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Association between acute kidney injury and neurological outcome or death at 6 months in out-of-hospital cardiac arrest: A prospective, multicenter, observational cohort study

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ABSTRACT

Purpose: This study aimed to evaluate the association between acute kidney injury (AKI) and 6 months neurological outcome after out-of-hospital cardiac arrest (OHCA).
Materials and methods: Prospective multi-center observational cohort included adult OHCA patients treated with targeted temperature management (TTM) across 20 hospitals in the South Korea between October 2015 and October 2017. The diagnosis of AKI was made using the Kidney Disease: Improving Global Outcomes criteria. The outcome was neurological outcome at 6 months evaluated using the modified Rankin scale (MRS).
Results: Among 5676 patients with OHCA, 583 patients were enrolled. AKI developed in 348 (60%) patients. Significantly more non-AKI patients had good neurological outcome at 6 months (MRS 0–3) than AKI patients (134/235 [57%] vs. 69/348 [20%], $P < .001$). AKI was associated with poor neurological outcome at six months in multivariate logistic regression analysis (adjusted odds ratio: 0.206 [95% confidence interval: 0.099–0.426], $P < .001$]). Cox regression analysis with time-varying covariate of AKI showed that patients with AKI had a higher risk of death than those without AKI (hazard ratio: 2.223; 95% confidence interval: 1.630–3.030, $P < .001$).
Conclusions: AKI is associated with poor neurological outcome (MRS 4–6) at 6 months in OHCA patients treated with TTM.
Trial registration: NCT02827422

1. Introduction

Acute kidney injury (AKI) is one of the major problems in the emergency and critical care setting and is prominently associated with hospital mortality [1,2]. Further, AKI affects patients who have successfully achieved return of spontaneous circulation (ROSC) from out-of-hospital cardiac arrest (OHCA). As complex mechanisms of ischemia–reperfusion injury begin just after ROSC, post-cardiac arrest syndrome (PCAS) develops in various organs including the kidneys and eventually results in multiple organ failure [3,4]. The natural courses and treatment recommendations for post-cardiac arrest myocardial dysfunction and brain injury are well established [5,6]. However, the reported incidences of AKI in PCAS patients are diverse and range from 12% to 80% because of

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; KDIGO, Kidney Disease: Improving Global Outcomes; KORHN, Korean Hypothermia Network; KORHN-PRO, Korean Hypothermia Network prospective registry; MRS, modified Rankin scale; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PCAS, post-cardiac arrest syndrome; ROSC, return of spontaneous circulation; RRT, renal replacement therapy; TTM, targeted temperature management.

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several reasons, such as different characteristics of patients in the cohort [7-16]. In addition, the associations between AKI and neurological outcome of cardiac arrest were heterogeneous among several single-center observational cohort studies, although the patients with AKI showed higher mortality than those without AKI [10,12,14,16].

The varied results and heterogeneous association between AKI and neurological outcome might be due to the diversity in the characteristics of study cohorts. As several factors such as witnessed arrest, bystander cardiopulmonary resuscitation (CPR), and shockable rhythm could affect survival following OHCA and are predetermined before AKI development, these factors should be controlled to precisely evaluate the effects of AKI [17]. Therefore, a prospective multicenter observational cohort study should evaluate the effect of AKI on long-term neurological outcome.

In 2002, two randomized clinical trials showed that using mild therapeutic hypothermia in comatose survivors of cardiac arrest significantly improved the neurological outcome [18,19]. In addition, Nielsen et al. reported that there were no differences in the outcomes between the two target temperatures (33 °C or 36 °C) [20]. Next, targeted temperature management (TTM) between 32 °C and 36 °C had been recommended to the comatose adult patients with ROSC after cardiac arrest [4,21]. Several physiologic changes affect the renal system during therapeutic hypothermia. For example, urine output increases during the induction phase and decrease in the maintenance and re-warming phase of therapeutic hypothermia [22]. These physiologic changes could affect the diagnosis of AKI. Therefore, this study aimed to evaluate the association between AKI and long-term neurological outcome after OHCA treated with TTM in a multicenter clinical setting.

2. Material and methods

2.1. Study design and setting

This was a prospective, multicenter, observational cohort study. Data were collected from the Korean Hypothermia Network (KORHN) prospective registry (KORHN-PRO). Established in 2011 and covering 32 hospitals in total, the KORHN is a multicenter clinical research consortium for TTM in South Korea. Among 32 hospitals of the KORHN, 20 hospitals participated in the KORHN-PRO. The participating institutions ($n = 20$) were evenly distributed throughout the entire country (Seoul, 10; Gyeonggi-do, 4; Chungcheong-do, 1; Gangwon-do, 1; Jeonra-do, 1; Gyeongsang-do, 1; Daegu, 1; Busan, 1). The study design and plan, including the informed consent form, were approved by the institutional review board (IRB) of all participating hospitals and registered at the International Clinical Trials Registry Platform (NCT02827422). In accordance with national requirements and the principles of the Declaration of Helsinki, written informed consent was obtained from all patients' legal surrogates.

2.2. Study population

All adult patients (≥18 years) with OHCA, regardless of the cause of arrest, who were unconscious after ROSC (Glasgow Coma Scale score < 8) and treated with TTM between October 2015 and October 2017 were enrolled. Patients with active intracranial bleeding, acute stroke, known limitations in therapy and do-not-resuscitate order, known pre-arrest cerebral performance category 3 or 4, known disease that would make survival at 6 months unlikely, and body temperature < 30 °C on admission were excluded from the study.

Enrolled patients received care for PCAS according to the standard operating procedure for OHCA at each hospital. The KORHN TTM protocol was recommended to be used in each hospital (supplementary information). Each principal investigator of participating hospitals reviewed the hospital records of OHCA survivors treated with TTM and collected data. The independent data input commission investigated the survival rate and neurological outcome at 6 months after ROSC. If patients died at 6 months after ROSC, the date of death was recorded.

2.3. Variables

All data were prospectively acquired from the web-based registry in accordance with the Utstein-style guidelines [23]. The primary outcome was neurological outcome at 6 months. The modified Rankin scale (MRS) was used to assess neurological outcome, with an MRS of 0–3 being regarded as good outcome and an MRS of 4–6 as poor outcome (MRS score of 6 indicates death) [24].

The predictors of interest were sex, age, medical history, witnessed arrest, bystander CPR, initial rhythm assessed by the emergency medical service personnel in the field (shockable rhythm or non-shockable rhythm), time interval from collapse to ROSC, epinephrine dose, post-ROSC plasma lactate level (first measured value in day 1), post-ROSC glucose level (first measured value in day 1), post-ROSC shock (a systolic blood pressure <90 mmHg for >30 min, or the need of supportive measures to maintain a blood pressure of 90 mmHg), advanced treatment (e.g., extracorporeal membrane oxygenation, coronary angiography, and renal replacement therapy [RRT]), targeted temperature and duration, serum creatinine level, urine output, peak C-reactive protein (mg/dL), and events within 7 days since ROSC (seizure, bleeding, infection, hypokalemia, hypophosphatemia, hypomagnesemia, hypoglycemia [blood glucose <60 mg/dl], sustained hyperglycemia [blood glucose>180 mg/dl for >4 h], tachycardia [>130/min], and bradycardia [<40/min]). Serum creatinine level and urine output were evaluated daily up to 7 days since ROSC considering the duration of PCAS [3].

2.4. Definition of AKI

The definition and staging of AKI were based on the diagnostic criteria stipulated in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Supplementary information) [25]. However, diagnosis and staging of AKI were made only by using the criteria for serum creatinine level, because the data on urine output was collected not by a 1-h interval but by a 1-day interval. In addition, the diagnosis and staging of AKI were made only in the first 7 days after OHCA, because the serum creatinine level was entered in the electronic case report form for only up to 7 days since ROSC. The study protocol recommended that the serum creatinine level was measured daily for up to 7 days since ROSC basically. However, when the serum creatinine level was checked twice or more in a day, only the highest value was entered. All patients undergoing RRT were considered to have stage 3 AKI. We chose the lowest serum creatinine level between the serum creatinine level on the first hospital day and the estimated baseline serum creatinine level in accordance with the KDIGO guidelines and the article by Bellomo et al. owing to the absence of information about the participants' prior kidney function [25,26].

2.5. Sample size

The sample size was calculated based on the relative risk precision using the relative risk of poor neurological outcome in the AKI group. Although the primary outcome in this study was neurological outcome at 6 months, no other studies have reported a cohort of AKI after OHCA with a neurological outcome at 6 months prior to the start of the KORHN-PRO. Therefore, the relative risk of poor neurological outcome at 3 months in the AKI group was used to calculate the sample size. A previous study reported that the proportion of those with poor neurological outcome at 3 months in the non-AKI group and the relative risk of AKI were 0.54 and 1.22, respectively [12]. The probability of type I error was set at 0.05, and the relative risk precision was set at 20%. Using these parameters, a web-based sample size calculator estimated a minimum sample size of 106 for each group [27].

2.6. Statistical methods

Descriptive statistics are reported as median (interquartile range) or means with standard deviation for continuous variables according to the normality of distribution. The normal distribution of data was analyzed using the Shapiro–Wilk test or Kolmogorov–Smirnov test. Categorical variables are 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 risk factor and outcome was quantified using odds ratio (OR) with 95% confidence interval (CI). To determine the factors associated with AKI development and 6-month survival and good neurological outcome, we performed multivariate logistic regression analysis initially including variables with *P*-value <.2; we then applied a stepwise backward selection of the variables which remained significant. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the logistic regression model. The Cox regression analysis with time-varying covariate was used in the survival analysis to calculate the hazard ratio of AKI with respect to mortality, because the impact of day of AKI development may have a varying impact on distant outcome. Kaplan-Meier survival curves were compared between the AKI and non-AKI groups using the log-rank test. A *P*-value <.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

From 5676 patients with OHCA screened during the study period, a total of 729 patients treated with TTM from 20 academic hospitals located in South Korea were enrolled to KORHN-PRO registry database (Fig. 1). Among them, the patients with chronic kidney disease (CKD) ($n = 52$), death within 48 h since ROSC ($n = 66$), and those with missing six-month MRS ($n = 20$), missing survival status at 6 months ($n = 7$), and missing serum creatinine value ($n = 1$) were excluded. In total, the data from 583 patients were analyzed. The baseline characteristics of the study population according to AKI development are summarized in Table 1.

3.2. Descriptive data

AKI developed in 348/583 (60%) OHCA patients treated with TTM. Most AKI developed within 3 days since ROSC (328/348 [94%]). AKI stages were as follows: stage 1 (136/348 [39%]), stage 2 (56/348 [16%]), and stage 3 (156/348 [45%]). Regarding the diagnostic criteria of AKI, 343/348 (99%) patients were diagnosed using the serum creatinine criteria and 5/348 (1%) patients were diagnosed as having AKI stage 3 using the RRT initiation criteria.

3.3. Outcomes

The 6-month survival rate was significantly higher in non-AKI patients than in AKI patients (162/235 [69%] vs. 101/348 [29%], $P < .001$). Significantly more non-AKI patients had good neurological outcome at 6 months (MRS 0–3) than AKI patients (134/235 [57%] vs. 69/348 [20%], $P < .001$). The distribution of MRS at 6 months was significantly different between non-AKI patients and AKI patients (MRS 0: 94/235 [40%] vs. 45/348 [13%]; MRS 1: 29/235 [12%] vs. 18/348 [5%]; MRS 2: 7/235 [3%] vs. 3/348 [1%]; MRS 3: 4/235 [2%] vs. 3/348 [1%]; MRS 4: 3/235 [1%] vs. 7/348 [2%]; MRS 5: 25/235 [11%] vs. 27/348 [8%]: MRS 6: 73/235 [31%] vs. 245/348 [70%], non-AKI patients vs. AKI patients, respectively, $P < .001$).

3.4. Factors associated with AKI development in multivariate analysis

In multivariate logistic regression analysis, 4 factors were associated with AKI development (Table 2). Age, collapse to ROSC interval, epinephrine dose, and Post-ROSC shock were independent predictors of AKI development.

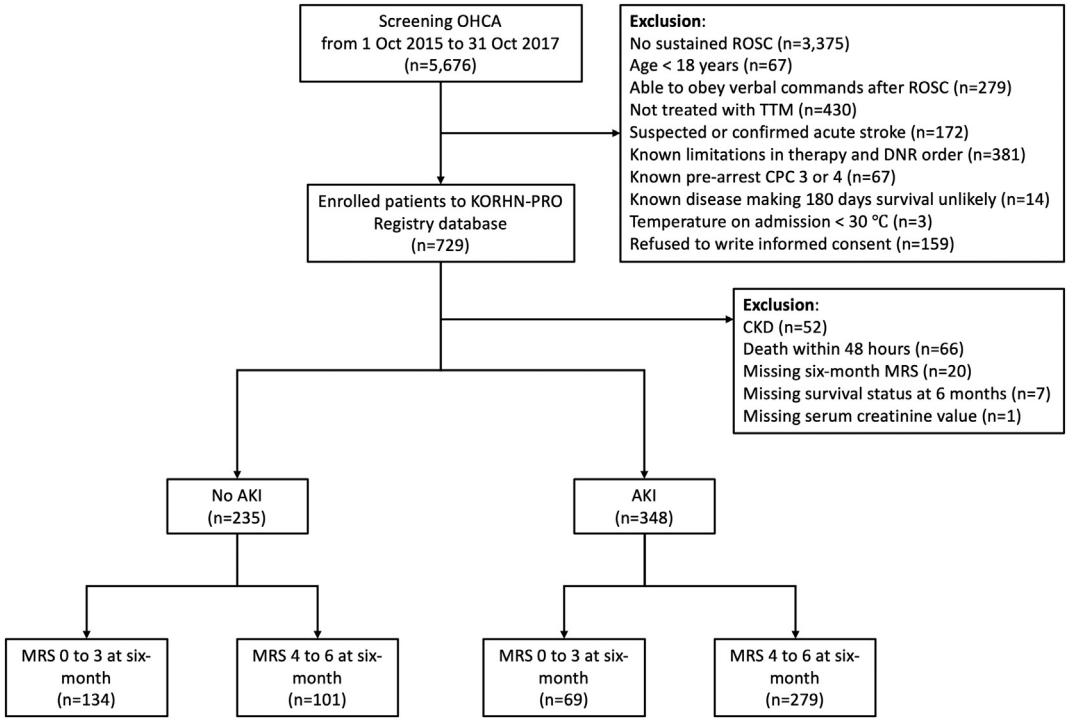

Fig. 1. Flow chart of the study population. AKI, acute kidney injury; CKD, chronic kidney disease; CPC, cerebral performance category; DNR, do-not-resuscitate; KORHN-PRO, Korean Hypothermia Network prospective registry; MRS, modified Rankin scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

Table 1
Baseline characteristics of the study population according to acute kidney injury development.

Variable	All patients ($n = 583$)	No AKI ($n = 235$)	AKI ($n = 348$)	*P*-value
Demographics				
Male sex	409/583 (70%)	160/235 (68%)	249/348 (72%)	0.370
Age (years)	57 (46, 69)	54 (42, 63)	61 (48, 72)	<**0.001**
Weight (kg)	65 (58, 74)	65 (55, 73)	67 (60, 75)	**0.017**
Medical history				
Heart failure	18/583 (3%)	3/235 (1%)	15/348 (4%)	**0.049**
Hypertension	217/583 (37%)	72/235 (31%)	145/348 (42%)	**0.007**
Diabetes mellitus	120/583 (21%)	35/235 (15%)	85/348 (24%)	**0.005**
Resuscitation				
Witnessed arrest	396/580 (68%)	168/233 (72%)	228/347 (66%)	0.105
Bystander CPR	365/579 (63%)	146/232 (63%)	219/347 (63%)	0.965
Shockable rhythm	200/491 (41%)	104/205 (51%)	96/286 (34%)	<**0.001**
Collapse to ROSC interval (min)	30 (18, 41)	21 (14, 33)	33 (22, 45)	<**0.001**
Epinephrine dose (mg)	2 (0, 4)	1 (0, 2)	2 (1, 5)	<**0.001**
Post-resuscitation				
Post-ROSC lactate (mmol/L)	10 (6, 13)	8 (5, 12)	11 (7, 14)	<**0.001**
Post-ROSC glucose (mg/dL)	261 (196, 335)	253 (180, 319)	272 (203, 344)	**0.003**
Post-ROSC shock	332/580 (57%)	96/234 (41%)	236/346 (68%)	<**0.001**
Coronary angiography	218/583 (37%)	99/235 (42%)	119/348 (34%)	0.052
ECMO	31/581 (5%)	1/235 (0%)	30/346 (9%)	<**0.001**
RRT	82/575 (14%)	0/230 (0%)	82/345 (24%)	<**0.001**
TT > 34 °C	127/583 (22%)	46/235 (20%)	81/348 (23%)	0.288
TTM duration >24 h	11/582 (2%)	2/235 (1%)	9/347 (3%)	0.214
[a]Seizure	163/583 (28%)	84/235 (36%)	79/348 (23%)	**0.001**
[a]Bleeding	31/582 (5%)	7/234 (3%)	24/348 (7%)	**0.040**
[a]Infection	335/583 (58%)	133/235 (57%)	202/348 (58%)	0.728
[a]Hypokalemia	234/583 (40%)	104/235 (44%)	130/348 (37%)	0.096
[a]Hypophosphatemia	221/574 (39%)	95/232 (41%)	126/342 (37%)	0.321
[a]Hypomagnesemia	185/572 (32%)	72/231 (31%)	113/341 (33%)	0.621
[a]Hypoglycemia	78/581 (13%)	17/233 (7%)	61/348 (18%)	<**0.001**
[a]Sustained hyperglycemia	306/582 (53%)	92/234 (39%)	214/348 (62%)	<**0.001**
[a]Tachycardia >130/min	132/583 (23%)	50/235 (21%)	82/348 (24%)	0.518
[a]Bradycardia <40/min	41/582 (7%)	17/234 (7%)	24/348 (7%)	0.865
Peak CRP (mg/dL)	16 (9, 25)	14 (8, 20)	18 (9, 28)	<**0.001**
AKI stage				
Stage 1	136/348 (39%)	0/235 (0%)	136/348 (39%)	N/A
Stage 2	56/348 (16%)	0/235 (0%)	56/348 (16%)	N/A
Stage 3	156/348 (45%)	0/235 (0%)	156/348 (45%)	N/A
Outcomes				
Six-month survival	263/583 (45%)	162/235 (69%)	101/348 (29%)	<**0.001**
MRS 0 to 3 at six-month	203/583 (35%)	134/235 (57%)	69/348 (20%)	<**0.001**

$P < .05$ are presented in bold.
AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; MRS, modified Rankin scale; N/A, not applicable; ROSC, return of spontaneous circulation; RRT, renal replacement therapy; TT, target temperature; TTM, targeted temperature management.
[a] Events recorded within 7 days since ROSC.

3.5. Factors associated with survival at 6 months

In the multivariate logistic regression analysis, 8 factors were associated with survival at 6 months (Table 3). Among them, witnessed arrest, shockable rhythm, and coronary angiography were found to be independent predictors of survival at 6 months, whereas collapse to ROSC interval, Post-ROSC shock, acute kidney injury (adjusted OR: 0.317; [95% CI: 0.181–0.554, $P < .001$]), Peak CRP, and sustained hyperglycemia were negatively associated with survival at 6 months.

Table 2
Factors associated with acute kidney injury development in multivariate analysis.

Factors	Odds ratio	95% confidence interval	*P*-value
Age	1.032	1.017, 1.047	<**0.001**
Weight	1.029	1.009, 1.048	**0.003**
Heart failure	5.342	0.603, 47.316	0.132
Shockable rhythm	0.620	0.387, 0.993	**0.047**
Collapse to ROSC interval	1.035	1.016, 1.053	<**0.001**
Epinephrine dose	1.124	1.015, 1.245	**0.025**
Post-ROSC shock	2.152	1.363, 3.399	**0.001**

$P < .05$ are presented in bold.
ROSC, return of spontaneous circulation.
Stepwise backward multivariate logistic regression initially including age, weight, heart failure, hypertension, diabetes mellitus, witnessed arrest, shockable rhythm, collapse to ROSC interval, epinephrine dose, Post-ROSC lactate, Post-ROSC glucose, Post-ROSC shock, and coronary angiography.
Hosmer and Lemeshow Test: Chi-square = 9.227; df = 8; $P = .323$.

3.6. Factors associated with neurological outcome at 6 months

In multivariate logistic regression analysis, 8 factors were associated with good neurological outcome at 6 months (Table 4). Among them, shockable rhythm, coronary angiography, and hypophosphatemia were independent predictors of good neurological outcome at 6 months, whereas collapse to ROSC interval, Post-ROSC glucose, AKI (adjusted OR: 0.206; [95% CI: 0.099–0.426, $P < .001$]), seizure, and sustained hyperglycemia were associated with poor neurological outcome at 6 months. Regarding the AKI stage, we divided the stages of AKI as lower (stage 1) and higher (stage 2 or 3) stages for statistical analysis. The results of the multivariate logistic regression analysis showed that the higher stage of AKI (stage 2 or 3) was associated with poor neurological outcome at 6 months (adjusted OR: 0.323; [95% CI: 0.123–0.851, $P = .022$], Table S1 in the supplementary information).

Table 3
Factors associated with 6 months survival.

Factors	Odds ratio	95% confidence interval	*P*-value
Witnessed arrest	2.389	1.263, 4.521	**0.007**
Shockable rhythm	2.591	1.355, 4.952	**0.004**
Collapse to ROSC interval	0.964	0.949, 0.980	<**0.001**
Post-ROSC shock	0.447	0.258, 0.774	**0.004**
Coronary angiography	4.499	2.275, 8.896	<**0.001**
[a]Hypomagnesemia	1.630	0.911, 2.917	0.100
[a]Sustained hyperglycemia	0.403	0.233, 0.694	**0.001**
Peak CRP	0.976	0.960, 0.993	**0.006**
Acute kidney injury	0.317	0.181, 0.554	<**0.001**

$P < .05$ are presented in bold.
CRP, C-reactive protein; ROSC, return of spontaneous circulation.
Stepwise backward multivariate logistic regression initially including age, hypertension, diabetes mellitus, witnessed arrest, shockable rhythm, collapse to ROSC interval, epinephrine dose, Post-ROSC lactate, Post-ROSC glucose, Post-ROSC shock, coronary angiography, targeted temperature management duration >24 h, bleeding, hypophosphatemia, hypomagnesemia, hypoglycemia, sustained hyperglycemia, peak C-reactive protein, and acute kidney injury.
Hosmer and Lemeshow Test: Chi-square = 8.837; df = 8; $P = .356$.
[a] Events recorded within 7 days since ROSC.

The distribution of the stages of AKI was significantly different between the poor and good neurological outcome groups ($P < .001$, Table S2).

3.7. Effects of target temperature on the development of AKI

Target temperature was not associated with the development of AKI (OR for target temperature > 34 °C: 1.246; [95% CI: 0.830–1.873, $P = .289$]).

3.8. Survival analysis

Cox regression analysis with time-varying covariate of AKI showed that the patients with AKI had a higher risk of death than those without AKI (hazard ratio: 2.223; 95% CI: 1.630–3.030, $P < .001$; Table 5). The Kaplan-Meier survival curves were significantly different between the AKI and non-AKI groups and among the stages of AKI (Fig. 2). In the pairwise comparisons among stages of AKI, a significant difference was found between stages 1 and 2 ($P < .001$) and between stages 1 and 3 ($P < .001$). However, no difference was observed between stages 2 and 3 ($P = .070$).

Table 4
Factors associated with 6 months good neurological outcomes (modified Rankin scale 0 to 3).

Factors	Odds ratio	95% confidence interval	*P*-value
Male sex	2.161	0.949, 4.925	0.067
Age	0.982	0.961, 1.004	0.102
Shockable rhythm	7.642	3.522, 16.580	<**0.001**
Collapse to ROSC interval	0.956	0.936, 0.975	<**0.001**
Post-ROSC glucose	0.995	0.991, 0.999	**0.010**
Coronary angiography	5.954	2.663, 13.310	<**0.001**
[a]Seizure	0.315	0.148, 0.671	**0.003**
[a]Hypophosphatemia	2.146	1.068, 4.312	**0.032**
[a]Sustained hyperglycemia	0.315	0.154, 0.643	**0.002**
Acute kidney injury	0.206	0.099, 0.426	<**0.001**

$P < .05$ are presented in bold.
ROSC, return of spontaneous circulation.
Stepwise backward multivariate logistic regression initially including male sex, age, weight, hypertension, diabetes mellitus, witnessed arrest, bystander cardiopulmonary resuscitation, shockable rhythm, collapse to ROSC interval, epinephrine dose, Post-ROSC lactate, Post-ROSC glucose, Post-ROSC shock, coronary angiography, target temperature >34 °C, targeted temperature management duration >24 h, seizure, bleeding, infection, hypokalemia, hypophosphatemia, hypomagnesemia, hypoglycemia, sustained hyperglycemia, bradycardia <40/min, peak C-reactive protein, and acute kidney injury.
Hosmer and Lemeshow Test: Chi-square = 12.374; df = 8; $P = .135$.
[a] Events recorded within 7 days since ROSC.

3.9. Subgroup analysis using the subpopulation with survival at discharge

Subgroup analysis using the subpopulation with survival at discharge was conducted to explore the impact of AKI specifically because the majority of deaths occurred in the early period after cardiac arrest (Table S3 and S4). In the subgroup analysis, AKI was still associated with poor neurological outcome (MRS 4–6) at 6 months (adjusted OR: 0.300; [95% CI: 0.122–0.734, $P = .008$]).

4. Discussion

To the best of our knowledge, the present study is the first report that evaluated the effect of AKI on long-term neurological outcome based on a prospective, multicenter, observation cohort of OHCA patients treated with TTM. Previous single-center studies have already reported that the development of AKI was significantly associated with poor long-term neurological outcome [14,16]. However, this association had not been confirmed in a meta-analysis (OR: 1.32; [95% CI: 0.83–2.08], $P = .24$) [13]. The reason for the inconsistent results might be caused by the heterogeneity among studies. Especially, well-known potent predictor of OHCA, such as the ratio of shockable rhythm, was different among studies (our cohort: 41% vs other studies: 67%) [14]. In South Korea, the ratio of initial shockable rhythm in OHCA patients was reported to be low (26% in the cohort between 2007 and 2012) [28]. Given that shockable rhythm itself was associated with a significantly lower risk of AKI development, the incidence of AKI was higher in our cohort than the weighted mean prevalence in the meta-analysis (60% vs 52%) [13]. To overcome this heterogeneity of the study cohort, multicenter clinical trials, including a large number of patients, was needed to confirm the association of the development of AKI and long-term neurological outcome of the OHCA patients.

Although the specific characteristics of the patient cohort in our study were different from those of the previous studies (e.g., incidence of AKI, ratio of good outcome, and ratio of shockable rhythm), the results of the present study confirm that the development of AKI after OHCA was strongly associated with long-term neurological outcome [13,14,16]. Interestingly, the distributions of AKI stage were significantly different between the good and poor neurological outcome groups. Although there were more patients with stage 1 AKI who had a good neurological outcome (67%), there were more patients with stage 3 AKI who had a poor neurological outcome (51%). The results of the multivariate analysis showed that the higher stage of AKI (stage 2 or 3) was associated with a poor neurological outcome at 6 months.

The majority of deaths occurred in the early period after cardiac arrest in our cohort. To explore the impact of AKI specifically, we have conducted subgroup analysis using the subpopulation with survival at discharge ($n = 341$). Although the differences in the medical history and shockable rhythm disappeared after excluding the patients with death at discharge, AKI was significantly associated with poor neurological outcome at 6 months.

We have conducted the Cox regression analysis with time-varying covariate of AKI development, because the impact of day of AKI development may have a varying impact on distant outcome. Although hazards ratio of AKI was calculated with consideration of the time varying covariate of the day of AKI development, the calculated value (hazards ratio: 2.223) was similar to that of a previous report, which was calculated using the Cox proportional hazards model (hazards ratio: 2.169) [16].

The development of AKI was not influenced by target temperature in our cohort. Recently, the post hoc analysis of TTM trial for evaluating the effect of target temperature on the development of AKI has been reported [20,29,30]. Although the incidence of AKI was higher in the TTM-33 group compared to that in the TTM-36 group (49% versus 40%), there was no association between the target temperature and development of AKI on the basis of results of the multivariate analysis [30]. Another study with a small sample size reported that mild therapeutic hypothermia had a protective effect on the development of AKI

Table 5
Cox regression analysis with time-varying covariate of development of acute kidney injury.

Variable	Coefficient	Standard Error	Wald	*P*-value	Hazards ratio	95% confidence interval
Shockable rhythm	−0.578	0.201	8.231	**0.004**	0.561	0.378, 0.833
Witnessed arrest	−0.309	0.147	4.390	**0.036**	0.734	0.550, 0.980
Collapse to ROSC interval	0.017	0.003	28.346	<**0.001**	1.017	1.011, 1.024
Post-ROSC shock	0.346	0.157	4.837	**0.028**	1.414	1.038, 1.925
Coronary angiography	−0.713	0.192	13.800	<**0.001**	0.490	0.336, 0.714
[a]Hypomagnesemia	−0.313	0.150	4.340	**0.037**	0.731	0.544, 0.982
[a]Hypoglycemia	0.438	0.193	5.141	**0.023**	1.549	1.061, 2.262
[a]Sustained hyperglycemia	0.416	0.148	7.935	**0.005**	1.516	1.135, 2.025
[b]T_COV_AKI	0.799	0.158	25.496	<**0.001**	2.223	1.630, 3.030

$P < .05$ are presented in bold.
AKI, acute kidney injury; ROSC, return of spontaneous circulation.
[a] Events recorded within 7 days since ROSC.
[b] T_COV_AKI means time-varying covariate of AKI development.

(adjusted OR: 0.424; [95% CI: 0.187–0.962. $P = .040$]) [15]. A further study will be needed to confirm the effect of TTM on the development of AKI after OHCA.

Factors associated with AKI in our cohort showed that the development of AKI was significantly linked with the extent of global hypoxic insults. All parameters, including collapse to ROSC interval, epinephrine dose, and post-ROSC shock, showed that longer arrest time could increase the risk of developing AKI. It means that the pathophysiology of AKI after OHCA might be different with other causes of AKI, such as sepsis. Therefore, the natural course of AKI after OHCA, including recovery

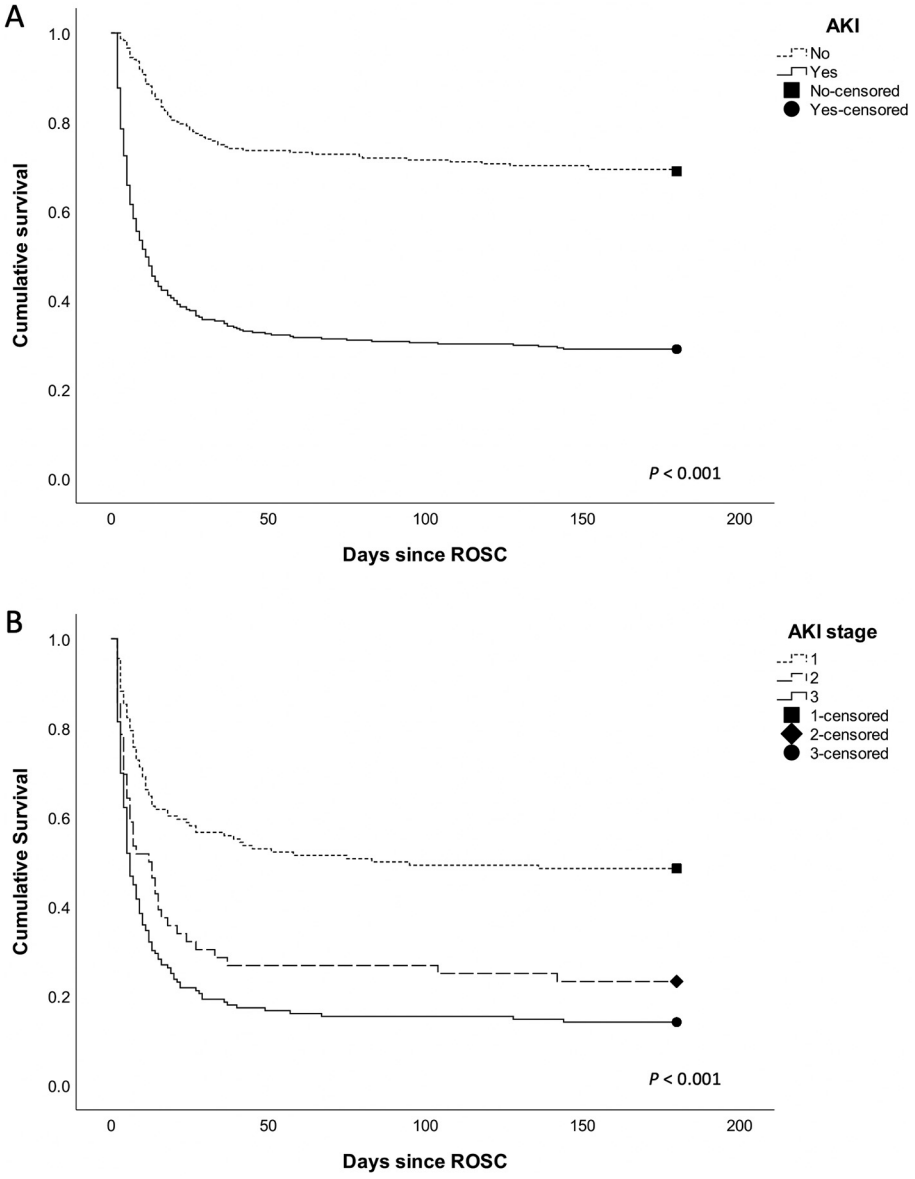

Fig. 2. Comparisons of the Kaplan-Meier survival curves. A. AKI group versus non-AKI group. B. Stages of AKI. AKI, acute kidney injury; ROSC, return of spontaneous circulation.

rate, effect of RRT, and development of chronic kidney disease, might be different with other causes of AKI despite similar clinical outcomes. Further cohort study, including long-term follow-up after development of AKI, will be needed.

The results of the present study might be helpful to clinicians when they make a treatment plan. Especially, our data will be helpful in predicting and explaining the course of PCAS to the patient's legal surrogate when AKI occurs after OHCA.

5. Limitations

The present study has several limitations. First, our registry recorded patients' serum creatinine level and urine output for only 7 days since ROSC. Therefore, AKI developing after 7 days might be lost. In addition, we determined the development of AKI by only using the serum creatinine criteria, because data of urine output was collected not by a 1-h interval but by a 1-day interval. Therefore, the underestimation of AKI development might have occurred. Second, there was a possibility of overestimation in the diagnosis of AKI because we selected the lowest value between the serum creatinine level at day 1 and the estimated baseline serum creatinine level as the baseline creatinine level. Third, regarding RRT, our registry did not have a protocol for the specific indication and time of initiation of RRT. Initiation of RRT was determined by the physicians in charge of managing the patients at each institution. In addition, the initiation time, duration, and long-term requirement of RRT had not been entered in the registry. Therefore, the time course of AKI had not been determined in the case of AKI diagnosis by initiation of RRT, and the effect of RRT on the outcome could not be determined in this study. Fourth, there was a lack of clinical factors affecting the development of AKI during treatments, including the fluid balance status or Input-Output status of the patient, the required dose of vasopressors, and the use of nephrotoxic drugs. In addition, although the study participants were treated according to standard care, in-hospital treatment strategies and decisions were not standardized between hospitals. Fifth, there were some missing values in the registry data set. For the purpose of statistical handling, we have excluded the patients who had missing values of six-month MRS ($n = 20$), survival status at 6 months ($n = 7$), and serum creatinine level ($n = 1$). However, the other missing data were not considered. Sixth, the patients with AKI could have died due to other causes (competing risk problems) rather than due to AKI. If we knew the exact cause of death, we could have handled this problem statistically. However, it was difficult to assume the cause of death in patients with PCAS. Multi-organ failure occurs frequently in patients with PCAS, because they are exposed to the global hypoxic insults after OHCA. We assumed that the patients who died within 48 h after ROSC had a higher risk of death, regardless of AKI development. Therefore, we excluded the patients who died within 48 h since ROSC to decrease the competing risk problems. Seventh, although the results of the present study showed that AKI occurrence was a potent predictor of poor long-term neurological outcome, we should interpret these results carefully because the characteristics of the OHCA patients are different from those of other critical patients. Global hypoxic insults during OHCA could lead to PCAS, including post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology [3]. Various factors including many confounders could affect the patient's outcome in the prehospital phase. Therefore, we should assess the OHCA patients carefully when the AKI will occur.

6. Conclusions

The development of AKI is associated with poor neurological outcome or death at 6 months in OHCA patients treated with TTM. The reasons for this association should be investigated in future studies.

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Author contribution

Wee JH contributed to study conception and design. Cho IS, Lee DH, Oh JH, Youn CS, Lee BK, Wee JH, Cha KC, Chae MK, Shin JH, and the KORHN investigators contributed to data acquisition. Cho IS, Lee DH, Oh JH, Youn CS, Lee BK, Wee JH, Cha KC, Chae MK, and Shin JH contributed to data analysis and interpretation. Oh JH contributed to acquisition of funding. Oh JH and Cho IS 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.

Data availability statement

We submitted minimal anonymized data set as a supporting information file.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Declaration of Competing Interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.08.029.

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