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## Clinical paper

# Current trends and outcomes of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest in Japan: A nationwide observational study



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## Abstract

**Aim:** The present study aimed to describe the prevalence, prognosis and annual trends of extracorporeal cardiopulmonary resuscitation (ECPR) for out-of-hospital cardiac arrest (OHCA) patients, using a nationwide inpatient database in Japan.

**Methods:** This was a nationwide retrospective cohort study, using the Japanese Diagnosis Procedure Combination inpatient database. We included OHCA patients registered in the database from July 2010 to March 2017 and analyzed the annual prevalence of OHCA patients who received ECPR. The outcomes included survival to hospital discharge and survival with favorable neurologic outcome at hospital discharge. The annual trends on the outcomes were also analyzed.

**Results:** We identified 217,907 eligible patients. OHCA patients were divided into patients with ECPR ( $n=5,612$ ) and conventional CPR ( $n=212,295$ ). The prevalence of ECPR performed in OHCA patients was 2.6%. ECPR prevalence significantly increased from 2.1% in 2010 to 3.0% in 2016 ( $P<0.001$ ). Overall survival to hospital discharge was 16.4% and 2.7% in patients with ECPR and conventional CPR, respectively. Prevalence of patients who were discharged from hospital with favorable neurologic outcome was 12.4% and 1.6% in those with ECPR and conventional CPR, respectively.

Increasing age was associated with progressively deteriorating outcomes. The trend of survival to hospital discharge significantly increased on an annual basis.

**Conclusions:** The annual prevalence of ECPR significantly increased from 2010 to 2016. Improvements in overall survival to hospital discharge were noted for ECPR in OHCA patients and there was a trend in the tendency for ECPR patients discharged from the hospital to have favorable neurologic outcomes.

**Keywords:** Out-of-hospital cardiac arrest, cardiopulmonary resuscitation, extracorporeal membrane oxygenation, extracorporeal

*Abbreviations:* CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest.

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## Introduction

Out-of-hospital cardiac arrest (OHCA) is a major global public health issue with more than 400,000 and 127,000 annual cases occurring in the United States and in Japan, respectively.<sup>1,2</sup> While substantial regional variations are observed, OHCA patients administered conventional cardiopulmonary resuscitation (CPR) generally gravitate towards unfavorable outcomes.

Extracorporeal cardiopulmonary resuscitation (ECPR) is defined as the application of veno-arterial extracorporeal membrane oxygenation (ECMO) in patients experiencing sudden and unexpected refractory cardiac arrest.<sup>3</sup> Several observational studies have suggested that ECPR—as a second line treatment in the event of conventional CPR failure—could enhance survival rates and neurologic outcomes in OHCA patients.<sup>4–6</sup> Therefore, ECPR has seen rapid worldwide dissemination over the past decade.<sup>7</sup>

Although the number of patients who received ECPR have been increasing, studies focusing on the trend of outcomes in OHCA patients with ECPR are limited. The ELSO registry (n=1796) reported that survival rates using ECPR have remained static from 2003 to 2014 despite advances in the provision of ECMO care and increasing comorbidities of patients over time.<sup>8</sup> However, the previous study was conducted in selected facilities and therefore the trend in outcomes at the nationwide level are unknown. In addition, the prevalence of ECPR for OHCA patients has yet to be widely examined due in part to limited real world data. The present study endeavored to describe the prevalence, prognosis and annual trends with regard to ECPR in OHCA patients using a nationwide inpatient database in Japan.

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## Materials and methods

### Ethical statement

This study was approved by the Institutional Review Board at The University of Tokyo (No.3501-1). Due to the anonymous nature of the data, the requirement for informed consent was waived.

### Data source

We performed a retrospective cohort study using the Diagnosis Procedure Combination database. The database includes discharge abstracts and administrative claims data from more than 1,000 acute-care hospitals. Approximately seven million patients are registered in the database on an annual basis. In particular, the database encompasses approximately 90% of all tertiary-care emergency hospitals in Japan.<sup>9</sup> The database has been well-described and numerous reports utilizing the information contained in the database have been published previously.<sup>10–12</sup> The database contains the following information for each patient: dates of admission and discharge; age; sex; diagnoses; and comorbidities. The diagnoses and comorbidities were recorded using the International Classification of Diseases, Tenth Revision (ICD-10) codes with text data entered in Japanese. The database also provides conscious level at admission and discharge; medical procedures performed, medications, and devices used during hospitalization; and discharge status (discharge to home, discharge to other facility, and in-hospital death).

### Variables

Patient characteristics included age, sex, diagnoses (ventricular tachycardia, ventricular fibrillation, acute coronary syndrome and pulmonary embolism), and procedures performed on the day of admission (defibrillation, intra-aortic balloon pumping, target temperature management and percutaneous coronary intervention). Based on a common classification, age was categorized into four groups: <65; 65–74; 75–84; and ≥85 years.<sup>13,14</sup> Conscious level at admission or discharge was evaluated using the Japan Coma Scale (JCS) score: 0, alert consciousness; 1–3, awake without any stimuli; 10–30, aroused by some stimuli; and 100–300, coma. Assessments via the JCS and Glasgow Coma Scale correlate well.<sup>15,16</sup> Diagnoses were defined in accordance with the following ICD-10 codes: ventricular tachycardia and fibrillation, I472 and I490; acute coronary syndrome, I20–23; and pulmonary embolism, I26.

### Patient selection and outcomes

We included OHCA patients registered in the database from April 2010 to March 2017. OHCA patients were defined as those who had received CPR on the day of admission and presenting with a JCS of 300 at admission – equivalent to a 3 on the Glasgow Coma Scale. We excluded patients with OHCA due to trauma (ICD-10 code, TX or SX) and/or those who underwent resuscitative thoracotomy on the day of admission.

First, we described the background characteristics of OHCA patients who were administered ECPR or only conventional CPR. ECPR patients were administered ECPR following conventional CPR for refractory cardiac arrest. Next, we analyzed the annual prevalence of OHCA patients who received ECPR. Third, the in-hospital outcomes and those stratified by age category were described. The outcomes included i) survival to hospital discharge and ii) survival with favorable neurologic outcome at hospital discharge. Finally, the annual trends on the outcomes were analyzed. Survival with favorable neurologic outcome was defined as patients who were discharged from the hospital with a JCS of 0 or single digit. A score of 0 or in the single digits under the JCS is roughly synonymous with a Cerebral Performance Category score of 1 or 2.<sup>17,18</sup>

### Statistical analysis

Data were presented as medians with interquartile ranges (IQR) for continuous variables and as proportions for categorical variables. Continuous variables were compared using Wilcoxon rank-sum tests and categorical variables were compared using Fisher's exact or Chi-square tests. Annual trends during the study period were evaluated with the Cochran Armitage tests. Two-sided *p*-values of <0.05 were considered statistically significant. All analyses were performed using Stata MP15 (Stata, College Station, TX, USA).

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## Results

We identified 217,907 eligible patients during the study period. The OHCA patients were divided into patients who were administered ECPR (n=5,612) or conventional CPR (n=212,295) (Supplementary Figure S1). The characteristics of the patients included in this study are shown in Table 1. Patients administered ECPR had a significantly lower median age than those with conventional CPR (62 vs. 78 years

**Table 1 – Characteristics of patients with out-of-hospital cardiac arrest.**

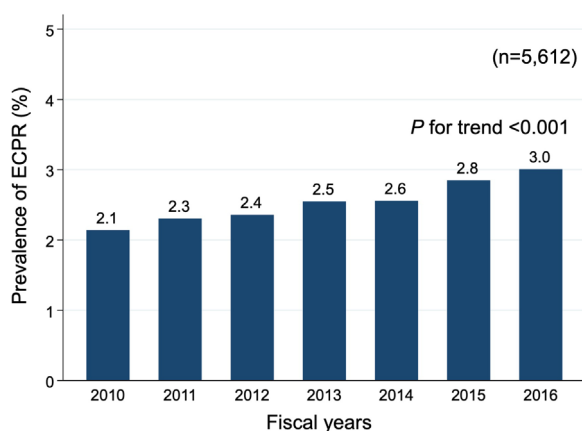
| Variables                                    | ECPR (n=5,612) |         | Conventional CPR (n=212,295) |         | P-value |
|--|----------------|---------|------------------------------|---------|---------|
| Age, years (IQR)                             | 62             | (50-71) | 78                           | (67-85) | <0.001  |
| Sex, male                                    | 4,425          | (78.8%) | 120,923                      | (57.0%) | <0.001  |
| Diagnoses                                    |                |         |                              |         |         |
| Ventricular tachycardia / fibrillation       | 2,536          | (45.2%) | 8,068                        | (3.8%)  | <0.001  |
| Acute coronary syndrome                      | 2,618          | (46.7%) | 18,331                       | (8.6%)  | <0.001  |
| Pulmonary embolism                           | 296            | (5.3%)  | 1,208                        | (0.6%)  | <0.001  |
| Procedures performed on the day of admission |                |         |                              |         |         |
| Defibrillation                               | 3,004          | (53.5%) | 22,874                       | (10.8%) | <0.001  |
| Intra-aortic balloon pumping                 | 600            | (10.7%) | 1,684                        | (0.8%)  | <0.001  |
| Target temperature management                | 1,464          | (26.1%) | 3,486                        | (1.6%)  | <0.001  |
| Percutaneous coronary intervention           | 2,097          | (37.4%) | 2,253                        | (1.1%)  | <0.001  |

CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; IQR, interquartile range.

of age, respectively). In comparison with conventional CPR patients, patients administered ECPR had a higher proportion of ventricular tachycardia/fibrillation (45.2%), acute coronary syndrome (46.7%) and pulmonary embolism (5.3%). In patients with ECPR, 53.5% and 37.4% underwent defibrillation and percutaneous coronary intervention, respectively, on the day of admission. The percentage of these procedures carried out in patients with ECPR were significantly higher than that observed in patients with conventional CPR.

Fig. 1 demonstrates the annual prevalence of ECPR performed in OHCA patients. The prevalence of ECPR performed in OHCA patients spanning the entire data spectrum (2010–2016) was 2.6% (5,612/217,970). The prevalence of ECPR significantly increased from 2.1% in 2010 to 3.0% in 2016 ( $P$  for trend <0.001). Fig. 2 shows the outcomes in patients with ECPR and those with conventional CPR. The overall survival to hospital discharge was 16.4% in patients with ECPR and 2.7% in patients with conventional CPR. The prevalence of patients who were discharged from hospital with favorable neurologic outcome was 12.4% in patients with ECPR and 1.6% in those with conventional CPR. These outcomes were associated with increasing age category.

Fig. 3 demonstrates the annual trends of the outcomes for patients treated with ECPR versus only conventional CPR. The survival to hospital discharge was significantly increased from 11.5% in 2010 to 18.6% in 2015 and 16.5% in 2016 for ECPR patients ( $P$  for trend=0.015). The prevalence of survival with favorable neurologic



**Fig. 1 – Annual prevalence of ECPR administered in patients with out-of-hospital cardiac arrest. ECPR, extracorporeal cardiopulmonary resuscitation.**

outcome at hospital discharge was also increased from 9.0% in 2010 to 14.4% in 2015 and 16.5% in 2016 but was not statistically significant for ECPR patients ( $P$  for trend=0.09). In patients only administered conventional CPR, no statistically significant trends were noted for neither survival to hospital discharge nor favorable neurological outcomes ( $P$  for trends, 0.09 and 0.21, respectively). Summary of patient characteristics and outcomes on an annual basis in OHCA patients with ECPR is shown in Supplementary Table S1.

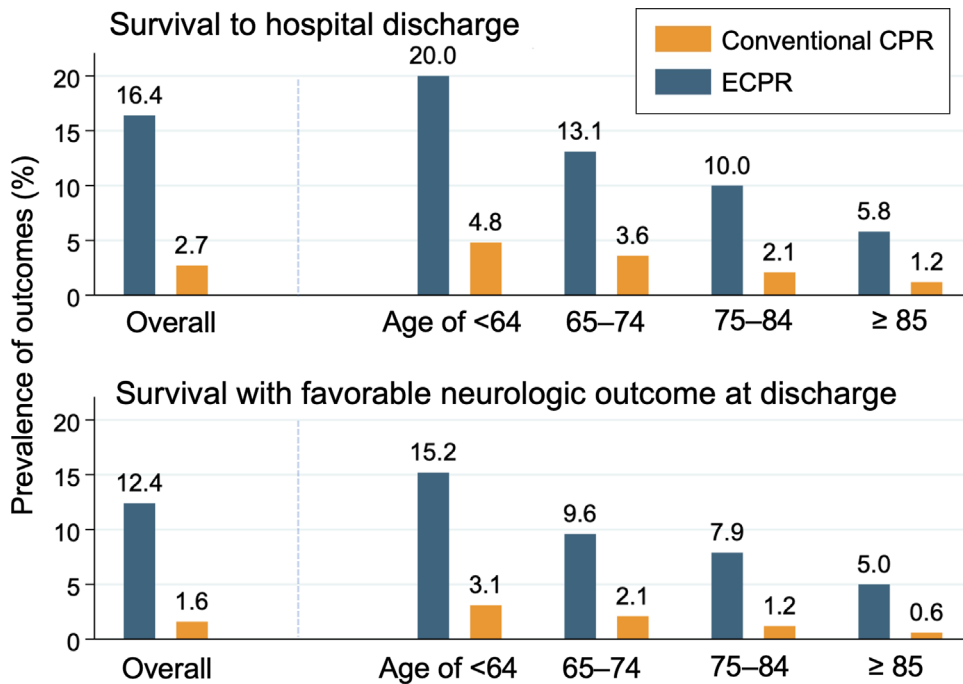
## Discussion

The prevalence of ECPR for OHCA patients in the present study was 2.6%, using a real-world nationwide database in Japan. The annual prevalence of ECPR significantly increased from 2010 to 2016. In patients with ECPR, the overall survival to hospital discharge was 16.4% and the prevalence of patients who were discharged from hospital with favorable neurologic outcome was 12.4%. These outcomes worsened with increasing age category.

ECPR has been rapidly adopted worldwide and Japan is one of leading countries in the field of ECPR<sup>7</sup>; however, the prevalence of ECPR and the annual trend have not widely examined. Our study demonstrated that the prevalence of ECPR in OHCA patients was significantly and steadily increased during the study period and reached 3% in 2006 in Japan. Increasing experience with ECPR in individual facilities along with the accumulation of evidence in support for ECPR around the world may have contributed to these results.

The overall survival to hospital discharge was 16.4% and the prevalence of patients who were discharged from hospital with favorable neurologic outcome was 12.4% in OHCA patients with ECPR. Conversely, even with ECPR in place, nearly 90% of OHCA patients did not return home with favorable neurologic outcome. In particular, survival with favorable neurologic outcome in the age category  $\geq 85$  years was a mere 5%. The indication of ECPR in older patients should be considered with caution.

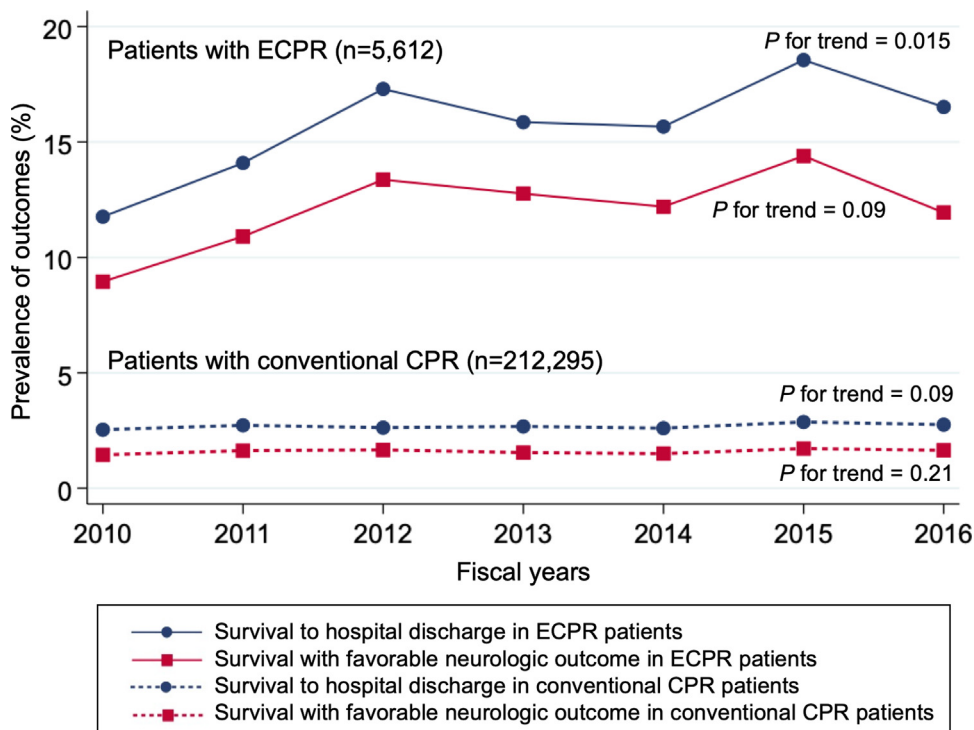
In the trend analyses, the survival to hospital discharge was significantly increased during the study period. Although the trend in survival with favorable neurologic outcome was not statistically significant, the observed trends appeared to mirror that of the survival to hospital discharge. The SAVE-J study conducted in 2008–2011 in Japan demonstrated a favorable neurologic outcome with a CPC of 1 or 2 at one month after cardiac arrest in 12.3% of patients with ECPR ( $n=260$ ).<sup>5</sup> No clear guidelines have been published to date in Japan with regard to ECPR and therefore the SAVE-J study serves as a



**Fig. 2 – Outcomes in patients with ECPR and conventional CPR by age category.**  
**ECPR, extracorporeal cardiopulmonary resuscitation; CPR, cardiopulmonary resuscitation.**

general reference in terms of ECPR eligibility. The same study excluded patients aged 75 years or older and the median age of participants was 56 in OHCA patients with ECPR. Although our study included older patients (median age of 62) in comparison with the SAVE-J study, the prevalence of survival with favorable neurologic

outcome at discharge was similar (12.4%). In addition, the median age of participants included our study increased on an annual basis. The indication for—and adaptation of—ECPR in OHCA patients has been gradually expanding and this may have positively impacted the outcomes.



**Fig. 3 – Annual trend of the outcomes for patients treated with ECPR versus only conventional CPR.**  
**ECPR, extracorporeal cardiopulmonary resuscitation; CPR, cardiopulmonary resuscitation.**

The recently updated 2019 guidelines describe the challenges of making recommendations for routine use of ECPR and evaluating the role of ECPR in patients with cardiac arrest due to a lack of robust evidence.<sup>1</sup> Although several observational studies reporting favorable outcomes have been published,<sup>4–6,19,20</sup> most of these studies were single center investigations with variability in the inclusion criteria. The results of our study will become a benchmark for further studies focused on ECPR in OHCA patients given the use of real world cases extracted from a nationwide database.

While the study offers a unique perspective into the subject, several limitations in the present study should be addressed. First, the DPC database does not include detailed clinical information such as bystander CPR attempt, initial cardiac rhythm, low-flow duration, arterial pH value and serum lactate concentration at hospital admission.<sup>21</sup> Therefore, we could not perform regression analyses to evaluate factors associated with the outcomes. Second, we were unable to obtain the patient's exact condition at the time of arrival at the hospital. OHCA was defined as patients who had received CPR on the day of admission and presenting with a JCS of 300 at admission – the worst score on the coma scale. A number of patients with in-hospital cardiac arrest may be included in the present study. Finally, the claims database only includes hospitalized patients and does not reflect out-of-hospital patients or prehospital treatments. However, in accordance with the universal insurance coverage system in Japan, hospitals can reimburse patients who underwent advanced life support during hospitalization even if spontaneous circulation failed to return in patients and they later died in the emergency department. The number of total OHCA patients may have been underestimated in the present study. The denominator (total number of OHCA) may affect the overall prevalence of ECPR.

## Conclusions

The most recently reported prevalence of ECPR for OHCA patients in 2016 was 3% using a real-world nationwide database in Japan. The annual prevalence of ECPR significantly increased from 2010 to 2016. In addition to the gradually increasing prevalence, improvements in overall survival to hospital discharge were noted for ECPR in OHCA patients. Although statistical significance could not be achieved, there was a trend in the tendency for ECPR patients discharged from the hospital to have favorable neurologic outcomes as well.

## Funding

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## Declaration of competing interest

None

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.resplu.2020.100048>.

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