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# Effect of Prehospital Epinephrine on Out-of-Hospital Cardiac Arrest Outcomes: A Propensity Score-Matched Analysis

Eunah Han[1], Taeyoung Kong[1], Je Sung You[1], Incheol Park[1], Goeun Park[2], Sujee Lee[2], Sung Phil Chung[1], and Korean Cardiac Arrest Research Consortium (KoCARC) Investigators

[1]Department of Emergency Medicine, Yonsei University College of Medicine, Seoul;
[2]Biostatistics Collaboration Unit, Medical Research Center, Yousei University College of Medicine, Seoul, Korea.

**Purpose:** A pilot project using epinephrine at the scene under medical control is currently underway in Korea. This study aimed to determine whether prehospital epinephrine administration is associated with improved survival and neurological outcomes in out-of-hospital cardiac arrest (OHCA) patients who received epinephrine during cardiopulmonary resuscitation (CPR) in the emergency department.

**Materials and Methods:** This retrospective observational study used a nationwide multicenter OHCA registry. Patients were classified into two groups according to whether they received epinephrine at the scene or not. The associations between prehospital epinephrine use and outcomes were assessed using propensity score (PS)-matched analysis. Multivariable logistic regression analysis was performed using PS matching. The same analysis was repeated for the subgroup of patients with non-shockable rhythm.

**Results:** PS matching was performed for 1084 patients in each group. Survival to discharge was significantly decreased in the patients who received prehospital epinephrine [odds ratio (OR) 0.415, 95% confidence interval (CI) 0.250–0.670, $p<0.001$]. However, no statistical significance was observed for good neurological outcome (OR 0.548, 95% CI 0.258–1.123, $p=0.105$). For the patient subgroup with non-shockable rhythm, prehospital epinephrine was also associated with lower survival to discharge (OR 0.514, 95% CI 0.306–0.844, $p=0.010$), but not with neurological outcome (OR 0.709, 95% CI 0.323–1.529, $p=0.382$).

**Conclusion:** Prehospital epinephrine administration was associated with decreased survival rates in OHCA patients but not statistically associated with neurological outcome in this PS-matched analysis. Further research is required to investigate the reason for the detrimental effect of epinephrine administered at the scene.

**Key Words:** Epinephrine, out-of-hospital cardiac arrest, survival, neurological outcome

## INTRODUCTION

Resuscitation guidelines recommend the use of epinephrine as part of advanced life support (ALS) for cardiac arrest. Early administration of epinephrine is recommended as soon as possible for patients with non-shockable rhythm; in patients with shockable rhythm, defibrillation needs to be performed first, while epinephrine is recommended if defibrillation fails.[1,2] In several countries, epinephrine can be used in prehospital settings. A recent randomized, double-blind trial comparing epinephrine to the placebo control group found improved survival at 30 days.[3] However, epinephrine did not improve neurological outcomes, consistent with previous randomized studies.[4,5]

In Korea, epinephrine used to be administered to patients after arrival at the hospital, as the emergency medical technician (EMT) could not use epinephrine according to the law. Since

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**Corresponding author:** Sung Phil Chung, MD, PhD, Department of Emergency Medicine, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: 82-2-2019-3030, Fax: 82-2-2019-4820, E-mail: emstar@yuhs.ac

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2014, EMTs have used epinephrine under medical control, as reported in a pilot project on smartphone-based advanced life support (SALS).[6,7] This approach reportedly significantly improved favorable neurological outcomes, from 1.9% to 6.9%, compared to the approach used during the pre-intervention period. The SALS project consisted of multidisciplinary interventions, including not only prehospital epinephrine administration but also advanced airway, video-based medical control, and multiple ambulance dispatch; therefore, it was difficult to differentiate the effect of epinephrine.

This study aimed to compare the outcomes of out-of-hospital cardiac arrest (OHCA) in patients who received epinephrine only after arriving at the hospital and those who received epinephrine at the scene in Korea. The authors hypothesized that prehospital epinephrine is associated with improved survival rate and neurologic outcomes when administered to OHCA patients.

## MATERIALS AND METHODS

### Study design and setting

A retrospective observational analysis was performed using data from the Korean Cardiac Arrest Research Consortium (KoCARC) registry from October 2015 to June 2020. The KoCARC is a nationwide OHCA research registry based on the Utstein templates and a hospital-based collaborative research network. The KoCARC registry included OHCA patients transported to the participating emergency departments (ED) via emergency medical services (EMS) with resuscitation efforts and those with a presumed medical etiology identified by emergency physicians. The registry excluded patients with a terminal illness documented in medical records, patients under hospice care, pregnant patients, and patients with a previously documented "Do Not Resuscitate" card. Patients with cardiac arrest due to definite non-medical etiologies were also excluded, including trauma, drowning, poisoning, burns, asphyxia, or hanging. Information about the KoCARC database, data elements, and quality assurance has been previously published.[8] The data were collected via a standardized form and uploaded to a web-based electronic database registry; the quality of this registry is controlled by the quality management committee.[8,9]

### Study population and data extraction

From the KoCARC registry, we excluded patients who were aged <18 years, those who were transferred from other hospitals to the enrolled hospital, those who did not receive epinephrine after arrival at the ED, and those without information about extracted variables: age, sex, witnessed, arrest location, bystander CPR status, first monitored electrocardiography (ECG) rhythm, prehospital defibrillation, prehospital advanced airway placement, ambulance dispatch type, prehospital return of spontaneous circulation (ROSC), survival at hospital discharge, neurological outcome at discharge, and prehospital epinephrine use. In this study, all patients who arrived at the hospital with cardiac arrest were administered epinephrine. Therefore, the difference between the two groups was whether epinephrine was administered during the prehospital stage or after arriving at the hospital.

### Outcome variables

The primary outcome was survival to hospital discharge. The secondary outcome was a favorable neurological outcome defined as a cerebral performance category (CPC) of 1 or 2 at the time of hospital discharge. Patients had a CPC of "1" if they had good cerebral performance and were conscious, alert, and able to work with a possible mild neurologic or psychological deficit. Patients had a CPC of "2" if they had a moderate cerebral disability and were conscious, had sufficient cerebral function for independent daily life activities, and were able to work in sheltered environments. This performance scale indicates mortality at a CPC of 5, defined as death or brain death.

### Statistical analysis

The KoCARC registry compiled and released data with a standard spreadsheet application (Excel 2016; Microsoft, Redmond, WC, USA). The patients who presented with cardiac arrest at the ED and received epinephrine during CPR were classified into two groups according to whether they received epinephrine at the scene or not. Propensity score (PS) matching was performed to reduce selection bias between the groups. Multivariable logistic regression analysis was used to calculate the estimated PS for survival from OHCA in each patient. Patient characteristics including age, sex, initial ECG rhythm, witness, bystander CPR, prehospital defibrillation, ambulance dispatch type, and prehospital airway placement were included in the multivariable analysis. PS matching was performed without replacement using the nearest neighbor method with a maximum caliper of 0.1 to generate matched 1:1 pairs.

The clinical characteristics of the study population were summarized using the mean±SD for continuous variables and the numbers with a percentage for categorical variables. The standardized mean differences were calculated to compare the group differences and assess the balance of the clinical characteristics of patients before and after PS matching. A standardized difference of ≤0.15 suggested an appropriate balance between the covariates. After PS matching, multivariable logistic regression analysis was performed to investigate the effect of prehospital epinephrine administration on survival to discharge and neurological outcome. For sensitivity analysis, PS matching was repeated for patients with non-shockable rhythms.

Data analyses were performed using the SAS program (version 9.4, SAS Institute Inc., Cary, NC, USA) and R software for Windows (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p<0.05$.


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### Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board (IRB) of the 62 participating hospitals in the KoCARC OHCA registry. Informed consent was waived by the IRB of Severance Hospital, Yonsei University Health System (3-2015-0290). This research project was registered at ClinicalTrials.gov (identifier: NCT03222999).

## RESULTS

Among 12321 OHCA patients on whom resuscitation was attempted during the study period, 6085 patients (49.3%) were finally included except for pediatric patients aged <18 years who did not receive epinephrine at the hospital, and the main variables were unknown (Fig. 1). Prehospital epinephrine was administered to 1085 patients (17.8%). The baseline characteristics of the overall population and the PS-matched population are shown in Table 1. Before matching, all variables except for

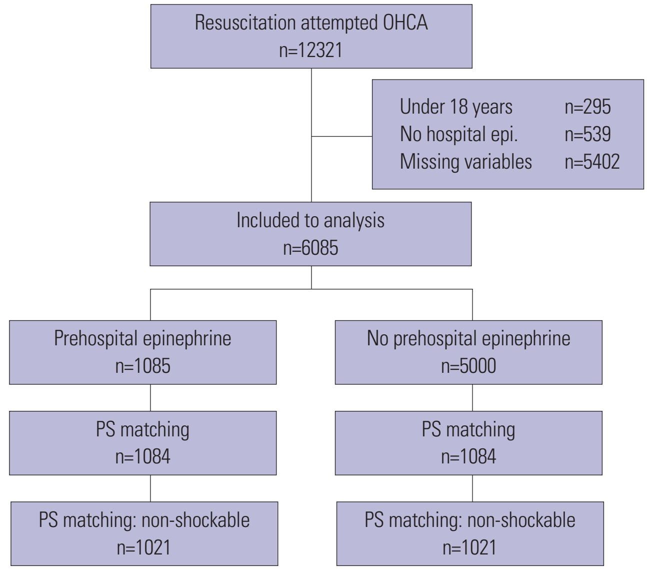


**Fig. 1.** Study flow chart. OHCA, out-of-hospital cardiac arrest; PS, propensity score.

**Table 1.** Baseline Characteristics of the Overall Population and PS-Matched Cohort Stratified by Prehospital Epinephrine Use

| Variables | Overall population | | | | PS-matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | No prehospital epinephrine (n=5000) | Prehospital epinephrine (n=1085) | SMD | *p* value | No prehospital epinephrine (n=1084) | Prehospital epinephrine (n=1084) | SMD | *p* value |
| Age (yr) | 70.3±15.1 | 67.6±15.2 | -0.175 | <0.001 | 68.9±14.9 | 67.6±15.2 | -0.080 | 0.060 |
| Sex | | | | <0.001 | | | | 0.963 |
| Male | 3104 (62.1) | 747 (68.8) | 0.146 | | 748 (69.0) | 746 (68.8) | -0.004 | |
| Female | 1896 (37.9) | 338 (31.2) | -0.146 | | 336 (31.0) | 338 (31.2) | 0.004 | |
| Initial ECG | | | | <0.001 | | | | 0.207 |
| Non-shockable | 4831 (96.6) | 1022 (94.2) | -0.104 | | 1035 (95.5) | 1021 (94.2) | -0.005 | |
| Shockable | 169 (3.4) | 63 (5.8) | 0.104 | | 49 (4.5) | 63 (5.8) | 0.005 | |
| Witness | | | | <0.001 | | | | 0.667 |
| No | 2754 (55.1) | 532 (49.0) | -0.121 | | 521 (48.1) | 532 (49.1) | 0.020 | |
| Yes | 2246 (44.9) | 553 (51.0) | 0.121 | | 563 (51.9) | 552 (50.9) | -0.020 | |
| Arrest place | | | | 0.981 | | | | 0.208 |
| Home | 3742 (74.8) | 813 (74.9) | -0.002 | | 838 (77.3) | 812 (74.9) | 0.055 | |
| Not home | 1258 (25.2) | 272 (25.1) | 0.002 | | 246 (22.7) | 272 (25.1) | -0.055 | |
| Bystander CPR | | | | <0.001 | | | | 0.058 |
| None | 2537 (50.7) | 673 (62.0) | 0.233 | | 690 (63.7) | 672 (62.0) | -0.034 | |
| Hands-only | 227 (4.5) | 25 (2.3) | -0.149 | | 11 (1.0) | 25 (2.3) | 0.086 | |
| Standard | 2236 (44.7) | 387 (35.7) | -0.189 | | 383 (35.3) | 387 (35.7) | 0.008 | |
| Prehospital defibrillation | | | | <0.001 | | | | 0.242 |
| No | 4195 (83.9) | 785 (72.4) | -0.258 | | 810 (74.7) | 785 (72.4) | -0.052 | |
| Yes | 805 (16.1) | 300 (27.6) | 0.258 | | 274 (25.3) | 299 (27.6) | 0.052 | |
| Ambulance team | | | | <0.001 | | | | 0.817 |
| Single | 2366 (47.3) | 182 (16.8) | -0.818 | | 177 (16.3) | 182 (16.8) | 0.012 | |
| Multiple | 2634 (52.7) | 903 (83.2) | 0.818 | | 907 (83.7) | 902 (83.2) | -0.012 | |
| Prehospital advanced airway | | | | <0.001 | | | | 0.559 |
| No | 850 (17.0) | 41 (3.8) | -0.690 | | 35 (3.2) | 41 (3.8) | 0.029 | |
| Yes | 4150 (83.0) | 1044 (96.2) | 0.690 | | 1049 (96.8) | 1043 (96.2) | -0.029 | |

PS, propensity score; SMD, standardized mean difference; ECG, electrocardiography; CPR, cardiopulmonary resuscitation.
Data are presented as mean±SD or n (%).

the arrest location–age, sex, initial ECG rhythm, witnessed, bystander CPR, prehospital defibrillation, and ambulance dispatch type–showed significant differences between the two groups. After the PS matching procedure, 1084 matched pairs were selected between the prehospital epinephrine and no epinephrine users. The differences in baseline characteristics related to OHCA were well-balanced between the PS-matched cohort (Table 1).

Survival rate to hospital discharge was significantly lower in the prehospital epinephrine group, in both overall (4.7% v.s 2.4%, *p*=0.001) and PS-matched cohort (5.2% vs. 2.4%, *p*=0.002), while prehospital ROSC was significantly higher in the prehospital epinephrine group before (2.3% vs. 9.9%, *p*<0.001) and after matching (2.7% vs. 9.9%, *p*<0.001). However, no statistical significance was observed between groups for the good neurological outcome (Table 2).

Multivariable logistic regression analysis using the PS-matched cohort revealed that survival to discharge was significantly decreased in the prehospital epinephrine group [odds ratio (OR) 0.415, 95% confidence interval (CI) 0.250–0.670, *p*<0.001]. However, no statistical significance was observed for the good neurological outcome (OR 0.548, 95% CI 0.258–1.123, *p*=0.105) (Table 3). Factors independently associated with survival and good neurological outcome at discharge were age, witness, and prehospital defibrillation (Fig. 2).

For the patient subgroups with non-shockable rhythm, 1021 PS-matched pairs were analyzed with a multivariable logistic regression model. Administration of prehospital epinephrine was associated with lower survival to hospital discharge (OR 0.514, 95% CI 0.306–0.844, *p*=0.010), while it showed no association with good neurological outcome (OR 0.709, 95% CI 0.323–1.529, *p*=0.382).

## DISCUSSION

The PS-matched analysis using a nationwide multicenter OHCA registry in Korea showed an association between prehospital epinephrine use and poor survival to discharge, even though there was a higher rate of prehospital ROSC. Moreover, the use of prehospital epinephrine was not associated with neurological outcomes. After adjusting for possible confounders, prehospital epinephrine was still associated with unfavorable survival outcomes.

The issue regarding the effectiveness of prehospital epinephrine administration has been controversial. A meta-analysis combining two randomized controlled trials showed that prehospital epinephrine administration was associated with increased survival to hospital discharge rate (OR 1.43, 95% CI 1.10–1.87).[10,11] The number of patients who would need treatment with epinephrine to prevent death following OHCA was calculated to be 112;[3] however, prehospital epinephrine was associated with a low survival rate in this study. Previous studies have reported that prehospital epinephrine use adversely affects the survival rate.[12-14] The reason for such different results between studies is presumed to be due to the different systems and performance of each prehospital EMS.

Although statistical significance was not demonstrated in this study, several studies have consistently reported that prehospital epinephrine use did not improve the neurological outcome. In the study conducted by Michelland, et al.[15] in France, non-traumatic OHCA patients who underwent early ALS did not show improvement in their neurological outcomes compared to those who underwent basic life support alone. A systematic review including 14 observational studies reported that prehospital epinephrine administration significantly increased the probability of ROSC (OR, 2.86), but decreased the rate of good neurological outcome at hospital discharge (OR, 0.51).[16] The reason why epinephrine administration worsens neurological outcomes despite a higher ROSC is not fully un-

**Table 2.** Comparison of Outcomes according to Prehospital Epinephrine Use in the Cohorts before and after Propensity Score Matching

| Variable | Before matching | | | After matching (1:1) | | |
|---|---|---|---|---|---|---|
| | No prehospital epinephrine (n=5000) | Prehospital epinephrine (n=1085) | *p* value | No prehospital epinephrine (n=1084) | Prehospital epinephrine (n=1084) | *p* value |
| Survival to discharge | | | 0.001 | | | 0.002 |
| No | 4764 (95.3) | 1059 (97.6) | | 1028 (94.8) | 1058 (97.6) | |
| Yes | 236 (4.7) | 26 (2.4) | | 56 (5.2) | 26 (2.4) | |
| Good neurological outcome | | | 0.310 | | | 0.293 |
| No | 4916 (98.3) | 1072 (98.8) | | 1064 (98.2) | 1071 (98.8) | |
| Yes | 84 (1.7) | 13 (1.2) | | 20 (1.8) | 13 (1.2) | |
| Prehospital ROSC | | | <0.001 | | | <0.001 |
| No | 4883 (97.7) | 978 (90.1) | | 1055 (97.3) | 977 (90.1) | |
| Yes | 117 (2.3) | 107 (9.9) | | 29 (2.7) | 107 (9.9) | |

ROSC, return of spontaneous circulation.
Data are presented n (%).


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**Table 3.** Multivariable Logistic Regression Analysis Using Propensity Score-Matched Cohort

| Variable | Survival to discharge | | Good neurological outcome | |
|---|---|---|---|---|
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Epinephrine | | | | |
| No | ref | | ref | |
| Yes | 0.415 (0.250–0.670) | <0.001 | 0.548 (0.258–1.123) | 0.105 |
| Age | 0.967 (0.952–0.982) | 0.001 | 0.959 (0.936–0.983) | 0.001 |
| Sex | | | | |
| Male | ref | | ref | |
| Female | 0.618 (0.310–1.139) | 0.144 | 0.598 (0.173–1.592) | 0.164 |
| Initial ECG | | | | |
| Non-shockable | ref | | ref | |
| Shockable | 0.773 (0.338–1.600) | 0.512 | 0.998 (0.355–2.427) | 0.764 |
| Witness | | | | |
| No | ref | | ref | |
| Yes | 2.219 (1.336–3.804) | 0.003 | 2.563 (1.134–6.567) | 0.033 |
| Bystander CPR | | | | |
| None | ref | | ref | |
| Hands-only | 0.678 (0.037–3.530) | 0.713 | 1.434 (0.076–8.179) | 0.739 |
| Standard | 0.901 (0.531–1.486) | 0.690 | 0.704 (0.274–1.606) | 0.431 |
| Prehospital defibrillation | | | | |
| No | ref | | ref | |
| Yes | 3.957 (2.415–6.599) | <0.001 | 14.384 (5.364–50.073) | <0.001 |
| Ambulance team | | | | |
| Single | ref | | ref | |
| Multiple | 1.149 (0.632–2.244) | 0.224 | 0.968 (0.405–7.907) | 0.169 |
| Prehospital advanced airway | | | | |
| No | ref | | ref | |
| Yes | 2.479 (0.884–5.945) | 0.058 | 3.272 (0.705–11.266) | 0.083 |

OR, odds ratio; CI, confidence interval; ECG, electrocardiography; CPR, cardiopulmonary resuscitation; ref, reference.

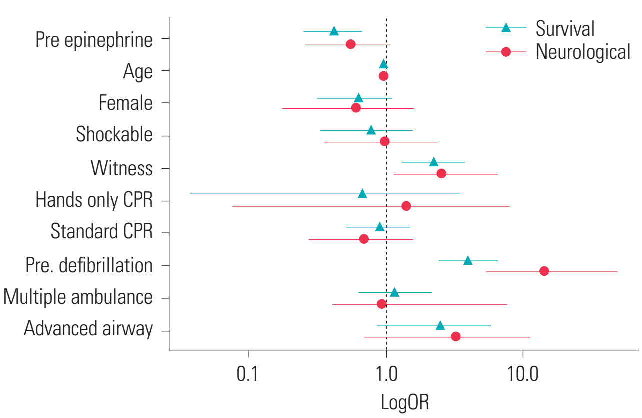


**Fig. 2.** ORs with 95% confidence intervals of survival and neurological outcomes for each variable from multivariable logistic regression analysis after propensity score matching. OR, odds ratio; CPR, cardiopulmonary resuscitation; pre, prehospital.

derstood. However, the brain is more sensitive to ischemic reperfusion injury from cardiac arrest and has lesser ability to recover functionally than other organs, including the heart.[17] The rationale for using epinephrine in cardiac arrest is the increase in coronary and cerebral perfusion associated with the α-adrenergic effect. However, epinephrine also has detrimental effects after cardiac arrest, including myocardial dysfunction, increased metabolic demand, ventricular arrhythmias, and abnormalities in the cerebral microcirculation.[18,19]

Several studies have suggested that the earlier the administration of epinephrine, the better the prognosis. For every minute epinephrine is administered to a patient from the time of arrival of EMS at the scene, the probability of survival decreases by 4%.[20] Studies have shown that prehospital epinephrine should be administered within 20 minutes to patients with non-shockable rhythm to improve survival or neurological outcome.[21-23] Those in the prehospital epinephrine group in this study showed poor survival rate even though epinephrine was administered earlier than the control group, who received epinephrine at a more delayed time after hospital arrival. The epinephrine group had a higher prehospital ROSC rate, but these patients did not survive until hospital discharge. A similar result was obtained when the subgroup with non-shockable rhythm, known to be more susceptible to epinephrine, was separately analyzed.

One of the possible reasons of poor outcome for prehospital epinephrine group is a longer scene time interval (STI). Many studies have been conducted on the association between the STI and neurological outcome in cardiac arrest patients. Coute, et al.[24] reported that the probability of worsening neurological outcomes increased when the STI exceeded 20 min in patients with bystander-witnessed OHCA. Park, et al.[25] reported that continuing CPR for more than 15 min on the scene was associated with a decreased chance of survival and good neurological outcomes in refractory OHCA patients with a shockable rhythm. Goto, et al.[26] reported that a call-to-hospital arrival time of less than 24 minutes was associated with favorable neurological outcomes at 1-month in OHCA patients transported to hospitals without a prehospital ROSC. Jang, et al.[27] reported that an STI greater than 19 min was associated with poor neurologic outcomes at hospital discharge. In this study, the STI in the prehospital epinephrine group was 22.3±8.6 min, which was significantly longer than that in the no-epinephrine group at 12.2±6.3 min. However, the effect of STI on survival or neurological outcome could not be included in the regression model, since there were a lot of missing values.

The reason for the improvement in survival and neurological outcome reported in the SALS pilot project in Korea may not be explained by prehospital epinephrine use. Perhaps, it seems to be due to the overall effect of multidisciplinary bundled interventions and smartphone-based medical control. However, in this study, multiple ambulance dispatch and placement of a prehospital advanced airway were not statistically associated with favorable survival and neurological outcomes. Therefore, additional studies are required to differentiate the beneficial effects of bundled interventions in the SALS project.

This study had several limitations. First, the patients administered epinephrine were not assigned in a randomized manner. Although we performed a statistical adjustment for confounders with a PS matching, unmeasured confounders could not be managed. Second, we did not have sufficient variables to allow us to perform further risk adjustment (e.g., CPR quality of EMS providers and administration timing of epinephrine). Third, important variables, such as the STI and targeted temperature management, had many missing values (46% and 17%, respectively), making it difficult to include the variables in the regression model to evaluate their association with the OHCA outcome. Fourth, the results may not be generalizable. Therefore, caution is needed when applying these results to other countries with different EMS systems. ALS procedures and drug administration by EMTs are not routinely performed in Korea.

In conclusion, this study suggested that prehospital epinephrine was associated with decreased survival rates in OHCA patients, but not statistically associated with neurological outcomes. Further research is required to investigate the reason for the detrimental effect of epinephrine administered at the scene, and to guide better indication and regimen for prehospital epinephrine use in Korea.

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## AUTHOR CONTRIBUTIONS

Conceptualization: Sung Phil Chung. Data curation: Eunah Han, Goeun Park, and Sujee Lee. Formal analysis: Sung Phil Chung, Goeun Park, and Sujee Lee. Investigation: Eunah Han and Sung Phil Chung. Methodology: Goeun Park and Sujee Lee. Project administration: Sung Phil Chung. Resources: KoCARC investigators. Software: Eunah Han, Goeun Park, and Sujee Lee. Supervision: Sung Phil Chung and Incheol Park. Validation: Sung Phil Chung and Incheol Park. Visualization: Sung Phil Chung, Goeun Park, and Sujee Lee. Writing—original draft: Eunah Han. Writing—review & editing: Taeyoung Kong, Je Sung You, Incheol Park, and Sung Phil Chung. Approval of final manuscript: all authors.

## ORCID iDs

| | |
|---|---|
| Eunah Han | https://orcid.org/0000-0001-7928-3901 |
| Taeyoung Kong | https://orcid.org/0000-0002-4182-7245 |
| Je Sung You | https://orcid.org/0000-0002-2074-6745 |
| Incheol Park | https://orcid.org/0000-0001-7033-766X |
| Goeun Park | https://orcid.org/0000-0002-6670-5500 |
| Sujee Lee | https://orcid.org/0000-0002-2473-3693 |
| Sung Phil Chung | https://orcid.org/0000-0002-3074-011X |

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