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ORIGINAL RESEARCH

Impact of the interval between cardiopulmonary resuscitation and veno-arterial extracorporeal membrane oxygenation on in-hospital mortality in adult patients after cardiac arrest

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can improve survival and neurological outcomes in patients with cardiac arrest. This study aimed to evaluate the association between the interval from cardiopulmonary resuscitation (CPR) initiation to VA-ECMO cannulation and in-hospital mortality in adult patients. **Methods**: Data from 279 adult patients who received VA-ECMO during CPR were retrospectively collected and the CPR-to-ECMO interval was stratified into tertiles: $\leq$14 minutes, 15–29 minutes, and $>$30 minutes. A multivariable logistic regression examined the relationship between the interval and in-hospital mortality, adjusting for potential confounders. **Results**: Among the 279 patients who underwent VA-ECMO, 179 died during hospitalization. VA-ECMO was initiated within 14 minutes in 44 patients, between 15 and 29 minutes in 52 patients, and after more than 30 minutes in 83 patients. A longer interval was independently associated with a higher risk of in-hospital mortality. Each additional minute of delay was associated with a 3% increase in mortality risk (adjusted odds ratio (aOR) 1.03; 95% confidence interval (CI), 1.01–1.04; $p = 0.002$). Compared to patients in the lowest tertile, those in the highest tertile had a 4.07-fold increased risk of death (aOR 4.07; 95% CI, 1.90–8.73; $p < 0.001$). **Conclusions**: In patients undergoing CPR, a shorter interval between CPR initiation and VA-ECMO cannulation was significantly associated with lower in-hospital mortality. These findings underscore the importance of minimizing delays in VA-ECMO initiation to improve survival outcomes following cardiac arrest.

Keywords

Cardiopulmonary resuscitation; Interval; Veno-arterial extracorporeal membrane oxygenation; Mortality; Cardiac arrest

1. Background

Cardiac arrest is characterized by the sudden cessation of effective cardiac output, resulting in the abrupt interruption of systemic blood circulation. This condition can rapidly lead to end-organ hypoperfusion and ischemia, frequently culminating in multi-organ dysfunction. In-hospital mortality following cardiac arrest remains high, ranging from 75% to 90% [1, 2]. Cardiopulmonary resuscitation (CPR) is a fundamental emergency intervention aimed at restoring circulation during cardiac arrest. However, when conventional CPR fails to achieve return of spontaneous circulation (ROSC), the probability of survival declines significantly with time [3]. Even among patients in whom ROSC is achieved, many develop post-cardiac arrest syndrome, a pathophysiological state characterized by hypoxic brain injury, myocardial dysfunction, systemic vasodilation, and renal and hepatic impairment [4]. Despite advances in supportive care, including optimization of ventilatory, hemodynamic, and metabolic parameters, in-hospital mortality in this population remains between 40% and 90% [5, 6]. Given these challenges, early and effective intervention is critical. Delays in initiating resuscitative efforts are strongly associated with decreased survival rates and an increased risk of irreversible neurological injury [7, 8]. Therefore, strategies aimed at minimizing time to advanced resuscitation may offer significant prognostic benefit in patients experiencing cardiac arrest.

The prompt initiation of CPR is essential for maintaining tissue perfusion and improving the likelihood of successful resuscitation [9, 10]. Evidence indicates that each minute of delay in initiating CPR and defibrillation is associated with a 7–10% decrease in survival probability [11, 12]. In cases

where conventional CPR fails to achieve sustained ROSC, extracorporeal membrane oxygenation (ECMO) may be required to provide temporary circulatory and respiratory support [13]. Although the use of ECMO has been associated with benefits in improving both survival and neurological outcomes in patients with refractory cardiac arrest [14, 15], the optimal timing and duration of CPR before the initiation of ECMO remain subjects of ongoing investigation and clinical debate.

To date, only a limited number of randomized controlled trials have evaluated the use of ECMO in critically ill patients, and the existing evidence supporting current ECMO-related guidelines remains relatively weak [16, 17]. Despite this, the clinical indications for ECMO have progressively evolved over the past decade. A previous study analyzing risk factors in patients who underwent extracorporeal cardiopulmonary resuscitation (ECPR) suggested that the interval between the initiation of CPR and the cannulation of ECMO may represent the only modifiable prognostic factor influencing ECPR outcomes, with the early initiation of ECMO during ECPR being associated with significant improvements in both short- and long-term survival [18]. However, a study by Tae Sun Ha reported no significant difference in the arrest-to-ECMO interval between survivors and non-survivors [19]. Currently, there is a lack of comprehensive data clarifying how the timing of ECMO initiation affects patient outcomes in the context of ECPR. The optimal timing for initiating veno-arterial ECMO (VA-ECMO) in patients with cardiac arrest remains unclear and is often influenced by a range of clinical and logistical considerations [20, 21]. Factors such as severity of the cardiac arrest, immediate patient response to conventional CPR, and the availability of ECMO equipment and trained personnel can all impact the timing of ECMO deployment [22].

Given the increasing use of ECMO in the management of post-cardiac arrest patients, a clearer understanding of the optimal CPR-to-ECMO interval is of paramount clinical relevance. Therefore, the present study was designed to evaluate the prognostic significance of the time interval between the initiation of CPR and the cannulation of ECMO support in patients who experienced cardiac arrest. By conducting a rigorous analysis and applying robust statistical methods to adjust for potential confounders, this study aims to address a critical gap in current knowledge and provide clinically relevant evidence to guide decision-making and improve outcomes in this high-risk patient population.

2. Materials and methods

2.1 Study design

This study was a secondary retrospective cohort analysis conducted using publicly available data from the Division of Vascular Surgery at Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea. The objective was to evaluate in-hospital mortality in relation to the interval between the initiation of CPR and the cannulation of VA-ECMO. The dataset, originally provided by Eunae Byun, is accessible via a public data repository at https://doi.org/10.1371/journal.pone.0300713.s010 [23]. The registry comprises detailed clinical data of patients who underwent ECMO during severe cardiac arrest between January 2015 and December 2019. The present analysis aimed to determine whether the duration of the CPR-to-ECMO interval was associated with in-hospital mortality outcomes.

2.2 Study population

All adult patients (aged $\geq$18 years) who experienced cardiac arrest, either in-hospital or out-of-hospital, and were subsequently transferred to Asan Medical Center were eligible for inclusion based on the following predefined criteria: (a) cardiac arrest patients aged 18 years or older, irrespective of the arrest location; (b) absence of sustained ROSC following conventional CPR, with sustained ROSC defined as the absence of chest compressions for at least 20 minutes; (c) patients who received VA-ECMO for refractory cardiac arrest, either in-hospital or out-of-hospital, with ECMO support maintained for a minimum duration of 24 hours; and (d) a witnessed collapse or a reliably estimated time of collapse. However, those with any of the following criteria were excluded: did not undergo CPR (n = 568), required re-initiation of ECMO (n = 12), and underwent veno-venous ECMO (n = 9). Of the 868 ECMO patients initially screened, a total of 279 met the inclusion criteria and were included in the analysis. The study flowchart is presented in Fig. 1.

2.3 Grouping and outcome definitions

Participants were classified into three groups according to the tertiles of the interval from the initiation of CPR to the cannulation of VA-ECMO. The tertile thresholds were defined as follows: tertile 1 (T1, n = 84), interval $<$14 minutes; tertile 2 (T2, n = 91), interval between 15 and 29 minutes; and tertile 3 (T3, n = 104), interval $\geq$30 minutes. The primary study endpoint was in-hospital mortality.

2.4 Demographic characteristics and other covariates

Variables included in the database file were demographic data, pre-existing comorbidities, laboratory findings, clinical characteristics, indications for VA-ECMO, and in-hospital mortality. Additionally, ECMO-specific variables extracted from procedural records included ECMO running time, placement of distal perfusion catheter, and complications related to VA-ECMO. VA-ECMO-related events were individually documented and included bleeding, thromboembolism, deep venous thrombosis, cannula-related local complications, pseudoaneurysm, arteriovenous fistula, arterial dissection, local wound infection, peripheral neurologic events, bowel ischemia, and pneumothorax. VA-ECMO-related vascular events specifically included thromboembolism, bleeding, deep venous thrombosis, cannula-related local complications, pseudoaneurysm, arteriovenous fistula, and arterial dissection.

2.5 Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation, while categorical variables are reported as frequencies

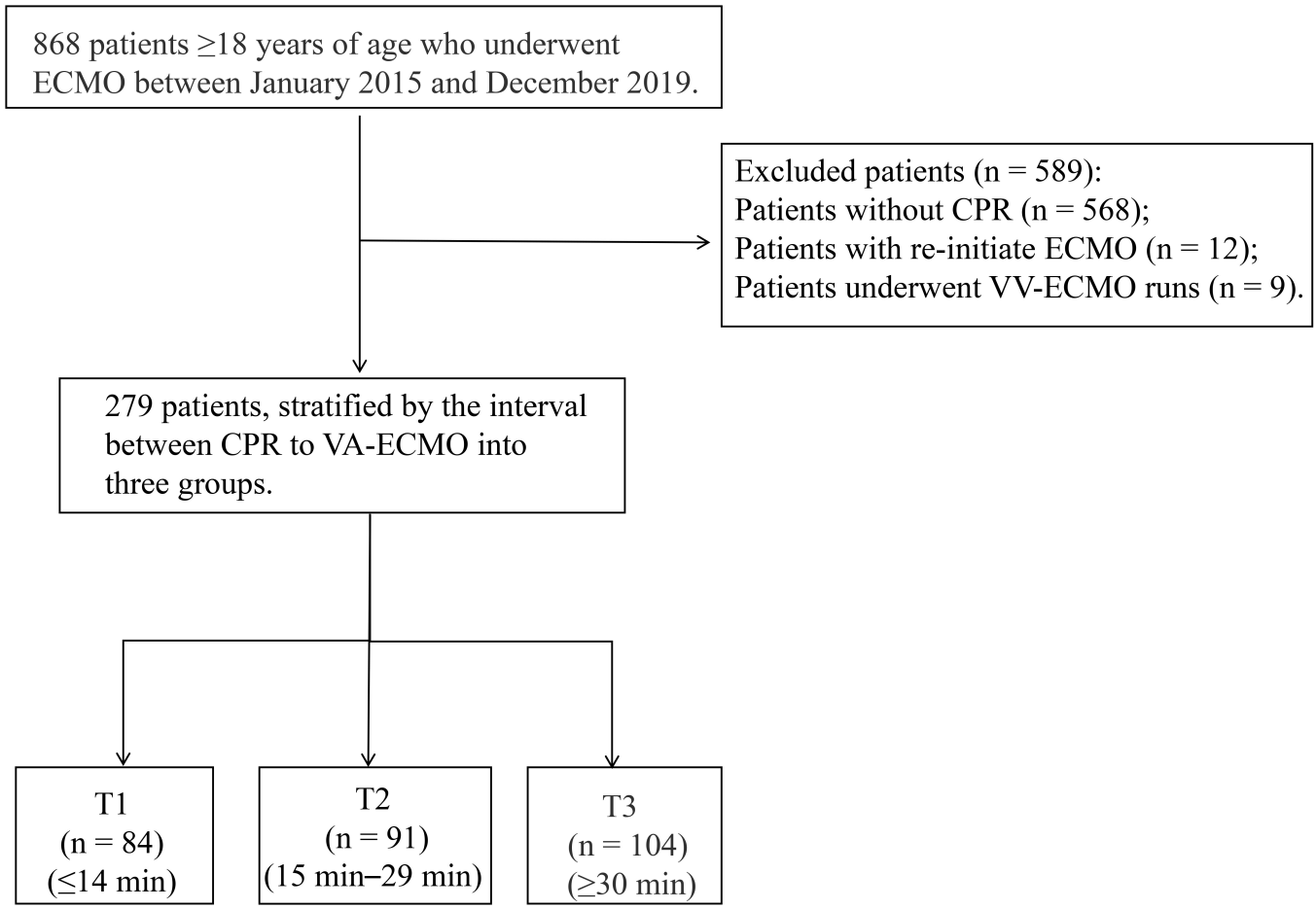

FIGURE 1. Screening criteria and study flow chart. CPR, cardiopulmonary resuscitation; VV-ECMO, veno-venous extracorporeal membrane oxygenation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

or percentages. Group comparisons across the CPR-to-ECMO interval categories were performed using one-way analysis of variance (ANOVA) for normally distributed variables, the Kruskal-Wallis H test for non-normally distributed variables, and the chi-square test for categorical variables.

Univariable and multivariable logistic regression models were used to assess the association between CPR-to-ECMO interval and in-hospital mortality. Three models were constructed: Model 1 was unadjusted; Model 2 adjusted for age, sex, and body mass index (BMI); and Model 3 further adjusted for age, sex, smoking status, BMI, diabetes mellitus, hypertension, chronic kidney disease, cerebrovascular accident, coronary artery disease, peripheral artery disease, C-reactive protein, preoperative hemoglobin, platelet count, partial thromboplastin time, international normalized ratio (INR), use of antiplatelet or anticoagulation therapy, VA-ECMO insertion site, VA-ECMO indication, VA-ECMO-related events, VA-ECMO-related vascular events, and ECMO running time.

Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported, and the dose-response relationship between CPR-to-ECMO interval and in-hospital mortality was further explored using curve fitting techniques. Stratified analyses were also conducted to evaluate the consistency of associations across subgroups and to ensure robustness of the findings.

All statistical analyses were performed using R software (version 4.3; http://www.r-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Characteristics of participants

A total of 279 adult patients were included in the final analysis. Baseline characteristics stratified by CPR-to-VA-ECMO interval tertiles are presented in Table 1. Patients in the higher tertiles were found to be more likely to have diabetes mellitus compared with those in the lowest tertile. No statistically significant differences were observed in most demographic variables across the three groups, with the exception of C-reactive protein levels, which differed significantly ($p = 0.036$). With regard to ECMO-related parameters, significant differences were observed in the indication for VA-ECMO insertion ($p = 0.020$), the location of VA-ECMO cannulation ($p = 0.050$), and VA-ECMO running time ($p < 0.001$).

Patient outcome variables also varied significantly, with differences observed in total hospital stay ($p < 0.001$), Intensive Care Unit (ICU) stay duration ($p < 0.001$), and in-hospital mortality ($p < 0.001$). The overall in-hospital mortality rate in the study cohort was 64.16% (179 of 279 patients). Follow-

TABLE 1. Characteristics of patients according to the interval between CPR and VA-ECMO initiation.

Variables	T1 (≤14 min) n = 84	T2 (15 min–29 min) n = 91	T3 (>30 min) n = 104	*p*
Gender (n (%))				
Male	64 (76.19%)	64 (70.33%)	78 (75.00%)	0.640
Female	20 (23.81%)	27 (29.67%)	26 (25.00%)	
Age (yr)	57.82 ± 13.66	61.37 ± 14.75	60.15 ± 14.08	0.127
BMI	24.14 ± 5.71	23.98 ± 4.27	24.12 ± 4.22	0.638
Smoking status (n (%))				
No	61 (72.62%)	65 (71.43%)	77 (74.04%)	0.919
Yes	23 (27.38%)	26 (28.57%)	27 (25.96%)	
Hypertension (n (%))				
No	38 (45.24%)	52 (57.14%)	54 (51.92%)	0.289
Yes	46 (54.76%)	39 (42.86%)	50 (48.08%)	
Diabetes mellitus (n (%))				
No	54 (64.29%)	70 (76.92%)	62 (59.62%)	0.033
Yes	30 (35.71%)	21 (23.08%)	42 (40.38%)	
Chronic kidney disease (n (%))				
No	66 (78.57%)	80 (87.91%)	87 (83.65%)	0.250
Yes	18 (21.43%)	11 (12.09%)	17 (16.35%)	
Cerebrovascular accident (n (%))				
No	73 (86.90%)	86 (94.51%)	95 (91.35%)	0.211
Yes	11 (13.10%)	5 (5.49%)	9 (8.65%)	
Coronary artery disease (n (%))				
No	59 (70.24%)	67 (73.63%)	77 (74.04%)	0.823
Yes	25 (29.76%)	24 (26.37%)	27 (25.96%)	
Peripheral artery disease (n (%))				
No	82 (97.62%)	88 (96.70%)	100 (96.15%)	0.851
Yes	2 (2.38%)	3 (3.30%)	4 (3.85%)	
CRRT (n (%))				
No	29 (34.52%)	30 (32.97%)	38 (36.54%)	0.871
Yes	55 (65.48%)	61 (67.03%)	66 (63.46%)	
C-reactive protein (mg/L)	2.15 ± 2.48	1.56 ± 1.53	1.79 ± 1.96	0.036
Preoperative hemoglobin (g/L)	11.12 ± 2.76	11.30 ± 2.75	11.31 ± 3.05	0.832
Preoperative platelet ($\times 10^9$/L)	187.27 ± 89.45	187.01 ± 115.63	170.86 ± 106.09	0.236
Preoperative partial thromboplastin time (s)	42.89 ± 33.00	45.64 ± 37.37	50.72 ± 43.84	0.369
Preoperative INR	1.49 ± 0.71	1.59 ± 1.67	1.86 ± 2.21	0.301
Preoperative anti-platelet therapy (n (%))				
No	54 (64.29%)	64 (70.33%)	77 (74.04%)	0.348
Yes	30 (35.71%)	27 (29.67%)	27 (25.96%)	
Preoperative anti-coagulation therapy (n (%))				
No	73 (86.90%)	79 (86.81%)	95 (91.35%)	0.523
Yes	11 (13.10%)	12 (13.19%)	9 (8.65%)	
Place of VA-ECMO insertion (n (%))				
Operation room	8 (9.52%)	6 (6.59%)	6 (5.77%)	0.050
ICU	44 (52.38%)	38 (41.76%)	35 (33.65%)	
Other	32 (38.10%)	47 (51.65%)	63 (60.58%)	

TABLE 1. Continued.

Variables	T1 (≤14 min) n = 84	T2 (15 min–29 min) n = 91	T3 (>30 min) n = 104	*p*
Indication of VA-ECMO insertion (n (%))				
Post-cardiotomy shock	11 (13.10%)	8 (8.79%)	4 (3.85%)	0.020
Cardiac failure	61 (72.62%)	72 (79.12%)	95 (91.35%)	
Other	12 (14.29%)	11 (12.09%)	5 (4.81%)	
Distal perfusion catheter (n (%))				
No	58 (69.05%)	64 (70.33%)	84 (80.77%)	0.125
Yes	26 (30.95%)	27 (29.67%)	20 (19.23%)	
VA-ECMO-related events (n (%))				
No	54 (64.29%)	55 (60.44%)	69 (66.35%)	0.689
Yes	30 (35.71%)	36 (39.56%)	35 (33.65%)	
VA-ECMO-related vascular events (n (%))				
No	69 (82.14%)	71 (78.02%)	86 (82.69%)	0.674
Yes	15 (17.86%)	20 (21.98%)	18 (17.31%)	
Time from cardiac arrest to VA-ECMO initiation (min)	7.15 ± 3.97	21.71 ± 4.47	48.47 ± 24.33	<0.001
VA-ECMO running time (min)	9561.67 ± 13,388.43	6959.07 ± 8864.54	5546.18 ± 11,458.09	<0.001
Hospital stay (d)	51.80 ± 80.30	40.86 ± 53.95	39.56 ± 128.05	<0.001
ICU stay (d)	26.61 ± 42.62	17.69 ± 23.78	15.54 ± 30.72	<0.001
In-hospital mortality (n (%))				
No	40 (47.62%)	39 (42.86%)	21 (20.19%)	<0.001
Yes	44 (52.38%)	52 (57.14%)	83 (79.81%)	

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; BMI, Body mass index; CRRT, continuous renal replacement therapy; INR, International Normalized Ratio; ICU, Intensive Care Unit.

ing tertile stratification, in-hospital mortality was 52.38% (44 deaths) in the lowest time interval group, 57.14% (52 deaths) in the middle group, and 79.81% (83 deaths) in the highest interval group.

3.2 Univariable analysis for in-hospital mortality

The results indicated a significant association between the interval from CPR to VA-ECMO initiation and in-hospital mortality. Each additional minute in the interval was associated with increased odds of in-hospital death (OR 1.02; 95% CI, 1.01–1.04; $p = 0.001$). No significant associations were observed for BMI ($p = 0.534$) or smoking status ($p = 0.622$). In contrast, higher preoperative hemoglobin levels were significantly associated with reduced in-hospital mortality (OR 0.83; 95% CI, 0.76–0.91; $p < 0.001$). A similar inverse relationship was observed for preoperative platelet count (OR 0.99; 95% CI, 0.99–1.00; $p < 0.001$). Female patients exhibited a significant trend toward increased in-hospital mortality (OR 2.02; 95% CI, 1.11–3.69; $p = 0.022$). In addition, patients who received continuous renal replacement therapy (CRRT) had a significantly higher risk of in-hospital death compared to those who did not (OR 2.29; 95% CI, 1.37–3.81; $p = 0.001$) (Table 2).

3.3 Relationship between the interval from CPR to VA-ECMO and in-hospital mortality

In the unadjusted model (Model 1), each one-minute increase in the interval from CPR to VA-ECMO initiation was associated with a 2% increase in the odds of in-hospital mortality (OR 1.02; 95% CI, 1.01–1.04; $p = 0.001$). This association remained statistically significant in the fully adjusted model (Model 3), in which the odds of mortality increased by 3% per minute delay (adjusted OR (aOR) 1.03; 95% CI, 1.01–1.04; $p = 0.002$), indicating that a longer interval is independently associated with higher in-hospital mortality risk.

Further analysis based on interval tertiles demonstrated that patients in the highest tertile (≥30 minutes) had significantly greater odds of in-hospital death compared with those in the lowest tertile (<14 minutes). After adjusting for all potential confounders, the aOR for in-hospital mortality in the highest tertile was 4.07 (95% CI, 1.90–8.73; $p < 0.001$), as shown in Table 3.

For the purpose of sensitivity analysis, we converted the interval into categorical variable according to tertile classification and calculated the p for trend. In the fully adjusted model (Model 3), the aORs for in-hospital mortality in T2 and T3 compared to T1 were 1.13 and 4.07, respectively. The p for trend was < 0.001, supporting the presence of a dose-response relationship. These findings are consistent with those

TABLE 2. Univariable logistic regression analysis of in-hospital mortality.

Variables	Statistics	OR (95% CI)	*p*
Gender			
Male	206 (73.84%)	Ref.	
Female	73 (26.16%)	2.02 (1.11, 3.69)	0.022
Age (yr)	59.85 ± 14.20	1.02 (1.00, 1.03)	0.076
BMI	24.08 ± 4.72	1.02 (0.96, 1.07)	0.534
Smoke (n (%))			
No	203 (72.76%)	Ref.	
Yes	76 (27.24%)	0.87 (0.51, 1.50)	0.622
Hypertension (n (%))			
No	144 (51.61%)	Ref.	
Yes	135 (48.39%)	1.32 (0.80, 2.15)	0.274
Diabetes mellitus (n (%))			
No	186 (66.67%)	Ref.	
Yes	93 (33.33%)	1.58 (0.92, 2.70)	0.095
Chronic kidney disease (n (%))			
No	233 (83.51%)	Ref.	
Yes	46 (16.49%)	1.97 (0.95, 4.07)	0.068
Cerebrovascular accident (n (%))			
No	254 (91.04%)	Ref.	
Yes	25 (8.96%)	1.21 (0.50, 2.90)	0.675
Coronary artery disease (n (%))			
No	203 (72.76%)	Ref.	
Yes	76 (27.24%)	0.94 (0.54, 1.63)	0.831
Peripheral artery disease (n (%))			
No	270 (96.77%)	Ref.	
Yes	9 (3.23%)	1.12 (0.27, 4.58)	0.873
CRRT (n (%))			
No	97 (34.77%)	Ref.	
Yes	182 (65.23%)	2.29 (1.37, 3.81)	0.001
C-reactive protein (mg/L)	1.82 ± 2.02	1.03 (0.90, 1.16)	0.696
Preoperative hemoglobin (g/L)	11.25 ± 2.86	0.83 (0.76, 0.91)	<0.001
Preoperative platelet ($\times 10^9$/L)	181.07 ± 104.64	0.99 (0.99, 1.00)	<0.001
Preoperative Partial Thromboplastin Time (s)	46.70 ± 38.73	1.02 (1.01, 1.03)	0.003
Preoperative INR	1.66 ± 1.70	1.43 (0.99, 2.08)	0.057
Preoperative anti-platelet therapy (n (%))			
No	195 (69.89%)	Ref.	
Yes	84 (30.11%)	0.94 (0.55, 1.59)	0.808
Preoperative anti-coagulation therapy (n (%))			
No	247 (88.53%)	Ref.	
Yes	32 (11.47%)	1.26 (0.57, 2.78)	0.565
Place of VA-ECMO insertion (n (%))			
Operation room	20 (7.17%)	Ref.	
ICU	117 (41.94%)	2.08 (0.80, 5.42)	0.134
Other	142 (50.90%)	1.73 (0.68, 4.43)	0.253

TABLE 2. Continued.

Variables	Statistics	OR (95% CI)	*p*
Indication of VA-ECMO insertion (n (%))			
Post-cardiotomy shock	23 (8.24%)	Ref.	
Cardiac failure	228 (81.72%)	1.66 (0.70, 3.94)	0.247
Other	28 (10.04%)	2.29 (0.72, 7.30)	0.161
Distal perfusion catheter (n (%))			
No	206 (73.84%)	Ref.	
Yes	73 (26.16%)	0.54 (0.31, 0.93)	0.027
VA-ECMO-related events (n (%))			
No	178 (63.80%)	Ref.	
Yes	101 (36.20%)	0.78 (0.47, 1.29)	0.324
VA-ECMO-related vascular events (n (%))			
No	226 (81.00%)	Ref.	
Yes	53 (19.00%)	0.82 (0.44, 1.51)	0.524
Time from cardiac arrest to VA-ECMO initiation (min)	27.30 ± 23.04	1.02 (1.01, 1.04)	0.001
VA-ECMO running time (min)	7215.98 ± 11,416.06	1.00 (1.00, 1.00)	0.063

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; INR, International Normalized Ratio; BMI, body mass index; ICU, Intensive Care Unit; Ref., reference range; OR, odds ratio; CI, confidence interval.

TABLE 3. Multivariable logistic regression analysis of the association between the interval from CPR to VA-ECMO and in-hospital mortality.

Exposure	Model 1		Model 2		Model	
	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Time from cardiac arrest to VA-ECMO initiation (min)	1.02 (1.01, 1.04)	0.001	1.03 (1.01, 1.04)	<0.001	1.03 (1.01, 1.04)	0.002
Time from cardiac arrest to VA-ECMO initiation (tertile)						
T1	Ref.		Ref.		Ref.	
T2	1.21 (0.67, 2.20)	0.527	1.08 (0.58, 2.00)	0.806	1.13 (0.55, 2.30)	0.745
T3	3.59 (1.89, 6.83)	<0.001	3.56 (1.85, 6.86)	<0.001	4.07 (1.90, 8.73)	<0.001
p for trend	<0.001		<0.001		<0.001	

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; OR, odds ratio; CI, confidence interval; Ref., reference range.

obtained when modeling the interval as a continuous variable, and suggest a potential linear association between increasing interval duration and in-hospital mortality risk.

3.4 Subgroup analysis for in-hospital mortality

Stratified analyses were conducted based on key clinical and procedural variables, including sex, smoking status, hypertension, diabetes mellitus, chronic kidney disease, cerebrovascular accident, Coronary artery disease (CAD), preoperative use of antiplatelet or anticoagulation therapy, VA-ECMO insertion site, indication for VA-ECMO, and use of a distal perfusion catheter. The results consistently demonstrated that a longer interval between CPR and VA-ECMO initiation was associated with an increased risk of in-hospital mortality across most subgroups.

In our cohort, the association between the CPR-to-ECMO interval and in-hospital mortality was not significantly modified by sex, smoking status, hypertension, diabetes mellitus, chronic kidney disease, ECMO insertion site, indication for ECMO, or use of a distal perfusion catheter (all p for interaction > 0.05). However, a significant interaction was observed between the presence of coronary artery disease and the interval-mortality association (p for interaction = 0.0344). Among patients with CAD, a longer interval was strongly associated with higher in-hospital mortality (OR 1.06; 95% CI, 1.02–1.10; $p = 0.003$) (Table 4).

TABLE 4. Subgroup analyses of the association between the interval from CPR to VA-ECMO and in-hospital mortality.

Variables	OR (95% CI)	*p*	*p* for interaction
Gender			
Male	1.03 (1.01–1.05)	0.001	0.2939
Female	1.01 (0.98–1.04)	0.518	
Smoking status			
No	1.02 (1.00–1.03)	0.053	0.1106
Yes	1.05 (1.01–1.08)	0.007	
Hypertension			
No	1.03 (1.01–1.06)	0.003	0.2514
Yes	1.02 (1.00–1.04)	0.101	
Diabetes mellitus			
No	1.02 (1.00–1.04)	0.013	0.6596
Yes	1.03 (1.00–1.06)	0.035	
Chronic kidney disease			
No	1.02 (1.01–1.04)	0.003	0.5980
Yes	1.04 (0.99–1.09)	0.117	
Coronary artery disease			
No	1.02 (1.00–1.03)	0.027	0.0344
Yes	1.06 (1.02–1.10)	0.003	
Place of VA-ECMO insertion			
Operation room	1.02 (0.97–1.07)	0.413	0.9759
ICU	1.03 (1.00–1.05)	0.060	
Other	1.03 (1.01–1.05)	0.008	
Indication of VA-ECMO insertion			
Post-cardiotomy shock	1.00 (0.95–1.06)	0.898	0.7331
Cardiac failure	1.03 (1.01–1.04)	0.001	
Other	1.02 (0.96–1.08)	0.517	
Distal perfusion catheter			
No	1.03 (1.01–1.05)	0.001	0.0512
Yes	1.00 (0.97–1.03)	0.964	

VA-ECMO, veno-arterial extracorporeal membrane oxygenation; ICU, Intensive Care Unit; OR, odds ratio; CI, confidence interval.

3.5 Relationships between the interval from CPR to VA-ECMO and in-hospital mortality by curve fitting analysis

In the present study, curve fitting analysis revealed a positive linear relationship between the duration of the interval from CPR to VA-ECMO initiation and the risk of in-hospital mortality. Specifically, longer intervals were associated with progressively higher mortality rates. After adjusting for a comprehensive set of potential confounders, including age, sex, smoking status, BMI, hypertension, diabetes mellitus, chronic kidney disease, cerebrovascular accident, CAD, peripheral artery disease, C-reactive protein, preoperative hemoglobin, platelet count, partial thromboplastin time, INR, preoperative antiplatelet and anticoagulation therapy, VA-ECMO insertion site and indication, VA-ECMO-related complications (general and vascular), and ECMO running time, a clear dose-response trend remained evident (Fig. 2).

4. Discussion

In this secondary retrospective study, we examined the association between the interval from CPR to VA-ECMO initiation and in-hospital mortality in patients with cardiac arrest. Our findings demonstrated a significant and independent association between longer CPR-to-ECMO intervals and increased risk of in-hospital mortality, which remained robust across multiple subgroup analyses. Notably, a stronger correlation was observed among patients with underlying CAD, suggesting that this population may be particularly more vulnerable to delays in ECMO initiation. Further analysis using interval-based tertile grouping confirmed that in-hospital mortality increased progressively with longer CPR-to-ECMO intervals.

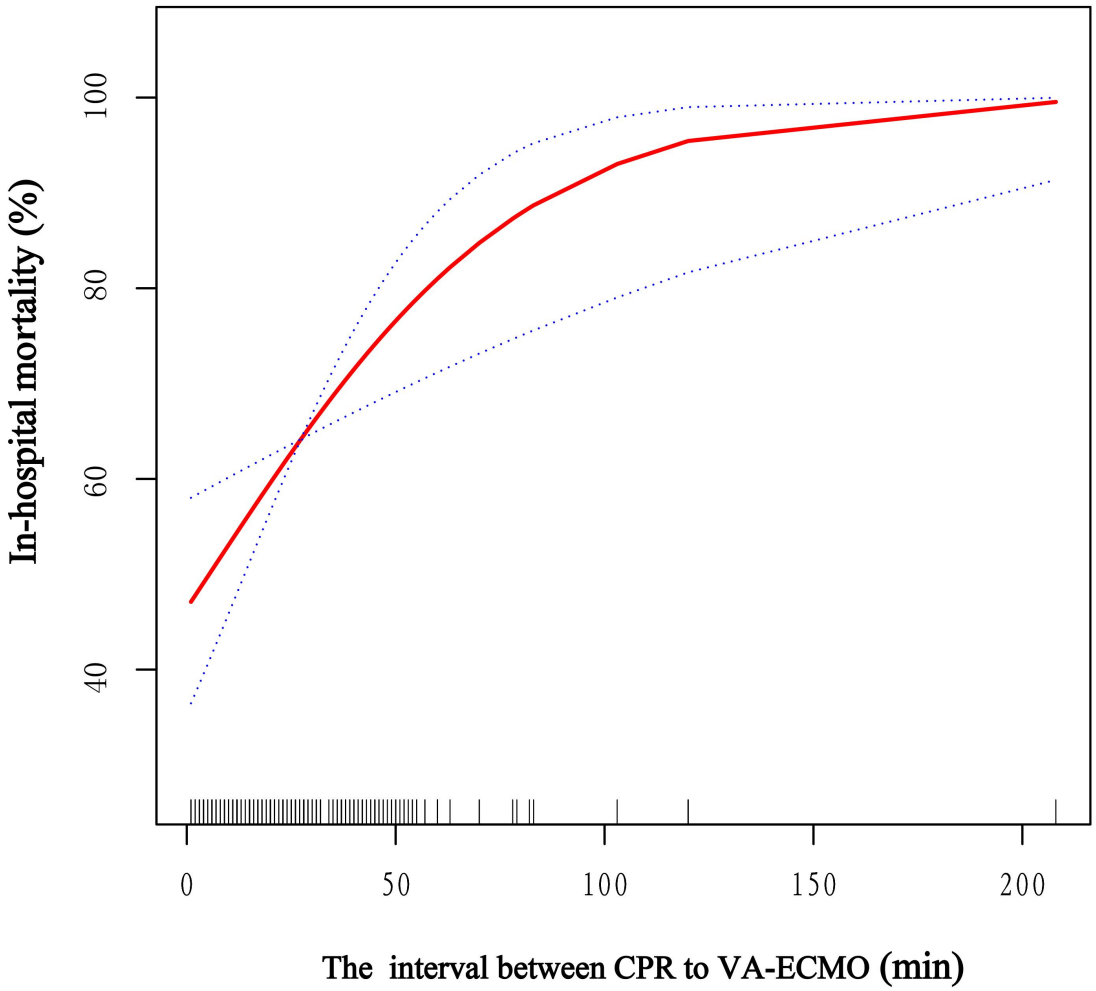

FIGURE 2. Association between the interval from CPR to VA-ECMO initiation and in-hospital mortality in the overall cohort. A linear relationship was observed between the interval duration and in-hospital mortality. The red line indicates the fitted regression curve, while the blue bands represent 95% confidence intervals. VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation.

This trend was statistically significant and supports the conclusion that earlier ECMO initiation may be associated with better clinical outcomes. Moreover, the observed dose-response relationship reinforces the prognostic importance of minimizing the low-flow duration during cardiac arrest.

Previous studies have shown that ECPR can maintain systemic organ perfusion in patients with refractory cardiac arrest, effectively reducing low-flow time compared to conventional CPR (CCPR). By decreasing the duration of inadequate perfusion, ECPR contributes to a lower incidence of irreversible multiorgan failure and hypoxic brain injury. Importantly, ECPR serves not only as a bridge to definitive diagnosis and treatment but also extends the therapeutic window, allowing for interventions that may not otherwise be feasible within the limited time frame of CCPR [14]. The time-dependent decline in survival during prolonged low-flow states has been consistently demonstrated. Existing evidence indicates that each additional minute of low-flow time is associated with a substantial reduction in survival probability [24]. Therefore, early initiation of ECMO during ongoing CPR may mitigate the physiological consequences of prolonged hypoperfusion, thereby improving survival prospects. Despite the increasing clinical experience and technological advancements in ECMO systems, the morbidity and mortality associated with ECMO remain high, with outcome variability observed across centers, patient populations, and indications [25, 26]. A study by Park *et al.* [27] identified multiple risk factors negatively affecting survival in patients undergoing ECPR, including age >66 years, non-shockable initial rhythms, prolonged CPR-to-ECMO time, low initial pulse pressure, and high initial Sequential Organ Failure Assessment (SOFA) scores, which align with our results and highlight the critical importance of minimizing delays in ECMO initiation. Consequently, in the context of ECPR, the time from the onset of CPR to ECMO pump-on represents a modifiable clinical factor with significant prognostic implications. Our findings emphasize that optimizing the timing of VA-ECMO initiation during cardiac arrest may serve as a key determinant in improving survival outcomes [18].

Our subgroup analysis demonstrated that a prolonged interval between CPR and ECMO initiation is significantly associated with increased in-hospital mortality among patients with CAD. Earlier studies have similarly suggested that early ECMO initiation can improve outcomes in patients with coro-

nary artery disease, underscoring the importance of minimizing the delay between circulatory collapse and mechanical support [28]. ECMO provides hemodynamic stabilization by bypassing cardiac function to maintain systemic perfusion, and has been shown to enhance neurologically favorable survival outcomes in this population [29]. The beneficial effects of ECMO are multifaceted. In the acute setting, ECMO mitigates ischemic injury and corrects metabolic derangements affecting vital organs, such as the brain and myocardium. Hemodynamic support via ECMO also facilitates timely treatment of the underlying cause of arrest, including the use of percutaneous coronary intervention (PCI) when clinically indicated. Early revascularization during cardiac arrest restores myocardial perfusion, stabilizes metabolic instability in the ischemic myocardium, reduces infarct size, and suppresses proarrhythmic triggers [30]. However, the underlying pathophysiology of CAD, characterized by systemic vascular inflammation and progressive atherosclerosis, is not fully addressed by focal revascularization. Although PCI may effectively alleviate flow-limiting stenoses, the diffuse and progressive nature of atherosclerotic disease predisposes patients to future vascular events and new lesion development [31]. Moreover, the technical complexity of ECMO cannulation represents a critical barrier to timely intervention [13]. This procedure requires specialized expertise and is often delayed by the physiological consequences of cardiac arrest, including persistent hypotension, hypovolemia, and vascular collapse, contributing to vascular stiffness, inflammation, and increased procedural difficulty [32, 33]. Delays may also arise from operator inexperience or inadequate preprocedural evaluation of vascular anatomy, including insufficient assessment of vessel diameter, stenosis, or malformations [34]. Additionally, the choice of cannulation strategy, *i.e.*, percutaneous versus surgical, affects procedural efficiency and outcomes. Successful ECMO initiation requires trained surgical teams and standardized intensive care protocols to ensure prompt and safe cannulation [35, 36]. While ECMO can be initiated relatively rapidly in controlled environments such as operating rooms or ICUs, its use in emergency departments or general wards is frequently delayed due to the need for interdisciplinary coordination, equipment mobilization, staffing logistics, and concurrent resuscitative efforts, all of which may extend the CPR-to-ECMO interval and reduce treatment efficacy [37].

The decision to initiate ECMO during CPR remains complex and is often based on the clinical judgment and experience of the treating physician, as it must frequently be made under extreme time pressure, underscoring the need for standardized recommendations and evidence-based guidelines to support timely and effective implementation [38]. The current lack of protocol standardization for ECMO initiation and management is a recognized limitation, which may reduce the reproducibility and applicability of resuscitative procedures across institutions [39]. In particular, the absence of structured training programs and institutional protocols, especially in settings where nursing staff and healthcare providers lack standardized VA-ECMO training, can compromise patient outcomes and hinder timely ECMO deployment and effective management in critical conditions such as cardiogenic shock or post-cardiac arrest syndrome [40]. Despite advancements in ECMO and comprehensive medical support, short-term mortality remains high, with reported rates ranging from 37% to 69% in ECMO-treated patients [41]. Furthermore, delays in obtaining informed consent from the patient's family may further extend the catheterization window, contributing to treatment delays.

Among intra-ECPR variables, the interval between CPR initiation and ECMO pump-on time remains the only consistently modifiable predictor of survival to hospital discharge. However, implementing ECMO during every CPR event, particularly in resource-limited environments, poses significant logistical and financial challenges. Given the complexity of ECMO systems and the high level of expertise required for safe operation, establishing a dedicated 24-hour extracorporeal life support (ECLS) team has been proposed as a pragmatic solution. Such a model facilitates rapid ECMO initiation, reduces ECPR start-up time, improves first-response efficiency, and minimizes procedural complications [37]. Comprehensive ECPR programs should incorporate structured protocols for cannulation, extremity reperfusion, left heart decompression, and contingency planning for procedural complications. Simulation-based training is essential to maintain multidisciplinary team proficiency in high-risk, time-sensitive interventions. The availability of pre-assembled ECMO carts stocked in the order of procedural use and placed in strategic hospital locations can streamline response times and improve procedural readiness [42]. Technological adjuncts also contribute to procedural efficiency, whereby pre-procedural assessment of axillary arteries and the aortic arch using multi-slice computed tomography (CT) angiography can guide appropriate catheter selection and placement depth, particularly for axillary artery access [43]. In addition, the use of real-time ultrasound guidance has been shown to reduce cannulation time and improve procedural accuracy in ECPR scenarios [43]. In one study, real-time ultrasound-guided cannulation was high, with shorter cannulation time for ECPR [44]. Ultimately, ECMO during CPR should be guided by careful consideration of pre-ECPR factors, including the reversibility of the underlying arrhythmic event, baseline organ dysfunction, and patient age [27]. Careful selection of ECMO candidates during CPR is essential to ensure appropriate and timely application, particularly in resource-constrained or emergency settings.

We acknowledge several limitations in this study. First, this was a single-center, retrospective, observational cohort study, and certain key variables, such as the inner diameter of the cannula and the ECMO flow rate, were not available. The absence of these data introduces potential information bias and may limit the precision of our findings. Second, most covariates included in the analysis were collected at baseline. Although these baseline measurements reflect patients' clinical status at the time of ECMO initiation, they do not capture dynamic changes during treatment, such as those resulting from clinical interventions, disease progression, or recovery, thereby restricting our ability to evaluate the influence of time-varying factors on patient outcomes. Third, the study lacked stratified data for in-hospital cardiac arrest (IHCA) versus out-of-hospital cardiac arrest (OHCA), as these categories were not independently recorded in the original dataset. The inability to distinguish between IHCA and OHCA hinders a more specific evaluation of the generalizability and relevance

of our findings across different cardiac arrest populations. Fourth, there was limited information regarding patient management during cardiac arrest. Specifically, we lacked details on whether basic or advanced life support was administered, whether mechanical CPR was employed, and which airway management or pharmacologic interventions were used. Post-ECMO care data were also unavailable, particularly regarding neurologic prognostication and decisions about withdrawal of life-sustaining treatment. These omissions reduce the ability to fully interpret the influence of clinical management on patient outcomes. Fifth, although in-hospital mortality is a widely used endpoint in ECMO research, it represents only one aspect of clinical prognosis. Survival is a multifactorial process influenced by underlying disease burden, comorbidities, immune and nutritional status, and the quality of post-resuscitation care. Importantly, in-hospital mortality does not capture long-term outcomes such as neurological function, organ recovery, or quality of life. Patients who survive till hospital discharge may experience substantial physical or cognitive impairment. Future studies should include more comprehensive outcome measures, such as validated functional scores, health-related quality-of-life assessments, and long-term follow-up data. Finally, this study represents a secondary analysis of a publicly available dataset covering a period from 2015 to 2019. As such, the dataset cannot be updated to include more recent cases, and the findings may not fully reflect current clinical practices or technological advancements. Furthermore, the retrospective design limits mechanistic insight into the observed association between CPR-to-ECMO interval and mortality. Thus, robust prospective studies incorporating biomarker analyses, time-resolved hemodynamic data, and multicenter validation are needed to elucidate the biological mechanisms underlying this relationship and to confirm the clinical utility of early ECMO initiation.

5. Conclusions

This study highlights the critical importance of timely VA-ECMO initiation during CPR in improving clinical outcomes among patients with cardiac arrest. A clear, dose-dependent relationship was observed between the duration of the CPR-to-ECMO interval and in-hospital mortality, with longer delays significantly associated with increased risk of adverse outcomes. These findings emphasize the necessity of minimizing time to ECMO initiation, particularly in patients with underlying coronary artery disease, who appear to be more sensitive to treatment delays.

ABBREVIATIONS

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; ICU, Intensive Care Unit; OR, odds ratio; CI, confidence interval; BMI, body mass index; INR, International Normalized Ratio; ROSC, return of spontaneous circulation; ECPR, extracorporeal cardiopulmonary resuscitation; CCPR, conventional cardiopulmonary resuscitation; CAD, Coronary artery disease; SOFA, Sequential Organ Failure Assessment; ECLS, Extracorporeal life support; Ref., reference range.

AVAILABILITY OF DATA AND MATERIALS

Please see the website (https://doi.org/10.1371/journal.pone.0300713.s010).

AUTHOR CONTRIBUTIONS

QFL, QL, SML and CJZ—designed the research study. HLH, RXB and XLG—analyzed the data. QFL, QL and CJZ—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is a secondary analysis of fully anonymized, publicly available data. The original data collection was approved by the Institutional Review Board of Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea (IRB No. 2020-0793), and the requirement for informed consent was waived due to the retrospective design and use of de-identified data. Because only publicly available, fully anonymized data were used and no individual participants could be identified, this secondary analysis was considered exempt from additional ethical review and informed consent by the Clinical Research Ethics Committee of Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China. All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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