Resuscitation Plus 20 (2024) 100831

Contents lists available at ScienceDirect

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

# Associations of long-term hyperoxemia, survival, and neurological outcomes in extracorporeal cardiopulmonary resuscitation patients undergoing targeted temperature management: A retrospective observational analysis of the SAVE-J II study

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ARTICLE INFO

*Keywords:*
Cardiopulmonary resuscitation
Induced hypothermia
Oxygen
Survival rate

ABSTRACT

*Background:* Extracorporeal cardiopulmonary resuscitation (ECPR) can improve survival rates and neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA). High levels of partial pressure of arterial oxygen ($PaO_2$) negatively affect survival and neurological outcomes in patients with OHCA. However, research on associations of hyperoxemia with survival and neurological outcomes after ECPR remains limited, especially considering targeted temperature management (TTM) administration to patients. Additionally, few reports have examined the impact of hyperoxemia beyond 24 h. In this study, we aimed to examine the effect of prolonged hyperoxemia on survival and neurological outcomes after ECPR for OHCA in patients undergoing TTM.

*Methods:* We performed a secondary observational analysis of data from the SAVE-J II study, a retrospective, multicenter registry study of ECPR of patients with OHCA. Data on arterial $PaO_2$ after ECPR for intensive care unit days 2–4 were collected and averaged. Patients were divided into two groups: hyperoxic ($PaO_2 \geq 300$ mmHg) and non-hyperoxic ($PaO_2 < 300$ mmHg). Each variable was compared between the groups. Additionally, survival and mortality rates at discharge were compared, and factors associated with survival (primary outcome) and neurological outcomes (secondary outcome) at discharge were examined.

*Results:* The multivariate analysis for survival at discharge showed that age, initial ventricular fibrillation/ventricular tachycardia (VF/VT) waveform, $P = 0.0004$), and hyperoxemia were significant factors. For neurological outcomes at discharge, significant factors included age, initial VF/VT waveform, hemoglobin level at presentation, and hyperoxemia.

*Conclusions:* Prolonged hyperoxemia was significantly associated with worse survival and neurological outcomes after ECPR for OHCA in patients who underwent TTM.

*Abbreviations:* AHA, American Heart Association; CI, confidence interval; CNS, central nervous system; CPC, cerebral performance category; ECPR, extracorporeal cardiopulmonary resuscitation; Hb, hemoglobin; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; $PaO_2$, partial pressure of arterial oxygen; PCAS, post-cardiac arrest syndrome; ROS, reactive oxygen species; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

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https://doi.org/10.1016/j.resplu.2024.100831
Received 4 September 2024; Received in revised form 11 November 2024; Accepted 14 November 2024

## Introduction

The current survival rate for out-of-hospital cardiac arrest (OHCA) is low, at approximately 10 %.[1] However, extracorporeal cardiopulmonary resuscitation (ECPR) is associated with improved survival rates and neurological outcomes in patients with OHCA.[2–4] The SAVE-J study conducted in Japan in 2014 established that ECPR is associated with improved neurological outcomes.[4] Moreover, the American Heart Association (AHA) has proposed the implementation of ECPR for cases that meet certain criteria.[5] Additionally, previous studies have reported that high levels of partial pressure of arterial oxygen ($PaO_2$) can have a negative effect on survival and neurological outcomes in patients with OHCA.[6–10] Therefore, monitoring oxygen levels to avoid hyperoxemia after ECPR is crucial.

Furthermore, targeted temperature management (TTM) affects neurological outcomes in patients with post-cardiac arrest syndrome (PCAS) after ECPR.[11] The 2020 AHA guidelines recommend maintaining a target body temperature between 32℃ and 36℃ for at least 24 h to prevent secondary brain injury.[12–14] However, little is known about the effects of prolonged (>24 h) hyperoxemia on survival and neurological outcomes after ECPR for OHCA in patients undergoing TTM. This study assessed the impact of prolonged hyperoxemia on survival and neurological outcomes after ECPR for OHCA in patients who received TTM.

## Materials and methods

In this study, we performed a secondary analysis of the SAVE-J II study, a retrospective, multicenter registry study conducted across 36 health centers in Japan; the study included patients admitted to these centers between January 1, 2013, and December 31, 2018.[15] The study design and data collection methods for the SAVE-J II study have been previously described.[15] The inclusion criteria were age ≥ 18 years and receipt of ECPR for OHCA. The exclusion criteria were incomplete TTM and missing data on $PaO_2$ at intensive care unit (ICU) days 2–4.

TTM completion in this study was defined as cases in which the target body temperature of 32–36 ℃ was maintained constant for at least 24 h according to the 2020 AHA guidelines.[12–14] The following patient information was collected from the SAVE-J II study database: age, sex, medical history (hypertension, diabetes, dyslipidemia, cardiovascular disease, central nervous system [CNS] disease, chronic kidney disease), initial ventricular fibrillation/ventricular tachycardia (VF/VT) waveform, witnessed OHCA, bystander CPR, loss of bilateral pupillary light reflex in the prehospital setting, prehospital emergency care, return of spontaneous circulation (ROSC) on arrival at the hospital, blood lactate and hemoglobin (Hb) levels on arrival at the hospital, extrinsic, cardiogenic, low flow time, $PaO_2$ after ECPR, length of ICU stay, ventilation duration, survival at discharge, cerebral performance category (CPC) at discharge, and CPC 30 days after discharge.

Data on $PaO_2$ after ECPR were collected and averaged for ICU days 2–4. We focused on the $PaO_2$ of patients with PCAS after ECPR during ICU stay; thus, we excluded day 1 values, measured immediately after ECPR, from the mean values. The hyperoxic group had an average $PaO_2$ ≥ 300 mmHg, whereas the non-hyperoxic group had an average $PaO_2$ < 300 mmHg. The cutoff value was set at 300 mmHg based on previous findings.[10,16–17] .

The primary outcome was survival at discharge, and the secondary outcome was neurological outcomes at discharge. Regarding neurological outcomes, CPC 1 or 2 was defined as good and CPC 3–5 as poor. With regard to setting the outcomes, the survival rate and mortality rate are considered the most important factors in the field of resuscitation; hence, the primary outcome was set as survival at discharge, based on previous findings.[10,16–17] .

For statistical analyses, we first compared each item between the hyperoxic and non-hyperoxic groups. Second, the survival and mortality rates of the groups at discharge were also compared, and factors associated with survival and neurological outcomes at discharge were examined. In addition, we performed using the Mann–Whitney U and Fisher's exact tests for continuous and categorical variables, respectively. Multiple logistic regression analysis was used to examine the effect of hyperoxemia on outcomes. Patient background and clinical information variables that showed an association with survival at discharge, with a $P$ value < 0.05, were used as adjustment factors. A $P$ value < 0.05 denoted statistical significance. Multi-collinearity was tested using the variance inflation factor, with values > 10.0 indicating the presence of multi-collinearity. Statistical analyses were performed using JMP® version 16 software (SAS Institute Inc., Cary, NC).

The SAVE-J II study was registered in the University Hospital Medical Information Network Clinical Trial Registry and Japan Clinical Trial Registry (registration number: UMIN000036490). This study was approved by the Ethics Review Committee of the Yokohama City University Medical Center (Ethics No.: K190300003; approval date: March 23, 2022). Owing to the retrospective nature of this study, the need for written informed consent was waived, per the Personal Information Protection Law and National Research Ethics Guideline in Japan. The study was conducted in accordance with the principles of the Declaration of Helsinki.

## Results

Among 2,157 patients enrolled in the database, TTM was completed in 619 patients. Of these, we calculated the average $PaO_2$ without missing the values measured on ICU days 2–4 for 440 patients, among whom 28 and 412 were classified as hyperoxic and non-hyperoxic, respectively (Fig. 1).

The median age of patients was 61 (interquartile range 49–67) years. Among the 440 patients, 377 (86 %) were male, 150 (34 %) had a history of hypertension, 101 (23 %) had a history of diabetes, 72 (16 %) had dyslipidemia, 125 (28 %) had a history of cardiovascular disease, 31 (7 %) had a history of CNS disease, and 22 (5 %) had chronic kidney disease. Prehospital information included initial VF/VT waveform in 315 (72 %) cases, witnessed in 365 (83 %), bystander CPR in 259 (60 %), loss of bilateral pupillary light reflex in 294 (88 %), and prehospital emergency care in 99 (23 %). On arrival at the hospital, 27 (6 %) patients had ROSC. The mean blood lactate level was 12.4 (9.4–16.0) mmol/L, and the mean Hb level was 13.2 (11.3–14.8) g/dL. Among the cases, 97 % were cases of non-traumatic cardiopulmonary arrest (CPA), with 361 (91 %) being cases of cardiogenic CPA. In addition, 13 (3 %) were cases of traumatic CPA. The mean low flow time was 52 (40–62) min, and percutaneous coronary intervention was performed in 220 (50 %) patients. The mean length of ICU stay and ventilation duration were 11 (7–16) days and 9 (6–15) days, respectively. A total of 254 (58 %) patients survived at discharge, 138 (31 %) had a CPC of 1 or 2 at discharge, and 132 (31 %) had a CPC of 1 or 2 at 30 days after discharge. The comparison between the hyperoxic and non-hyperoxic groups revealed significant differences in the loss of bilateral paired light reflexes and survival at discharge ($P$ < 0.05) (Table 1). Factors associated with survival at discharge included age, history of diabetes, initial VF/VT waveform, hyperoxemia, Hb level on arrival, and low flow time (Table 2).

In the multivariate analysis for survival at discharge, age (odds ratio [OR] = 0.97, 95 % confidence interval [CI] [0.96–0.99], $P$ = 0.0007), initial VF/VT waveform (OR = 2.33, 95 % CI [1.46–3.73], $P$ = 0.0004), and hyperoxemia (OR = 0.15, 95 % CI [0.05–0.43], $P$ = 0.0004) were significant factors (Table 3). Similarly, the multivariate analysis for neurological outcomes at discharge showed that age (OR = 0.97, 95 % CI [0.96–0.99], $P$ = 0.0021), initial VF/VT waveform (OR = 1.77, 95 % CI [1.03–3.02], $P$ = 0.0380), Hb level at presentation (OR = 1.11, 95 % CI [1.02–1.21], $P$ = 0.0207), and hyperoxemia (OR = 0.22, 95 % CI [0.06–0.82], $P$ = 0.0235) were significant factors (Table 4). No multicollinearity was observed in all analyses.

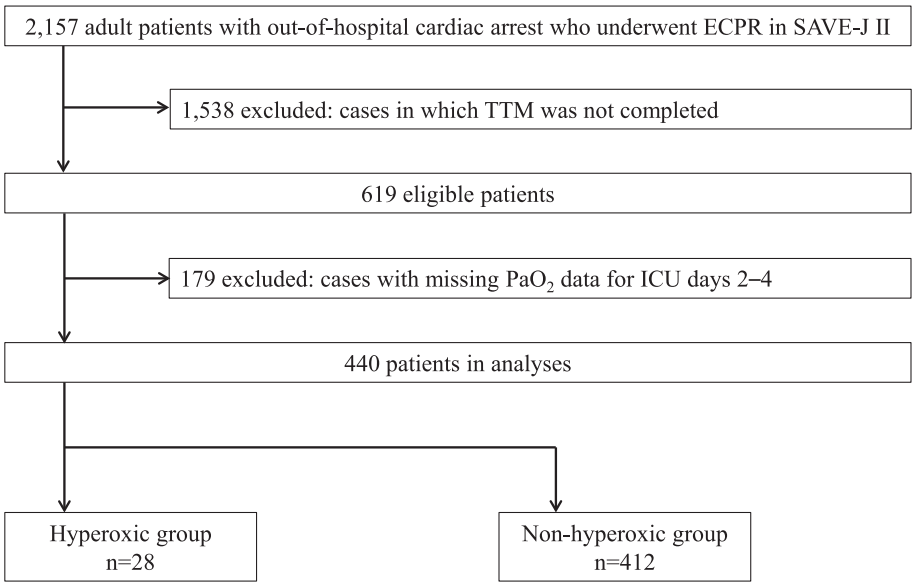


**Fig. 1.** Flow diagram depicting patient selection procedure ECPR: extracorporeal cardiopulmonary resuscitation; TTM: targeted temperature management.

**Table 1**
Comparison of variables between the hyperoxic and non-hyperoxic groups.

| Median (interquartile range)/frequency (%) | Number of valid cases (hyper/non-hyper)* | All patients (n = 440) | | Hyperoxic group (n = 28) (≥300 mmHg) | | Non-hyperoxic group (n = 412) (<300 mmHg ) | | *P* value |
|---|---|---|---|---|---|---|---|---|
| ***Patient background*** | | | | | | | | |
| Age | (28/412) | 59 | (49–67) | 63.5 | (44–69) | 59 | (49–67) | 0.5015 |
| Male (%) | (28/412) | 377 | (86 %) | 23 | (82 %) | 354 | (86 %) | 0.5769 |
| ***Comorbidities*** | | | | | | | | |
| Hypertension | (28/412) | 150 | (34 %) | 10 | (36 %) | 140 | (34 %) | 0.8393 |
| Diabetes | (28/412) | 101 | (23 %) | 6 | (21 %) | 95 | (23 %) | 1.0000 |
| Dyslipidemia | (28/412) | 72 | (16 %) | 5 | (18 %) | 67 | (16 %) | 0.7931 |
| Cardiovascular disease | (28/412) | 125 | (28 %) | 10 | (36 %) | 115 | (28 %) | 0.3899 |
| CNS disease | (28/412) | 31 | (7 %) | 1 | (4 %) | 30 | (7 %) | 0.7098 |
| Chronic kidney disease | (28/412) | 22 | (5 %) | 2 | (7 %) | 20 | (5 %) | 0.6426 |
| ***Prehospital information*** | | | | | | | | |
| Initial VF/VT waveform | (28/409) | 315 | (72 %) | 17 | (61 %) | 298 | (73 %) | 0.1915 |
| Witnessed | (28/410) | 365 | (83 %) | 23 | (82 %) | 342 | (83 %) | 0.7962 |
| Bystander CPR | (28/406) | 259 | (60 %) | 20 | (71 %) | 239 | (59 %) | 0.2338 |
| Loss of bilateral pupillary light reflex | (25/310) | 294 | (88 %) | 16 | (64 %) | 278 | (90 %) | 0.0012 |
| Prehospital emergency care | (28/412) | 99 | (23 %) | 7 | (25 %) | 92 | (22 %) | 0.8150 |
| ***Hospital arrival*** | | | | | | | | |
| ROSC | (28/411) | 27 | (6 %) | 2 | (7 %) | 25 | (6 %) | 0.6870 |
| Lac (mmol/L) | (26/380) | 12.4 | (9.4–16.0) | 13.1 | (7.8–15.1) | 12.4 | (9.4–16.0) | 0.6225 |
| Hb (g/dL) | (27/409) | 13.2 | (11.3–14.8) | 13.9 | (11.9–15.0) | 13.1 | (11.3–14.8) | 0.1951 |
| Traumatic | (24/372) | 13 | (3 %) | 0 | (0 %) | 13 | (3 %) | 1.0000 |
| Cardiogenic | (24/372) | 361 | (91 %) | 24 | (100 %) | 337 | (91 %) | 0.1508 |
| Low flow time (min) | (27/398) | 52 | (40–62) | 56 | (41–70) | 52 | (40–61) | 0.1114 |
| PCI | (28/408) | 220 | (50 %) | 13 | (46 %) | 207 | (51 %) | 0.6996 |
| ***ICU*** | | | | | | | | |
| Length of ICU stay (days) | (28/404) | 11 | (7–16) | 7.5 | (5–13.5) | 11 | (7–16) | 0.0550 |
| Ventilation duration (days) | (28/404) | 9 | (6–15) | 8.5 | (5–17.75) | 9 | (6–15) | 0.5797 |
| ***Outcome*** | | | | | | | | |
| Survival at discharge | (28/412) | 254 | (58 %) | 6 | (21 %) | 248 | (60 %) | <0.0001 |
| CPC 1 or 2 at discharge | (28/412) | 138 | (31 %) | 4 | (14 %) | 134 | (33 %) | 0.0565 |
| CPC 1 or 2 at 30 days after discharge | (28/404) | 132 | (31 %) | 4 | (14 %) | 128 | (32 %) | 0.0575 |

*(): Number of valid cases in each group; CNS: central nervous system, CPR: cardiopulmonary resuscitation, ROSC: return of spontaneous circulation; PCI: percutaneous coronary intervention, ICU: intensive care unit, CPC: cerebral performance category, VF/VT: ventricular fibrillation/ventricular tachycardia.

**Table 2**
Comparison of variables between the survival and death groups at discharge.

| Median (interquartile range)/frequency (%) | Number of valid cases (survival/death)* | All patients (n = 440) | | Survival group (n = 254) | | Death group (n = 186) | | *P* value |
|---|---|---|---|---|---|---|---|---|
| ***Patient background*** | | | | | | | | |
| Age | (254/186) | 59 | (49–67) | 57 | (46–66) | 62 | (53–69) | <0.0001 |
| Male (%) | (254/186) | 377 | (86 %) | 213 | (84 %) | 164 | (88 %) | 0.2175 |
| ***Comorbidities*** | | | | | | | | |
| Hypertension | (254/186) | 150 | (34 %) | 80 | (32 %) | 70 | (38 %) | 0.1871 |
| Diabetes | (254/186) | 101 | (23 %) | 48 | (19 %) | 53 | (28 %) | 0.0216 |
| Dyslipidemia | (254/186) | 72 | (16 %) | 44 | (17 %) | 28 | (15 %) | 0.6022 |
| Cardiovascular disease | (254/186) | 125 | (28 %) | 65 | (26 %) | 60 | (32 %) | 0.1349 |
| CNS disease | (254/186) | 31 | (7 %) | 18 | (7 %) | 13 | (7 %) | 1.0000 |
| Chronic kidney disease | (254/186) | 22 | (5 %) | 11 | (4 %) | 11 | (6 %) | 0.5097 |
| ***Prehospital information*** | | | | | | | | |
| Initial VF/VT waveform | (251/186) | 315 | (72 %) | 203 | (81 %) | 112 | (60 %) | <0.0001 |
| Witnessed | (252/186) | 365 | (83 %) | 209 | (83 %) | 156 | (84 %) | 0.8969 |
| Bystander CPR | (250/184) | 259 | (60 %) | 151 | (60 %) | 108 | (59 %) | 0.7666 |
| Loss of bilateral pupillary light reflex | (189/146) | 294 | (88 %) | 163 | (86 %) | 131 | (89 %) | 0.4016 |
| Prehospital emergency care | (254/186) | 99 | (23 %) | 60 | (24 %) | 39 | (21 %) | 0.5639 |
| ***Hospital arrival*** | | | | | | | | |
| ROSC | (254/185) | 27 | (6 %) | 17 | (7 %) | 10 | (5 %) | 0.6889 |
| Lac (mmol/L) | (236/170) | 12.4 | (9.4–16.0) | 12.7 | (9.8–16.0) | 12.2 | (9.0–16.1) | 0.3800 |
| Hb (g/dL) | (253/183) | 13.2 | (11.3–14.8) | 13.4 | (11.7–15.0) | 12.9 | (10.9–14.6) | 0.0333 |
| Traumatic | (228/168) | 13 | (3 %) | 10 | (4 %) | 3 | (2 %) | 0.2529 |
| Cardiogenic | (228/168) | 361 | (91 %) | 210 | (92 %) | 151 | (90 %) | 0.4766 |
| Low flow time (min) | (243/182) | 52 | (40–62) | 49 | (39–61) | 54 | (42–63) | 0.0431 |
| PCI | (252/184) | 220 | (50 %) | 122 | (48 %) | 98 | (53 %) | 0.3333 |
| ***ICU*** | | | | | | | | |
| Hyperoxemia** | (254/186) | 28 | (6 %) | 6 | (2 %) | 22 | (12 %) | <0.0001 |

*(): Number of valid cases in each group; **Hyperoxemia: an average $PaO_2$ of ≥ 300 mmHg.
CNS: central nervous system, CPR: cardiopulmonary resuscitation, ROSC: return of spontaneous circulation; PCI: percutaneous coronary intervention, ICU: intensive care unit, CPC: cerebral performance category, VF/VT: ventricular fibrillation/ventricular tachycardia.

**Table 3**
Multivariate analysis for survival at discharge.

| Explanatory variable | OR | 95 % CI | *P* value |
|---|---|---|---|
| Age | 0.97 | (0.96–0.99) | 0.0007 |
| Diabetes | 0.61 | (0.38–1.00) | 0.0501 |
| Initial VF/VT waveform | 2.33 | (1.46–3.73) | 0.0004 |
| Hb (arrival at hospital) | 1.04 | (0.96–1.13) | 0.3096 |
| Low flow time | 1.00 | (0.99–1.01) | 0.7151 |
| Hyperoxemia | 0.15 | (0.05–0.43) | 0.0004 |

OR: odds ratio, CI: confidence interval, VF/VT: ventricular fibrillation/ventricular tachycardia.
Hyperoxemia: an average $PaO_2$ of ≥ 300 mmHg.

**Table 4**
Multivariate analysis for neurological outcomes at discharge.

| Explanatory variable | OR | 95 % CI | *P* value |
|---|---|---|---|
| Age | 0.97 | (0.96–0.99) | 0.0021 |
| Diabetes | 0.73 | (0.43–1.26) | 0.2661 |
| Initial VF/VT waveform | 1.77 | (1.03–3.02) | 0.0380 |
| Hb (arrival at hospital) | 1.11 | (1.02–1.21) | 0.0207 |
| Low flow time | 1.01 | (1.00–1.01) | 0.1840 |
| Hyperoxemia | 0.22 | (0.06–0.82) | 0.0235 |

OR: odds ratio, CI: confidence interval, VF/VT: ventricular fibrillation/ventricular tachycardia.
Hyperoxemia: an average $PaO_2$ of ≥ 300 mmHg.

## Discussion

Prolonged hyperoxemia may affect survival and neurological outcomes at discharge in patients undergoing ECPR and TTM. Although hyperoxemia worsens survival and neurological outcomes at discharge,[6–10] most previous studies were conducted at 24 h or earlier. Here, we focused on patients with ECPR undergoing TTM and hyperoxemia exceeding 24 h. The results suggest that prolonged hyperoxemia may affect survival and neurological outcomes after ECPR for OHCA in patients who undergo TTM.

ECPR for OHCA has gained popularity in the past few years and may significantly improve survival over conventional CPR in patients with refractory CPA.[18–19] In addition, guidelines for treatment after cardiac arrest recommend TTM because it contributes to good neurological outcomes.[20] The combination of appropriate implementation of ECPR after OHCA followed by TTM may improve survival and neurological outcomes. Hyperoxemia after ECPR has been reported to worsen survival and neurological outcomes at discharge.[6–10] Therefore, $PaO_2$ levels must be properly managed after ECPR while considering oxygen toxicity.

Oxygen toxicity has been recognized since the 19th century,[21] and concepts of tissue and cellular damage by reactive oxygen species (ROS), especially from oxidative stress and ischemia–reperfusion injury, have been recently elucidated.[22] The mechanisms of failure and the role of ROS in resuscitation are as follows. When oxygen supply is disrupted, energy is quickly lost from the brain; however, when blood flow resumes, it rapidly recovers and returns to pre-ischemic values.[23] However, when ischemic tissues undergo reperfusion, excessive production of ROS, nitric oxide (NO), and other substances results in vascular endothelial and microcirculatory damage associated with inflammatory responses, leading to progressive organ damage.[24] In cells exposed to ischemic conditions, anaerobic glycolysis and acidosis due to oxygen deprivation decrease the intracellular pH and increase the intracellular $Na^+$ concentration owing to the activation of the $Na^+/H^+$ exchange system and decreased activity of $Na^+/K^+$-ATPase because of decreased

ATP levels, thereby increasing intracellular $Ca^{2+}$ concentration. This increase in $Ca^{2+}$ concentration is involved in the development of various ischemia–reperfusion disorders, such as arrhythmias and myocardial cell damage in cardiomyocytes.[24] Therefore, treatment must assume that this ischemia–reperfusion injury is systemic in patients resuscitated following cardiac arrest.

TTM, formerly known as therapeutic hypothermia, is associated with lowering further brain damage.[25–26] TTM may reduce brain metabolism by decreasing the consumption of oxygen and glucose by brain cells, thereby reducing the inflammatory response induced by reperfusion.[27] In addition to stabilizing cellular enzymes, TTM may also reduce intracranial pressure.[28] TTM is used for head trauma, stroke, meningitis, and acute respiratory distress syndrome, in addition to post-resuscitation care.[29] Thus, appropriate ECPR and subsequent TTM for OHCA are associated with improved survival and neurological outcomes. However, previous studies exploring the relationship of $PaO_2$ with survival and neurological outcomes after ECPR have been limited to patients who completed TTM. To address this limitation, we included only patients who underwent TTM. Furthermore, $PaO_2$ data in previous studies were recorded immediately after ECPR, at 30 min, and at 24 h.[7,10,30–31] Most previous studies examined $PaO_2$ within 24 h. This may be due to past studies showing that early hyperoxemia is more detrimental than late hyperoxemia[32] and that oxidative stress after cardiac arrest occurs rapidly.[33] However, within 24 h of consideration, patients who died early were included, which may have affected survival at discharge. In our study, we included patients with complete data up to day 4 and excluded those with missing data on days 2–4. Therefore, we did not include patients who died early after ECPR, and we had an advantage over previous studies in that we had a larger sample size and used longer-term $PaO_2$. The results showed that even prolonged hyperoxemic management was associated with worse survival at discharge and worse neurologic outcomes.

The main causes of death during ECPR were early circulatory failure and delayed neuropathy, as reported by Bonnemain et al..[31] Patients who died due to early circulatory failure tended to have higher initial lactate levels, whereas those who died due to delayed neuropathy tended to have lower initial lactate levels. Hyperoxemia may cause reperfusion injury in the former and hyperoxic neuropathy in the latter. In other words, initial lactate levels may influence the effects of hyperoxemia.[31] As the cause of death was not mentioned in this study, evaluating the causal relationship between hyperoxemia and death is impossible, and this should be the focus of future studies.

This study showed significant differences in hyperoxemia, age, and initial VF/VT waveform factors related to survival at discharge. Among these factors, hyperoxemia was strongly and significantly different from other factors, with an OR of 0.15. This indicates that, even with TTM, oxygen toxicity must be carefully considered, and it is possible that its management may need to be adhered to over time. In summary, minimizing brain cell metabolism through TTM and appropriate ECPR and avoiding hyperoxemia-induced toxicity not only early but also in the long term is the key to saving patients with OHCA.

This study has certain strengths. First, $PaO_2$ values were calculated using data from ICU days 2–4. Second, the sample size was large. Third, only patients with complete TTM were included in the analysis.

However, this study has some limitations. First, it was conducted in Japan; thus, the findings cannot be generalized to patients in other countries. Second, the results cannot be generalized to patients who received ECPR but not TTM. Third, ECPR protocols and management differed among health centers. Fourth, missing data may have caused selection bias. Fifth, blood sampling for blood gas analysis in patients from the database was insufficient (once daily), potentially confounding the results as variations in vital signs, ventilator settings, and other parameters can affect blood gas analysis. Sixth, the site of blood sampling was not mentioned. Because the mixing zone changes according to cardiac function during extracorporeal membrane oxygenation (ECMO), the interpretation of the results differs depending on the sampling site, even for the same patient. Seventh, although the cutoff value was set at 300 mmHg based on previous studies, whether this value was appropriate is unknown. Eighth, the percentage of patients with cardiogenic CPA was high (91 %), potentially leading to analytical bias. Therefore, the results may not reflect outcomes in patients with non-cardiogenic CPA. Ninth, extreme hyperoxemia may occur in patients with reduced cardiac function. A high $PaO_2$ level determined by blood gas analysis of the right radial artery could have been primarily obtained through ECMO flow. Thus, it is unclear whether the worse clinical outcomes are due to hyperoxemia or impaired cardiac function; detailed records of cardiac function would have provided more information on outcomes. Tenth, early hyperoxemia in patients surviving at least 4 days was not considered. Additionally, although hyperoxemia was shown to be significantly associated with the primary outcome of survival at discharge, the underlying mechanism remains unclear. Moreover, the effect of hyperoxemia on neurological outcomes may involve partial pressure of carbon dioxide and $PaO_2$. Further studies are warranted to overcome these limitations.

## Conclusion

This study showed that hyperoxemia on day 2–4 after cardiac arrest is associated with lower odds of survival to hospital discharge and survival with favorable neurological outcomes.

## Author contributions

TT was a major contributor to the writing of the manuscript. TA supported the statistical analysis. HT and AI acquired the data. HH, IT, TH, TS, and YK gave final approval for the version to be published. All authors read and approved the final manuscript.

## Authors' contributions

Tomoaki Takeda was a major contributor to the writing of the manuscript. Takeru Abe supported the statistical analysis. Hayato Taniguchi and Akihiko Inoue acquired the data. Hiroshi Honzawa, Ichiro Takeuchi, Toru Hifumi, Tetsuya Sakamoto, and Yasuhiro Kuroda gave final approval of the version to be published. All authors read and approved the final manuscript.

## CRediT authorship contribution statement

**Tomoaki Takeda:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Hayato Taniguchi:** Methodology, Formal analysis, Conceptualization. **Hiroshi Honzawa:** Project administration, Investigation, Conceptualization. **Takeru Abe:** Methodology, Formal analysis, Data curation. **Ichiro Takeuchi:** Validation, Supervision, Conceptualization. **Akihiko Inoue:** Validation, Supervision, Resources, Conceptualization. **Toru Hifumi:** Validation, Supervision, Resources, Conceptualization. **Tetsuya Sakamoto:** Validation, Supervision, Conceptualization. **Yasuhiro Kuroda:** Validation, Supervision, Conceptualization.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## 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.

## Acknowledgement

We thank all members of the SAVE-J II study group: Hirotaka Sawano, M.D., Ph.D. (Osaka Saiseikai Senri Hospital), Yuko Egawa, M. D., Shunichi Kato, M.D. (Saitama Red Cross Hospital), , Naofumi Bunya, M.D., Takehiko Kasai, M.D. (Sapporo Medical University), Shinichi Ijuin, M.D., Shinichi Nakayama, M.D., Ph.D. (Hyogo 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 Hospital of Medicine), Kunihiko Maekawa, M.D. (Hokkaido University Hospital), Takafumi Shimizu, M.D., Satoshi Nara, M.D. (Teine Keijinkai Hospital), Michitaka Nasu, M.D., Kuniko Takahashi, M.D. (Urasoe General Hospital), Yoshihiro Hagiwara, M.D., M.P.H. (Imperial Foundation Saiseikai, Utsunomiya Hospital), Shigeki Kushimoto, M.D., Ph.D. (Tohoku University Graduate School of Medicine), Reo Fukuda, M.D. (Nippon Medical School Tama Nagayama Hospital), Takayuki Ogura, M.D., Ph.D. (Japan Red Cross Maebashi Hospital), Shin-ichiro Shiraishi, 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), Tomohisa Shoko, M.D., Ph.D. (Tokyo Women's Medical University Medical Center East), Nobuya Kitamura, M.D., Ph.D. (Kimitsu Chuo Hospital), Takayuki Otani, M.D. (Hiroshima City Hiroshima Citizens Hospital), Yoshinori Matsuoka, M.D., Ph.D. (Kobe City Medical Center General Hospital), Makoto Aoki, M.D., Ph.D. (Gunma University Graduate School of Medicine), Masaaki Sakuraya, M.D., M.P.H. (JA 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), Hiroshi 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).

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## Glossary

*AHA:* American Heart Association
*CI:* confidence interval
*CNS:* central nervous system
*CPA:* cardiopulmonary arrest
*CPC:* cerebral performance category
*ECPR:* extracorporeal cardiopulmonary resuscitation
*Hb:* hemoglobin
*ICU:* intensive care unit
*OHCA:* out-of-hospital cardiac arrest
*OR:* odds ratio
*$PaO_2$:* partial pressure of arterial oxygen
*PCAS:* post-cardiac arrest syndrome
*ROS:* reactive oxygen species
*ROSC:* return of spontaneous circulation
*TTM:* targeted temperature management