

Original Article

Variability of extracorporeal cardiopulmonary resuscitation practice in patients with out-of-hospital cardiac arrest from the emergency department to intensive care unit in Japan

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Aim: A lack of known guidelines for the provision of extracorporeal cardiopulmonary resuscitation (ECPR) to patients with out-of-hospital cardiac arrest (OHCA) has led to variability in practice between hospitals even in the same country. Because variability in ECPR practice has not been completely examined, we aimed to describe the variability in ECPR practice in patients with OHCA from the emergency department (ED) to the intensive care units (ICU).

Methods: An anonymous online questionnaire to examine variability in ECPR practice was completed in January 2020 by 36 medical institutions who participated in the SAVE-J II study. Institutional demographics, inclusion and exclusion criteria, initial resuscitation management, extracorporeal membrane oxygenation (ECMO) initiation, initial ECMO management, intra-aortic balloon pumping/endo-tracheal intubation/management during coronary angiography, and computed tomography criteria were recorded.

Results: We received responses from all 36 institutions. Four institutions (11.1%) had a hybrid emergency room. Cardiovascular surgery was always involved throughout the entire ECMO process in only 14.7% of institutions; 60% of institutions had formal inclusion criteria and 50% had formal exclusion criteria. In two-thirds of institutions, emergency physicians carried out cannulation. Catheterization room was the leading location of cannulation (48.6%) followed by ED (31.4%). The presence of formal exclusion criteria significantly increased with increasing ECPR volume (P for trend <0.001). Intra-aortic balloon pumping was routinely initiated in only 25% of institutions. Computed tomography was routinely carried out before coronary angiography in 25% of institutions.

Conclusions: We described the variability in ECPR practice in patients with OHCA from the ED to the ICU.

Key words: Emergency department, extracorporeal cardiopulmonary resuscitation, out-of-hospital cardiac arrest

INTRODUCTION

THE PREVALENCE OF extracorporeal cardiopulmonary resuscitation (ECPR) in patients with out-of-hospital cardiac arrest (OHCA) has been rapidly increasing worldwide, and countries in East Asia, such as Japan, Korea, and Taiwan, are leading in the field of ECPR, followed by European countries and the USA.¹

Although ECPR has been provided in many countries, guidelines do not determine the details of ECPR practice. Therefore, ECPR practice varies in each individual hospital even in the same country, and the variability of ECPR practice has been examined only in Korea and the USA.^{2,3} However, as several studies have reported ECPR since the 1980s in Japan^{4,5} and Sakamoto *et al.* undertook a prospective observational study (i.e., the SAVE-J study) to evaluate the effectiveness of ECPR and conventional cardiopulmonary resuscitation (CPR) for patients with OHCA,⁶ the variability

of ECPR practice has not been fully described. At present, we are preparing for the next SAVE-J II study to provide real-world data on ECPR in Japan and to examine the indications, management, and prediction of neurologic outcomes.

This study aimed to describe the variability of ECPR practice in patients with OHCA from the emergency department (ED) to the intensive care unit (ICU) based on their responses on questionnaires from institutions in the SAVE-J II study and also to clarify the points for improvement in ECPR practice through the present study.

METHODS

THE INSTITUTIONAL REVIEW board approved this survey-based study (approval number 19-R155). The local committee waived the approval of review boards in participating institutions because the present questionnaire survey did not contain individual patients' information.

Study setting

We prepared a questionnaire to examine the variability of ECPR practice from ED to ICU. The basic questionnaire was distributed to 36 medical institutions who participated in the SAVE-J II study (UMIN-ID, UMIN000036490), which is a retrospective multicenter observational study to examine the effectiveness of ECPR in Japan. The survey

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was carried out using an anonymous questionnaire system through the Internet⁷ (Appendix S1) and was distributed in January 2020 and collected by February 2020.

Data collection

In the basic questionnaire, the following parameters were recorded: demographics of institutions, inclusion and exclusion criteria, initial resuscitation management, drug administration for persistent ventricular fibrillation/pulseless ventricular tachycardia, chest compression methods during the cannulation process, venoarterial extracorporeal membrane oxygenation (VA-ECMO) initiation, initial ECMO management, intra-aortic balloon pumping (IABP)/endotracheal intubation/management during coronary angiography (CAG), and computed tomography (CT) criteria. The questions are shown in Appendix S1.

Definitions

Hybrid emergency room

Based on the concept of combining “examination” and “treatment” in the same space, the hybrid emergency room (ER) is equipped with a multislice interventional radiology–CT system in the ER.^{8,9} Emergency physicians (EPs) carry out ECPR.

Study end-points

The primary end-point of the present study was to describe the variability of ECPR practice in patients with OHCA from ED to ICU in Japan.

Primary data analysis

Data are summarized as absolute values and percentages. Demographics of institutions, inclusion and exclusion criteria, initial resuscitation management, ECMO initiation, initial ECMO management, IABP/endotracheal intubation/management during CAG, and CT criteria are described. Missing data were not imputed. We used the Cochran–Armitage test for trend of categorical variables. Statistical analyses were undertaken using JMP statistical software (version 12; SAS Institute, Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant for all analyses.

RESULTS

WE RECEIVED RESPONSES from all 36 institutions (Fig. 1). Most participating institutions were

distributed in the surrounding areas of big cities such as Tokyo and Osaka.

Demographics of institutions

The details of study institution demographics are described in Table 1. Four institutions (11.1%) who responded had a hybrid ER. The leading historical number of ECPR per year was 10–19 cases, followed by 5–9 cases. Cardiovascular surgery always involved the entire ECMO process in only 14.7% of institutions.

Inclusion and exclusion criteria

Approximately 60% of institutions had a formal inclusion criterion, and no limitation on age was provided in 40% of institutions (Table 2). Half of the institutions had a formal exclusion criterion. No institutions responded that obesity, cachexia, or initial rhythm pulseless electrical activity were the exclusion criteria of ECPR in the present study, and only 10% of institutions responded that ECPR was not carried out in patients with unwitnessed or no bystander CPR.

Initial resuscitation management

Approximately 90% of institutions initiated blood drawing during CPR, and C-reactive protein and fibrinogen degradation products/d-dimer were evaluated in nearly all institutions (Table 3).

Extracorporeal membrane oxygenation initiation

Vascular access was obtained percutaneously using ultrasound (47.2%), followed by percutaneously without ultrasound (44.4%). No institution reported cut-down vascular access (Table 4). In two-thirds of institutions, EPs carried out the cannulation. The catheterization room for CAG (48.6%) was the leading location of cannulation, followed by the ED (31.4%).

With regard to the typical cannula size range, 19–21 Fr was used in approximately 70% of institutions for venous ECMO and 15–17 Fr was used in >70% of institutions for arterial ECMO.

Initial ECMO management

Only one-quarter of institutions routinely placed distal limb perfusion catheters (Table S1). Seventy percent of EPs actually carried out the placement of distal limb perfusion catheters.

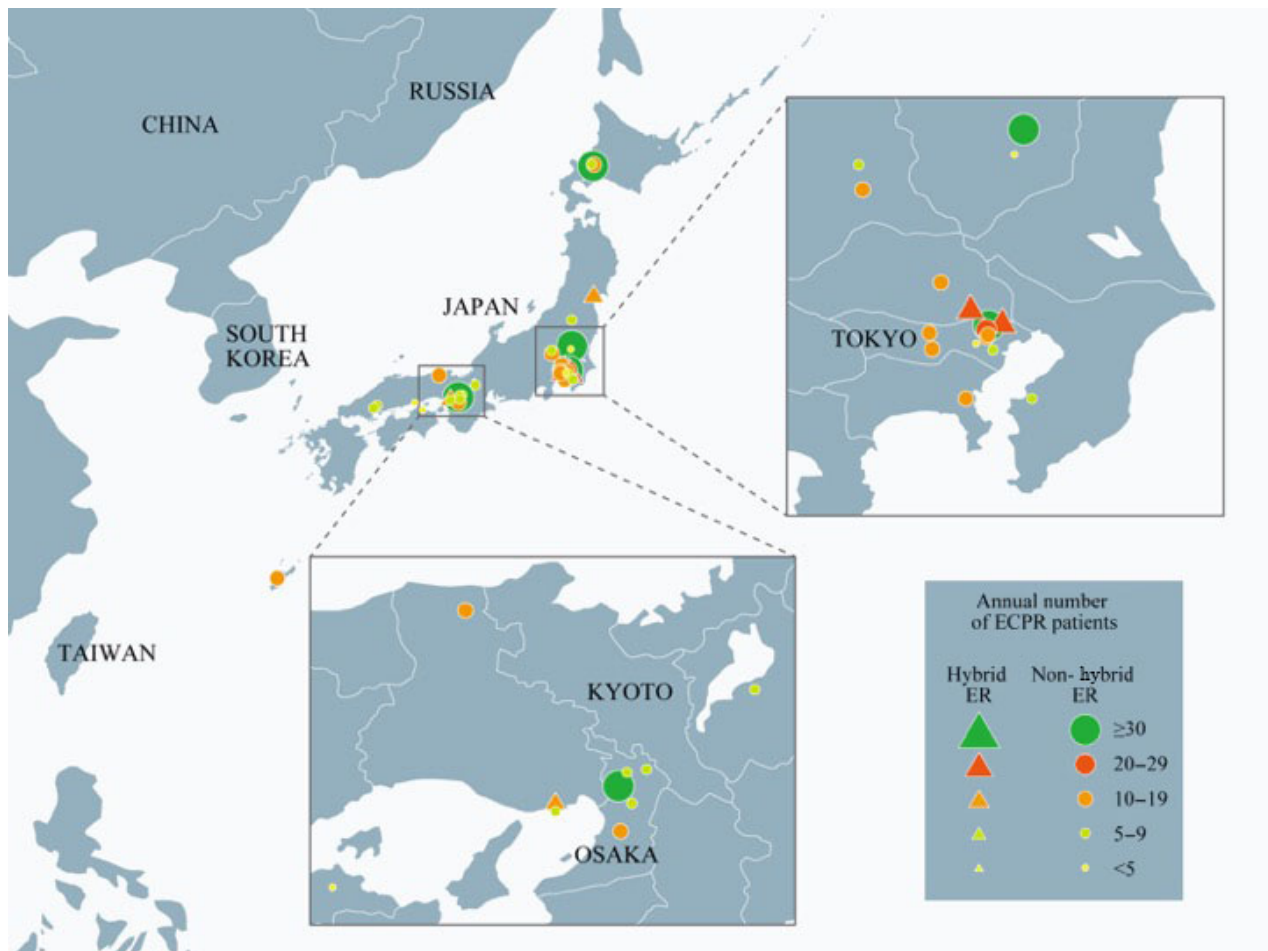


Fig. 1. Thirty-six medical institutions in Japan were included in the SAVE-J II study. ECPR, extracorporeal cardiopulmonary resuscitation; ER, emergency room.

Intra-aortic balloon pumping/endotracheal intubation/management during CAG

Intra-aortic balloon pumping is routinely initiated in only 25% of institutions. In approximately 10% of institutions, IABP was placed by EPs, who are responsible for airway management during CAG (Table S2).

Computed tomography

Computed tomography was routinely undertaken before CAG in 25% of institutions, and nine institutions routinely carried out CT after CAG (Table S3). Head and whole-body non-contrast CTs were mainly carried out with consideration of contrast CT as needed in both situations (before and after CAG).

Trend of presence of formal inclusion and exclusion criteria for ECPR volume

The presence of formal exclusion criteria significantly increased with increasing ECPR volume (P for trend <0.001; Fig. 2A), but the presence of formal inclusion criteria did not (P for trend = 0.646; Fig. 2B).

DISCUSSION

THE DETAILS OF VA-ECMO, such as inclusion and exclusion criteria, initial resuscitation management, ECMO initiation, initial ECMO management, IABP/endotracheal intubation/management during CAG, and CT criteria differed in each participating institution.

Table 1. Demographics of institutions that participated in the SAVE-J II study

Variable	Level	%	N
Hybrid ER versus nonhybrid ER	Hybrid ER	11.1	4
	Non-hybrid ER	88.9	32
Historical rate of ECPR per year	<5/year	11.1	4
	5–9/year	33.3	12
	10–19/year	36.1	13
	20–29/year	8.3	3
Historical rate of arrival of CPA patients per year in the emergency department	<100/year	16.7	6
	100–199/year	36.1	13
	200–299/year	22.2	8
	≥300/year	25.0	9
Historical rate of VA-ECMO in patients with circulatory failure after ROSC per year	<5/year	44.4	16
	5–9/year	38.9	14
	10–19/year	13.9	5
Service involved throughout the entire ECMO process	≥20/year	2.8	1
	Emergency medicine	Yes, always	91.7
Cardiology	Yes, as needed	5.6	2
	No	2.8	1
	Yes, always	52.8	19
Cardiovascular surgery (missing obs. = 2)	Yes, as needed	44.4	16
	No	2.8	1
	Yes, always	14.7	5
Radiology (missing obs. = 2)	Yes, as needed	61.8	21
	No	23.5	8
	Yes, always	3.0	1
	Yes, as needed	29.4	10
	No	67.6	23

CPA, cardiopulmonary arrest; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ER, emergency room; obs., observations; ROSC, return of spontaneous circulation; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Table 2. Inclusion and exclusion criteria of extracorporeal cardiopulmonary resuscitation reported by 36 Japanese medical institutions

Variable	Level	%	n
Formal inclusion criteria	Yes	61.1	22
Age (years) (included number = 10)	<80	10.0	1
	<75	50.0	5
	No limitation of age	40.0	4
Time from witnessed to hospital arrival (min) (included number = 10)	<30	10.0	1
	<45	30.0	3
	<60	20.0	2
	No limitation of time	40.0	4
Formal exclusion criteria	Yes	50.0	18
Exclusion criteria (any) (included number = 18)	Age	55.6	10
	Obesity	0.0	0
	Cachexia	0.0	0
	Impaired ADL	66.7	12
	Apparent dialysis access	22.2	4
	Concomitant major trauma	5.6	1
	Suspected drug overdose	0.0	0
	Unwitnessed	11.1	2
	No bystander CPR	11.1	2
	Initial rhythm PEA	0.0	0
	Initial rhythm Asystole	22.2	4
	Time from collapse to hospital arrival	27.8	5
	Terminal state of cancer	77.8	14
DNAR	88.9	16	
Terminal state of pre-existing disease	72.2	13	
Children	5.6	1	

ADL, activities of daily living; CPR, cardiopulmonary resuscitation; DNAR, do not attempt resuscitation; PEA, pulseless electrical activity.

Demographics of institutions

In the present study, approximately 10% of institutions had the so-called hybrid ER. Several studies on ECPR in hybrid ER have been recently reported.^{8,10} This system has the possibility of seamless ECPR from ECMO induction to CAG, followed by percutaneous coronary intervention without any patient transfer.¹⁰ Regarding the historical rate of ECPR, more than one-third of institutions carried out ECPR on 10–19 patients/year, which was higher than that of the former study with 40% of institutions having 0–1 patients/year in the USA in 2016.³ Recently, excellent data regarding the effectiveness of ECPR for OHCA patients has been

reported,¹¹ and ECPR will continue to be provided in institutions around the world.

Inclusion and exclusion criteria

Less than half of institutions do not limit the age in the inclusion criteria of ECPR. This is closely related to the national health insurance system in Japan.¹² Because the Japanese government mainly pays the medical bills, physicians in charge do not pay attention to the unpaid medical bills in the ECPR initiation. A systematic review provides

Table 3. Initial resuscitation management reported by 36 Japanese medical institutions

Variables	Level	%	<i>n</i>
Timing of blood drawing	During CPR (from arrival to VA-ECMO initiation)	86.1	31
	After VA-ECMO initiation	13.9	5
Blood drawing item (any)	CBC	100	36
	Chemistry	100	36
	Blood gas	100	36
	CRP	97.2	35
	FDP/D-dimer	94.4	34
	AT-III	38.9	14
Defibrillation for persistent VF/pulseless VT	Following ACLS algorithm	33.3	12
	If DC was applied three times in the prehospital setting, no initiation of further DC	13.9	5
	Limited use of DC	11.9	4
	No further initiation of DC	13.9	5
	Decision by physicians in charge	27.8	10
Drug administration (epinephrine, amiodarone) for persistent VF/pulseless VT	Following ACLS algorithm	72.2	26
	Limited use	8.3	3
	No use	5.6	2
	Use epinephrine only	0.0	0
	Use amiodarone only	8.3	3
	Others	5.6	2
Chest compression methods during the cannulation process	Mechanical	33.3	12
	Hand	44.4	16
	Both (mechanical and hand)	22.2	8

ACLS, advanced cardiovascular life support; AT-III, antithrombin III; CBC, complete blood count; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; DC, direct current; FDP, fibrin/fibrinogen degradation products; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.

age cut-offs, usually <75 years,¹³ and Otani *et al.* also recently addressed the inclusion criteria of those aged ≤75 years.¹⁴ Goto *et al.* examined elderly patients with OHCA who were treated with ECPR and concluded that ECPR might not be beneficial for patients aged ≥70 years who had OHCA.¹⁵ Thus, the limitation of age <75 years in the inclusion criteria of ECPR could be warranted. Regarding exclusion criteria, only 50% of institutes have a formal exclusion criterion, which is a lower figure than that in the USA or Korea.² The establishment of inclusion and exclusion criteria is fundamentally required to provide a universally acceptable algorithm in ECPR. To date, it is difficult to create specific inclusion and exclusion criteria due to low certainty of evidence.

Initial resuscitation management

Blood drawing, including not only complete blood count and blood gas but also C-reactive protein and fibrinogen degradation products/D-dimer, was undertaken during CPR in almost all institutions in the present study. This mainly

reflects the characteristics of clinical practice in Japan.^{16,17} Because Otani *et al.* reported that the D-dimer level could predict major bleeding in ECPR on admission,¹⁸ evaluating these markers could have some significance in predicting the outcomes.

Extracorporeal membrane oxygenation initiation

Venous cut-down was not used to obtain vascular access in this study. More than one-third of institutions use this procedure for vascular access in the USA.³ We speculate that because the number of obese patients is relatively low in Japan compared with other developed countries,¹⁹ vascular access can be obtained percutaneously. Regarding the role of the cannulator, EPs carried out cannulation in two-thirds of institutions, but the proportion is only 10% in the USA.³ This is mainly due to the unavailability of cardiothoracic surgeons throughout the entire ECMO process in Japan. Approximately 50% of institutions in the present survey carried out cannulation in the catheterization room, whereas cannulation

Table 4. Extracorporeal membrane oxygenation (ECMO) initiation reported by 36 Japanese medical institutions

Variables	Level	%	N
Vascular access obtained by	Percutaneous access with ultrasound	47.2	17
	Percutaneous access without ultrasound	44.4	16
	Cut-down	0	0
	Modified (percutaneous + cut-down)	5.6	2
	Others	2.8	1
Role of cannulator (check all that apply)	Emergency medicine	66.7	24
	Cardiology	63.9	23
	Vascular surgery	0	0
Locations where cannulation has been performed at the institution (missing obs. = 1)	Emergency department	31.4	11
	Hybrid ER	8.6	3
	Catheter room	48.6	17
	Operating room	2.9	1
	Others	8.6	3
Cannula selection: typical arterial cannula size range (Fr)	<15	5.6	2
	15–17	72.2	26
	19–21	16.7	6
Cannula selection: typical venous cannula size range (Fr)	23–25	5.6	2
	<15	5.6	2
	15–17	5.6	2
Priming of ECMO (check all that apply)	19–21	69.4	25
	23–25	19.4	7
	Clinical engineering technologist	94.4	34
Timing of priming of ECMO	Emergency medicine	11.1	4
	Cardiology	5.6	2
	Before patient arrival	11.1	4
	Within 5 min after arrival	69.4	25
	5–10 min after arrival	16.7	6
	After 10 min	2.8	1

ER, emergency room; obs., observations.

was undertaken mainly in the ED and operating room in the USA.³ With regard to the typical cannula size range, 19–21 Fr was used in venous ECMO and 15–17 Fr was used in arterial ECMO in approximately 70% of institutions in the present study. However, 23–25 Fr is used in venous and 19–21 Fr is used in arterial ECMO in approximately 50% of institutions in the USA.³ Safe cannulation using larger catheters could be preferable for ECPR in Japan.

Initial ECMO management

With regard to the placement of distal limb perfusion catheters, routine catheter placement was carried out in only 25%

of institutions, whereas >90% was routinely initiated in the USA.³ This is mainly due to patient size, degree of obesity,¹⁹ and catheter size.²⁰ Limb ischemia is less likely due to smaller catheter use without distal limb perfusion flows compared with Europe or North America.^{20,21} Approximately 90% of distal limb perfusion catheters are used by cardiothoracic surgeons in the USA, whereas >70% are used by Eps, including acute care surgeons trained in cardiovascular surgery, in Japan.³

Intra-aortic balloon pumping/endotracheal intubation/management during CAG

Intra-aortic balloon pumping is recognized as the bundle treatment option used during ECPR,^{13,22} however, to our knowledge, ours is the first questionnaire to determine the details of IABP. Intra-aortic balloon pumping was routinely initiated in only 25% of institutions, initiated as needed in 60%, and in 15% for cardiac origin only. This could reflect the variance of ECPR strategies in each participating hospital.

Computed tomography

Japan has the highest number of CT scanners worldwide,²³ thus, CTs were commonly used in the present survey and might be useful for diagnosis and prognostic prediction in ECPR.²⁴

Current issues and future challenges in ECPR in Japan

Regarding the low rates of inclusion and exclusion criteria, only high-volume centers tend to have the latter. Considering the cost of ECPR, universally acceptable exclusion criteria need to be accepted, even at low-volume centers. Establishing inclusion and exclusion criteria is a first step toward organizing a universal algorithm. To this end, the results of the upcoming SAVE-J II study, with >2,000 ECPR cases, will therefore provide a robust conclusion in terms of the inclusion and exclusion criteria.

Approximately 10% of institutions had a hybrid ER, and the number of hybrid ERs will continue to increase. The advantages of ECPR initially carried out in a hybrid ER are considered to be earlier initiation of ECMO, safer procedures (cannulation under the X-ray system), and shorter time required for the completion of percutaneous coronary intervention. These advantages could contribute to the development of better outcomes in Japan. Moreover, considering these advantages, the inclusion/exclusion criteria and management strategies in those facilities could be optimized.

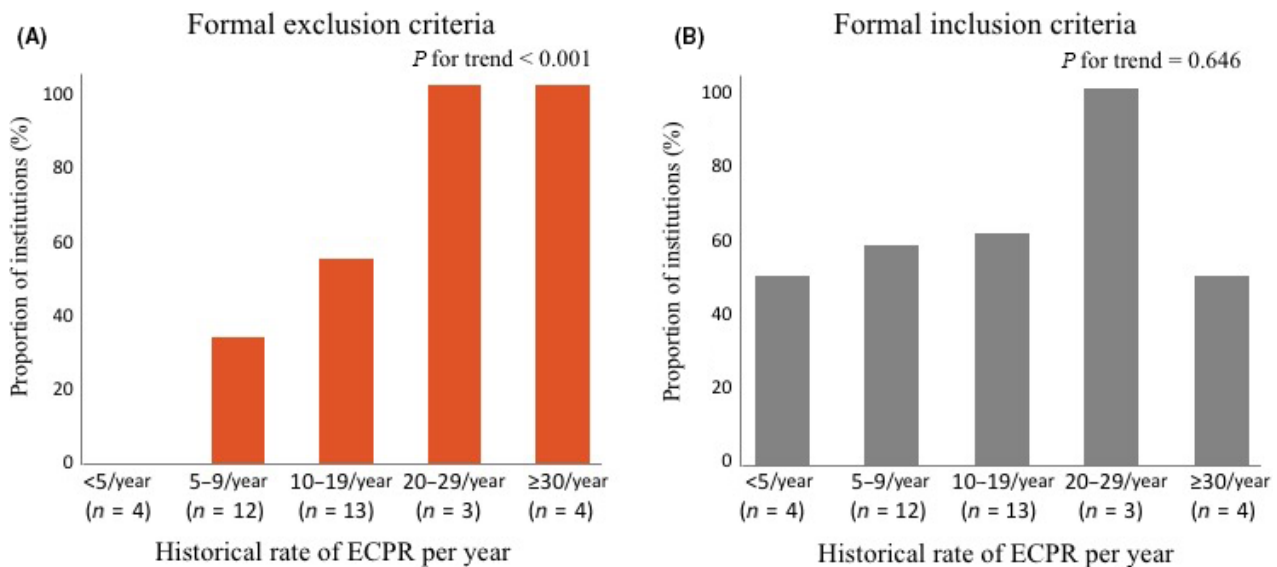


Fig. 2. Trend of presence of (A) inclusion and (B) exclusion criteria for extracorporeal cardiopulmonary resuscitation (ECPR) volume in 36 medical institutions in Japan.

Although aggressive blood drawing and routinely obtained CT before admittance to the ICU are among Japan's ECPR strengths, more data are required to make the argument more effective in ECPR. As the present study showed that EPs carried out the cannulation in 66.7% of the surveyed institutions, the findings should be applicable to the USA and other countries. As mentioned above, the results of the SAVE-J II study will also determine the association between cannulation by EPs in the ED and complications or good outcomes.

Limitations

This study had several limitations. First, because this is a questionnaire survey, more detailed clinical practice on ECPR was not obtained. For example, three-choice questions answerable with "Yes, always", "Yes, as needed", and "No" did not obtain detailed information. Second, although 36 institutions were included in the present study, a previous report suggested that 69 institutes were capable of ECPR in Japan.²⁵ Therefore, not all Japanese ECPR facilities took part in the present study. However, almost all high-volume ECPR centers are included in the present SAVE-J II study, and responses were received from all 36 participating facilities. Finally, ICU management was not evaluated in the current study; therefore, an advanced questionnaire containing questions arising from ICU management of ECPR is being designed for future studies.

CONCLUSIONS

THE VARIABILITY OF ECPR practice in patients with OHCA from ED to ICU has been described. We have some advantages with regard to hospital facilities, such as the availability of hybrid ER and CT; therefore, clinical research using the data of those Japanese facilities needs to be better coordinated. Extracorporeal cardiopulmonary resuscitation practice varied; therefore, establishing the inclusion/exclusion criteria will be required to provide the most appropriate and standardized management strategies in ECPR practice.

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DISCLOSURE

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Animal studies: N/A.

Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Details of the questionnaire regarding extracorporeal cardiopulmonary resuscitation practice in patients with out-of-hospital cardiac arrest in Japan.

Table S1. Initial extracorporeal membrane oxygenation (ECMO) management. CT, computed tomography; ICU, intensive care unit.

Table S2. Intra-aortic balloon pumping (IABP)/endotracheal intubation/management during coronary angiography (CAG). CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; PAC, pulmonary artery catheter.

Table S3. Computed tomography. CAG, coronary angiography.