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Shockable Rhythm, Gasping, Body Movement, and Pupillary Reflex as Independent Predictors of Neurological Recovery in ECPR-Treated Out-of-Hospital Cardiac Arrest

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Abstract

To determine which characteristics are associated with favourable neurological recovery among adults receiving extracorporeal cardiopulmonary resuscitation (ECPR) following out-of-hospital cardiac arrest (OHCA). This retrospective observational investigation drew on a secondary assessment of the SAVE-J II registry, incorporating information from 36 Japanese hospitals. Between 2013 and 2018, the registry documented 2157 OHCA patients treated with ECPR; 1823 fulfilled the criteria for inclusion. Adults aged ≥18 years who underwent ECPR prior to intensive care unit admission were analysed. The principal endpoint was neurological status at discharge, defined by a Cerebral Performance Category score of 1 or 2. Multivariate logistic regression was applied to explore how scene-level or arrival-time variables related to favourable outcomes. Multivariable modelling demonstrated that a shockable rhythm encountered at the scene [odds ratio (OR) 2.11; 95% confidence interval (CI) 1.16–3.95] and upon arrival (OR 2.59; 95% CI 1.60–4.30), CPR delivered by a bystander (OR 1.63; 95% CI 1.03–1.88), body movement during resuscitation (OR 7.10; 95% CI 1.79–32.90), gasping (OR 4.33; 95% CI 2.57–7.28), reactive pupils at arrival (OR 2.93; 95% CI 1.73–4.95), and male sex (OR 0.43; 95% CI 0.24–0.75) were significantly associated with neurological outcome. Shockable rhythm, intervention by a bystander, movement detected during resuscitation, gasping activity, pupillary responsiveness, and sex all showed associations with favourable neurological recovery in OHCA patients managed with ECPR.

Keywords: Extracorporeal cardiopulmonary resuscitation, Neurological outcome, Out-of-hospital cardiac arrest, Pupillary reflex, Body movement, Gasping

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) has been described as offering potential advantages for individuals experiencing out-of-hospital cardiac arrest (OHCA) when compared with conventional cardiopulmonary resuscitation (CCPR) [1-4]. More recently, three randomised trials evaluating ECPR in the OHCA setting produced conflicting conclusions [5-7]. The ARREST study ended ahead of schedule because ECPR demonstrated marked superiority over CCPR [5]. In contrast, the Prague OHCA and INCEPTION trials did not show statistically meaningful gains in survival accompanied by good neurological function [6, 7]. Given that ECPR requires substantially greater financial and resource investments than CCPR, careful identification of appropriate candidates is essential [8].Although earlier recommendations and prior investigations have proposed criteria for ECPR consideration [9, 10], the same guidance notes that the evidence base remains insufficient to clearly identify which patients are most likely to benefit [9].

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Various features—such as increasing age, the presence of an initial shockable rhythm, whether the event was witnessed, and the length of low-flow time—have been suggested as potential predictors of favourable neurological status after ECPR [11–20]. However, available studies involve relatively small populations, with the largest including roughly 500 participants and systematic reviews totalling under 1000 cases [12, 18, 20]. As a result, agreement on standardised eligibility criteria for ECPR has not yet been achieved [9].

The present work sought to determine predictors linked to favourable neurological outcomes by examining data from the multicentre, retrospective SAVE-J II registry (Study of Advanced Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan). Identifying such predictors is a key step toward developing consistent selection strategies and unified ECPR protocols.

Materials and Methods

Ethical approval and consent to participate

The SAVE-J II project was listed in both the University Hospital Medical Information Network Clinical Trials Registry and the Japanese Clinical Trial Registry (UMIN000036490). Approval for the study was granted by the Institutional Review Board of Kagawa University (approval number: 2018–110) as well as by each participating site, including the Nippon Medical School Hospital (approval number: R1-05–1125). The present analysis was additionally authorised by the Institutional Review Board of the Nippon Medical School Hospital (approval number: B-2022–633). Because the study relied on retrospective data, informed consent requirements were waived across all centres. Reporting followed the STROBE guidelines for observational studies.

Study design

This investigation represents a secondary analysis of the SAVE-J II registry, a retrospective multicentre dataset capturing cases of OHCA treated with ECPR in 36 Japanese institutions between 1 January 2013 and 31 December 2018 [21].

Study sample

Eligible participants were adults (age ≥18 years) who experienced OHCA and underwent ECPR before admission to the intensive care unit. Exclusion criteria included: (1) initiation of veno-arterial extracorporeal membrane oxygenation (ECMO) after ICU admission; (2) discontinuation of the cannulation procedure before ECMO activation due to return of spontaneous circulation (ROSC); (3) cardiac arrest caused by external factors such as hypoxia, intoxication, trauma, suffocation, drowning, or similar non-cardiac events; (4) ROSC achieved either upon arrival at the hospital or at the start of ECMO; (5) transfer from another medical facility; and (6) missing neurological outcome data. Hypothermia was defined as a recorded temperature below 30 °C or a physician's diagnosis at the time of arrival [21].

Data collection

The SAVE-J II registry was created after the fact by extracting information from hospital charts at every participating site, using a unified reporting template developed by the coordinating investigator. Patient information was derived from documented histories, examinations, and clinical records. Each site's clinicians and staff entered data independently. Whenever an entry appeared incomplete or inconsistent, the central study team contacted the institution directly—by email, telephone, virtual meetings, or on-site visits—to clarify or correct the record. Details regarding the hospitals involved and their selection standards have been described previously [22]. The dataset included demographic information (age and sex), cause of cardiac arrest, first documented rhythm in the field and on arrival, whether the event was witnessed, whether bystander CPR was performed, whether defibrillation was attempted, ROSC status, presence of gasping, pupil size, light reflex on arrival, initial blood gas parameters (pH, oxygen and carbon dioxide tensions, lactate, haemoglobin), rhythm immediately before ECMO cannulation, and multiple timing variables relevant to ECPR. Shockable rhythm at first assessment was defined as ventricular fibrillation, pulseless ventricular tachycardia, or a rhythm judged shockable by automated external defibrillation administered by EMS personnel [21]. ROSC required persistent palpable circulation for at least one minute [21]. Transient ROSC referred to any return of pulse or blood pressure before arrival that was lost again upon hospital presentation [23]. Body movement during resuscitation was defined as a Glasgow Coma Scale–Motor Score ≥2 among patients still in cardiac arrest at hospital arrival [24].

Outcome variables included ICU stay, total hospitalization length, survival status, and neurological recovery. Time intervals were computed as: (1) EMS activation to hospital arrival, (2) hospital arrival to ECMO initiation, and (3) EMS activation to ECMO initiation. Estimated low-flow time was defined based on arrest location: if the arrest occurred inside the ambulance, the interval was measured from arrest onset to ECMO start; for all other locations, it was measured from the EMS call to ECMO initiation [21]. Because the various time-related intervals showed multicollinearity (assessed using variance inflation factors), only the estimated low-flow time was retained for regression modelling. Defibrillation was also excluded from the adjusted models because of its strong clinical dependency on having an initial shockable rhythm.

Outcome

The main outcome of interest was neurological status at discharge, evaluated using the cerebral performance category (CPC) scale [25]. A CPC score of 1 or 2 was classified as favourable, whereas scores of 3–5 were considered unfavourable.

Statistical analysis

Baseline characteristics and ECPR outcomes were summarised using standard descriptive methods. Continuous variables were reported as medians with interquartile ranges; categorical variables were presented as counts and percentages. Between-group comparisons used the Mann–Whitney U test for continuous data and either the chi-squared test or Fisher's exact test for categorical data. Logistic regression (univariate and multivariable) was applied to identify predictors of favourable neurological recovery. Only variables known to clinicians from first patient contact through ECMO initiation were eligible for inclusion.

The multivariable models adjusted for: age, sex, arrest aetiology (cardiogenic versus non-cardiogenic), initial rhythms at the scene and on arrival (shockable vs non-shockable), witnessed collapse, bystander CPR, transient ROSC, estimated low-flow duration, presence of purposeful movement, gasping on arrival, pupil size and reflex, and initial blood gas values. These variables were chosen based on prior work indicating potential prognostic relevance in ECPR-treated OHCA [1, 10, 11, 13–19]. Findings considered clinically important were highlighted in the Results, and those with strong statistical effects (odds ratio >2 or <0.5) were elaborated upon in the Discussion. Two-sided P values <0.05 defined statistical significance. Analyses were conducted using R version 4.2.0 (R Foundation for Statistical Computing).

Results and Discussion

During the study period (2013–2018), 2157 adults with OHCA treated with ECPR were initially registered in the SAVE-J II database. After applying the predefined criteria, 1823 patients remained for the final analysis **(Figure 1)**.

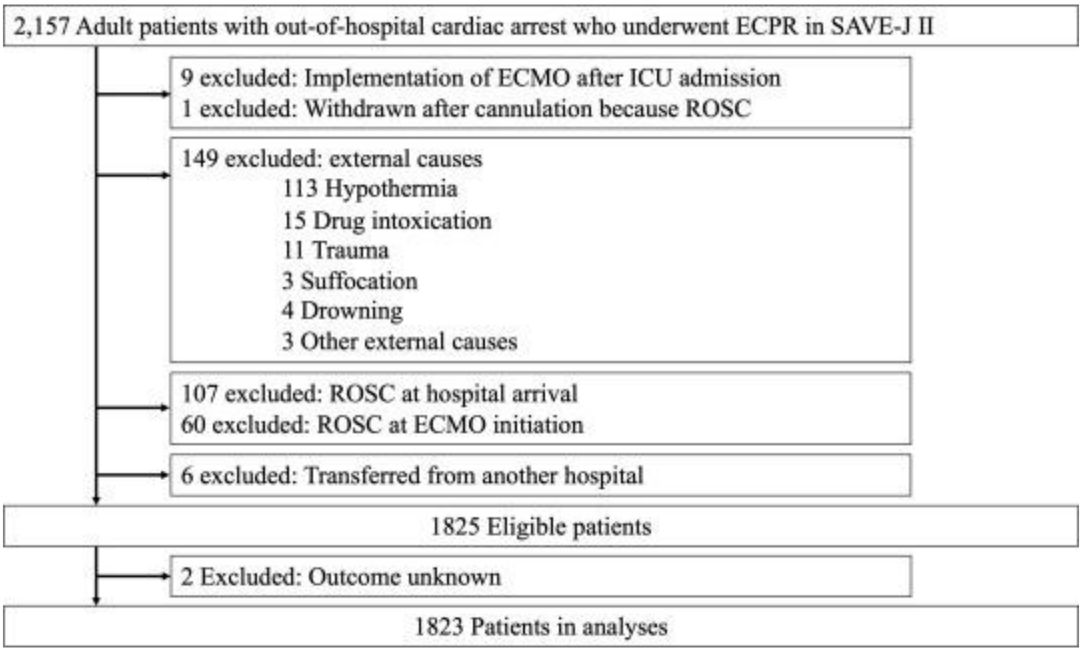

Figure 1. Flow chart depicting application of inclusion and exclusion criteria. Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation; SAVE-J II, Study of Advanced Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan; ICU, intensive care unit; ROSC, return of spontaneous circulation

Patient characteristics

Table 1 compares baseline findings in relation to neurological status at discharge. Patients who ultimately had favourable neurological recovery showed a markedly higher proportion of shockable rhythms recorded both at the event location (81.6% vs 61.7%) and when arriving at the hospital (73.5% vs 41.9%). Transient ROSC also occurred more frequently in this group (16.2% vs 8.3%). Gasping was observed far more often among those with favourable outcomes (25.6% vs 6.9%). In addition, they typically exhibited smaller pupillary diameters [4.0 (3.0–5.0) mm vs 5.0 (4.0–6.0) mm] and a greater likelihood of having a present pupillary reflex (28.2% vs 6.5%).

Table 1. Baseline demographic and clinical data [a].

Characteristic	Unfavorable neurological outcome (CPC 3–5) (n = 1589)	Favorable neurological outcome (CPC 1–2) (n = 234)	Total (n = 1823)
Age, years	61 (50–69)	56 (45–66)	60 (49–69)
Male sex	1339 (84.3)	187 (79.9)	1526 (83.7)
Etiology of cardiac arrest			
Cardiogenic	1215 (76.5)	205 (87.6)	1420 (77.9)
Non-cardiogenic	258 (16.2)	19 (8.1)	277 (15.2)
Initial recorded rhythm at scene			
Non-shockable	594 (37.4)	40 (17.1)	634 (34.8)
Shockable	981 (61.7)	191 (81.6)	1172 (64.3)
Cardiac arrest witnessed	1232 (77.5)	200 (85.5)	1432 (78.6)
Bystander-initiated CPR	879 (55.3)	165 (70.5)	1044 (57.3)
Transient return of spontaneous circulation before hospital	132 (8.3)	38 (16.2)	170 (9.3)
Estimated low-flow duration, minutes	55 (46–67)	51 (41–62)	55 (45–67)
Cardiac rhythm on hospital arrival			
Non-shockable	918 (57.8)	62 (26.5)	980 (53.8)
Shockable	666 (41.9)	172 (73.5)	838 (46.0)
Spontaneous body movements during ECPR/resuscitation	11 (0.7)	13 (5.6)	24 (1.3)
Gasping observed on hospital arrival	110 (6.9)	60 (25.6)	170 (9.3)
Pupil size on hospital arrival, mm	5.0 (4.0–6.0)	4.0 (3.0–5.0)	5.0 (4.0–6.0)
Pupillary light reflex present on arrival	103 (6.5)	66 (28.2)	169 (9.3)
Arterial blood gas on hospital arrival			
pH	6.92 (6.81–7.03)	6.96 (6.83–7.09)	6.93 (6.81–7.04)
$PaCO_2$, mmHg	69.5 (49.5–90.0)	56.3 (44.6–71.4)	67.4 (48.6–88.5)
PaO_2, mmHg	79.5 (34.0–278.0)	136.7 (47.1–327.1)	82.0 (34.8–289.0)
Serum lactate, mg/dL	116.1 (91.8–143.0)	120.6 (87.4–144.2)	117.0 (91.1–144.0)
Hemoglobin, g/dL	12.7 (10.8–14.5)	13.5 (11.7–15.4)	12.8 (10.9–14.6)

ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; Hb, haemoglobin.
Missing values: Age = 1, Sex = 0, Aetiology = 126, Initial rhythm at scene = 17, Witnessed = 6, Bystander CPR = 28, Transient ROSC = 28, Estimated low-flow time = 108, Rhythm on arrival = 5, Motor response during resuscitation = 18, Gasping = 214, Pupil size = 221, Pupillary reflex = 240, pH = 99, $PaCO_2$ = 102, PaO_2 = 110, Lactate = 212, Hb = 64.
[a]Continuous variables are summarised as medians with quartiles; categorical variables as counts and percentages. [b]Low-flow time was determined based on arrest location: for arrests occurring inside an ambulance, the interval spanned from arrest onset to ECMO initiation; otherwise, it was calculated from the EMS call to ECMO initiation.

Clinical outcome data

Table 2 displays clinical outcomes across neurological groups. Of the total cohort, 234 individuals achieved a favourable neurological status. Median ICU stay for the entire sample was 3 (1–10) days, but those with favourable outcomes remained substantially longer [11 (8–16) vs 2 (1–7) days, P < 0.001]. The same pattern appeared in the overall hospital admission duration, which had an overall median of 3 (1–17) days but extended markedly among the favourable-outcome group [35 (22–53) vs 2 (1–8) days, P < 0.001]. Overall in-hospital mortality was 75.0%.

Table 2. Clinical results according to neurological outcome [a].

Outcome / Variable	Unfavorable neurological outcome (CPC 3–5) (n = 1589)	Favorable neurological outcome (CPC 1–2) (n = 234)	P value	Total (n = 1823)
Duration of ICU stay, days	2 (1–7)	11 (8–16)	<0.001	3 (1–10)

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Duration of ICU stay among hospital survivors, days	14 (10–19)	11 (8–16)	<0.001	12 (9–17)
Total length of hospital stay, days	2 (1–8)	35 (22–53)	<0.001	3 (1–17)
Length of hospital stay among patients surviving to discharge, days	37 (22–58)	35 (22–53)	0.321	36 (22–56)
In-hospital mortality, n (%)	1368 (87.1)	0 (0)	<0.001	1368 (75.0)

[a]Medians with quartiles for continuous variables; counts and percentages for categorical variables.

Logistic regression analysis for favourable neurological outcomes at discharge

We employed univariate and multivariable logistic regression to identify factors linked to favourable neurological outcomes **(Table 3)**. In adjusted analyses, several parameters showed significant associations: a shockable rhythm noted at the scene [OR 2.11; 95% CI 1.16–3.95] and at hospital arrival [OR 2.59; 95% CI 1.60–4.30], bystander-initiated CPR [OR 1.63; 95% CI 1.03–1.88], observable motor activity during resuscitation [OR 7.10; 95% CI 1.79–32.90], gasping when first evaluated [OR 4.33; 95% CI 2.57–7.28], and the presence of a pupillary light response [OR 2.93; 95% CI 1.73–4.95]. Male sex showed an inverse association [OR 0.43; 95% CI 0.24–0.75].

Table 3. Logistic regression findings for favourable neurological outcomes.

Variable	**Multivariable adjusted analysis**		**Univariate analysis**	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 1-year increase)	0.97 (0.95–0.98)	<0.001	0.97 (0.97–0.98)	<0.001
Male sex	0.43 (0.24–0.75)	0.002	0.74 (0.53–1.06)	0.09
Etiology of cardiac arrest				
Cardiogenic	Reference		Reference	
Non-cardiogenic	1.03 (0.46–2.16)	0.95	0.44 (0.26–0.69)	<0.001
Initial rhythm at scene				
Non-shockable	Reference		Reference	
Shockable	2.11 (1.16–3.95)	0.017	2.89 (2.05–4.18)	<0.001
Witnessed arrest	1.04 (0.59–1.88)	0.90	1.85 (1.27–2.80)	0.002
Bystander-performed CPR	1.63 (1.03–1.88)	0.039	1.98 (1.47–2.70)	<0.001
Transient ROSC before hospital arrival	1.67 (0.86–3.16)	0.12	2.15 (1.44–3.15)	<0.001
Estimated low-flow duration (per 1-min increase)	0.99 (0.98–1.00)	0.10	0.99 (0.98–0.99)	0.002
Cardiac rhythm on hospital arrival				
Non-shockable	Reference		Reference	
Shockable	2.59 (1.60–4.30)	<0.001	3.82 (2.83–5.23)	<0.001
Spontaneous body movement during resuscitation	7.10 (1.79–32.90)	0.007	8.42 (3.72–19.4)	<0.001
Gasping observed on hospital arrival	4.33 (2.57–7.28)	<0.001	4.52 (3.15–6.43)	<0.001
Pupil diameter on arrival (per 1-mm increase)	0.76 (0.65–0.89)	<0.001	0.66 (0.59–0.74)	<0.001
Pupillary light reflex present on arrival	2.93 (1.73–4.95)	<0.001	6.22 (4.35–8.89)	<0.001
Arterial blood gas on arrival				
pH (per 0.1-unit increase)	0.25 (0.06–1.06)	0.059	3.43 (1.55–7.58)	<0.001
$PaCO_2$ (per 1-mmHg increase)	0.98 (0.97–0.99)	<0.001	0.99 (0.98–0.99)	<0.001
PaO_2 (per 1-mmHg increase)	1.00 (1.00–1.00)	0.84	1.00 (1.00–1.00)	0.017
Serum lactate (per 1-mg/dL increase)	1.00 (0.99–1.00)	0.25	1.00 (1.00–1.00)	0.92
Hemoglobin (per 1-g/dL increase)	1.21 (1.10–1.34)	<0.001	1.15 (1.09–1.21)	<0.001

OR, odds ratio; CI, confidence interval; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; GCS-MS, Glasgow Coma Scale–Motor Score; Hb, haemoglobin.
[a]Low-flow time definitions were identical to those described in Table 1.

In this retrospective cohort analysis, we identified links between favourable neurological recovery and several clinical observations documented at hospital entry. The key contribution of this work is its broad evaluation of known prognostic indicators using a large dataset, allowing clearer estimation of their influence on neurological outcomes. Factors showing a positive association with good neurological status included shockable rhythms both prehospital and on arrival, bystander CPR, visible body movement during resuscitation, gasping, and preserved pupillary reflexes at arrival. Male sex was negatively associated with favourable outcomes. Although body movement, gasping, and pupillary reflexes carried high odds ratios, these findings were uncommon, occurring in only 1.3–9.3% of cases.

Compared with the inclusion criteria used in three earlier randomised trials of ECPR [5-7], our cohort differed in several ways: fewer witnessed arrests (78.6%), lower bystander CPR rates (57.3%), and more non-shockable rhythms at the scene (34.8%). As a result, only 12.8% of patients achieved favourable neurological outcomes, lower than the 20–40% reported in trials applying stricter enrolment rules [5- 7]. Still, we found that beyond shockable rhythms, signs of life—body movement during resuscitation, gasping, and pupillary reflex—were also linked to better outcomes. Their overall frequency remained low (1.3–9.3%), yet including such elements in selection criteria might improve the proportion of patients achieving favourable recovery.

Our findings showed that shockable rhythms, spontaneous movement, gasping, and pupillary responses exhibited the strongest odds ratios among variables measurable between arrival and ECMO initiation. Prehospital shockable rhythm remained a robust predictor. Any occurrence of a shockable rhythm between collapse and ECMO cannulation may reflect salvageable physiology. A recent randomised trial demonstrated that gasping during CPR correlates with favourable long-term survival and neurological status [25]. Gasping observed during transport also predicts neurological recovery among OHCA patients receiving ECPR [26]. Gasping likely reflects partial preservation of cerebral perfusion. When combined with shockable rhythms, gasping acts as a powerful natural biomarker for predicting favourable outcomes [25]. Pupillary reflexes during and after resuscitation likewise hold prognostic value [27], as they directly reflect brainstem activity [27]. Prior work has highlighted the usefulness of "signs of life," a collective term encompassing movement, gasping, and pupillary response [15, 20]. Integrating multiple such findings may enable more accurate outcome prediction.

A recent systematic review summarised prognostic factors associated with favourable neurological outcomes in ECPR-treated OHCA patients [28], analysing 29 studies with 7,397 participants [28]. Our results align with identified predictors such as sex, shockable rhythm, and bystander CPR, while adding further evidence regarding signs of life—including body movement, gasping, and pupillary reflexes. These findings support informed ECPR selection and underscore the need for further investigation. Importantly, this study focused on the potential advantages of applying broad inclusion criteria rather than restrictive exclusion criteria; the absence of these favourable predictors should not automatically preclude ECPR.

Limitations

This study has several limitations. First, the retrospective observational nature introduces risks of selection and recall bias. Second, ECPR initiation was determined by clinicians at each site without predefined criteria, meaning patients with predicted poor outcomes may have been excluded. Third, no comparison group without ECPR was available, preventing assessment of treatment effectiveness. Fourth, long-term neurological follow-up was not collected. Fifth, time-dependent variables such as ROSC count or total ROSC duration before ECMO initiation were unavailable, limiting interpretation of transient ROSC quality. Low-flow time estimates may also differ from true values, especially in patients with intermittent ROSC. Sixth, our cohort differs from typical ECMO populations: 34.8% initially had non-shockable rhythms, 61.2% received defibrillation prehospital, and 57.3% had bystander CPR. These differences may limit generalisability. Seventh, missing data may have introduced uncertain bias. Lastly, the presumed cardiogenic or non-cardiogenic cause of arrest may have been misclassified.

Conclusion

This multicentre retrospective cohort study indicates that shockable rhythm, bystander CPR, spontaneous movement during resuscitation, gasping, pupillary response, and sex correlate with favourable neurological outcomes among OHCA patients undergoing ECPR. These results may help refine patient selection for ECPR. Prospective studies are needed to confirm these observations.

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