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Clinical paper

Impact of mechanical circulatory support on out-of-hospital cardiac arrest outcomes stratified by vasoactive-inotropic score: A retrospective cohort study

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Abstract

Aims: To assess whether mechanical circulatory support (MCS), including intra-aortic balloon pump (IABP) or veno-arterial extracorporeal membrane oxygenation (ECMO), can help improve neurological outcomes in patients with out-of-hospital cardiac arrest (OHCA).

Methods: This is a retrospective observational cohort study performed in China Medical University Hospital, Taichung, Taiwan. Adult patients with OHCA admitted between January 2015 and June 2023. Quantitative score of vasoactive-inotropic agents and qualitative interventions of MCS, including IABP and ECMO after OHCA. Multivariate regression evaluated the efficacy of each MCS approach in patients stratified by the vasoactive-inotropic score (VIS).

Results: A total of 334 patients were included and analyzed, 122 (36.5%) had favorable neurological outcomes and 215 (64.4%) survived ≥ 90 days. These patients were stratified by VIS: 0–25, 26–100, 101–250, and >250 . In patients with a VIS > 100 , ECMO with or without IABP ensured favorable neurological outcomes and survival after OHCA compared to non-MCS interventions ($p < 0.001$). For patients with a VIS ≤ 100 , IABP alone was beneficial, with no significant outcome difference from non-MCS interventions ($p > 0.05$).

Conclusions: ECMO with or without IABP therapy may improve post-OHCA neurological outcomes and survival in patients with an expected VIS-24 h > 100 (e.g., epinephrine dose reaches 3 mg during CPR).

Keywords: Out-of-hospital cardiac arrest, Vasoactive-inotropic score, Mechanical circulatory support, Extracorporeal membrane oxygenation, Intra-aortic balloon pump

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant concern due to its high mortality risk and poor neurological outcomes.^{1,2} Only a quarter of patients achieve a return of spontaneous circulation

(ROSC) during hospitalization for OHCA, and about one-third of the hospitalized patients survive till discharge, with favorable neurological outcomes.²

In addition to immediate cardiopulmonary resuscitation (CPR) and early defibrillation, vasopressors and inotropic agents are often administered to patients with cardiac arrest to maintain adequate

Abbreviations: CPC, cerebral performance category, CPR, cardiopulmonary resuscitation, ECMO, extracorporeal membrane oxygenation, IABP, intra-aortic balloon pump, MCS, mechanical circulatory support, OHCA, out-of-hospital cardiac arrest, ROSC, return of spontaneous circulation, SOFA, sequential organ failure assessment, VIS, vasoactive-inotropic score

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blood pressure and tissue perfusion. The severity of cardiac arrest and the associated risk of mortality are indicated by the vasoactive-inotropic score (VIS); a higher score correlates with a worse outcome.^{3,4} Mechanical circulatory support (MCS) therapies, such as intra-aortic balloon pump (IABP) and veno-arterial extracorporeal membrane oxygenation (ECMO), can be used in patients with cardiac arrest due to inadequate perfusion⁵. Owing to the pulsatile flow and feasibility of IABP, this therapy has been used as a circulatory adjunct in OHCA treatment. However, IABP does not improve neurological outcomes or extend survival⁶. Survival rates are higher, and consequently, mortality rates are lower in patients receiving ECMO after OHCA than in those receiving IABP therapy^{5,7,8}. ECMO is superior to standard defibrillation in patients with OHCA and refractory ventricular fibrillation⁹. However, recent large-scale randomized clinical trials on refractory OHCA have indicated that extracorporeal CPR and conventional CPR result in similar outcomes, with no favorable neurological outcomes^{10,11}. This failure may be attributed to the duration of resuscitation and severity of the sustained shock. Although measuring the doses of vasopressors and inotropic agents can facilitate the accurate estimation of ailment severity, the association between the combined VIS and MCS remains unclear^{3,4}. Information on their association could inform clinical practice.

This study aimed to investigate the effect of MCS therapies (IABP alone vs. ECMO with or without IABP) on the clinical outcomes of OHCA in adult patients stratified using VIS, which indicates the degree of ailment severity.

Material and methods

Study design, setting, and cohort

This study included hospitalized adults (age ≥ 18 years) who received OHCA treatment at the Cardiology Intensive Care Unit or Stroke and Neurology Critical Care Unit of the China Medical University Hospital, Taichung, Taiwan between January 2015 and June 2023. The hospital is accredited by Taiwan's Ministry of Health and Welfare. Patients with OHCA of a cardiac origin were included but those with noncardiac OHCA or metastatic cancer were excluded.

Data collection

Patients with OHCA immediately received CPR before and after emergency department (ED) arrival, followed by intravenous epinephrine at 1 mg/3 min at ED until heartbeat was restored. Higher proportion of witnessed cardiac arrest and bystander CPR to confirm mean shorter no-flow time <5 min. CPR time was estimated as low-flow time, whether CPR was performed by bystanders, family members, emergency medical technicians, ED staff, or CPR machines. The attending physician administered a continuous intravenous dose of vasopressors (norepinephrine or vasopressin) or inotropic agents (dopamine or dobutamine) based on the clinical situation. The primary goal was maintaining a systolic blood pressure >90 mmHg and heart rate >60 bpm, and the secondary goal was maintaining organ perfusion by evaluating the adequacy of heart contractility through echocardiography.

Modified VIS-24 h was calculated using the maximum dosing rates of vasoactive and inotropic medications ($\mu\text{g}/\text{kg}/\text{min}$ or $\text{unit}/\text{kg}/\text{min}$) during the first 24 h after OHCA⁴. The VIS was calculated as follows: (epinephrine [$\mu\text{g}/\text{kg}/\text{min}$] $\times 100$) + (norepinephrine [$\mu\text{g}/\text{kg}/\text{min}$] $\times 100$) + (vasopressin [$\text{unit}/\text{kg}/\text{min}$] $\times 10,000$) + (dopamine

[$\mu\text{g}/\text{kg}/\text{min}$] + (dobutamine [$\mu\text{g}/\text{kg}/\text{min}$] + (milrinone [$\mu\text{g}/\text{kg}/\text{min}$] $\times 10$) + (levosimendan [$\mu\text{g}/\text{kg}/\text{min}$] $\times 50$)³. In fact, the flow rate of epinephrine was estimated by assuming a 1-hour average administration of the total dose of epinephrine. All the data were reviewed and validated by two independent researchers. MCS, such as IABP therapy alone or ECMO with or without IABP therapy, is commonly used if ROSC is not achieved, or systolic blood pressure, heart rate, or adequate organ perfusion is not maintained after ROSC.

Study outcomes

Primary outcomes were favorable neurological outcomes and 90-day survival after hospitalization. The Cerebral Performance Category (CPC) is a tool that assesses brain awareness. Grades 1, 2, 3, 4, and 5 indicate normal or mild cerebral disability, moderate cerebral disability, severe cerebral disability, coma or vegetative state, and brain death or mortality, respectively. A CPC grade of 1 or 2 suggests favorable neurological outcomes, whereas that of 3, 4 or 5 indicates poor neurological outcomes.

Statistical analysis

The VIS-stratified groups were compared for patient characteristics and clinical outcomes. Continuous variables are presented as mean \pm SD or median (first quartile, third quartile) and were compared using the analysis of variance or Kruskal–Wallis test. Categorical variables are presented as numbers and percentages and were compared using the chi-square test or Fisher exact test. Survival rates were compared using the Kaplan–Meier survival curve and log-rank test. IABP therapy, ECMO, and non-MCS interventions were compared using a 2-sided Student *t*-test. A 2-tailed *p*-value of <0.05 indicated statistical significance. Statistical analyses were performed using SPSS (version 22.0; IBM Armonk, NY, USA) or SAS (version 9.4; SAS Institute, Cary, NC, USA).

Ethics

The study was approved by the Institutional Review Board of China Medical University Hospital, Taichung, Taiwan on March 4, 2023 (approval number: CMUH112-REC3-016). The requirement for informed consent was waived due to the retrospective nature of this study. The requirement for informed consent was waived because of the retrospective nature of this study.

Results

This study included 427 adult patients who experienced OHCA between January 2015 and June 2023. Patients with OHCA of noncardiac origin (asphyxia or pneumonia, intracranial hemorrhage or infarction, trauma, drugs, or toxins) and those with metastatic cancer were excluded, leaving 334 patients with OHCA of cardiac origin in the final analysis. Patients were stratified into the following four groups based on the VIS: 0–25 (78 patients), 26–100 (80 patients), 101–250 (95 patients), and >250 (81 patients). Fig. 1 presents a flowchart depicting group allocation.

Table 1 displays the baseline characteristics of the study groups. Between-group similarities were observed in age (58.3–61.6 years); sex (male, 71.3–85.9%); body weight (68.0–72.2 kg); and comorbidities, such as coronary artery disease, cerebrovascular disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and end-stage renal disease. The incidence rate of initial shockable rhythm, including pulseless ventricular tachycardia and

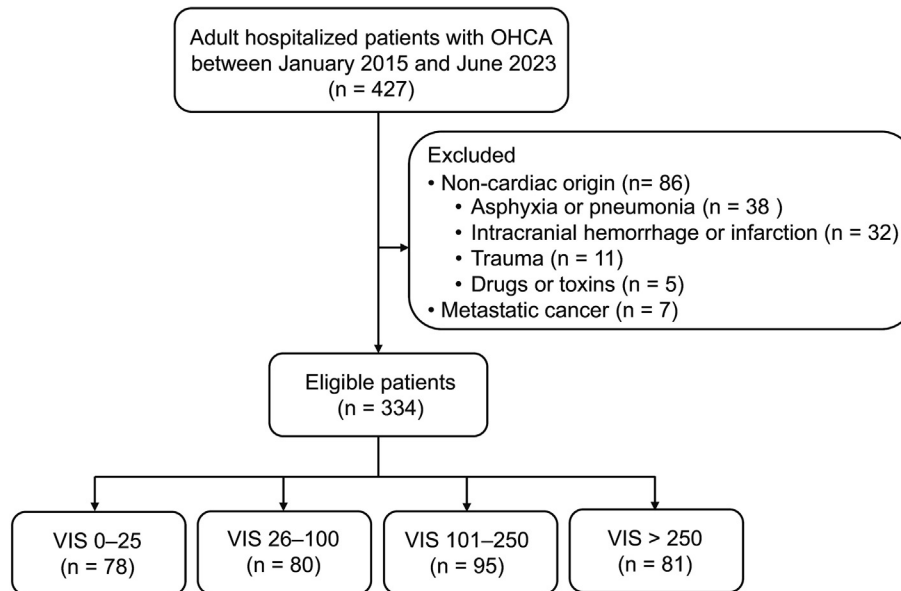


Fig. 1 – Flowchart depicting group allocation. A total of 427 consecutive patients admitted to the cardiac intensive care unit between January 2015 and June 2023 were screened. Patients who had OHCA of a noncardiac origin or metastatic cancer were excluded from the analysis. Eligible patients ($n = 334$)—adults hospitalized for OHCA of a cardiac origin—were stratified into four groups by the maximum VIS to evaluate ailment severity during the first 24 h after OHCA. The four groups were as follows: patients with a VIS of 0–25, 26–100, 101–250, and >250. Abbreviations: OHCA, out-of-hospital cardiac arrest; VIS, vasoactive-inotropic score.

Table 1 – Baseline characteristics of patients across four groups based on the vasoactive-inotropic score.

Baseline characteristics	VIS 0–25 ($n = 78$)	VIS 26–100 ($n = 80$)	VIS 101–250 ($n = 95$)	VIS > 250 ($n = 81$)	p -value
Age, y , mean \pm SD	60.6 \pm 13.1	61.6 \pm 12.5	60.0 \pm 17.1	58.3 \pm 14.1	0.54
Male, n (%)	67 (85.9)	57 (71.3)	74 (77.9)	68 (84.0)	0.09
Body weight (kg), median (IQR)	68.0 (59.9, 80.0)	68.1 (60.2, 80.0)	68.0 (58.0, 78.1)	72.2 (60.0, 80.0)	0.82
Witnessed cardiac arrest, n (%)	64 (82.1)	58 (72.5)	63 (66.3)	62 (76.5)	0.12
Bystander CPR, n (%)	43 (55.1)	45 (56.3)	39 (41.1)	41 (50.6)	0.16
Initial shockable rhythm, n (%)	64 (82.1)	51 (71.3)	56 (58.9)	56 (69.1)	0.01
Medical history, n (%)					
Chronic heart failure	28 (35.9)	13 (16.3)	22 (23.2)	18 (22.2)	0.03
Coronary artery disease	13 (16.7)	8 (10.0)	24 (25.3)	16 (19.8)	0.07
Cerebrovascular disease	2 (2.6)	5 (6.3)	7 (7.4)	3 (3.7)	0.46
Hypertension	39 (50.0)	36 (45.0)	47 (49.5)	31 (38.3)	0.40
Diabetes mellitus	20 (25.6)	30 (37.5)	35 (36.8)	21 (25.9)	0.18
Chronic obstructive pulmonary disease	3 (3.8)	4 (5.0)	1 (1.1)	3 (3.7)	0.51
End-stage renal disease	13 (16.9)	14 (17.5)	11 (11.6)	10 (12.4)	0.60
Lowest pH, median (IQR)	7.3 (7.1, 7.4)	7.1 (7.0, 7.3)	7.0 (6.8, 7.1)	6.9 (6.8, 7.1)	<0.001
Lactate (mmol/L), median (IQR)	7.1 (4.5, 10.6)	11.0 (7.9, 15.0)	13.1 (9.2, 16.7)	15.6 (12.3, 20.7)	<0.001
LVEF (%), median (IQR)	44.7 (34.6, 55.3)	43.0 (31.9, 54.7)	37.3 (26.9, 50.1)	25.5 (17.2, 32.3)	<0.001

Abbreviations: VIS, vasoactive-inotropic score; LVEF, left ventricular ejection fraction

fibrillation, was higher among patients with a VIS ≤ 100 than that among those with a VIS > 100 (71.3–82.1% vs. 58.9–69.1%, respectively; $p = 0.01$). Patients with a VIS > 250 had the lowest pH (6.9) and left ventricular ejection fraction (25.5%), and highest lactate level (15.6 mmol/L); all parameters varied significantly from those of patients with a VIS 0–25 (7.3, 44.7%, and 7.1 mmol/L, respectively; all $p < 0.001$). Patients with higher VIS exhibited significant trends toward severe acidemia, lactic acidosis, and poor heart contractility compared to those with lower VIS.

Table 2 presents treatment characteristics. Increasing VIS was significantly correlated with prolonged CPR (high VIS vs. low VIS: 18.0–40.0 vs. 12.0–12.0 min) and elevated ECMO frequency (high VIS vs. low VIS: 40.0–71.6% vs. 6.4–26.3%, respectively) ($p < 0.001$). The groups had similar rates of targeted temperature management (65.4–72.6%) and IABP therapy alone (10.0–17.9%). Further analyses revealed that the use of stronger vasopressors or inotropic agents within the first 24 h after OHCA, particularly the administration of high-dose epinephrine during emergency CPR,

Table 2 – Treatment characteristics of patients across four groups based on the vasoactive-inotropic score.

Treatment characteristics	VIS 0–25 (n = 78)	VIS 26–100 (n = 80)	VIS 101–250 (n = 95)	VIS > 250 (n = 81)	p-value
CPR time (min), median (IQR)	12.0 (5.0, 20.0)	12.0 (6.0, 20.0)	18.0 (10.0, 27.0)	40.0 (25.0, 60.0)	<0.001
Percutaneous coronary intervention, n (%)	38 (48.7)	44 (55.0)	54 (56.8)	57 (70.4)	0.04
Targeted temperature management, n (%)	51 (65.4)	58 (72.5)	69 (72.6)	54 (66.7)	0.64
IABP alone, n (%)	14 (17.9)	8 (10.0)	12 (12.6)	11 (13.6)	0.53
ECMO with or without IABP, n (%)	5 (6.4)	21 (26.3)	38 (40.0)	58 (71.6)	<0.001
Vasoactive inotropic agents, median (IQR)					
Epinephrine (mg)	0.0 (0.0, 0.0)	2.0 (0.5, 3.0)	5.0 (3.0, 7.0)	13.0 (10.0, 17.0)	<0.001
Epinephrine (µg/kg/min)	0.0 (0.0, 0.0)	0.5 (0.1, 0.7)	1.3 (0.9, 1.7)	3.1 (2.5, 3.8)	<0.001
Norepinephrine (µg/kg/min)	0.0 (0.0, 0.0)	0.2 (0.0, 0.3)	0.2 (0.0, 0.4)	0.3 (0.0, 0.4)	<0.001
Vasopressin (unit/kg/min)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.50
Dopamine (µg/kg/min)	0.0 (0.0, 0.0)	3.3 (0.0, 9.9)	7.9 (0.0, 15.0)	9.5 (0.0, 17.8)	<0.001
Dobutamine (µg/kg/min)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.05
Milrinone (µg/kg/min)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00
Levosimendan (µg/kg/min)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00
VIS, median (IQR)	0.0 (0.0, 11.0)	65.4 (46.1, 85.9)	157.1 (113.4, 204.1)	343.6 (285.2, 408.3)	<0.001

Abbreviations: CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VIS, vasoactive-inotropic score.

resulted in higher VIS ($p < 0.001$). Similar results were obtained with norepinephrine and dopamine ($p < 0.001$).

Regarding 90-day clinical outcomes, higher VIS was associated with poorer neurological outcomes and survival rates. Among patients with VISs of 0–25, 26–100, 101–250, and >250, the rate of favorable neurological outcomes was 59.0%, 52.5%, 29.5%, and 7.4%, and that of survival was 85.9%, 81.3%, 60.0%, and 32.1%, respectively. The CPC grade was strongly correlated with VIS during the first 24 h after OHCA ($p < 0.001$) and the Sequential Organ Failure Assessment (SOFA) score in the admission days of 3, 5, 7 ($p < 0.001$) (Table 3). The Kaplan–Meier curve for 90-day survival indicated that VIS during the first 24 h after OHCA was directly

proportional to survival for 2 weeks; then, the association was stable and persisted for 90 days (Fig. 2).

Fig. 3 displays the median VISs of patients stratified using the CPC grade. Patients with a CPC grade of 1 or 2 had a median VIS of 109.2 for ECMO, 59.9 for IABP therapy, and 24.6 for non-MCS intervention. ECMO was associated with favorable neurological outcomes in patients with a VIS > 100. Patients with a CPC grade of 3 or 4 had median a VIS of 274.4 for ECMO, 94.5 for IABP therapy, and 80.8 for non-MCS intervention. ECMO was associated with improved survival in patients with a VIS > 250. Guidelines for ECMO or IABP use were developed based on these findings (Table 3).

Table 3 – Clinical outcomes and applications of mechanical circulatory support in patients across four groups based on the vasoactive-inotropic score.

Clinical outcomes	VIS 0–25 (n = 78)	VIS 26–100 (n = 80)	VIS 101–250 (n = 95)	VIS > 250 (n = 81)	p-value
90-day CPC, n (%)					
CPC 1 or 2	46 (59.0)	42 (52.5)	28 (29.5)	6 (7.4)	<0.001
CPC 3 or 4	21 (26.9)	23 (28.8)	29 (30.5)	20 (24.7)	0.87
CPC 5	11 (14.1)	15 (18.8)	38 (40.0)	55 (67.9)	<0.001
Hospitalization LOS (days), median (IQR)	22.0 (12.0, 49.0)	31.5 (16.0, 55.5)	24.0 (5.0, 36.0)	5.0 (2.0, 36.0)	<0.001
Sequential organ failure assessment score, median (IQR)					
Day 1	11.0 (9.0, 13.0)	12.0 (10.5, 14.0)	12.0 (9.0, 16.0)	15.0 (13.0, 16.0)	<0.001
Day 3	9.0 (6.0, 12.0)	10.0 (8.0, 12.5)	12.0 (8.0, 19.0)	16.0 (14.0, 24.0)	<0.001
Day 5	8.0 (5.0, 11.0)	9.0 (7.0, 11.0)	11.0 (7.0, 24.0)	24.0 (13.0, 24.0)	<0.001
Day 7	7.0 (5.0, 10.0)	8.0 (6.0, 11.0)	12.0 (9.0, 16.0)	24.0 (12.0, 24.0)	<0.001
Clinical application					
CPC 1 or 2	Non-MCS	Non-MCS or IABP alone	ECMO with or without IABP	No valid data in this study	
CPC 3 or 4	Non-MCS	Non-MCS or IABP alone	ECMO and/or IABP	ECMO with or without IABP	

Abbreviations: CPC, cerebral performance category; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LOS, length of stay; MCS, mechanical circulatory support; VIS, vasoactive-inotropic score.

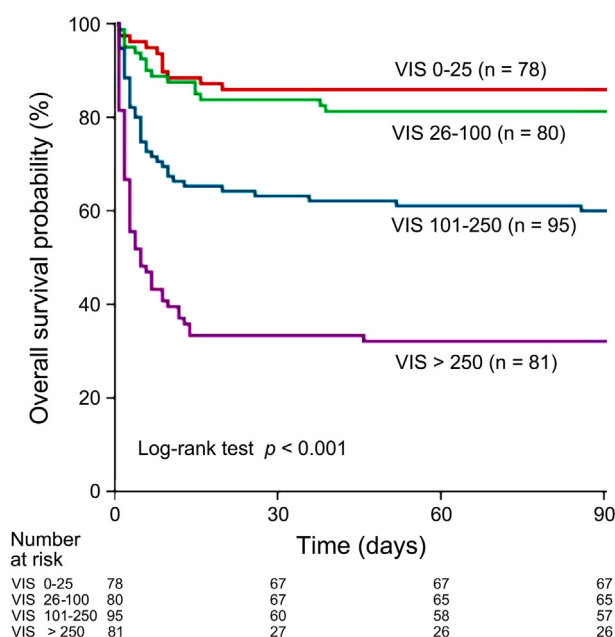


Fig. 2 – Kaplan-Meier curve depicting 90-day survival in patients stratified using the VIS. Patients with a modified VIS-24 h of 0–25: 67/78 (85.9%); 26–100: 65/80 (81.3%); 101–250: 57/95 (60.0%); and >250: 26/81 (32.1%). Log-rank test $p < 0.001$. Abbreviation: VIS, vasoactive-inotropic score.

Discussion

Our findings revealed that the VIS in adults hospitalized for OHCA is strongly and positively correlated with mortality risk, arterial blood pH level, lactate level, left ventricular ejection fraction within the first 24 h after OHCA, and SOFA score in the admission days of 3, 5, 7. Among patients with a VIS > 100, ECMO with or without IABP therapy resulted in favorable neurological outcomes and survival beyond 90 days. For patients with a VIS \leq 100, IABP therapy alone may be beneficial; however, post-treatment clinical outcomes may not be significant. Our study is the first to analyze the effects of MCS, including ECMO and IABP therapy, on the outcomes of OHCA in patients stratified by the VIS.

Patients with critical illness often require vasopressors and inotropic agents. VIS reflects the degree of hemodynamic support required, with a strong negative correlation between VIS and clinical outcomes.^{3,4} Vasopressors are harmful to the vascular endothelium, whereas inotropic agents are harmful to the myocardium. These drugs induce catecholamine release, thereby directly damaging the vascular endothelium and inducing a systemic inflammatory response. Epinephrine plays a dual role by serving as a vasopressor and an inotropic agent, potentially accelerating heart rate recovery, but also increasing VIS rapidly.^{12–14}

IABP therapy neither improved neurological outcomes nor extended survival in patients with OHCA.⁶ Although IABP therapy alone can improve the clinical outcomes of OHCA in patients with a VIS \leq 100, the benefits were nonsignificant (Fig. 3; $p > 0.05$). IABP therapy is beneficial only in certain clinical conditions, such as ventricular septal rupture and acute mitral regurgitation after myocardial infarction.¹⁵

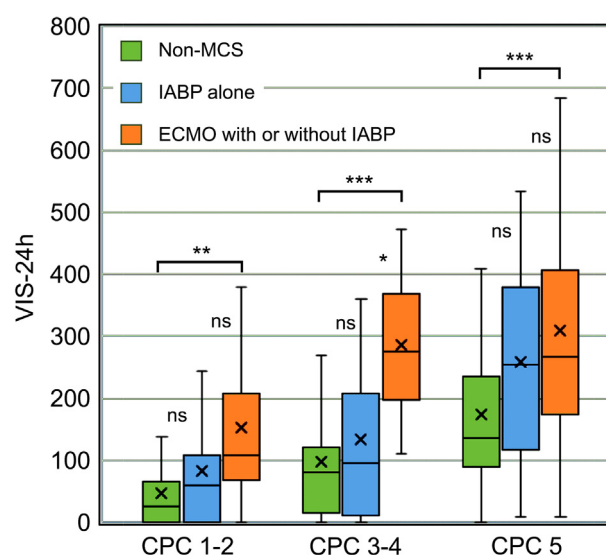


Fig. 3 – Median VIS for various interventions in patients stratified using the CPC grade. Among patients with a CPC grade 1 or 2 (survival with favorable neurological outcomes), the median VIS was 109.2 for ECMO, 59.9 for IABP therapy, and 24.6 for non-MCS intervention. Among patients with a CPC grade 3 or 4 (survival with poor neurological outcomes), the median VIS was 274.4 for ECMO, 94.5 for IABP therapy, and 80.8 for non-MCS intervention. Abbreviations: CPC, Cerebral Performance Category; ECMO, extracorporeal membrane oxygenation; MCS, mechanical circulatory support; IABP, intra-aortic balloon pump; VIS, vasoactive-inotropic score.

Known for its beneficial role in cardiogenic shock, ECMO has been increasingly used for the treatment of cardiac arrest because of the patho-mechanistic similarity of cardiac arrest with ischemia-reperfusion injuries and systemic inflammatory responses.^{8,16} For cardiac arrest, the American Heart Association recommends intravenous administration of 1 mg/3 min epinephrine during CPR to increase coronary perfusion pressure.¹⁷ Regarding the early prediction of mortality in patients receiving ECMO, some researchers have used only epinephrine data rather than the VIS because epinephrine is typically administered during CPR, but the maximum VIS usually be estimated the first 24 h after OHCA.^{18,19} Nonetheless, the total dose of epinephrine administered during CPR can be used to estimate the VIS because of continuous epinephrine administration is harmful.^{18,19} In this study, among patients with a VIS > 100, which corresponds to ≥ 3 mg epinephrine (Table 2), early ECMO support not only reduced the required dose of epinephrine, but also improved 90-day clinical outcomes (Fig. 3). ECMO should be initiated immediately after the administration of the third dose of epinephrine (3 mg) during CPR, approximately 6 min after ED arrival.

Compared with conventional CPR, extracorporeal CPR leads to increased systemic perfusion, thereby improving survival rates. Consequently, more adult patients with OHCA are receiving extracorporeal CPR.^{20–22} Compared with conventional CPR, extracorporeal CPR for 30 and 60 min can significantly improve survival from 10% to 30%.^{23–25} ECMO implantation should be scheduled if ROSC is not achieved within 15 min of CPR, although the optimal timing for

ECMO initiation remains unclear.²⁶ In this study, patients with a VIS \leq 100 typically achieved ROSC within 15 min after the administration of <3 mg of epinephrine. However, patients with a VIS between 101 and 250 required ≥ 3 mg of epinephrine to achieve ROSC usually between 15 and 30 min, and those with a VIS $>$ 250 always failed to achieve ROSC within 30 min despite a high dose of epinephrine. Due to a variability in CPR quality, it is reasonable to initiate ECMO earlier if up to 3 mg of epinephrine has been administered. If low-flow time persists for >30 min after OHCA, left ventricular unloading strategies should be considered to mitigate the severely impaired contractility of the heart in addition to ECMO implantation. IABP is easily added to ECMO for left ventricular unloading. However, ECMO with IABP resulted in only limited clinical benefit compared with ECMO without IABP in the subgroup analysis while VIS $>$ 250 (survival rate: 37.5% vs. 32.4%, odds ratio: 1.25, $p = 0.68$). IABP therapy is not clinically effective because it alleviates the afterload of the heart; thus, effective left ventricular unloading strategies that alleviate the preload of the left ventricle should be adopted.^{27,28} These strategies include percutaneous balloon atrial septostomy,²⁹ percutaneous left ventricular assist device [(Impella®) ECPPELLA],^{30,31} surgical left atrial venting (LAVA ECMO), and surgical left ventricle apical venting.²⁹

This study had some limitations. First, the single-center design limits the generalizability of these findings. Second, this was a retrospective study and not a randomized clinical trial, warranting further studies. Finally, the maximum VIS (>100) was calculated during the first 24 h after OHCA in lieu of pre-ECMO VIS for accuracy, but loss of emergency effectiveness of ECMO implantation; therefore, future studies should focus on the rapid initiation and completion of ECMO support and the benefits of left ventricular unloading stronger than IABP.

Conclusions

The findings suggest that ECMO with or without IABP therapy can improve neurological outcomes and survival while hospitalized patients with a VIS $>$ 100 within the first 24 h after OHCA. Clinicians should consider initiating ECMO once the epinephrine dose reaches 3 mg during CPR.

CRedit authorship contribution statement

Da-Long Chen: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yu-Kai Lin:** Data curation, Conceptualization. **Chia-Ing Li:** Visualization, Investigation, Formal analysis, Conceptualization. **Guei-Jane Wang:** Writing – review & editing, Supervision. **Kuan-Cheng Chang:** Writing – review & editing, Supervision.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

- Ong ME, Shin SD, De Souza NN, et al. Outcomes for out-of-hospital cardiac arrests across 7 countries in Asia: the pan Asian resuscitation outcomes study (PAROS). *Resuscitation* 2015;96:100–8. <https://doi.org/10.1016/j.resuscitation.2015.07.026>.
- Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation* 2017;110:133–40. <https://doi.org/10.1016/j.resuscitation.2016.10.030>.
- Belletti A, Lerose CC, Zangrillo A, Landoni G. Vasoactive-inotropic score: evolution, clinical utility, and pitfalls. *J Cardiothorac Vasc Anesth* 2021;35:3067–77. <https://doi.org/10.1053/j.jvca.2020.09.117>.
- Tabi M, Burstein BJ, Ahmed A, Dezfulian C, Kashani KB, Jentzer JC. Shock severity and hospital mortality in out of hospital cardiac arrest patients treated with targeted temperature management. *Shock* 2021;55:48–54. <https://doi.org/10.1097/SHK.0000000000001600>.
- Wong ASK, Sin SWC. Short-term mechanical circulatory support (intra-aortic balloon pump, Impella, extracorporeal membrane oxygenation, TandemHeart): a review. *Ann Transl Med* 2020;8:829. <https://doi.org/10.21037/atm-20-2171>.
- Kishimori T, Matsuyama T, Yamada T, et al. Intra-aortic balloon pump and survival with favorable neurological outcome after out-of-hospital cardiac arrest: a multicenter, prospective propensity score-matched study. *Resuscitation* 2019;143:165–72. <https://doi.org/10.1016/j.resuscitation.2019.07.002>.
- Ouweneel DM, Schotborgh JV, Limpens J, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:1922–34. <https://doi.org/10.1007/s00134-016-4536-8>.

8. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. *Circ Heart Fail* 2018;11:e004905. <https://doi.org/10.1161/CIRCHEARTFAILURE.118.004905>.
9. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet* 2020;396:1807–16. [https://doi.org/10.1016/S0140-6736\(20\)32338-2](https://doi.org/10.1016/S0140-6736(20)32338-2).
10. Belohlavek J, Smalцова J, Rob D, et al. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2022;327:737–47. <https://doi.org/10.1001/jama.2022.1025>.
11. Suverein MM, Delnoij TSR, Lorusso R, et al. Early extracorporeal CPR for refractory out-of-hospital cardiac arrest. *N Engl J Med* 2023;388:299–309. <https://doi.org/10.1056/NEJMoa2204511>.
12. Hyun J, Kim AR, Lee SE, et al. Vasoactive-inotropic score as a determinant of timely initiation of venoarterial extracorporeal membrane oxygenation in patients with cardiogenic shock. *Circ J* 2022;86:687–94. <https://doi.org/10.1253/circi.CJ-21-0614>.
13. Choi KH, Yang JH, Park TK, et al. Differential prognostic implications of vasoactive inotropic score for patients with acute myocardial infarction complicated by cardiogenic shock according to use of mechanical circulatory support. *Crit Care Med* 2021;49:770–80. <https://doi.org/10.1097/CCM.0000000000004815>.
14. Na SJ, Chung CR, Cho YH, et al. Vasoactive inotropic score as a predictor of mortality in adult patients with cardiogenic shock: medical therapy versus ECMO. *Rev Esp Cardiol (Engl Ed)* 2019;72:40–7. <https://doi.org/10.1016/j.rec.2018.01.003>.
15. Kettner J, Sramko M, Holek M, Pirk J, Kautzner J. Utility of intra-aortic balloon pump support for ventricular septal rupture and acute mitral regurgitation complicating acute myocardial infarction. *Am J Cardiol* 2013;112:1709–13. <https://doi.org/10.1016/j.amicard.2013.07.035>.
16. Li W, Yang D. Extracorporeal membrane oxygenation in refractory cardiogenic shock. *Heart Surg Forum* 2020;23:E888–94. <https://doi.org/10.1532/hsf.3263>.
17. Gough CJR, Nolan JP. The role of adrenaline in cardiopulmonary resuscitation. *Crit Care* 2018;22:139. <https://doi.org/10.1186/s13054-018-2058-1>.
18. Zotzmann V, Rillinger J, Lang CN, et al. Epinephrine, inodilator, or no inotrope in venoarterial extracorporeal membrane oxygenation implantation: a single-center experience. *Crit Care* 2019;23:320. <https://doi.org/10.1186/s13054-019-2605-4>.
19. Massart N, Mansour A, Ross JT, et al. Epinephrine administration in venoarterial extracorporeal membrane oxygenation patients is associated with mortality: a retrospective cohort study. *ESC Heart Fail* 2021;8:2899–906. <https://doi.org/10.1002/ehf2.13370>.
20. Bartos JA, Grunau B, Carlson C, et al. Improved survival with extracorporeal cardiopulmonary resuscitation despite progressive metabolic derangement associated with prolonged resuscitation. *Circulation* 2020;141:877–86. <https://doi.org/10.1161/CIRCULATIONAHA.119.042173>.
21. Inoue A, Hifumi T, Sakamoto T, Kuroda Y. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest in adult patients. *J Am Heart Assoc* 2020;9:e015291. <https://doi.org/10.1161/JAHA.119.015291>.
22. Daubin C, Brunet J, Huet J, et al. Extracorporeal cardiopulmonary resuscitation and survival after refractory cardiac arrest: Is ECPR beneficial? *ASAIO J* 2021;67:1232–9. <https://doi.org/10.1097/MAT.0000000000001391>.
23. Wengenmayer T, Rombach S, Ramshorn F, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Crit Care* 2017;21:157. <https://doi.org/10.1186/s13054-017-1744-8>.
24. Hutin A, Abu-Habsa M, Burns B, et al. Early ECPR for out-of-hospital cardiac arrest: Best practice in 2018. *Resuscitation* 2018;130:44–8. <https://doi.org/10.1016/j.resuscitation.2018.05.004>.
25. Mandigers L, Boersma E, den Uil CA, et al. Systematic review and meta-analysis comparing low-flow duration of extracorporeal and conventional cardiopulmonary resuscitation. *Interact Cardiovasc Thorac Surg* 2022;35:ivac219. <https://doi.org/10.1093/icvts/ivac219>.
26. Conrad SA, Rycus PT. Extracorporeal membrane oxygenation for refractory cardiac arrest. *Ann Card Anaesth* 2017;20(Supplement): S4–S10. <https://doi.org/10.4103/0971-9784.197790>.
27. Baldetti L, Gramegna M, Beneduce A, et al. Strategies of left ventricular unloading during VA-ECMO support: A network meta-analysis. *Int J Cardiol* 2020;312:16–21. <https://doi.org/10.1016/j.ijcard.2020.02.004>.
28. Ezad SM, Ryan M, Donker DW, et al. Unloading the left ventricle in venoarterial ECMO: in whom, when, and how? *Circulation* 2023;147:1237–50. <https://doi.org/10.1161/CIRCULATIONAHA.122.062371>.
29. Donker DW, Brodie D, Henriques JPS, Broomé M. Left ventricular unloading during veno-arterial ECMO: a review of percutaneous and surgical unloading interventions. *Perfusion* 2019;34:98–105. <https://doi.org/10.1177/0267659118794112>.
30. Unoki T, Kamentani M, Nakayama T, et al. Impact of extracorporeal CPR with transcatheter heart pump support (ECPELLA) on improvement of short-term survival and neurological outcome in patients with refractory cardiac arrest – a single-site retrospective cohort study. *Resusc Plus* 2022;10:100244. <https://doi.org/10.1016/j.resplu.2022.100244>.
31. Thevathasan T, Füreder L, Fechtner M, et al. Left-ventricular unloading with Impella during refractory cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. *Crit Care Med* 2024;52:464–74. <https://doi.org/10.1097/CCM.0000000000006157>.