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Clinical paper

Prehospital advanced airway management for paediatric patients with out-of-hospital cardiac arrest: A nationwide cohort study

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Abstract

Background: Although prehospital advanced airway management (AAM) (i.e., endotracheal intubation [ETI] and insertion of supraglottic airways [SGA]) has been performed for paediatric out-of-hospital cardiac arrest (OHCA), the effect of AAM has not been fully studied. We evaluated the association between prehospital AAM for paediatric OHCA and patient outcomes.

Methods: We conducted an observational cohort study, using the All-Japan Utstein Registry between 2014 and 2016. We included paediatric patients (age <18 years) with OHCA. We calculated time-dependent propensity score at each minute after initiation of cardiopulmonary resuscitation by EMS providers, using a Fine-Gray regression model. We sequentially matched patients who received AAM during cardiac arrest to patients at risk of receiving AAM within the same minute (risk-set matching). The primary outcome was 1-month survival. Secondary outcome was 1-month survival with favourable functional status, defined as Cerebral Performance Category score of 1 or 2.

Results: We analysed 3801 paediatric patients with OHCA. 481 patients (12.7%) received AAM and 3320 (87.3%) did not. Among the 3801 analysed patients, 912 patients underwent risk-set matching. In the matched cohort, AAM was not associated with 1-month survival (AAM: 52/456 [11.4%] vs. no AAM: 44/456 [9.6%]; risk ratio [RR], 1.15 [95% CI, 0.76–1.73]; risk difference [RD], 1.5% [−3.0 to 6.1%]) or favourable functional status (AAM: 9/456 [2.0%] vs. no AAM: 10/456 [2.2%]; RR, 0.69 [95% CI, 0.26–1.79]; RD, −0.8% [−2.9 to 1.3%]).

Conclusion: Among paediatric patients with OHCA, we found that prehospital AAM was not associated with 1-month survival or favourable functional status.

Keywords: Out-of-hospital cardiac arrest, Paediatrics, Advanced airway management, Time-dependent propensity score analysis, Risk-set matching

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Introduction

Paediatric out-of-hospital cardiac arrest (OHCA) is a major public health problem worldwide, annually affecting more than 7000 children in the United States and 1700 in Japan with high mortality.[1,2] Public health burden of paediatric OHCA remains high because of the greater number of lost years of productivity per individual.[3] Although recent studies showed improving secular trends in patient outcomes after adult OHCA,[4–8] survival among paediatric OHCA has not significantly changed,[9,10] suggesting that paediatric OHCA care may need further improvement.

Advanced airway management (AAM) such as endotracheal intubation (ETI) and insertion of supraglottic airway (SGA) has been performed for paediatric OHCA in the prehospital setting.[9] However, evidence to support the effectiveness of prehospital AAM for paediatric OHCA is limited, with conflicting study results.[11–14] One major limitation of prior studies is "resuscitation time bias" (i.e., patients undergoing longer resuscitation for cardiac arrest tend to have intra-arrest interventions [e.g., AAM]).[15] Since longer resuscitation for cardiac arrest is associated with worse outcome,[16,17] the results are biased toward a harmful effect of the intra-arrest interventions unless the timing of the interventions is accounted for.[15]

To address resuscitation time bias and time-varying confounders, time-dependent propensity score and risk-set matching have been used recently for airway research in cardiac arrest.[18–20] However, there are no prior studies that assessed the effect of prehospital AAM for paediatric OHCA using this methodology. We therefore evaluated the association between prehospital AAM and patient outcomes after paediatric OHCA, using time-dependent propensity score and risk-set matching.

Methods

Study design and setting

We conducted a secondary analysis of All-Japan Utstein Registry, a prospective, nationwide, population-based OHCA registry.[7,8,14,19] Cardiac arrest was defined as lack of cardiac mechanical activity confirmed by lack of clinical evidence of circulation.[21–23] In Japan, municipal governments provide almost uniform emergency medical services (EMS) system through fire departments that include dispatch centres.[7,8,14,19] Ambulances are allocated to fire departments and dispatched from the closest fire department.[7,8,14,19] Each ambulance crew consists of 3 EMS providers, including at least 1 emergency life-saving technician (ELST) who has completed extensive training in prehospital care.[7,8,14,19] ELSTs are permitted to perform insertion of SGA for patients with OHCA under on-line medical direction.[19] Since 2004, specially trained and certified ELSTs have been permitted to perform ETI under on-line medical direction after completion of additional training as described in the Supplemental Methods.[19] Therefore, while standard ELSTs can insert only SGA, specially trained, certified ELSTs can perform ETI and insert SGA.[19] EMS providers are not legally permitted to terminate resuscitation in the field.[7,8,14,19] Additional details of study setting are provided in the Supplemental Methods.

Study participants

This study included paediatric patients with traumatic and non-traumatic OHCA (age <18 years) on whom EMS attempted resuscitation from January 2014 through December 2016 (the most recent publicly available data as of May 2019, the time of the analysis) with subsequent transport to hospitals. We defined attempted resuscitation as external shock delivery (by laypersons or EMS providers) or chest compression by EMS providers.[21–23]

We excluded (1) EMS-witnessed arrest; (2) OHCA without ELST involvement; (3) OHCA with unknown initial rhythm; (4) OHCA with unknown or negative values in resuscitation interval variables (e.g., interval between initiation of cardiopulmonary resuscitation [CPR] by EMS providers and successful placement of advanced airway device [interval between EMS CPR and AAM], interval between initiation of EMS CPR and first shock delivery by EMS providers [only for those with shockable rhythm], interval between initiation of EMS CPR and epinephrine administration by EMS providers [only for those with epinephrine administration], interval between initiation of EMS CPR and prehospital ROSC [only for those who had prehospital ROSC], interval between emergency call and initiation of EMS CPR, and interval between initiation of EMS CPR and hospital arrival); and (5) OHCA with interval between emergency call to initiation of EMS CPR ≥30 min.[19] We excluded EMS-witnessed arrest because of collinearity between EMS-witnessed status and layperson interventions (layperson CPR and public access automated external defibrillator [AED] shock delivery); i.e., EMS-witness arrest perfectly predicts absence of layperson interventions. We excluded OHCA without ELST involvement because those had no risk of being exposed to AAM.

Outcomes

The primary outcome was 1-month survival. Secondary outcome was 1-month survival with favourable functional status, defined as a Cerebral Performance Category (CPC) score of 1 or 2.[21–23] Functional outcome was determined by the physician responsible for the care of the patient at a follow-up interview at 1 month after successful resuscitation using the CPC scale.[19] Further details of data collection and quality control of the registry are provided in the Supplemental Methods. We used CPC because Paediatric CPC was not available.

Statistical analyses

We characterized the study population with descriptive statistics. We presented continuous variables as medians with interquartile ranges (IQRs) and categorical variables as counts with proportions. We performed Wilcoxon rank sum test for continuous variables and chi-squared test for categorical variables to examine differences in baseline patient characteristics.

The main exposure was successful AAM placement by EMS providers during cardiac arrest. To evaluate the association between successful AAM placement and outcomes, we performed time-dependent propensity score and risk-set matching analysis, accounting for the timing of AAM and adjusting for potential confounders. Similar methodology was previously used to evaluate the effectiveness of airway management for cardiac arrest.[18–20] We calculated propensity scores as the estimated risk scores which predict probability of receiving successful AAM placement using a Fine-Gray regression model with time-dependent covariates, time-independent covariates, and competing risk events.[19,24] In the regression model, we included prehospital ROSC before AAM as a competing risk because EMS providers are not allowed to perform AAM after ROSC in Japan and prehospital ROSC is an informative

Table 1 – Characteristics of the study population.

	No AAM	AAM			P values for AAM vs. no AAM
	n = 3320	All AAM n = 481	ETI n = 63	SGA n = 418	
Patient demographics					
Age group, n (%)					<0.001
Infants (<1 y)	1445 (43.5)	75 (15.6)	2 (3.2)	73 (17.5)	
Children (1 y–12 y)	1116 (33.6)	123 (25.6)	9 (14.3)	114 (27.3)	
Adolescents (>12 y)	759 (22.9)	283 (58.8)	52 (82.5)	231 (55.3)	
Sex, n (%)					0.007
Male	1978 (59.6)	318 (66.1)	39 (61.9)	279 (66.7)	
Arrest characteristics					
Year of arrest, n (%)					0.064
2014	1110 (33.4)	177 (36.8)	22 (34.9)	155 (37.1)	
2015	1102 (33.2)	169 (35.1)	23 (36.5)	146 (34.9)	
2016	1108 (33.4)	135 (28.1)	18 (28.6)	117 (28.0)	
Day of arrest, n (%)					0.95
Weekday (Monday to Friday)	2854 (86.0)	413 (85.9)	53 (84.1)	360 (86.1)	
Weekend (Saturday and Sunday)	466 (14.0)	68 (14.1)	10 (15.9)	58 (13.9)	
Time of arrest, n (%)					0.435
Daytime (9:00–16:59)	1028 (31.0)	158 (32.8)	21 (33.3)	137 (32.8)	
Night time (17:00–8:59)	2292 (69.0)	323 (67.2)	42 (66.7)	281 (67.2)	
Tertiles of prefecture preference for performing AAM					<0.001
Tertile 1 (0–7.3%)	1148 (34.6)	49 (10.2)	8 (12.7)	41 (9.8)	
Tertile 2 (7.4%–13.8%)	892 (26.9)	99 (20.6)	15 (23.8)	84 (20.1)	
Tertile 3 (13.9%–38.2%)	1280 (38.6)	333 (69.2)	40 (63.5)	293 (70.1)	
Aetiology, n (%)					<0.001
Medical[a]	2446 (73.7)	258 (53.6)	24 (38.1)	234 (56.0)	
Non-medical	874 (26.3)	223 (46.4)	39 (61.9)	184 (44.0)	
Witness status, n (%)					0.062
Layperson witnessed	870 (26.2)	146 (30.4)	24 (38.1)	122 (29.2)	
Unwitnessed	2450 (73.8)	335 (69.6)	39 (61.9)	296 (70.8)	
First rhythm, n (%)					0.471
Shockable	119 (3.6)	21 (4.4)	5 (7.9)	16 (3.8)	
Nonshockable	3201 (96.4)	460 (95.6)	58 (92.1)	402 (96.2)	
Layperson interventions					
Layperson CPR, n (%)					0.013
Chest compression only CPR	1455 (43.8)	245 (50.9)	34 (54.0)	211 (50.5)	
Chest compression with ventilation	531 (16.0)	65 (13.5)	7 (11.1)	58 (13.9)	
No layperson CPR	1334 (40.2)	171 (35.6)	22 (34.9)	149 (35.6)	
Public access AED shock delivery, n (%)	40 (1.2)	5 (1.0)	1 (1.6)	4 (1.0)	0.93
EMS interventions					
Prehospital physician involvement, n (%)	280 (8.4)	39 (8.1)	10 (15.9)	29 (6.9)	0.879
Interval between emergency call and initiation of EMS CPR, median (IQR), minutes	9 (7–11)	9 (7–11)	9.5 (8–13)	9 (7–11)	0.055
Interval between initiation of EMS CPR and AAM, median (IQR), minute	N/A	7 (5–11)	11 (7–14.5)	7 (4–11)	N/A
Epinephrine administration, n (%)	65 (2.0)	88 (18.3)	31 (49.2)	57 (13.6)	<0.001
Interval between initiation of EMS CPR and epinephrine administration, median (IQR), minutes	14 (12–20)	15 (9.75–19.25)	17 (11–20)	14 (9–19)	0.759
EMS shock delivery, n (%)	153 (4.6)	35 (7.3)	11 (17.5)	24 (5.7)	0.016
Interval between initiation of EMS CPR and EMS shock delivery, median (IQR), minutes	2 (1–5)	3 (1.5–8)	6 (2–9.5)	2.5 (1–7)	0.042

AAM indicates advanced airway management; SGA, supraglottic airway; ETI, endotracheal intubation; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; EMS, emergency medical services; IQR, interquartile range; N/A, not applicable.
[a] The aetiology of arrest was presumed to be medical origin unless aetiology was trauma, drug overdose, drowning, electrocution, or asphyxia, based on the updated Utstein template.[23]

censoring. We also modelled hospital arrival as a non-informative censoring because our main exposure was prehospital AAM, prehospital termination of resuscitation is not legally permitted in Japan, and data after hospital arrival were not available in the registry.

The time-dependent and time-independent covariates are shown in Table 1 and described in the Supplementary Method. We applied spline functions (B-spline) for continuous variables (age and interval between emergency call and initiation of EMS CPR). The aetiology of

arrest was presumed to be medical origin unless aetiology was trauma, drug overdose, drowning, electrocution, or asphyxia, based on the updated Utstein template.[23] Prefectures are the jurisdictional and administrative division levels in Japan, and we included the prefecture categories, based on the tertiles of proportion of patients who received AAM at each prefecture, to account for regional variation in outcomes.[25] These covariates were chosen a priori based on their association with survival from prior studies, biologic plausibility, and adequate ascertainment.[9,10,25–27]

Using the predicted time-dependent propensity scores, each patient receiving AAM at any given minute (from min 0 to min 59) after initiation of CPR by EMS providers was sequentially matched with a patient who was at risk of receiving AAM and had the nearest propensity score within the same minute in a one-to-one fashion without replacement — those who were still undergoing CPR and had not yet received AAM before or within the same minute (risk-set matching).[15,18–20] Patients matched as at-risk of receiving AAM therefore also included those who received AAM later because the matching should not be dependent on future events.[15,18–20,28,29] At-risk patients could have been subsequently matched multiple times as at-risk patients or as patients receiving AAM (if the patient received AAM) in order to reduce the number of unmatched patients as described in a recent study of endotracheal intubation for paediatric in-hospital cardiac arrest.[18] We set the calliper-width for the nearest neighbour matching at 0.2 standard deviations of the propensity scores in the logit scale.[30,31] Risk-set matching is known to account for resuscitation time bias.[15,29] To evaluate the performance of the risk-set matching, we calculated standardized differences for each covariate. We considered standardized difference less than 0.25 as a well-matched balance.[31]

Using the original cohort, we estimated unadjusted risk ratios (RRs) with 95% confidence intervals (CIs) of AAM for the primary and secondary outcomes by univariable regression with log-binomial link function. In the matched cohort, we applied log-binomial link function in generalized estimating equations (GEE) to calculate RRs with 95% CIs of AAM for the primary and secondary outcomes.[32] We used GEE to address potential correlation within-pair of risk-set matches because some patients could have been duplicated in AAM and no AAM groups (i.e., patients matched as no AAM could have been matched as no AAM or AAM later [if they received AAM later]). We used frequency weighting adjustment to account for number of the duplications between patients with AAM and no AAM.[31] We did not include covariates in the models in the original and matched cohorts to avoid overfitting given our limited sample size. We also calculated risk differences (difference between outcomes in AAM and no AAM) with 95% CIs in the original and matched cohorts, based on the binomial regression models and the GEE with identity link.

We performed stratified analyses by types of AAM (SGA or ETI) and similarly assessed the associations between each type of AAM and outcomes in the original and matched cohorts. As the timing of AAM may change the effect size of AAM, we further carried out another stratified analysis in the matched cohort, based on the tertiles of interval between EMS CPR and AAM (i.e., timing of matching). We additionally performed a sensitivity analysis, not allowing matched at-risk patients to be subsequently matched multiple times in the time-dependent propensity score analysis. We also conducted subgroup analyses by age group and initial rhythm. In the subgroup analyses, using the original and matched cohorts, we recalculated RRs with 95% CIs for 1-month survival. All statistical analyses were performed with R software, version 3.5.1 (www.r-project.org). All tests were 2-tailed, and P values of less than 0.05 were considered statistically significant.

Results

We observed 4834 paediatric patients with OHCA (Fig. 1). After excluding those who met exclusion criteria, 3801 patients were eligible for our study. 481 patients (12.7%) received AAM and 3320 (87.3%) did not receive AAM. Among those with AAM, 418 underwent SGA insertion (86.9%) and 63 had ETI (13.1%).

We present patient characteristics in Table 1. Among those who had AAM, more than half were adolescents (58.8%), while approximately one quarter of those who did not receive AAM were adolescents (22.9%). Among both AAM and no AAM groups, more

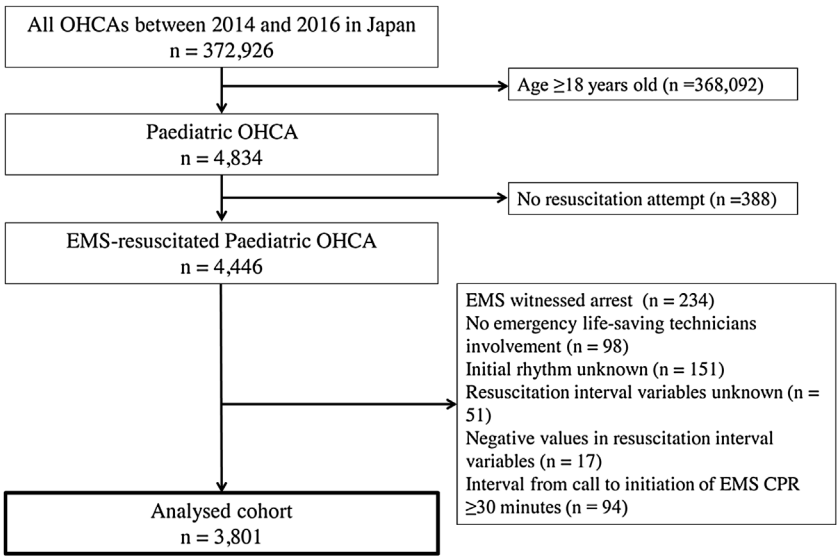

Fig. 1 – Study participant flowchart.
OHCA indicates out-of-hospital cardiac arrest; EMS, emergency medical services; CPR, cardiopulmonary resuscitation.

Table 2 – Characteristics of the study population in the matched cohort.

	No AAM n = 456	AAM n = 456	Standardized difference
Patient demographics			
Age group, n (%)			0.04
Infants (<1 y)	80 (17.5)	74 (16.2)	
Children (1 y–12 y)	111 (24.3)	117 (25.7)	
Adolescents (>12 y)	265 (58.1)	265 (58.1)	
Sex, n (%)			0.03
Male	313 (68.6)	306 (67.1)	
Arrest characteristics			
Year of arrest, n (%)			0.05
2014	161 (35.3)	168 (36.8)	
2015	158 (34.6)	160 (35.1)	
2016	137 (30.0)	128 (28.1)	
Day of arrest, n (%)			0.04
Weekday (Monday to Friday)	396 (86.8)	390 (85.5)	
Weekend (Saturday and Sunday)	60 (13.2)	66 (14.5)	
Time of arrest, n (%)			0.02
Daytime (9:00–16:59)	154 (33.8)	150 (32.9)	
Night time (17:00–8:59)	302 (66.2)	306 (67.1)	
Tertiles of prefecture preference for performing AAM			0.03
Tertile 1 (0–7.3%)	45 (9.9)	44 (9.6)	
Tertile 2 (7.4%–13.8%)	87 (19.1)	92 (20.2)	
Tertile 3 (13.9%–38.2%)	324 (71.1)	320 (70.2)	
Aetiology, n (%)			0.07
Medical[a]	230 (50.4)	246 (53.9)	
Non-medical	226 (49.6)	210 (46.1)	
Witness status, n (%)			0.08
Bystander witnessed	119 (26.1)	136 (29.8)	
Unwitnessed	337 (73.9)	320 (70.2)	
First rhythm, n (%)			0.03
Shockable	21 (4.6)	18 (3.9)	
Nonshockable	435 (95.4)	438 (96.1)	
Layperson interventions			
Layperson CPR, n (%)			0.16
Chest compression only CPR	203 (44.5)	234 (51.3)	
Chest compression with ventilation	81 (17.8)	59 (12.9)	
No layperson CPR	172 (37.7)	163 (35.7)	
Public access AED shock delivery, n (%)	9 (2.0)	4 (0.9)	0.09
EMS interventions			
Prehospital physician involvement, n (%)	45 (9.9)	37 (8.1)	0.06
Interval between emergency call and initiation of EMS CPR, median (IQR), minutes	9 (7–11)	9 (7–11)	0.03
Interval between initiation of EMS CPR and AAM, median (IQR), minutes	N/A	7.5 (5–11)	N/A
Epinephrine administration, n (%)	15 (3.3)	17 (3.7)	0.02
Interval between initiation of EMS CPR and epinephrine administration, median (IQR), minutes	14 (10–21)	16 (10–19.75)	0.07
EMS shock delivery, n (%)	22 (4.8)	23 (5.0)	0.01
Interval between initiation of EMS CPR and EMS shock delivery, median (IQR), minutes	4.5 (1.25–7.5)	2.5 (1.25–7.75)	0.06
Timing of matching (Interval between EMS CPR and matching), n (%)			
<5 min	95 (20.8)	95 (20.8)	
5–9 min	193 (42.3)	193 (42.3)	
10–14 min	113 (24.8)	113 (24.8)	
15–19 min	32 (7.0)	32 (7.0)	
20–24 min	18 (3.9)	18 (3.9)	
25–29 min	2 (0.4)	2 (0.4)	
>29 min	3 (0.7)	3 (0.7)	

AAM indicates advanced airway management; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; EMS, emergency medical services; IQR, interquartile range; N/A, not applicable.

[a] The aetiology of arrest was presumed to be medical origin unless aetiology was trauma, drug overdose, drowning, electrocution, or asphyxia, based on the updated Utstein template.[23]

than half were male (66.1% in AAM and 59.6% in no AAM), more than one quarter had layperson witnessed arrest (30.4% in AAM and 26.2% in no AAM), over 95% had nonshockable initial rhythm (95.6% in AAM and 96.4% in no AAM), and more than half had layperson CPR (64.4% in AAM and 59.8% in no AAM). Median interval between initiation of EMS CPR and AAM was 7 min (IQR, 5–11). Among those who had ETI, we observed more adolescents (82.5%) than among those with SGA (55.3%).

912 patients underwent risk-set matching. 702 patients were matched once, 84 patients were matched twice, 10 patients were matched three times, and 3 patients were matched four times. We present patient characteristics of the matched cohort in Table 2. Standardized differences were within 0.25 for all variables, indicating good post-matching balance.

In the original cohort, there were no significant differences in 1-month survival (AAM: 57/481 [11.9%] vs. no AAM: 387/3320 [11.7%]; unadjusted RR, 1.02 [95% CI, 0.78–1.32]; risk difference, 0.2% [95% CI, −2.9% to 3.3%]) and 1-month survival with favourable functional status (AAM: 10/481 [2.1%] vs. no AAM: 108/3320 [3.3%]; unadjusted RR, 0.64 [95% CI, 0.34–1.21]; risk difference, −1.2% [95% CI, −2.6% to 0.2%]) (Table 3). In the matched cohort, we observed no significant differences between AAM and no AAM groups in 1-month survival (AAM: 52/456 [11.4%] vs. no AAM: 44/456 [9.6%]; RR, 1.15 [95% CI, 0.76–1.73]; risk difference, 1.5% [95% CI, −3.0%–6.1%]) and favourable functional status (AAM: 9/456 [2.0%] vs. no AAM: 10/456 [2.2%]; RR, 0.69 [95% CI, 0.26–1.79]; risk difference, −0.8% [95% CI, −2.9% to 1.3%]).

In the stratified analyses by types of AAM (Table 3), we did not observe the associations between SGA and 1-month survival in the original cohort (unadjusted RR, 1.05 [95% CI, 0.80–1.38]) and in the matched cohort (RR, 1.32 [95% CI, 0.86–2.04]) nor between ETI and 1-month survival in the original cohort (unadjusted RR, 0.82 [95% CI, 0.38–1.74]) and in the matched cohort (RR, 0.55 [95% CI, 0.19–1.63]). In the analysis stratified by the timing of matching, we did not observe the associations between AAM and outcomes regardless of the timing of matching (Table 4). In the sensitivity analysis not allowing multiple matching, we did not observe the associations between AAM and outcomes (Supplemental Table). We did not observe the association between AAM and 1-month survival across age groups and initial rhythms (Table 5).

Discussion

In this cohort study with time-dependent propensity score and risk-set matching, using the prospective, nationwide, population-based OHCA registry, we did not detect significant differences in 1-month survival nor favourable functional status between those who received prehospital AAM and those who did not.

Comparison with prior studies

Among those who underwent AAM, we observed that SGA insertion was more common than ETI, while prior studies in the US showed that

Table 3 – Outcomes for patients with out-of-hospital cardiac arrest with vs. without advanced airway management.

	Number of patients with outcome/total patients (%)		Risk ratio (95% CI) vs. no AAM	Risk difference,[b] % (95% CI)
	No AAM	AAM		
Original cohort				
Primary analysis (AAM vs. no AAM)				
1-month survival	387/3320 (11.7)	57/481 (11.9)	1.02 (0.78–1.32)	0.2 (−2.9 to 3.3)
1-month survival with favourable functional status	108/3320 (3.3)	10/481 (2.1)	0.64 (0.34–1.21)	−1.2 (−2.6 to 0.2)
Stratified analysis				
SGA vs. no AAM				
1-month survival	387/3320 (11.7)	51/418 (12.2)	1.05 (0.80–1.38)	0.5 (−2.8 to 3.9)
1-month survival with favourable functional status	108/3320 (3.3)	10/418 (2.4)	0.74 (0.39–1.39)	−0.9 (−2.4 to 0.7)
ETI vs. no AAM				
1-month survival	387/3320 (11.7)	6/63 (9.5)	0.82 (0.38–1.74)	−2.1 (−9.4 to 5.1)
1-month survival with favourable functional status	108/3320 (3.3)	0/63 (0)	[a]	[a]
Time-dependent propensity score-matched cohort				
Primary analysis (AAM vs. no AAM)				
1-month survival	44/456 (9.6)	52/456 (11.4)	1.15 (0.76–1.73)	1.5 (−3.0 to 6.1)
1-month survival with favourable functional status	10/456 (2.2)	9/456 (2.0)	0.69 (0.26–1.79)	−0.8 (−2.9 to 1.3)
Stratified analysis				
SGA vs. no AAM				
1-month survival	36/396 (9.1)	46/396 (11.6)	1.32 (0.86–2.04)	3.0 (−1.6 to 7.6)
1-month survival with favourable functional status	6/396 (1.5)	9/396 (2.3)	1.38 (0.45–4.26)	0.6 (−1.3 to 2.4)
ETI vs. no AAM				
1-month survival	8/60 (13.3)	6/60 (10.0)	0.55 (0.19–1.63)	−7.6 (−21.8 to 6.6)
1-month survival with favourable functional status	4/60 (6.7)	0/60 (0)	[a]	[a]

AAM indicates advanced airway management; SGA, supraglottic airway; ETI, endotracheal intubation; CI, confidence interval.
[a] The models did not converge.
[b] Difference of outcomes in AAM and no AAM (Outcome in AAM− Outcome in No AAM).

Table 4 – Outcomes for patients with out-of-hospital cardiac arrest with vs. without advanced airway management in time dependent propensity score-matched cohort, according to the time of matching.

	Number of patients with outcome/total patients (%)		Risk ratio (95% CI) vs. no AAM	Risk difference,[b] % (95% CI)
	No AAM	AAM		
Timing of matching: tertile 1 (0–5.9 min)				
1-month survival	15/142 (10.6)	17/142 (12.0)	1.13 (0.59–2.18)	1.4 (−6.0 to 8.8)
1-month survival with favourable functional status	5/142 (3.5)	6/142 (4.2)	1.20 (0.37–3.86)	0.7 (−3.8 to 5.2)
Timing of matching: tertile 2 (6.0–9.9 min)				
1-month survival	16/146 (11.0)	17/146 (11.6)	1.06 (0.56–2.03)	0.7 (−6.6 to 8.0)
1-month survival with favourable functional status	2/146 (1.4)	3/146 (2.1)	1.50 (0.25–8.89)	0.7 (−2.3–3.7)
Timing of matching: tertile 3 (10.0–36 min)				
1-month survival	13/168 (7.7)	18/168 (10.7)	1.38 (0.70–2.74)	3.0 (−3.2 to 9.2
1-month survival with favourable functional status	3/168 (1.8)	0/168 (0)	[a]	[a]

AAM indicates advanced airway management; CI, confidence interval.
[a] The models did not converge.
[b] Difference of outcomes in AAM and no AAM (Outcome in AAM – Outcome in No AAM).

Table 5 – 1-month survival for patients with out-of-hospital cardiac arrest with vs. without advanced airway management in subgroup analyses.

	Number of patients with 1-month survival/total patients (%)		Risk ratio (95% CI) vs. no AAM	Risk difference,[a] % (95% CI)
	No AAM	AAM		
Original cohort				
Age group				
Infants (<1 y)	145/1445 (10.0)	8/75 (10.7)	1.06 (0.54–2.09)	0.6 (−6.6 to 7.8)
Children (1 y–12 y)	145/1116 (13.0)	17/123 (13.8)	1.06 (0.67–1.70)	0.8 (−5.6 to 7.3)
Adolescents (>12 y)	97/759 (12.8)	32/283 (11.3)	0.88 (0.61–1.29)	−1.5 (−5.9 to 2.9)
Initial rhythm				
Shockable	68/119 (57.1)	9/21 (42.9)	0.75 (0.47–1.20)	−14.3 (−35.3 to 6.7)
Nonshockable	319/3201 (10.0)	48/460 (10.4)	1.05 (0.79–1.40)	0.5 (−2.5 to 3.5)
Time-dependent propensity score-matched cohort				
Age group				
Infants (<1 y)	7/80 (8.8)	8/74 (10.8)	1.24 (0.47–3.26)	2.1 (−7.4 to 11.5)
Children (1 y–12 y)	13/111 (11.7)	16/117 (13.7)	1.17 (0.59–2.32)	2.0 (−6.7 to 10.6)
Adolescents (>12 y)	24/265 (9.1)	28/265 (10.6)	1.17 (0.69–1.96)	1.5 (−3.6 to 6.6)
Initial rhythm				
Shockable	10/21 (47.6)	8/18 (44.4)	0.93 (0.46–1.88)	−3.2 (−35.3 to 29.0)
Nonshockable	34/435 (7.8)	44/438 (10.0)	1.29 (0.84–1.97)	2.2 (−1.6 to 6.0)

AAM indicates advanced airway management; CI, confidence interval.
[a] Difference of 1-month survival in AAM and no AAM (Survival in AAM – Survival in No AAM), % (95% CI).

ETI was performed more often than SGA.[9,13] Possible explanations of this difference include that, in our study population, standard ELSTs can only choose SGA as AAM, while specially trained, certified ELSTs can perform SGA and ETI. Another possibility is that SGA might be used as a rescue airway for failed ETI. As we acknowledged in the limitation, the data on training level of ELSTs and failed airway were not available.

A clinical trial to compare prehospital ETI to bag-valve-ventilation reported no significant differences in survival to hospital discharge (Odds ratio [OR], 0.96 [95% CI, 0.53–1.73]) or in good neurological outcome (OR, 1.47 [95% CI, 0.65–3.32]) among paediatric patients with OHCA.[33] Although this is the only existing trial of prehospital ETI in paediatrics, it was conducted between 1994 and 1997, and change in resuscitation care limits generalizability of the results to current practice. Two recent observational studies assessed effectiveness of prehospital AAM for paediatric OHCA and showed inconsistent results.[13,14] A secondary analysis of the same Japanese registry between 2011 and 2012 using traditional propensity score matching (not time-dependent propensity score with risk-set matching) reported that prehospital AAM was not associated with 1-month survival (OR, 1.44 [95% CI, 0.92–2.27]) or 1-month survival with favourable functional status, defined as CPC 1 or 2 (OR, 0.74 [95% CI, 0.35–1.59]) among 2157 paediatric patients with OHCA.[14] Using traditional propensity score analysis, another observational study of the Cardiac Arrest Registry to Enhance Survival registry in the United States showed that prehospital ETI (OR, 0.39 [95% CI, 0.26 to 0.59]) and SGA (OR, 0.32 [95% CI, 0.12 to 0.84]) were associated with decreased odds of survival to hospital discharge among 1724

paediatric patients with OHCA, compared with bag-valve-mask ventilation.[13] A recent systematic review and meta-analysis of AAM for paediatric cardiac arrest demonstrated that AAM was not associated with patient outcomes (survival to hospital discharge and good neurologic function at discharge), compared with bag-valve-mask ventilation, highlighting low to very low certainty of existing evidence on AAM for paediatric OHCA.[12]

Strengths of this study

Our study has several strengths. First, no prior studies accounted for the timing of AAM for paediatric patients with OHCA, which could have led to a critical resuscitation time bias. Patients who undergo longer resuscitation are more likely to receive an intra-cardiac arrest interventions.[15] Because length of resuscitation is strongly associated with worse outcome,[16,17] simple comparisons will usually find that exposure to intra-cardiac arrest interventions is biased toward a harmful effect.[15] A secondary analysis of a multicentre registry of in-hospital cardiac arrest in the US found that ETI was associated with decreased rate of survival to hospital discharge among paediatric cases, addressing resuscitation time bias with time-dependent propensity score and risk-set matching.[18] However, the current study is the first attempt to evaluate association between AAM and patient outcomes in paediatric OHCA, accounting for this bias. Second, no prior studies that investigated the effectiveness of AAM for paediatric patients with OHCA adjusted for potential time-varying confounders (e.g., shock delivery by EMS and epinephrine administration) as time-dependent covariates. We dealt with these potential time-varying confounders using time-dependent propensity score with risk-set matching, which has been used in several cardiac arrest studies.[18–20] Third, we used a competing risk model to accurately estimate time-dependent propensity scores of AAM during CPR. In our study, we defined prehospital ROSC before AAM as a competing risk because ROSC is an informative censoring. If we modelled prehospital ROSC as a non-informative censoring, the propensity scores for patients with ROSC before AAM would be overestimated.[34] Fourth, we reported risk differences in outcomes with 95% CIs. The point estimates for the magnitude of risk differences that we observed are important to quantify and to help understand the potential effect size of AAM, but uncertainty in this estimate does not exclude clinically trivial effect size because the 95% CIs cross 0%. Using a robust statistical approach, our study expands current knowledge of prehospital AAM for paediatric patients with OHCA.

Implications

Since we did not observe the associations between prehospital AAM and patient outcomes, our findings support the American Heart Association resuscitation guideline; "in the prehospital setting, it is reasonable to ventilate and oxygenate infants and children with a bag-mask device, especially if transport time is short (Class IIa, LOE B)".[11] As we did not observe superiority nor inferiority of AAM, our study may imply that prehospital airway management for paediatric OHCA should be based on multiple factors such as difficulty of bag-valve-mask ventilation, skill and experience of providers, and expected transport time.[11,35] Another implication is that prehospital airway research on paediatric OHCA may need to mostly rely on well-designed observational studies rather than clinical trials. Our study showed that point estimates for the effect size of AAM on patient outcomes were small despite large sample size and robust statistical approach. Future clinical trials with appropriate sample size of AAM for paediatric OHCA may not be practical, given the low incidence (5465 patients with EMS-treated paediatric OHCA in the US per year).[1]

Limitations

There are several limitations to our study. First, the number of attempted AAM and of failed AAM were not available in the registry. As failed intubation for patients with OHCA is known to be associated with poor outcomes,[36] failed AAM could have counted as no AAM and might have biased the results. Second, some potential confounders such as patient comorbidities and premorbid function, location of arrest, quality of CPR, and level of ELSTs (standard or certified) were not available in the registry, and we were not able to adjust for these unmeasured confounders. As data on quality of CPR and level of ELSTs (i.e., standard versus specially trained, certified ELSTs) were not available in the registry, we were unable to assess the relationship between quality of CPR and level of ELSTs. This could have biased our results because it is possible that higher level of ELSTs may have provided higher quality of CPR. Third, our inference may not be fully generalizable to other EMS systems because the effectiveness of AAM could be modified by EMS providers' skill and EMS protocol. Fourth, we used CPC to evaluate functional status because Paediatric CPC (PCPC) was not available. We defined CPC 1 or 2 (to correspond to PCPC 1–3) as a favourable functional status based on common report in adult OHCA studies.[14] Lastly, as with all epidemiological studies, data integrity, validity, and ascertainment bias are potential limitations.

Conclusion

In this secondary analysis of a prospective, nationwide, population-based OHCA registry in Japan, we found that prehospital AAM was not associated with 1-month survival or 1-month survival with favourable functional status in paediatric OHCA.

Author contributions

Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Okubo.
Critical revision of the manuscript: All authors.
Statistical analysis: Komukai, Izawa, Gibo.
Study supervision: Iwami, Callaway, Kitamura.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the

previous three years, no other relationships or activities that could appear to have influenced the submitted work. The authors declare that they have no conflict of potential.

Ethical approval

The medical institutional review board of Osaka University Graduate School of Medicine approved this study and waived the need for informed consent because of de-identified data.

Data sharing

No additional data available.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.09.007.

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