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High incidence of acute kidney injury in extracorporeal resuscitation, Leading to poor prognosis

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A B S T R A C T

Background: Extracorporeal membrane oxygenation (ECMO) patients have a high incidence of acute kidney injury (AKI). Extracorporeal cardiopulmonary resuscitation (ECPR) patients are more likely to develop AKI than ECMO patients because of serious injury during cardiac arrest (CA).
Objectives: This study aims to assess the occurrence and outcomes of AKI in ECPR and ECMO, and to identify specific risk factors and clinical implications of AKI in ECPR.
Methods: This is a retrospective observational study from a single tertiary care hospital in Gwangju, Korea. Adults (≥18 years) who received ECMO with cardiac etiology in the emergency and inpatient departments from January 2015 to December 2021 were included. The patients (n = 169) were divided into two groups, ECPR and ECMO without CA, and the occurrence of AKI was investigated. The primary outcome of the study was in-hospital mortality, and the secondary outcomes were six-month cerebral performance category (CPC) and AKI during hospitalization.
Results: The incidence of AKI was significantly higher with ECPR (67.5 %) than with ECMO without CA (38.4 %). ECPR was statistically significant for Expire (adjusted OR (aOR) 2.45, 95 % CI 1.28–4.66) and Poor CPC (2.59, 1.32–5.09). AKI was also statistically significant for Expire (6.69, 3.37–13.29) and Poor CPC (5.45, 2.73–10.88). AKI was the determining factor for the outcomes of ECPR (p = 0.01).
Conclusions: ECPR patients are more likely to develop AKI than ECMO without CA patients. In ECPR patients, AKI leads to poor outcomes. Therefore, clinicians should be careful not to develop AKI in ECPR patients.

1. Introduction

The use of Veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) has increased over the past decade [1]. ECMO has been most commonly used in patients with cardiogenic shock [2–6], and has recently been used as a salvage treatment in patients with cardiac arrest (CA) [7–10]. The implementation of ECMO in ongoing cardiopulmonary resuscitation (CPR) is known as extracorporeal cardiopulmonary resuscitation (ECPR). Unfortunately, the survival rate of ECPR patients is worse than in ECMO patients with cardiogenic shock [1,11,12]. The difference in survival rates is due to ECPR patients suffering serious injuries during CA.

ECPR patients suffer from both ECMO and CPR-related injuries. The use of ECMO has caused various injuries to patients [13]. One of the most common injuries is acute kidney injury (AKI) [13]. AKI occurs because of hemodynamic, inflammatory, and pathophysiological abnormalities that result from the ECMO cycle and maintaining a state of shock, which is required for the ECMO treatment

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[14,15]. CA can also cause AKI and other related injuries. These injuries are because CA patients have unstable hemodynamic conditions and ischemic reperfusion injuries [16]. Therefore, ECPR patients are presumed to have a higher incidence of AKI than ECMO patients with cardiogenic shock. However, there are no studies that compare the incidence of AKI between ECPR and ECMO.

AKI is associated with mortality and poor neurological outcome in CA patients without ECMO [17–21]. AKI has also been reported to be associated with mortality in ECMO patients with cardiogenic shock [13,14]. Therefore, AKI is likely to be associated with the prognosis of ECPR patients. However, several studies on ECPR patients have inconsistent results regarding the association between AKI and patient outcomes [22,23].

We hypothesized that ECPR patients develop more AKI than ECMO patients without CA, and that AKI in ECPR patients is associated with poor outcomes. Therefore, we compared the occurrence of AKI in ECPR and ECMO patients without CA and investigated their associations with patient outcomes. Additional analyses examined whether AKI was associated with the outcomes of ECPR patients. Finally, we investigated the factors of CA that cause AKI in ECPR patients.

2. Method

2.1. Study design

This is a retrospective observational study that included patients treated with ECMO for cardiac etiology at Chonnam National University Hospital between January 2015 and December 2021. Chonnam National University Hospital is a tertiary center whose emergency department (ED) treats 40,000 to 45,000 patients per year. This study was approved by the institutional review board of Chonnam National University Hospital (CNUH-2022-238).

2.2. Patients and definitions

This study included patients over the age of 18 who received an ECMO treatment with cardiac etiology in the emergency and inpatient departments of Chonnam National University Hospital. Exclusion criteria were as follows: 1) Recovery of spontaneous circulation (ROSC) after CA prior to the ECMO procedure 2) Death within 24 h after the ECMO procedure 3) A ECMO procedure for shock treatment after cardiac surgery 4) Diagnosed with ESRD and received a dialysis treatment 5) AKI diagnosis or renal replacement therapy (RRT) before the ECMO procedure. Finally, ECMO patients with cardiogenic shock and ECPR patients due to CA were enrolled, and were divided into two groups, ECPR and ECMO without CA.

2.3. Cardiac etiology

Presumed cardiac etiology, including all medical etiologies and excluding traumatic CA, was defined as cardiac etiology according to the Utstein criteria [24]. In all patients, Cardiac Angiography (CAG) or Transthoracic Echocardiogram (TTE) was performed before or after ECMO by a cardiologist, and heart diseases such as myocardial infarction (MI), heart failure, myocarditis, and tamponade were diagnosed. Patients that had an ECMO performed during hospitalization due to other complications such as sepsis were not included in the study, although a cardiac problem was the initial diagnosis.

2.4. ECMO

VA ECMO was performed in patients with cardiogenic shock, and whether to use ECMO as a treatment was decided by two or more physicians, including a cardiologist. Cardiogenic shock was defined as hypotension (<90/60 mmHg) for more than 30 min, a need for vasopressors or inotropes to maintain a systolic blood pressure over 90 mmHg, pulmonary congestion, elevated left-ventricular filling pressure, or evidence of end organ hypoperfusion, including cool extremities, oliguria, and lactic acidosis [25].

2.5. ECPR

ECPR was defined as the ROSC due to VA ECMO in CA patients. Chonnam National University Hospital has the following ECPR criteria, which is initiated by the decision of two or more physicians, including an emergency medicine specialist: 1) over the age of 18, 2) Suspected cardiac origin as the cause of the CA, 3) Refractory ventricular fibrillation (VF), VF, or pulseless ventricular tachycardia (VT) on the initial electrocardiogram (ECG), 4) No sustained ROSC for the first 10 min, and 5) No flow time for less than 5 min, or a low flow time less than 60 min. The exclusion criteria were as follows: 1) Terminal malignancy, 2) uncontrollable bleeding, or 3) Poor levels of daily activity before CA.

2.6. ECMO cannulation and maintenance

The ECMO device was implanted by percutaneous or surgical cannulation, using a 14–17 Fr cannula for the femoral artery and a 21–24 Fr cannula for the femoral vein, in the emergency room, catheterization room, or coronary care unit. This study used a Rotaflow centrifugal pump (Maquet, Rastatt, Germany) with a Quadrox membrane oxygenator (Maquet, Rastatt, Germany) and the PLS2050 circuit system (Maquet, Rastatt, Germany). For patients without life-threatening bleeding, anticoagulation was provided by the intravenous administration of unfractionated heparin, which aimed for a partial thromboplastin time between 50 and 60 s. The

anticoagulatory protocol includes the intravenous infusion of unfractionated heparin, with a target activated clotting time of 180–200 s and a PTT between 60 and 80 s.

2.7. Inpatient management

According to the guidelines, CAG was performed immediately or after a delay according to the findings of the ECG and TTE, and percutaneous coronary intervention or thrombolytic therapy was performed in MI [26]. If ECPR patients did not recover consciousness after ROSC, Target Temperature management (TTM) was performed while the patient was unconscious. Unconsciousness was defined as not being able to obey verbal commands and not having a verbal response to pain [27]. In the case of severe bleeding tendency, TTM was performed at 36°, and in all other cases, it was performed at 33°. All treatments after admission to the intensive care unit (ICU) were performed according to the protocols set by a verified specialist.

2.8. AKI

AKI was defined according to the Kidney Disease Improving Global Outcomes criteria [28]. Stage 1 AKI was defined as a 1.5–1.9 fold increase in serum creatinine concentrations within seven days or a serum creatinine concentration over 0.3 mg/dL (26.5 μmol/L) within 48 h, a urine excretion less than 0.5 mL/kg/hour over a 6-h period. Stage 2 AKI was defined as a serum creatinine 3.0 times the baseline, a serum creatinine concentration over 4.0 mg/dL, initiation of renal replacement therapy (RRT), a urine excretion less than 0.3 mL/kg/hour, or a urine excretion less than 0.5 mL/kg/hour over a 12-h period Stage 3 AKI was defined by a urine excretion less than 0.5 mL/kg/hour over a 24-h period or anuria that lasts more than 12 h. If there was a creatinine measurement within three months, it was used as the baseline creatinine concentration [29], and if there was no record of a baseline creatinine concentration, it was the result of a hospitalization. RRT implementation was performed by a nephrologist in the ICU. Continuous venovenous hemodiafiltration was conducted through the integration of the ECMO circuit, via a Luer lock connection, to the oxygenator. Anticoagulation use was directed by the cardiology service per the ECMO protocol. AKI was investigated in cases diagnosed within 72 h after ECPR or ECMO.

2.9. Data collection and study endpoints

The following medical record information was collected from Chonnam National University Hospital records: age; weight; underlying disease, such as hypertension, diabetes mellitus, chronic kidney disease, previous PCI, other cardiovascular diseases, previous coronary artery bypass graft surgery, cerebrovascular disease and pulmonary diseases; CA information, such as out of hospital CA (OHCA), CA witnesses, bystander cardiopulmonary resuscitation (BLS), initial shockable rhythm, time from collapse to ECMO initiation (ECPR time), and time from collapse to ROSC (total CA time); laboratory data, including platelet count (Plt), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urine nitrogen (BUN), creatine kinase (CK), serial creatine (Cr), lactate, total bilirubin (T-bil), bicarbonate, and base excesses; and length of stay in the ICU and the hospital.

The primary outcome of the study was ECPR and ECMO without CA in-hospital mortality, and the secondary outcomes were a six-month cerebral performance category (CPC) score of 3 or higher and an AKI during the hospitalization.

2.10. Statistical analysis

The characteristics of the study population were expressed as a percentage of the mean ± the standard deviation (*SD*) for continuous variables and percentages for categorical variables. Continuous variables were compared using *t*-tests with unequal variances, and categorical variables were compared using the chi-square or Fisher's exact tests. Odds ratio (OR) and 95 % CI were calculated by performing a logistic regression analysis between AKI and ECPR prognosis, and the adjusted OR was calculated by using age and sex, variables known to affect the prognosis of ECMO patients. A mediation analysis was done to further explore possible causal mechanisms between ECPR (exposure), AKI (mediator) and the outcome (outcome). The mediation analysis used a binomial (probit) model using the mediation R package and the following settings: variables with a significant univariable association: ECPR, AKI, and clinically important variables: age and sex. The interaction term for ECPR*AKI was included as the association between AKI and mortality and may be different depending on the severity of the physiological derangement. The linear regression fit with least squares and the probit regression were used for the mediator and outcome models, respectively. Heteroscedasticity was allowed for the covariance matrix, and 5000 simulations were performed using the Monte Carlo method. A subgroup analysis was performed to calculate the OR and 95 % CI to compare the effects of AKI on the outcomes in the ECPR group and the ECMO without CA group, respectively. In addition, whether the factors in CA were associated with the prognosis of ECPR was investigated. A regression analysis was performed using backward elimination by inputting variables from the univariable analysis on the outcome with P values of 0.2 or less. Data were analyzed using R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria). For statistical significance, a two-sided P value of less than 0.05 was used.

3. Results

3.1. Characteristics of ECPR patients versus ECMO without CA

A total of 248 patients (ECPR 134, ECMO without CA 114) were enrolled in this study, and 79 patients were excluded. Out of the final total of 169 patients enrolled in this study, there were 83 ECPR patients and 86 ECMO patients without CA. The ratio of males (P = 0.02) was significantly higher in the ECPR group, and the average age was significantly lower in the ECPR group than in the ECMO without CA group (63.1 vs. 71.1, respectively; P = 0.02). The rate of acute MI was significantly higher in the ECPR group than in the ECMO without CA group (81.9 % vs. 62.8 %, respectively; P = 0.01). The incidence of AKI was significantly higher in the ECPR group than in the ECMO without CA group (67.5 % vs. 38.4 %, respectively), and the rate of stage 2–3 was higher in the ECPR than in the ECMO without CA group (57.8 % vs. 30.2 %, respectively). In the laboratory data, AST, ALT, lactate, bicarbonate, and base excess were statistically associated with poorer outcomes in the ECPR group than in the ECMO without CA group (P < 0.01). The ECPR group had significantly worse outcomes in in-hospital mortality (59.0 % vs. 38.4 %, P = 0.01) and poor neurological outcomes (66.3 % vs. 47.7 %, P = 0.02) (Table 1).

Table 1
Patient characteristics according to Extracorporeal cardiopulmonary resuscitation implementation.

Variables	Total	ECMO	ECPR	P value
	(N = 169)	(N = 86)	(N = 83)	
Demographics				
Sex, male	124 (73.4 %)	56 (65.1 %)	68 (81.9 %)	0.02
Age, years	68.0 [55.0; 74.1]	71.1 [59.0; 76.1]	63.1 [53.1; 72.1]	0.02
Weight, kg	65.0 [58.0; 73.0]	63.0 [55.0; 70.0]	68.0 [60.0; 75.0]	0.01
Comorbid diseases				
Hypertension	84 (49.7 %)	44 (51.2 %)	40 (48.2 %)	0.82
Diabetes mellitus	68 (40.2 %)	28 (32.6 %)	40 (48.2 %)	0.06
Chronic kidney disease	4 (2.4 %)	3 (3.5 %)	1 (1.2 %)	0.64
Previous PCI	43 (25.4 %)	16 (18.6 %)	27 (32.5 %)	0.06
Other cardiovascular	33 (19.5 %)	17 (19.8 %)	16 (19.3 %)	1.00
Previous CABG	5 (3.0 %)	5 (5.8 %)	0 (0.0 %)	0.08
Cerebrovascular disease	19 (11.2 %)	8 (9.3 %)	11 (13.3 %)	0.57
Pulmonary disease	10 (5.9 %)	6 (7.0 %)	4 (4.8 %)	0.79
Cause of ECMO insertion, acute MI	122 (72.2 %)	54 (62.8 %)	68 (81.9 %)	0.01
ECMO duration, hours	116.6 [57.8; 203.0]	121.8 [69.3; 211.8]	96.2 [48.1; 182.6]	0.13
Renal characteristics				
AKI	89 (52.7 %)	33 (38.4 %)	56 (67.5 %)	<0.01
KDIGO				<0.01
0	80 (47.3 %)	53 (61.6 %)	27 (32.5 %)	
1	15 (8.9 %)	7 (8.1 %)	8 (9.6 %)	
2	1 (0.6 %)	0 (0.0 %)	1 (1.2 %)	
3	73 (43.2 %)	26 (30.2 %)	47 (56.6 %)	
Outcome				
ICU stay, days	10.1 [5.5; 20.6]	11.8 [6.9; 21.1]	9.1 [4.1; 17.3]	0.14
Hospital stay, days	16.9 [7.9; 29.2]	17.8 [9.9; 30.8]	14.6 [5.0; 25.8]	0.11
In-hospital death	82 (48.5 %)	33 (38.4 %)	49 (59.0 %)	0.01
Poor neurological outcome	96 (56.8 %)	41 (47.7 %)	55 (66.3 %)	0.02
Laboratory findings				
Platelet, × 103/μL	145.0 [112.0; 191.0]	140.5 [108.0; 177.0]	154.0 [114.0; 202.0]	0.21
Blood urea nitrogen, mg/dl	24.5 [19.2; 31.6]	25.4 [20.3; 31.8]	23.2 [18.8; 30.5]	0.30
Creatinine, mg/dL	1.2 [0.9; 1.6]	1.2 [0.8; 1.7]	1.3 [1.0; 1.6]	0.29
AST, U/L	352.0 [156.0; 928.0]	295.5 [112.0; 733.0]	544.0 [235.5; 1059.0]	0.01
ALT, U/L	122.0 [57.0; 311.0]	79.5 [34.0; 250.0]	176.0 [94.0; 351.5]	<0.01
Total bilirubin, mg/dL	0.9 [0.6; 1.3]	1.0 [0.7; 1.4]	0.8 [0.5; 1.2]	0.05
Creatine kinase, IU/L	2336.0 [610.0; 7032.0]	1580.0 [543.0; 3441.0]	2736.5 [916.5; 8111.5]	0.09
Lactate, mmol/L	8.9 [4.4; 13.9]	4.5 [2.5; 8.5]	12.5 [10.0; 15.0]	<0.01
Bicarbonate, mmol/L	12.9 ± 6.2	16.8 ± 4.8	8.8 ± 4.7	<0.01
Base excess, mmol/L	−16.0 ± 8.6	−10.9 ± 6.8	−21.4 ± 6.8	<0.01

'Other cardiovascular' comprises: congestive heart failure, ischemic heart disease, mitral valve disorder, arrythmia. 'Respiratory' comprises: chronic obstructive lung disease, asthma, pulmonary emphysema. 'Cerebrovascular' comprises: cerebral hemorrhage, cerebral infarction, cerebrovascular accident, cerebrovascular disease.

ECMO, extra corporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CA, cardiac arrest; MI, myocardial infarction; AKI, acute kidney injury; KDIGO, kidney disease improving global outcomes; CRRT, continuous renal replacement therapy; ICU, intensive care unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

3.2. Characteristics of patients with AKI

There was no significant difference in sex and age between the AKI and non-AKI groups and no significant difference in Comorbid diseases. ECPR in the AKI group was 62.9 %, which was significantly higher than that in the non-AKI group (33.8 %). In the AKI group, stage 3 was the most common among the Kidney Disease: Improving Global Outcomes (KDIGO) classifications (N = 73, 82.0 %). There were significant differences in BUN, Cr, AST, ALT, CK, lactate, bicarbonate, and base excess in the laboratory finding. Length of ICU stay and Hospitalization were significantly shorter in the AKI group compared with the non-AKI group. In-hospital mortality was significantly higher in the AKI group than in the non-AKI group (69.7 % vs. 25.0 %, respectively), and poor neurologic outcome was significantly higher in the AKI group than in the non-AKI group (77.5 % vs. 37.5 %, respectively), indicating a poor prognosis (Table 2).

3.3. Association for outcomes of ECPR and AKI

A logistic regression was performed to determine whether ECPR and AKI occurrences were associated with outcomes. The aOR and 95 % CI of ECPR was statistically significant for each outcome: mortality 2.45 (1.28–4.66), Poor CPC 2.59 (1.32–5.09), and AKI incidence 3.37 (1.75–6.49). The aOR of AKI occurrence was also statistically significant for mortality 6.69 (3.37–13.29) and Poor CPC 5.45 (2.73–10.88) (Table .3).

Table 2
Patient characteristics according to Acute kidney injury occurrence.

Variables	Total	No AKI	AKI	P value
	(N = 169)	(N = 80)	(N = 89)	
Demographics				
Sex, male	124 (73.4 %)	54 (67.5 %)	70 (78.7 %)	0.10
Age, years	68.0 [55.0; 74.1]	68.1 [54.0; 74.0]	67.0 [58.1; 75.1]	0.47
Weight, kg	65.0 [58.0; 73.0]	65.0 [58.0; 74.0]	65.0 [58.0; 72.0]	0.70
Comorbid diseases				
Hypertension	84 (49.7 %)	41 (51.2 %)	43 (48.3 %)	0.70
Diabetes mellitus	68 (40.2 %)	27 (33.8 %)	41 (46.1 %)	0.10
Chronic kidney disease	4 (2.4 %)	2 (2.5 %)	2 (2.2 %)	0.91
Previous PCI	43 (25.4 %)	21 (26.2 %)	22 (24.7 %)	0.82
Other cardiovascular	33 (19.5 %)	13 (16.2 %)	20 (22.5 %)	0.31
Previous CABG	5 (3.0 %)	2 (2.5 %)	3 (3.4 %)	0.74
Cerebrovascular disease	19 (11.2 %)	7 (8.8 %)	12 (13.5 %)	0.33
Pulmonary disease	10 (5.9 %)	4 (5.0 %)	6 (6.7 %)	0.63
Cause of ECMO insertion, acute MI	122 (72.2 %)	56 (70.0 %)	66 (74.2 %)	0.55
ECPR	83 (49.1 %)	27 (33.8 %)	56 (62.9 %)	<0.01
ECMO duration, hours	116.6 [57.8; 203.0]	118.7 [57.1; 222.7]	107.6 [57.8; 194.2]	0.58
Renal characteristics				
AKI				
KDIGO				<0.01
0	80 (47.3 %)	80 (100.0 %)	0 (0.0 %)	
1	15 (8.9 %)	0 (0.0 %)	15 (16.9 %)	
2	1 (0.6 %)	0 (0.0 %)	1 (1.1 %)	
3	73 (43.2 %)	0 (0.0 %)	73 (82.0 %)	
Outcome				
ICU stay, days	10.1 [5.5; 20.6]	11.8 [7.5; 20.6]	8.8 [3.1; 20.6]	0.03
Hospital stay, days	16.9 [7.9; 29.2]	20.2 [13.7; 30.3]	11.7 [3.1; 26.3]	<0.01
In-hospital death	82 (48.5 %)	20 (25.0 %)	62 (69.7 %)	<0.01
Poor neurological outcome	99 (58.6 %)	30 (37.5 %)	69 (77.5 %)	<0.01
Laboratory findings				
Platelet, × 103/μL	145.0 [112.0; 191.0]	149.0 [115.5; 194.0]	142.0 [108.0; 184.0]	0.46
Blood urea nitrogen, mg/dl	24.5 [19.2; 31.6]	22.9 [17.8; 28.1]	26.1 [20.9; 34.0]	0.02
Creatinine, mg/dL	1.2 [0.9; 1.6]	1.0 [0.8; 1.3]	1.5 [1.1; 1.9]	<0.01
AST, U/L	352.0 [156.0; 928.0]	288.0 [125.5; 583.0]	602.0 [244.0; 1098.0]	<0.01
ALT, U/L	122.0 [57.0; 311.0]	90.0 [36.5; 154.0]	222.0 [81.0; 397.0]	<0.01
Total bilirubin, mg/dL	0.9 [0.6; 1.3]	0.9 [0.6; 1.2]	0.9 [0.6; 1.5]	0.89
Creatine kinase, IU/L	2336.0 [610.0; 7032.0]	1271.5 [417.0; 3499.0]	3049.0 [1084.0; 8245.5]	0.01
Lactate, mmol/L	8.5 [4.4; 13.4]	7.2 [3.4; 11.7]	9.5 [5.5; 14.9]	0.05
Bicarbonate, mmol/L	12.9 [7.8; 18.0]	15.4 [9.1; 18.2]	11.4 [6.8; 16.8]	0.02
Base excess, mmol/L	−15.2 [-22.6;-9.2]	−13.0 [-21.6;-8.3]	−17.5 [-23.6;-10.3]	0.05

'Other cardiovascular' comprises: congestive heart failure, ischemic heart disease, mitral valve disorder, arrythmia. 'Respiratory' comprises: chronic obstructive lung disease, asthma, pulmonary emphysema. 'Cerebrovascular' comprises: cerebral hemorrhage, cerebral infarction, cerebrovascular accident, cerebrovascular disease.

AKI, acute kidney injury; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CA, cardiac arrest; MI, myocardial infarction; ECMO, extra corporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; KDIGO, kidney disease improving global outcomes; CRRT, continuous renal replacement therapy; ICU, intensive care unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3
Multivariable logistic regression models for outcomes of Extracorporeal cardiopulmonary resuscitation and Acute kidney injury.

Outcome	N	%	Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
ECPR	83			
Expire	49	59 %	2.31 (1.25–4.29)	2.45 (1.28–4.66)
Poor CPC	55	66.3 %	2.16 (1.16–4.01)	2.59 (1.32–5.09)
AKI	56	67.5 %	3.33 (1.77–6.27)	3.37 (1.75–6.49)
AKI	89			
Expire	62	69.7 %	6.89 (3.5–13.58)	6.69 (3.37–13.29)
Poor CPC	67	75.3 %	5.36 (2.76–10.39)	5.45 (2.73–10.88)

Adjusted for age and sex.
OR, odds ratio; CI, confidence intervals; ECPR, extracorporeal cardiopulmonary resuscitation; CPC, cerebral performance category; AKI, acute kidney injury Expire indicates an in-hospital death; Poor CPC indicates a poor neurological outcome (CPC 3–5).

3.4. Mediation effect of AKI on ECPR and outcome

A causal mediation analysis was performed to explore the causal mechanism, and AKI was designated as the mediator. The causal mediation analysis divided the total effects into direct and indirect effects, in which indirect effects represented the causal mechanism through AKI, and direct effects represented all other mechanisms. ECPR influenced the in-hospital survival through mediating the effect of AKI, where the average causal mediation effect (ACME) was 0.16 (95 % CI, 0.05–0.28), the average direct effect (ADE) was 0.06 (−0.09–0.22), and the proportion of the mediated effect was 55 % (0.20–1.61) (Table 4), indicating that this relationship was completely mediated by AKI. The relationship between ECPR and poor CPC was also completely mediated by AKI.

3.5. Subgroup analysis

A logistic regression was performed to determine whether AKI was associated with outcomes by dividing patients into ECPR and ECMO without CA groups. In the ECPR group, the aOR for mortality of the AKI group was 11.52 (3.81–34.81) compared with the non-AKI group, and the aOR of the AKI group was 3.29 (1.27–8.54) in the ECMO without CA group. In ECPR, the aOR for the poor neurologic outcome of the AKI group was 7.09 (2.52–19.95), and the aOR of the AKI group was 2.89 (1.07–7.80) in the ECMO without CA group (Table 5). The aOR for the outcome in the occurrence of AKI was higher in the ECPR group than the ECMO without CA group.

3.6. Prediction of outcomes in ECPR

For ECPR patients, a logistic regression was performed to investigate the outcome and association with CA variables identified in previous studies. In the univariable analysis, only the total CA time was statistically significant for each outcome: AKI 1.04 (95 % CI, 1.01–1.08), in-hospital mortality 1.04 (1.01–1.07), and poor neurological outcome 1.04 (1.01–1.07) (Table .6).

4. Discussion

ECPR was associated with more AKI occurrence than ECMO without CA, and ECPR was also associated with a higher mortality (59 % vs. 38.4 %; P = 0.01) and poorer neurologic outcome with a CPC score of three or higher (66.3 % vs. 47.7 %; P = 0.02), and the outcome of patients with AKI was higher in the ECPR group than in the ECMO without CA group (aOR 11.52 [3.81–34.81] vs. 3.29 [1.27–8.54], respectively). The mediation analysis suggested that AKI completely mediated the relationship between ECPR and the outcome (P = 0.01), suggesting a possible causal association. The variable related to the prognosis of ECPR was the total CA time. ECPR causes various injuries during CA, worsening the patient's prognosis. This study particularly found that AKI mediates the prognosis of ECPR patients, suggesting that injury to the patient should be minimized during CA and CPR. Efforts should be made to reduce kidney damage before and after the start of ECMO to improve the prognosis of the patients.

In ECPR and ECMO without CA, AKI showed a difference of 67.55 % and 38.4 %, respectively. In previous studies, AKI in ECMO was reported to be 32.9–83.1 % [13,14], and in ECPR, it was reported to be 63–72 % [22,23,30]. Since ECPR is clearly defined as ROSC resulting from ECMO implementation, there is little difference between studies. This study showed AKI to be 67.55 %, which was not

Table 4
Mediation effects of Acute kidney injury on the relationship between Extracorporeal cardiopulmonary resuscitation and Outcome.

Outcome	Indirect effect (ACME, 95 % CI)	Direct effect (ADE, 95 % CI)	Total effect (95 % CI)	P value	Proportion mediated (95 % CI)
Expire[a]	0.16 (0.05–0.28)	0.06 (−0.09–0.22)	0.22 (0.06–0.38)	<0.01	0.55 (0.20–1.61)
Poor CPC[b]	0.12 (0.04–0.23)	0.08 (−0.08–0.25)	0.20 (0.06–0.36)	<0.01	0.49 (0.16–1.57)

Total effect: the sum of the direct and indirect effects. Proportion mediated: the coefficient of the indirect and total effects. ACME, average causal mediation effect; ADE, average direct effect; CI, confidence intervals.
[a] Expire indicates an in-hospital death.
[b] Poor CPC indicates a poor neurological outcome (CPC 3–5).

Table 5
Multivariable logistic regression for outcomes of Acute kidney injury, subgroup analysis according to whether or not Extracorporeal cardiopulmonary resuscitation was performed.

Outcome	Non-AKI	AKI	
		Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Expire[a]			
ECPR	ref.	11.58 (3.86–34.75)	11.52 (3.81–34.81)
ECMO without CA	ref.	3.78 (1.50–9.50)	3.29 (1.27–8.54)
Poor CPC[b]			
ECPR	ref.	6.95 (2.50–19.33)	7.09 (2.52–19.95)
ECMO without CA	ref.	3.58 (1.43–8.94)	2.89 (1.07–7.80)

Adjusted for Age, Sex.
AKI, acute kidney injury; OR, odds ratio; CI, confidence intervals; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; CA, cardiac arrest; CPC, cerebral performance category.
[a] Expire indicates an in-hospital death.
[b] Poor CPC indicates a poor neurological outcome (CPC 3–5).

Table 6
Univariable logistic regression analysis for each outcome of Cardiac arrest related variables (ECPR patients only).

Variables	AKI			In-hospital death			Neurological outcome		
	No AKI (N = 27)	AKI (N = 56)	Odds ratio (95 % CI)	survival (N = 34)	death (N = 49)	Odds ratio (95 % CI)	good (N = 28)	poor (N = 55)	Odds ratio (95 % CI)
Age, years	63.4 ± 11.3	62.8 ± 12.3	1.00 (0.96–1.04)	63.0 ± 12.3	63.0 ± 11.7	1.00 (0.96–1.04)	61.8 ± 12.2	63.6 ± 11.8	1.01 (0.97–1.05)
Sex, male	21 (77.8 %)	47 (83.9 %)	1.49 (0.47–4.73)	26 (76.5 %)	42 (85.7 %)	1.85 (0.60–5.69)	22 (78.6 %)	46 (83.6 %)	1.39 (0.44–4.41)
OHCA	1 (3.7 %)	12 (21.4 %)	7.09 (0.87–57.72)	4 (11.8 %)	9 (18.4 %)	1.69 (0.47–6.01)	4 (14.3 %)	9 (16.4 %)	1.17 (0.33–4.21)
Witness	27 (100.0 %)	51 (91.1 %)	0 (0–0)	32 (94.1 %)	46 (93.9 %)	0.96 (0.15–6.07)	27 (96.4 %)	51 (92.7 %)	0.47 (0.05–4.44)
BLS	27 (100.0 %)	50 (89.3 %)	0 (0–0)	33 (97.1 %)	44 (89.8 %)	0.27 (0.03–2.39)	27 (96.4 %)	50 (90.9 %)	0.37 (0.04–3.33)
Shockable	11 (40.7 %)	23 (41.1 %)	1.01 (0.40–2.58)	15 (44.1 %)	19 (38.8 %)	0.80 (0.33–1.95)	14 (50.0 %)	20 (36.4 %)	0.57 (0.23–1.44)
Total CA time[a]	23.0 [15.0; 41.0]	36.0 [25.0; 49.5]	1.04 (1.01–1.08)	26.5 [17.0; 42.0]	38.0 [25.0; 50.0]	1.04 (1.01–1.07)	24.5 [15.0; 43.5]	36.0 [25.0; 47.5]	1.04 (1.01–1.07)
ECPR time[b]	23.0 [14.5; 34.0]	28.5 [20.5; 38.0]	1.02 (0.98–1.05)	25.9 ± 13.3	30.6 ± 14.4	1.03 (0.99–1.06)	25.5 ± 14.2	30.2 ± 13.9	1.03 (0.99–1.06)

AKI, acute kidney injury; CI, confidence intervals; OHCA, Out of hospital cardiac arrest; Witness, Arrest witnessed; BLS, bystander cardiopulmonary resuscitation; Shockable, Initial shockable rhythm; CA, cardiac arrest; ECPR, extracorporeal cardiopulmonary resuscitation.
[a] Total CA time (minutes) is defined as the time from collapse to recovery of spontaneous circulation (ROSC).
[b] ECPR time (minutes) is defined as the time from collapse to extracorporeal membrane oxygenation (ECMO) initiation.

significantly different from the previous studies. However, the incidence of AKI in ECMO varies widely among reports. This is because each study has different enrollment criteria. The results of the ECMO studies differed depending on whether each study included severe patients, such as CA, even if they were not ECPR. Since this study compared ECPR and ECMO to determine the effect of CA, only patients with cardiogenic shock, excluding complications from the operation and CA, were included in the ECMO group. As a result, the incidence of AKI was low at 38.4 %.

In addition to ECMO-induced injuries, ECPR patients also suffer from CA injuries, which we hypothesized to affect the incidence of AKI. In this study, the AKI group was defined as the occurrence of AKI within 72 h after ECMO application. This definition of AKI was used because, in previous AKI and CA studies, it was reported that most AKIs occur within one to three days after CA [17,19]. AKIs that occurred long after ECMO procedures should not be included in studies. AKIs that occur long after the ECMO procedure are caused by the patient's status during ECMO maintenance or after ECMO removal and are unlikely to be caused by CA.

In this study, there was a significant difference in the incidence of AKI between ECPR and ECMO without CA. CA patients receive ischemic injury due to little to no blood supply during CPR and even after ROSC. Tissue hypoperfusion and multiple organ dysfunction due to the myocardial dysfunction and systemic ischemia and reperfusion are known to cause AKI [16], and these impairments occur in ECPR. In this study, ECPR patients had significantly worse laboratory results immediately after ECMO compared with those who performed ECMO with cardiogenic shock, which indirectly proves that injury in the CA process had an effect. In addition, ECMO without CA is considered a 'shock with flow' state, which is different from the possibly more dangerous no-flow or low-flow state experienced during ECPR.

ECPR was associated not only with the occurrence of AKI but also with the outcome. In ECPR, AKI completely mediated the outcome, and the OR for the outcome was higher in patients with ECPR than in ECMO patients without CA. This suggests that the injury caused by CA affects the outcome through AKI. There are many studies proving that AKI is associated with outcomes such as mortality and CPC in CA [18,19,31–34]. However, there are few studies on the association between AKI and mortality in ECPR patients. Gaisendrees et al. reported a higher in-hospital mortality in the non-AKI group in ECPR patients. (86 % with no AKI and 70 % with AKI) [22]. However, the results of this study are difficult to accept. The outcome of the non-AKI group was that the ICU and hospital stay period were only one day, and the in-hospital mortality of 86 % and the good neurological outcome of 66.7 % were opposite results. In another study, Ravipati et al. reported the mortality of AKI in ECPR patients to be 67 % and 75 % depending on RRT [23], which is similar to our study.

The total CA time was a significant factor related to CPR that could cause AKI. In addition to the incidence of AKI, total CA time was also associated with mortality and poor neurologic outcome [30,35]. ECPR time is a risk factor for AKI in ECPR. However, in this study, ECPR time did not correlate with prognosis but with total CA time. The results from previous studies were from in-hospital CA (IHCA), and this study included not only IHCA but also OHCA. In this study, the time difference between the ED and the decision to apply ECPR occurred in OHCA. Therefore, the low flow time and total arrest time for IHCA were almost identical, but for OHCA, it was not. Fast decision-making and fast procedure are required to reduce the total CA time of the ECPR.

We found that reducing AKI before and after ECMO initiation can help improve patient outcomes. During arrest, the risk of AKI increases due to no-flow or low-flow conditions, which can only be improved by reducing the total time of arrest. This was shown by the correlation between the occurrence of AKIs and total CA time observed in the present study [16]. As a solution to this problem, we propose that ROSC should be performed promptly by reducing the decision and procedure time of ECPR. In addition, we suggest that proper fluid management should be performed, which is discussed in the previous literature [33], and other methods should be further studied.

4.1. Limitation

This study had several limitations. First, it was a retrospective study conducted by a single institution. More patients and multicenter studies should be performed in the future. Second, organ failures other than AKI were not investigated. ECPR can cause various injuries due to CA and will result in injury to all organs. This can be inferred from this study's laboratory results, which were performed by the lab immediately after ECMO in ECPR. However, all the injuries to various organs, such as acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and acute liver failure (ALF). The study was conducted focusing on AKI among various organs because AKI is a serious and frequently occurring complication in CA. Third, AKI was diagnosed when continuous renal replacement therapy (CRRT) was applied due to metabolic acidosis, pulmonary edema, or other renal failure diseases. Cases requiring CRRT due to the deterioration of systemic conditions caused by ECMO and AKI may have been overestimated due to kidney injuries. However, this problem was addressed when the study defined AKI using the KDIGO standard. The KDIGO standard is currently the most widely agreed diagnostic standard for AKI. Lastly, data on CA without ECMO was not included in the study and thus the differences caused by ECMO during CA could not be investigated. However, since the critical variable affecting outcome (including AKI) in the ECPR process is CA rather than ECMO, this limitation is minimized.

5. Conclusion

ECPR showed increased in-hospital mortality and poorer neurologic outcomes than ECMO without CA. ECPR has a higher incidence of AKI than ECMO, and AKI is associated with poor outcomes by completely mediating these effects. Therefore, clinicians should be careful not to develop AKI in ECPR patients.

Article summary

1. Why is this topic important?

This topic holds significant clinical importance due to the elevated incidence of acute kidney injury (AKI) observed in patients undergoing extracorporeal membrane oxygenation (ECMO) and extracorporeal cardiopulmonary resuscitation (ECPR), necessitating effective management strategies for improved outcomes.

2. What does this study attempt to show?

This study aims to provide a comprehensive review highlighting the higher occurrence of AKI in ECPR patients compared to ECMO patients without cardiac arrest, emphasizing the association between AKI and unfavorable clinical outcomes in the ECPR setting.

3. What are the key findings?

The key findings underscore a significantly increased incidence of AKI in ECPR patients, demonstrating its correlation with elevated in-hospital mortality rates and inferior cerebral performance outcomes.

4. How is patient care impacted?

The study's implications for patient care emphasize the critical importance of diligent AKI monitoring and prevention measures specifically tailored to ECPR patients, with the ultimate goal of enhancing patient prognosis.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Dong Ki Kim: Writing – review & editing, Writing – original draft, Conceptualization. **Young Soo Cho:** Supervision, Formal analysis, Data curation, Conceptualization. **Byung Kook Lee:** Investigation, Funding acquisition, Formal analysis. **Kyung Woon Jeung:** Visualization, Validation. **Yong Hun Jung:** Visualization, Validation. **Dong Hun Lee:** Writing – review & editing, Writing – original draft. **Min Chul Kim:** Software, Resources. **Yong whan Lim:** Software, Resources. **Do Wan Kim:** Funding acquisition, Formal analysis. **Kyo Seon Lee:** Investigation, Funding acquisition. **In Seok Jeong:** Project administration, Methodology, Investigation. **Jeong Mi Moon:** Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Byeong Jo Chun:** Visualization, Validation, Software, Resources, Project administration. **Seok Jin Ryu:** Writing – review & editing, Writing – original draft.

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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