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ORIGINAL ARTICLE

Early versus late advanced airway management for adult patients with out-of-hospital cardiac arrest: A time-dependent propensity score–matched analysis

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Abstract

Objective: The objective was to investigate whether early advanced airway management during the entire resuscitation period is associated with favorable neurological outcomes and survival in patients with out-of-hospital cardiac arrest (OHCA).

Methods: We performed a retrospective cohort study of patients with OHCA aged ≥18 years enrolled in OHCA registry in Japan who received advanced airway management during cardiac arrest between June 2014 and December 2020. To address resuscitation time bias, we performed risk set matching analyses in which patients who did and did not receive advanced airway management were matched at the same time point (min) using the time-dependent propensity score; further, we compared early (≤10 min) and late (>10 min) advanced airway management. The primary and secondary outcome measures were favorable neurological outcomes using Cerebral Performance Category scores and survival at 1 month after cardiac arrest.

Results: Of the 41,101 eligible patients, 21,446 patients received early advanced airway management. Thus, risk set matching was performed with a total of 42,866 patients. In the main analysis, early advanced airway management was significantly associated with favorable neurological outcomes (risk ratio [RR] 0.997, 95% confidence interval [CI] 0.995–0.999) and survival (RR 0.990, 95% CI 0.986–0.994) at 1 month after cardiac arrest. In the sensitivity analysis with early advanced airway management defined as ≤5 min and ≤20 min, the results were comparable.

Conclusions: Although early advanced airway management was statistically significant for improved neurological outcomes and survival at 1 month after cardiac arrest, the RR was very close to 1, indicating that the timing of advanced airway management has minimal impact on clinical outcomes, and decisions should be made based on the individual needs of the patient.

KEYWORDS
airway management, cardiopulmonary resuscitation, heart arrest, intubation

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INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a major public health problem owing to its high mortality rate and serious sequelae.[1–3] Improving the neurologic survival of patients with OHCA is an important issue. Advanced airway management, encompassing tracheal intubation, placement of a supraglottic device, and the use of esophageal obturators, represents an important resuscitation technique that provides a more reliable airway than bag–mask ventilation.[4–6] Several studies in the prehospital setting have reported that early advanced airway management improves the probability of return of spontaneous circulation (ROSC) and neurological outcomes.[7–9]

Resuscitation time bias, also known as immortal time bias, is a form of systematic error indicates during cardiopulmonary resuscitation (CPR), the group with a longer CPR duration is more likely to receive interventions such as advanced airway management.[10,11] If resuscitation time bias is not addressed, interventions will be biased toward poor outcomes, as a longer duration of arrest is associated with poorer outcomes. Therefore, resuscitation time bias may bias patients with late advanced airway management toward poorer outcomes. Resuscitation time bias has been recently shown to be effectively addressed by risk set matching with time-dependent propensity scores.[12–16] While there have been studies using rigorous methods for in-hospital cardiac arrest,[12,13] research on advanced airway management in OHCA attempting to address resuscitation time bias is limited. Moreover, these studies have only examined the presence or absence of advanced airway management in the prehospital setting,[14] or they involved relatively small sample sizes.[16] Furthermore, evidence for the impact of early advanced airway management on OHCA outcomes throughout the prehospital and in-hospital resuscitation periods is lacking, and a systematic review by the International Liaison Committee on Resuscitation's Advanced Life Support Task Force was unable to identify the optimal timing of advanced airway management.[17]

Determining the effectiveness of early advanced airway management on survival and neurological intact survival is critical for appropriate application of resuscitation strategies in patients with OHCA. The Japanese Association for Acute Medicine (JAAM) OHCA Registry, a large data set with comprehensive resuscitation time information including pre- and in-hospital information, has the potential to fill the current knowledge gap.

To examine whether early advanced airway management in the total period of resuscitation is associated with favorable neurological outcomes and survival in adult patients with OHCA, we compared early and late advanced airway management using risk set matching with time-dependent propensity scores and multivariate analysis to address resuscitation time bias and prehospital and in-hospital confounders.

METHODS

Study design and setting

We conducted a retrospective examination of data for June 2014 to December 2020 sourced from the JAAM-OHCA Registry, a nationwide, multicenter initiative in Japan that prospectively gathers both prehospital and in-hospital data of patients experiencing OHCA. The registry encompasses all OHCA patients transported to affiliated medical centers.

Ethical approval for the registry protocol was granted by the institutional review board of each participating institution. Given the observational nature of the study and the assurance of data anonymity, the need for patient-specific informed consent was waived. The study report was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18]

Management of OHCA in Japanese emergency medical services

In Japan, local governments manage emergency medical services (EMS) systems under the oversight of the Japanese Fire and Disaster Management Agency.[19,20] The Japan Resuscitation Council provides CPR training guidelines for all EMS staff, aligning with the International Liaison Committee on Resuscitation's statement.[21,22] The EMS team is composed of three members, with at least one being a highly trained emergency medical technician (EMT) skilled in prehospital care. The composition of EMS teams, specifically the number of EMTs in each team, varies across regions based on the availability of certified EMTs. Emergency personnel other than EMTs are trained in first aid. All EMTs have the ability to utilize upper airway tools such as laryngeal tubes (esophageal obturator) and laryngeal mask airways. However, only EMTs with specific training and certification can perform tracheal intubations, which is performed only when the patient has experienced cardiac arrest. In Japan, there are 42,495 qualified EMTs, with 29,389 working as EMTs (as of April 1, 2023).[23] Of the qualified EMTs, 15,977 are certified to perform tracheal intubation. Certification as an EMT in the performance of tracheal intubation requires completion of a program approved by a regional medical control committee. This program consists of 62 sessions, with each session lasting 50 min. In addition, the practical aspect of the training requires the completion of more than 30 successful intubations in the operating room under the supervision of experienced attending physicians. Legally, Japanese EMS personnel cannot cease on-site resuscitation; every OHCA patient is taken to a medical facility unless resuscitation is unquestionably futile and has not commenced. In the context of EMS in Japan, a patient is considered nontransportable if he or she meets all of the following six criteria: (1) a level of consciousness of Japan Coma Scale 300; (2) complete absence of respiration; (3) no palpable pulse in the carotid arteries; (4) dilated pupils and no light reflex; (5) coldness and no temperature sensation; and (6) rigor mortis in the extremities or livor mortis.

Study population

OHCA patients aged ≥ 18 years who were part of the JAAM-OHCA Registry and received advanced airway management during cardiac arrest were included in this study. Exclusion criteria included cases where time to advanced airway management was missing, 0 min, ≥60 min, or inconsistent (i.e., negative values) and cases where time-dependent variables or outcome data were missing.

Measurements and definitions

The JAAM-OHCA Registry, which integrates prehospital and in-hospital data, served as the source of the study data. Prehospital data were collected by the EMS personnel based on the Utstein-style template.[19] In-hospital data, as well as evaluations of the etiology of cardiac arrest, were collected by the medical staff. The physician at the hospital to which the patient was transported determined the etiology of the cardiac arrest based on the patient's history, clinical course, and examination findings. The JAAM-OHCA Registry Committee combined these data.[20]

The exposure was early advanced airway management versus late advanced airway management during cardiac arrest. Advanced airway management was defined as tracheal intubation, placement of a supraglottic device, or the use of an esophageal obturator. Early advanced airway management was defined as placement of an advanced airway within 10 min or less following the initial contact between the patient and EMS. Based on a previous study[8] and the feasibility of advanced airway management in adult patients with OHCA, we determined a cutoff time of 10 min. To ensure that the 10-min criterion was appropriate, we also examined at the median and distribution of the time to advanced airway management prior to the analysis. In cases where cardiac arrest was directly observed by the EMS staff, the time intervals for advanced airway placement, adrenaline administration, and shock delivery were calculated from the moment of witnessing the cardiac event rather than from the initial EMS–patient contact.

The primary outcome was favorable neurological outcome 1 month after cardiac arrest, and the secondary outcome was survival 1 month after cardiac arrest. A favorable neurological outcome was defined as a Cerebral Performance Category (CPC) score of 1 or 2.[24] The CPC score encompasses five distinct outcomes: (1) good cerebral recovery, (2) moderate cerebral disability, (3) severe cerebral disability, (4) coma or vegetative state, and (5) death or brain death.

Weeks were divided into weekdays and weekend. The times of emergency calls were categorized as 7:00–14:59 h, 15:00–22:59 h, and 23:00–6:59 h.[25] Witness status was categorized as none, EMS personnel, and others. Bystander CPR was categorized as present, absent, and present including rescue breathing. The initially monitored cardiac rhythms were categorized as ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, asystole, and others. The causes of cardiac arrest were classified as cardiogenic, respiratory, asphyxiation, traumatic, other intrinsic factors, and other extrinsic factors. Prehospital advanced airway management was classified as laryngeal masks, esophageal obturators, and endotracheal tubes.

Data analysis

Descriptive statistics were calculated for all the relevant variables. Continuous data were presented as median and interquartile range (IQR), whereas categorical variables were presented as counts and percentages. Standardized differences between the two groups in the initial cohort indicated differences in baseline characteristics.

Risk set matching using a time-dependent propensity score analysis was performed to examine the relationship between early advanced airway management and outcomes. A Fine–Gray regression model, including time-dependent covariates, time-independent covariates, and competing risk events, was used to calculate a propensity score that represented an estimated risk score predicting the likelihood of early advanced airway management. Similar methods have been used in previous cardiac arrest treatment trials and have been shown to be effective in reducing resuscitation time bias.[14–16,26] Because this study aimed to evaluate the effectiveness of early advanced airway management in cardiac arrest, this Fine–Gray regression model considered ROSC before advanced airway management as a competing risk and informative censoring. The time-dependent and time-independent covariates used to calculate time-dependent propensity scores are listed in Table 1. The time-dependent covariates included the presence or absence of adrenaline administration, time from EMS–patient contact to adrenaline administration, presence or absence of shock delivery, and time from EMS–patient contact to shock delivery. As in-hospital treatments (percutaneous coronary intervention, extracorporeal membrane oxygenation, intra-aortic balloon pump, and target temperature management) could not be included in the propensity score, they were adjusted using multivariate analysis after matching. These covariates were selected based on their importance and medical relevance to the exposure and outcomes from the guidelines and previous studies.[14–16,27–29]

Each patient who underwent advanced airway management at any time between 1 and 59 min after EMS contact was matched by caliper matching to a patient undergoing resuscitation who was at risk for advanced airway management and had not yet received an advanced airway management during the same time period (risk set matching). The caliper width for the

TABLE 1 Demographics and characteristics of original cohort.

	Early advanced airway management (*n* = 21,446)	Late advanced airway management (*n* = 19,655)	Standardized difference
Age (years)	77 (66–85)	74 (61–84)	−0.187
Male	12,730 (59.4)	12,149 (61.8)	0.05
Day of week			0.011
Weekday	14,366 (67.0)	13,064 (66.5)	
Weekend	7080 (33.0)	6591 (33.5)	
Time of emergency call			0.038
7:00–14:59	8988 (41.9)	7947 (40.4)	
15:00–22:59	8072 (37.6)	7417 (37.7)	
23:00–6:59	4386 (20.5)	4291 (21.8)	
Witness status			0.072
None	11,887 (55.4)	10,190 (51.8)	
EMS personnel	1704 (7.9)	1686 (8.6)	
Others	7855 (36.6)	7779 (39.6)	
Bystander CPR			0.097
Presence	8496 (39.6)	7435 (37.8)	
Absence	11,219 (52.3)	11,034 (56.1)	
Presence including rescue breathing	1731 (8.1)	1186 (6.0)	
Initial monitored cardiac rhythm			0.073
VF	1585 (7.4)	1765 (9.0)	
Pulseless VT	26 (0.1)	44 (0.2)	
PEA	5622 (26.2)	5306 (27.0)	
Asystole	13,457 (62.7)	11,797 (60.0)	
Other	756 (3.5)	743 (3.8)	
Cause of cardiac arrest			0.252
Cardiogenic	11,789 (55.0)	10,160 (51.7)	
Respiratory	1263 (5.9)	963 (4.9)	
Asphyxiation	1323 (6.2)	1331 (6.8)	
Traumatic	743 (3.5)	1739 (8.8)	
Other intrinsic	4626 (21.6)	3523 (17.9)	
Other extrinsic	1702 (7.9)	1940 (9.9)	
Time from emergency call to start of CPR (min)	9 (7–11)	9 (7–12)	0.066
Time from the patient contact by EMS to arrival at the hospital (min)	24 (20–30)	24 (18–31)	−0.01
Adrenaline administration before advanced airway management	649 (3.0)	1293 (6.6)	0.167
Time from the patient contact by EMS to adrenaline administration before advanced airway management (min)	6 (5–7)	8 (7–9)	1.04
Shock delivery before advanced airway management	1721 (8.0)	2181 (11.1)	0.105
Time from the patient contact by EMS to shock delivery before advanced airway management (min)	2 (1–3)	2 (1–3)	0.232
Prehospital advanced airway management	19,862 (92.6)	7088 (36.0)	1.46
Prehospital advanced airway management type			1.65
Laryngeal mask	2288 (10.7)	273 (1.4)	
Esophageal obturator	14,835 (69.2)	4959 (25.2)	
Endotracheal tube	3458 (16.1)	2016 (10.2)	
Physician during emergency transport	1925 (9.0)	1409 (7.2)	0.066
Prehospital advanced life support by physician	2375 (11.1)	2202 (11.2)	0.004

TABLE 1 (Continued)

	Early advanced airway management (*n* = 21,446)	Late advanced airway management (*n* = 19,655)	Standardized difference
In-hospital variables			
Percutaneous coronary intervention	625 (2.9)	623 (3.2)	0.015
Extracorporeal membrane oxygenation	959 (4.5)	907 (4.6)	0.008
Intra-aortic balloon pump	729 (3.4)	696 (3.5)	0.015
Target temperature management	1226 (5.7)	1268 (6.5)	0.031

Note: Data are reported as median (IQR) or *n* (%).

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medicine service; IQR, interquartile range; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

caliper matching was set to 0.2. When configuring pairs through nearest neighbor matching, a specific caliper is set; if the width is less than or equal to the value calculated based on the caliper, the pair is configured. Narrowing the caliper width will enhance the alignment of characteristics between both groups for comparison but decreases the number of matched patients, leading to a loss of patients from the matching cohort. In the present study, the caliper width was determined based on recommendations from statisticians in previous literature and studies that employed similar methods.[14–16,30,31] Since matching should not be based on future events, patients who subsequently received advanced airway management were also considered to be at risk for advanced airway management. Although the matched controls were independent within the risk strata at each time point (min), several patients in the control group overlapped within the matched cohort across all combined strata. This issue was addressed by adjusting the frequency weighting to indicate the number of duplicates when analyzing the results. Risk set matching assumes that matched pairs are correlated at the same time point. Therefore, a generalized estimating equation (GEE) was used to analyze the results and estimate the risk ratio (RR) while accounting for intrapair correlation.

To assess the effectiveness of the risk set matching, standardized differences were calculated for each covariate. A well-matched balance was defined as a balance with an absolute value of <0.20 and the standardized difference.[30] RRs between early and late advanced airway management outcomes were estimated using GEE with a modified Poisson regression with robust variance. The correlation matrix was considered as "exchangeable." All tests were two-tailed and considered statistically significant if the 95% confidence interval (CI) did not cross 1. Data were analyzed using the R software version 4.1.3 (www.r-project.org).

Sensitivity analysis

To assess whether changes in cutoff values alter the effect of early advanced airway management, we performed analyses defining early advanced airway management as ≤5 min and ≤20 min using the same methodology as the main analysis. These cutoffs were established based on a previous study[7] and the quartile range of the time to advanced airway management. To evaluate only patients who require advanced airway management before arriving to the hospital, we performed analyses that included only patients who underwent prehospital advanced airway management.

Subgroup analysis

Subgroup analyses of patients under 60 years of age and witnessed cases were performed because of the potential benefits of analyzing the age group with a better chance of improving outcomes and witnessed cases, in which the time since cardiac arrest is considered to be more consistent.[7,8] In addition, because current international guidelines advocate the use of two different algorithms depending on the initial rhythm monitored, with separate suggestions for the timing of advanced airway management, we performed a subgroup analysis of shockable and nonshockable rhythm cases.[14] In addition, given the uncertainty surrounding optimal airway management practices in OHCA—in terms of both the preferred device and the ideal timing for device placement—we performed subgroup analyses for laryngeal mask, esophageal obturator, and tracheal intubation.

RESULTS

Patients

A total of 60,348 patients with cardiac arrest were enrolled in the JAAM-OHCA Registry (Figure 1). Among them, 59,107 patients were aged ≥18 years. A total of 15,167 exclusions were made based on the time to advanced airway management, with 7796 cases not receiving advanced airway management and 5933 having missing data for the time to advanced airway management. After cases that met other exclusion criteria were excluded, 41,101 cases were included in the final analysis.

Patient characteristics

Among the 41,101 patients, 21,446 (52.2%) underwent early advanced airway management and 19,655 (47.8%) underwent late advanced airway management (Table 1). In comparison with late advanced airway management, early advanced airway management was less likely to be used in cases with traumatic causes (early advanced airway management 3.5%, late advanced airway management 8.8%).

To address the concern that patients with missing advanced airway management time might bias the data, information from such patients is presented in Table S1. Importantly, there were no noteworthy characteristics that would introduce substantial bias in the excluded patient groups with missing advanced airway management time.

Main results

The demographics and traits of the time-dependent propensity score–matched cohort are presented in Table 2. After risk set matching with a time-dependent propensity score, 42,866 patients were matched. With this group, 27,518 patients were matched uniquely, while 10,475 were matched multiple times. Except for the time from EMS contact to the injection of adrenaline before advanced airway management, for which only some patients were included, the standardized difference was 0.20 for all variables, demonstrating good balance after matching.

The outcomes of the original and time-dependent propensity score–matched cohorts are shown in Table 3. Among the eligible patients, 1064 (2.6%) had a favorable neurological outcome and 2524 (6.1%) survived at 1 month after cardiac arrest.

The outcomes after risk set matching for the main analysis, in which early advanced airway management was defined as ≤10 min, and for the sensitivity analysis, in which early advanced airway management was defined as ≤5 min and ≤20 min, are shown in Table 3. In the main analysis, early advanced airway management was significantly associated with favorable neurological outcomes (RR 0.997 [95% CI 0.995–0.999]) and survival (RR 0.990 [95% CI 0.986–0.994]) at 1 month after cardiac arrest. In the sensitivity analysis with early advanced airway management defined as ≤5 min, early advanced airway management was significantly associated with favorable neurological outcome (RR 0.995 [95% CI 0.991–0.999]) and survival (RR 0.991 [95% CI 0.985–0.998]) at 1 month after cardiac arrest. In the sensitivity analysis with early advanced airway management defined as ≤20 min, no significant differences were observed for favorable neurological outcomes at 1 month after cardiac arrest (RR 0.999 [95% CI 0.997–1.001]), but early advanced airway management was significantly associated with survival at 1 month after cardiac arrest (RR 0.994 [95% CI 0.991–0.997]).

Sensitivity analysis

In the sensitivity analysis, which only included patients with prehospital advanced airway management, no significant difference was observed between early advanced airway management and favorable neurological outcome at 1 month after cardiac arrest in all analyses. This includes scenarios defined as early advanced airway management ≤10 min (RR 0.998 [95% CI 0.995–1.001]), 5 min (RR 0.999 [95% CI 0.997–1.001]), or 20 min (RR 0.999 [95% CI 0.997–1.001]; see Table S2). Moreover, early advanced airway management was significantly associated with survival at 1 month after cardiac arrest in all analyses. This correlation remained consistent whether early advanced airway management was defined as ≤10 min (RR 0.990 [95% CI 0.985–0.995]), 5 min (RR 0.983 [95% CI 0.975–0.990]), or 20 min (RR 0.994 [95% CI 0.990–0.998]).

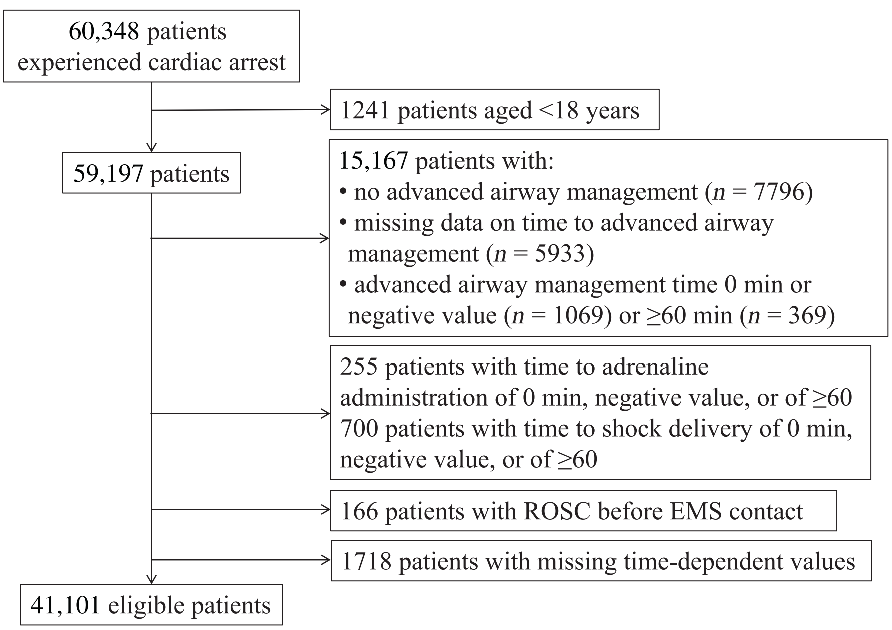

FIGURE 1 Study flowchart. EMS, emergency medical service; ROSC, return of spontaneous circulation.

TABLE 2 Demographics and characteristics of the time-dependent propensity score–matched cohort.

	Early advanced airway management (*n* = 21,433)	Late advanced airway management (*n* = 21,433)	Standardized difference
Age (years)	77 (66–85)	77 (66–85)	0.006
Male	12,722 (59.4)	12,683 (59.2)	0.004
Day of week			0.004
Weekday	14,358 (67.0)	14,400 (67.2)	
Weekend	7075 (33.0)	7033 (32.8)	
Time of emergency call			0.007
7:00–14:59	8981 (41.9)	8948 (41.9)	
15:00–22:59	8067 (37.6)	8067 (37.6)	
23:00–6:59	4385 (20.5)	4449 (20.8)	
Witness status			0.013
None	11,886 (55.5)	11,878 (55.4)	
EMS personnel	1694 (7.9)	1767 (8.2)	
Others	7853 (36.6)	7788 (36.3)	
Bystander CPR			0.008
Presence	8494 (39.6)	8483 (39.6)	
Absence	11,209 (52.3)	11,175 (52.1)	
Presence including rescue breathing	1730 (8.1)	1767 (8.2)	
Initial monitored cardiac rhythm			0.01
VF	1584 (7.4)	1546 (7.2)	
Pulseless VT	26 (0.1)	23 (0.1)	
PEA	5621 (26.2)	5671 (26.5)	
Asystole	13,455 (62.8)	13,462 (62.8)	
Other	747 (3.5)	732 (3.4)	
Cause of cardiac arrest			0.013
Cardiogenic	11,786 (55.0)	11,872 (55.4)	
Respiratory	1262 (5.9)	1280 (6.0)	
Asphyxiation	1323 (6.2)	1341 (6.3)	
Traumatic	743 (3.5)	716 (3.3)	
Other intrinsic	4618 (21.5)	4568 (21.3)	
Other extrinsic	1701 (7.9)	1656 (7.7)	
Time from emergency call to start of CPR (min)	9 (7–11)	9 (7–11)	0.011
Time from the patient contact by EMS to arrival at the hospital (min)	24 (20–30)	25 (20–30)	0.006
Adrenaline administration before advanced airway management	649 (3.0)	565 (2.6)	0.024
Time from the patient contact by EMS to adrenaline administration before advanced airway management (min)[a]	6 (5–7)	8 (6–9)	0.695
Shock delivery before advanced airway management	1721 (8.0)	1696 (7.9)	0.004
Time from the patient contact by EMS to shock delivery before advanced airway management (min)[a]	2 (1–3)	2 (1–3)	0.08
Prehospital advanced airway management	19,849 (92.6)	19,849 (92.6)	0
Prehospital advanced airway management type			0.011
Laryngeal mask	2275 (10.6)	2212 (10.3)	
Esophageal obturator	14,835 (69.2)	14,876 (69.4)	

(Continues)

TABLE 2 (Continued)

	Early advanced airway management (*n* = 21,433)	Late advanced airway management (*n* = 21,433)	Standardized difference
Endotracheal tube	3458 (16.1)	3492 (16.3)	
Physician during emergency transport	1918 (8.9)	1977 (9.2)	0.01
Prehospital advanced life support by physician	2369 (11.1)	2420 (11.3)	0.008
In-hospital variables			
Percutaneous coronary intervention	624 (2.9)	564 (2.6)	0.017
Extracorporeal membrane oxygenation	958 (4.5)	922 (4.3)	0.008
Intra-aortic balloon pump	728 (3.4)	703 (3.3)	0.006
Target temperature management	1226 (5.7)	1138 (5.3)	0.018

Note: Data are reported as median (IQR) or *n* (%).

Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Because the variable is only for patients who received that treatment, matching does not necessarily improve the balance.

TABLE 3 Outcomes between early and late advanced airway management in risk-set matching using time-dependent propensity score.

	No. of patients with outcome		
	Early advanced airway management	Late advanced airway management	RR (95% CI)
Original cohort	*n* = 21,446	*n* = 19,655	
Favorable neurological outcome at 1 month after cardiac arrest	402 (1.9)	662 (3.4)	NA
Survival at 1 month after cardiac arrest	1262 (6.4)	1262 (5.9)	NA
Time-dependent propensity score-matched cohort			
Early advanced airway management defined as ≤10 min	*n* = 21,433	*n* = 21,433	
Favorable neurological outcome at 1 month after cardiac arrest	402 (1.9)	327 (1.5)	0.997 (0.995–0.999)
Survival at 1 month after cardiac arrest	1260 (5.9)	1014 (4.7)	0.990 (0.986–0.994)
Sensitivity analysis			
Early advanced airway management defined as ≤5 min	*n* = 8716	*n* = 8716	
Favorable neurological outcome at 1 month after cardiac arrest	188 (2.2)	139 (1.6)	0.995 (0.991–0.999)
Survival at 1 month after cardiac arrest	562 (6.4)	463 (5.3)	0.991 (0.985–0.998)
Early advanced airway management defined as ≤20 min	*n* = 31,243	*n* = 31,243	
Favorable neurological outcome at 1 month after cardiac arrest	596 (1.9)	578 (1.9)	0.999 (0.997–1.001)
Survival at 1 month after cardiac arrest	1747 (5.6)	1497 (4.8)	0.994 (0.991–0.997)

Note: Data are reported as *n* (%).

Abbreviation: RR, risk ratio.

Subgroup analysis

In the subgroup analyses of patients aged ≤60 years or >60 years, with or without witness, and shockable rhythm or nonshockable rhythm, early advanced airway management was significantly associated with neurological outcomes or survival in some subgroups (Table 4). However, the RR was very close to 1 in all analyses, potentially suggesting less clinical importance.

In a subgroup analysis focusing on different devices for advanced airway management, laryngeal mask, esophageal obturator, and endotracheal intubation had RRs very close to 1 in each analysis for the association with favorable neurological outcome and survival at

1 month after cardiac arrest, with no apparent differences observed across the devices (Table 5).

DISCUSSION

This study reviewed data from the JAAM-OHCA Registry, which includes prehospital and in-hospital data and addressed resuscitation time bias by sequential matching using time-dependent propensity scores to determine whether early advanced airway management in the overall resuscitation time is associated with the outcomes for OHCA patients. In analyses where early advanced airway management was defined as ≤5 and 10 min, it showed a significantly association with favorable neurological outcome and survival at 1 month. When early advanced airway management was defined as ≤20 min, it was significantly associated with survival at 1 month, but not with favorable neurological outcome. However, the RR was very close to 1 in all analysis, indicating that timing of advanced airway management has little effect on clinical outcomes and should be tailored to the individual needs of the patient.

In this study, early advanced airway management showed little clinical association with the outcomes. In two observational studies on adult OHCA patients who received prehospital advanced airway management in Japan, early advanced airway management was found to be associated with favorable neurological outcomes.[7,8] A secondary analysis of the Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance Valve and Early versus Delayed (ROC PRIMED) study conducted in the United States and Canada showed that early advanced airway management was associated with an increased probability of

TABLE 4 Outcomes between early and late advanced airway management in risk-set matching using time-dependent propensity score in subgroup analysis.

	18–60 years of age	>60 years of age
Early advanced airway management defined as ≤10 min	$n=7441$	$n=35{,}425$
Favorable neurological outcome at 1 month after cardiac arrest	0.995 (0.986–1.004)	0.998 (0.995–1.000)
Survival at 1 month after cardiac arrest	0.989 (0.978–1.001)	0.991 (0.986–0.995)
Early advanced airway management defined as ≤5 min	$n=2891$	$n=14{,}541$
Favorable neurological outcome at 1 month after cardiac arrest	0.998 (0.983–1.013)	0.995 (0.991–0.999)
Survival at 1 month after cardiac arrest	0.997 (0.978–1.018)	0.990 (0.983–0.998)
Early advanced airway management defined as ≤20 min	$n=11{,}655$	$n=50{,}831$
Favorable neurological outcome at 1 month after cardiac arrest	1.000 (0.992–1.007)	0.999 (0.998–1.001)
Survival at 1 month after cardiac arrest	0.998 (0.988–1.008)	0.994 (0.990–0.997)
	Witness	No witness
Early advanced airway management defined as ≤10 min	$n=19{,}102$	$n=23{,}764$
Favorable neurological outcome at 1 month after cardiac arrest	0.994 (0.989–0.999)	0.999 (0.997–1.001)
Survival at 1 month after cardiac arrest	0.980 (0.971–0.999)	0.998 (0.994–1.001)
Early advanced airway management defined as ≤5 min	$n=7816$	$n=9616$
Favorable neurological outcome at 1 month after cardiac arrest	0.993 (0.985–1.002)	0.997 (0.994–1.000)
Survival at 1 month after cardiac arrest	0.981 (0.968–0.995)	0.998 (0.993–1.004)
Early advanced airway management defined as ≤20 min	$n=28{,}472$	$n=34{,}014$
Favorable neurological outcome at 1 month after cardiac arrest	0.997 (0.994–1.001)	1.001 (0.999–1.002)
Survival at 1 month after cardiac arrest	0.985 (0.979–0.992)	1.001 (0.998–1.004)
	Shockable rhythm	Non-shockable rhythm
Early advanced airway management defined as ≤10 min	$n=3178$	$n=39{,}688$
Favorable neurological outcome at 1 month after cardiac arrest	0.984 (0.957–1.012)	0.998 (0.996–1.000)
Survival at 1 month after cardiac arrest	0.969 (0.931–1.008)	0.992 (0.988–0.995)
Early advanced airway management defined as ≤5 min	$n=1285$	$n=16{,}147$
Favorable neurological outcome at 1 month after cardiac arrest	0.956 (0.914–0.999)	0.998 (0.995–1.001)
Survival at 1 month after cardiac arrest	0.978 (0.913–1.048)	0.992 (0.986–0.998)
Early advanced airway management defined as ≤20 min	$n=4495$	$n=57{,}991$
Favorable neurological outcome at 1 month after cardiac arrest	0.990 (0.966–1.014)	1.000 (0.999–1.001)
Survival at 1 month after cardiac arrest	0.983 (0.950–1.016)	0.995 (0.992–0.998)

Note: Data are reported as RR (95% CI).

Abbreviation: RR, risk ratio.

TABLE 5 Outcomes between early and late advanced airway management in risk set matching using time-dependent propensity score in a subgroup analysis of different devices for advanced airway management.

	Laryngeal mask
Early advanced airway management defined as ≤10 min	n = 4487
Favorable neurological outcome at 1 month after cardiac arrest	0.997 (0.989–1.005)
Survival at 1 month after cardiac arrest	0.984 (0.972–0.997)
Early advanced airway management defined as ≤5 min	n = 2561
Favorable neurological outcome at 1 month after cardiac arrest	0.990 (0.981–1.000)
Survival at 1 month after cardiac arrest	0.988 (0.972–1.004)
Early advanced airway management defined as ≤20 min	n = 4872
Favorable neurological outcome at 1 month after cardiac arrest	0.999 (0.991–1.006)
Survival at 1 month after cardiac arrest	0.991 (0.980–1.002)
	Esophageal obturator
Early advanced airway management defined as ≤10 min	n = 29,711
Favorable neurological outcome at 1 month after cardiac arrest	0.996 (0.993–0.998)
Survival at 1 month after cardiac arrest	0.992 (0.993–0.999)
Early advanced airway management defined as ≤5 min	n = 12,276
Favorable neurological outcome at 1 month after cardiac arrest	0.996 (0.991–1.001)
Survival at 1 month after cardiac arrest	0.994 (0.986–1.003)
Early advanced airway management defined as ≤20 min	n = 38,723
Favorable neurological outcome at 1 month after cardiac arrest	0.997 (0.995–0.999)
Survival at 1 month after cardiac arrest	0.993 (0.990–0.997)
	Endotracheal tube
Early advanced airway management defined as ≤10 min	n = 8668
Favorable neurological outcome at 1 month after cardiac arrest	1.001 (0.996–1.008)
Survival at 1 month after cardiac arrest	0.987 (0.977–0.998)
Early advanced airway management defined as ≤5 min	n = 2595
Favorable neurological outcome at 1 month after cardiac arrest	0.998 (0.985–1.011)
Survival at 1 month after cardiac arrest	0.981 (0.960–1.002)
Early advanced airway management defined as ≤20 min	n = 18,891
Favorable neurological outcome at 1 month after cardiac arrest	1.007 (1.002–1.012)
Survival at 1 month after cardiac arrest	1.000 (0.993–1.007)

Note: Data are reported as RR (95% CI).
Abbreviation: RR, risk ratio.

ROSC in adult OHCA patients who were witnessed and received prehospital advanced airway management.[9] Although these studies reported that early advanced airway management was associated with better outcomes, they did not address resuscitation time bias, which may have influenced these results. Patients with a later advanced airway management tended to have longer resuscitation times than those with an earlier advanced airway management. Since longer periods of arrest are associated with worse outcomes, resuscitation time bias may lead to poorer outcomes in patients with late advanced airway management.[10,11] Therefore, resuscitation time bias is an important consideration when examining the effectiveness of treatments such as advanced airway management during resuscitation.

A Japanese observational study of prehospital advanced airway management in 310,620 patients with OHCA that addressed resuscitation time bias using risk set matching with time-dependent propensity scores reported that advanced airway management was associated with better survival in patients with a nonshockable rhythm.[14] However, that study only assessed whether prehospital advanced airway management was performed and did not examine the timing of advanced airway management. A secondary analysis of 2146 patients enrolled in the Pragmatic Airway Resuscitation Trial (PART), a clinical trial comparing the effects of epiglottis tubes and endotracheal intubation on the outcomes after OHCA in adults, used risk set matching with a time-dependent propensity score to compare patients who received advanced airway management within 5, 5–10, 10–15, and 15–20 min of advanced life support arrival to those who did not.[16] The results showed that the timing of an advanced airway placement attempt was not associated with survival to hospital discharge, which is consistent with the results of this study.

This study used a large registry that included both prehospital and in-hospital data to compare early and late advanced airway management in terms of overall resuscitation time. Additionally, we addressed the resuscitation time bias and adjusted for confounding and time-dependent confounding factors by risk set matching using time-dependent propensity score matching. The Fine–Gray model was used to estimate time-dependent propensity scores, and ROSC before advanced airway management was considered a competing risk. Therefore, we rigorously evaluated the effects of advanced airway management during CPR. The results showed that early advanced airway management was significantly associated with survival and favorable neurological outcomes. However, the large sample size was considered the reason for the significant difference, and the effect sizes suggest that early advanced airway management is not clinically associated with improved outcomes. The sensitivity analysis using different cutoff times and the sensitivity analysis focusing solely on cases that received prehospital advanced airway management yielded robust results. The subgroup analysis based on patient characteristics showed no notable significant effect modifiers. Additionally, the subgroup analysis considering the devices used for advanced airway management showed no clear differences among the devices. Prior studies have reported no clear difference in efficacy among these techniques in the prehospital setting.[32,33]

Building on these preliminary findings, our analysis provides an insight into the potential lack of distinct device-specific variations in timing. These results suggest that prioritizing advanced airway placement may not be necessary for all patients with OHCA and that its timing should be based on the individual needs of the patient.

LIMITATIONS

Our study has several limitations. First, although the findings adjusted for many confounding factors, the possibility of unknown or unmeasured confounders could not be ruled out because this was an observational study. Potential confounders not addressed in this study included difficulty in ventilation during CPR, underlying disease, first-pass success, and the number of failed intubations. In addition, confounding by indication, which is important consideration in such studies, could not be completely excluded. Each patient's detailed characteristics and medical history may influence the timing of advanced airway management, which may have also affected the outcomes. To further clarify the causal relationship between early and late airway management and outcomes, randomized controlled trials are needed to address these confounding issues. Second, EMS systems vary from country to country and region to region, which limited the generalizability of our study results. For example, in Japan, guidelines for terminating resuscitation in the scene are strict, often resulting in patients being transported to medical facilities despite limited prospects for successful resuscitation. While this study excluded nonintubated cases and individuals less likely to be resuscitated, it may still affect reported survival rates and neurological outcomes. Third, patients with cardiac arrest constitute a highly heterogeneous population.[34] No apparent effect modification was observed in the subgroup analysis performed in this study (age, with or without a witness, shockable, nonshockable). However, there may be an effect modifier, such as early advanced airway management being more effective in certain patients. Fourth, to mitigate resuscitation time bias, risk group matching was performed using time-dependent propensity scores. This approach precluded the analysis of advanced airway management time as a continuous variable, necessitating the use of a cutoff to compare the two groups. The main analysis was performed with a cutoff of 10 min, and sensitivity analyses were performed with cutoffs of 5 and 20 min. However, it is difficult to determine the optimal value for the cutoffs.

CONCLUSIONS

In this observational study of out-of-hospital cardiac arrest in Japan, although early advanced airway placement was significantly associated with improved neurological outcomes or survival at 1 month after cardiac arrest, the effect size suggested that the timing of advanced airway management has minimal impact on clinical outcomes. Health care professionals should determine the timing of advanced airway management based on individual patient needs. Future randomized control trials are needed to better clarify the effect of early advanced airway placement in out-of-hospital cardiac arrest.

AUTHOR CONTRIBUTIONS

Study concept and design: Shunsuke Amagasa, Masahiro Kashiura, Hideto Yasuda , and Yuki Kishihara. Acquisition of the data: Shunsuke Amagasa. Analysis and interpretation of the data: Shunsuke Amagasa and Shintaro Iwamoto. Drafting of the manuscript: Shunsuke Amagasa. Critical revision of the manuscript for important intellectual content: Shintaro Iwamoto, Masahiro Kashiura, Hideto Yasuda, Yuki Kishihara, Satoko Uematsu, and Takashi Moriya. Statistical expertise: Shintaro Iwamoto. Acquisition of funding: None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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