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Clinical paper

Corticosteroid use with extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A nationwide observational study

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Abstract

Aim: Several studies have reported that corticosteroid administration for cardiac arrest patients may improve outcomes. However, these previous studies have not examined the effect of corticosteroid use in out-of-hospital cardiac arrest (OHCA) patients administered extracorporeal cardiopulmonary resuscitation (ECPR). Therefore, we aimed to examine the effectiveness of corticosteroids in OHCA patients administered ECPR.

Methods: Using the Japanese Diagnosis Procedure Combination inpatient database, we included OHCA patients who were administered ECPR on the day of admission between July 2010 and March 2019. The patients were categorized into the corticosteroid and control groups according to whether they received corticosteroids on the day of admission or not. The primary outcome was in-hospital mortality and the secondary outcomes included percentages of neurologically favorable survival, major bleeding complications, and infection-related complications. We compared the outcomes using a propensity score matching analysis.

Results: We identified 6,142 eligible patients (459 vs 5,683, the corticosteroid and control group, respectively). One-to-four propensity score matching analysis (457 vs 1,827) showed in-hospital mortality was significantly higher in the corticosteroid group compared with the control group (82.1% vs 76.6%; risk difference, 5.5%; 95% CI, 1.5 to 9.5%). Neurologically favorable outcomes did not differ between the two groups (13.6% vs 16.9%; risk difference, −3.3%; 95% CI, −6.9 to 0.3%). The percentage of major bleeding complications and infection-related complications did not significantly differ between the two groups.

Conclusions: The results of this study demonstrated that administration of corticosteroids on the day of admission to OHCA patients administered ECPR was associated with increased in-hospital mortality.

Keywords: Cardiac arrest, Corticosteroid, Extracorporeal cardiopulmonary resuscitation

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major public health challenge.[1,2] Prognosis for OHCA remains poor and the survival rate at the time of hospital discharge is approximately 10% and 2.6% in the United States and Japan, respectively.[1,3] Extracorporeal cardiopulmonary resuscitation (ECPR) has been added to the armamentarium of life-saving procedures for OHCA patients. Previous studies have shown that ECPR in OHCA patients could improve survival rates at one and twelve months in comparison with conventional CPR.[4–6]

Abbreviations: OHCA, out-of-hospital cardiac arrest, CPR, cardiopulmonary resuscitation, ECPR, extracorporeal cardiopulmonary resuscitation, CPB, cardiopulmonary bypass, RCT, randomized controlled trial, IHCA, in-hospital cardiac arrest, ROSC, return of spontaneous circulation, ICU, intensive care unit, ICD-10, International Classification of Diseases, 10th Revision, JCS, Japan Coma Scale, BMI, body mass index, SD, standard deviation, IQR, interquartile ranges, CI, confidence interval

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Several studies have reported that corticosteroid and vasopressin supplementation—in addition to epinephrine—during CPR may improve outcomes for cardiac arrest.[7–11] A previously conducted population-based retrospective cohort study on OHCA patients in Taiwan showed that corticosteroid administration during CPR may be associated with improved survival-to-admission, survival to hospital discharge, and one-year survival.[7] A recent randomized controlled trial (RCT) of in-hospital cardiac arrest (IHCA) demonstrated that supplementation of methylprednisolone and vasopressin in addition to epinephrine during CPR, compared with epinephrine alone, improved the rate of return of spontaneous circulation (ROSC).[9] Two other RCTs examining IHCA showed consistent benefits of methylprednisolone administration during CPR and hydrocortisone administration in post-cardiac arrest shock.[10,11] In patients with cardiac arrest, adrenal insufficiency and low serum cortisol concentration during and after CPR have been associated with systemic inflammatory response.[12,13] Given these findings, corticosteroid administration for cardiac arrest patients was hypothesized to help maintain vascular tone and amplify the effects of vasopressors.[10,11]

No studies, however, have examined the efficacy of corticosteroids for OHCA patients administered ECPR. In the previous RCTs, the targeted patient population was IHCA—and not OHCA—patients. Moreover, the most recent RCT excluded patients administered ECPR.[9] ECPR may lead to more potent systemic inflammatory responses than conventional CPR due to the added cardiopulmonary bypass (CPB) component of treatment.[14] Thus, corticosteroids may also be beneficial in patients administered ECPR. Therefore, the present study was designed to examine the effectiveness of corticosteroid use in OHCA patients administered ECPR, using a Japanese nationwide inpatient database.

Methods

Ethical statement

This study was approved by the Institutional Review Board of The University of Tokyo (approval number 3501-3). The requirement for informed consent was waived due to the anonymous nature of the data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

Data source

The present study was a retrospective observational analysis using the Japanese Diagnosis Procedure Combination inpatient database. This database includes administrative claims data and discharge abstracts from more than 1,200 acute-care hospitals and covers approximately 90% of all tertiary-care emergency hospitals in Japan.[16] The database also includes information on dates of admission and discharge, age, sex, height, weight, ambulance use, primary and secondary diagnosis, comorbidities at admission, complication after admission, surgical and nonsurgical procedures with procedure date, date and dose of drugs, intensive care unit (ICU) admission, level of consciousness at admission and discharge, and discharge status. The primary diagnosis, comorbidities at admission and complication after admission are recorded in accordance with the International Classification of Diseases, 10th Revision (ICD-10) codes and Japanese text.

Study population

We identified OHCA patients who were administered ECPR on the day of admission and registered in the database from July 2010 to March 2019. OHCA patients were defined as those who were administered CPR on the day of admission and presented with a Japan Coma Scale (JCS) of 300 at admission.[2] A JCS of 300 is equivalent to a Glasgow Coma Scale of 3. Exclusion criteria were defined as follows: (1) patients who were aged < 18 years; (2) trauma patients (ICD-10 codes of main diagnoses, SX or TX); (3) patients who underwent resuscitative thoracotomy on the day of admission; (4) patients who underwent cardiac surgery on the day of admission (to exclude use of CPB during cardiac surgery); (5) patients discharged on the day of admission (to avoid immortal time bias);[17] or (6) missing value of outcomes.

Variables

We identified the following variables: age; sex; body mass index (BMI) at admission; comorbidities;[18] the Charlson comorbidity index;[19] teaching hospital admission; ICU admission; admission fiscal year; diagnoses;[20] procedures performed on the day of admission; medications used on the day of admission including corticosteroid, and blood product use. BMI (kg/m^2) was categorized as <18.5, 18.5–24.9, 25.0–29.9, $\geq$30.0, or missing data. The Charlson comorbidity index was calculated with the ICD-10 code-based comorbidities on admission and was categorized as 0, 1, 2, or $\geq$3.[19] The ICD-10 codes used to identify comorbidities and diagnoses are shown in Supplementary Table 1.

Exposure and outcomes

The main exposure was whether the patient received corticosteroids on the day of admission (corticosteroid group) or did not (control group). Corticosteroid administration was defined as intravenous administration of hydrocortisone, methylprednisolone, prednisolone, betamethasone, and/or dexamethasone regardless of dosage. The dosage of corticosteroids was described in the corticosteroid group. The dosage was converted into methylprednisolone equivalencies.[21]

The primary outcome was in-hospital mortality. The secondary outcomes were percentages of neurologically favorable survival, major bleeding complications, and infection-related complications. Neurologically favorable survival was defined as patients who were discharged from the hospital with a JCS of 0 or single digit. JCS of 0 or single digit are roughly equivalent to a Cerebral Performance Category score of 1 or 2.[2,20,22] Major bleeding complications was defined using post-admission complication ICD-10 code as intracranial bleeding (ICD-10 code, I61), intraspinal bleeding (G951), pericardial hematoma (I312), intra-abdominal hematoma or retroperitoneal hematoma (K661), intra-articular bleeding (M250), intraocular bleeding (H448), and compartment syndrome (M622) during hospitalization.[23] Infection-related complications were defined as the onset of pneumonia (ICD-10 code, J15 and J18), sepsis (A40, A41, and R65), surgical site infection (T814–6, T827, T857 and T880), urinary tract infection (N30 and N39), and other infections (A04, G00, I31, O86 and Y93).[24]

Statistical analysis

We used propensity score matching analyses to account for the differences in baseline demographics and characteristics between the corticosteroid and control groups. The propensity scores for corticosteroid use on the day of admission were calculated using a multivari-

able logistic regression model. To account for clustering within hospitals, a generalized estimating equation was linked to the model. Predictor variables included age, sex, BMI category at admission, comorbidity at admission (diabetes mellitus, hypertension, obstructive lung disease, rheumatic disease and vasculitis, and interstitial pneumonia), the Charlson comorbidity index, teaching hospital admission, ICU admission on the day of admission, fiscal year of admission, diagnoses, procedures performed on the day of admission, and medications used on the day of admission. We conducted a one-to-four matching with replacement using the nearest available match within 20% of the standard deviation (SD) of the estimated propensity score on the logit scale.[25] We assessed the balance of the covariates between the two groups before and after propensity score matching using the absolute standardized difference. An absolute standardized difference of <10% was considered as balanced.[26]

We conducted two sensitivity analyses. First, the overlap weighting method was performed to examine the robustness of the results of the propensity score matching analysis. Overlap weighting is one of the weighting methods utilizing the propensity score.[27,28] Under this method, treated patients (corticosteroids group) were weighted by the probability of not receiving treatment (1 − propensity score) and untreated patients (control group) were weighted by the probability of receiving treatment (propensity score). Since these weights are smaller for extreme propensity score values, outliers who are almost always treated (propensity score close to 1) or never treated (propensity score close to 0) do not dominate the results and worsen accuracy, as occurs with inverse probability weighting.[27] The target of overlap weighting focuses on patients with the most pronounced overlap in observed characteristics and its corresponding estimand is the average effect of treatment in the overlap population.[29] Second, considering the possibility of the minimal involvement of immortal time bias and the effect of the reduced number of patients due to exclusions, we performed a one-to-four propensity score matching analysis including patients who were discharged on the day of admission.

Continuous variables were expressed as medians with interquartile ranges (IQR) and categorical variables as numbers and proportions. The patient demographics and characteristics between the corticosteroid and control groups were compared using the absolute standardized difference. We calculated risk differences and their 95% confidence intervals (CIs) for the outcomes. Two-sided values of $p < 0.05$ were considered statistically significant in all hypothesis tests. All statistical analyses were performed using Stata MP version 15.0 software (Stata Corp, College Station, TX, USA).

Results

Study population

We identified 6,142 eligible patients during the study period from 445 facilities (Fig. 1). Among these patients, the corticosteroid and control groups consisted of 459 and 5,683 patients, respectively. After a one-to-four propensity score matching, we compared 457 and 1,827 patients in the corticosteroid and control groups, respectively. The C-statistics for the propensity score model was 0.78.

The summary of baseline characteristics before and after propensity score-matching are shown in Table 1. A more comprehensive compilation of the baseline characteristics is shown in Supplementary Table 2. Before propensity score matching, patients in the corticosteroid group were more likely to have a higher percentage of BMI < 18.5, BMI ≥ 30.0, BMI of missing, obstructive lung disease, ICU admission, central venous catheter use coronary angiography, bronchoscopy, renal replacement therapy, temperature modulating device use, tracheostomy, and medications used on the day of admission (dobutamine, norepinephrine, vasopressin, atropine, sodium bicarbonate solution, magnesium sulfate, propofol, and blood products). On the other hand, patients in the corticosteroid group were likely to have a lower percentage of BMI of 18.5–24.9 and 25.0–29.9, hypertension, ventricular fibrillation, acute coronary syndrome, aortic dissection, pulmonary embolism, subarachnoid hemorrhage, defibrillation, percutaneous coronary intervention, and amiodarone use. After propensity score matching, the covariates were balanced between the two groups except for the proportion of BMI of missing, temperature modulating device use, and dopamine use. The median dosage of corticosteroids on the day of admission (converted into methylprednisolone equivalency) in the corticosteroid group was 100 mg (IQR, 40–915 mg).

Outcomes

The outcomes after propensity score-matching are shown in Table 2. In-hospital mortality was significantly higher in the corticosteroid group compared with the control group (82.1% vs 76.6%; risk difference, 5.5%; 95% CI, 1.5 to 9.5%). Neurologically favorable outcomes did not differ between the two groups (13.6% vs 16.9%; risk difference, –3.3%; 95% CI, –6.9 to 0.3%). The percentage of major bleeding complications did not significantly differ between the two groups (0.9% vs 1.5%; risk difference, –0.7%; 95% CI, –1.7 to 0.4%). The percentage of infection-related complications also did not significantly differ between the two groups (14.7% vs 15.7%; risk difference, –1.0%; 95% CI, –4.6 to 2.7%).

In the sensitivity analysis using overlap weighting, the patient characteristics after weighting are provided in Supplementary Table 3. Table 3 shows the results of the sensitivity analysis. In-hospital mortality was significantly higher in the corticosteroid group compared with the control group (82.2% vs 76.0%; risk difference, 6.2%; 95% CI, 4.2 to 8.2%). Neurologically favorable outcomes were significantly lower in the corticosteroid group compared with the control group (13.6% vs 18.1%; risk difference, –4.6%; 95% CI, –6.4 to –2.7%). The percentage of major bleeding complications was significantly lower in the corticosteroid group compared with the control group (0.8% vs 1.5%; risk difference, –0.7%; 95% CI, –1.2 to –0.1%). The percentage of infection-related complications did not significantly differ between the two groups (14.5% vs 14.8%; risk difference, –0.3%; 95% CI, –2.0 to 1.5%).

The sensitivity analysis of one-to-four matching, including patients who were discharged on the day of admission, showed similar results to the main analysis with regard to the primary outcome. In-hospital mortality was significantly higher in the corticosteroid group compared with the control group (84.9% vs 79.7%; risk difference, 5.2%; 95% CI, 1.7 to 8.6%). Neurologically favorable outcomes were significantly lower in the corticosteroid group compared with the control group (11.4% vs 15.4%; risk difference, –4.0%; 95% CI, –7.1 to –0.9%). The percentage of major bleeding complications did not significantly differ between the two groups (1.1% vs 1.7%; risk difference, –0.6%; 95% CI, –1.6 to 0.5%). The percentage of infection-related complications also did not significantly differ between the two groups (1.1% vs 1.7%; risk difference, –0.6%; 95% CI, –1.6 to 0.5%).

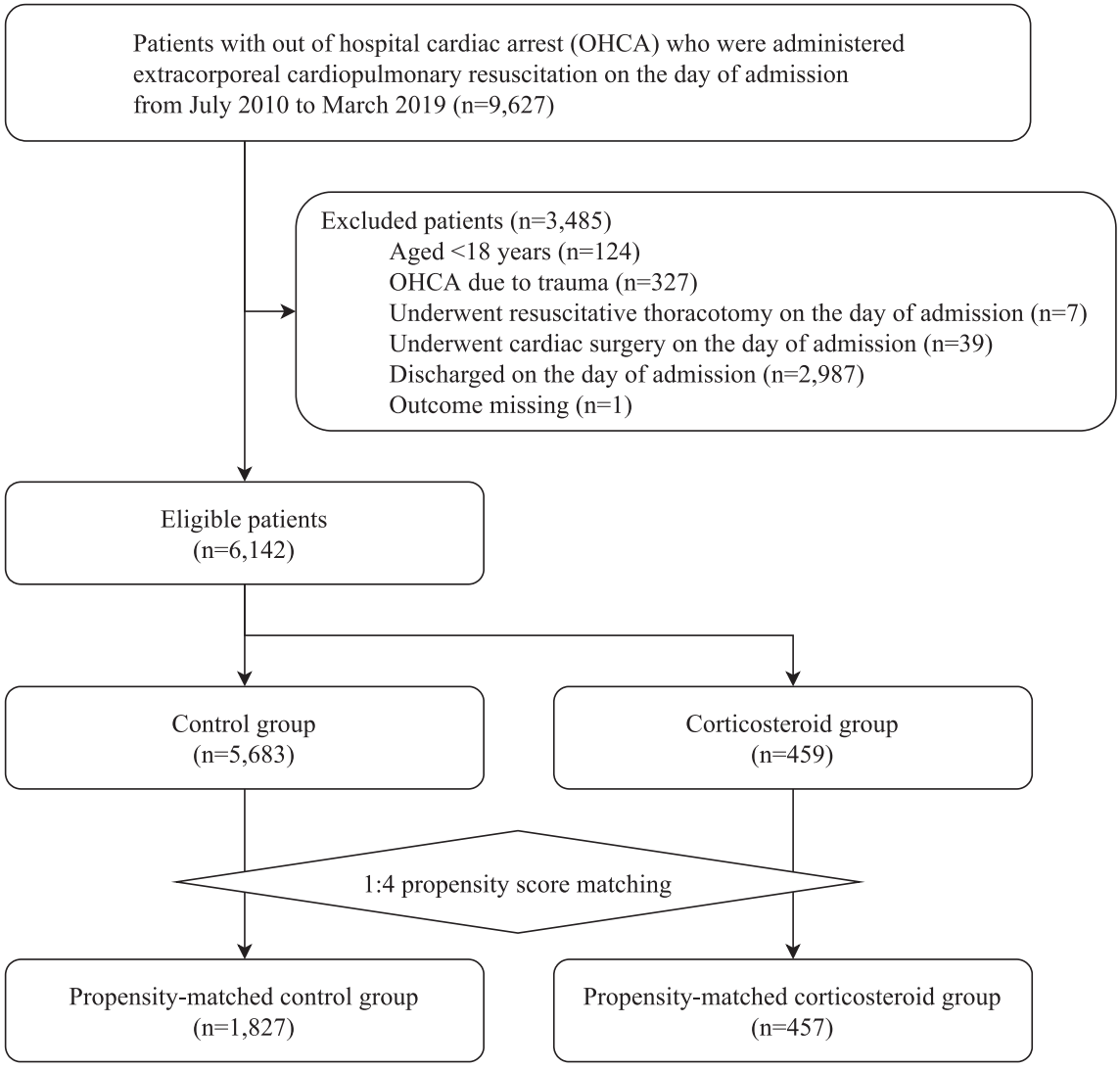

Fig. 1 – Patient flowchart.

Discussion

This nationwide observational study focused on the effectiveness of corticosteroid use in OHCA patients who were administered ECPR. The major finding of the present study was that administration of corticosteroids on the day of admission for OHCA patients administered ECPR was associated with increased in-hospital mortality.

The difference in outcomes observed between the present and previous studies could have arisen due to the population targeted in the present study being limited to OHCA patients who were administered ECPR. When it comes to using CPB, our findings are similar to those of several previous RCTs examining the efficacy of corticosteroid use in cardiac surgery with CPB.[30–32] CPB induces a systemic inflammatory response, which is associated with adverse clinical outcomes.[14] Although corticosteroids were shown to attenuate this inflammatory response,[33] three previous RCTs on cardiac surgery using CPB did failed to demonstrate the efficacy of corticosteroids.[30–32] Several hypotheses were raised as to the reason for these findings.[31] First, corticosteroid-induced insulin resistance may exacerbate myocardial ischemia by preventing glucose from entering the myocardial cells. Second, the inflammatory response is imperative in the body's natural ability to heal, however, corticosteroids may impede this process. A previous study reported that corticosteroid use after myocardial infarction increased the infarct size.[34] While previous RCTs included only 10–30% of patients with a shockable rhythm,[7–11] the present study included approximately 50% of patients with a shockable rhythm and acute coronary syndrome. Therefore, our study was limited to ECPR cases, which included a large number of patients with cardiogenic cardiac arrest.

On the other hand, a recent RCT reported a lack of hemodynamic benefit associated with corticosteroid administration in IHCA patients.[35] In this previous study, mean arterial pressure was slightly higher within the first 4 hours post-ROSC in the corticosteroid group; however, this marginal benefit could not be documented at subsequent follow-up. Early resistance to corticosteroids was suggested as a potential cause of these results. A similar—albeit unidentified—underlying mechanism could have influenced the outcome of our study.

The results of this study do not support the recommendation for routine corticosteroid use in OHCA patients administered

Table 1 – Summary of baseline patient characteristics before and after propensity score matching.

Variables	Before propensity score matching					After propensity score matching				
	Control group (n = 5683)		Corticosteroid group (n = 459)		Standardized difference (%)	Control group (n = 1827)		Corticosteroid group (n = 457)		Standardized difference (%)
Age, median (IQR)	61	(50, 70)	61	(49, 69)	–8.1	59	(48, 70)	61	(49, 69)	0.0
Male	4558	(80.2)	360	(78.4)	–4.4	1390	(76.1)	359	(78.6)	5.9
Comorbidity										
Diabetes mellitus	697	(12.3)	48	(10.5)	–5.7	192	(10.5)	48	(10.5)	0.0
Hypertension	701	(12.3)	37	(8.1)	–14.2	158	(8.6)	37	(8.1)	–2.0
Obstructive lung disease	649	(11.4)	86	(18.7)	20.5	378	(20.7)	85	(18.6)	–5.3
Rheumatic disease and vasculitis	11	(0.2)	2	(0.4)	4.3	7	(0.4)	2	(0.4)	0.9
Interstitial pneumonia	4	(0.1)	1	(0.2)	3.9	7	(0.4)	1	(0.2)	–3.0
Charlson comorbidity index										
0	2997	(52.7)	237	(51.6)	–2.2	1017	(55.7)	236	(51.6)	–8.1
1	1757	(30.9)	142	(30.9)	0.0	539	(29.5)	142	(31.1)	3.4
2	596	(10.5)	47	(10.2)	–0.8	159	(8.7)	46	(10.1)	4.7
≥3	333	(5.9)	33	(7.2)	5.4	112	(6.1)	33	(7.2)	4.4
Ventricular fibrillation	2918	(51.3)	188	(41.0)	–20.9	697	(38.1)	188	(41.1)	6.1
Ventricular tachycardia	302	(5.3)	16	(3.5)	–8.9	62	(3.4)	16	(3.5)	0.6
Acute coronary syndrome	3125	(55.0)	205	(44.7)	–20.8	771	(42.2)	204	(44.6)	4.9
Aortic dissection	93	(1.6)	2	(0.4)	–11.9	5	(0.3)	2	(0.4)	2.8
Pulmonary embolism	375	(6.6)	18	(3.9)	–12.0	104	(5.7)	18	(3.9)	–8.2
Subarachnoid hemorrhage	109	(1.9)	3	(0.7)	–11.2	9	(0.5)	3	(0.7)	2.2
Procedures performed on the day of admission										
Coronary angiography	1357	(23.9)	137	(29.8)	13.5	476	(26.1)	137	(30.0)	8.7
Renal replacement therapy	630	(11.1)	137	(29.8)	47.8	474	(25.9)	135	(29.5)	8.0
Temperature modulating device	1688	(29.7)	162	(35.3)	12.0	491	(26.9)	162	(35.4)	18.6
Defibrillation	3054	(53.7)	217	(47.3)	–12.9	859	(47.0)	217	(47.5)	0.9
Percutaneous coronary intervention	2688	(47.3)	154	(33.6)	–28.3	595	(32.6)	154	(33.7)	2.4
Intra-aortic balloon pump	738	(13.0)	56	(12.2)	–2.4	229	(12.5)	56	(12.3)	–0.9
Medications used on the day of admission										
Epinephrine	4978	(87.6)	394	(85.8)	–5.2	1629	(89.2)	393	(86.0)	–9.6
Dopamine	2026	(35.7)	166	(36.2)	1.1	757	(41.4)	166	(36.3)	–10.5
Dobutamine	1550	(27.3)	151	(32.9)	12.3	650	(35.6)	150	(32.8)	–5.8
Norepinephrine	3226	(56.8)	343	(74.7)	38.5	1382	(75.6)	341	(74.6)	–2.4
Vasopressin	247	(4.3)	105	(22.9)	56.1	373	(20.4)	103	(22.5)	5.2
Atropine	456	(0.8)	53	(11.5)	11.9	214	(11.7)	53	(11.6)	–0.4
Amiodarone	2835	(49.9)	186	(40.5)	–18.9	810	(44.3)	186	(40.7)	–7.4
Transfusions used on the day of admission										
Red blood cells	2796	(49.2)	330	(71.9)	47.7	1349	(73.8)	328	(71.8)	–4.6
Fresh frozen plasma	2263	(39.8)	278	(60.6)	42.4	1167	(63.9)	276	(60.4)	–7.2
Platelets	392	(6.9)	67	(14.6)	25.0	297	(16.3)	65	(14.2)	–5.7
Albumin	2510	(44.2)	244	(53.2)	18.1	1043	(57.1)	243	(53.2)	–7.9

IQR, interquartile range; ICU, intensive care unit.

Data are shown as number (%) otherwise specified.

Table 2 – Outcomes after propensity score matching.

Outcomes	Control group		Corticosteroid group		Risk difference	(95% confidence interval)	p-value
In-hospital mortality	76.6%	(1399/1827)	82.1%	(375/457)	5.5%	(1.5% to 9.5%)	0.012
Neurologically favorable outcomes	16.9%	(308/1827)	13.6%	(62/457)	–3.3%	(–6.9% to 0.3%)	0.09
Major bleeding complications	1.5%	(28/1827)	0.9%	(4/457)	–0.7%	(–1.7% to 0.4%)	0.29
Infection-related complications	15.7%	(286/1827)	14.7%	(67/457)	–1.0%	(–4.6% to 2.7%)	0.60

ECPR. The strength of the present study lies in its internal validity utilizing a large nationwide database with several statistical analyses. For the primary outcome, the results were consistent in the main statistical analysis and in the two additional sensitivity analyses. Even though the results of this study were different from previous studies investigating cardiac arrest patients, no RCTs to date have examined the effect of corticosteroids on OHCA patients, nor on OHCA patients administered ECPR cases. Thus, the present study serves as the justification for conducting further RCTs.

Table 3 – Outcomes after overlap weighting.

Outcomes	Control group		Corticosteroid group		Risk difference	(95% confidence interval)	*p*-value
In-hospital mortality	76.0%	(2327/3064)	82.2%	(2529/3078)	6.2%	(4.2% to 8.2%)	<0.001
Neurologically favorable outcomes	18.1%	(556/3064)	13.6%	(418/3078)	–4.6%	(–6.4% to –2.7%)	<0.001
Major bleeding complications	1.5%	(47/3063)	0.8%	(26/3079)	–0.7%	(–1.2% to –0.1%)	0.013
Infection-related complications	14.8%	(452/3064)	14.5%	(446/3079)	–0.3%	(–2.0% to 1.5%)	0.77

The present study has several limitations. First, confounding of indication may have inadvertently occurred. Information on cardiac arrest (i.e., presence of witness, bystander CPR and duration of cardiac arrest) in the pre-hospital setting and vital signs after ROSC were unavailable due to the nature of the administrative database. Therefore, the patients with unstable hemodynamics and poor general condition may have favorably received corticosteroids. Second, detailed information on timing and purpose of corticosteroids were unavailable. In particular, it was unclear whether corticosteroids were administered during CPR or after ROSC. However, efficient circulation would be re-established within a relatively short interval after arrival at the hospital because the patients in the present study were limited to those who were administered ECPR. Thus, the percentage of cases involving corticosteroid use during CPR (prior to establishing extracorporeal circulation) would be limited. Although the history of corticosteroid medication prior to admission was also unavailable due to the nature of the database, we obtained surrogate variables of past medical history indicative of prior corticosteroid use. Third, defining ECPR in OHCA patients using procedure codes may lead to misclassification. We defined ECPR cases as patients who received CPR and were placed on extracorporeal life support on the day of admission. We also defined OHCA cases as patients who received CPR on the day of admission and presented with a JCS of 300 at admission. Therefore, the definition adopted in our study may encompass patients placed on extracorporeal life support due to heart failure after ROSC but not cardiac arrest. The same may also be true for cases involving the use of veno-venous extracorporeal membrane oxygenation due to respiratory failure after cardiac arrest.

Conclusions

This nationwide observational study revealed that administration of corticosteroids on the day of admission to OHCA patients administered ECPR was associated with increased in-hospital mortality. The results of this study do not support the recommendation for routine corticosteroid use in OHCA patients administered ECPR. Although we adjusted for numerous confounding factors via the propensity score method, randomized controlled trials are warranted to confirm our findings.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

None.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at The University of Tokyo (Approval number 3501-3, December 2017). The requirement for informed consent was waived due to the anonymous nature of the data.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100308.

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