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Posted Date: 19 March 2025

doi: 10.20944/preprints202503.1406.v1

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Article

Effect of Levosimendan Use on All-Cause Mortality in Out-of-Hospital Cardiac Arrest Survivors After Extracorporeal Cardiopulmonary Resuscitation

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Abstract: Background: Out-of-hospital cardiac arrest (OHCA) survivors after extracorporeal cardiopulmonary resuscitation (ECPR) have a 50-70% mortality rate. However, the use of vasoactive inotropes during the first 24 h worsened the mortality rate. Because of administering inodilators (e.g., levosimendan and milrinone) within 72 h of ECPR could facilitate extracorporeal membrane oxygenation (ECMO) weaning, it is crucial to determine whether the use of inodilators could improve mortality rates. **Methods:** This retrospective cohort study included 158 patients with OHCA of cardiac origin who had undergone ECPR and were hospitalized between January 2015 and December 2024. This study was conducted in the intensive care unit of China Medical University Hospital, Taichung, Taiwan. Twenty-three patients received levosimendan within 72 h, whereas the others did not receive an inodilator. Primary endpoints included ECMO weaning failure and the 90-day all-cause mortality rate. Kaplan-Meier survival curve analysis was also performed. Possible covariates for all-cause mortality were estimated using Cox regression modeling. **Results** The levosimendan group exhibited lower rates of ECMO weaning failure and 90-day all-cause mortality than the control group (13.0% vs. 52.6% and 17.4% vs. 57.0%, respectively; both $p < 0.001$). The 90-day survival curve analysis revealed that the levosimendan and control groups had survival rates of 0.83 and 0.43, respectively (log-rank $p < 0.001$). Administration of levosimendan within 72 h resulted in a hazard ratio of 0.30 (95% confidence interval: 0.12–0.75, $p = 0.01$). **Conclusions** Administering levosimendan within 72 h of ECPR could be a protective factor in improving all-cause mortality.

Keywords: out-of-hospital cardiac arrest; extracorporeal cardiopulmonary resuscitation; levosimendan inodilator; extracorporeal membrane oxygenation

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is estimated to occur at a rate of 50–100 per 100,000 person-years worldwide [1]. Notably, half of the patients with cardiac arrests of cardiac origin receive temporary mechanical circulatory support, with 70% of patients experiencing acute myocardial infarction [2].

Although initial cardiopulmonary resuscitation (CPR) is crucial during sudden cardiac arrest, the mortality rate remains markedly high [3]. Despite bystander CPR and early defibrillation improving survival rates, they remain sub-optimal [4,5]. Considering data on CPR duration, the mortality rate is as high as 80–90% for non-shockable rhythms after epinephrine administration for > 10 min or shockable rhythms after defibrillation and epinephrine for > 20 min [6]. Because CPR only supplies a low-flow status, a CPR duration of > 15 min is considered refractory cardiac arrest, and new strategies need to be developed to improve survival [7].

The application of extracorporeal CPR (ECPR) is gaining widespread momentum owing to its capacity for more appropriate blood flow and improvement in ischemia/reperfusion injury after OHCA [8]. In recent years, ECPR was reported to substantially enhance survival compared with conventional CPR, although the benefit in terms of awakening rate remains poorly clarified [9,10,11,12]. In patients with refractory cardiac arrest, ECPR was found to be associated with a markedly high mortality rate (50–70%) compared with conventional CPR [6].

Levosimendan, an inodilator, increases both heart contractility and vasodilatation to improve systemic perfusion [13]. Levosimendan has been used in acute cardiac care, including coronary artery bypass graft surgery, advanced heart failure, and rescue therapy for cardiogenic shock [13,14]. Recently, levosimendan was administered during weaning from extracorporeal membrane oxygenation (ECMO) [14,15]. However, survival benefits associated with the use of levosimendan during ECPR remain unclear. In the current study, we examined the potential effects of levosimendan use on all-cause mortality in patients with OHCA who underwent ECPR.

2. Materials and Methods

2.1. Study Design and Population

This observational, retrospective cohort study included 158 patients with OHCA who underwent ECPR and were consecutively admitted to the intensive care unit of China Medical University Hospital, Taichung, Taiwan, between January 2015 and December 2024. Patients with OHCA of non-cardiac origin or metastatic cancer were excluded (STROBE flowchart; Figure 1). The study design conformed to the ethical guidelines of the Institutional Review Board of China Medical University Hospital (CMUH112-REC3-016).

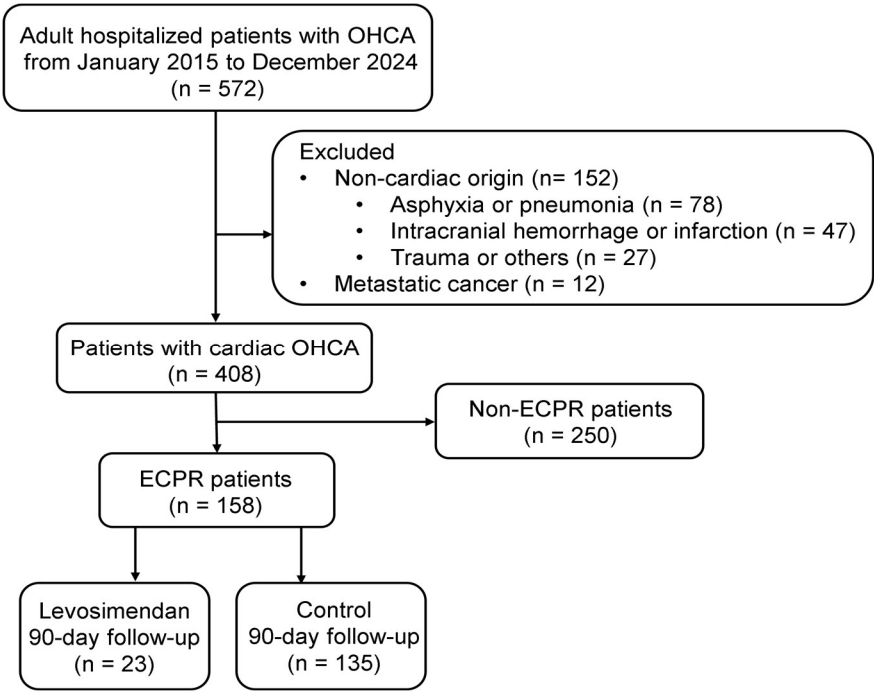


Figure 1. STROBE flow chart for OHCA survivors. A total of 572 adult patients with OHCA, hospitalized between January 2015 and December 2024, were enrolled for further evaluation. Subsequently, 164 patients with OHCA of non-cardiac origin or metastatic cancer were excluded, and 408 eligible patients were analyzed. However, 250 patients did not receive ECMO support. A total of 158 patients who received ECPR underwent further analyses. Additionally, 23 and 135 patients in the levosimendan and control groups, respectively, underwent a 90-day follow-up. ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest.

2.2. Variables, Data, Sources, and Measurements

Data were retrieved from electronic hospital records and included the following covariables: age, sex, CPR duration, initial shockable or non-shockable rhythm, first 24-h vasoactive-inotropic score (VIS), previous chronic medication, coronary angiography and mechanical circulatory support (e.g., intra-aortic balloon pump or extracorporeal membrane oxygenation), and echocardiography data.

2.3. Vasopressors (Epinephrine, Norepinephrine, and Vasopressin)

Epinephrine acts on the β_1 , β_2 , and α_1 adrenergic receptors to promote inotropy and cardiac pumping and induce vasoconstriction. During the first phase of cardiopulmonary resuscitation, high-dose epinephrine is commonly used to facilitate the restoration of cardiac pumping. Norepinephrine acts on α_1 and β_1 adrenergic receptors. Because of its high affinity for α_1 receptors, norepinephrine is typically administered as the first-line vasoconstrictor in a state of shock. Vasopressin acts on the V1 receptor. Owing to its high potency for vasoconstriction, vasopressin is often used as a second-line vasoconstrictor when norepinephrine fails to adequately improve blood pressure.

2.4. Inotropes (Dopamine and Dobutamine)

Dopamine and dobutamine primarily act on the β_1 adrenergic receptor. Dopamine exerts a dose-dependent. Low-dose dopamine (2–5 $\mu\text{g/kg/min}$) acts on dopaminergic and β_1 adrenergic receptors to enhance renal and interstitial circulation; medium-dose dopamine (5–10 $\mu\text{g/kg/min}$) acts on β_1 adrenergic receptors to increase heart rate and cardiac contractility; and high-dose dopamine (10–20 $\mu\text{g/kg/min}$) act on α_1 and β_1 adrenergic receptors, increasing not only heart rate and cardiac contractility but also blood pressure. Unlike dopamine, dobutamine acts on β_1 and β_2 adrenergic receptors to increase cardiac contractility and is commonly used in patients with acute heart failure or low cardiac output syndrome.

2.5. Inodilators (Milrinone and Levosimendan)

Milrinone is a phosphodiesterase 3 inhibitor that inhibits phosphodiesterase activity, suppressing the hydrolysis of the secondary messenger (cAMP), thereby increasing the cAMP concentration in cells. Milrinone exerts cardiac contractile and vasodilatory effects. Levosimendan is a calcium sensitizer that promotes the binding of myocardial troponin C to calcium, thereby enhancing cardiac contractility. Unlike other inotropes, OR-1855 and OR-1896 maintain cardiac contractility for 1–2 weeks and aid in cardiac recovery after low cardiac output, cardiac arrest, or coronary artery bypass grafting. Levosimendan has been found to exert additional effects on smooth muscles and mitochondria through K_{ATP} channels, thereby dilating blood vessels and protecting the heart.

2.6. First 24-h VIS

The first 24-h VIS was calculated using the maximum dosing rates of vasoactive and inotropic agents ($\mu\text{g/kg/min}$ or unit/kg/min) administered during the first 24 h after OHCA [16]. The maximal VIS was calculated as follows: (epinephrine [$\mu\text{g/kg/min}$] $\times 100$) + (norepinephrine [$\mu\text{g/kg/min}$] $\times 100$) + (vasopressin [unit/kg/min] $\times 10,000$) + (dopamine [$\mu\text{g/kg/min}$]) + (dobutamine

[$\mu\text{g/kg/min}$]) + (milrinone [$\mu\text{g/kg/min}$] \times 10) + (levosimendan [$\mu\text{g/kg/min}$] \times 50) [17]. Vasopressors can lead to inadequate perfusion, resulting in increased lactate concentrations. Inotropic agents can induce arrhythmia as a side effect, while inodilators cause hypotension due to vasodilatation. VIS-24 has been used to evaluate the severity of cardiogenic shock [18]. A VIS-24 h value of ≤ 100 indicated mild to moderate severity; 101–250 indicated severe severity; > 250 indicated critical severity.

2.7. Left Ventricular Function Test at 24 h After OHCA

Data on left ventricular ejection fraction (LVEF) 24 h after OHCA were acquired echocardiography using the Simpson method under an apical 4-chamber view and confirmed by two specialists. LVEF $\leq 40\%$ indicates systolic heart failure. Left ventricular cardiac index (LVCI) data were also acquired using echocardiography via the velocity-time integral of the left ventricular outflow tract. LVCI ≤ 2.2 L/min/M² indicates low cardiac output. Cardiac power output (CPO) is the product of cardiac output and the mean arterial pressure divided by 451; a CPO of < 0.6 W indicates cardiogenic shock.

2.8. Levosimendan Use Within 72 h of ECPR

Levosimendan within 72 h of ECPR was administered at the discretion of the specialist if the systolic blood pressure was > 90 mmHg without vasopressor use. Levosimendan was administered as a 12.5 mg dose diluted to 500 mL in 5% dextrose and maintained at 0.05–0.1 $\mu\text{g/kg/min}$ without loading. Following continuous infusion, coadministration of low-dose norepinephrine vasopressors, inotropic agents, or beta-blockers was permitted.

2.9. Statistical Analysis

Data values are expressed as mean \pm standard deviation (SD) or absolute number and percentages. Student's *t*-test was used to determine *p*-values, with a *p*-value of < 0.05 deemed statistically significant. Kaplan-Meier 90-day survival curves were used to compare the levosimendan and control groups. Multivariate Cox logistic regression analysis was performed to identify the independent risk factors for ECPR mortality. The model passed the proportional hazards hypothesis test, and the variance inflation factor of these covariates was set to < 10 to avoid multicollinearity. The 90-day hazard ratio, 95% confidence interval (CI), and related significant values obtained from the regression analysis are reported. Statistical significance was set at 5%. All statistical analyses were performed using SPSS version 30.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Clinical Characteristics

Table 1 summarizes the baseline clinical characteristics of the study population, which was classified based on levosimendan administration after ECPR. The mean patient age at diagnosis was 54.3 ± 13.9 years, and most were male (87.3%). Primary medical history included hypertension, hyperlipidemia, diabetes mellitus, chronic heart failure, and coronary artery disease as possible risk factors for ECPR.

Despite the high proportion of witnessed cardiac arrest (69.0%), bystander CPR (43.7%), and initial shockable rhythm (75.3%), the no-flow time was 4.8 ± 1.7 min, CPR duration was 34.8 ± 23.9 min, and initial arterial pH was 7.01 ± 0.18 . The cardiac arrest hospital prognosis score was 151.8 ± 39.4 .

The leading cause of cardiac OHCA after ECPR was coronary heart disease (67.11%), including left mainstem disease (14.6%) and triple-vessel disease (35.4%). Patients with ST-segment elevation myocardial infarction (42.4%) and non-ST-segment elevation myocardial infarction with hemodynamic instability (20.3%) underwent percutaneous coronary intervention (62.7%).

Approximately 31.0% of patients received intra-aortic balloon pumps on ECMO, and 71.5% received targeted temperature management.

The first 24-h VIS was as high as 244.4 ± 171.8 . Echocardiography at 24 h after ECPR revealed that LVEF was $31.1 \pm 14.9\%$, LVCI was 1.62 ± 0.99 L/min/M², and CPO was 0.49 ± 0.33 W. The levosimendan and control groups had similar baseline clinical characteristics.

Table 1. Baseline clinical characteristics of study subjects depending on whether levosimendan was administered after ECPR.

	Levosimendan (n = 23)	Control (n = 135)	p-value
Age (y), mean \pm SD	54.1 \pm 12.9	54.3 \pm 14.1	0.96
Male sex, n (%)	21 (91.3)	117 (86.7)	0.54
BMI (kg/m²), mean \pm SD	27.7 \pm 4.1	26.8 \pm 4.8	0.34
Medical history, n (%)			
Hypertension	13 (56.5)	52 (38.5)	0.11
Hyperlipidemia	9 (39.1)	49 (36.3)	0.66
Diabetes mellitus	5 (21.7)	28 (20.7)	0.91
Chronic heart failure	4 (17.4)	20 (14.8)	0.75
Coronary artery disease	4 (17.4)	26 (19.3)	0.83
End-stage renal disease	1 (4.3)	7 (5.2)	0.87
Cerebrovascular disease	1 (4.3)	3 (2.2)	0.55
Chronic obstructive pulmonary disease	1 (4.3)	1 (0.7)	0.15
Witnessed cardiac arrest, n (%)	17 (74.3)	92 (68.2)	0.48
Bystander CPR, n (%)	12 (52.2)	57 (42.2)	0.29
Initial shockable rhythm, n (%)	2 (91.3)	98 (72.6)	0.05
No-flow time (min), mean \pm SD	4.6 \pm 1.5	4.9 \pm 0.4	0.51
CPR duration (min), mean \pm SD	30.7 \pm 13.7	35.5 \pm 25.3	0.37
Initial arterial pH, mean \pm SD	7.04 \pm 0.16	7.01 \pm 0.19	0.39
CAHP score, mean \pm SD	140.3 \pm 26.7	153.8 \pm 7.1	0.13
CHD, n (%)			
Coronary angiography	15 (65.2)	92 (68.1)	0.78
Left main disease	6 (26.1)	17 (12.6)	0.09
Triple-vessel disease	9 (39.1)	47 (34.8)	0.69
AMI, n (%)			
Percutaneous coronary intervention	14 (60.9)	85 (63.0)	0.85
ST-elevation myocardial infarction	12 (52.2)	55 (40.7)	0.31
Intra-aortic balloon pump, n (%)	11 (47.8)	38 (28.1)	0.06
Targeted temperature management, n (%)	17 (73.9)	96 (71.1)	0.78
Cardiogenic shock, n (%)	22 (95.7)	129 (95.6)	0.98
SCAI Stage C, n (%)	2 (8.7)	29 (21.5)	
SCAI Stage D, n (%)	9 (39.1)	37 (27.4)	
SCAI Stage E, n (%)	11 (47.8)	63 (46.7)	

The first 24-h VIS, mean ± SD	235.7 ± 128.0	245.9 ± 178.6	0.79
Vasopressin (I/kg/min), mean ± SD	0.0 ± 0.0	0.0 ± 0.0	
Norepinephrine (µg/kg/min), mean ± SD	0.3 ± 0.2	0.2 ± 0.2	
Epinephrine (µg/kg/min), mean ± SD	2.0 ± 1.3	2.1 ± 1.7	
Dopamine (µg/kg/min), mean ± SD	6.3 ± 7.7	8.1 ± 9.3	
Dobutamine (µg/kg/min), mean ± SD	0.5 ± 1.5	0.2 ± 0.9	
LVEF at 24 h (%), mean ± SD	31.2 ± 12.2	31.0 ± 15.4	0.97
LVCI at 24 h (L/min/M²), mean ± SD	1.73 ± 0.83	1.60 ± 1.02	0.56
CPO at 24 h (W), mean ± SD	0.54 ± 0.26	0.48 ± 0.35	0.41

AMI, acute myocardial infarction; BMI, body mass index; CPR, cardiopulmonary resuscitation; CAHP, cardiac arrest hospital prognosis; CHD, coronary heart disease; CPO, cardiac power output; ECPR, extracorporeal cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; LVCI, left ventricular cardiac index; SD, standard deviation; VIS, vasoactive-inotropic score.

3.2. Follow-Up of Laboratory Tests on the Day of Admission

The results of laboratory tests at 6 and 24 h after OHCA are shown in Table 2. Blood counts were performed on the day of admission. On the first day after ECPR, the white blood cell count increased from 13.9 to 15.3 K/µL, particularly the neutrophil count from 7.8 to 13.1 K/µL. A decrease in hemoglobin from 12.7 to 11.2% and platelet count from 188.3 to 132.9K/µL was attributed to inflammation-related consumption.

Among the biochemical indices, markers related to heart, liver, and kidney function were significantly elevated following OHCA and ECPR because of organ damage. Although the mean lactate level decreased from 15.7 to 6.9 mmol/L, it remained above the threshold value of 5 mmol/L for critical status. The levosimendan and control groups had similar baseline blood counts and biochemical indices.

Table 2. Baseline blood counts and biochemical indices of study subjects at 6 and 24 h depending on whether levosimendan was administered after ECPR.

	Levosimendan (n = 23)	Control (n = 135)	p-value
Blood counts			
WBC (K/µL) at 6 h, mean ± SD	14.0 ± 6.8	13.9 ± 6.0	0.98
WBC (K/µL) at 24 h, mean ± SD	14.4 ± 7.8	15.5 ± 7.0	0.51
Neutrophils (K/µL) at 6 h, mean ± SD	7.6 ± 5.8	7.9 ± 5.0	0.78
Neutrophils (K/µL) at 24 h, mean ± SD	12.4 ± 7.4	13.2 ± 6.5	0.57
Hemoglobin (%) at 6 h, mean ± SD	13.2 ± 2.4	12.5 ± 2.6	0.05
Hemoglobin (%) at 24 h, mean ± SD	12.1 ± 1.9	11.0 ± 2.5	0.06
Platelet (K/µL) at 6 h, mean ± SD	182.5 ± 74.8	189.3 ± 140.8	0.82
Platelet (K/µL) at 24 h, mean ± SD	123.5 ± 53.3	134.6 ± 72.0	0.48
Biochemical indices			

Troponin-I (ng/mL) at 6 h, mean ± SD	6.9 ± 5.7	4.3 ± 3.8	0.08
Troponin-I (ng/mL) at 24 h, mean ± SD	110.2 ± 100.3	80.1 ± 80.8	0.11
AST (U/L) at 6 h, mean ± SD	249.6 ± 198.8	305.4 ± 311.4	0.46
AST (U/L) at 24 h, mean ± SD	577.6 ± 287.7	812.6 ± 1872.8	0.58
ALT (U/L) at 6 h, mean ± SD	125.2 ± 105.4	150.8 ± 177.6	0.53
ALT (U/L) at 24 h, mean ± SD	232.6 ± 180.3	272.7 ± 566.0	0.74
BUN (mg/dL) at 6 h, mean ± SD	21.0 ± 7.7	24.8 ± 20.6	0.41
BUN (mg/dL) at 24 h, mean ± SD	26.2 ± 6.1	28.9 ± 17.6	0.47
Creatinine (mg/dL) at 6 h, mean ± SD	1.5 ± 0.4	2.0 ± 2.0	0.22
Creatinine (mg/dL) at 24 h, mean ± SD	1.7 ± 0.4	2.0 ± 1.5	0.29
Lactate (mmol/L) at 6 h, mean ± SD	14.0 ± 6.3	16.0 ± 6.8	0.21
Lactate (mmol/L) at 24 h, mean ± SD	5.1 ± 2.8	7.2 ± 6.2	0.12

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; ECPR, extracorporeal cardiopulmonary resuscitation; WBC, white blood cells.

3.3. Analyses of Sequential Organ Failure Assessment (SOFA), Length of Stay, Clinical Outcomes, and Cerebral Performance Category (CPC)

The SOFA score uses six parameters, namely the heart, lung, brain, liver, kidney, and platelet levels, to assess organ perfusion. The mean SOFA score on day 1 was 14.3. After levosimendan administration, the SOFA score improved, decreasing to 11.6 on day 7. However, the SOFA score increased in the absence of levosimendan administration, reaching 16.2 on day 7. Hospital stay was longer in the levosimendan group than in the control group (38.0 days vs. 24.5 days, $p < 0.001$). The rates of ECMO weaning failure and 90-day mortality were significantly lower in the levosimendan group than in the control group (13.0% vs. 52.6% and 17.4% vs. 57.0%, respectively; all $p < 0.001$).

CPC is used to evaluate neurological outcomes as follows: CPC 1: normal or mild disability; CPC 2: moderate disability; CPC 3: severe disability; CPC 4: vegetative status or coma; CPC 5: brain death. Patients with CPC 1–2 had favorable neurological outcomes, while those assigned CPC 3–5 had poor neurological outcomes. Although the levosimendan group has a lower incidence of poor neurological outcomes than the control group, the difference was statically non-significant (47.8% vs. 71.8%, $p = 0.06$).

Table 3. Sub-analyses of SOFA, length of stay, clinical outcomes, and CPC for the study population based on whether levosimendan was administered after ECPR.

	Levosimendan (n = 23)	Control (n = 135)	p-value
SOFA on day 1, mean ± SD	14.1 ± 1.9	14.4 ± 2.5	0.64
SOFA on day 3, mean ± SD	13.4 ± 2.6	15.8 ± 5.2	0.03
SOFA on day 5, mean ± SD	12.7 ± 3.3	16.0 ± 6.2	0.01
SOFA on day 7, mean ± SD	11.6 ± 3.4	16.2 ± 7.0	0.003
Hospital stay (days), mean ± SD	38.0 ± 21.7	24.5 ± 26.0	0.02
ECMO weaning failure, n (%)	3 (13.0)	71 (52.6)	< 0.001

90-day mortality, n (%)	4 (17.4)	77 (57.0)	< 0.001
90-day poor neurological outcomes, n (%)	11 (47.8)	97 (71.8)	0.06
CPC sub-analyses at 90-day follow-up			
CPC 1, n (%)	6 (26.1)	27 (20.0)	
CPC 2, n (%)	6 (26.1)	11 (8.1)	
CPC 3, n (%)	5 (21.7)	7 (5.2)	
CPC 4, n (%)	2 (8.7)	13 (9.6)	
CPC 5, n (%)	4 (17.4)	77 (57.0)	

CPC, Cerebral Performance Category; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

3.4. Kaplan-Meier Survival Curves of ECPR

ECPR analysis was conducted using Kaplan-Meier survival curves. The 90-day follow-up analysis revealed the survival rate was 0.83 in the levosimendan group but only 0.43 in the control group, indicating a significant difference (log-rank $p < 0.001$; Figure 2).

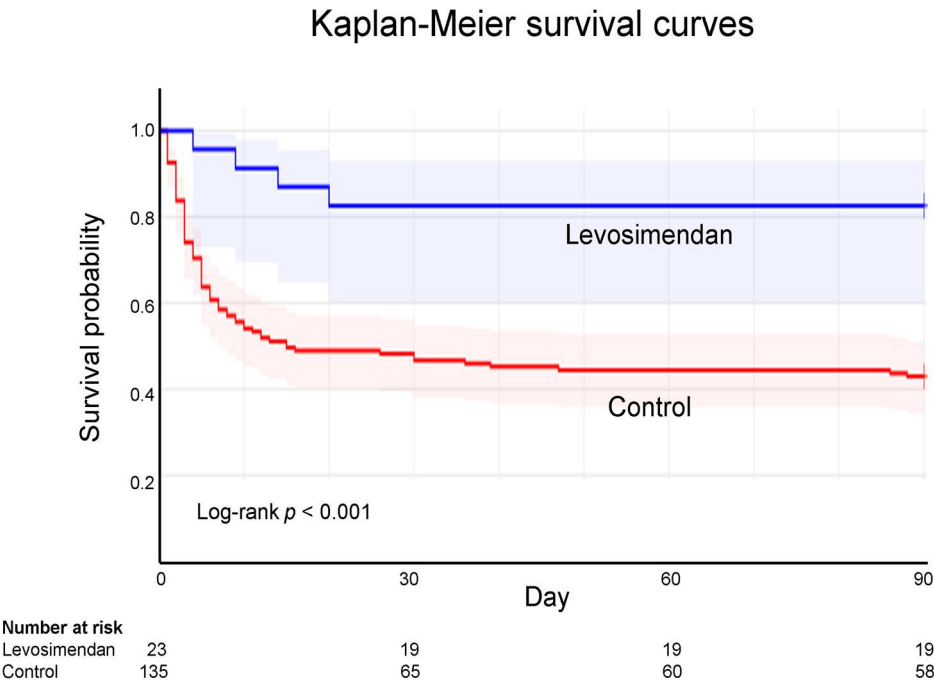


Figure 2. Kaplan-Meier survival curves for extracorporeal cardiopulmonary resuscitation according to levosimendan administration. According to Kaplan-Meier curve analysis, the 90-day survival rate following ECPR is 0.83 and 0.43 for the levosimendan and control groups, respectively.

3.5. Ninety-Day Mortality Rate-Adjusted Covariables Using Cox Regression Model

Figure 3 illustrates several covariates analyzed as risk factors for 90-day mortality after ECPR. Risk factors in descending order were as follows: lactate > 5 mmol/L (hazard ratio: 2.92, 95% CI: 1.86–4.57, $p < 0.001$); first 24-h VIS > 250 (hazard ratio: 1.82, 95% CI: 1.16–2.86, $p = 0.01$); CPR duration > 30 min (hazard ratio: 1.58, 95% CI: 1.01–2.46, $p = 0.05$). Age, sex, coronary heart disease, and add-on intra-aortic balloon pump did not significantly impact the 90-day mortality. Importantly, initial

shockable rhythm (hazard ratio: 0.53, 95% CI: 0.31–0.91, $p = 0.01$) and levosimendan within 72 h (hazard ratio: 0.30, 95% CI: 0.12–0.75, $p = 0.01$) were identified as protective factors.

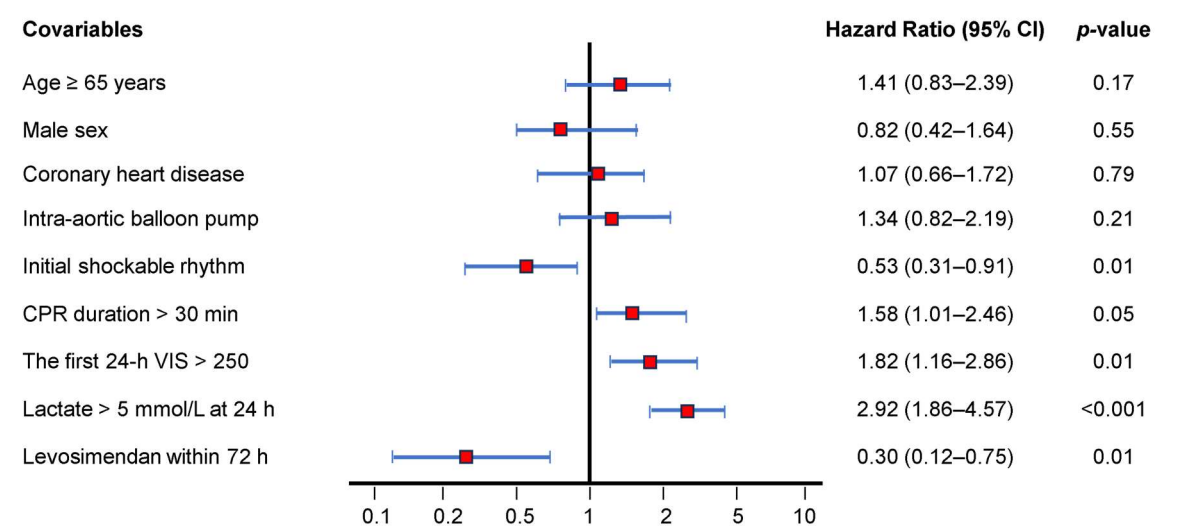


Figure 3. Ninety-day mortality rate-adjusted covariables of OHCA survivors after ECPR using the Cox regression model. Several covariables were analyzed as risk factors for 90-day mortality. Covariables include age ≥ 65 years (hazard ratio: 1.41, 95% CI: 0.83–2.39), male sex (hazard ratio: 0.82, 95% CI: 0.42–1.64), coronary heart disease (hazard ratio: 1.07, 95% CI: 0.66–1.72), intra-aortic balloon pump (hazard ratio: 1.34, 95% CI: 0.82–2.19), initial shockable rhythm (hazard ratio: 0.53, 95% CI: 0.31–0.91), CPR duration > 30 min (hazard ratio: 1.58, 95% CI: 1.01–2.46), the first 24-h VIS > 250 (hazard ratio: 1.82, 95% CI: 1.16–2.86), lactate > 5 mmol/L at 24 h (hazard ratio: 2.92, 95% CI: 1.86–4.57), and levosimendan administration within 72 h (hazard ratio: 0.19, 95% CI: 0.11–0.34). CPR, cardiopulmonary resuscitation; VIS, vasoactive-inotropic score; OHCA, out-of-hospital cardiac arrest; ECPR, extracorporeal cardiopulmonary resuscitation.

4. Discussion

In the current study, we evaluated the potential protective factors that could improve all-cause mortality after ECPR in patients with OHCA. In this retrospective study, we found that the use of levosimendan within 72 h yielded a good survival benefit. However, the appropriate timing and conditions for use warrant further investigation.

OHCA involves both myocardial ischemia and cerebral hypoxia and induces severe ischemia-reperfusion injury. ECPR is performed with shock to reduce ischemia/reperfusion injuries [8]. Considering the high mortality (between 50 and 70%), a new strategy is required to improve these poor outcomes [6].

As an inodilator, levosimendan has been widely used to treat acute and advanced heart failure in Europe and Asia for the past two decades [19,20,21]. Levosimendan, a novel myofilament calcium sensitizer, binds myocardial troponin C with calcium to enhance heart contractility. The circulating metabolites OR-1855 and OR-1896 are formed slowly and maintain heart contractility after 24 h for 1–2 weeks. Levosimendan can also induce smooth muscle relaxation via K_{ATP} activation to enhance vasodilation and protect the heart via mitochondrial K_{ATP} activation [19,20]. Therefore, maximal pulmonary capillary wedge pressure was reduced 6 h after infusion, and maximal cardiac output was enhanced 24 h after infusion [20,21]. Additionally, levosimendan has been employed to address other conditions, including cardiac surgery (especially in coronary artery bypass grafting), right heart failure, tachycardia, postpartum cardiomyopathy, stunned myocardium, calcium channel blocker toxicity, and sepsis, benefiting not only for the heart but also providing systemic support [22]. In recent years, levosimendan has been successfully used in cardiogenic shock as an adjunct therapy with vasopressors or antiarrhythmic drugs [23].

Weaning from ECMO can be challenging because of poor heart recovery. Although dopamine inotropy was frequently attempted 10 years ago, the ECMO weaning failure rate was high owing to the adverse effects of ventricular arrhythmias. In recent years, the use of dobutamine has been recommended as a dopamine replacement and the first inotropic agent for ECMO weaning, given the fewer ventricular arrhythmias and mild vasodilatory effects [24]. Milrinone, an inodilator, has been shown to exert similar results despite inducing greater vasodilatation [25]. Levosimendan is the most recent successful inodilator used in ECMO weaning, inducing inotropic and vasodilatory effects similar to milrinone, with a lower myocardial oxygen demand than milrinone or dobutamine [25]. Although milrinone is more likely to lower the pH, it could be advantageous over milrinone in terms of ECMO weaning. In addition to eliciting a more sustained inodilatory effect, levosimendan prevents intracellular calcium overload and myocardial oxygen demand, thereby promoting ECMO weaning [23,26]. ECPR combines ECMO and CPR after cardiac arrest. OHCA of cardiac origin is commonly attributed to acute myocardial infarction, heart failure, or idiopathic ventricular arrhythmia. Levosimendan exerts inotropic and vasodilatory effects during ECMO weaning and facilitates cardiac recovery from CPR-related myocardial stunning [27,28]. The all-cause mortality rate markedly decreased as the ECMO weaning rate increased [29,30]. The increased perfusion due to levosimendan use also improves cardiac and multiorgan function. Meta-analyses have confirmed the overall decline in all-cause mortality after levosimendan administration [31,32].

Myocardial dysfunction is a key factor governing the response to levosimendan. Because of its inotropic effect, levosimendan improves LVEF, particularly in the stunned myocardium. Moreover, levosimendan improves low cardiac output syndrome owing to its combined inotropic and vasodilatory effects [33]. Follow-up data obtained echocardiography at 24 h post-ECPR revealed a mean LVEF of 31.2% ($< 40\%$), LVCI of 1.73 L/min/m² (< 2.2 L/min/m²), and CPO of 0.54 W (< 0.6 W). Notably, a poor systolic function (LVEF $< 25\%$) can impact prognosis [34]. In this situation, given the lack of viable myocardium, a left ventricular assist device or heart transplantation should be considered in addition to levosimendan [35].

In addition to the heart, levosimendan improves perfusion in other organs. Recently, levosimendan was shown to improve renal function through renal vasodilation, particularly in patients with cardiorenal syndrome [36,37]. In our study, the levosimendan group had lower SOFA scores than the control group on days 3, 5, and 7 (13.4 vs. 15.8, $p = 0.03$; 12.7 vs. 16.0, $p = 0.01$; 11.6 vs. 16.2, $p = 0.003$, respectively). This finding could be largely attributed to cardiac and kidney functional recovery. The downward trend in the incidence of poor neurological outcomes was statistically non-significant (47.8% vs. 71.8%, $p = 0.06$). This finding implies that, in addition to increased cerebral perfusion (e.g., ECMO and levosimendan) and targeted temperature management, other factors must be explored for brain recovery. Lactate levels are indicative of multiorgan perfusion status. For a lactate level of > 5 mmol/L 24 h post-ECPR affecting the clinical outcome, the hazard ratio was 2.92, consistent with the findings of previous studies [38].

Early administration of levosimendan is crucial because myocardial dysfunction and ischemia/reperfusion injury can affect outcomes in the first 72 h. In the current study, the use of levosimendan within 72 h enhanced inotropy and vasodilatation and improved clinical outcomes. Along with supportive ECMO, levosimendan administration within 24 h does not induce side effects, such as hypotension, and could effectively improve clinical outcomes [39]. Conversely, delaying levosimendan administration for > 72 h failed to improve ECMO weaning rates or clinical outcomes [40].

This study has some limitations. First, the number of patients who received ECPR with levosimendan administration was markedly small, restricting the confidence level. Second, this study was conducted at a single center and may be non-applicable to other hospitals. Third, lactate levels > 5 mmol/L 24 h after OHCA notably impacted the accuracy of the 90-day mortality rate. Finally, the retrospective cohort study design reduced the real-world reliability compared with prospective cohort studies or randomized clinical trials.

5. Conclusions

In the current study, the levosimendan group had lower rates of ECMO weaning failure and 90-day all-cause mortality than the control group (13.0% vs. 52.6% and 17.4% vs. 57.0%, respectively; both $p < 0.001$). According to the 90-day Kaplan-Meier survival curve analysis, the survival rates for the levosimendan and control groups were 0.83 and 0.43, respectively (log-rank $p < 0.001$). The hazard ratio for levosimendan administration within 72 h was 0.30 (95% CI: 0.12–0.75, $p = 0.01$). Based on these findings, levosimendan should be included as a protective agent for patients undergoing ECPR after OHCA.

Author Contributions: Conceptualization, D. C. and Y. L.; methodology, D. C.; data curation, D. C. and Y. L.; formal analysis, D. C.; investigation, D. C.; writing – original draft, D. C.; writing – review and editing, G. W. and K. C.; supervision, G. W. and K. C. All authors have read and agreed to the published version of the manuscript.

Funding: This study received no external funding.

Institutional Review Board Statement: This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH104-REC3-058 and CMUH112-REC3-016) for data collection and analysis.

Informed Consent Statement: Verbal and written informed consent were obtained from all participants.

Data Availability Statement: The original contributions presented in this study are included in the article, and further inquiries can be directed to the corresponding authors.

Acknowledgments: All authors would like to thank Dr. Ching-Yi Chou, Dr. Wen-De Tang, Dr. Ching-Fen Chang, Dr. Kee-Koon Ng, and Dr. Yi-Jiun Jou at the China Medical University Hospital for their excellent clinical team support.

Conflicts of Interest: The authors declare no conflict of interest. The authors declare no financial interests.

Abbreviations

CAHP	Cardiac arrest hospital prognosis
CI	Confidence interval
CPC	Cerebral Performance Category
CPO	Cardiac power output
CPR	Cardiopulmonary resuscitation
ECPR	Extracorporeal cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
LVEF	Left ventricular ejection fraction
LVCi	Left ventricular cardiac index
OHCA	Out-of-hospital cardiac arrest
SOFA	Sequential Organ Failure Assessment
VIS	Vasoactive-inotropic score

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