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ORIGINAL RESEARCH

Recovery from acute kidney injury is an independent predictor of survival at 30 days only after out-of-hospital cardiac arrest who were treated by targeted temperature management

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Abstract

Background: Development of acute kidney injury (AKI) after out-of-hospital cardiac arrest (OHCA) is associated with mortality and poor neurological outcome. However, the effect of recovery from AKI after OHCA is uncertain. This study investigates whether recovery from AKI was associated with the rate of survival and neurological outcome at 30 days after OHCA.

Methods: This is a prospective multicentre observational cohort study of adult OHCA patients treated with targeted temperature management (TTM) across five hospitals in South Korea between February 2019 and July 2020. AKI was diagnosed using the Kidney Disease: Improving Global Outcomes criteria. The primary outcome was the rate of survival at 30 days, and the secondary outcome was the rate of survival with a favourable neurological outcome at 30 days, defined by a score of 3 or less on the modified Rankin scale.

Results: Among the 2,018 patients with OHCA, 79 were treated with TTM. After excluding two patients with incomplete data on outcomes, 77 were analysed. AKI developed in 43 (56%) patients. Among them, 22 (51%) recovered from AKI. Although the rate of survival at 30 days for the recovery group was superior to the non-recovery group (82% vs. 24%, $P < 0.001$), the rate of survival with a favourable neurological outcome at 30 days for the recovery group was not different than that for the non-recovery group (32% vs. 10%, $P = 0.132$). Recovery from AKI was an independent predictor of survival at 30 days after OHCA in the multivariate analysis (adjusted odds ratio, 22.737; 95% confidence interval, 3.814-135.533; $P = 0.001$); however, it was not associated with a favourable neurological outcome at 30 days after OHCA in the multivariate analysis.

Conclusion: Recovery from AKI was an independent predictor of survival at 30 days only after OHCA who were treated by TTM.

Keywords

Acute kidney injury; Out-of-hospital cardiac arrest; Targeted temperature management; Therapeutic hypothermia

1. Introduction

Acute kidney injury (AKI) is associated with increased risk of death and poor neurological outcome after out-of-hospital cardiac arrest (OHCA) [1, 2]. Because AKI has been confirmed as a risk factor of mortality, recovery from AKI might be associated with a good outcome. In case of critically ill patients, the rate of survival of patients who recovered from AKI was significantly higher than those who did not recover [3]. However, the effect of recovery from AKI after OHCA is uncertain. Although one retrospective cohort study reported that the recovery from AKI was a potent predictor of survival and good neurological outcome at discharge, there were several limitations to the study, including that the development of AKI and recovery from AKI were determined retrospectively and the outcomes could not be determined at the same time point among the patients [4]. To address these limitations, our prospective cohort study aims to identify the effect of recovery from AKI on the rate of survival and good neurological outcome at 30 days after OHCA. We hypothesised that the rate of survival at 30 days after OHCA in patients who recovered from AKI was superior to the patients who did not recover from AKI.

2. Materials and methods

2.1 Study design and setting

This is a prospective multicentre observational cohort study. Data were collected from five academic hospitals in South Korea between February 2019 and July 2020. The development of AKI and recovery from AKI were defined prospectively considering both the serum creatinine level and hourly urine output. The study design and plan, including the informed consent form, were approved by the institutional review board of each hospital and were registered at the International Clinical Trials Registry Platform (Clinical Research Information Service; Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare, Osong, Chungcheongbuk-do, Republic of Korea, (https://cris.nih.go.kr [registered No. KCT0003544])) on February 21, 2019. The first participant was enrolled on March 18, 2019, and the last participant was enrolled on July 22, 2020.

2.2 Study population

All adult patients with OHCA irrespective of the cause of arrest who were unconscious after the return of spontaneous circulation (ROSC) and treated with targeted temperature management (TTM) were enrolled in the registry. Patients aged $<$ 19 years, those who were dead on arrival to the hospital and did not receive cardiopulmonary resuscitation (CPR), those who did not achieve ROSC despite cardiopulmonary resuscitation, those who did not receive TTM despite achieving ROSC, those diagnosed with end-stage renal disease with dialysis (peritoneal dialysis or haemodialysis) before developing cardiac arrest, those who had a Do-Not-Attempt-Resuscitation (DNAR) order, those who had acute intracranial haemorrhage or acute ischaemic stroke, and those who had active bleeding were excluded. In addition, patients were excluded from the study when patients' legal surrogates refused to participate or withdrew informed consent during the study period. Enrolled patients received care for post-cardiac arrest syndrome according to the standard operating procedures for OHCA at each hospital. The principal investigator of each participating hospital collected data from the hospital records of OHCA survivors treated with TTM and determined the development of AKI and recovery from AKI prospectively. The independent data input researcher investigated survival status and modified Rankin scale (MRS) at 30 days after OHCA. If patients died before 30 days, the death date was recorded.

2.3 Indication and contraindication of TTM

Regardless of the initial rhythm, patients who did not show meaningful responses to verbal commands after ROSC for more than 20 minutes were treated with TTM. Cardiac arrest associated with trauma, severe sepsis, having poor cognition or poor neurological condition before cardiac arrest, pregnancy, arrhythmia not responding to treatment or coronary vasospasm, refractory shock not responding to fluid or vasopressors, active bleeding or thrombolytic use, and therapeutic hypothermia were relatively contraindicated; thus, TTM could be decided by the institution's expert. However, TTM was contraindicated for patients with terminal illness before cardiac arrest, those who had a DNAR order, and those with other aetiologies for coma.

2.4 Definition of AKI

The development and staging of AKI were defined using the Kidney Disease: Improving Global Outcomes criteria [5]. AKI was defined when one of the following conditions were fulfilled. First, an increase in serum creatinine more than 1.5 times baseline within 7 days after OHCA. Second, an increase in serum creatinine more than 0.3 mg/dL within 48 hours. Third, a decrease in hourly urine output lower than 0.5 mL/kg/h for 6 hours. The baseline serum creatinine was defined as the last available serum creatinine level within the last 3 months. If the last available serum creatinine level within the last 3 months was unknown, the baseline serum creatinine level was defined as the lowest value between the post-ROSC value and estimated serum creatinine value through the use of the Modification of Diet in Renal Disease equation [5]. Recovery from AKI was defined when all the AKI criteria were not fulfilled (decrease in the serum creatinine level within 150% of the baseline serum creatinine level without oliguria [hourly urine output $\geq$ 0.5 mL/kg/h for 6 h]).

2.5 Variables

The primary outcome was the rate of survival at 30 days, and the secondary outcome was the rate of survival with a favourable neurological outcome at 30 days, which was defined by a score of 3 or less on the MRS. Other variables were as follows: age (years), sex (male or female), weight (kg), past medical history (hypertension, diabetes mellitus, heart failure), witnessed cardiac arrest (witnessed or not witnessed), bystander CPR (yes or no), first monitored rhythm (shockable or non-shockable), CPR time (min), epinephrine dose (mg), coronary angiography (yes or no), extracorporeal membrane oxygenation (yes or no), urine output (mL/kg/h) in the intensive care unit, event of shock (mean arterial pressure $<$ 70 mmHg) after OHCA, daily serum creatinine level (mg/dL), renal replacement therapy (yes or no), survival status at 30 days after OHCA, MRS at 30 days after OHCA, and the date of death if the patient died within 30 days after OHCA. If the serum creatinine level was checked two or more times a day, the highest value was recorded. All dates were calculated from the day of the OHCA. The MRS was used for assessing neurological outcomes, with an MRS of 0-3 considered as a good outcome and an MRS of 4-6 as a poor outcome [6]. The MRS was calculated using a 9-question telephone survey (modifiedrankin.com) [7]. The telephone survey was performed by independent data input researcher.

2.6 Sample size

The sample size was calculated on the basis of relative risk precision using the relative risk of survival rate for the AKI recovery group. Although the primary outcome was the rate of survival at 30 days, no other studies have reported a cohort of AKI recovery group after OHCA with a rate of survival at 30 days prior to the start of this study. Therefore, the relative risk

of the rate of survival at discharge for the AKI recovery group was used for calculating the sample size. A previous study reported that the proportion of the AKI non-recovery group and the relative risk of survival at discharge for the AKI recovery group were 0.61 and 4, respectively [4]. The probability of type I error was set at 0.05, and the relative risk precision was set at 10%. Using these parameters, a web-based sample size calculator estimated a minimum sample size of 18 for each group [8]. Therefore, 36 patients with AKI after OHCA would be needed.

2.7 Statistical methods

Descriptive statistics were reported as median (interquartile range) or mean ± standard deviation for continuous variables according to the normality of distribution. Data normality was analysed using the Shapiro-Wilk test or Kolmogorov-Smirnov test. Categorical variables were reported as frequency (percentage). Demographics and clinical differences between the groups were assessed using Pearson's chi-squared test, Fisher's exact test, independent sample *t*-test, or Mann-Whitney *U* test, as appropriate. The association between predictors and outcome was quantified using the odds ratio (OR) with 95% confidence interval (CI). To determine the independent factors associated with the outcomes, the multivariate logistic regression analysis was performed, which included all variables with a *P*-value of < 0.2; a stepwise backward selection of the variables was then applied, which remained significant. The Hosmer-Lemeshow test was used for evaluating the goodness of fit of the logistic regression model. Differences in the Kaplan-Meier survival curves between the groups (non-AKI group vs. AKI group and AKI recovery group vs. AKI non-recovery group) were compared using the log-rank test. A *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1 Study population

Of the 2,018 patients with OHCA screened during the study period, 79 were treated with TTM at five academic hospitals (Fig. 1). After excluding two patients with incomplete data on outcomes, 77 were analysed. The baseline characteristics of the patients according to AKI and recovery status from AKI are summarised in Table 1.

3.2 Descriptive data

The mean age of the patients was 58 ± 16 years, and their mean weight was 68 ± 12 kg, with most patients being men (56/77, 73%). The median duration of CPR was 26 ± 18 mins, and the median dose of adrenaline (epinephrine) was 1 mg (0-4 mg). The baseline serum creatinine was 1.00 (1.00-1.10) mg/dL.

3.3 Clinical course of AKI

AKI developed in 43/77 (56%) patients, and 22/43 (51%) recovered from AKI. In total, 35/43 (81%) patients were diagnosed with AKI based on serum creatinine level, and 8/43 (19%) were diagnosed on the basis of the hourly urine output criteria. In all the cases, AKI developed within 3 days since ROSC (29/43 [68%] on day 1, 7/43 [16%] on day 2, and 7/43 [16%] on day 3). Renal recovery occurred in 6 (3-7) days after OHCA, and the median duration of AKI was 4 (2-10) days. The duration of AKI was significantly longer for the AKI non-recovery group than for the AKI recovery group (7 [3-13] vs. 4 [2-6] days; $P = 0.02$). The distribution of AKI stages was as follows: stage 1, 18/43 (42%); stage 2, 7/43 (16%); and stage 3, 18/43 (42%). The recovery rate from AKI was significantly different among the stages of AKI (14/18 [78%] in stage 1, 5/7 [71%] in stage 2, 3/18 [17%] in stage 3, $P < 0.001$) (Fig. 2). Renal replacement therapy (RRT) was conducted in 14/43 (33%) patients. The most common modality of RRT was continuous renal replacement therapy (13/14 [93%]). The median duration of RRT was 9 ± 6 days. There were no differences in the duration of RRT according to renal recovery (10 ± 8 days in recovery group vs. 9 ± 6 days in non-recovery group, $P = 0.787$). None of the RRT patients required RRT at 30 days after ROSC. Among 14 RRT patients, eight expired, three recovered from AKI, two stopped RRT by withdrawing life sustaining therapy, and one converted to chronic kidney disease.

3.4 Rate of survival at 30 days after OHCA

In total, 51/77 (66%) patients survived at 30 days after OHCA. The rate of survival at 30 days after OHCA for the non-AKI group was significantly higher than that for the AKI group (28/34 [82%] vs. 23/43 [54%], $P = 0.008$); the rate of survival was significantly different according to the stages of AKI (14/18 [78%] in stage 1, 3/7 [43%] in stage 2, and 6/18 [33%] in stage 3, $P = 0.008$) (Fig. 3). For the AKI group, the rate of survival at 30 days after OHCA for the recovery group was significantly higher than that for the non-recovery group (18/22 [82%] vs. 5/21 [24%], $P < 0.001$). Recovery from AKI and shock were independent predictors of survival at 30 days after OHCA in patients with AKI (recovery from AKI: adjusted OR 22.737, 95% CI 3.814-135.533, $P = 0.001$; shock: adjusted OR 0.112, 95% CI 0.015-0.807, $P = 0.030$; Hosmer and Lemeshow test: chi-square = 0.366; df = 2; $P = 0.833$).

3.5 Survival analysis

The Kaplan-Meier survival curves differed significantly between the non-AKI and AKI groups ($P = 0.006$) (Fig. 4). In the AKI group, the Kaplan-Meier survival curves differed significantly between the recovery and non-recovery groups ($P < 0.001$) (Fig. 5). However, there was no difference between the non-AKI and AKI recovery groups ($P = 0.99$) (Fig. 5).

3.6 Favourable neurological outcome at 30 days after OHCA

The distribution of MRS at 30 days after OHCA according to the group are summarised in Table 2. In total, 32/77 (42%) patients had a score of 3 or less on the MRS at 30 days after OHCA. The rate of favourable neurological outcome at 30 days after OHCA for the non-AKI group was significantly higher than that for the AKI group (23/34 [68%] vs. 9/43 [21%],

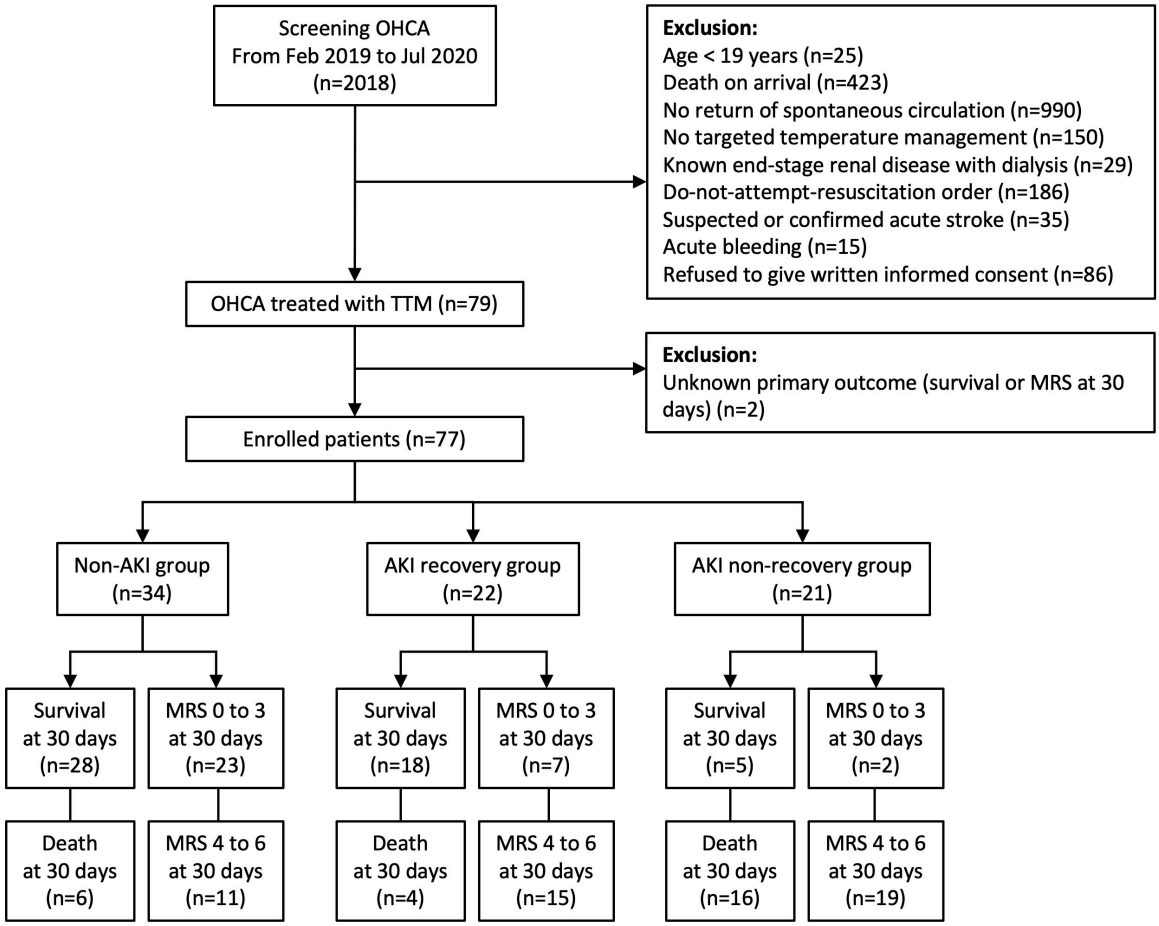

FIGURE 1. Study flow diagram. AKI, acute kidney injury; OHCA, out-of-hospital cardiac arrest; MRS, modified Rankin scale; TTM, targeted temperature management.

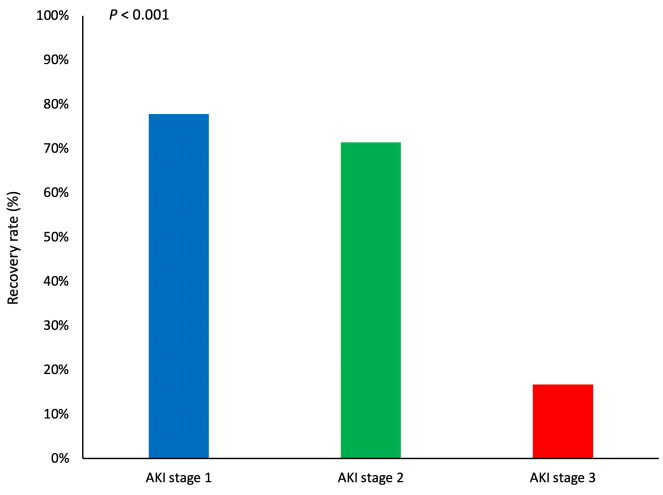

FIGURE 2. Recovery rate from different stages of acute kidney injury. AKI, acute kidney injury.

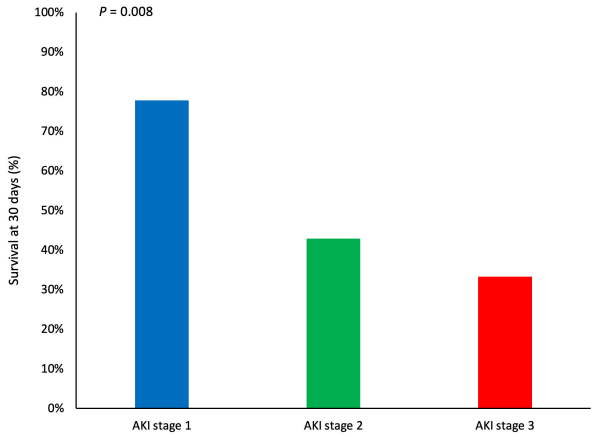

FIGURE 3. Rate of survival at 30 days for different stages of acute kidney injury. AKI, acute kidney injury.

$P < 0.001$), and the rate of favourable neurological outcome was significantly different according to the stages of AKI (8/18 [44%] in stage 1, 0/7 [0%] in stage 2, and 1/18 [6%] in stage 3, $P = 0.005$). For the AKI group, the rate of favourable neurological outcome at 30 days after OHCA for the recovery group was not different than that for the non-recovery group (7/22 [32%] vs. 2/21 [10%], $P = 0.13$) (Fig. 6). There were no independent predictors of favourable neurological outcome at 30 days after OHCA in patients with AKI.

TABLE 1. Baseline characteristics according to the groups

Variables	Non-AKI group (n = 34)	AKI group (n = 43)		*P* value
		AKI recovery group (n = 22)	AKI non-recovery group (n = 21)	
Demographics				
Male sex	20 (59)	18 (82)	18 (86)	**0.02**
Age (years)	52 ± 16	61 ± 15	62 ± 14	**0.04**
Weight (kg)	66 ± 14	69 ± 8	71 ± 13	0.27
Medical history				
Hypertension	14 (41)	11 (50)	8 (38)	0.71
Diabetes mellitus	4 (12)	8 (36)	7 (33)	0.05
Heart failure	2 (6)	2 (9)	1 (5)	0.93
Baseline sCr (mg/dL)	1.10 (0.90-1.10)	1.00 (1.00-1.10)	1.00 (1.00-1.10)	0.76
Resuscitation				
Witnessed arrest	23 (68)	18 (82)	15 (71)	0.66
Bystander CPR	20 (61)	14 (64)	16 (76)	0.49
Shockable rhythm	19 (70)	7 (37)	3 (18)	< **0.001**
CPR time (min)	20 (9-30)	30 (19-38)	37 (17-40)	**0.004**
Epinephrine dose (mg)	0 (0-3)	2 (0-4)	3 (1-6)	**0.03**
Post-resuscitation				
TT of 33 °C	23 (32)	4 (18)	11 (52)	0.204
TT of 36 °C	11 (68)	18 (82)	10 (48)	0.204
TTM of 24-hour	27 (79)	20 (91)	14 (67)	0.363
TTM of 48-hour	7 (20)	2 (9)	7 (33)	0.363
Shock	21 (62)	15 (68)	15 (71)	0.74
Coronary angiography	19 (56)	8 (36)	4 (19)	**0.01**
ECMO	0 (0)	0 (0)	2 (5)	0.16
AKI stage				< **0.001**
Stage 1	N/A	14 (64)	4 (19)	
Stage 2	N/A	5 (23)	2 (10)	
Stage 3	N/A	3 (14)	15 (71)	
CRRT	N/A	2 (9)	11 (52)	< **0.001**
Outcome				
Survival at 30 days	28 (82)	18 (82)	5 (24)	< **0.001**
Good MRS (0 to 3) at 30 days	23 (68)	7 (32)	2 (10)	< **0.001**

Values are expressed as number (%) or mean ± standard deviation (or median [interquartile range]).
P < 0.05 are presented in bold.
AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MRS, modified Rankin scale; N/A, not applicable; sCr, serum creatinine; TT, targeted temperature; TTM, targeted temperature management.

TABLE 2. Modified Rankin scales at 30 days after cardiac arrest according to the groups

Modified Rankin Scale	Total (n = 77)	Non-AKI group (n = 34)	AKI group (n = 43)	
			AKI recovery group (n = 22)	AKI non-recovery group (n = 21)
1	17 (22)	12 (35)	4 (18)	1 (5)
2	11 (14)	9 (26)	2 (9)	0 (0)
3	4 (5)	2 (6)	1 (5)	1 (5)
4	3 (4)	2 (6)	1 (5)	0 (0)
5	15 (19)	3 (9)	10 (45)	2 (10)
6	27 (35)	6 (18)	4 (18)	17 (81)

Values are expressed as number (%).

4. Discussion

In this prospective multicentre observational cohort study, we found that recovery from AKI was an independent predictor of survival at 30 days after OHCA. However, it was not associated with a favourable neurological outcome at 30 days after OHCA. Although brain injury has been identified as the leading cause of death after OHCA, AKI is a well-known risk

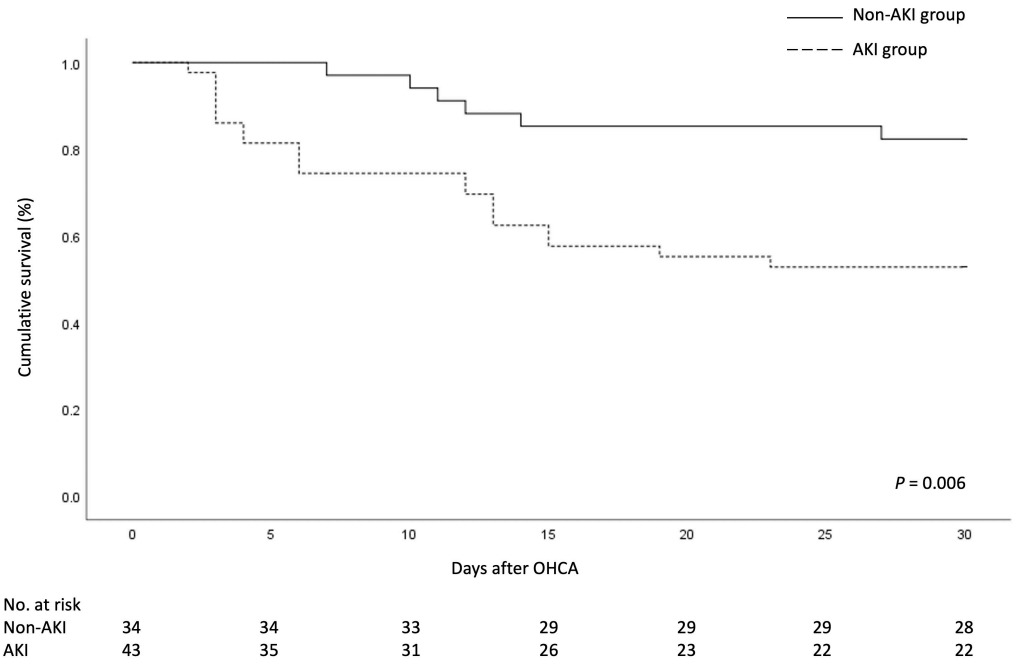

FIGURE 4. Thirty-day cumulative survival for patients with or without acute kidney injury after out-of-hospital cardiac arrest. AKI, acute kidney injury; OHCA, out-of-hospital cardiac arrest.

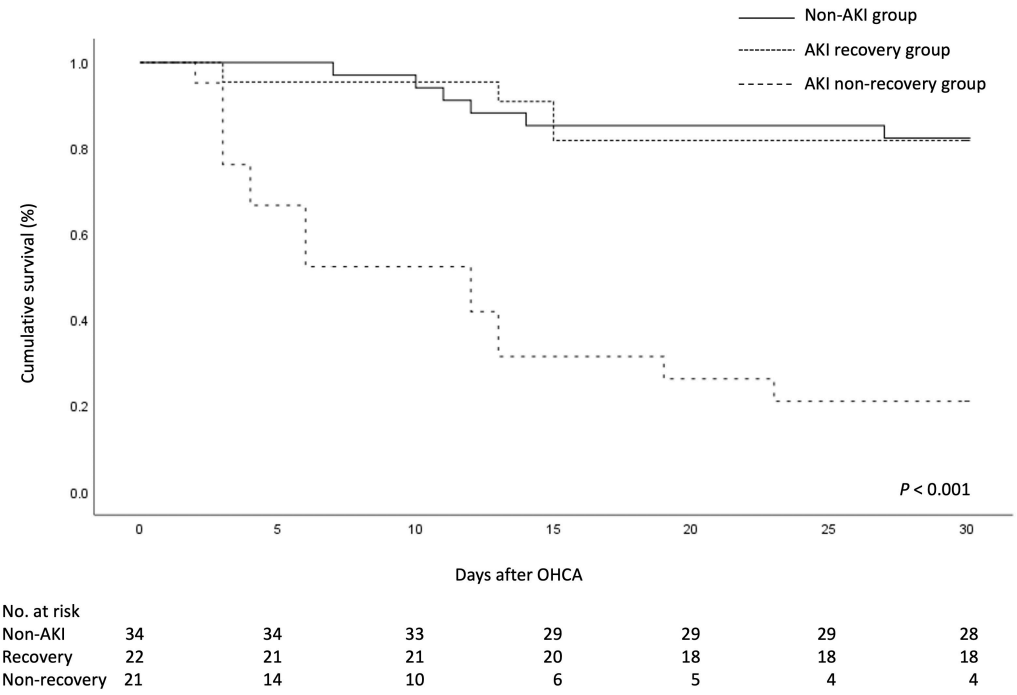

FIGURE 5. Thirty-day cumulative survival according to recovery status from acute kidney injury after out-of-hospital cardiac arrest. AKI, acute kidney injury; OHCA, out-of-hospital cardiac arrest.

factor for mortality in critically ill patients, including those with post-cardiac arrest [9–15]. Even mild reversible AKI, such as stage 1 AKI, could increase the risk of death [2, 5, 11]. In the epidemiologic studies of critically ill patients, the rate of recovery after AKI was markedly higher for survivors, and the rate of survival was significantly higher for the group of recovery after AKI [3, 16]. Therefore, maximising recovery of renal function is the goal of any AKI prevention and treatment strategy in the critical care area [17].

In our cohort, recovery from AKI played an important role in improving patients' outcome. Considering the results of previous retrospective study, it was expected that the rate of survival would be higher for the AKI recovery group than for the AKI non-recovery group [4]. We could not expect that the rate of survival for the AKI recovery group was similar to that for the non-AKI group because even stage 1 AKI could increase mortality. However, the rate of survival at 30 days after OHCA for the AKI recovery group was not different than

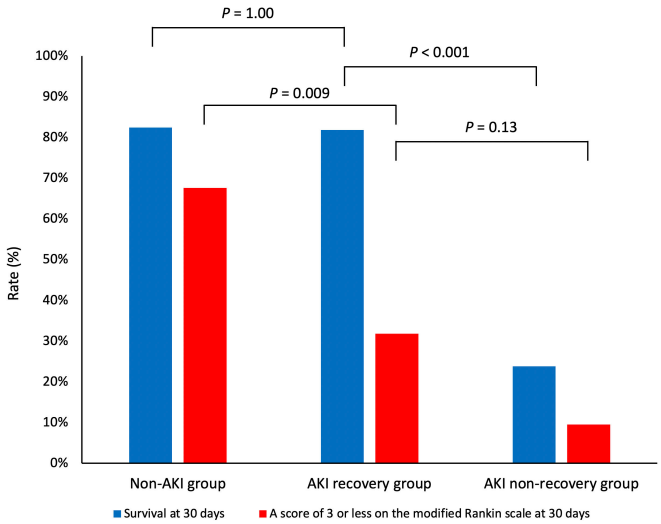

FIGURE 6. Differences of outcomes among the groups. AKI, acute kidney injury.

that for the non-AKI group (P = 1.00) (Fig. 6). In addition, there were no differences in the Kaplan-Meier survival curves between the non-AKI group and AKI recovery group (Fig. 5). These unexpected results suggested that renal recovery could be a treatment target for improving the rate of survival after OHCA. Furthermore, renal recovery could be used as a survival predictor when AKI develops after OHCA.

However, the rate of favourable neurological outcome at 30 days after OHCA for the AKI recovery group was significantly lower than that for the non-AKI group and was not different than that for the non-recovery group (Fig. 6). Discrepant results between the rate of survival and the favourable neurological outcome show the potential and limitation of renal recovery for its usage as an outcome predictor and treatment goal. In addition, the dilemma remains that recovery from AKI might be a significant independent predictor only for short-term survival of OHCA patients and not for long-term outcome. This issue should be evaluated in the additional study by using long-term primary outcome such as survival and neurological outcome at 6-month or 12-month after OHCA.

A previous retrospective study reported renal recovery as a potent predictor of survival and favourable neurological outcome at discharge [4]. Several factors might contribute to the differences in the results between our study and those of previous studies. First, although the previous study assessed the outcomes at different time points according to patients (e.g., at discharge), the assessment of outcome in our study was determined at the same time point (30 days after OHCA). Second, although the development of AKI and renal recovery had been determined considering both the serum creatinine and hourly urine output in both studies, there were limitations in defining AKI on the basis of hourly urine output in the retrospective cohort because of incomplete data. While 19% of AKI was diagnosed by applying hourly urine output criteria in our study, only 3% of AKI was diagnosed using urine output criteria in the previous study. This difference might affect the defining process of AKI and recovery from AKI.

Another interesting result was the difference in the recovery rate according to the stages of AKI (Fig. 2). Especially, the recovery rate in the AKI stage 3 was only 17%. It was significantly lower than that of the stage 1 or 2 AKI. Recovery from AKI itself was an independent predictor of survival outcome; a significantly lower recovery rate of AKI stage 3 could affect the lower rate of survival at 30 days for the AKI stage 3 (33.3%) (Fig. 3). A chicken-or-egg question might arise here. The severity of AKI stage 3 itself might decrease the rate of renal recovery because a more severe AKI was a risk factor for non-recovery [3, 17]. However, a lower recovery rate in stage 3 AKI might be a reason for high mortality. Further research will be needed for investigating the role of renal recovery for different stages of AKI and clinical outcomes.

5. Limitations

Our study has several limitations. First, the predictor of renal recovery could not be determined because the number of participants was small. Another clinical trial, including a large number of patients, will be needed for determining the factors associated with renal recovery. Second, although 'recovery from AKI' was defined as the absence of AKI criteria, using this definition might underestimate or overestimate renal recovery [17]. New biomarkers for accurate estimation of renal recovery will be needed for overcoming this limitation. Third, a significant number of patients (n = 150) were excluded from the screening process because they were not treated with TTM. Although TTM had been regarded as a standard treatment after cardiac arrest, it was not provided to some patients because of several reasons, including relative contraindications of TTM and financial issues [4]. Additionally, a relatively large number of patients (n = 86) were excluded because their legal surrogates refused to participate in the study. As a result, there was a possibility in the occurrence of selection bias. Although this study was not an interventional but an observational study, legal surrogates hesitated to provide written informed consent. Therefore, the possibility of selection bias exists.

6. Conclusions

Recovery from AKI was an independent predictor of survival at 30 days only after OHCA who were treated by TTM.

AUTHOR CONTRIBUTIONS

Oh JH contributed to the study conception and design. Cha KC, Cho IS, Oh JH, Park YS, Choi YH, Kim SJ, and Kim TY contributed to data acquisition. Cha KC, Cho IS, and Oh JH contributed to data analysis and interpretation. Oh JH contributed to statistical analysis and revisions. Oh JH contributed to funding acquisition. Cha KC, Cho IS, and Oh JH contributed to the drafting of the manuscript and its critical revision for important intellectual content. All authors have read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study design and plan, including the informed consent form, were approved by the institutional review board (IRB) of each hospital (Approval No, Chung-Ang University Hospital IRB: 1803-014-348, Yonsei University Health System Severance Hospital IRB: 4-2018-1199, Ewha Womans University Mokdong Hospital IRB: EUMC-2018-11-020-002, Hanil General Hospital IRB: HGH-2018-OBS-018, and Yonsei University Wonju Severance Cristian Hospital IRB: CR318107). According to the national requirements and the principles of the Declaration of Helsinki, written informed consent was obtained from all patients' legal surrogates.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed for this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1351449359038726144/attachment/SV2020120902_Supplementary_material.docx.

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