Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Setting, Data Collection, Definition, Exposures, and Risk-Set Matching Analysis

JAAM-OHCA registry

The JAAM-OHCA registry is a nationwide prospective registry of out-of-hospital cardiac arrest (OHCA) patients maintained by the Japanese Association of Acute Medicine (JAAM). The detailed methodology of the JAAM-OHCA registry is described in a previous report.[1] In brief, this registry consists of prehospital data collected using the Utstein-style template[2,3] and in-hospital data, including patient characteristics, resuscitation and intensive care procedures, and outcomes. The neurological status of the survivors was evaluated by the medical staff at each institution 1 month after the event. As quality control, if the data form of the JAAM-OHCA registry was incomplete, the JAAM-OHCA registry committee, composed of specialists in the fields of emergency medicine and epidemiology, returned it to the respective institution requesting that it be completed to the best extent possible, which resulted in no loss of follow-up to determine the outcomes at 30 days among the patients included in this study.

Emergency medical service (EMS) system in Japan

An ambulance carries three emergency providers and at least one emergency life-saving technician who is skilled at intravenous (IV) catheterization, IV epinephrine administration, and advanced airway management (AAM). EMS personnel do not place intraosseous access. Cardiopulmonary resuscitation (CPR) is conducted according to the Japanese guidelines, which are compliant with the international resuscitation guidelines.[4] Termination-of-resuscitation (TOR) can be implemented only when patients satisfy all of the following requirements: patients in a terminal state, patients who have provided advance directive (AD) against resuscitation attempts, patients' family members expressing their wish to withhold CPR, and physicians in charge directing the EMS personnel to terminate CPR in a direct communication. The EMS personnel can withhold CPR only for cases in which death is obvious, such as cases of decapitation, incineration, late postmortem changes (decomposition, mummification, etc) and early postmortem changes (rigor mortis, postmortem lividity, etc).[5]

Data collection, definition, and exposures

Characteristics of the patients, OHCA event, resuscitative procedures and outcomes were collected from the JAAM-OHCA registry. AAM, IV catheterization, and IV epinephrine administration were defined as the prehospital advanced life support (ALS) procedures. IV epinephrine administration, tracheal intubation, and targeted temperature management (TTM) were defined as in-hospital ALS procedures. The main exposure variables were year of OHCA and prehospital ALS procedures (AAM and IV epinephrine administration). Because of the collinearity between IV catheterization and IV epinephrine administration, we did not include IV catheterization as an exposure variable. In addition, we calculated the time spent on CPR procedures until return of spontaneous circulation (ROSC) was achieved in the prehospital and in-hospital settings as indices of medical resource consumption.

Advanced life support termination-of-resuscitation (ALS-TOR) rule[6] and TOR in the in-hospital setting

Regarding ALS-TOR rule, patients are regarded as candidates for TOR when all the following 5 criteria are met: (1) event not witnessed by the EMS personnel; (2) no automated external defibrillator (AED) used or manual shock applied in the out-of-hospital setting; (3) no ROSC in the out-of-hospital setting; (4) no bystander witness of the arrest; (5) no bystander-administered CPR. As for in-hospital TOR, there are no established criteria in Japan.[4] The Japan Resuscitation Council Resuscitation guidelines 2020 suggest that $EtCO_2$ ≥10 mmHg at 20 minutes after the initial measurement or initiation of resuscitation is a potential predictor of ROSC and survival at hospital discharge.[4] Therefore, physicians often judge whether to terminate or continue resuscitation efforts based on several predictive factors, including the $EtCO_2$, measured at a certain time (such as 20 minutes) after the initiation of resuscitation.

Risk-set matching analysis with time-dependent propensity score (PS)

PS indicating the time-varying probability of receiving the prehospital procedures was calculated by a competing risk time-to-event analysis using the Fine-Gray regression model.[7-11] In the model, time to receiving the procedures was the dependent variable, and arrival of the EMS personnel was set as time 0 because the patients were at-risk of receiving the procedure only after this time-point. We fit two models: one with the dependent variable of time-to-AAM and the other with the dependent variable of time-to-IV

epinephrine administration. We included age, sex, witness status[7,12] (family, friend, colleague, passers-by, others, or no witness), bystander-initiated CPR, year of occurrence, day of occurrence (weekday or weekend), time of occurrence (daytime or nighttime), external etiology of the cardiac arrest, prehospital involvement of physician and time from the emergency call to arrival of the EMS personnel as the time-independent covariates. In the analysis, we did not include the data of patients who were not in cardiac arrest at the time of arrival of the EMS personnel (but subsequently suffered from cardiac arrest while being treated by the EMS personnel), because patients with a non-asystole rhythm as the first-documented rhythm were excluded from the study. The time-dependent covariates included the remaining prehospital procedures (AAM or IV epinephrine administration) and shock delivery by the EMS personnel.

We performed 1:1 risk-set matching with replacement of each of the prehospital procedures using the calculated time-dependent PS.[13,14] A patient who underwent the prehospital procedures at any given minute after arrival of the EMS personnel was sequentially matched with a patient who was likely to have received prehospital procedures and had a similar PS in the same minute. These at-risk patients could have subsequently undergone the prehospital procedures after the matching or never undergone prehospital procedures, because the matching should be independent of future events.[13,14] At-risk patients could have been matched multiple times as at-risk patients or patients undergoing the prehospital procedures (only if the patients underwent the prehospital procedures) until undergoing the prehospital procedures (matching with replacement).[15] We set the caliper width for the nearest neighbor matching at 0.2 SD of the PS in the logit scale.[16] To assess the performance of the risk-set matching, we calculated a standardized difference for each covariate. A standardized difference of less than 0.25 was regarded as a well-balanced match.[15] We created two PS-matched cohorts: one for AAM and the other for IV epinephrine administration. In each of the matched cohorts, we fitted a conditional logistic model with matched pairs to calculate the odds ratios (ORs) with 95% confidence intervals (CIs).[17] The ORs represented the estimated magnitude of the association of the prehospital procedures with the outcomes as compared with that of those at risk of undergoing prehospital procedures.

eTable 1. Secular Trends in the Patient Outcomes at 30 days

A All Patients Included in Analysis

	No. (%) of patients (n = 35 843)								
	2014 (n = 1848)	**2015 (n = 4984)**	**2016 (n = 5513)**	**2017 (n = 5706)**	**2018 (n = 5999)**	**2019 (n = 5901)**	**2020 (n = 5892)**	***P* value**	**Total (n = 35 843)**
CPC ≤2	2 (0.1)	9 (0.2)	9 (0.2)	12 (0.2)	15 (0.3)	9 (0.2)	11 (0.2)	.69	67 (0.2)
CPC ≤3	5 (0.3)	23 (0.5)	21 (0.4)	27 (0.5)	30 (0.5)	38 (0.6)	28 (0.5)	.11	172 (0.5)
Survival	30 (1.6)	68 (1.4)	87 (1.6)	76 (1.3)	79 (1.3)	84 (1.4)	73 (1.2)	.24	497 (1.4)
ROSC	424 (22.9)	1122 (22.5)	1274 (23.1)	1314 (23.0)	1349 (22.5)	1360 (23.0)	1178 (20.0)	.003	8021 (22.4)

B Patients Older Than 80 years

	No. (%) of patients (n = 14 453)								
	2014 (n = 693)	**2015 (n = 1919)**	**2016 (n = 2159)**	**2017 (n = 2347)**	**2018 (n = 2444)**	**2019 (n = 2446)**	**2020 (n = 2445)**	***P* value**	**Total (n = 14 453)**
CPC ≤2	0 (0)	3 (0.2)	0 (0)	3 (0.1)	2 (0.1)	1 (0.04)	3 (0.1)	.81	12 (0.1)
CPC ≤3	1 (0.1)	5 (0.3)	5 (0.2)	9 (0.4)	7 (0.3)	13 (0.5)	10 (0.4)	.08	50 (0.3)
Survival	9 (1.3)	25 (1.3)	27 (1.3)	20 (0.9)	19 (0.8)	30 (1.2)	28 (1.1)	.56	158 (1.1)
ROSC	174 (25.1)	452 (23.6)	517 (23.9)	533 (22.7)	576 (23.6)	596 (24.4)	520 (21.3)	.10	3368 (23.3)

(continued)

eTable 1. (continued)

C Patients Without ROSC at Hospital Arrival

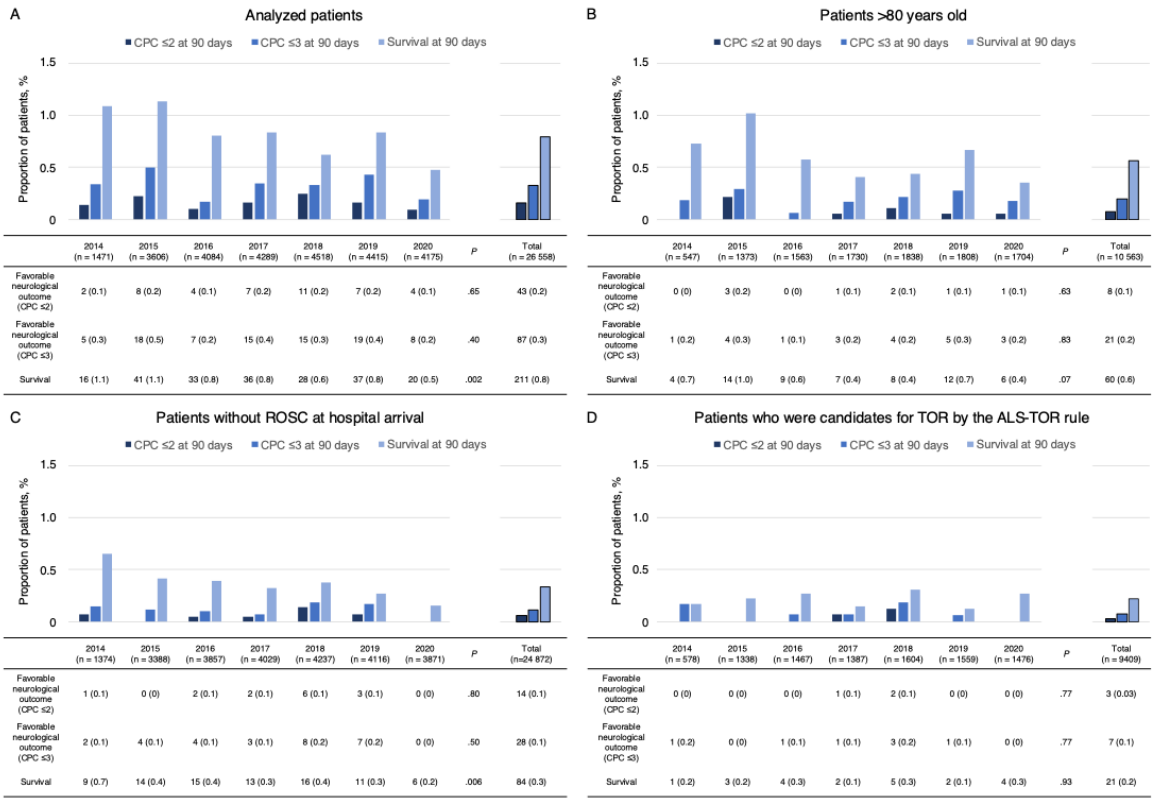
	No. (%) of patients (n = 33 466)								
	2014 (n = 1718)	**2015 (n = 4698)**	**2016 (n = 5182)**	**2017 (n = 5337)**	**2018 (n = 5598)**	**2019 (n = 5470)**	**2020 (n = 5463)**	***P* value**	**Total (n = 33 466)**
CPC ≤2	1 (0.1)	0 (0)	4 (0.1)	5 (0.1)	7 (0.1)	4 (0.1)	2 (0.04)	.57	23 (0.1)
CPC ≤3	2 (0.1)	6 (0.1)	7 (0.1)	11 (0.2)	16 (0.3)	9 (0.2)	6 (0.1)	.74	57 (0.2)
Survival	13 (0.8)	24 (0.5)	36 (0.7)	31 (0.6)	34 (0.6)	29 (0.5)	25 (0.5)	.21	192 (0.6)
ROSC	294 (17.1)	836 (17.8)	943 (18.2)	945 (17.7)	948 (16.9)	929 (17.0)	749 (13.7)	<.001	5644 (16.9)

D Patients Who Were Candidates for TOR by The ALS-TOR Rule

	No. (%) of patients (n = 12 731)								
	2014 (n = 748)	**2015 (n = 1863)**	**2016 (n = 1973)**	**2017 (n = 1899)**	**2018 (n = 2142)**	**2019 (n = 2059)**	**2020 (n = 2047)**	***P* value**	**Total (n = 12 731)**
CPC ≤2	0 (0)	0 (0)	2 (0.1)	3 (0.2)	3 (0.1)	0 (0)	0 (0)	.73	8 (0.1)
CPC ≤3	1 (0.1)	0 (0)	2 (0.1)	4 (0.2)	5 (0.2)	1 (0.04)	1 (0.04)	.99	14 (0.1)
Survival	2 (0.3)	5 (0.3)	5 (0.3)	6 (0.3)	9 (0.4)	6 (0.3)	7 (0.3)	.55	40 (0.3)
ROSC	94 (12.6)	231 (12.4)	271 (13.7)	232 (12.2)	269 (12.6)	245 (11.9)	205 (10.0)	.007	1547 (12.2)

Abbreviations: CPC, Cerebral Performance Category; ROSC, return of spontaneous circulation; TOR, termination of resuscitation; ALS-TOR, advanced life support-termination of resuscitation.

eFigure 1. Secular trends in the patient outcomes at 90 days



eFigure 1. Secular Trends in the Patient Outcomes at 90 days

A Secular trends in the proportion of patients who showed a favorable neurological outcome (CPC ≤2 and CPC ≤3) at 90 days and survived at 90 days among the analyzed patients.

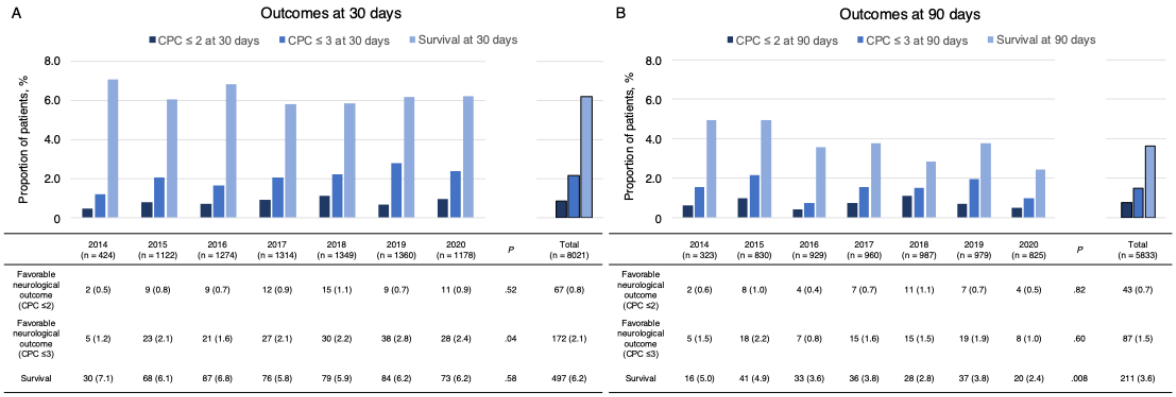
B Secular trends in the patients aged >80 years old.

C Secular trends in the patients without ROSC at hospital arrival.

D Secular trends in the patients who were candidates for TOR by the ALS-TOR rule.

CPC indicates Cerebral Performance Category; ROSC, return of spontaneous circulation; TOR, termination-of-resuscitation; ALS-TOR, advanced life support termination-of-resuscitation.

eFigure 2. Secular trends in the outcomes among patients with ROSC at any time



	2014 (n = 424)	2015 (n = 1122)	2016 (n = 1274)	2017 (n = 1314)	2018 (n = 1349)	2019 (n = 1360)	2020 (n = 1178)	*P*	Total (n = 8021)
Favorable neurological outcome (CPC ≤2)	2 (0.5)	9 (0.8)	9 (0.7)	12 (0.9)	15 (1.1)	9 (0.7)	11 (0.9)	.52	67 (0.8)
Favorable neurological outcome (CPC ≤3)	5 (1.2)	23 (2.1)	21 (1.6)	27 (2.1)	30 (2.2)	38 (2.8)	28 (2.4)	.04	172 (2.1)
Survival	30 (7.1)	68 (6.1)	87 (6.8)	76 (5.8)	79 (5.9)	84 (6.2)	73 (6.2)	.58	497 (6.2)

	2014 (n = 323)	2015 (n = 830)	2016 (n = 929)	2017 (n = 960)	2018 (n = 987)	2019 (n = 979)	2020 (n = 825)	*P*	Total (n = 5833)
Favorable neurological outcome (CPC ≤2)	2 (0.6)	8 (1.0)	4 (0.4)	7 (0.7)	11 (1.1)	7 (0.7)	4 (0.5)	.82	43 (0.7)
Favorable neurological outcome (CPC ≤3)	5 (1.5)	18 (2.2)	7 (0.8)	15 (1.6)	15 (1.5)	19 (1.9)	8 (1.0)	.60	87 (1.5)
Survival	16 (5.0)	41 (4.9)	33 (3.6)	36 (3.8)	28 (2.8)	37 (3.8)	20 (2.4)	.008	211 (3.6)

eFigure 2. Secular Trends in the Outcomes Among Patients With ROSC at Any Time

A Secular trends in the proportion of patients who showed a favorable neurological outcome (CPC ≤2 and CPC ≤3) at 30 days and survived at 30 days among the patients who achieved ROSC at any time during the resuscitation process.

B Secular trends in the proportion of patients who showed a favorable neurological outcome (CPC ≤2 and CPC ≤3) at 90 days and survived at 90 days among the patients who achieved ROSC at any time during the resuscitation process.

ROSC indicates return of spontaneous circulation; CPC, Cerebral Performance Category.

eTable 2. Secular Trends in the Performance of Prehospital and In-Hospital Advanced Life Support (ALS) Procedures in the Analyzed Patients

A Prehospital Procedure

	No. (%) of patients (n = 35 843)								
	2014 (n = 1848)	**2015 (n = 4984)**	**2016 (n = 5513)**	**2017 (n = 5706)**	**2018 (n = 5999)**	**2019 (n = 5901)**	**2020 (n = 5892)**	***P* value**	**Total (n = 35 843)**
AAM	938 (50.8)	2279 (45.7)	2815 (51.1)	3090 (54.2)	3224 (53.7)	3090 (52.4)	3216 (54.6)	<.001	18 652 (52.0)
IV catheterization	724 (39.2)	2015 (40.4)	2047 (37.1)	2483 (43.5)	2508 (41.8)	2488 (42.2)	2506 (42.5)	<.001	14 771 (41.2)
Epinephrine	454 (24.6)	1159 (23.3)	1305 (23.7)	1526 (26.7)	1784 (29.7)	1909 (32.4)	1989 (33.8)	<.001	10 126 (28.3)

B In-hospital Procedure

	No. (%) of patients (n = 35 843)								
	2014 (n = 1848)	**2015 (n = 4984)**	**2016 (n = 5513)**	**2017 (n = 5706)**	**2018 (n = 5999)**	**2019 (n = 5901)**	**2020 (n = 5892)**	***P* value**	**Total (n = 35 843)**
Epinephrine	1572 (85.1)	4153 (83.3)	4687 (85.0)	4854 (85.1)	4939 (82.3)	4798 (81.3)	4516 (76.6)	<.001	29 519 (82.4)
Tracheal intubation	1215 (65.7)	3204 (64.3)	3638 (66.0)	3542 (62.1)	3663 (61.1)	3702 (62.7)	3135 (53.2)	<.001	22 099 (61.7)
TTM	35 (1.9)	88 (1.8)	89 (1.6)	88 (1.5)	85 (1.4)	79 (1.3)	61 (1.0)	<.001	525 (1.5)

Abbreviations: AAM, advanced airway management; IV, intravenous; TTM, targeted temperature management.

eTable 3. Characteristics of Patients With OHCA and an Initial Rhythm of Asystole Who Received Prehospital AAM and Were at Risk of Receiving AAM in the Time-Dependent Propensity Score-Matched Cohort[a]

	No. (%) of patients		
	Control group (n = 18 135)	**AAM group (n = 18 135)**	**Standardized difference**
Age, median (IQR), y	76 (62-85)	78 (67-86)	0.145
Sex			
Male	10 516 (58.0)	10 426 (57.5)	0.010
Female	7619 (42.0)	7709 (42.5)	
External cause of arrest	2188 (12.1)	1391 (7.7)	0.148
Witness category			
Family	2609 (14.4)	3007 (16.6)	0.048
Friend	234 (1.3)	278 (1.5)	
Colleague	124 (0.7)	108 (0.6)	
Passer-by	445 (2.5)	213 (1.2)	
Others	1719 (9.5)	1552 (8.6)	
No witness	13 004 (71.7)	12 977 (71.6)	
Category of bystander CPR			
Chest compression only	7486 (41.3)	7641 (42.1)	0.052
Chest compression with ventilation	709 (3.9)	906 (5.0)	
No bystander CPR	9940 (54.8)	9588 (52.9)	
Year of occurrence			
2014	913 (5.0)	930 (5.1)	0.035
2015	2660 (14.7)	2265 (12.5)	
2016	2776 (15.3)	2781 (15.3)	
2017	2873 (15.8)	3049 (16.8)	
2018	3121 (17.2)	3191 (17.6)	
2019	3022 (16.7)	3053 (16.8)	
2020	2770 (15.3)	2866 (15.8)	

(continued)

eTable 3. (continued)

	No. (%) of patients		
	Control group (n = 18 135)	AAM group (n = 18 135)	Standardized difference
Day of occurrence			
Weekday	12 052 (66.5)	11 986 (66.1)	0.008
Weekend	6083 (33.5)	6149 (33.9)	
Time of occurrence			
Daytime	7305 (40.3)	7226 (39.8)	0.009
Nighttime	10 830 (59.7)	10 909 (60.2)	
Prehospital involvement of physician	1533 (8.5)	1057 (5.8)	0.102
Response time, median (IQR), min[b]	9 (7-11)	9 (7-10)	0.043

Abbreviations: AAM, advanced airway management; CPR, cardiopulmonary resuscitation.

[a] Continuous variables were expressed as medians (interquartile range [IQR]: 25-75), and categorical variables were expressed as proportions (%).

[b] Time from call to contact with the patient.

eTable 4. Characteristics of Patients With OHCA and an Initial Rhythm of Asystole Who Received Prehospital Epinephrine Administration and Were at Risk of Receiving Prehospital Epinephrine Administration in the Time-Dependent Propensity Score-Matched Cohort[a]

	No. (%) of patients		
	Control group (n = 9714)	Epinephrine group (n = 9714)	Standardized difference
Age, median (IQR), y	77 (64-85)	78 (67-86)	0.118
Sex			
Male	5575 (57.4)	5772 (59.4)	0.041
Female	4139 (42.6)	3942 (40.6)	
External cause of arrest	1098 (11.3)	714 (7.4)	0.136
Witness category			
Family	1316 (13.5)	2023 (20.8)	0.095
Friend	129 (1.3)	149 (1.5)	
Colleague	74 (0.8)	83 (0.9)	
Passer-by	204 (2.1)	137 (1.4)	
Others	828 (8.5)	1011 (10.4)	
No witness	7163 (73.7)	6311 (65.0)	
Category of bystander CPR			
Chest compression only	4030 (41.5)	4291 (44.2)	0.064
Chest compression with ventilation	431 (4.4)	484 (5.0)	
No bystander CPR	5253 (54.1)	4939 (50.8)	
Year of occurrence			
2014	499 (5.1)	447 (4.6)	0.094
2015	1290 (13.3)	1150 (11.8)	
2016	1483 (15.3)	1274 (13.1)	
2017	1531 (15.8)	1486 (15.3)	
2018	1673 (17.2)	1754 (18.1)	
2019	1691 (17.4)	1868 (19.2)	
2020	1547 (15.9)	1735 (17.9)	

(continued)

eTable 4. (continued)

	No. (%) of patients		
	Control group (n = 9714)	Epinephrine group (n = 9714)	Standardized difference
Day of occurrence			
Weekday	6467 (66.6)	6479 (66.7)	0.003
Weekend	3247 (33.4)	3235 (33.3)	
Time of occurrence			
Daytime	3859 (39.7)	3994 (41.1)	0.028
Nighttime	5855 (60.3)	5720 (58.9)	
Prehospital involvement of physician	739 (7.6)	687 (7.1)	0.021
Response time, median (IQR), min[b]	8 (7-10)	9 (7-11)	<.001

Abbreviations: CPR, cardiopulmonary resuscitation.

[a] Continuous variables were expressed as medians (interquartile range [IQR]: 25-75), and categorical variables were expressed as proportions (%).

[b] Time from call to contact with the patient.

eTable 5. Association Between Prehospital ALS Procedures and Patient Outcomes at 90 Days

	AAM			Epinephrine		
	Patients with outcome, No./total No. (%)			Patients with outcome, No./total No. (%)		
Outcome	Control group	AAM group	OR (95% CI)	Control group	Epinephrine group	OR (95% CI)
CPC ≤2	17/18 135[a] (0.1)	20/18 135[a] (0.1)	1.67 (0.73-3.81)	14/9714[b] (0.1)	7/9714[b] (0.1)	0.60 (0.22-1.65)
CPC ≤3	41/18 135[a] (0.2)	44/18 135[a] (0.2)	1.29 (0.78-2.11)	22/9714[b] (0.2)	25/9714[b] (0.3)	1.13 (0.57-2.27)
Survival	99/18 135[a] (0.5)	110/18 135[a] (0.6)	1.17 (0.85-1.61)	51/9714[b] (0.5)	80/9714[b] (0.8)	1.54 (1.01-2.36)

[a] There were 9079 missing data for outcome at 90 days in the risk-set matched cohort.

[b] There were 5131 missing data for outcome at 90 days in the risk-set matched cohort.

Abbreviations: ALS, advanced life support; AAM, advanced airway management; OR, odds ratio; CPC, Cerebral Performance Category.

eTable 6. Time Spent on CPR Procedures Until ROSC

	Hour (min)			
	Analyzed patients (n = 35 843)		Patients who were candidates for TOR (n = 12 731)	
	Total time	Time incurred to obtain one patient with CPC ≤2 at 30 days	Total time	Time incurred to obtain one patient with CPC ≤2 at 30 days
Prehospital	20 928[a] (1 255 685)	312[a] (18 742)	7568[d] (454 089)	946[d] (56 761)
In-hospital	14 506[b] (870 348)	217[b] (12 990)	5271[e] (316 266)	659[e] (39 533)
Total	35 434[c] (2 126 033)	529[c] (31 732)	12 839[f] (770 355)	1605[f] (96 294)

[a] There were 5 missing data.

[b] There were 828 missing data.

[c] There was 1 missing data.

[d] There was 1 missing data.

[e] There were 293 missing data.

[f] There was 1 missing data.

Abbreviations: CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; TOR, termination-of-resuscitation; CPC, Cerebral Performance Category.

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