Clinical paper

Transient return of spontaneous circulation related to favourable outcomes in out-of-hospital cardiac arrest patients resuscitated with extracorporeal cardiopulmonary resuscitation: A secondary analysis of the SAVE-J II study

Takayuki Otani, Toru Hifumi, Akihiko Inoue, Toshikazu Abe, Tetsuya Sakamoto, Yasuhiro Kuroda, the SAVE-J II study group, Hirotaka Sawano, Yuko Egawa, Kazuhiro Sugiyama, Maki Tanabe, Naofumi Bunya, Takehiko Kasai, Shinichi Ijuin, Shinichi Nakayama, Jun Kanda, Seiya Kanou, Toru Takiguchi, Shoji Yokobori, Hiroaki Takada, Kazushige Inoue, Ichiro Takeuchi, Hiroshi Honzawa, Makoto Kobayashi, Tomohiro Hamagami, Wataru Takayama, Yasuhiro Otomo, Kunihiro Maekawa, Takafumi Shimizu, Satoshi Nara, Michitaka Nasu, Kuniko Takahashi, Yoshihiro Hagiwara, Shigeki Kushimoto, Reo Fukuda, Takayuki Ogura, Shin-ichiro Shiraishi, Ryosuke Zushi, Norio Otani, Migaku Kikuchi, Kazuhiro Watanabe, Takuo Nakagami, Tomohisa Shoko, Nobuya Kitamura, Takayuki Otani, Yoshinori Matsuoka, Makoto Aoki, Masaaki Sakuraya, Hideki Arimoto, Koichiro Homma, Hiromichi Naito, Shunichiro Nakao, Tomoya Okazaki, Yoshio Tahara, Hiroshi Okamoto, Jun Kunikata, Hideto Yokoi

Abbreviations: CI, confidence interval, CPA, cardiopulmonary arrest, CPC, cerebral performance category, CPR, cardiopulmonary resuscitation, ECMO, extracorporeal cardiopulmonary membrane oxygenation, EMS, emergency medical service, OHCA, out-of-hospital cardiac arrest, OR, odds ratio, ROSC, return of spontaneous circulation, ECPR, extracorporeal cardiopulmonary resuscitation

E-mail address: sonnyboy@tempo.ocn.ne.jp (T. Otani).

* Corresponding author at: Department of Emergency Medicine, Hiroshima City Hiroshima Citizens Hospital, 7-33 Motomachi, Naka-ku, Hiroshima-city, Hiroshima 730-8518, Japan.

E-mail address: sonnyboy@tempo.ocn.ne.jp (T. Otani).

https://doi.org/10.1016/j.resplu.2022.100300

Received 28 June 2022; Received in revised form 3 August 2022; Accepted 29 August 2022

Available online xxxx

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**Abstract**

**Aim:** This study aimed to investigate the relationship between transient return of spontaneous circulation (ROSC) before extracorporeal membrane oxygenation (ECMO) initiation and outcomes in out-of-hospital cardiac arrest (OHCA) patients, who were resuscitated with extracorporeal cardiopulmonary resuscitation (ECPR).

**Methods:** This was a secondary analysis of the SAVE-J II study, which was a retrospective multicentre registry study involving 36 participating institutions in Japan. We classified patients into two groups according to the presence or absence of transient ROSC before ECMO initiation. Transient ROSC was defined as any palpable pulse of ≥1 min before ECMO initiation. The primary outcome was favourable neurological outcomes (cerebral performance categories 1–2).

**Results:** Of 2,157 patients registered in the SAVE-J II study, 1,501 met the study inclusion criteria; 328 (22%) experienced transient ROSC before ECMO initiation. Patients with transient ROSC had better outcomes than those without ROSC (favourable neurological outcome, 26% vs 12%; P < 0.001; survival to hospital discharge, 46% vs 24%, respectively; P < 0.001). A Kaplan–Meier plot showed better survival in the transient ROSC group (log-rank test, P < 0.001). In multiple logistic analyses, transient ROSC was significantly associated with favourable neurological outcomes and survival (favourable neurological outcomes, adjusted odds ratio, 3.34 [95% confidence interval, 2.35–4.73]; survival, adjusted odds ratio, 3.99 [95% confidence interval, 2.95–5.40]).

**Conclusions:** In OHCA patients resuscitated with ECPR, transient ROSC before ECMO initiation was associated with favourable outcomes. Hence, transient ROSC is a predictor of improved outcomes after ECPR.

**Keywords:** Out-of-hospital cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Transient return of spontaneous circulation

### Introduction

Patient outcomes for those with out-of-hospital cardiac arrest (OHCA) remain poor; however, key predictors associated with favourable outcomes in OHCA patients have been reported, including younger age, shorter arrest duration, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), and shockable initial cardiac rhythm. Achieving return of spontaneous circulation (ROSC) in the field is also known to be a particularly strong predictor of favourable outcomes. However, some OHCA patients experience refractory cardiopulmonary arrest (CPA), i.e., they do not achieve ROSC through conventional CPR. Even those who achieve transient ROSC with conventional CPR may experience re-arrest, leading to refractory CPA.

It has been reported that extracorporeal cardiopulmonary membrane oxygenation (ECMO) assisted resuscitation, also known as extracorporeal resuscitation (ECPR), is potentially effective for refractory CPA. The 2020 American Heart Association guidelines for Class IIb recommend the use of ECPR for refractory CPA with a potentially reversible aetiology. While ideal candidates for ECPR initiation and its optimal timing are currently being investigated, the outcome-related factors in patients who receive ECPR are similar to those of OHCA patients who achieve ROSC with conventional CPR, such as younger age, shorter arrest duration (time from arrest to ECMO initiation), witnessed arrest, and shockable initial cardiac rhythm. In addition, recent ECPR-related studies have reported that the experience of transient ROSC before ECMO initiation was also associated with favourable outcomes in refractory CPA; however, the numbers of included patients were relatively small. Furthermore, details concerning when transient ROSC was achieved (before or after hospital arrival) were not reported in these studies.

Therefore, the relationship between the presence or absence of transient ROSC before ECMO initiation and outcomes has not been well understood. Moreover, even if transient ROSC is achieved, it remains largely unclear what timing concerning ROSC, i.e., before or after hospital arrival, is most prognostic.

To address this knowledge gap, we used the largest ECPR registry data of OHCA in Japan to investigate the relationship between transient ROSC during resuscitation before ECMO initiation and outcomes in OHCA patients resuscitated with ECPR.

### Methods

**Study design and setting**

This study was a secondary analysis of the SAVE-J II study, which was a retrospective multicentre registry study of OHCA patients resuscitated with ECPR, involving 36 participating institutions in Japan. The study design and data collection methods of the SAVE-J II study have been previously described. The SAVE-J II study included consecutive OHCA patients aged ≥18 years who were resuscitated with ECPR. They were admitted to the participating institutions between 1 January 2013 and 31 December 2018. In this study, ECPR was defined as resuscitation using ECMO for patients with refractory CPA. The inclusion criterion was cardiac arrest when ECMO was initiated. The exclusion criteria were as follows: (1) patients who were transferred from another hospital; (2) patients with sustained ROSC when ECMO was initiated; and (3) aetiologies of arrest comprising non-cardiac conditions, such as acute aortic syndromes, hypothermia, primary cerebral disorders, infection, drug intoxication, trauma, suffocation, and drowning. In addition, we excluded patients with a time of >60 minutes from hospital arrival to ECMO initiation, because these patients may have achieved ROSC for a long period before ECMO initiation. We also excluded patients with missing data on transient ROSC, timing of ROSC, arrest to ECMO initiation time interval, and outcomes.

The SAVE-J II study was registered at the University Hospital Medical Information Network Clinical Trials Registry and the Japanese Clinical Trial Registry (registration number: UMIN000036490). This study was approved by the Institutional Review Board of Kagawa University (approval number: 2018-110) and each participating institution, including the Hiroshima City Hiroshima Citizens Hospital (approval number: 2019-80). This secondary analysis of de-identified data was approved by the Institutional Review Board of Hiroshima City Hiroshima Citizens Hospital (approval number: 2021-157). The need for written informed consent was waived due to the retrospective nature of this study.
The following patient data were collected from the SAVE-J II study database: age, sex, incidence of witnessed cardiac arrest and bystander-initiated CPR, initial cardiac rhythm at the scene, time interval (call or time of arrests witnessed by the emergency medical service [EMS] to hospital arrival and hospital arrival to ECMO initiation), aetiology of cardiac arrest, timing of ROSC (pre-hospital [before hospital arrival] only, in-hospital [after hospital arrival] only, or both pre- and in-hospital) in patients with transient ROSC, and outcomes. Time interval was calculated from the emergency call for those who arrested before EMS arrival, and calculated from arrest witnessed by EMS for those who arrested after EMS arrival to hospital arrival and ECMO initiation. The definition of cardiac arrest aetiology was based on a previous report.21 Initial shockable rhythm was defined as ventricular fibrillation or pulseless ventricular tachycardia. Transient ROSC was defined as any palpable pulse or measurable blood pressure ≥1 min before ECMO initiation, either before and after hospital arrival.22 The primary outcome was a favourable neurological outcome, and the secondary outcome was survival to hospital discharge. A favourable neurological outcome was defined as a cerebral performance category (CPC) of 1–2, whereas an unfavourable outcome was defined as a CPC of 3–5.

Statistical analysis
The study patients were divided into two groups according to the presence or absence of transient ROSC before ECMO initiation. We examined the relationship between transient ROSC and patient characteristics and outcomes. To investigate the association between transient ROSC and the outcomes, we performed univariate analyses. Continuous variables were presented as medians and interquartile ranges (IQR), whereas categorical variables were presented as numbers and percentages. Continuous variables were compared using a Mann–Whitney U test, and categorical variables were compared using chi-squared or Fisher’s exact tests. We also depicted the association between transient ROSC and survival to hospital discharge using Kaplan–Meier survival curves, with a log-rank test to present the differences. Additionally, we performed multiple logistic analyses adjusted for patient characteristics and cardiac arrest status. Covariates were selected based on previous studies, including age, sex, bystander witness, bystander-initiated CPR, initial cardiac rhythm (shockable or not), time interval from call or EMS witnessed to ECMO initiation, and the causes of cardiac arrest (cardiac causes or not).5–22 Data were reported as odds ratios (ORs) with 95% confidence intervals (CIs). For the subgroup analysis, we selected only patients who had transient ROSC. We stratified the patients according to timing of transient ROSC (pre-hospital only [group 1], in-hospital only [group 2], or both pre and in-hospital [group 3]), and the categories were mutually exclusive. We then compared patient characteristics and outcomes. Continuous variables were compared using a Kruskal–Wallis test, and categorical variables were compared using a chi-squared test. Furthermore, we performed multiple logistic analyses adjusted for patient characteristics and cardiac arrest status. Covariates were selected as in the primary analysis. All statistical analyses were performed using R software package version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at two-sided \( P < 0.05 \).
was no difference in age, frequency of witnessed arrest, shockable initial cardiac rhythm, or aetiology of arrest. Further, bystander-initiated CPR was less frequent in group 2 than in the other groups (64%, 53%, and 72% in groups 1, 2, and 3, respectively; \( P = 0.02 \)). Call or EMS witnessed to ECMO initiation time was the longest in group 3 (57 min [IQR 47–67], 59 min [IQR 49–70], and 63 min [IQR 53–75] in groups 1, 2, and 3, respectively; \( P = 0.03 \)). The frequency of favourable neurological outcomes (23%, 25%, and 33% in groups 1, 2, and 3, respectively; \( P = 0.03 \)) and survival to hospital discharge (41%, 45%, and 58% in groups 1, 2, and 3, respectively; \( P = 0.07 \)) did not differ among the three groups. The relationship between the timing of transient ROSC and outcomes in univariate and multivariate analyses showed that group 3 had a significantly higher chance of survival to hospital discharge than group 1 (unadjusted OR, 1.99 [95% CI 1.06–3.72]; adjusted OR, 2.50 [95% CI 1.21–5.14]) (Table 4). The full adjusted model is presented in Supplementary Table A2.

**Discussion**

The major finding of this study was that, according to data obtained from the largest ECPR registry of OHCA in Japan, transient ROSC was independently associated with favourable outcomes in ECPR patients, regardless of the timing of transient ROSC.

ECPR has been reported as an advanced resuscitation technique for cases of refractory CPA that do not achieve ROSC with conventional CPR.8–25 Previous studies have reported that ECPR improved neurological outcomes and survival; however, its benefit is limited and it should be considered for selected patients with reversible causes of CPA and potential for survival.8–12 Selecting patients who are likely to benefit from ECPR is important and most ECPR studies have included younger patients with fewer comorbidities. Some studies restricted their inclusion criteria for patients with ECPR and witnessed arrest, shockable initial cardiac rhythms, shorter CPR duration, and required a certain period of conventional CPR prior to ECMO initiation;8,10,23,24 however, the vast majority of the ECPR studies involved single centres with varying inclusion criteria and settings. Therefore, there is currently no strong evidence to define who the “selected patients” should comprise.8 Therefore, there is a need to identify patients who are likely to benefit from ECPR.

The time from cardiac arrest to ROSC is known to be one of the key factors associated with favourable outcomes in patients who experience OHCA.1–6 Conventional CPR is most effective within the first 20 min, at which time 90% of patients with favourable neurological outcomes have achieved ROSC.1 Moreover, prolonged duration of CPR decreases the chances of survival. The acceptable duration (upper limit) of CPR for the achievement of favourable outcomes is approximately 40 min in patients who receive conventional CPR.1–3 OHCA patients who have achieved transient ROSC with conventional CPR may experience re-arrest, which is known to be associated with a worse outcome;2 whereas, OHCA patients who had experienced transient ROSC before hospital arrival and finally achieved sustained ROSC were reported to have favourable outcomes even if their CPR duration was \( \geq 40 \) min.4,11,12 Similarly, in patients with ECPR, the time from cardiac arrest to ECMO initiation...
could be an important factor related to their outcomes.  

ECPR may enhance survival after prolonged arrest duration; however, previous studies have suggested that >60 min of CPR duration was associated with poor outcomes even with ECPR. It is clear that prolonged cardiac arrest without ROSC precludes the possibility of ECPR; however, some reports have described patients with ECPR having had favourable outcomes even with a CPR time >60 min. As mentioned above, re-arrest, patients who have previously achieved ROSC but who experience arrest again during resuscitation, is associated with a worse outcome; however, this is only for CPA patients resuscitated with conventional CPR. Transient ROSC has been associated with favourable outcomes in patients with ECPR, with approximately 7–27% of such patients achieving transient ROSC before ECMO initiation; however, the details of ROSC during CPR were not clearly reported and CPR duration was defined differently among these studies, with some defining it as the time from CPA to ROSC or ECMO initiation, while others defined it as the sum of times performing CPR. Patients resuscitated with ECPR who had received prolonged CPR may have experienced transient ROSC during conventional CPR, which may have led to favourable outcomes.

Our study found that patients with transient ROSC before ECMO initiation had more frequent favourable neurological outcomes and survival than those without, even though they included older patients, less frequent shockable initial cardiac rhythm, and longer call-to-

| Table 1 – Comparisons between patients with and without transient ROSC prior to ECMO initiation. |
|-------------------------------------------------|-------------------------------------------------|-----------------|
| Transient ROSC | No ROSC | P-value |
|-----------------------------------------------|--------|---------|
| Age, years | 63 (52–70) | 60 (48–68) | 0.001 |
| Males | 263 (80) | 1,007 (86) | 0.01 |
| Witnessed arrest | 262 (80) | 932 (80) | 0.93 |
| EMS witnessed arrest | 46 (14) | 118 (10) | 0.04 |
| Bystander-initiated CPR | 197 (61) | 671 (58) | 0.40 |
| Initial cardiac rhythm | <0.001 |
| Shockable | 202 (63) | 841 (72) |
| Pulseless electrical activity | 101 (31) | 239 (21) |
| Asystole | 20 (6) | 85 (7) |
| Cardiac rhythm at ECMO initiation | <0.001 |
| Shockable | 171 (52) | 635 (54) |
| Pulseless electrical activity | 133 (41) | 340 (29) |
| Asystole | 24 (7) | 198 (17) |
| Call or EMS witnessed to hospital arrival, min | 30 (23–38) | 30 (24–37) | 0.89 |
| Hospital arrival to ECMO, min | 27 (19–37) | 21 (15–29) | <0.001 |
| Call or EMS witnessed to ECMO, min | 59 (49–70) | 53 (44–63) | <0.001 |
| Aetiology of arrest | <0.001 |
| Cardiac causes of arrest | 272 (83) | 1,017 (87) |
| Acute coronary syndrome | 194 (59) | 691 (59) |
| Arrhythmia | 48 (15) | 164 (14) |
| Myopathy | 12 (4) | 78 (7) |
| Other cardiac causes | 18 (6) | 84 (7) |
| Non-cardiac causes of arrest | 39 (12) | 65 (6) |
| Pulmonary embolism | 31 (10) | 28 (2) |
| Other non-cardiac causes | 8 (2) | 37 (3) |
| Unknown | 17 (5) | 91 (8) |
| Favourable neurological outcomes | 85 (26) | 136 (12) | <0.001 |
| Survival to hospital discharge | 152 (46) | 283 (24) | <0.001 |
| Data are presented as the number (column %) of patients or median (interquartile range). CPR, cardiopulmonary resuscitation; EMS, emergency medical service; ECMO, extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation. The following data were missing: 2 witnessed arrest, 3 EMS witnessed arrest, 17 bystander-initiated CPR, and 13 initial cardiac rhythm. |

Fig. 2 – Kaplan–Meier survival curves with the log-rank test for presenting the differences between patients with and without transient ROSC The bold line indicates patients with transient ROSC and the thin line indicates patients without transient ROSC. The Kaplan–Meier plot showed significantly better survival in the transient ROSC group (log-rank test, P < 0.001). ROSC, return of spontaneous circulation.
ECMO or EMS-witnessed-to-ECMO time. In addition, transient ROSC was independently associated with favourable outcomes, regardless of the timing of the ROSC (before and/or after hospital arrival). Moreover, even if transient ROSC was achieved for the first time after hospital arrival, there was a chance of good outcomes. In the subgroup analysis with groups divided according to the timing of ROSC, patients with transient ROSC both before and after hospital arrival (group 3) were more likely to survive to hospital discharge than patients with transient ROSC before hospital arrival only (group 1). This result may reflect that a higher frequency of transient ROSC or a longer total ROSC time before ECMO initiation is associated with favourable outcomes. The results of our study using data from the largest ECPR registry in Japan support findings in previous reports.18–21 Inclusion criteria for ECPR were not defined in the SAVE-J II study, and OHCA patients who experienced transient ROSC may have been more likely to receive ECPR; however, transient ROSC could be a predictor of favourable outcomes in patients with ECPR. Therefore, ECPR should be considered if transient ROSC was achieved at any time even when the CPR duration was prolonged.

Table 2 – Unadjusted and adjusted association between transient ROSC and clinical outcomes.

|                                | Unadjusted odds ratios | Adjusted odds ratios* |
|--------------------------------|------------------------|-----------------------|
|                                | Odds ratio (95% CI)    | P-value               |
| Favourable neurological outcomes|                        |                       |
| No ROSC                        | 1 (Reference)          | 1 (Reference)         |
| Transient ROSC                 | 2.67 (1.94–3.65)       | <0.001                |
| Survival to hospital discharge |                        |                       |
| No ROSC                        | 1 (Reference)          | 1 (Reference)         |
| Transient ROSC                 | 2.71 (2.09–3.53)       | <0.001                |

CI, confidence interval; ROSC, return of spontaneous circulation.
* Adjusted according to age, sex, bystander witness, bystander-initiated cardiopulmonary resuscitation, initial cardiac rhythm (shockable or not), time interval from call or emergency medical service witnessed to extracorporeal membrane oxygenation initiation, and the causes of cardiac arrest (cardiac causes or not).

Table 3 – Comparisons among groups divided according to timing of transient ROSC.

|                                | Pre-hospital only (Group 1) | In-hospital only (Group 2) | Pre- and in-hospital (Group 3) | P-value |
|--------------------------------|-----------------------------|---------------------------|-------------------------------|---------|
|                                | n = 102                    | n = 159                   | n = 67                        |         |
| Age, years                     | 63 (51–71)                 | 62 (53–69)                | 64 (55–70)                    | 0.62    |
| Males                          | 77 (76)                    | 132 (83)                  | 54 (81)                       | 0.33    |
| Witnessed arrest               | 79 (78)                    | 126 (79)                  | 57 (85)                       | 0.46    |
| EMS witnessed arrest           | 15 (15)                    | 20 (13)                   | 11 (16)                       | 0.71    |
| Bystander-initiated CPR        | 65 (64)                    | 85 (53)                   | 47 (72)                       | 0.02    |
| Initial cardiac rhythm         |                            |                           |                               | 0.82    |
| Shockable                      | 64 (63)                    | 100 (63)                  | 38 (60)                       |         |
| Pulseless electrical activity  | 32 (32)                    | 50 (31)                   | 19 (30)                       |         |
| Asystole                       | 5 (5)                      | 9 (6)                     | 6 (10)                        |         |
| Call or EMS witnessed to hospital arrival, min | 33 (24–44) | 28 (22–35) | 33 (25–40) | 0.001 |
| Hospital arrival to ECMO, min  | 21 (14–31)                 | 29 (21–40)                | 29 (22–41)                    | <0.001  |
| Call or EMS witnessed to ECMO, min | 57 (47–67) | 59 (49–70) | 63 (53–75) | 0.03 |
| Aetiology of arrest            |                            |                           |                               | 0.36    |
| Cardiac causes of arrest       | 88 (86)                    | 131 (82)                  | 53 (79)                       |         |
| Acute coronary syndrome        | 63 (62)                    | 90 (57)                   | 41 (61)                       |         |
| Arrhythmia                     | 14 (14)                    | 27 (17)                   | 7 (10)                        |         |
| Myopathy                       | 4 (4)                      | 4 (3)                     | 4 (6)                         |         |
| Other cardiac causes           | 7 (7)                      | 10 (6)                    | 1 (2)                         |         |
| Non-cardiac causes of arrest   | 10 (10)                    | 17 (11)                   | 12 (18)                       |         |
| Pulmonary embolism             | 7 (7)                      | 15 (9)                    | 9 (13)                        |         |
| Other non-cardiac causes       | 3 (3)                      | 2 (1)                     | 3 (5)                         |         |
| Unknown                        | 4 (4)                      | 11 (7)                    | 2 (3)                         |         |
| Favourable neurological outcome| 23 (23)                    | 40 (25)                   | 22 (33)                       | 0.30    |
| Survival to hospital discharge | 42 (41)                    | 71 (45)                   | 39 (58)                       | 0.07    |

Data are presented as the number (column %) of patients or median (interquartile range).
* CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; EMS, emergency medical service; ROSC, return of spontaneous circulation.
* The following data were missing: 3 bystander-initiated CPR, and 5 initial cardiac rhythm.
In OHCA patients resuscitated with ECPR, transient ROSC before ECMO initiation was independently associated with favourable outcomes. Transient ROSC should be evaluated as a potential indication for ECPR in OHCA patients with refractory CPA.

### Conclusions

In OHCA patients resuscitated with ECPR, transient ROSC before ECMO initiation was independently associated with favourable outcomes. Transient ROSC should be evaluated as a potential indication for ECPR in OHCA patients with refractory CPA.

### Conflicts of interest

The authors declare that they have no conflicts of interests.

### Data statement

Please contact the author for data requests.

### Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We thank Editage for the English language editing. We also thank all the members of the SAVE-J II study group who participated in this study: Hirotaka Sawano, M.D., Ph.D. (Osaka Saiseikai Senri Hospital), Yoko Egawa, M.D., Shunichi Kato, M.D. (Saitama Red Cross Hospital), Kazuhiro Sugiyama, M.D., Maki Tanabe, M.D. (Tokyo Metropolitan Bokutoh Hospital), Naofumi Bunya, M.D., Takehiko Kasai, M.D. (Sapporo Medical University), Shinichi Ijim, M.D., Shinichi Nakayama, M.D., Ph.D. (Hyo-Ri Emergency Medical Center), Jun Kanda, M.D., Ph.D., Seiya Kanou, M.D. (Teikyo University Hospital), Toru Takiguchi, M.D., Shoji Yokobori, M.D., Ph.D. (Nippon Medical School), Hiroaki Takada, M.D., Kazushige Inoue, M.D. (National Hospital Organization Disaster Medical Center), Ichiro Takeuchi, M.D., Ph.D., Hiroshi Honzawa, M.D. (Yokohama City University Medical Center), Makoto Kobayashi, M.D., Ph.D., Tomohiro Hamagami, M.D. (Toyooka Public Hospital), Wataru Takayama, M.D., Yasuhiro Otomo, M.D., Ph.D. (Tokyo Medical and Dental University of Medicine), Kunihiko Maekawa, M.D. (Hokkaido University Hospital), Takafumi Shimizu, M.D., Satoshi Nara, M.D. (Teine Keijinkai Hospital), Michioka Nasu, M.D., Kuniko Takahashi, M.D. (Urasoe General Hospital), Yoshihiro Hagimiwa, M.D., M.P.H. (Imperial Foundation Saiseikai, Utsunomiya Hospital), Shigeki Kushimoto, M.D., Ph.D. (Tohoku University Graduate School of Medicine), Ryo Fukuda, M.D. (Nippon Medical School Tama Nagayama Hospital), Takayuki Ogura, M.D., Ph.D. (Japan Red Cross Maebashi Hospital),

### Table 4 – Unadjusted and adjusted association between timing of transient ROSC and clinical outcomes.

| Favourable neurological outcomes | Unadjusted odds ratios | Adjusted odds ratios* |
|----------------------------------|------------------------|-----------------------|
|                                 | Odds ratio (95% CI)    | P-value               | Odds ratio (95% CI)    | P-value               |
|                                 |                        |                       |                        |                       |
| ROSC pre-hospital only (Group 1) | 1 (Reference)          |                       | 1 (Reference)          |                       |
| ROSC in-hospital only (Group 2)  | 1.15 (0.64–2.08)       | 0.63                  | 1.14 (0.59–2.18)       | 0.70                  |
| ROSC pre- and in-hospital (Group 3) | 1.68 (0.84–3.35)   | 0.14                  | 1.93 (0.88–4.20)       | 0.09                  |
| Survival to hospital discharge  |                        |                       |                        |                       |
| ROSC pre-hospital only (Group 1) | 1 (Reference)          |                       | 1 (Reference)          |                       |
| ROSC in-hospital only (Group 2)  | 1.15 (0.70–1.91)       | 0.58                  | 1.10 (0.62–1.94)       | 0.74                  |
| ROSC pre- and in-hospital (Group 3) | 1.99 (1.06–3.72)     | 0.03                  | 2.50 (1.21–5.14)       | 0.01                  |

CI, confidence interval; ROSC, return of spontaneous circulation.

* Adjusted according to age, sex, bystander witness, bystander-initiated cardiopulmonary resuscitation, initial cardiac rhythm (shockable or not), time interval from call or emergency medical service witnessed to extracorporeal membrane oxygenation initiation, and the causes of cardiac arrest (cardiac causes or not).
Shin-ichiro Shiraiishi, M.D. (Aizu Central Hospital), Ryosuke Zushi, M.D. (Osaka Mishima Emergency Critical Care Center), Norio Otani, M.D. (St. Luke’s International Hospital), Migaku Kikuchi, M.D., Ph.D. (Dokkyo Medical University), Kazuhiro Watanabe, M.D. (Nihon University Hospital), Takuo Nakagami, M.D. (Omihachiman Community Medical Center), Tomohiro Shoko, M.D., Ph.D. (Tokyo Women’s Medical University Medical Center East), Nobuya Kitamura, M.D., Ph.D., Makoto Aoki, M.D., Ph.D. (Gunma University Graduate School of Medicine), Masaaki Sakuraya, M.D., Ph.D. (J.A. Hiroshima General Hospital Hiroshima), Hideki Arimoto, M.D. (Osaka City General Hospital), Koichiro Homma, M.D., Ph.D. (Keio University School of Medicine), Hiromichi Naito, M.D., Ph.D. (Okayama University Hospital), Shunichiro Nakao, M.D., Ph.D. (Osaka University Graduate School of Medicine), Tomoya Okazaki, M.D., Ph.D. (Kagawa University Hospital), Yoshio Tahara, M.D., Ph.D. (National Cerebral and Cardiovascular Center), Hiroki Okamoto, M.D., M.P.H. (St. Luke’s International Hospital), Jun Kunikata, M.D., Ph.D., Hideto Yokoi, M.D., Ph.D. (Kagawa University Hospital).

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100300.

Author details

the SAVE-J II study group

Department of Emergency Medicine, Hiroshima City Hiroshima Citizens Hospital, 7-33 Motomachi, Naka-ku, Hiroshima-city, Hiroshima 730-8518, Japan

Department of Emergency and Critical Care Medicine, St. Luke’s International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan

Department of Emergency and Critical Care Medicine, Hyogo Emergency Medical Center, 1-3-1 Wakinohamakaiogandori, Chuo-ku, Kobe 651-0073, Japan

Department of Emergency and Critical Care Medicine, Tsukuba Memorial Hospital, 1187-299 Kaname, Tsukuba, Ibaraki 300-2622, Japan

Department of Health Services Research, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8577, Japan

Department of Emergency Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Ibaraki-Ku, Tokyo 173-8606, Japan

Department of Emergency, Disaster and Critical Care Medicine, Kagawa University Hospital, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

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