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Clinical paper

Impact of first documented rhythm on cost-effectiveness of extracorporeal cardiopulmonary resuscitation

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Abstract

Objectives: Recommendations for extracorporeal cardiopulmonary resuscitation (ECPR) state that appropriate patient selection is important for the sake of efficacy and cost-effectiveness of ECPR. It is not known whether first documented rhythm plays a prominent role in economic outcomes of patients with cardiac arrest who received ECPR.

Methods and results: We reviewed the medical records of 120 consecutive patients who received extracorporeal membrane oxygenation (ECMO) assisted CPR due to refractory circulatory collapse between 2008 and 2016 in Urasoe General Hospital. The patients presented with ventricular fibrillation or pulseless ventricular tachycardia (VF/VT; n = 59, 49.2%) or with asystole or pulseless electric activity (ASY/PEA; n = 61, 50.8%) as the first documented rhythm. Multivariate logistic regression analysis identified shorter duration from collapse to ECMO initiation (odds ratio, 1.95 per 10 min; 95% confidence interval, 1.32–2.89, p = 0.001), bystander CPR (odds ratio, 5.53; 95% confidence interval, 1.36–22.5, p = 0.017), and first documented rhythm of VF/VT (odds ratio, 3.93; 95% confidence interval, 1.30–11.8, p = 0.015) as clinical predictors for neurologically intact survival. Total hospital cost per life saved by ECPR for ASY/PEA was approximately twice that for VF/VT ($213,656 vs. $101,669). ECPR yielded Quality adjusted life years (QALYs) of 3.32 at a mean total cost of $39,634 for VF/VT and QALYs of 1.17 at a mean cost of $35,609 for ASY/PEA. The cost per QALYs was $11,081 for VF/VT and $29,447 for ASY/PEA. The incremental cost-effectiveness ratio of ECPR vs. conventional CPR was estimated to be $ 16,246 per QALY gained.

Conclusion: ECPR for patients presenting with VF/VT was found to be highly cost-effective and ECPR for patients presenting with ASY/PEA was borderline cost-effective.

Keywords: Extracorporeal cardiopulmonary resuscitation, Cardiac arrest, Cost-effectiveness

Introduction

Early delivery of defibrillation shock improves chances of survival for cardiac arrest victims with witnessed shockable rhythms, such as ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT).[1,2] Previous studies have confirmed the poor prognosis of patients with refractory circulatory collapse who have shock-resistant rhythms or non-shockable rhythms, such as pulseless electrical activity (PEA) or asystole treated with conventional cardiopulmonary resuscitation (CCPR) with chest compression and administration of inotropic agents.[3–6]

Observational studies have reported that the use of extracorporeal cardiopulmonary resuscitation (ECPR) improved the survival rate of cardiac arrest victims compared to CCPR.[7,8] However, there is no data on the use of ECPR from randomized controlled trials. The

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2015 guidelines by both the American Heart Association and the European Resuscitation Council recommend the appropriate use of ECPR for selected cardiac arrest patients for whom suspected etiology is potentially reversible in the institutions that are capable of rapid deployment of extracorporeal membrane oxygenation (ECMO).[9,10] These guidelines made no mention of ECPR adaptation concerning the first documented rhythm of patients with cardiac arrest. ECPR is expensive and staff-intensive; hence, identification of circumstances in which it provides the most benefit is essential. We hypothesized that the first documented rhythm would influence the cost-effectiveness of ECPR.

Methods

Study design and setting

This Japanese single-center, retrospective, observational study was conducted at Urasoe General Hospital over a period of nine years (2008–2016). This study was approved by the institutional review boards of Urasoe General Hospital. We analyzed data from the ECPR registry, collecting detailed information about long-term follow-up of cardiac arrest patients who received resuscitation with use of ECMO.

Outcome definitions and measures

The ECPR registry has 100 variables describing the demographic and clinical characteristics of the patients, number of administered shocks, the precise details of the ECPR procedure, additional therapies, and medical expense for hospitalization, as well as data about intensive care and long-term outcomes. Emergency medical services reported data of out-of-hospital cardiac arrest according to the Utstein style.[11] First documented rhythm was defined as the first electrocardiogram rhythm documented at the time the patient became pulseless and, for those patients with unwitnessed/unmonitored arrests, it represented the first rhythm documented at the time a monitor arrived and was applied. We defined the pre-ECMO period as the time between collapse and ECMO initiation and the post-ECMO period as the time between ECMO initiation and exit time from the catheterization laboratory. The SYNTAX score was calculated for all patients who underwent coronary angiography.[12] The primary outcome was neurologically intact survival, defined as cerebral performance category score of 1 or 2. Secondary outcomes were 24-h survival, 30-day survival, survival to hospital discharge, successful ECMO weaning, and cost-effectiveness. We defined successful ECMO weaning as separation from ECMO support without reimplementation of ECMO or subsequent mortality in the next 48 h.

Indications and management of ECPR in Urasoe General Hospital

Selection criteria for ECPR in our hospital include refractory circulatory collapse, age $\leq$75 years, and arrival at the hospital within 45 min from the onset of cardiac arrest. An emergency physician was permanently stationed in our hospital and the information about institutional indication for ECPR was disclosed at the emergency room. In some cases, however, we performed rapid-response ECPR for patients in cardiac arrest before verification of patient's identity or confirmation of background investigations. We excluded patients with cognitive decline, terminal non-cardiac disease, severe immobility, a Do-Not-Attempt-Resuscitation order, or irreversible signs of death. We used two self-priming ECMO machines (Capiox emergency bypass system; Terumo Inc., Tokyo, Japan). ECPR was performed in the catheterization laboratory and the ECMO cannulae were inserted under fluoroscopic guidance. A venous cannula (21 Fr) was placed in the common femoral vein for extraction and an arterial cannula (15 Fr) was placed in the common femoral artery for infusion. Out-of-hospital cardiac arrest patients bypassed the emergency department and were transported directly to the catheterization laboratory during regular office hours. The ECMO patients were treated in the intensive care unit after procedures were performed in the catheterization laboratory. Patients were weaned from ECMO support if hemodynamic stability was maintained and echocardiographic parameters improved after a series of procedures such as PCI, insertion of intra-aortic balloon pump, and continuous hemodiafiltration.

Patient disposition

During the study period, 120 consecutive patients with refractory circulatory collapse underwent ECPR. First documented rhythm was VF in 55 (45.8%), pulseless VT in 4 (3.3%), asystole in 23 (19.2%), and PEA in 38 (31.7%). The first documented rhythms were divided into two groups: shockable rhythm (VF or pulseless VT; n = 59, 49.2%) and non-shockable rhythm (asystole or PEA; n = 61, 50.8%).

Cost effectiveness

Costs were estimated for all patients based on observed healthcare resource usage during the hospitalization period. Per-patient cost was calculated by dividing the sum of total hospitalization expense by the number of patients. Cost per life saved to discharge was calculated by dividing the sum of total hospitalization expense by the number of survivors.

The incremental differences between the groups in costs and quality adjusted life years (QALYs) were computed and incremental cost-effectiveness ratio (ICER) was extrapolated. We assumed that all patients had a baseline utility value of '0', which is equivalent to dead. We then assumed a linear transition from '0' in cardiac arrest to the utility value at hospital discharge and similarly from the hospital discharge to the 12-month utility value. Based on prior reports, a good neurological outcome defined by a Cerebral Performance Categories scale of 1 or 2 was assigned a multiplier of 0.75, and a poor neurological outcome defined by a Cerebral Performance Categories scale score of 3 or 4 was assigned a weight of 0.39.[13,14] We multiplied the utility value by the number of years of expected additional life in Japan.[15] Then half of the product was assigned to QALYs of the study patients because QALYs of patients after cardiac arrest are assumed to be lower than general population. ICER was calculated by dividing the difference in mean cost between the two groups by the difference in mean QALYs between the two groups. We used the conversion rate for currency at an average of US $1 = ¥97.5 for the study duration. Total treatment costs included procedure fee, device cost of ECPR, and all expenses associated with additional therapies such as PCI, therapeutic hypothermia, insertion of intra-aortic balloon pump, and blood transfusion. To understand the scale of expenditure on ECMO use in Japan, please refer to the following hospital cost in Japan: acute myocardial infarction treated with PCI: approximately $20,000; multivessel or left main coronary artery disease revascularized using on-pump coronary artery bypass grafting: $30,000–$40,000.[16,17]

Statistical analysis

We compared the two groups using univariate analysis with regard to patient demographics, ECMO data, additional therapies, and clinical outcomes. Data normality was tested using the Kolmogorov–Smirnov test. If data had nonparametric distribution, we reported median and interquartile ranges. Differences between the two groups were analyzed using the Mann-Whitney U test for continuous variables and chi-square test for categorical data. We performed Wilcoxon signed-rank test for matched numbers of pre-ECMO and post-ECMO shock delivery. Kaplan–Meier estimate with log-rank test was used to compare the survival functions between the groups. Multivariate logistic regression examined the association between each explanatory variable and outcome. Results yielding a two-tailed p-value of less than 0.05 were regarded statistically significant. All statistical calculations were performed with SPSS software, version 24.0 (IBM).

Results

In the period of study, there were no drastic changes in medical service or health economics at both regional and national levels in Japan. There was no correlation between the total hospital cost of ECPR per patient and time course of the study ($r = 0.10$, $p = 0.27$). Table 1 summarizes the baseline characteristics and Table 2 shows a summary of ECMO and adjunctive therapies according to the first documented rhythm. The patients presenting with VF or pulseless VT had better prognoses than the patients presenting with asystole or PEA in terms of all clinical outcomes (Table 3 and Fig. 1). Multivariate logistic regression analysis revealed shorter duration from collapse to ECMO initiation, bystander CPR, and presenting rhythm of VF/VT as clinical predictors for neurologically intact survival (Fig. 2).

Cost effectiveness

We treated patients presenting with VF or pulseless VT at a median cost of $31,736 and patients presenting with asystole or PEA at a median cost of $23,564 during the entire hospitalization period associated with ECPR. The median hospitalization period of non-survivors was within a few days. In contrast, survivors stayed in the hospital for longer than a month, which contributed to an increase in total hospital cost regardless of the first documented rhythm. Although per-patient costs were comparable between patients presenting with VF or pulseless VT and patients presenting with asystole or PEA, the cost of saving patients' lives till the time of discharge was twice as high for patients presenting with asystole or PEA than for patients presenting with VF or pulseless VT ($213,656 vs. $101,669, Table 4).

The mean life expectancy was 13.7 years for CPC 1–2 and 11.5 years for CPC 3–4 among patients presenting with VF or pulseless VT, and it was 11.1 years for CPC 1–2 and 8.3 years for CPC 3–4 among patients presenting with asystole or PEA. The average QALYs were 3.32 in patients presenting with VF or pulseless VT and 1.16 in patients presenting with asystole or PEA. The cost per QALYs was $11,081 for patients presenting with VF or pulseless VT and $29,447 for patients presenting with asystole or PEA.

The mean total cost associated with ECPR per patient was $39,633 in patients presenting with VF or pulseless VT and $35,609 in patients presenting with asystole or PEA and the difference in the cost per patient between the groups was $4024. Comparing ECPR for patients presenting with VF or pulseless VT to ECPR for patients presenting with asystole or PEA, the ICER was extrapolated to be $1872 per QALY gained.

Discussion

To the best of our knowledge, this is the first report to demonstrate the impact of the first documented rhythm on cost-effectiveness of ECPR for patients with refractory circulatory collapse by comparing shockable and non-shockable initial rhythms. Aggressive application of ECMO to cardiac arrest victims with the first documented rhythm of asystole or PEA resulted in high mortality. The cost per saved life among patients presenting with asystole or PEA was estimated to be double the cost per saved life among

Table 1 – Demographic and baseline characteristics of patients receiving ECPR grouped by first documented rhythm.

	VF/VT (n = 59)	ASY/PEA (n = 61)	p value
Age, median (IQR), y	66.0 (52.0–74.0)	64 (53.5–73.5)	0.80
Male sex, n (%)	50 (84.7)	49 (80.3)	0.52
Witnessed, n (%)	55 (93.2)	54 (88.5)	0.37
Prodromal chest pain/discomfort, n (%)	19 (32.2)	11 (18.0)	0.073
Bystander CPR, n (%)	35 (60.3)	40 (65.6)	0.56
Out-of-hospital cardiac arrest, n (%)	43 (72.9)	36 (59.0)	0.11
Dispatch of doctor car, n (%)	11 (18.6)	10 (16.4)	0.75
Off-hours ECPR, n (%)	30 (50.8)	29 (47.5)	0.72
Loss of pupillary light reflex at ECMO initiation, n (%)	28 (48.3)	39 (65.0)	0.067
Lactate levels at ECMO initiation, median (IQR), mg/dl	11.2 (7.1–14.3)	11.9 (7.6–15.0)	0.46
Cardiac etiology, n (%)	52 (88.1)	37 (62.7)	0.001
Acute myocardial infarction, n (%)	37 (62.7)	26 (42.6)	0.028
Number of pre-ECMO defibrillation shocks, median (IQR)*	4 (2–5)	0 (0–1.5)	<0.001
Number of post-ECMO defibrillation shocks, median (IQR)†	1 (0–2)	0 (0–0)	0.001

ASY/PEA, asystole or pulseless electrical activity; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; IQR, interquartile range; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.
*†We defined the pre-ECMO period as the time between collapse and ECMO initiation and the post-ECMO period as the time between ECMO initiation and exit time from the catheterization laboratory.

Table 2 – Adjunctive therapeutic interventions and complications of ECMO grouped by first documented rhythm.

	VF/VT (n = 59)	ASY/PEA (n = 61)	p value
Coronary angiography, n (%)	57 (96.6)	53 (86.9)	0.054
SYNTAX score in IHD patients, median (IQR)	21.5 (10.0, 24.5)	27.5 (14.5–36.3)	0.064
PCI, n (%)	36 (61.0)	29 (47.5)	0.14
Angiographic success rate of PCI[a]	97.2% (35/36)	82.8% (24/29)	0.081
Insertion of intra-aortic balloon pump, n (%)	45 (76.3)	43 (70.5)	0.47
Therapeutic hypothermia, n (%)	34 (60.7)	30 (57.7)	0.75
Continuous hemodiafiltration, n (%)	9 (15.3)	6 (9.8)	0.37
Collapse-to-ECMO time, median (IQR), minutes	49.0 (39.9–67.2)	53.0 (42.0–66.5)	0.40
Duration of ECMO, median (IQR), days	1.94 (0.45–2.96)	1.05 (0.30–2.33)	0.12
Complications on ECMO, n (%)			
Pneumonia	5 (8.5)	4 (6.6)	0.74
Leg ischemia	8 (13.6)	6 (9.8)	0.53
Sepsis	1 (1.7)	6 (9.8)	0.11
Disseminated intravascular coagulation	11 (18.6)	12 (19.7)	0.89
Bleeding	20 (33.9)	21 (34.4)	0.95
Red blood cell transfusion, median (IQR), ml/day	349 (0, 1176)	362 (0, 1114)	0.73

ASY/PEA, asystole or pulseless electrical activity; ECMO, extracorporeal membrane oxygenation; IHD, ischemic heart disease including acute and old myocardial infarction; IQR, interquartile range; PCI, percutaneous coronary intervention; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.
[a] We defined successful PCI in ECPR as angiographic success: <50% residual in-segment stenosis in the presence of thrombolysis in myocardial infarction (TIMI) 3 flow[14].

Table 3 – Clinical outcomes of ECPR in accordance with first documented rhythm.

	VF/VT (n = 59)	ASY/PEA (n = 61)	p value
24-h survival, n (%)	44 (74.6)	36 (59.0)	0.071
30-day survival, n (%)	24 (41.4)	13 (21.3)	0.018
Survival to discharge, n (%)	23 (39.0)	10 (16.4)	0.006
Successful weaning from ECMO, n (%)*	28 (49.1)	17 (27.9)	0.018
Neurologically intact survival, n (%)†	19 (32.8)	9 (14.8)	0.021

ASY/PEA, asystole or pulseless electrical activity; ECMO, extracorporeal cardiopulmonary resuscitation; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.
*†We defined successful ECMO weaning as separation from ECMO support without reimplementation of ECMO or subsequent mortality in the next 48 h and neurologically intact survival as cerebral performance category score of 1 or 2.

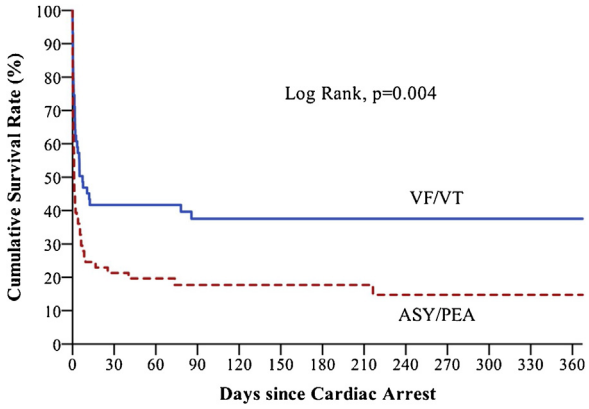

Fig. 1 – Kaplan-Meier estimates of survival following ECPR in accordance with first documented rhythm. ASY/PEA, asystole or pulseless electrical activity; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.

patients presenting with VF or pulseless VT. The ICER was $1872 per QALY gained for ECPR offered to patients presenting with VF or pulseless VT vs. ECPR offered to patients presenting with asystole or PEA.

Our findings support some observational studies that have described initial shockable rhythm as a predictor for neurologically favorable outcomes and initial rhythm of asystole as a strong predictor of subsequent mortality.[18,19] Asystole or PEA as presenting rhythms

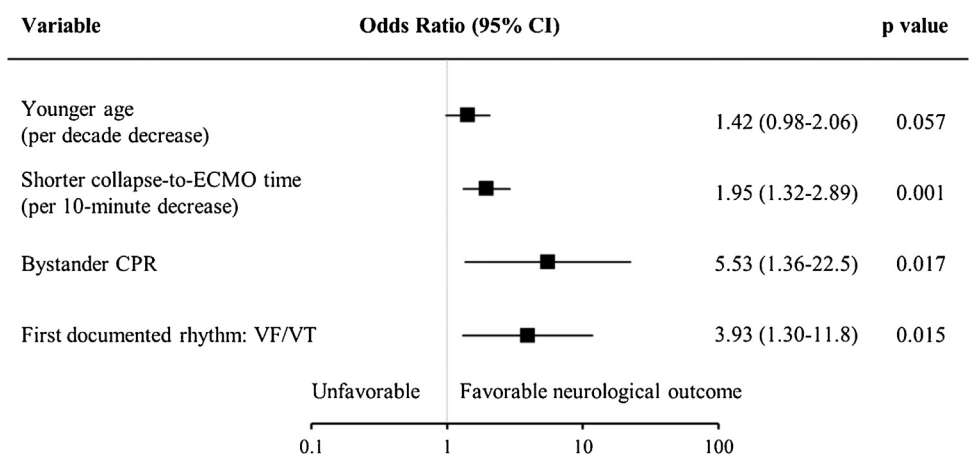

Fig. 2 – Multivariate logistic regression analysis for neurologically intact survival.
CI, confidence interval; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.

Table 4 – Cost-effectiveness of ECPR in accordance with first documented rhythm.

	VF/VT			ASY/PEA		
	Overall (n = 59)	Survivors (n = 23)	Non-survivors (n = 36)	Overall (n = 61)	Survivors (n = 10)	Non-survivors (n = 51)
Hospitalization period, median (IQR), days	5 (1–30)	33 (19–61)	1.5 (0–4.75)	1 (0–13)	43.5 (32.3–57.8)	1 (0–3)
Total hospital cost per day, median (IQR)	$4582 (1697–8546)	$1687 (1103–2003)	$7396 (5017–10475)	$6619 (2829–9821)	$1561 (1065–2114)	$8276 (5043–17816)
Total hospital cost, median (IQR)	$31,736 (19472–58689)	$51,523 (36049–72354)	$22,871 (11231–34905)	$23,564 (11625–54986)	$68,303 (57444–102765)	$19,436 (10467–58218)
Total cost per life saved to discharge[a]	$101,669			$213,656		
Life expectancy, mean (95% CI), years	10.5 (5.93–15.02)			3.34 (1.24–5.82)		
QALYs, mean (95% CI)	3.32 (1.61–5.04)			1.16 (0.31–2.02)		
Total hospital cost per QALYs[b]	$11,081			$29,447		

ASY/PEA, asystole or pulseless electrical activity; CI, confidence internal; IQR, interquartile range; QALYs, quality adjusted life years; VF/VT, ventricular fibrillation or pulseless ventricular tachycardia.
[a] Total cost per life saved to discharge was calculated by dividing the sum of total hospital cost by the number of lives saved.
[b] Total hospital cost per QALYs was calculated by dividing the sum of total hospital cost by the sum of QALYs.

of cardiac arrest had a critical impact on cerebral resuscitation. The pupillary light reflex was more commonly absent in patients presenting with asystole or PEA than in patients presenting with VF or pulseless VT, even though the two groups had similar incidences of witnessed collapse, bystander CPR, and equivalent collapse-to-ECMO time. Previous studies have identified the absence of pupillary light reflex as a reliable indicator of poor prognosis.[20] Patients with asystole or PEA may already have suffered progressive brain damage induced by hypoxia and hypoperfusion, compared to patients with VF or pulseless VT at the time of first cardiac rhythm monitoring.

Forced circulation by ECMO improves hypoxemia and hemodynamics, so deployment of ECMO might lead to lowering shock resistance of VF or VT.[21,22] Most patients with an initial shockable rhythm received two or more defibrillation shocks in the pre-ECMO setting, suggesting that patients with an initial shockable rhythm developed an electrical storm of VF. Repetitive electrical cardioversion applied to recurrent VF or VT induces myocardial damage.[23] The shock-less strategy with ECMO support provided the cardiac arrest victims with an initial shockable rhythm the best chance of restoring an organized rhythm, imposing the smallest shock delivery burden.

The high mortality rate of ECMO patients presenting with asystole or PEA resulted in less cost-effectiveness compared to ECPR performed for those with VF or pulseless VT. Cardiac arrest patients who underwent ECPR had a median overall hospital cost of $27,456 (interquartile range $13,864–$55,661). The total hospitalization cost associated with ECPR was comparable to what has been previously reported from Taiwan.[24] The cost-effectiveness threshold differs between countries.[25] The UK has ICER criteria of £20,000–£30,000 British pounds per QALY gained. The United States is willing to pay around $50,000–$100,000 per QALY gained, and in Japan is around 5,000,000–6,000,000 yen per QALY gained. Previous studies about resuscitation for cardiac arrest showed overall survival of approximately 6% and favorable neurological outcomes of 3%.[26] In the current study, the patients were resistant to median 50 min of CCPR

before implementation of ECPR, suggesting they had extremely low possibility of survival otherwise. If we assume that CCPR yields overall survival (CPC 1–4) of 3% and favorable neurological outcomes (CPC 1–2) of 1.5% for the patients with similar background of our registry, QALYs of patients who undergo CCPR are estimated to be 0.09 and QALYs gained by ECPR over CCPR are 2.11. If we extrapolate that mean total cost of CCPR is $30,000 in survivors (CPC 1–4) and $2500 in non-survivors, the incremental cost associated with implementation of ECPR is $34,280.[27] The ICER of ECPR over conventional CPR is estimated to be $ 16,246 per QALYs gained. It is challenging to estimate life time QALYs among cardiac arrest patients who undergo CPR including ECPR because there is a lack of clinical data about their long-term prognosis. We also explored other factors potentially influencing economic outcomes of ECPR. The ICER of ECPR for cardiac arrest with bystander CPR over without bystander CPR was $11,750 per QALYs gained. In addition, compared with ECPR implemented over 50 min, ECPR implemented within 50 min have ICER of $4729 per QALYs gained. ECPR should be rapidly performed in order to achieve cost-effectiveness because the prognosis improvement by shortening the time directly influences the economic outcomes.

In the current study, ECPR for patients presenting with VF or pulseless VT was found to be highly cost-effective and ECPR for patients presenting with asystole or PEA was borderline cost-effective. From an economic perspective, ECPR is a very strong indication for patients presenting with VF or pulseless VT and it can be still considered for patients presenting with asystole or PEA if there is no other therapeutic choice. Considering clinical efficacy and cost-effectiveness, the indications for ECPR might be classified into different levels in accordance with the first documented rhythms. A possible indication for ECPR in the treatment of refractory circulatory collapse with the first documented rhythm of asystole or PEA includes young, active, otherwise healthy patients who are expected to reintegrate into community life as before the collapse.

Limitations

This was a single-center, retrospective, cohort study in which selection bias and information bias might have occurred. However, in this study, cardiologists and emergency physicians at various levels performed ECPR, suggesting that these findings might be generalized to other institutes dedicated to tertiary care. We did not always perform ECPR for patients with unwitnessed cardiopulmonary collapse, persistent asystole, and prolonged time interval between circulatory collapse to CPR. ECPR might not be homogeneously applied in considering the presentation times. It was difficult to assess the extent to which the patients received intensive care. Although both groups of patients similarly underwent invasive procedures and intensive care in early phase of treatment, we withdrew intensive care more often in patients presenting with asystole or PEA than in patients presenting with VF or pulseless VT (19.7% vs. 5.1%; $p = 0.016$). This was possibly caused as the result of high mortality rate in patients presenting with asystole or PEA. Prolonged prehospital delay discouraged us from performing ECPR, particularly during night shifts and weekends, because we had to begin with activation of the catheterization laboratory during off-hours. Potential confounders such as CPR quality, time interval of circulatory collapse without attempting CPR, and location of arrest might have influenced outcomes.

Conclusions

ECPR provided a higher survival rate for patients presenting with VF or pulseless VT than for patients presenting with asystole or PEA. Prevention of death in cardiac arrest victims presenting with asystole or PEA by performing ECPR cost about twice as much as that for patients presenting with VF or pulseless VT. ECPR for patients presenting with VF or pulseless VT was found to be highly cost-effective and ECPR for patients presenting with asystole or PEA was borderline cost-effective.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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