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Clinical paper

Evaluation of the optimal timing for advanced airway management for adult patients with out-of-hospital cardiac arrest: A retrospective observational study from a multicenter registry

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Abstract

Aim: We aimed to investigate the appropriate timing for advanced airway management (AAM) in witnessed adult non-traumatic out-of-hospital cardiac arrest (OHCA) by adjusting for resuscitation time bias and limiting the analysis to witnessed OHCA.

Methods: This retrospective observational study used a multicentre OHCA registry involving 99 participating hospitals in Japan and included adult patients with witnessed non-traumatic OHCA who underwent AAM during resuscitation. The primary and secondary outcomes were favourable 30-day neurological outcomes and survival, respectively. The time from emergency medical service contact to AAM was categorised as follows: 1–5, 6–10, 11–15, 16–20, 21–25, and 26–30 min. In each group, we calculated the time-dependent propensity score using a Fine-Gray regression model. After propensity score matching, we used a generalised estimating equation (GEE).

Results: A total of 16,448 patients who underwent AAM were matched with patients at risk of requiring AAM. AAM was associated with favourable 30-day neurological outcomes when performed at 6–10 and 16–20 min with RRs (95% CIs) of 1.41 (1.12–1.78), but not at 16–20 min (0.74 [0.56–0.99]), respectively. AAM was associated with improved 30-day survival at 1–5 and 6–10 min (1.22 [1.05–1.41], 1.33 [1.16–1.54], respectively), but not at 16–20 min (0.78 [0.62–0.97].

Conclusions: Performing AAM within 10 min was associated with improved outcomes compared with those at risk of receiving AAM. However, the results were not consistent across all groups, therefore, careful interpretation is required.

Keywords: Airway management, Cardiopulmonary resuscitation, Emergency medical services, Intubation, intratracheal, Out-of-hospital cardiac arrest

Introduction

Out-of-hospital cardiac arrest (OHCA) is still responsible for numerous deaths worldwide.[1,2] Advanced airway management (AAM), including supraglottic airway and tracheal intubation is an important resuscitation technique.[3–5] Early AAM might improve prognosis after OHCA.[6–9]

Various studies have been conducted to date, however, the appropriate AAM timing is unclear, and there is a growing interest

Abbreviations: AAM, advanced airway management, CPC, cerebral performance category, CI, confidence interval, CPR, cardiopulmonary resuscitation, EMS, emergency medical service, EMT, emergency medical technician, GEE, generalised estimating equation, IQR, interquartile ranges, JAAM, Japanese Association for Acute Medicine, OHCA, out-of-hospital cardiac arrest, PS, propensity score, PSM, propensity score matching, PEA, pulseless electrical activity, ROSC, return of spontaneous circulation, RR, risk ratio, SD, standardised dierence, VF, ventricular fibrillation, VT, pulseless ventricular tachycardia

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in the AAM timing when maximum effects can be obtained.[6–14] Despite adjusting for the resuscitation time bias, which could potentially explain the worsened outcomes in patients who received interventions at later stages, Okubo et al. did not detect an association between the timing of AAM and patient prognosis.[11] This might have been due to an insufficient sample size.[11] Moreover, they included unwitnessed OHCA, and the inability to calculate the exact time from OHCA to AAM may have biased the results.[11] Our previous study also compared the outcomes of early and late AAM in adult OHCA, and the subgroup analysis suggested significant AAM effectiveness in witnessed OHCA; however, this was the subgroup and not the main analysis.[12]

Therefore, the association between AAM timing and outcomes should be investigated in a larger patient group, limited to witnessed OHCA, with resuscitation time bias adjustments. Furthermore, in the current study, we used the Japanese Association for Acute Medicine (JAAM)-OHCA registry, which includes not only the information from the all-Utstein registry but also additional data collected after hospital arrival. Compared to the all-Utstein registry, the JAAM-OHCA registry contains a greater amount of information, making it a more comprehensive data source for our analysis. If this study indicates an appropriate AAM timing, future resuscitation practices may be influenced by measures, such as performing AAM more quickly or prioritising rapid transport to hospitals without AAM. Furthermore, patient outcomes could be improved. Therefore, our objective was to investigate the appropriate timing for AAM in a large patient group limited to witnessed OHCA, with adjustments for resuscitation time bias.

Methods

Study design

We conducted a multicentre retrospective observational study using the JAAM-OHCA registry. This registry includes OHCA patients transported to 99 hospitals in Japan between June 2014 and December 2021 and collects prehospital and posthospital information. Prehospital information was collected from the All-Japan Utstein Registry of the Fire and Disaster Management Agency, and posthospital information was collected by medical personnel at each institution. This information was registered in a web-based system by medical personnel at each institution, and the outcome assessors were not blinded.

The ethics committee of each participating hospital approved the collection of JAAM-OHCA information, and the specific Ethics Committee approved this study (approval number: S19–016). The requirement for informed consent was waived, as this study involved no interventions that diverged from standard cardiopulmonary resuscitation (CPR) practices. We provided an opt-out process on the website. This study was conducted according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines and Declaration of Helsinki and its later amendments (e-Table 1 in Additional file 1).[15]

Participants

The inclusion criteria were as follows: 1) witnessed OHCA, 2) resuscitation by emergency medical service (EMS) personnel, and 3) AAM during resuscitation. Based on a similar previous study, the exclusion criteria were as follows: 1) OHCA caused by trauma, 2) < 18 years, 3) missing data on the time from EMS contact to AAM, 4) time from EMS contact to AAM was 0 min, ≥ 60 min, or inconsistent (i.e., negative values), 5) missing data on covariates for the Fine-Gray regression model or outcomes.[12] Details of the covariates are described in the Statistical Analysis section.

Japanese EMS in OHCA cases

In Japan, the Japan Resuscitation Council provides CPR guidelines to EMS staff based on the International Liaison Committee on Resuscitation's statement.[16] Each EMS team comprises three individuals, including at least one advanced emergency medical technician (EMT) proficient in prehospital care. All EMTs can perform AAM using laryngeal tubes and masks. However, only EMTs with specialised training and certification can perform tracheal intubation, which is restricted to OHCA. Legally, Japanese EMS personnel are not authorised to terminate resuscitation efforts at the scene; therefore, every OHCA patient is transported to a hospital unless it is unequivocally clear that resuscitation attempts would be futile.

Data collection

The following data were collected: age, sex, time of emergency call (7:00–14:59, 15:00–22:59, 23:00–6:59 h), transportation by vehicular or air ambulance with a physician present, witness status (none, EMS personnel, others), bystander CPR (presence, absence, presence including rescue breathing), initial monitored cardiac rhythm (ventricular fibrillation [VF], pulseless ventricular tachycardia [VT], pulseless electrical activity [PEA], asystole, other), cause of cardiac arrest (cardiogenic, respiratory, other intrinsic factors), adrenaline administration before AAM, time from EMS contact to adrenaline administration before AAM, shock delivery before AAM, time from EMS contact to shock delivery before AAM, prehospital AAM (laryngeal mask, oesophageal obturator, endotracheal tube), prefecture performance rates of prehospital AAM, time from EMS contact to AAM, time from scene to EMS contact, time from emergency call to physician contact, 30-day cerebral performance category (CPC), and survival.[17] Based on a previous study, the emergency call time was categorised into three time intervals and AAM includes both supraglottic airway and tracheal intubation, since which are considered to have comparable efficacy.[18,19]

Outcome measures

The primary outcome was a favourable 30-day neurological outcome following OHCA, which was defined as a CPC score of 1 or 2.[17] The secondary outcome was 30-day survival.

Statistical analyses

Continuous variables were described using medians and interquartile ranges (IQR), and categorical variables, using absolute counts and percentages (%). We did not impute missing data and only analysed complete cases. Based on a previous study, we categorised the time from EMS contact to AAM into the following groups and performed statistical analyses for each: 1–5, 6–10, 11–15, 16–20, 21–25, and 26–30 min.[20] Exposure was categorised as the interval between EMS contact and AAM. Additionally, for cases of OHCA occurring directly in the presence of EMS, we treated the scene to AAM time as EMS contact to AAM.

First, we used a Fine-Gray regression model to calculate the time-dependent propensity score (PS)—an estimated risk score that predicts AAM likelihood. We considered the return of spontaneous circulation (ROSC) before AAM as a competing risk and an informative censoring event because we aimed to verify AAM efficacy during resuscitation. Moreover, AAM was used as a response

variable, and the following explanatory variables, including time-dependent and time-independent covariates, were identified.[6,13] Time-dependent covariates included adrenaline administration before AAM, time from EMS contact to adrenaline administration, shock delivery before AAM, and time from EMS contact to shock delivery. Time-independent covariates included age, sex, emergency call timing, witness status, bystander CPR, time from scene to EMS contact, time from scene to CPR initiation, time from EMS contact to hospital arrival, initial cardiac rhythm, transportation by road or air ambulance with a physician present, tertiles of prefecture performance rates of prehospital AAM, and OHCA cause. In Japan, there are a few regional differences in CPR practice. Therefore, to adjust for regional differences, we divided the prefectures into tertiles based on the AAM rate, as described previously.[13] After calculating the time-dependent PS, to perform time-dependent PS matching (PSM), patients administered AAM and those at a risk of requiring AAM were matched in a 1:1 ratio, with the calliper width set to 0.2. We confirmed that the covariates were balanced using standardised differences (SDs). A value of < 0.2 was used as the cut-off SD.[21]

Second, we used a generalised estimating equation (GEE) to adjust for within-patient clustering. A hierarchical structure was set at the level of each patient, and the correlation matrix for GEE was treated as "exchangeable." We treated favourable 30-day neurological outcomes or survival as response variables. Effect estimates were described using risk ratios (RR) and 95% confidence intervals (CI). We calculated the risk ratios with 95% confidence intervals for outcomes at each time interval (1–5, 6–10, 11–15, 16–20, 21–25, and 26–30 min) by comparing patients who received AAM during that specific time interval with those who had not yet received AAM and were still at risk of receiving AAM thereafter. In other words, our analysis did not treat a particular time interval as a fixed reference group.

We used the R package Matching and geepack (version 4.1.3) (The R Project for Statistical Computing, Vienna, Austria), and a two-sided p-value < 0.05 was considered significant.

Subgroup analysis

We performed a subgroup analysis in shockable and non-shockable rhythm cases because current international guidelines advocate the use of two different algorithms depending on the initial monitored rhythm, with different suggestions for AAM.[8].

Sensitivity analysis

We performed a sensitivity analysis limited to the patients who underwent endotracheal intubation because we considered that AAM using an endotracheal tube might be more effective compared to other devices.

Results

Patient enrolment

Among 18,233 included patients, 4,172 (22.9%) received AAM within 1–5 min, 5,668 (31.1%) within 6–10 min, 2,846 (15.6%) within 11–15 min, 1,546 (8.5%) within 16–20 min, 1,261 (6.9%) within 21–25 min, and 1,009 (5.5%) within 26–30 min (Fig. 1). Details of missing data are provided in Supplementary Table 1.

Patient characteristics

Patient characteristics are shown in Table 1 and Supplementary Tables 2–7. In original cohort in Table 1, the median age (IQR) was 76 (65–84) years, 11 and 542 patients (63.3%) were male, and 12,135 (66.6%) received prehospital AAM. Additionally, 3,386 patients (18.6%) experienced shock delivery before AAM and the median time from EMS contact to shock delivery was 2 (1–3) min (Table 1).

In the overall cohort after time-dependent PSM, the SDs for all variables were within 0.2 (Table 1, Supplementary Tables 2–7). In total, 12,056 (73.3%) patients received prehospital AAM. Adrenaline was administered to 2,601 patients (15.8%) before AAM. The median time from EMS contact to adrenaline administration was 12 (8–17) min. Shocks were delivered to 2,855 patients (17.4%) before AAM, and the median time from EMS contact to shock delivery was 2 (1–3) min (Table 1).

Analyses involving timing variables and GEE

AAM was associated with favourable 30-day neurological outcomes at 6–10 min (RR [95% CI]: 1.41 [1.12–1.78]) but not at 16–20 min (RR [95% CI]: 0.74 [0.56–0.99]) (Table 2, Fig. 2). Additionally, AAM was associated with improved 30-day survival at 1–5 and 6–10 min (RRs [95% CI]: 1.22 [1.05–1.41] and 1.33 [1.16–1.54], respectively), but not at 16–20 min (RR [95% CI]: 0.78 [0.62–0.97]) (Table 2, Fig. 3).

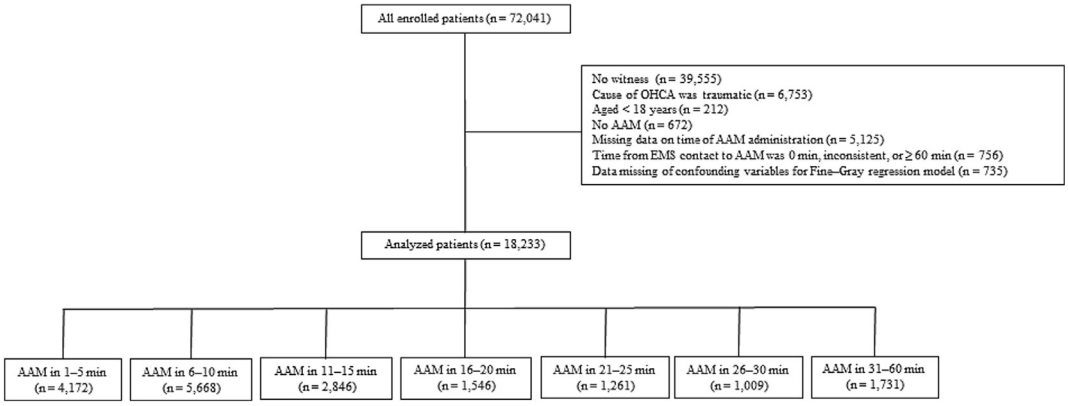

Fig. 1 – Flowchart of the screening and enrolment process within the current study. Abbreviations: AAM, advanced airway management; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

Table 1 – Demographics and characteristics of original cohort.

Variables	Original cohort (n = 18,233)	After maching		
		AAM (n = 16,448)	At risk of receiving AAM (n = 16,448)	SD
Age, median (IQR)	76 (65–84)	76 (65–84)	76 (65–84)	0.01
Male, n (%)	11,542 (63.3)	10,351 (62.9)	10,300 (62.6)	0.01
Time of emergency call, n (%)				0.01
7:00–14:59	7,677 (42.1)	6,960 (42.3)	6,869 (41.8)	
15:00–22:59	6,607 (36.2)	5,947 (36.2)	5,970 (36.3)	
23:00–6:59	3,949 (21.7)	3,541 (21.5)	3,609 (21.9)	
Tertiles of prefecture performance rates of out-of-hospital advanced airway management, n (%)				0.02
<42.4	5,145 (28.2)	4,210 (25.6)	4,315 (26.2)	
42.4–63.4	6,214 (34.1)	5,568 (33.9)	5,648 (34.3)	
>63.4	6,874 (37.7)	6,670 (40.6)	6,485 (39.4)	
Witness status, n (%)				0.02
EMS personnel	3,387 (18.6)	3,117 (19.0)	3,262 (19.8)	
Others	14,846 (81.4)	13,331 (81.0)	13,186 (80.2)	
Bystander CPR, n (%)				0.01
Presence	6,627 (36.4)	5,968 (36.3)	5,916 (36.0)	
Absence	10,404 (57.1)	9,394 (57.1)	9,429 (57.3)	
Presence including rescue breathing	1,202 (6.6)	1,086 (6.6)	1,103 (6.7)	
Initial monitored cardiac rhythm, n (%)				0.04
VF	2,838 (15.6)	2,432 (14.8)	2,191 (13.3)	
Pulseless VT	47 (0.3)	41 (0.2)	33 (0.2)	
PEA	6,561 (40.9)	6,730 (40.9)	6,846 (41.6)	
Asystole	5,971 (36.0)	5,953 (36.2)	6,061 (36.8)	
Other	1,428 (7.8)	1,292 (7.9)	1,317 (8.0)	
Cause of cardiac arrest, n (%)				0.01
Cardiogenic	12,109 (66.4)	10,827 (65.8)	10,893 (66.2)	
Respiratory	1,400 (7.7)	1,296 (7.9)	1,266 (7.7)	
Other intrinsic disease	4,724 (25.9)	4,325 (26.3)	4,289 (26.1)	
Time from scene to EMS contact, min, median (IQR)	9 (7–10)	9 (7–10)	9 (7–10)	0.02
Time from scene to initiation of CPR, min, median (IQR)	9 (8–12)	9 (8–12)	10 (8–13)	0.04
Time from EMS contact to AAM, min, median (IQR)	10 (6–19)	–*	–*	–*
Time from EMS contact to hospital arrival, min, median (IQR)	25 (20–31)	25 (19–31)	25 (20–31)	0.03
Adrenaline administration before AAM, n (%)	3,375 (18.5)	2,601 (15.8)	2,812 (17.1)	0.04
Time from the patient contact by EMS to adrenaline administration before AAM, median min (IQR)*	13 (8–19)	12 (8–17)	14 (9–19)	0.24
Shock delivery before AAM, n (%)	3,386 (18.6)	2,855 (17.4)	2,619 (15.9)	0.04
Time from the patient contact by EMS to shock delivery before AAM, median min (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.08
Prehospital AAM, n (%)	12,135 (66.6)	12,056 (73.3)	11,979 (72.8)	0.01
Prehospital AAM type, n (%)				
Laryngeal mask	1,105 (6.1)	1,091 (6.6)	1,069 (6.5)	0.03
Esophageal obturator	9,131 (50.1)	9,078 (55.2)	8,878 (54.0)	
Endotracheal tube	2,235 (12.3)	2,220 (13.5)	2,350 (14.3)	
Physician during emergency transport, n (%)	1,901 (10.4)	1,781 (10.8)	1,764 (10.7)	< 0.01

Abbreviations: AAM, advanced airway management; CPR, cardiopulmonary resuscitation; IQR, interquartile range; EMS, emergency medicine service; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; SD, standardized difference.

* Since we performed time-dependent propensity score matching based on the time from EMS contact to AAM, this variable was not adjusted for in the overall analysis.

Subgroup analysis in shockable and non-shockable rhythm cases

Among patients with shockable cardiac rhythms, AAM was associated with improved 30-day survival at 6–10 min (RR [95% CI]: 1.25 [1.05–1.50]) but not at 26–30 min (RR [95% CI]: 0.73 [0.57–0.94]) (Table 3). Among patients with non-shockable cardiac rhythms, AAM was associated with favourable 30-day neurological outcomes at 6–10 min (RR [95% CI]: 1.58 [1.05–2.39]), but not at 16–20 min (RR [95% CI]: 0.56 [0.35–0.90]) (Table 3). Additionally, AAM was associated with improved 30-day survival at 1–5 and 6–10 min

Table 2 – Outcomes in time-dependent propensity score matched cohort.

Outcomes	Number of patients with outcome/total number of patients (%)		Risk ratio (95% CI)
	AAM	At risk of receiving AAM	
Analyses with timing variable			
30-day favorable neurological outcome			
1–5 min	176/4,160 (4.2)	138/4,160 (3.3)	1.18 (0.93–1.50)
6–10 min	192/5,664 (3.4)	150/5,664 (2.6)	1.41 (1.12–1.78)
11–15 min	87/2,840 (3.1)	83/2,840 (2.9)	1.09 (0.78–1.53)
16–20 min	90/1,538 (5.9)	130/1,538 (8.5)	0.74 (0.56–0.99)
21–25 min	93/1,244 (7.4)	114/1,244 (9.0)	0.88 (0.67–1.17)
26–30 min	98/1,002 (9.7)	97/1,002 (9.6)	1.05 (0.79–1.41)
30-day survival			
1–5 min	416/4,160 (10.0)	327/4,160 (7.8)	1.22 (1.05–1.41)
6–10 min	503/5,664 (8.9)	373/5,664 (6.6)	1.33 (1.16–1.54)
11–15 min	207/2,840 (7.3)	180/2,840 (6.3)	1.20 (0.97–1.49)
16–20 min	152/1,538 (9.8)	195/1,538 (12.6)	0.78 (0.62–0.97)
21–25 min	150/1,244 (11.9)	169/1,244 (13.4)	0.95 (0.76–1.18)
26–30 min	145/1,002 (14.4)	160/1,002 (15.9)	0.94 (0.75–1.18)

Abbreviations: AAM, advanced airway management; CI, confidence interval.

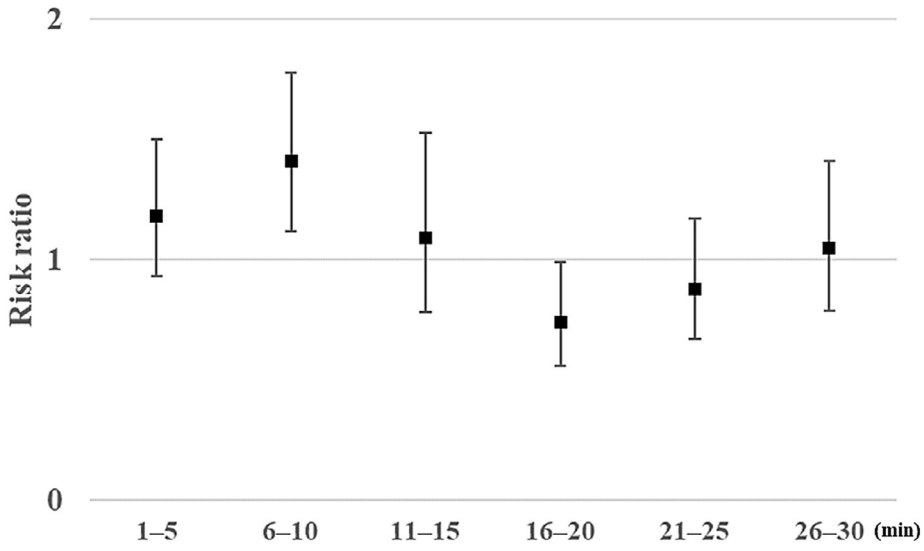

Fig. 2 – The 30-day favourable neurological outcome stratified by the timing of AAM. Abbreviations: AAM, advanced airway management.

(RRs [95% CI]: 1.28 [1.04–1.59] and 1.38 [1.13–1.69], respectively), but not at 16–20 min (RR [95% CI]: 0.62 [0.45–0.86]) (Table 3).

Sensitivity analysis

AAM was associated with improved 30-day survival at 6–10 min (RR [95% CI]: 1.45 [1.01–2.06]) (Supplementary Tables 8).

Discussion

On analysing timing variables and GEE, AAM within 10 min from EMS contact was associated with improved outcomes. Additionally, AAM after 16 min was associated with worse outcomes in some groups.

Our current results were similar to those of our previous study comparing early and late AAM in adult OHCA.[12] In the subgroup analysis for witnessed OHCA, early AAM was significantly associated with prognosis.[12] Meanwhile, the current results differed from those of another study in adult OHCA, indicating early AAM was not significantly associated with prognosis.[11] Several interpretations can be considered regarding these similarities and differences between the current and previous studies.[11,12] First, the difference in the number of patients may have influenced the detection of significant differences. Okubo et al. included 2,146 patients, while our previous and current studies included 41,101 and 18,223 patients, respectively.[11,12] In Okubo et al.'s study, each group included 923 patients, and the incidence of outcomes was 2.2% and 1.7% in the AAM and at risk of requiring AAM groups, respectively.[7] To achieve a power of 0.8, detecting a significant difference would require over 10,000 patients per group. Second, heterogeneity based on whether OHCA was witnessed may have influenced the detection of significant differences. Okubo et al.'s analysis was not limited to witnessed OHCA, and both our previous and cuurent studies conducted analy-

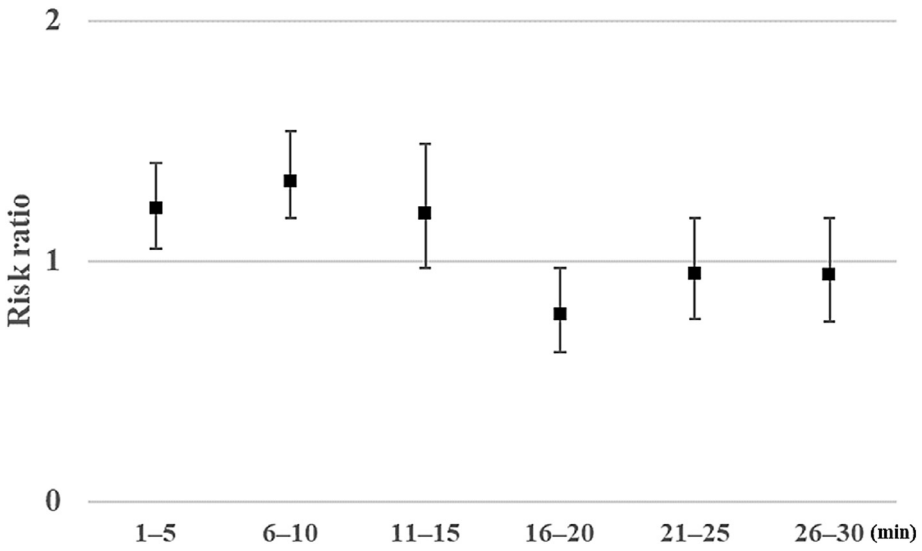

Fig. 3 – Thirty-day survival stratified by the timing of AAM. Abbreviations: AAM, advanced airway management.

Table 3 – Outcomes for subgroup analysis in time-dependent propensity score matched cohort.

Outcomes	Number of patients with outcome/total number of patients (%)		Risk ratio (95% CI)
	AAM	At risk of receiving AAM	
Shockable cardiac rhythms			
30-day favorable neurological outcome			
1–5 min	113/599 (18.9)	96/573 (16.8)	1.11 (0.85–1.45)
6–10 min	122/789 (15.5)	102/779 (13.1)	1.29 (0.99–1.70)
11–15 min	58/376 (15.4)	49/316 (15.5)	0.97 (0.66–1.45)
16–20 min	61/248 (24.6)	69/214 (32.2)	0.83 (0.60–1.15)
21–25 min	65/241 (27.0)	66/186 (35.5)	0.84 (0.62–1.15)
26–30 min	69/220 (31.4)	66/156 (42.3)	0.79 (0.59–1.06)
30-day survival			
1–5 min	203/599 (33.9)	169/573 (29.5)	1.14 (0.95–1.37)
6–10 min	238/789 (30.2)	193/779 (24.8)	1.25 (1.05–1.50)
11–15 min	94/376 (25.0)	78/316 (24.7)	1.02 (0.76–1.36)
16–20 min	86/248 (34.7)	85/214 (39.7)	0.90 (0.69–1.17)
21–25 min	89/241 (36.9)	81/186 (43.5)	0.97 (0.74–1.25)
26–30 min	87/220 (39.5)	86/156 (55.1)	0.73 (0.57–0.94)
Non-shockable cardiac rhythms			
30-day favorable neurological outcome			
1–5 min	63/3,561 (1.8)	42/3,587 (1.2)	1.33 (0.88–2.00)
6–10 min	70/4,875 (1.4)	48/4,885 (1.0)	1.58 (1.05–2.39)
11–15 min	29/2,464 (1.2)	34/2,524 (1.4)	1.00 (0.59–1.69)
16–20 min	29/1,290 (2.3)	61/1,324 (4.6)	0.56 (0.35–0.90)
21–25 min	28/1,003 (2.8)	48/1,058 (4.5)	0.69 (0.42–1.13)
26–30 min	29/782 (3.7)	31/846 (3.7)	1.04 (0.61–1.78)
30-day survival			
1–5 min	213/3,561 (6.0)	158/3,587 (4.4)	1.28 (1.04–1.59)
6–10 min	265/4,875 (5.4)	180/4,885 (3.7)	1.38 (1.13–1.69)
11–15 min	113/2,464 (4.6)	102/2,524 (4.0)	1.22 (0.91–1.64)
16–20 min	66/1,290 (5.1)	110/1,324 (8.3)	0.62 (0.45–0.86)
21–25 min	61/1,003 (6.1)	88/1,058 (8.3)	0.77 (0.55–1.09)
26–30 min	58/782 (7.4)	74/846 (8.8)	0.90 (0.63–1.29)

Abbreviations: AAM, advanced airway management; CI, confidence interval.

ses limited to witnessed OHCA.[11,12] A large-scale epidemiological study involving 38,227 OHCA patients reported that the incidence of mortality at the scene in witnessed OHCA was 62.4% compared to 53.0% in unwitnessed OHCA.[22] Furthermore, the rate of favourable neurological outcomes was 1.3% in witnessed OHCA and 0.2% in unwitnessed OHCA; these differences suggest a high degree of heterogeneity between these patients.[22] And in unwitnessed OHCA, it is impossible to accurately determine and evaluate the time from OHCA to AAM. Therefore, an analysis which treats these groups identically may not be appropriate.

Conversely, AAM within 10 min was associated with improved outcomes and after 16 min was associated with worse outcomes in the current study. From a pathophysiological perspective, which might have been attributed to the beneficial effects of early AAM and oxygen supply. Although the specific time remains unclear, the American Heart Association guidelines state that the oxygen stored in the body is depleted within few minutes after cardiac arrest.[23] Therefore, our findings suggest that administering AAM and thereby supplying fresh oxygen within 10 min made it possible to minimise systemic damage due to hypoxia, which could have improved the neurological outcome and survival. Furthermore, after 16 min, hypoxic injury to tissues—particularly the brain—may become irreversible, which could have contributed to the observed deterioration in outcomes.

Our investigation is novel, as we adjusted for resuscitation bias, included a large number of patients, and limited the analysis to witnessed OHCA. Based on our current results, AAM within 10 min from EMS contact might improve outcomes. On the other hand, delayed AAM particularly after 16 min may be associated with worse outcomes. However, AAM within 1–5 min from EMS contact produced no significant difference in favourable 30-day neurological outcomes and after 11 min, the presence or absence of significant differences within each group was inconsistent, resulting in a lack of uniform results. And all of the 95% CIs of the RRs were close to one; therefore, careful interpretation is needed when assessing the clinical utility of the current study. Furthermore, as detailed in the following limitation statement, important confounding factors such as environment, airway characteristics, failed airway attempts, and operator experience were not statistically adjusted for in the current study. Therefore, careful attention should be paid to the possibility that the findings of our study may not be accurate.

The current study has some limitations. First, owing to selection bias, internal and external validity may have been compromised. Data on the time to AAM were missing in approximately 7% of patients. While this percentage was not substantial, the type of missing data may be missing not at random (MNAR). If the missing data was indeed MNAR, the exclusion of these data from the analysis could introduce selection bias and potentially reduce internal and external validity.[24] Second, differences in EMS proficiency may have biased the results. The AAM timing might be a surrogate for EMS performance (i.e., high-performing EMS personnel may be able to perform AAM more swiftly).[11] Therefore, we adjusted for regional differences in current study by using tertiles of prefecture prehospital AAM performance rates. However, due to the absence of EMS information in the OHCA registry, it was challenging to statistically adjust for patient clustering within EMS systems. Therefore, our current results may not be sufficiently accurate. Third, adjustments for covariates may not have been sufficient. As our current study was a retrospective observational study the use of variables that were not collected by the OHCA registry was not possible. For instance, serious comorbidities, such as cirrhosis, were considered to affect outcomes, yet they were not included in the registry. Moreover, the JAAM-OHCA registry does not include information on failed AAM attempts, such as the number of unsuccessful airway placements, scene/environment, airway anatomic complexity, airway soiling, and vascular access challenges. These factors are likely to be associated with both later AAM placement and decrements in CPR quality and chest compression fraction. And these factors may also have an impact on patient outcomes. Therefore, statistical analyses including additional covariates may yield results that differ from those of our current study. Fourth, in the current study, the type of AAM was not recorded in 31.5% of cases. We conducted a sensitivity analysis limited to cases involving endotracheal intubation; however, due to the small number of cases, we were unable to obtain results that allow for sufficient interpretation. In other words, if the proportion of missing data regarding the type of AAM had been lower, the results of the sensitivity analysis might have been different. Finally, The statistically significant differences identified in the current study may have arisen by chance. The analysis did not demonstrate consistent results regarding the effect of AAM across the various time intervals. Furthermore, in the subgroup analysis, AAM within 6–10 min was not associated with favorable 30-day neurological outcomes. These inconsistencies raise the possibility that the observed findings may have been the result of random variation rather than a true effect.

Conclusions

The current study showed that AAM within 10 min from EMS contact was associated with improved outcomes compared with those at risk of receiving AAM. However, the results were not consistent across all groups, and the 95% CIs of the RRs were close to one; therefore, careful interpretation is needed when considering the study's clinical utility.

CRediT authorship contribution statement

Yuki Kishihara: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shunsuke Amagasa:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Hideto Yasuda:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Masahiro Kashiura:** Writing – review & editing, Methodology, Conceptualization. **Yutaro Shinzato:** Writing – review & editing, Methodology, Conceptualization. **Takashi Moriya:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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