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Clinical paper

Association between gasping and survival among out-of-hospital cardiac arrest patients undergoing extracorporeal cardiopulmonary resuscitation: The SOS-KANTO 2017 study

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Abstract

Aim: This study aimed to assess the association between gasping and survival among out-of-hospital cardiac arrest (OHCA) patients requiring extracorporeal cardiopulmonary resuscitation (ECPR).

Methods: This prospective, multicenter, observational study was conducted between 2019 and 2021. We categorized adult patients requiring ECPR into those with or without gasping prior to hospital arrival. The primary outcome was the 30-day survival. We performed multivariable logistic regression analyses fitted with generalized estimating equations and subgroup analyses based on the initial rhythm and age.

Results: Of the 9,909 patients with OHCA requiring ECPR, 332 were enrolled in the present study, including 92 (27.7%) and 240 (72.3%) with and without gasping, respectively. The 30-day survival was higher in patients with gasping than in those without gasping (35.9% [33/92] vs. 16.2% [39/240]). In the logistic regression analysis, gasping was significantly associated with improved 30-day survival (adjusted odds ratio: 3.01; 95% confidence interval, 1.64–5.51). Subgroup analyses demonstrated similar trends in patients with an initial non-shockable rhythm and older age.

Conclusions: Gasping was associated with improved survival in OHCA patients requiring ECPR, even those with an initial non-shockable rhythm and older age. Clinicians may select the candidates for ECPR appropriately based on the presence of gasping.

Keywords: Out-of-hospital cardiac arrest, Cardiopulmonary resuscitation, Extracorporeal cardiopulmonary resuscitation, Gasping, Sign of life

Background

Out-of-hospital cardiac arrest (OHCA) is a severe medical condition with a low survival rate (i.e., 8%).[1] In particular, refractory cardiac arrest, defined as prolonged cardiac arrest without return of spontaneous circulation (ROSC), is associated with poor clinical outcomes (i.e., < 4%).[2,3]

In patients with OHCA, extracorporeal cardiopulmonary resuscitation (ECPR) can be initiated to restore perfusion and prevent further hypoxic brain injury, followed by the identification and treatment of the underlying cause of cardiac arrest.[4] However, the benefits of ECPR in cases of refractory cardiac arrest are still unclear.[56] Considering the invasiveness, cost, and need for substantial human resources with ECPR,[8–10] its indications should be considered carefully.[7]

Gasping is common in the first few minutes after cardiac arrest[8] and is associated with improved survival in OHCA patients.[89] A meta-analysis reported that OHCA patients with gasping were

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3.5-fold more likely to survive than those without gasping.[10] However, the association between gasping and survival in OHCA patients receiving ECPR is unclear. A recent study showed that an initial shockable rhythm and younger age are important prognostic factors in OHCA patients undergoing ECPR.[11] However, it remains unclear whether gasping is associated with improved survival in OHCA patients undergoing ECPR who have an initial non-shockable or older age.

Therefore, this study evaluated the relationship between gasping and survival in OHCA patients receiving ECPR, particularly those with an initial non-shockable rhythm or older age. We hypothesized that gasping was associated with improved survival in OHCA patients requiring ECPR, even those with an initial non-shockable rhythm or older age.

Methods

The SOS-KANTO 2017 study was a prospective, multicenter (42emergencyhospitals), observational study conducted among OHCA patients in the Kanto area of Japan between September 2019 and March 2021. The SOS-KANTO study group has investigated multiple clinical issues related to OHCA since 2002 and regularly performs prospective observational studies with preregistered research hypotheses.[12] Previous report examined the average 30-day survival rate in the SOS-KANTO 2017 study between before and after Covid-19 pandemic and the rate was 5.6~7.2%,[13] which was comparable to outcome among other developed countries.[1] The institutional review board of each participating hospital approved the study protocol, including the institutional review board of Gunma University Hospital (HS2019-004). The requirement of informed consent was waived because of the anonymous nature of the data used. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and a complete checklist has been provided in Supplementary Table 1.

Study setting and design

Cardiac arrest was defined as the cessation of mechanical heart activity, confirmed by the absence of signs of circulation. The study included OHCA patients undergoing ECPR. We excluded patients aged $\leq$ 16 years and those with traumatic cardiac arrest or subarachnoid hemorrhage. As an observational study using an existing dataset, formal sample calculations were not conducted, and the inclusion of as many patients as possible was prioritized.

Study variables

Out-of-hospital information regarding OHCA was prospectively collected by emergency medical service (EMS) providers using the standard Utstein-style template.[14] In-hospital information was collected by the treating physicians at each institution. The collected data included: age; sex; out-of-hospital information, including witness status, presence of bystander, receipt of public defibrillation, initial cardiac rhythm on EMS arrival, and presence of gasping prior to admission; in-hospital information, including presence of gasping at admission and cardiac rhythm at admission; time variables, including time of witness of cardiac arrest, emergency call, cardiopulmonary resuscitation (CPR) initiation, and return of spontaneous circulation; therapeutic measures; dates of admission and discharge; and cause of cardiac arrest determined by treating physicians. The presence of gasping prior to admission was confirmed and prospectively recorded by EMS providers, and the presence of gasping on admission was recorded by treating physicians. Low-flow time was defined as the interval between CPR initiation and ROSC. The time of ROSC was recorded before and after hospital arrival. Data on the survival status and Pittsburgh Cerebral Performance Categories for neurological function were recorded at hospital discharge and 30 days after admission. We categorized eligible patients into those with and without gasping prior to admission.

Outcomes

The primary outcome was the 30-day survival. The secondary outcome was favorable neurological outcome at 30 days, defined as Cerebral Performance Categories 1 (good recovery) and 2 (moderate disability).[15]

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables are presented as numbers and percentages.

We used a multiple imputation method to handle missing data. Missing data were replaced with a set of substituted plausible values by creating 20 completely filled datasets using a Markov chain Monte Carlo algorithm, known as chained equations imputation.[16] Multiple imputation assumes that data are missing at random and that any systematic differences between the missing and observed values can be explained by differences in the observed data.[17]

To evaluate the associations between gasping and study outcomes, we performed multivariable logistic regression analyses fitted with generalized estimating equations (GEE) to adjust for patient demographics and out-of-hospital information (age, sex, witness, bystander CPR, public defibrillation, ROSC on EMS arrival, and initial shockable rhythm), while also adjusting for within-hospital clustering. Regarding GEE, we used a binomial distribution, employed the logit link function, and assumed an exchangeable working correlation structure.

Subgroup analyses were performed based on age (<65 or $\geq$ 65 years), initial cardiac rhythm (shockable or non-shockable), and timing of ECPR initiation (prior to or after ROSC) to evaluate the association between gasping and primary outcome. Additionally, sensitivity analysis was conducted by creating a mixed effects model with complete case analysis to assess the robustness of the primary results. In this model, the same variables as those in the primary analysis were adjusted as fixed effect variables, and the hospital's unique identifier was adjusted as a random effect variable.

Statistical analyses were performed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) and the used packages were mice for multiple imputation, geepack for GEE and lme4 for mixed effects. All estimates were calculated with 95% confidence intervals (CIs). The α level was set at 0.05 for statistical significance.

Results

Fig. 1 presents a flow diagram for patient selection. We identified 332 eligible patients, including 92 with gasping and 240 without gasping. The proportions of missing data on gasping and 30-day survival were 28.9% and 2.4%, respectively. Among patients with gasping prior to admission (n = 92), gasping at admission was observed in 20 patients (22%).

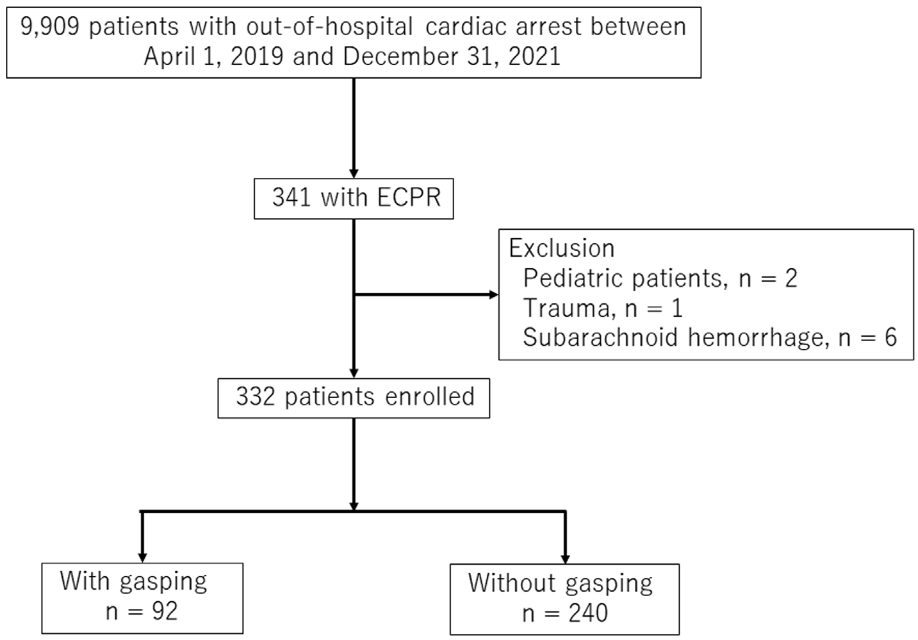

Fig. 1 – Flow diagram of patient selection. ECPR, extracorporeal cardiopulmonary resuscitation.

The median age was 58 years (IQR: 49–69), and 83% were males. The proportion of initial shockable rhythm was 53.9% (179/332), and the timing of ECPR initiation prior to ROSC was 75.3% (250/332). The proportion of 30-day survival was 21.7% (72/332).

Table 1 presents the baseline characteristics of patients in both groups. The proportions of witnesses, bystander CPR, public defibrillation, and initial shockable rhythm in patients with gasping were higher than in those without gasping. Furthermore, the proportions of ROSC were 13.0% and 6.2% in patients with and without gasping, respectively.

Outcome analyses

The proportion of 30-day survival was higher in patients with gasping than in those without gasping (35.9% vs. 16.2%). The proportion of a favorable neurological outcome was also higher in patients with gasping than in those without gasping (15.2% vs. 4.6%). Table 2 presented the unadjusted and adjusted models of logistic regression

Table 1 – Characteristics of ECPR patients with and without gasping at the time of EMS arrival.

Variables	Overall (n = 332)	With gasping (n = 92)	Without gasping (n = 240)
Demographics			
Age, years, median (interquartile range)	58 (49–69)	58 (50–70)	58 (49–68)
Sex, male n (%)	276 (83.1)	78 (84.8)	198 (82.5)
Cause of arrest, cardiogenic, n (%)	291 (87.6)	84 (91.3)	207 (86.2)
Out-of-hospital information, n (%)			
Witness cardiac arrest	263 (79.2)	79 (85.9)	184 (76.7)
Bystander CPR	159 (47.8)	47 (51.1)	112 (46.7)
Public defibrillation	25 (7.5)	10 (10.9)	15 (6.2)
ROSC on EMS arrival	56 (16.8)	16 (17.4)	40 (16.7)
Initial shockable rhythm	179 (53.9)	54 (58.7)	125 (52.1)
Cardiac rhythm at admission, n (%)			
ROSC	27 (8.1)	12 (13.0)	15 (6.2)
VF or pulseless VT	123 (37.0)	31 (33.6)	92 (38.3)
Pulse electrical activity	104 (31.3)	32 (34.8)	72 (30.0)
Asystole	78 (23.4)	17 (18.5)	61 (25.4)
Low-flow duration, min	37 (19–58)	37 (12–57)	37 (20–59)
VA-ECMO timing			
Prior to ROSC	250 (75.3)	69 (75.0)	181 (75.4)
After ROSC	82 (24.7)	23 (25.0)	59 (24.6)

ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia; VA-ECMO, veno-arterial extracorporeal membrane oxygenation

Table 2 – Full models of multivariable logistic regression analysis for 30-day survival.

Model	Unadjusted		Adjusted	
Variables	OR	95% CI	OR	95% CI
Age	1.00	0.98–1.02	1.00	0.98–1.02
Sex, male	1.57	0.82–3.01	1.70	0.85–3.41
Witness	0.89	0.47–1.69	0.61	0.34–1.09
Bystander CPR	1.59	0.94–2.69	1.63	0.85–3.10
Public defibrillation	1.45	0.58–3.61	1.10	0.45–2.65
ROSC on EMS arrival	1.57	0.82–3.01	2.28	1.05–4.95
Initial shockable rhythm	1.26	0.74–2.13	1.73	0.84–3.55
Gasping	2.88	1.67–4.98	3.01	1.64–5.51

ORs, odds ratios; CIs, confidence intervals; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EMS, emergency medical services.

analysis for 30-day survival. Gasping was significantly associated with an improved 30-day survival in both the unadjusted model(odds ratio [OR]: 2.88; 95% confidence interval [CI]: 1.67–4.98 and the adjusted model (OR: 3.01; 95% CI: 1.64.5.51). Table 3 presented the unadjusted and adjusted models of logistic regression analysis for favorable neurological outcome at 30 days. Gasping was significantly associated with an improved favorable neutological outcome in both the unadjusted model (OR: 3.74; 95% CI: 1.63–8.57) and the adjusted model (OR: 3.98; 95% CI: 1.41–11.20). Sensitivity analysis showed the result remained unchanged when using the mixed effects model (Supplemental Table 2).

Subgroup analyses

Fig. 2 presents the results of subgroup analyses. Gasping was associated with an improved 30-day survival, regardless of age and timing of ECPR. Furthermore, gasping was also associated with an increased 30-day survival among OHCA patients with an initial non-shockable rhythm.

Discussion

This multicenter, prospective, observational study demonstrated that gasping was associated with an improved 30-day survival and favorable outcomes among OHCA patients receiving ECPR. Furthermore, the 30-day survival was also improved in patients with an initial non-shockable rhythm or older age.

Our research had two advantages by taking advantage of the characteristics of prospective, multicenter study. First, we included the entire population of OHCA patients requiring ECPR. A previous study only focused on young patients undergoing ECPR who had an initial shockable rhythm.[11] Our study demonstrated that gasping was associated with improved 30-day survival among OHCA patients with an initial non-shockable or older age. Although ECPR is effective for patients with an initial non-shockable rhythm,[20–22] the indication for ECPR in these patients is unclear. Furthermore, the latest guidelines have not included OHCA patients with an initial non-shockable rhythm as potential candidates for ECPR.[18] Our results suggest that gasping is an indication for ECPR even among OHCA patients with an initial non-shockable rhythm. Our study also revealed that gasping was associated with improved survival in older OHCA patients receiving ECPR. A recent study demonstrated that the survival rate after cardiac arrest was significantly decreased in patients aged $\geq$ 65 years.[19] Our study results suggest that gasping may be an indication for ECPR in patients aged $\geq$ 65 years. Second, we adjusted for both patient- and hospital-level covariates using multivariable regression analyses fitted with GEE. Currently, the initiation of ECPR depends on institutional protocols.[20,21] A recent study demonstrated variations in ECPR application among OHCA patients in Japan, such as the presence of formal protocols, specialty of cannulator, and ECPR location.[20]

Previous studies have reported that gasping is not only an indicator of survival among OHCA patients, but also has beneficial cardiopulmonary effects. Gasping augments pulmonary gas exchange,[22] improves cardiac output and cardiac contractility,[23]

Table 3 – Full models of multivariable logistic regression analysis for favorable neurological outcome at 30 days.

Model	Unadjusted		Adjusted	
Variable	OR	95% CI	OR	95% CI
Age	1.02	0.98–1.05	1.02	0.99–1.04
Sex, male	2.54	1.04–6.21	3.66	1.66–8.08
Witness	1.05	0.38–2.92	0.57	0.21–1.53
Bystander CPR	3.78	1.47–9.72	3.99	1.63–9.78
Public defibrillation	2.59	0.81–8.25	1.10	0.32–3.71
ROSC on EMS arrival	0.40	0.09–1.78	0.45	0.05–3.97
Initial shockable rhythm	1.90	0.79–4.54	1.71	0.49–5.93
Gasping	3.74	1.63–8.57	3.98	1.41–11.20

ORs, odds ratios; CIs, confidence intervals; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; EMS, emergency medical services.

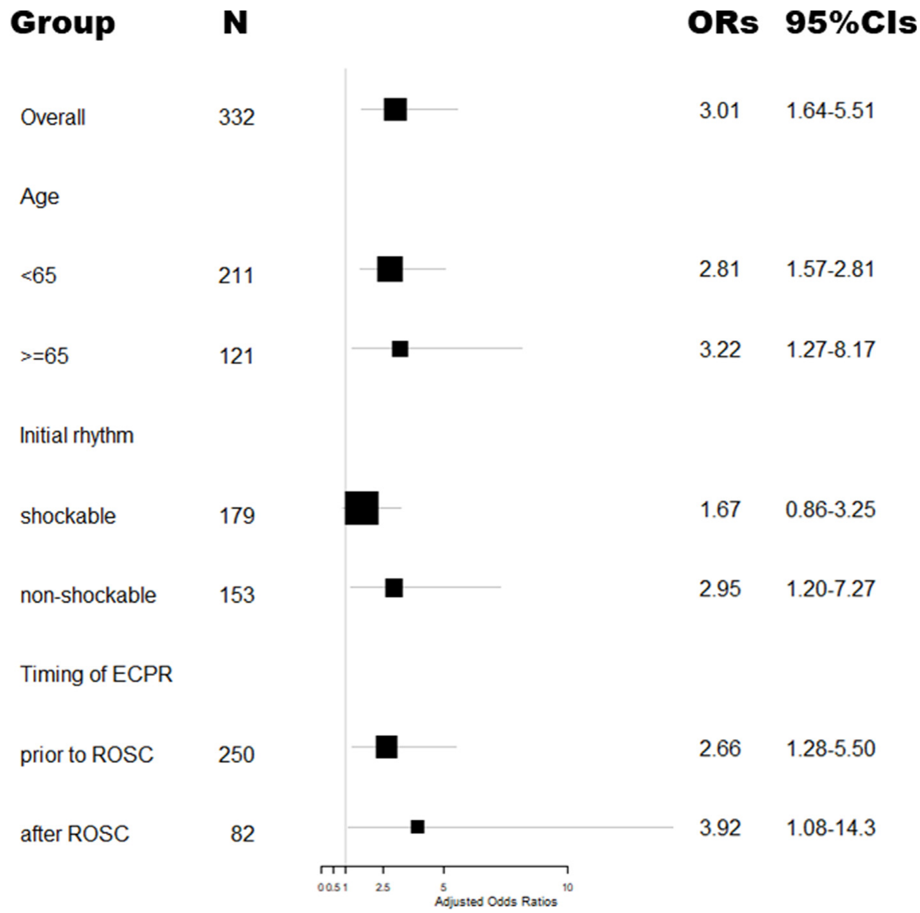

Fig. 2 – Multivariable logistic regression analyses for 30-day survival in patient subgroups. ECPR, extracorporeal cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; OR, odds ratio; CI, confidence interval.

and decreases intracranial pressure, while increasing the cerebral perfusion pressure.[24] These beneficial cardiopulmonary effects may have improved the prognosis of OHCA patients with an initial non-shockable rhythm or older age, who are considered to have a poor prognosis.

The clinical implication of our study is that the selection of ECPR candidates can be improved by incorporating the gasping status into the decision-making process. Okada et al. recently developed scoring systems based on multiple prognostic factors to better identify potential ECPR candidates,[25] and reported difficulties in predicting better outcomes in patients with an initial non-shockable rhythm.[26] These scoring systems may be improved by incorporating the gasping status of patients.

We acknowledge several limitations of our study. First, although gasping was associated with improved survival, causality cannot be inferred because this study was based on an observational design. However, randomized controlled trials may not be feasible for assessing the association between gasping and outcomes among OHCA patients requiring ECPR. Second, the presence of gasping prior to admission was recorded by EMS providers, based on a partially subjective evaluation, which may potentially lead to misclassification of the gasping group. Additionally, approximately 30% of gasping had missingness. We performed multiple imputation with GEE and complete case analysis with mixed effects model, and confirmed the results were not altered.

Conclusions

Gasping was associated with improved survival in OHCA patients receiving ECPR. Furthermore, similar results were observed even among patients with an initial non-shockable rhythm and age $\geq$ 65 years. Clinicians may select the candidates for ECPR more appropriately by considering the presence of gasping.

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CRediT authorship contribution statement

Makoto Aoki: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shotaro Aso:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Yohei Okada:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Akira Kawauchi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Tomoko Ogasawara:** Writing – review & editing, Supervision, Project administration. **Takashi Tagami:** Writing – review & editing, Visualization, Supervision, Project administration. **Yusuke Sawada:** Writing – review & editing, Writing – original draft, Investigation. **Hideo Yasunaga:** Writing – review & editing, Methodology, Formal analysis. **Nobuya Kitamura:** Writing – review & editing, Visualization, Project administration. **Kiyohiro Oshima:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yohei Okada has received a research grant from the JSPS-KAKENHI and the ZOLL Foundation, and overseas scholarships from the FUKUDA Foundation for Medical Technology and the International Medical Research Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100622.

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