 These associations between advanced age and poor outcomes were consistent in the  
4  
5 2 sensitivity analysis using decades of age as a categorical variable. Although larger studies are  
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7 3 required to confirm these results, our findings suggest that ECPR may not be beneficial for  
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9 4 OHCA patients aged  $\geq 75$  years. In addition, clinicians should carefully select patients up to  
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11 5 age 70-75. While the eligibility of ECPR should not be determined by age as a single  
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13 6 variable, our findings might not only help improve the survival rate and neurological  
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15 7 outcomes of elderly patients with OHCA but also facilitate further observation, intervention,  
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17 8 and discussion regarding the utilization of ECPR for elderly patients with OHCA.  
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27 11 **List of abbreviations:** out-of-hospital cardiac arrest, OHCA; extracorporeal  
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29 12 cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal  
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31 13 membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation  
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33 14 ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY;  
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35 15 confidence interval, CI  
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39 17 **DISCLOSURES:**

40 18 **Ethics approval and consent to participate and Consent for publication:** The institutional  
41  
42 19 review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of  
43  
44 20 informed consent.  
45

46 21 **Availability of data and materials:** The data used in this study were not publically  
47  
48 22 available.  
49

50 23 **Competing interests:** There are no conflict of interest.

51  
52 24 **Funding:** None  
53

54  
55 25 **Authors' contributions:** TG, SM, NT, HS, YH and Tkai planned the study. TKit supervised  
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1 and provided statistical advice on study design. TG analysed the data. TG drafted the  
2 manuscript, and all authors contributed substantially to its revision. TG takes responsibility  
3 for the paper as a whole. All authors read and approved the final manuscript.

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## 7 REFERENCES

- 8 1. 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency  
9 Cardiovascular Care Science With Treatment Recommendations. *Circulation*.  
10 2010;122:S250-S605.
- 11 2. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and  
12 emergency cardiovascular care. *Circulation*. 2010;122:S639-S946.
- 13 3. European Resuscitation Council Guidelines for Resuscitation 2010. *Resuscitation*.  
14 2010;81:1219-1451.
- 15 4. Ambulance Service Planning Office of Fire and Disaster Management Agency of  
16 Japan. Effect of first aid for cardiopulmonary arrest. .  
17 [http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218\\_1houdou/01\\_houdoushiryou.pdf](http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218_1houdou/01_houdoushiryou.pdf)  
18 Accessed March 03, 2015.
- 19 5. Kitamura T, Morita S, Kiyohara K, et al. Trends in survival among elderly patients  
20 with out-of-hospital cardiac arrest: a prospective, population-based observation from  
21 1999 to 2011 in Osaka. *Resuscitation*. 2014;85(11):1432-1438.
- 22 6. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future.  
23 *Gerontologist*. 2011;51(4):425-432.
- 24 7. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences  
25 between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary  
26 resuscitation using extracorporeal life support. *Resuscitation*. 2010;81(8):968-973.
- 27 8. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary  
28 resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a

- 1  
2  
3  
4 1 propensity-matched study and predictor analysis. *Crit Care Med.*  
5 2 2013;41(5):1186-1196.  
6  
7 3 9. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy  
8 4 for out-of-hospital and emergency department cardiac arrest. *Resuscitation.*  
9 5 2014;85(11):1527-1532.  
10  
11 6 10. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary  
12 7 resuscitation versus conventional cardiopulmonary resuscitation in adults with  
13 8 out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation.*  
14 9 2014;85(6):762-768.  
15  
16 10 11. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for  
17 11 Resuscitation 2010 Section 1. Executive summary. *Resuscitation.*  
18 12 2010;81(10):1219-1276.  
19  
20 13 12. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to  
21 14 extracorporeal cardiopulmonary resuscitation for predicting good neurological  
22 15 outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study.  
23 16 *Crit Care.* 2014;18(5):535.  
24  
25 17 13. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal  
26 18 cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with  
27 19 that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation.*  
28 20 2014;85(9):1219-1224.  
29  
30 21 14. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal  
31 22 cardiopulmonary resuscitation in adults. *Resuscitation.* 2015;91:73-75.  
32  
33 23 15. Choi DH, Kim YJ, Ryoo SM, et al. Extracorporeal cardiopulmonary resuscitation  
34 24 among patients with out-of-hospital cardiac arrest. *Clin Exp Emerg Med.*  
35 25 2016;3(3):132-138.  
36  
37 26 16. Kolla S, Lee WA, Hirschl RB, Bartlett RH. Extracorporeal life support for  
38 27 cardiovascular support in adults. *ASAIO J.* 1996;42(5):M809-819.  
39  
40 28 17. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life  
41 29 support for prolonged cardiac arrest. *Ann Thorac Surg.* 2005;79(1):178-183;

- 1  
2  
3  
4 1 discussion 183-174.  
5  
6 2 18. Mendiratta P, Wei JY, Gomez A, et al. Cardiopulmonary resuscitation requiring  
7  
8 3 extracorporeal membrane oxygenation in the elderly: a review of the Extracorporeal  
9  
10 4 Life Support Organization registry. *ASAIO J.* 2013;59(3):211-215.  
11  
12 5 19. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal  
13  
14 6 cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac  
15  
16 7 arrest. A systematic review and meta-analysis. *Resuscitation.* 2017;112:1-10.  
17  
18 8 20. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life  
19  
20 9 support: 2010 American Heart Association Guidelines for Cardiopulmonary  
21  
22 10 Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 Suppl  
23  
24 11 3):S729-767.  
25  
26 12 21. Prohl J, Rother J, Kluge S, et al. Prediction of short-term and long-term outcomes  
27  
28 13 after cardiac arrest: a prospective multivariate approach combining biochemical,  
29  
30 14 clinical, electrophysiological, and neuropsychological investigations. *Crit Care Med.*  
31  
32 15 2007;35(5):1230-1237.  
33  
34 16 22. Chen YS, Yu HY, Huang SC, et al. Extracorporeal membrane oxygenation support can  
35  
36 17 extend the duration of cardiopulmonary resuscitation. *Crit Care Med.*  
37  
38 18 2008;36(9):2529-2535.  
39  
40 19 23. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during  
41  
42 20 cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac  
43  
44 21 arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary  
45  
46 22 intervention. *Circ J.* 2010;74(1):77-85.  
47  
48 23 24. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated  
49  
50 24 cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation.*  
51  
52 25 2007;116(25):2900-2907.  
53  
54 26 25. Kim C, Becker L, Eisenberg MS. Out-of-hospital cardiac arrest in octogenarians and  
55  
56 27 nonagenarians. *Arch Intern Med.* 2000;160(22):3439-3443.  
57  
58 28 26. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation  
59  
60 29 efforts and functional outcome after out-of-hospital cardiac arrest: when should we



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4 1 change to novel therapies? *Circulation*. 2013;128(23):2488-2494.
- 5  
6 27. Asaka K; Aoki N. ECPR Indication Criteria -From the Cost Effective Analysis in  
7  
8 3 SAVE-J Study- [Abstract]. *Circulation* 2013;128:A305.
- 9  
10 28. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other  
11  
12 5 factors influence its decisions? A binary choice analysis. *Health Econ*.  
13  
14 6 2004;13(5):437-452.
- 15  
16 29. Fukuda T, Yasunaga H, Horiguchi H, et al. Health care costs related to out-of-hospital  
17  
18 8 cardiopulmonary arrest in Japan. *Resuscitation*. 2013;84(7):964-969.
- 19  
20 30. Wuerz RC, Holliman CJ, Meador SA, Swope GE, Balogh R. Effect of age on  
21  
22 10 prehospital cardiac resuscitation outcome. *Am J Emerg Med*. 1995;13(4):389-391.  
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Tadahiro Goto

ECPR for elderly OHCA

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6 **1 Table 1. Indications for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre**

7 Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.

8 Indication criteria

9 Absolute indication Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)

10 Relative indication Presumed treatable conditions with PEA/Asystole\*

11 Hypothermia

12 Drug intoxication

13 Exclusion criteria

14 Stroke

15 Terminal malignancy

16 Cirrhosis

17 Chronic obstructive pulmonary disease

18 Poor activities of daily living

19 In a case who the team leader judged "inadequate indication" for ECPR

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

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28 **2 \* Judged by an emergency physician who treats the patient with physician-staffed ambulance according to he initial rhythm.**

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**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%)

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Tadahiro Goto	ECPR for elderly OHCA		
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.

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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 ratios (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)

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ECPR for elderly OHCA

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  $\geq 75$  years survived with neurologically favourable outcomes.

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ECPR for elderly OHCA

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5 **FIGURE LEGENDS**

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

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8 **Supplemental Figure 1.** Patients receiving extracorporeal cardiopulmonary resuscitation

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### Figure 1

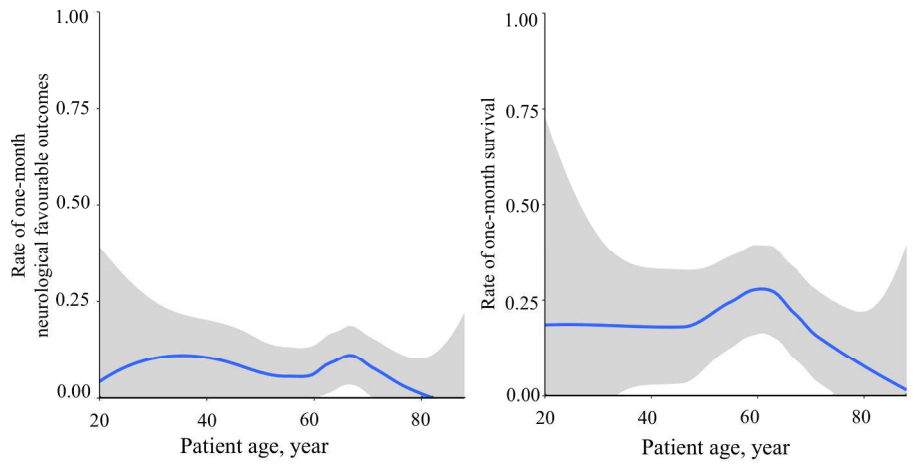
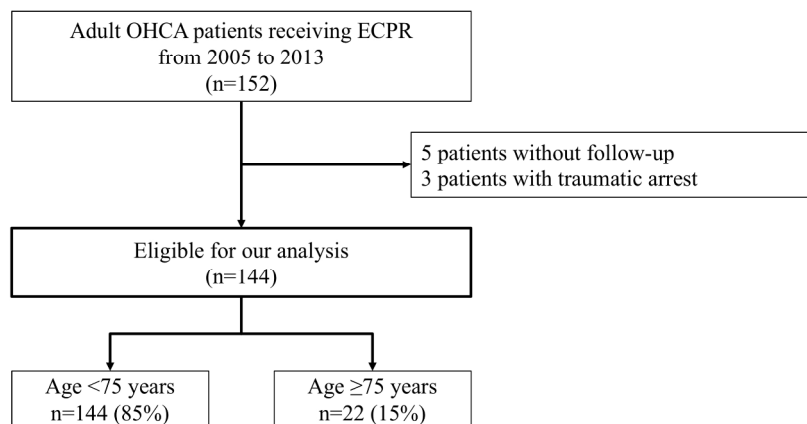


Figure 1

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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	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age ≥ 80
	years	years	years	years	years	years
	(n=12)	(n=11)	(n=35)	(n=44)	(n=31)	(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%)
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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  $\geq 20$  minutes during transportation.

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§ Aortic dissection, structural heart disease, and arrhythmia

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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	2-3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7-8

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Resuscitation, Emergency Medicine, cardiac arrest, elderly, Extracorporeal membrane oxygenation

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3 **1 Impact of Extracorporeal Cardiopulmonary Resuscitation on Outcomes of Elderly**  
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5 **2 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  $\geq 18$  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  $\geq 75$  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  $\geq 75$  years. Among OHCA patients aged  $\geq 75$  years, no patient survived with neurologically favourable outcomes, whereas 8% of patients aged  $< 75$  years survived with neurologically favourable outcomes

1 (0% [95%CI 0%-0%] vs. 8% [95%CI 4%-15%]). Likewise, the proportion of one-month survival was lower in patients aged  $\geq 75$  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.

6 **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  $\geq 75$  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  $\geq 75$  years.

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

### 14 **Strengths and limitations of this study**

- 15 1. This study is the first study investigating the impact of age on outcomes among OHCA patients treated with ECPR, including patients aged  $\geq 75$  years.
- 17 2. There are consistent findings in the sensitivity analyses using decade of age as a categorical variable.
- 19 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.

### 23 **1. Introduction**

24 Out-of-hospital cardiac arrest (OHCA) is a major, global public health problem.<sup>1-3</sup> In 2014, 25 the national annual number of OHCA of cardiac origin was 70,000 in Japan,<sup>4</sup> with an increase

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3 1 in the number of elderly patients.<sup>5</sup> As the aging population is expected to grow further in  
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5 2 Japan<sup>6</sup> as well as other developed nations, the increased incidence of OHCA in elderly  
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7 3 patients will become a further burden.<sup>5</sup> There is, therefore, a compelling need to develop  
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9 4 optimal management strategies and policies to treat OHCA in elderly patients.

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11 5 To date, encouraging results of extracorporeal cardiopulmonary resuscitation (ECPR)  
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13 6 for patients with OHCA have been shown as a highly advanced medical treatment.<sup>7-10</sup> The  
14  
15 7 recommendation of ECPR for cardiac arrest is class 2b based on the 2015 *American Heart*  
16  
17 8 *Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular*  
18  
19 9 *Care Science*.<sup>1</sup> In addition, the *European Resuscitation Council Guidelines for Resuscitation*  
20  
21 10 recommends the consideration of ECPR for cases such as paediatric resuscitation and  
22  
23 11 asthma-related cardiac arrest.<sup>11</sup> Further, subsequent observational studies have demonstrated  
24  
25 12 that the utilization of ECPR was associated with improved survival compared to conventional  
26  
27 13 cardiopulmonary resuscitation (CPR) in OHCA patients with potentially treatable  
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29 14 conditions.<sup>12,13</sup> The indication of ECPR for OHCA might, therefore, be extended in the future.  
30  
31 15 However, the utilization of ECPR for elderly patients — a population with limited  
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33 16 cardiovascular and pulmonary reserve — remains controversial.<sup>14</sup> Indeed, ECPR clinical  
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35 17 protocols are likely to include an age limit as a contraindication of ECPR, whereas there is  
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37 18 not sufficient supporting evidence.<sup>15</sup> Although some reports suggest that an age of  $\geq 75$  years  
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39 19 should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,<sup>16,17</sup>  
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41 20 a literature using the international Extracorporeal Life Support Organization registry  
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43 21 suggested that age should not be a bar against the consideration of the utilization of ECMO in  
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45 22 elderly patients.<sup>18</sup> Furthermore, a recent systematic review of prognostic factors for ECPR  
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47 23 recipients following OHCA has failed to establish a link between age and poor prognosis  
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49 24 following ECPR.<sup>19</sup>

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55 25 To address this knowledge gap in the literature, we assessed the neurological  
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1 outcomes and mortality of elderly patients with OHCA who underwent ECPR, using  
2 consecutive data from a critical care centre in Osaka, the second largest prefecture in Japan.

## 3 4 **2. Material and Methods**

### 5 *2.1. Study design and settings*

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

### 17 18 *2.2. Selection of participants and data collection*

19 We abstracted data from medical records of consecutive OHCA patients aged  $\geq 18$  years old  
20 who underwent ECPR between January 2005 and September 2013. In our centre, all OHCA  
21 patients including EMS-witnessed cases are recorded in the form of an electronic medical  
22 chart as our data resource. We abstracted necessary data from the medical chart for this study.  
23 For all OHCA patients, the emergency physician assessed the indications for ECPR during  
24 transportation and then informed the hospital medical staff in the emergency department via  
25 telephone. To confirm the eligibility of ECPR for OHCA patients, in our critical care medical

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3 1 centre, the on-site physicians used mobile phones to discuss the eligibility of ECPR with  
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5 2 other in-hospital attending physicians. In the present study, approximately 80% of OHCA  
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7 3 cases were transported by physician-staffed ambulances, and all patients were treated by  
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9 4 emergency physicians and the Advanced Cardiac Life Support guidelines of the emergency  
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11 5 department.<sup>20</sup>  
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13  
14 6 Indications of ECPR for OHCA patients are shown in **Table 1**. Absolute indications  
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16 7 for ECPR were OHCA patients with refractory ventricular fibrillation (Vf), defined as  
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18 8 sustained Vf after three attempts of defibrillation with potentially treatable conditions.  
19  
20 9 Relative indications for ECPR were OHCA patients with presumably treatable conditions  
21  
22 10 with pulseless electrical activity or asystole, hypothermia, and drug intoxication. Patient age  
23  
24 11 was not considered when using ECPR. Patients with the following were excluded: stroke,  
25  
26 12 terminal malignancy, cirrhosis, severe chronic obstructive pulmonary disease, poor daily  
27  
28 13 living activities, and assessed as “inadequate indications” for ECPR by the team leader.  
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### 31 32 33 15 *2.3. ECMO management and post-resuscitation care*

34  
35 16 The final decision to initiate ECPR depended on the opinions of the attending physicians.  
36  
37 17 To achieve successful and rapid implementation, the ECMO team consisted of emergency  
38  
39 18 physicians, cardiologists, and clinical engineers. Chest compression was continued until  
40  
41 19 starting ECMO. The percutaneous cannulation technique for venous and arterial ECMO  
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43 20 accesses was used to deliver ECMO with a 13.5 F arterial cannulae or a 19.5 F venous  
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45 21 cannulae via femoral artery or vein. The cannulation was performed in the ED or ED  
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47 22 adjoining cardiac catheterization room. Urgent coronary angiography was performed for  
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49 23 OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial  
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51 24 infarction were performed a primary percutaneous intervention with conventional technique  
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53 25 for culprit lesions. All post-resuscitated patients after implementation of ECMO received  
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3 1 guideline recommended care,<sup>1</sup> regardless of age and clinical diagnosis. The patients were  
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5 2 provided adequate oxygenation, vasopressors and fluid administration to maintain systolic  
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7 3 arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature  
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9 4 management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the  
10  
11 5 patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of  
12  
13 6 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage  
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15 7 equivalent to brain death, withdrawal of ECMO was considered.  
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#### 20 9 *2.4 Data collection and Quality control*

21  
22 10 The measured variables were patient demographics, prehospital characteristics (i.e.,  
23  
24 11 time-course, initial rhythm, presence of return of spontaneous circulation, and managements),  
25  
26 12 resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic  
27  
28 13 balloon pumping), and the cause of cardiac arrest. The attending physician at the morning  
29  
30 14 conference decided the most likely cause of cardiac arrest. Prehospital variables were  
31  
32 15 collected by the information from paramedics and the emergency physicians who treated the  
33  
34 16 patient with physician-staffed ambulance. The resuscitation time-course was collected by the  
35  
36 17 emergency physician who treated the patient with the physician-staffed ambulance and  
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38 18 medical staff in the emergency department. Other measurements including post resuscitation  
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40 19 care were recorded by the attending physician using a standardized data collection form.  
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#### 46 21 *3.5. Outcomes*

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48 22 Outcomes of interest were one-month neurologically favourable outcomes and survival.  
49  
50 23 Neurologically favourable outcomes were defined as a Cerebral Performance Categories  
51  
52 24 (CPC) score of 1 or 2.<sup>21</sup> The attending physician in-charge of the rounds or the outpatient  
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54 25 determined the CPC score.  
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5 2 *2.6. Statistical analyses*

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7 3 To assess the association between advanced age and outcomes, “elderly” patients were  
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9 4 defined as those aged  $\geq 75$  years, as previously reported.<sup>2,22,23</sup> Patients characteristics and  
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11 5 outcomes were compared between those aged  $< 75$  years and those aged  $\geq 75$  years.  
12  
13 6 Continuous data were presented as the median (interquartile) with differences analysed using  
14  
15 7 the Mann-Whitney test, while categorical data were expressed in percentages (n/N) with  
16  
17 8 differences analysed using chi-square test or Fischer’s exact test as appropriate. We also  
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19 9 illustrated the associations between age and each outcome by using a LOWESS smoother  
20  
21 10 with calculating 95% confidence interval using a bootstrap method.

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23  
24 11 A multivariable logistic regression model was fitted to study the association between  
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26 12 patient age and outcomes. Potential confounding factors based on biological plausibility and  
27  
28 13 previous studies were included.<sup>2,8,10,24</sup> Variables included gender, shockable rhythm,  
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30 14 witnessed arrest, and CPR by bystanders. Shockable rhythm was defined as Vf and pulseless  
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32 15 ventricular tachycardia (VT) at the initial assessment of paramedics or staff physicians. Odds  
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34 16 ratios (ORs) and confidence intervals (CIs) were then calculated. In the sensitivity analysis,  
35  
36 17 to assess the consistency of the associations between advanced age and outcomes, we further  
37  
38 18 repeated the analysis using age as a categorical variable: age  $\leq 39$ , 40-49, 50-59, 60-69, 70-79,  
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40 19 and  $> 80$  years. We also analysed data with excluding patients who were implemented ECMO  
41  
42 20 potentially due to persistent hypotension after ROSC (i.e., patients who had a temporal  
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44 21 ROSC during transportation or any comments in the medical record regarding response to the  
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46 22 resuscitation). We analyzed data using STATA 15.0 (StataCorp, College Station, TX) and R  
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48 23 statistical software (version 3.4.0).

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25 **3. Results**

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3 1 During the study period, 152 consecutive OHCA patients underwent ECPR. Among them we  
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5 2 excluded five patients without follow-up as they were transported to another hospital for  
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7 3 further advanced care (e.g., implementation of left ventricular assistive device) and another  
8  
9 4 three patients with traumatic arrest, leaving 144 patients eligible for our analysis (122  
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11 5 patients in the <75 years group and 22 patients in the ≥75 years group; **Supplemental Figure**  
12  
13 6 **1**).

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16 7 Overall, median patient age was 63 (interquartile range [IQR], 55-71) years, and 15%  
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18 8 of patients were women (**Table 2**). In 38% of cases, a bystander performed CPR. Shockable  
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20 9 rhythm (i.e., Vf and pulseless VT) accounted for 61% of cases. Physician-staffed ambulances  
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22 10 transported 81% of cases. The median time from call to arrival at the hospital was 41 min  
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24 11 (IQR, 33-50 min), and from call to implementation of ECMO was 57 min (IQR, 49-70 min).  
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26 12 On admission, the median pH value was 6.95 and median serum lactate level was 12.5  
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28 13 mmol/L. For post-resuscitation therapy, therapeutic hypothermia was completed in 44% of  
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30 14 patients, and an intra-aortic balloon pumping was used for 77% of patients. Approximately  
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32 15 70% of cardiac arrests were caused by acute myocardial infarction. There were no significant  
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34 16 differences in prehospital characteristics, resuscitation time-course, interventions, and causes  
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36 17 of cardiac arrest between patients aged ≥75 years and those aged <75 years, while the pH  
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38 18 value and serum lactate level were preferable (i.e., high pH value and low lactate level) in  
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40 19 patients aged ≥75 years, compared to those aged <75 years. Detailed information on patient  
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42 20 characteristics according to decades of age is shown in **Supplemental Table 1**.

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46 21 Overall, the proportion of neurologically favourable outcomes was 7% (95% CI,  
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48 22 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. **Figure 1**  
49  
50 23 illustrates the associations between age and each outcome. The rate of one-month  
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52 24 neurologically favourable outcomes remained around 8% between 18 and 70 years and  
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54 25 decreased as age increased. Likewise, the rate of one-month survival remained around 20%



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

3 **Table 3** demonstrates the associations between age and outcomes. Among patients  
4 aged  $\geq 75$  years, no patient survived with neurologically favourable outcomes, although 8% of  
5 patients aged  $< 75$  years survived with neurologically favourable outcomes (0% [95CI  
6 0%-0%] vs. 8% [95%CI 4%-15%]). The proportion of one-month survival was lower in  
7 patients aged  $\geq 75$  years than in those aged  $< 75$  years (14% [95%CI 4%-36%] vs. 20%  
8 [95%CI 14%-29%]). These associations remained in the unadjusted and adjusted models.

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

#### 17 18 **4. Discussion**

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

1 elderly patients with OHCA in the aging era.

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

15 The reasons for the observed lack of effectiveness of ECPR among elderly patients  
16 are likely multifactorial. First, consistent with the elderly being the population with limited  
17 cardiovascular and pulmonary reserve, the survival rate of OHCA patients was lower in older  
18 patients than in younger patients.<sup>25</sup> An observational study in the US demonstrated that  
19 advanced age was a factor associated with lower survival rate at discharge among OHCA  
20 patients (19.4% for  $\leq 80$  years vs. 9.4% for 80-89 years, and 4.4% for  $\geq 90$  years).<sup>25</sup> Second,  
21 shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a  
22 critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an  
23 observational study in the US, shorter duration of CPR was associated with neurologically  
24 favourable outcomes – 90% of patients with neurologically favourable outcomes required  
25 less than 16 minutes of CPR.<sup>26</sup> In our findings, the median time from cardiac arrest to ROSC

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3 1 or implementing of ECMO was 54 min, which is considerably longer than in the previous  
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5 2 study in the US.<sup>26</sup> However, patients who require ECPR are “non-responders” to  
6  
7 3 conventional CPR within 20 minutes.<sup>12</sup> In addition, another ECPR study also showed a  
8  
9 4 lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our  
10  
11 5 findings.<sup>8</sup> Due to the vulnerability of elderly patients, elderly patients might not withstand the  
12  
13 6 prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable  
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15 7 population and a longer CPR duration may help explain the lack of effectiveness of ECPR for  
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17 8 elderly patients with OHCA in the present study.

19  
20 9 Importantly, the cost burden of ECPR is also significant. In Japan, the incremental  
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22 10 cost-effectiveness ratio (ICER) of ECPR was approximately £57,000 per quality-adjusted  
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24 11 life-year (QALY).<sup>27</sup> Considering the acceptable ICER for introducing a new treatment is  
25  
26 12 approximately £20,000-30,000,<sup>28</sup> this financial burden is unacceptably high. Further, another  
27  
28 13 Japanese study suggested that the average cost for treating an OHCA patient was  
29  
30 14 approximately £1,250.<sup>29</sup> Aging, and its associated costs are increasing, constituting an  
31  
32 15 enormous financial burden throughout the developed world. Given this significant financial  
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34 16 burden and our present observations (i.e. the low rate of neurologic outcomes and survival in  
35  
36 17 patients aged  $\geq 75$ ), indications of ECPR in elderly patients with OHCA might be limited with  
37  
38 18 respect to cost-effectiveness. Our observations facilitate further investigations to elucidate the  
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40 19 cost-effectiveness of ECPR for elderly patients with OHCA.

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44 20 Despite the significant healthcare resource burden of ECPR, the present study did not  
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46 21 demonstrate the effectiveness of ECPR for elderly patients with OHCA. However, this does  
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48 22 not indicate that CPR should not be utilized for elderly patients. Although advanced age  
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50 23 could be a factor associated with poor outcomes in OHCA patients in the present study, this  
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52 24 factor alone does not appear to be a well established criterion to deny patients for  
53  
54 25 conventional CPR based on a previous report.<sup>25</sup> Additionally, experts say that decisions

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3 1 regarding termination of resuscitation should not be based on age.<sup>30</sup> However, given our  
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5 2 present findings regarding poor outcomes among elderly patients and the extremely high cost  
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7 3 of ECPR, the indication of ECPR for elderly patients should be carefully considered in this  
8  
9 4 aging era.

## 6 **Limitations**

7 We acknowledge several potential limitations to our study. First, as our sample consisted of  
8 retrospective data from a single centre in Japan, our inferences might not be generalizable to  
9 other healthcare settings. However, the observed association not only has plausible  
10 mechanisms but also persisted across different analytical assumptions. Although formal  
11 validation of the study in other healthcare settings is warranted, our inferences likely present  
12 in different practical settings. Second, there was lack of data on daily living activities,  
13 medication use, comorbidities before cardiac arrest including a poorer neurological state  
14 pre-arrest. In addition, information on whether the ECPR was implemented during active  
15 chest compressions and on the results of percutaneous coronary intervention was also not  
16 available. However, an experienced emergency physician or cardiologist assessed whether  
17 the cause of cardiac arrest was treatable and appropriate for ECPR based on information  
18 gained from the person accompanying the patient and the situation of cardiac arrest. Third,  
19 because no patient survived with neurologically favourable outcomes among patients aged  
20  $\geq 75$  years, multivariable logistic regression model did not fit to examine the association  
21 between age  $\geq 75$  and neurologically favourable outcomes. Nevertheless, the impact of our  
22 finding — no patient survived with neurologically favourable outcomes — might be  
23 supported by the underlying biological vulnerability among elderly patients. In addition, the  
24 nonstatistical differences in the outcomes between age  $< 75$  group and age  $\geq 75$  group might  
25 be attributable to the small sample size in age  $\geq 75$  group (n=22). Fourth, our study might

1 include ECMO cases for persistent hypotension after ROSC. However, there are consistent  
2 results after excluding patients who were implemented ECMO potentially due to persistent  
3 hypotension after ROSC in the ED. Finally, although the indication for ECPR was assessed  
4 based on the protocol and by experienced physicians, our data are subject to selection bias. In  
5 general, however, the indication of ECPR for elderly patients was stricter than that for  
6 younger patients, which might have biased our conclusions toward the null.

7

## 8 **Conclusions**

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

22

23

24 **List of abbreviations:** out-of-hospital cardiac arrest, OHCA; extracorporeal  
25 cardiopulmonary resuscitation, ECPR; cardiopulmonary resuscitation, CPR; extracorporeal

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2  
3 1 membrane oxygenation, ECMO; ventricular fibrillation, Vf; return of spontaneous circulation  
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5 2 ROSC; incremental cost-effectiveness ratio, ICER; quality-adjusted life-year, QALY;  
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7 3 confidence interval, CI  
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11 5 **DISCLOSURES:**

12  
13 6 **Ethics approval and consent to participate and Consent for publication:** The institutional  
14  
15 7 review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of  
16  
17 8 informed consent.

18  
19 9 **Availability of data and materials:** The data are not allowed for public use by institutional  
20  
21 10 review board.

22  
23 11 **Competing interests:** There are no conflict of interest.

24  
25 12 **Funding:** None

26  
27 13 **Authors' contributions:** TG, SM, NT, HS, YH and Tkai planned the study. TKit supervised  
28  
29 14 and provided statistical advice on study design. TG analysed the data. TG drafted the  
30  
31 15 manuscript, and all authors contributed substantially to its revision. TG takes responsibility  
32  
33 16 for the paper as a whole. All authors read and approved the final manuscript.

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36  
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44 20 **REFERENCES**

- 45  
46  
47 21 1. 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency  
48  
49 22 Cardiovascular Care Science With Treatment Recommendations. *Circulation*.  
50  
51 23 2010;122:S250-S605.  
52  
53 24 2. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and  
54  
55 25 emergency cardiovascular care. *Circulation*. 2010;122:S639-S946.  
56  
57 26 3. European Resuscitation Council Guidelines for Resuscitation 2010. *Resuscitation*.

- 1  
2  
3  
4 1 2010;81:1219-1451.
- 5  
6 2 4. Ambulance Service Planning Office of Fire and Disaster Management Agency of  
7  
8 3 Japan. Effect of first aid for cardiopulmonary arrest. .  
9  
10 4 [http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218\\_1houdou/01\\_houdoushiryou.pdf](http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218_1houdou/01_houdoushiryou.pdf)  
11  
12 5 Accessed March 03, 2015.
- 13  
14 6 5. Kitamura T, Morita S, Kiyohara K, et al. Trends in survival among elderly patients  
15  
16 7 with out-of-hospital cardiac arrest: a prospective, population-based observation from  
17  
18 8 1999 to 2011 in Osaka. *Resuscitation*. 2014;85(11):1432-1438.
- 19  
20 9 6. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future.  
21  
22 10 *Gerontologist*. 2011;51(4):425-432.
- 23  
24 11 7. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences  
25  
26 12 between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary  
27  
28 13 resuscitation using extracorporeal life support. *Resuscitation*. 2010;81(8):968-973.
- 29  
30 14 8. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary  
31  
32 15 resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a  
33  
34 16 propensity-matched study and predictor analysis. *Crit Care Med*.  
35  
36 17 2013;41(5):1186-1196.
- 37  
38 18 9. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy  
39  
40 19 for out-of-hospital and emergency department cardiac arrest. *Resuscitation*.  
41  
42 20 2014;85(11):1527-1532.
- 43  
44 21 10. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary  
45  
46 22 resuscitation versus conventional cardiopulmonary resuscitation in adults with  
47  
48 23 out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation*.  
49  
50 24 2014;85(6):762-768.
- 51  
52 25 11. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for  
53  
54 26 Resuscitation 2010 Section 1. Executive summary. *Resuscitation*.  
55  
56 27 2010;81(10):1219-1276.
- 57  
58 28 12. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to  
59  
60 29 extracorporeal cardiopulmonary resuscitation for predicting good neurological

- 1  
2  
3  
4 1 outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study.  
5 2 *Crit Care*. 2014;18(5):535.  
6  
7 3 13. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal  
8 4 cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with  
9 5 that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation*.  
10 6 2014;85(9):1219-1224.  
11  
12 7 14. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal  
13 8 cardiopulmonary resuscitation in adults. *Resuscitation*. 2015;91:73-75.  
14  
15 9 15. Choi DH, Kim YJ, Ryoo SM, et al. Extracorporeal cardiopulmonary resuscitation  
16 10 among patients with out-of-hospital cardiac arrest. *Clin Exp Emerg Med*.  
17 11 2016;3(3):132-138.  
18  
19 12 16. Kolla S, Lee WA, Hirschl RB, Bartlett RH. Extracorporeal life support for  
20 13 cardiovascular support in adults. *ASAIO J*. 1996;42(5):M809-819.  
21  
22 14 17. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life  
23 15 support for prolonged cardiac arrest. *Ann Thorac Surg*. 2005;79(1):178-183;  
24 16 discussion 183-174.  
25  
26 17 18. Mendiratta P, Wei JY, Gomez A, et al. Cardiopulmonary resuscitation requiring  
27 18 extracorporeal membrane oxygenation in the elderly: a review of the Extracorporeal  
28 19 Life Support Organization registry. *ASAIO J*. 2013;59(3):211-215.  
29  
30 20 19. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal  
31 21 cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac  
32 22 arrest. A systematic review and meta-analysis. *Resuscitation*. 2017;112:1-10.  
33  
34 23 20. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life  
35 24 support: 2010 American Heart Association Guidelines for Cardiopulmonary  
36 25 Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl  
37 26 3):S729-767.  
38  
39 27 21. Prohl J, Rother J, Kluge S, et al. Prediction of short-term and long-term outcomes  
40 28 after cardiac arrest: a prospective multivariate approach combining biochemical,  
41 29 clinical, electrophysiological, and neuropsychological investigations. *Crit Care Med*.



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2  
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4 1 2007;35(5):1230-1237.
- 5  
6 2 22. Chen YS, Yu HY, Huang SC, et al. Extracorporeal membrane oxygenation support can  
7  
8 3 extend the duration of cardiopulmonary resuscitation. *Crit Care Med.*  
9  
10 4 2008;36(9):2529-2535.
- 11  
12 5 23. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during  
13  
14 6 cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac  
15  
16 7 arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary  
17  
18 8 intervention. *Circ J.* 2010;74(1):77-85.
- 19  
20 9 24. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated  
21  
22 10 cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation.*  
23  
24 11 2007;116(25):2900-2907.
- 25  
26 12 25. Kim C, Becker L, Eisenberg MS. Out-of-hospital cardiac arrest in octogenarians and  
27  
28 13 nonagenarians. *Arch Intern Med.* 2000;160(22):3439-3443.
- 29  
30 14 26. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation  
31  
32 15 efforts and functional outcome after out-of-hospital cardiac arrest: when should we  
33  
34 16 change to novel therapies? *Circulation.* 2013;128(23):2488-2494.
- 35  
36 17 27. Asaka K; Aoki N. ECPR Indication Criteria -From the Cost Effective Analysis in  
37  
38 18 SAVE-J Study- [Abstract]. *Circulation* 2013;128:A305.
- 39  
40 19 28. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other  
41  
42 20 factors influence its decisions? A binary choice analysis. *Health Econ.*  
43  
44 21 2004;13(5):437-452.
- 45  
46 22 29. Fukuda T, Yasunaga H, Horiguchi H, et al. Health care costs related to out-of-hospital  
47  
48 23 cardiopulmonary arrest in Japan. *Resuscitation.* 2013;84(7):964-969.
- 49  
50 24 30. Wuerz RC, Holliman CJ, Meador SA, Swope GE, Balogh R. Effect of age on  
51  
52 25 prehospital cardiac resuscitation outcome. *Am J Emerg Med.* 1995;13(4):389-391.  
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ECPR for elderly OHCA

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5 **1 Table 1. Indications for Extracorporeal Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest at Senri Critical Care Medical Centre**

6 Following indications are applied when it is expected that ECMO be implemented within 45 min after cardiac arrest.  
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8 Indication criteria

9 Absolute indication	Refractory Vf (Persistent Vf following at least 3 unsuccessful countershocks)
10 Relative indication	Presumed treatable conditions with PEA/Asystole*
	11 Hypothermia
	12 Drug intoxication

13 Exclusion criteria

14 Stroke  
15 Terminal malignancy  
16 Cirrhosis  
17 Chronic obstructive pulmonary disease  
18 Poor activities of daily living

19 In a case who the team leader judged "inadequate indication" for ECPR

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

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

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Tadahiro Goto	ECPR for elderly OHCA		
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 haemorrhage.

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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 ratios (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)

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ECPR for elderly OHCA

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  $\geq 75$  years survived with neurologically favourable outcomes.

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ECPR for elderly OHCA

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5 **FIGURE LEGENDS**

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

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8 **Supplemental Figure 1.** Patients receiving extracorporeal cardiopulmonary resuscitation

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### Figure 1

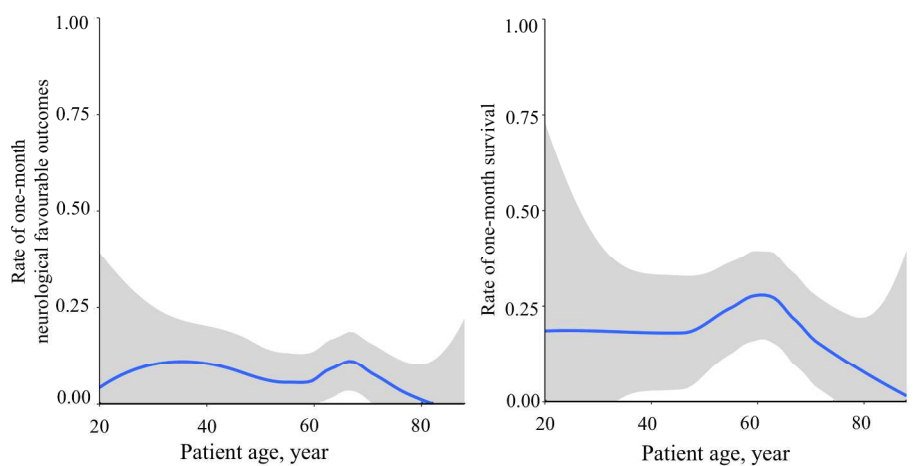
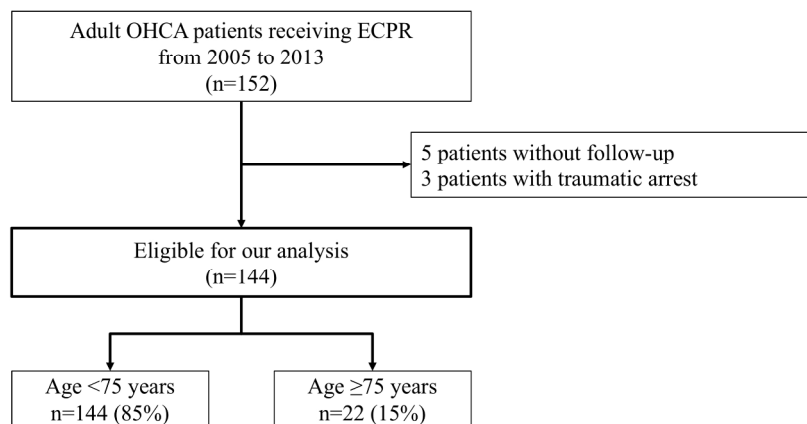


Figure 1

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## Supplemental Figure 1



253x190mm (300 x 300 DPI)

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

	Age 18-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	Age ≥ 80
	years	years	years	years	years	years
	(n=12)	(n=11)	(n=35)	(n=44)	(n=31)	(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%)
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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  $\geq 20$  minutes during transportation.

‡ Defined as spontaneous circulation sustained for  $\geq 20$  minutes.

§ Aortic dissection, structural heart disease, and arrhythmia

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

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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	2-3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7-8

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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**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  $\geq 18$  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 categorical variable (<50 years, 50-59 years, 60-69 years, and  $\geq 70$  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

1 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  $\geq 70$  was non-significantly associated with poor neurological outcomes (adjusted OR 0.08 [95%CI 0.01-1.00]; P=0.051), whereas age  $\geq 70$  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  $\geq 70$  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  $\geq 75$  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.<sup>1-3</sup> In 2014, the national annual number of OHCA of cardiac origin was 70,000 in Japan,<sup>4</sup> with an increase in the number of elderly patients.<sup>5</sup> As the aging population is expected to grow further in Japan<sup>6</sup> as well as other developed nations, the increased incidence of OHCA in elderly patients will become a further burden.<sup>5</sup> 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.<sup>7-10</sup> 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*.<sup>1</sup> 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.<sup>11</sup> 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.<sup>12,13</sup> 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.<sup>14</sup> Indeed, ECPR clinical protocols are likely to include an age limit as a contraindication of ECPR, whereas there is not sufficient supporting evidence.<sup>15</sup> Although some reports suggest that an age of  $\geq 75$  years should be a contraindication for extracorporeal membrane oxygenation (ECMO) support,<sup>16,17</sup> 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.<sup>18</sup> Furthermore, a recent systematic review of prognostic factors for ECPR

1 recipients following OHCA has failed to establish a link between age and poor prognosis  
2 following ECPR.<sup>19</sup>

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

## 6 7 **2. Material and Methods**

### 8 *2.1. Study design and settings*

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

### 20 21 *2.2. Selection of participants and data collection*

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

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

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

### 18 *2.3. ECMO management and post-resuscitation care*

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

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3 1 OHCA patients with a suspected cardiac origin. The patients diagnosed as acute myocardial  
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5 2 infarction were performed a primary percutaneous intervention with conventional technique  
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7 3 for culprit lesions. All post-resuscitated patients after implementation of ECMO received  
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9 4 guideline recommended care,<sup>1</sup> regardless of age and clinical diagnosis. The patients were  
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11 5 provided adequate oxygenation, vasopressors and fluid administration to maintain systolic  
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13 6 arterial pressure at 90 mmHg and/or mean atrial pressure at 65 mmHg, target temperature  
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15 7 management at 34 degrees Celsius. The weaning criteria of ECMO were as follows: 1) the  
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17 8 patient was haemodynamically stable and 2) adequately oxygenated with an ECMO flow of  
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19 9 1,500 mL/min. In cases of irreversible multiple organ failure or severe neurological damage  
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21 10 equivalent to brain death, withdrawal of ECMO was considered.  
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#### 26 12 *2.4 Data collection and Quality control*

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29 13 The measured variables were patient demographics, prehospital characteristics (i.e.,  
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31 14 time-course, initial rhythm, presence of return of spontaneous circulation, and managements),  
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33 15 resuscitation time-course, therapeutic intervention (therapeutic hypothermia and intra-aortic  
34  
35 16 balloon pumping), and the cause of cardiac arrest. The attending physician at the morning  
36  
37 17 conference decided the most likely cause of cardiac arrest. Prehospital variables were  
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39 18 collected by the information from paramedics and the emergency physicians who treated the  
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41 19 patient with physician-staffed ambulance. The resuscitation time-course was collected by the  
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43 20 emergency physician who treated the patient with the physician-staffed ambulance and  
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45 21 medical staff in the emergency department. Other measurements including post resuscitation  
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47 22 care were recorded by the attending physician using a standardized data collection form.  
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#### 52 24 *3.5. Outcomes*

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55 25 Outcomes of interest were one-month neurologically favourable outcomes and survival.  
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1 Neurologically favourable outcomes were defined as a Cerebral Performance Categories  
2 (CPC) score of 1 or 2.<sup>21</sup> The attending physician in-charge of the rounds or the outpatient  
3 determined the CPC score.

## 4 5 *2.6. Statistical analyses*

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

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

1 TX) and R statistical software (version 3.4.0).

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### 3 *2.7. Patient and Public Involvement*

4 Patients and public were not involved in this study.

5

## 6 **3. Results**

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

20 Overall, the proportion of neurologically favourable outcomes was 7% (95% CI,  
21 4%-13%) while survival was 19% (95%CI 14%-27%) in patients with OHCA. Patients with  
22 neurologically favourable outcomes were more likely to have re-arrest after ROSC during  
23 transportation compared to those without (P=0.03). For one-month survival, survived patients  
24 were more likely to have shockable rhythm, re-arrest after ROSC during transportation, and  
25 to be treated with therapeutic hypothermia compared to non-survived patients (all, P<0.05).



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

6 **Table 3** demonstrates the association between age and outcomes. Overall, in the  
7 unadjusted models using age as a continuous variable, age was non-significantly associated  
8 with the worse one-month neurological outcomes and survival. After the adjustment for  
9 potential confounders, while advanced age was non-significantly associated with worse  
10 neurological outcomes (adjusted OR 0.96 [95%CI 0.91-1.01]; P=0.08), the association  
11 between advanced age and poor survival rate was significant (adjusted OR 0.96 [95%CI  
12 0.93-0.99]; P=0.04). Similar associations were found in the analyses using age as a  
13 categorical variable. Compared to age <50 years, age  $\geq 70$  was associated with poor  
14 neurological outcomes (adjusted OR 0.08 [95%CI 0.01-1.00]; P=0.051) and significantly  
15 associated with the worse survival in the adjusted model (adjusted OR 0.14 [95%CI  
16 0.03-0.80]; P=0.03). Among patient aged 75 years, which is the suggested upper limitation of  
17 age for implementation of ECPR, only 3 patients survived and no patients survived with  
18 neurologically favourable outcomes.

#### 19 20 **4. Discussion**

21 In this retrospective analysis from an urban critical care hospital, we found that  
22 advanced age was associated with the lower rate of one-month survival and neurologically  
23 favourable outcomes in patients with OHCA who underwent ECPR. The rate of  
24 neurologically favourable outcomes and one-month survival decreased after age 70 years old.  
25 In addition, no patient aged  $\geq 75$  years survived with neurologically favourable outcomes at

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3 1 one-month after cardiac arrest. These findings provide valuable clues for creating optimal  
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5 2 strategy for elderly patients with OHCA in the aging era.

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7 3 Our study observed that age  $\geq 70$  was associated with the lower survival rate and no  
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9 4 patients aged  $\geq 75$  years survived with neurologically favourable outcomes at one-month after  
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11 5 cardiac arrest. Although previous studies reported that ECPR was more effective in treating  
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13 6 OHCA patients than conventional CPR, these studies did not assess the effect of advanced  
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15 7 age – their findings were based on studies limited to patients aged  $< 75$  years.<sup>9,10</sup> A  
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17 8 multicentre prospective observational study in Japan demonstrated that the survival rate at  
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19 9 one-month after cardiac arrest was significantly higher in the ECPR group than in the  
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21 10 non-ECPR group (27% vs. 6%) and that the proportion of neurologically favourable  
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23 11 outcomes was also significantly higher in the ECPR group (12.3% vs. 1.5%).<sup>10</sup> Our results  
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25 12 that overall one-month survival rate of 20% and one-month survival with neurologically  
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27 13 favourable outcomes of 8% are comparable results with these previous findings,<sup>9,10</sup> despite  
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29 14 we included patients aged  $\geq 75$  years. Therefore, focusing on the elderly patients, our findings  
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31 15 might suggest limitations in using ECPR to treat elderly patients with OHCA.  
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35 16 The reasons for the observed lack of effectiveness of ECPR among elderly patients  
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37 17 are likely multifactorial. First, consistent with the elderly being the population with limited  
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39 18 cardiovascular and pulmonary reserve, the survival rate of OHCA patients was lower in older  
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41 19 patients than in younger patients.<sup>23</sup> An observational study in the US demonstrated that  
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43 20 advanced age was a factor associated with lower survival rate at discharge among OHCA  
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45 21 patients (19.4% for  $\leq 80$  years vs. 9.4% for 80-89 years, and 4.4% for  $\geq 90$  years).<sup>23</sup> Second,  
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47 22 shorter duration from cardiac arrest to return of spontaneous circulation (ROSC) was a  
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49 23 critical factor for neurologically favourable outcomes among OHCA patients. Indeed, in an  
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51 24 observational study in the US, shorter duration of CPR was associated with neurologically  
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53 25 favourable outcomes – 90% of patients with neurologically favourable outcomes required  
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1 less than 16 minutes of CPR.<sup>24</sup> In our findings, the median time from cardiac arrest to ROSC  
2 or implementing of ECMO was 54 min, which is considerably longer than in the previous  
3 study in the US.<sup>24</sup> However, patients who require ECPR are “non-responders” to  
4 conventional CPR within 20 minutes.<sup>12</sup> In addition, another ECPR study also showed a  
5 lengthy median time from arrest to ROSC of 50 min in OHCA patients, consistent with our  
6 findings.<sup>8</sup> Due to the vulnerability of elderly patients, elderly patients might not withstand the  
7 prolonged CPR compared to younger age. Taken together, advanced age as a vulnerable  
8 population and a longer CPR duration may help explain the lack of effectiveness of ECPR for  
9 elderly patients with OHCA in the present study.

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

20 Despite the significant healthcare resource burden of ECPR, the present study did not  
21 demonstrate the effectiveness of ECPR for elderly patients with OHCA. However, this does  
22 not indicate that CPR should not be utilized for elderly patients. Although advanced age  
23 could be a factor associated with poor outcomes in OHCA patients in the present study, this  
24 factor alone does not appear to be a well established criterion to deny patients for  
25 conventional CPR based on a previous report.<sup>23</sup> Additionally, experts say that decisions

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3 1 regarding termination of resuscitation should not be based on age.<sup>28</sup> However, given our  
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5 2 present findings regarding poor outcomes among elderly patients and the extremely high cost  
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7 3 of ECPR, the indication of ECPR for elderly patients should be carefully considered in this  
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9 4 aging era.

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## 12 6 **Limitations**

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15 7 We acknowledge several potential limitations to our study. First, as our sample consisted of  
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17 8 retrospective data from a single centre in Japan, our inferences might not be generalizable to  
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19 9 other healthcare settings. However, the observed association not only has plausible  
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21 10 mechanisms but also persisted across different analytical assumptions. Although formal  
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23 11 validation of the study in other healthcare settings is warranted, our inferences likely present  
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25 12 in different practical settings. Second, there was lack of data on daily living activities,  
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27 13 medication use, comorbidities before cardiac arrest including a poorer neurological state  
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29 14 pre-arrest. In addition, information on whether the ECPR was implemented during active  
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31 15 chest compressions and on the results of percutaneous coronary intervention was also not  
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33 16 available. However, an experienced emergency physician or cardiologist assessed whether  
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35 17 the cause of cardiac arrest was treatable and appropriate for ECPR based on information  
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37 18 gained from the person accompanying the patient and the situation of cardiac arrest. Third,  
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39 19 our study might include ECMO cases for persistent hypotension after ROSC. However, the  
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41 20 association was significant after adjusting for the potential persistent hypotension after ROSC  
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43 21 (i.e., re-arrest after ROSC during transportation). Finally, although the indication for ECPR  
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45 22 was assessed based on the protocol and by experienced physicians, our data are subject to  
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47 23 selection bias. In general, however, the indication of ECPR for elderly patients was stricter  
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49 24 than that for younger patients, which might have biased our conclusions toward the null.  
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## 1 **Conclusions**

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

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

## 20 **DISCLOSURES:**

21  
22 **Ethics approval and consent to participate and Consent for publication:** The institutional  
23 review board of Osaka Saiseikai Senri Hospital approved this study and granted a waiver of  
24 informed consent.

25 **Availability of data and materials:** The data are not allowed for public use by institutional

Tadahiro Goto

ECPR for elderly OHCA

1 review board.

2 **Competing interests:** There are no conflict of interest.

3 **Funding:** None

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

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10

## 11 REFERENCES

- 12 1. 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency  
13 Cardiovascular Care Science With Treatment Recommendations. *Circulation*.  
14 2010;122:S250-S605.
- 15 2. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and  
16 emergency cardiovascular care. *Circulation*. 2010;122:S639-S946.
- 17 3. European Resuscitation Council Guidelines for Resuscitation 2010. *Resuscitation*.  
18 2010;81:1219-1451.
- 19 4. Ambulance Service Planning Office of Fire and Disaster Management Agency of  
20 Japan. Effect of first aid for cardiopulmonary arrest. .  
21 [http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218\\_1houdou/01\\_houdoushiryou.pdf](http://www.fdma.go.jp/neuter/topics/houdou/h25/2512/251218_1houdou/01_houdoushiryou.pdf)  
22 Accessed March 03, 2015.
- 23 5. Kitamura T, Morita S, Kiyohara K, et al. Trends in survival among elderly patients  
24 with out-of-hospital cardiac arrest: a prospective, population-based observation from  
25 1999 to 2011 in Osaka. *Resuscitation*. 2014;85(11):1432-1438.
- 26 6. Muramatsu N, Akiyama H. Japan: super-aging society preparing for the future.  
27 *Gerontologist*. 2011;51(4):425-432.

- 1  
2  
3  
4 1 7. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences  
5  
6 2 between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary  
7  
8 3 resuscitation using extracorporeal life support. *Resuscitation*. 2010;81(8):968-973.
- 9  
10 4 8. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary  
11  
12 5 resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a  
13  
14 6 propensity-matched study and predictor analysis. *Crit Care Med*.  
15  
16 7 2013;41(5):1186-1196.
- 17  
18 8 9. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy  
19  
20 9 for out-of-hospital and emergency department cardiac arrest. *Resuscitation*.  
21  
22 10 2014;85(11):1527-1532.
- 23  
24 11 10. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary  
25  
26 12 resuscitation versus conventional cardiopulmonary resuscitation in adults with  
27  
28 13 out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation*.  
29  
30 14 2014;85(6):762-768.
- 31  
32 15 11. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for  
33  
34 16 Resuscitation 2010 Section 1. Executive summary. *Resuscitation*.  
35  
36 17 2010;81(10):1219-1276.
- 37  
38 18 12. Kim SJ, Jung JS, Park JH, Park JS, Hong YS, Lee SW. An optimal transition time to  
39  
40 19 extracorporeal cardiopulmonary resuscitation for predicting good neurological  
41  
42 20 outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study.  
43  
44 21 *Crit Care*. 2014;18(5):535.
- 45  
46 22 13. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal  
47  
48 23 cardiopulmonary resuscitation for out-of-hospital cardiac arrest--a comparison with  
49  
50 24 that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation*.  
51  
52 25 2014;85(9):1219-1224.
- 53  
54 26 14. Riggs KR, Becker LB, Sugarman J. Ethics in the use of extracorporeal  
55  
56 27 cardiopulmonary resuscitation in adults. *Resuscitation*. 2015;91:73-75.
- 57  
58 28 15. Choi DH, Kim YJ, Ryoo SM, et al. Extracorporeal cardiopulmonary resuscitation  
59  
60 29 among patients with out-of-hospital cardiac arrest. *Clin Exp Emerg Med*.

- 1  
2  
3  
4 1 2016;3(3):132-138.
- 5  
6 2 16. Kolla S, Lee WA, Hirschl RB, Bartlett RH. Extracorporeal life support for  
7  
8 3 cardiovascular support in adults. *ASAIO J.* 1996;42(5):M809-819.
- 9  
10 4 17. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life  
11  
12 5 support for prolonged cardiac arrest. *Ann Thorac Surg.* 2005;79(1):178-183;  
13  
14 6 discussion 183-174.
- 15  
16 7 18. Mendiratta P, Wei JY, Gomez A, et al. Cardiopulmonary resuscitation requiring  
17  
18 8 extracorporeal membrane oxygenation in the elderly: a review of the Extracorporeal  
19  
20 9 Life Support Organization registry. *ASAIO J.* 2013;59(3):211-215.
- 21  
22 10 19. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal  
23  
24 11 cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac  
25  
26 12 arrest. A systematic review and meta-analysis. *Resuscitation.* 2017;112:1-10.
- 27  
28 13 20. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life  
29  
30 14 support: 2010 American Heart Association Guidelines for Cardiopulmonary  
31  
32 15 Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 Suppl  
33  
34 16 3):S729-767.
- 35  
36 17 21. Prohl J, Rother J, Kluge S, et al. Prediction of short-term and long-term outcomes  
37  
38 18 after cardiac arrest: a prospective multivariate approach combining biochemical,  
39  
40 19 clinical, electrophysiological, and neuropsychological investigations. *Crit Care Med.*  
41  
42 20 2007;35(5):1230-1237.
- 43  
44 21 22. Iwami T, Kawamura T, Hiraide A, et al. Effectiveness of bystander-initiated  
45  
46 22 cardiac-only resuscitation for patients with out-of-hospital cardiac arrest. *Circulation.*  
47  
48 23 2007;116(25):2900-2907.
- 49  
50 24 23. Kim C, Becker L, Eisenberg MS. Out-of-hospital cardiac arrest in octogenarians and  
51  
52 25 nonagenarians. *Arch Intern Med.* 2000;160(22):3439-3443.
- 53  
54 26 24. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation  
55  
56 27 efforts and functional outcome after out-of-hospital cardiac arrest: when should we  
57  
58 28 change to novel therapies? *Circulation.* 2013;128(23):2488-2494.
- 59  
60 29 25. Asaka K; Aoki N. ECPR Indication Criteria -From the Cost Effective Analysis in



- 1  
2  
3  
4 1 SAVE-J Study-. *Circulation*. 2013;128:A305.  
5  
6 2 26. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other  
7  
8 3 factors influence its decisions? A binary choice analysis. *Health Econ*.  
9  
10 4 2004;13(5):437-452.  
11  
12 5 27. Fukuda T, Yasunaga H, Horiguchi H, et al. Health care costs related to out-of-hospital  
13  
14 6 cardiopulmonary arrest in Japan. *Resuscitation*. 2013;84(7):964-969.  
15  
16 7 28. Wuerz RC, Holliman CJ, Meador SA, Swope GE, Balogh R. Effect of age on  
17  
18 8 prehospital cardiac resuscitation outcome. *Am J Emerg Med*. 1995;13(4):389-391.  
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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.

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

	Overall (n=144)	Neurologically favourable outcomes			Survival outcome		P value
		CPC 1-2 (n=10)	CPC 3-5 (n=134)	P value	Survived (n=28)	Not survived (n=116)	
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

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5	Causes of cardiac arrest, n (%)				0.68		0.59
6							
7	Acute myocardial infarction	100 (69%)	7 (70%)	93 (70%)		19 (68%)	81 (70%)
8	Structural heart disease	11 (8%)	0 (0%)	11 (8%)		2 (7%)	9 (8%)
9	Aortic dissection	6 (4%)	0 (0%)	6 (4%)		0 (0%)	6 (5%)
10	Arrhythmia	6 (4%)	2 (20%)	4 (3%)		3 (11%)	3 (3%)
11	Asphyxia	3 (2%)	0 (0%)	3 (2%)		0 (0%)	3 (3%)
12	Other§	7 (5%)	0 (0%)	7 (5%)		1 (4%)	6 (5%)
13	Unknown	12 (8%)	1 (10%)	11 (8%)		3 (11%)	9 (8%)
14							
15	Admission year				0.32		0.20
16							
17	2005	4 (3%)	1 (10%)	3 (2%)		2 (7%)	2 (2%)
18	2006	18 (13%)	1 (10%)	17 (13%)		5 (18%)	13 (11%)
19	2007	15 (10%)	0 (0%)	15 (11%)		2 (7%)	13 (11%)
20	2008	19 (13%)	2 (20%)	17 (13%)		3 (11%)	16 (14%)
21	2009	7 (5%)	0 (0%)	7 (5%)		2 (7%)	5 (4%)
22	2010	19 (13%)	1 (10%)	18 (13%)		3 (11%)	16 (14%)
23	2011	26 (18%)	1 (10%)	25 (19%)		3 (11%)	23 (20%)
24	2012	22 (15%)	1 (10%)	21 (16%)		2 (7%)	20 (17%)
25	2013	14 (10%)	3 (30%)	11 (8%)		6 (21%)	8 (7%)

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

33 \* Including witnessed by emergency medical service

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

35 \*\*\* Ventricular fibrillation and pulseless ventricular tachycardia.

36 † Defined as re-cardiac arrest after spontaneous circulation sustained for  $\geq 20$  minutes during transportation.

37 ‡ Defined as spontaneous circulation sustained for  $\geq 20$  minutes.

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

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5 **FIGURE LEGENDS**

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

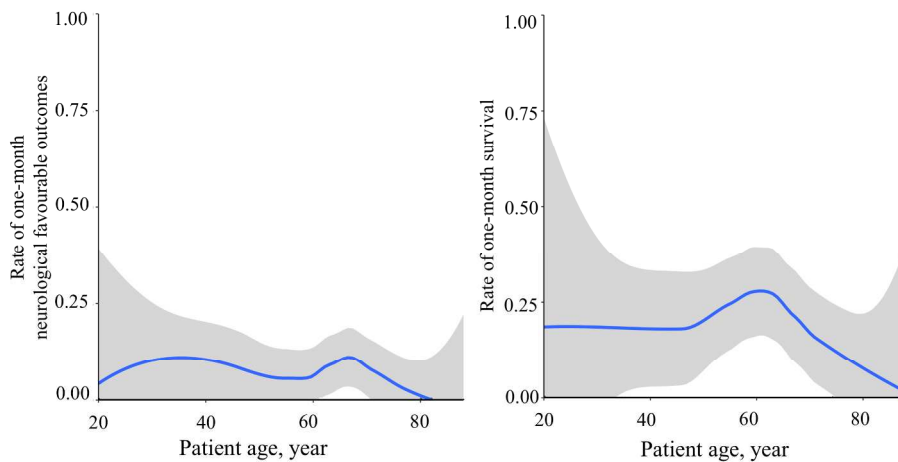


Figure 1

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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	2-3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5-7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7-8

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8-10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).