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## Clinical paper

# Neurologic outcome and location of cardiac arrest in out-of-hospital cardiac arrest patients who underwent extracorporeal cardiopulmonary resuscitation: A multicentre retrospective cohort in Japan

Kazuhiro Shirakawa<sup>a</sup>, Yoshinori Matsuoka<sup>a,b,\*</sup>, Yosuke Yamamoto<sup>b</sup>, Akihiko Inoue<sup>c</sup>, Ryo Takahashi<sup>c</sup>, Yoshie Yamada<sup>b</sup>, Koichi Ariyoshi<sup>a</sup>, Toru Hifumi<sup>d</sup>, Tetsuya Sakamoto<sup>e</sup>, Yasuhiro Kuroda<sup>f</sup>, The SAVE-J II study group<sup>1</sup>

### Abstract

**Aim:** We examined the association between the location of cardiac arrest and outcomes of patients with out-of-hospital cardiac arrest (OHCA) who underwent extracorporeal cardiopulmonary resuscitation (ECPR).

**Methods:** This was a secondary analysis of SAVE-J II, a multicentre retrospective registry with 36 participating institutions across Japan, which enrolled adult patients with OHCA who underwent ECPR. The outcomes of interest were favourable neurologic outcome at discharge. We compared the outcome between OHCA cases that occurred at residential and public locations, using a multilevel logistic regression model allowing for the random effect of each hospital.

**Results:** Among 1,744 enrolled OHCA, 809 and 935 occurred at residential (house: 603; apartment: 206) and public (street: 260; workplace: 210; others: 465) locations, respectively. The proportion of favourable neurologic outcomes was lower in OHCA at residential locations than those at public locations (88/781 (11.3%) vs. 131/891 (14.7%); adjusted odds ratio, 0.72 [95% confidence interval, 0.53–0.99]). However, subgroup analyses for patients with EMS aged <65 years call to hospital arrival within 30 minutes or during daytime revealed less difference between residential and public locations.

**Conclusion:** When cardiac arrests occurred at residential locations, lower proportions of favourable neurologic outcomes were exhibited among patients with OHCA who underwent ECPR. However, the event's location may not affect the prognosis among appropriate and select cases when transported within a limited timeframe.

**Keywords:** Extracorporeal cardiopulmonary resuscitation, Out-of-hospital cardiac arrest, Location of cardiac arrest, Cardiopulmonary resuscitation

## Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of death worldwide, affecting approximately 379,000 people in the United States, 275,000 people in Europe, and 126,000 people in Japan

annually.<sup>1–3</sup> Despite recent advances in cardiopulmonary resuscitation and post-cardiac arrest care, the prognosis of patients with cardiac arrests has remained dismal.<sup>4–6</sup> Among significant progress made in resuscitative interventions for OHCA, extracorporeal cardiopulmonary resuscitation (ECPR) has been gathering attention as an emerging resuscitative method that can increase coronary

\* Corresponding author at: Department of Emergency Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-Minamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan.

E-mail address: [matsuoka.yoshinori.f99@kyoto-u.jp](mailto:matsuoka.yoshinori.f99@kyoto-u.jp) (Y. Matsuoka).

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perfusion pressures and provide sufficient systemic organ perfusions to vital organs.<sup>7</sup> Until now, studies from various countries have been challenged to prove the effectiveness and efficacy of ECPR and ended up with controversial results.<sup>8–10</sup> At this time, it is important to select an appropriate candidate for ECPR, and factors, such as younger age, short low-flow time, and initial shockable rhythm are considered to be helpful in predicting patient outcomes.<sup>11–13</sup>

Although increasing numbers of studies have been conducted on the efficacy and effectiveness of ECPR, little is known regarding prognosis by location of occurrence among patients with OHCA who underwent ECPR. Previous studies have shown that cardiac arrest locations are associated with the outcomes of patients with OHCA. Low proportions of bystander cardiopulmonary resuscitation (CPR), automated external defibrillator (AED) usage, and a lack of human resources might be attributed to poor prognosis when cardiac arrests occurred at residential locations.<sup>14–17</sup> While the association between prognosis and site of cardiac arrests among OHCA has been well studied, we have scarce knowledge about the association in select patients with OHCA who underwent ECPR.

In Japan, a multicentre, retrospective observational study of ECPR for OHCA (SAVE-J II) was conducted recently, and we aimed to examine a knowledge gap of associations between the neurologic outcome of patients with OHCA with ECPR and locations of cardiac arrests by analysing data from the SAVE-J II study. Findings and insight from the present study would facilitate the development of EMS protocols or provide useful information in selecting the candidate for ECPR.

## Methods

### Study design and setting, population, and data collection

This was a secondary analysis of a nationwide multicentre retrospective registry, SAVE-J II, which enrolled adult patients (aged 18 years and older) with OHCA who underwent ECPR across 36 participating institutions in Japan between 1 January 2013 and 31 December 2018.<sup>18</sup> The study design and data collection methods of the SAVE-J II study were previously described in detail.<sup>18</sup>

From the original registry, we excluded patients with implementation of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) after intensive care unit (ICU) admission and withdrew after cannulation because of return of spontaneous circulation (ROSC). Patients who achieved ROSC on hospital arrival or at ECMO initiation were also excluded. Finally, we excluded those who collapsed into cardiac arrest in ambulances or after arriving at hospitals, those with unknown cardiac arrest locations, and those who were transferred from another hospital.

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 Kobe City Medical Center General Hospital (approval number: zn200304). The need for written informed consent was waived due to the retrospective nature of this study.

### Definition of location of cardiac arrest

We classified sites of cardiac arrest into residential (house, apartment) and public (street, workplace, and other public places) locations.

### Outcome measures

The primary outcome measure of the present study was favourable neurologic outcomes at discharge. Favourable neurologic outcomes were defined as a Cerebral Performance Category score (CPC) of 1 or 2, based on previous studies.<sup>19–21</sup> Cerebral Performance Category scores are categorised into: categories 1 (good performance); 2 (moderate disability); 3 (severe cerebral disability); 4 (coma/vegetative state); and 5 (death/brain death).<sup>22</sup>

### Statistical analysis

The baseline characteristics were stratified by the cardiac arrest location (house, apartment, street, workplace, and other public places). We assessed counts and proportions for categorical variables and medians with interquartile ranges for continuous variables.

In the primary analysis, we used the complete data set and evaluated the association between the outcome and location of cardiac arrest (residential or public) using a multilevel logistic regression model, which allows for the random effect of each hospital (a random-intercept model). We calculated adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) by adjusting possible confounding factors based on clinical plausibility and preexisting knowledge.<sup>16,21,23</sup> Covariates included in the model were as follows: age (5-yearly increments), gender, medical history (diabetes mellitus, heart disease, and chronic kidney disease), bystander witness status (yes or no), bystander CPR (yes or no), initial shockable rhythm (yes or no), time of EMS call (daytime [9:00–16:59] or nighttime [0:00–08:59 and 17:00–23:59]), and time from EMS call to hospital arrival.

We conducted several sensitivity analyses. First, we conducted an analysis for select patients who met SAVE-J criteria: age  $\leq 75$  years, initial shockable rhythm of cardiac arrest, and time from emergency medical service call to hospital  $\leq 45$  minutes. Second, we conducted a sensitivity analysis which aimed to account for potential influence by the hospital characteristics. Here, we constructed a statistical model by adding two more covariates related to the characteristics of hospitals to the statistical model of the primary analysis: annual cases of ECPR (categorized into tertiles) and hospital types (university, public, or private). Finally, we conducted an analysis for missing covariates with multiple imputations by chained equations. In this analysis, we generated 20 imputed data sets using all measured data, including outcomes, on the assumption that the data were missing at random.

Further, we performed an a priori subgroup analysis. In the subgroup analysis, we defined the subgroup as follows: time from EMS call to hospital arrival ( $\leq 30$  min, 31–44 min or  $\geq 45$  min), age ( $< 65$  years or  $\geq 65$  years), and time of EMS call (0:00–8:59, 9:00–16:59, or 17:00–23:59).

All statistical analyses were performed using IBM SPSS software, version 27 (IBM Corp., Armonk, New York, United States) and STATA, version 17.0 (StataCorp, College Station, Texas, United States).

## Results

In total, 2,157 patients were registered in the SAVE-J II registry. From the registry, we enrolled 1,744 patients in the present study after excluding patients as follows: 9 patients with implementation of ECMO after ICU admission, 1 with withdrawal after cannulation because of ROSC, 96 with ROSC at hospital arrival, 58 with ROSC

at ECMO initiation, 205 OHCA cases which occurred in ambulances, 33 OHCA cases which occurred in hospitals, 6 with unknown locations of cardiac arrest, and 5 which were transferred from another hospital. Finally, 1,672 patients with complete data sets were eligible for the primary analysis (Fig. 1).

Table 1 shows the baseline characteristics of patients with OHCA who underwent ECPR according to the location of cardiac arrest: residential and public locations. Of the 1,744 individuals, 809 OHCA cases occurred at residential locations (house: 603; apartment: 206) and 935 cases at public locations (street: 260; workplace: 210; others: 465) (Supplement Table). The median age was 60 years (IQR, 49–69), and 1,453 (83.3%) were male. Patients were less likely to receive bystander CPR, be witnessed, and have initial shockable rhythm when OHCA cases occurred at residential locations than at public locations.

Less than half of OHCA cases in residential locations occurred during the daytime (46.5%), and the time from the EMS call to hospital arrival was longer in OHCA cases at residential locations than those at public locations (34 minutes [IQR, 28–42] vs. 30 minutes [IQR, 24–37], respectively).

Fig. 2 shows the primary outcomes in patients with OHCA who underwent ECPR and the results of the statistical analyses. In the primary analysis, the proportion of favourable neurologic outcomes was significantly lower in the patients who collapsed at residential locations than in those who collapsed at public locations (88/781 (11.3%) vs. 131/891 (14.7%); unadjusted odds ratio, 0.74 [95% confidence interval [CI], 0.55–0.98]; adjusted odds ratio, 0.72 [95% CI, 0.53–0.99]).

In the sensitivity analyses, we obtained similar results to those obtained from the primary analysis. The analysis for select patients

who met SAVE-J criteria revealed a similar point estimate of an adjusted odds ratio but showed wider 95% CIs. The analysis using the modified model revealed almost the same results as the primary analysis. Finally, the sensitivity analysis for missing covariates showed comparable results between the analysis with imputed data sets and the analysis with the complete data set (Table 2).

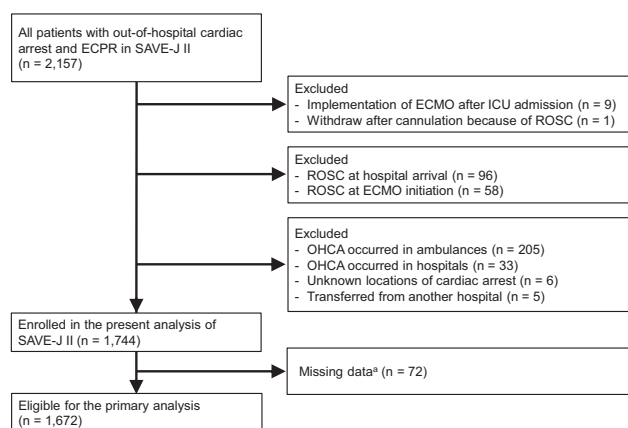
In the subgroup analyses, we compared the primary outcome in each predefined subgroup. When the time from EMS call to hospital arrival was within 30 minutes, the proportion of the primary outcome was comparable between cases at residential and public locations (39/248 (15.7) vs. 67/419 (16.0); adjusted odds ratio, 0.93 (0.58–1.49)). Among the subgroup of younger age (<65 years) or daytime cases (9:00–16:59), the point estimates of adjusted odds ratio were closer to one when compared with other categories (adjusted odds ratio, 0.81 (0.55–1.19) and 0.93 (0.61–1.42), respectively) (Fig. 2).

## Discussion

In our secondary analysis of the nationwide multicentre registry in Japan, patients with OHCA resuscitated with ECPR were more likely to develop unfavourable neurologic outcomes at discharge when cardiac arrests occurred at residential locations than at public locations. Conversely, we did not observe such a difference between residential and public locations when we restricted cases to those with time from EMS call to hospital arrival within 30 minutes or those aged <65 years.

Previous studies have reported that OHCA cases at residential locations were associated with poor outcomes, and it could be explained, to some extent, by the factors such as lower receipt of bystander CPR, lower proportion of initial shockable rhythm, and higher proportion of cases that occurred at night.<sup>14–16,24,25</sup> Indeed, we also observed that initial shockable rhythm was lower, and more patients collapsed at night in cases at residential locations in this study. However, even after adjusting for these factors, the proportion of favourable neurologic outcomes remained significantly lower in patients with cardiac arrests that occurred in residential locations. Our results were inconsistent with a multicentre retrospective cohort in Japan that reported that such deterioration of prognosis was not observed among patients with OHCA with initial shockable rhythm and residential locations.<sup>17</sup> In the paper, they suggested that these patients would not have much influence on incidence locations because the deleterious effects of reduced quality of chest compressions due to incidence locations were mitigated as there were some patients with cardiac arrest with ROSC after successful defibrillation. Considering that our target population is mainly patients with refractory cardiac arrests, the quality of CPR still retains much importance. Above these discussions, we believe that the results of the present study were plausible and added a new finding about the association between prognosis and locations of cardiac arrests in a new population, patients with OHCA and ECPR.

Our subgroup analysis revealed that even patients with OHCA at residential locations might have comparable prognoses to those at public locations when the cases were limited to those with time from EMS call to hospital arrival within 30 minutes, ages lower than 65 years, and time of EMS call of 9:00 to 16:59. The reasons of delay in EMS call to the hospital might be explained by the difficulty of reaching at the scene driving through narrow and winding streets or removing patients to outside residences of multi-unit buildings in urban areas. Further quality of CPR would be affected by several



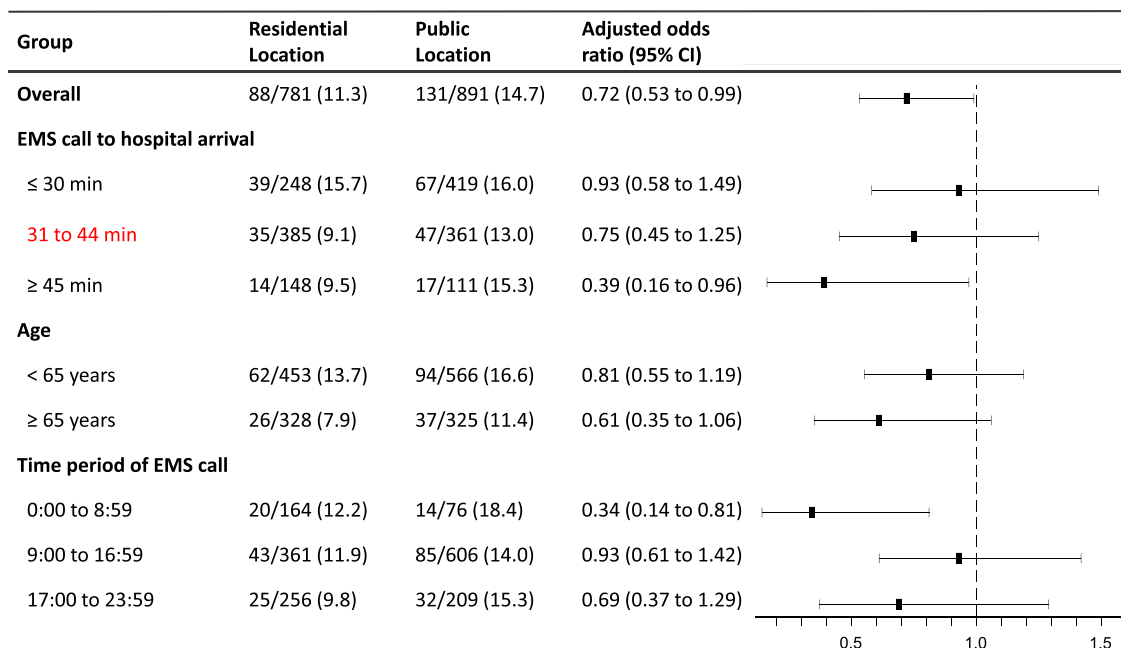
**Fig. 1 – Flow chart of the study.** <sup>a</sup>For the primary analysis, we precluded patients with missing data for the multilevel logistic regression model as follows: age, gender, past medical history, witness status, bystander cardiopulmonary resuscitation, initial rhythm of cardiac arrest, time of cardiac arrest, time from EMS call to hospital arrival, location of cardiac arrest, and favourable neurologic outcomes at discharge. ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

**Table 1 – Characteristics of out-of-hospital cardiac arrest patients who underwent extracorporeal cardiopulmonary resuscitation.**

Characteristics	Total (n = 1,744)	Residential location (n = 809)	Public location (n = 935)
Age, median (IQR)	60 (49–69)	61 (48–69)	60 (50–68)
Male, n (%)	1,453 (83.3%)	628 (77.6%)	825 (88.2%)
Medical history, n (%)			
Diabetes mellitus	319 (18.3%)	132 (16.3%)	187 (20.0%)
Heart disease	400 (22.9%)	175 (21.6%)	225 (24.1%)
Chronic kidney disease	77 (4.4%)	39 (4.8%)	38 (4.1%)
Witnessed, n (%)	1,282 (73.8%)	586 (72.8%)	696 (74.7%)
Bystander CPR, n (%)	899 (52.5%)	399 (50.5%)	500 (54.2%)
Initial shockable rhythm, n (%)	1,152 (66.7%)	514 (64.0%)	638 (69.0%)
Time period of EMS call, n (%)			
0:00–8:59	244 (14.2%)	167 (20.8%)	77 (8.4%)
9:00–16:59	998 (58.1%)	374 (46.5%)	624 (68.3%)
17:00–23:59	475 (27.7%)	263 (32.7%)	212 (23.2%)
Time from EMS call to hospital arrival, median (IQR), min	32 (26–39)	34 (28–42)	30 (24–37)
Time from hospital arrival to ECMO circuit establishment, median (IQR), min	22 (15–33)	23 (16–33)	22 (15–32)
Etiology of cardiac arrest, n (%)			
Cardiac causes	1,283 (74.6%)	557 (70.2%)	726 (78.4%)
External causes	244 (14.2%)	142 (17.9%)	102 (11.0%)
Others	193 (11.2%)	95 (12.0%)	98 (10.6%)
Favorable neurologic outcome at discharge, n (%)	227 (13.0%)	90 (11.1%)	137 (14.7%)
Survival at discharge, n (%)	436 (25.0%)	180 (22.3%)	256 (27.4%)

IQR, interquartile range; CPR, cardiopulmonary resuscitation; EMS, emergency medical service.

Missing data: witnessed status = 7, bystander CPR = 32, initial shockable rhythm = 16, time period of EMS call = 27, time from EMS call to hospital arrival = 28, time from hospital arrival to ECMO circuit establishment = 79, etiology of cardiac arrest = 24, favorable neurologic outcome at discharge = 1, survival at discharge = 1.



**Fig. 2 – Primary and subgroup analyses for outcomes of patients with out-of-hospital cardiac arrest and ECPR: Residential locations vs. Public locations. We compared outcomes of patients with OHCA who underwent ECPR using a multilevel logistic regression model. We adjusted for age, gender, past medical history, witness status, bystander cardiopulmonary resuscitation, initial rhythm of cardiac arrest, time of cardiac arrest, time from EMS call to hospital arrival, and location of cardiac arrest. The subgroups were predefined as follows: time from EMS call to hospital arrival (≤30 min, 31–44 min or ≥45 min), age (<65 years or ≥65 years) and time period of EMS call (0:00–8:59, 9:00–16:59, or 17:00–23:59). CI, confidence interval; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.**

**Table 2 – Sensitivity analyses for outcomes of patients with out-of-hospital cardiac arrest and ECPR: Residential locations vs. Public locations.**

	Residential locations	Public locations	Unadjusted odds ratio	Adjusted odds ratio
Primary analysis	88/693 (11.3)	131/891 (14.7)	0.74 (0.55–0.98)	0.72 (0.53–0.99)
Analysis for select patient who met SAVE-J criteria	54/363 (14.9)	92/510 (18.0)	0.79 (0.55–1.15)	0.78 (0.51–1.17)
Modified model with the hospital characteristics	88/693 (11.3)	131/891 (14.7)	–	0.73 (0.53–1.00)
Imputed data set	90/809 (11.1)	137/935 (14.7)	0.73 (0.55–0.97)	0.72 (0.53–0.98)

We performed three sensitivity analyses. First, we analysed select patients who met SAVE-J criteria: age  $\leq 75$  years, initial shockable rhythm of cardiac arrest, and time from emergency medical service call to hospital  $\leq 45$  minutes. Second, we constructed a statistical model by adding two more covariates to the statistical model of the primary analysis: annual cases of ECPR (categorized into tertiles) and hospital types (university, public, or private). Finally, we imputed the missing covariates with multiple imputations by chained equations. In the sensitivity analyses for missing covariates, we analysed using the same multilevel logistic regression model as the main analysis.

factors, including efforts to transport patients to the streets with lifts or stairs and restricted space for resuscitation.<sup>17,26</sup> Furthermore, it is also clinically important that we expect encouraging outcomes among younger patients and cases during the daytime, even when cardiac arrests occur at residential locations. Thus, focusing on younger patients or those collapsing during the day, or minimizing transportation time, might improve outcomes irrespective of the location of cardiac arrests. To achieve this, enhancing EMS awareness of ECPR indications and strengthening coordination between EMS and medical institutions may be essential.

### Limitations

Our study had some limitations. First, we could not account for factors such as the quality of the bystander CPR, which may have affected our findings. Previous studies have shown that there is a positive correlation between the number of bystanders and the quality of basic life support<sup>25–28</sup>; however, in cases where OHCA occurs in residential locations, the number of witnesses is usually limited to family members, which may have limited the quality of BLS and affected the proportions of favourable neurologic outcomes. Second, since our study is retrospective and observational in nature, it is subject to potential biases and confounding factors; therefore, our findings should be interpreted with caution. Finally, the data were collected from a single country and may not be generalisable to other settings. To improve the prognosis of OHCA treated with ECPR, further global studies are needed to evaluate the proportions and quality of bystander CPR, particularly in cases that occur in residential locations, as well as factors associated with an increase in time from emergency calls to the hospital arrival.

### Conclusions

The secondary analysis of a multicentre retrospective cohort in Japan revealed that the proportion of favourable neurologic outcomes was significantly lower in patients with OHCA who received ECPR when it occurred at residential locations than at public locations. However, the present study also added the finding that the prognosis might be similar regardless of the location of the event when the times from EMS call to hospital arrival were within 30 minutes, or patients with OHCA were aged  $< 65$  years. These findings underscore the importance of transporting patients to receiving hospitals as much as possible and facilitate EMS protocols of possible candidates of ECPR.

### CRedit authorship contribution statement

**Kazuhiro Shirakawa:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Yoshinori Matsuoka:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Yosuke Yamamoto:** Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision. **Akihiko Inoue:** Conceptualization, Investigation, Resources, Data curation, Writing – review & editing. **Ryo Takahashi:** Conceptualization, Investigation, Writing – review & editing. **Yoshie Yamada:** Investigation, Writing – review & editing. **Koichi Ariyoshi:** Writing – review & editing, Supervision. **Toru Hifumi:** Investigation, Resources, Data curation, Writing – review & editing, Supervision. **Tetsuya Sakamoto:** Investigation, Resources, Data curation, Writing – review & editing, Supervision. **Yasuhiro Kuroda:** Investigation, Resources, Data curation, Writing – review & editing, Supervision.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary material to this article can be found online at <https://doi.org/10.1016/j.resplu.2023.100468>.

## Author details

The SAVE-J II study group<sup>1</sup> <sup>a</sup>*Department of Emergency Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatogima-Minamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan* <sup>b</sup>*Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan* <sup>c</sup>*Department of Emergency and Critical Care Medicine, Hyogo Emergency Medical Center, 1-3-1 Wakinohama-kaigandori, Chuo-ku, Kobe, Hyogo 651-0073, Japan* <sup>d</sup>*Department of Emergency and Critical Care Medicine, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan* <sup>e</sup>*Teikyo University School of Medicine, Department of Emergency Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan* <sup>f</sup>*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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