

# 学位論文

Neurological outcomes associated with  
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to foreign body airway obstruction

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## Clinical paper

# Neurological outcomes associated with prehospital advanced airway management in patients with out-of-hospital cardiac arrest due to foreign body airway obstruction



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### Abstract

**Objectives:** Several studies have examined the association between advanced airway management (AAM) and survival for arrest that is non-shockable, noncardiac in origin, or due to suffocation; however, the efficacy of prehospital AAM compared with no AAM following foreign body removal by emergency medical services (EMS) has not been examined. We aimed to compare neurological outcomes in patients after out-of-hospital cardiac arrest (OHCA) due to foreign body airway obstruction (FBAO) managed with and without AAM after foreign body removal.

**Methods:** This retrospective observational cohort study used all emergency transportation data of Japan and the All-Japan Utstein Registry. We included patients with OHCA aged  $\geq 18$  years undergoing resuscitation and removal of airway foreign bodies by EMS from January 2015 to December 2017. The exposure of interest was prehospital AAM by EMS after foreign body removal, and the primary outcome was a favorable neurological outcome at hospital discharge (i.e., a cerebral performance category of 1–2).

**Results:** Overall, 329,098 adults had OHCA and 23,060 had foreign bodies removed from their airways; 3681 adult patients met our eligibility criteria and were divided as: AAM (2045) and non-AAM (1636) groups. Propensity score matching resulted in 1210 matched pairs with balanced baseline characteristics between the groups. The rate of favorable neurological outcome was significantly lower in the AAM group than in the non-AAM group (OR 0.34, 95% CI 0.19–0.62). However, survival was not significantly different between the two groups (OR 1.08, 95% CI 0.84–1.37).

**Conclusions:** We have not demonstrated the benefit of AAM for patients with OHCA due to FBAO. Further study will be required to confirm the efficacy of AAM for those patients.

**Keywords:** Foreign body airway obstruction, Pre-hospital, Cardiac arrest, Airway management, Neurological outcome, OHCA

## Introduction

Accidents are the sixth leading cause of death in Japan, with more than 9000 deaths from suffocation recorded annually.<sup>1</sup> Despite the poor 1 month survival rate of out-of-hospital cardiac arrest (OHCA)

from noncardiac cause in Japan,<sup>2</sup> suffocation has a higher survival rate than other causes.<sup>3,4</sup> Japan ranks first in all the countries worldwide with the largest percentage of older adults, and individuals aged  $\geq 80$  years account for more than half of all suffocation cases.<sup>5</sup>

Prehospital management by emergency medical services (EMS) serves as a bridge between basic life support at the scene and

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<http://dx.doi.org/10.1016/j.resplu.2021.100140>

Received 20 February 2021; Received in revised form 15 May 2021; Accepted 15 May 2021

Available online xxx

advanced hospital care following out-of-hospital cardiac arrest (OHCA) and is considered a fundamental element in the chain of survival.<sup>6,7</sup> Cardiac arrest caused by foreign body airway obstruction (FBAO) should immediately be treated by removing any foreign body from the airway during basic life support.<sup>8,9</sup> There is still an ongoing debate as to whether bag valve mask or advanced airway management (AAM), which includes endotracheal intubation (ETI) or the insertion of a supraglottic airway (SGA), is more effective for OHCA.<sup>10,11</sup>

In the present study, we aimed to compare neurological outcomes in patients after OHCA due to FBAO managed with and without AAM after foreign body removal.

## Methods

### Study design and setting

We performed a retrospective observational cohort study for the period from January 1, 2015, to December 31, 2017, using databases published by the Fire and Disaster Management Agency (FDMA).<sup>12</sup> These include all emergency transportation data of Japan and the All-Japan Utstein Registry. Researchers can use these data with permission from the FDMA. The study was approved by the ethics committees of Kagawa University School of Medicine and Kagawa Prefectural Central Hospital, and the need for informed consent was waived (approval numbers 2019-134 and 1012).

### Dataset

All emergency transportation data collected from fire departments in Japan are collected in an annual report. This includes information about ambulance dispatch (e.g., EMS time lapse from call to hospital arrival), patients (e.g., age, sex, location of occurrence, and severity of injuries and illnesses), and emergency treatment by EMS (e.g., cardiopulmonary resuscitation, foreign body removal, airway management, ventilation and infusions). The all emergency transportation data of Japan did not include detailed information on cardiac arrest (e.g., outcomes at 1 month, discharge, etc.). However, this information was available in the All-Japan Utstein Registry. This is a prospective, national, population-based registry of OHCA that was established by the FDMA in 2005 according to the relevant ethical guidelines in Japan. The registry uses Utstein-style data collection methods and it benefits from the participation of all fire stations with dispatch centers and all collaborating medical institutions. All data are transferred and stored in the nationwide database developed by the FDMA.

We obtained data on cases involving individuals aged  $\geq 18$  years who received emergency services including cardiopulmonary resuscitation (CPR) and removal of foreign bodies from the all emergency transportation data of Japan. Software for matching two data sets was not available. Therefore, with the help from the Medical Informatic Division of Kagawa Prefectural Central Hospital, Microsoft Access 2010 was used to link data items in the two datasets that matched perfectly with each other in terms of date of occurrence, location (prefecture), and patient characteristics (such as age and sex). We then assessed whether the time course of the linked patient data (time of calling the ambulance, time of arrival at the scene, and time of arrival at the hospital) was consistent. In addition, if the data for an airway management item in each data set did not match, it was treated as mismatch data. Patients with similar date of occurrence, location

(prefecture), demographic characteristics (e.g., age, sex), time course, and airway management data were identified (Supplemental).

Data extracted from the All-Japan Utstein Registry allowed us to evaluate cardiac arrest-specific data, including favorable neurological outcome and survival at 1 month or discharge.

### Study participants

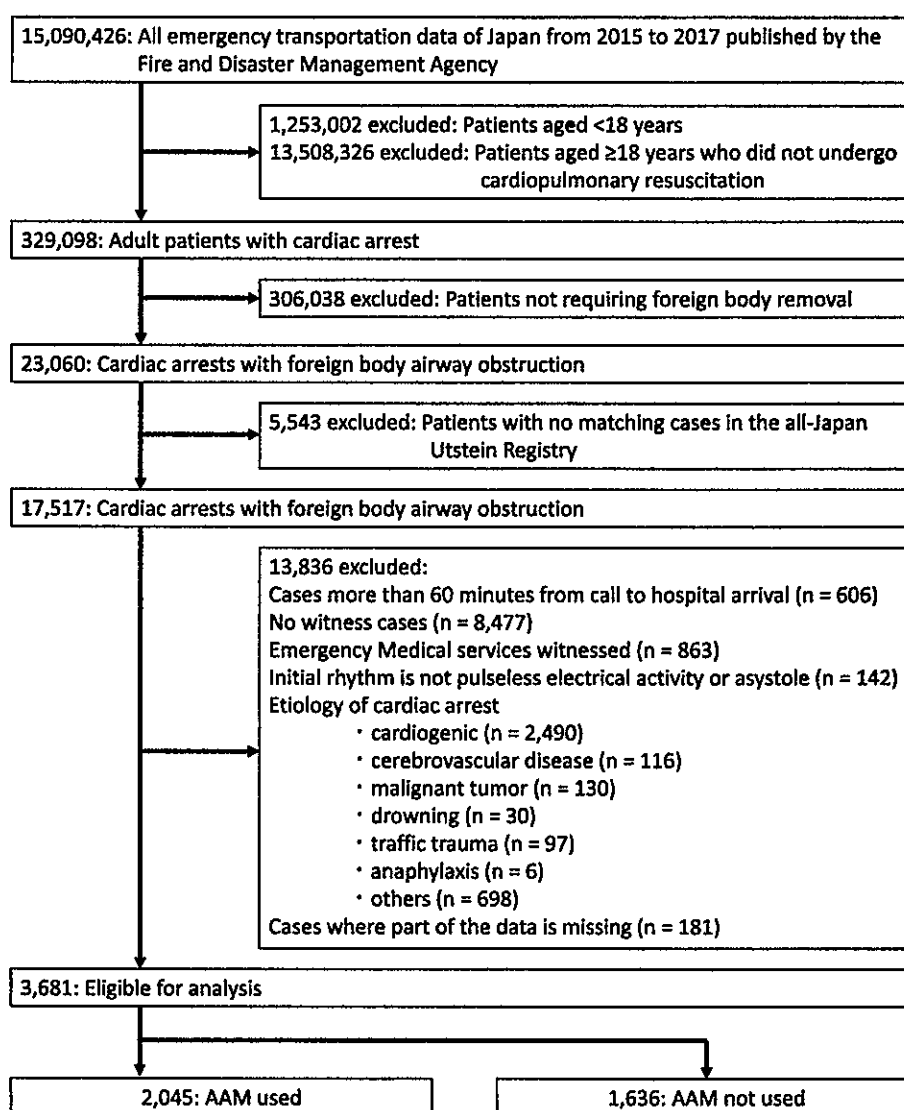
The study included patients aged  $\geq 18$  years who had foreign bodies removed during EMS resuscitation for OHCA during the study period. Foreign body removal was collected from all emergency transportation data of Japan. In this dataset, foreign body removal is checked when the airway obstruction caused by the foreign body is released, for example, foreign body removal using Magill forceps, back blows or abdominal thrusts. We excluded patients with missing or contradictory data, times exceeding 60 min from call to hospital arrival<sup>13</sup> and unwitnessed arrest. We excluded cases of shockable rhythms in which the EMS team should prioritize defibrillation over foreign body removal upon arrival at the scene and cases of cardiac arrest during transport. Only cases with initial cardiac rhythm with pulseless electrical activity (PEA) and asystole were included in the analysis. FBAO was not considered a cause of death in the All-Japan Utstein Registry. Cardiac arrest due to FBAO are commonly classified as external causes or respiratory problems caused by aspiration. To select cases of OHCA due to FBAO, we excluded cases in which the causes of cardiac arrest were cardiogenic conditions, cerebrovascular disease, malignant tumor, drowning, traffic trauma, anaphylaxis, among others (Fig. 1).

### Details of AAM under the EMS system in Japan

The prehospital EMS system in Japan is provided 24 h a day by fire departments throughout Japan. Emergency life-saving technicians (ELSTs) deliver prehospital care in this study, and under the direction of online medical control, they can administer epinephrine and secure advanced airways in cases of OHCA. The options for AAM are ETI placement or the establishment of SGA; however, although the SGA can be placed by all ELSTs, only certified ELSTs can place an ETI during cardiac arrest. ELSTs can establish a peripheral intravenous line. However, only certified ELSTs can administer epinephrine. In Japan, ELSTs are not usually allowed to interrupt resuscitation outside the hospital, and as such, all resuscitated patients are taken to hospital. Resuscitation is not attempted when the case is judged to be deceased, such as decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis. Cardiac arrest is treated according to the Japanese resuscitation guidelines,<sup>8,9</sup> which in turn, are based on the Consensus on Science with Treatment Recommendations by the International Liaison Committee on Resuscitation.<sup>14,15</sup>

### Data collection

We collected the following data from all emergency transportation data of Japan: cardiac arrest year and date, patient age and sex, time of call to the fire department, arrival time at the scene, departure time from the scene, arrival time at the hospital, whether CPR was performed by EMS, whether a foreign body was removed (with or without instrument), and airway management methods (no-AAM, SGA, ETI). We have confirmed that all other data are consistent with the All-Japan Utstein Registry, although the data on foreign body



**Fig. 1 – Flowchart of enrolment of the study participants.**

removal are unique to the all emergency transportation data of Japan. We collected the following data related to cardiac arrest from the All-Japan Utstein Registry: bystander CPR, bystander witness status, dispatcher instructions, ELST presence in ambulance, physician presence in ambulance, initial cardiac rhythm, the time of CPR started by EMS, administration of epinephrine, ROSC, survival 1 month after cardiac arrest or at discharge, and the neurological outcome at 1 month after cardiac arrest or at discharge.

### Study endpoints

The primary endpoint was a favorable neurological outcome at 1 month or at discharge from hospital within 1 month, defined as a Glasgow–Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability).<sup>16,17,18</sup> The secondary outcome was survival at 1 month or at discharge from hospital within 1-calendar month.

### Statistical analysis

Patients were divided into groups who underwent airway management with and without AAM (AAM and non-AAM groups, respectively). To compare baseline characteristics and EMS records, we used the  $\chi^2$  test or Fisher's exact test (expected value < 5) for categorical variables and the Wilcoxon rank sum test for continuous variables.

Potential confounders were adjusted by propensity score matching. Using a multivariate logistic regression model, the propensity score for receiving prehospital AAM in each patient was evaluated. The following variables were included in the model: year of cardiac arrest, age, sex, bystander CPR, dispatcher instructions, presence of ELST in the ambulance, presence of physician in the ambulance, initial cardiac rhythm, removal of foreign body from the airway using an instrument,<sup>19</sup> administration of epinephrine, prehospital ROSC, time from call to CPR performed by EMS, and time from call to hospital

arrival. We performed 1:1 nearest-neighbor matching and set the caliper width for nearest-neighbor matching at 0.2 standard deviations of the propensity score in the logit scale, as recommended. Standardized differences were calculated to evaluate the balance of variables in each predicted propensity score matched cohort, considering the balance to be adequate between groups if these were less than 0.1.

We also performed subgroup analyses for the primary endpoint based on whether or not prehospital epinephrine was administered. Logistic regression analyses were performed to assess the association between the use of AAM and the endpoints. The P for interaction in subgroup analyses was calculated using likelihood ratio test. Finally, odds ratios (ORs) and their 95% confidence intervals (95%CI) were calculated. All statistical analyses were performed using JMP Pro (version 15; SAS Institute INS., Cary, NC, USA), all tests were two-sided, and a P-value of <0.05 was considered statistically significant in all cases.

## Results

We screened all emergency transportation data of Japan published by the FDMA during the study period (n = 15,090,426) and identified 329,098 that concerned adults with documented OHCA. Of the 23,060 that involved the removal of foreign body from the airway, 17,517 were matched with the All-Japan Utstein Registry. Finally, 3681 met the eligibility criteria for this study and were divided into the AAM group (n = 2045) and non-AAM group (n = 1636) (Fig. 1).

### Findings before propensity score matching (PSM)

The characteristics of adult OHCA patients with foreign bodies removed with or without AAM during resuscitation are shown in Table 1. Compared with the non-AAM group, the AAM group had significantly higher rates of bystander CPR (67.0 % vs. 62.3%, p = 0.003) and

**Table 1 – Characteristics before and after propensity score matching according to the use of advanced airway management during resuscitation for out-of-hospital cardiac arrest caused by airway obstruction.**

	Before PSM			Standardized difference	After PSM			Standardized difference
	AAM group n = 2045	Non-AAM group n = 1636	p-value		AAM group n = 1210	Non-AAM group n = 1210	p-value	
Number of patients per year, n (%)			0.063			0.921		
2015	663 (32.4)	553 (33.8)		0.029	406 (33.6)	414 (34.2)	0.014	
2016	628 (30.7)	540 (33.0)		0.049	375 (31.0)	367 (30.3)	0.014	
2017	754 (36.9)	543 (33.2)		0.077	429 (35.5)	429 (35.5)	0.000	
Age, median (IQR) <sup>a</sup>	83 (76–89)	82 (74–88)	0.193	0.060	82 (75–88)	83 (75–89)	0.868	
Male sex, n (%)	1138 (55.7)	908 (55.5)	0.929	0.003	649 (53.6)	667 (55.1)	0.463	
Bystander CPR, n (%)	1371 (67.0)	1019 (62.3)	0.003	0.099	795 (65.7)	798 (66.0)	0.898	
Witness status, n (%)			0.283				0.954	
Family	1221 (59.7)	989 (60.5)		0.015	724 (59.8)	737 (60.9)	0.022	
Friend	49 (2.4)	41 (2.5)		0.007	29 (2.4)	32 (2.6)	0.015	
Colleague	7 (0.3)	10 (0.6)		0.039	6 (0.5)	7 (0.6)	0.011	
Passerby	17 (0.8)	23 (1.4)		0.055	13 (1.1)	12 (1.0)	0.008	
Others	751 (36.7)	573 (35.0)		0.035	438 (36.2)	422 (34.9)	0.028	
Dispatcher instruction, n (%)	1552 (75.9)	1203 (73.5)	0.101	0.054	899 (74.3)	904 (74.7)	0.816	
Presence of ELST in the ambulance, n (%)	2035 (99.5)	1603 (98.0)	<0.001	0.138	1202 (99.3)	1200 (99.2)	0.636	
Presence of physician in the ambulance, n (%)	73 (3.5)	90 (5.5)	0.004	0.096	54 (4.5)	54 (4.5)	1.000	
Initial cardiac rhythm, n (%)			0.008	0.088			1.000	
PEA	908 (44.4)	798 (48.8)			564 (46.6)	564 (46.6)		
Asystole	1137 (55.6)	838 (51.2)			646 (53.4)	646 (53.4)		
Foreign body removal, n (%)								
Use of an instrument	1950 (95.4)	1519 (92.9)	0.001	0.106	1145 (94.6)	1146 (94.7)	0.928	
Administration of epinephrine, n (%)	866 (42.4)	257 (15.7)	<0.001	0.614	280 (23.1)	255 (21.1)	0.221	
Prehospital ROSC, n (%)	390 (19.1)	236 (14.4)	<0.001	0.125	172 (14.2)	186 (15.4)	0.423	
Time from call to CPR performed by the EMS team, median (IQR), min <sup>a</sup>	9 (7–11)	9 (7–10)	0.003	0.108	9 (7–11)	9 (7–11)	0.225	
Time from call to hospital arrival, median (IQR), min <sup>b</sup>	34 (29–41)	29 (24–35)	<0.001	0.557	32 (27–36)	31 (26–38)	0.788	

Abbreviations: AAM = advanced airway management; CPR = cardiopulmonary resuscitation; ELST = emergency life-saving technician; EMS = emergency medical services; IQR = interquartile range; PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; SD = standard deviation.

We used the following independent variables in the logistic regression analysis for calculating propensity scores: number of patients per year, age, sex, bystander CPR, dispatcher instruction, presence of ELST and physician in the ambulance, initial cardiac rhythm, removal of a foreign body from the airway using an instrument, administration of epinephrine, prehospital ROSC, time from call to CPR performed by the EMS team, time from call to hospital arrival.

<sup>a</sup> Normal distribution.

<sup>b</sup> Unequal distribution.

asystole as the initial cardiac rhythm (55.6% vs. 51.2%,  $p = 0.008$ ). The AAM group also had a significantly higher proportion of participants with foreign bodies removed using instruments (95.4% vs. 92.9%,  $p = 0.001$ ), requiring epinephrine at the scene (and 42.4% vs. 15.7%,  $p < 0.001$ ), and having prehospital ROSC (19.1% vs. 14.4%,  $p < 0.001$ ). The time from call to hospital arrival was significantly longer in the AAM group than in the non-AAM group (34 min vs. 29 min,  $p < 0.001$ ).

Table 2 shows the outcomes by whether or not AAM was used. Notably, this shows that the proportion of patients with favorable neurological outcomes was significantly lower in the AAM (1.3%) group than in the non-AAM group (4.3%), with an OR of 0.28 (95% CI, 0.18–0.45). Nevertheless, survival was not significantly different between the AAM group (12.0%) and non-AAM group (13.9%), with an OR of 0.85 (95% CI, 0.70–1.03).

### Findings after PSM

Propensity score matching resulted in 1210 matched pairs with balanced baseline characteristics between the two groups (standardized difference  $< 0.1$ ) (Table 1). Outcomes were similar to those before matching, with a significantly lower percentage of favorable neurological outcomes in the AAM group compared with the non-AAM group (1.2% vs. 3.6%; OR 0.34 [95% CI, 0.19–0.62]) and no significant difference in survival (13.3% vs. 12.5%, respectively; OR 1.08 [95% CI, 0.84–1.37]) (Table 2).

### Subgroup analyses

In the subgroup analyses, the percentage of favorable neurological outcome was lower in the AAM group (1.6%) than in the non-AAM group (4.2%) among patients not receiving prehospital epinephrine administration, with an OR of 0.38 (95% CI, 0.21–0.68). However, no significant differences were observed between the two groups among patients requiring prehospital epinephrine (Table 3).

The percentage of 1 month survival was significantly higher in the AAM group (15%) with epinephrine administration; however, the AAM and non-AAM groups showed no significant differences in terms of patients not receiving epinephrine (Table 3).

## Discussion

In this study, we showed that favorable neurological outcomes occurred significantly less often when AAM was used than when it was

not after the removal of foreign bodies by ELSTs from airways following OHCA due to FBAO. However, in patients who underwent epinephrine administration in the subgroup analysis, there was no significant difference in neurological outcome between AAM and non-AAM groups, and 1 month survival was significantly better in AAM group.

As several reports have shown, pre-hospital epinephrine use is associated with survival, but not neurological outcomes.<sup>20,21,22</sup> A subgroup analysis was performed to determine if there was a difference in the effect of AAM with and without epinephrine on both outcomes. In this study, the percentage of patients in the AAM group who received epinephrine was reduced after PSM adjustment, and the rate of epinephrine administration is low worldwide. The reasons why epinephrine is not administered in Japan may be early ROSC, refusal of the family for epinephrine administration, intravenous failure, and absence of ELST who could administer epinephrine. Therefore, the non-epinephrine group may be a mixture of the early ROSC and difficult-to-resuscitate groups. Since early epinephrine administration is recommended for the treatment of PEA and asystole,<sup>23</sup> caution should be exercised in interpreting the results of this study. Moreover, in our results, the odds ratios of survival (1.08) and neurologically intact survival (0.34) were different. The reason for this discrepancy is that the epinephrine-treated patients who received AAM had the best survival (15%) and the worst favorable neurological outcome (0%), which may have been influenced by the therapeutic effects of epinephrine (Table 3), and post-hospitalization treatment may have affected the results. The data did not show how much targeted temperature management was conducted after admission.<sup>24</sup> It is also possible that the families of the elderly intubated patients refused active treatment, such as targeted temperature management, after hospitalization and received only life-sustaining treatment. In Japan, once a patient is intubated, it is rarely removed, and artificial respiration is often continued.

The effects of prehospital AAM on the neurological outcomes of patients experiencing OHCA have previously been examined.<sup>11,25</sup> Consistent with the current study, it has been reported that prehospital AAM is associated with poor neurological outcomes in cases of respiratory OHCA,<sup>26</sup> but it has also been reported that early AAM for OHCA may improve the 1 month survival among patients with non-shockable rhythms.<sup>2</sup> Our study is the first observational study to examine the effect of AAM specifically after foreign body removal of

**Table 2 – Outcomes for out-of-hospital cardiac arrest with foreign body removal by the use of advanced airway management.**

Outcomes <sup>a</sup>	Before PSM				After PSM			
	AAM n = 2045	Non-AAM n = 1636	p-value	OR (95% CI)	AAM n = 1210	Non-AAM n = 1210	p-value	OR (95% CI)
Favorable neurological outcome, n (%)	26 (1.3)	71 (4.3)	<0.001	0.28 (0.18–0.45)	15 (1.2)	43 (3.6)	<0.001	0.34 (0.19–0.62)
Survival, n (%)	246 (12.0)	227 (13.9)	0.096	0.85 (0.70–1.03)	161 (13.3)	151 (12.5)	0.544	1.08 (0.84–1.37)

Abbreviations: AAM = advanced airway management; CI = confidence interval; OR = odds ratio; PSM = propensity score matching.

<sup>a</sup> At 1 month or at hospital discharge within 1 month.

**Table 3 – Subgroup analyses after propensity score matching: outcomes with and without epinephrine use.**

Outcomes <sup>a</sup>	Subgroups	AAM n = 1210	Non-AAM n = 1210	p-value	OR (95% CI)	p for interaction
Favorable neurological outcomes, n (%)	Epinephrine	0/280 (0.0)	3/255 (1.2)	0.108	0.13 (0.01–1.38) <sup>b</sup>	0.156
	Non-epinephrine	15/930 (1.6)	40/955 (4.2)	<0.001	0.38 (0.21–0.68)	
Survival, n (%)	Epinephrine	42/280 (15.0)	23/255 (9.0)	0.035	1.78 (1.04–3.05)	0.038
	Non-epinephrine	119/930 (12.8)	128/955 (13.4)	0.696	0.95 (0.73–1.24)	

Abbreviations: AAM = advanced airway management; CI = confidence interval; OR = odds ratio.  
<sup>a</sup> At 1 month or at hospital discharge within 1 month.  
<sup>b</sup> Corrected odds ratio.

OHCA by FBAO, although we have not been able to examine the time of AAM.

Foreign body removal from the airway and bystander CPR have been associated with improved neurological outcomes patients following FBAO.<sup>27,28</sup> The immediate removal of foreign body is essential in the management of airway obstruction.<sup>29</sup> AAM is performed when ventilation is difficult even after foreign body removal and may delay the achievement of effective ventilation compared to the non-AAM group. Our study did not provide detailed information on the time of foreign body removal and ventilation assessment. In patients with suspected FBAO, the following factors should be considered: whether the dispatcher instructed the bystander to attempt abdominal thrusts or back blow, whether the foreign body had already been removed upon arrival of the EMS team, the time between FBAO and foreign body removal, and the ventilation status after foreign body removal. Recently, methods and devices to remove foreign bodies have been investigated,<sup>30,31,32</sup> and such major interventions have been reported to successfully reduce FBAO.<sup>33</sup> Soroudi et al. showed that the mortality rate is 3.3% in cases in which suffocation was managed before the arrival of the EMS team.<sup>34</sup> Bystander interventions should be considered with factors that influence the prognosis of FBAO. In the future, randomized controlled trials and observational cohort studies will be needed to evaluate the effectiveness of prehospital AAM for FBAO patients presenting with OHCA.<sup>35</sup>

The current study had several limitations that should be addressed. First, this was a retrospective observational study; therefore, we considered the risk of selection bias and the effects of uncontrolled confounding factors. In addition, PSM was performed. However, the effects of residual confounding factors, particularly that caused by indication, were not completely eliminated. Moreover, the rate of prehospital ROSC was adjusted by PSM, but the time to ROSC was not, so resuscitation time bias existed and caution should be taken in interpreting the results. Second, we only considered patients with initial cardiac rhythm with PEA or asystole upon arrival of the EMS team, yet in animals, it has been reported that hypoxia caused by asphyxiation can induce ventricular fibrillation or tachycardia. Given that most lethal arrhythmias are thought to be cardiogenic, no studies have considered the use of defibrillation or other treatments when arrhythmia is caused by asphyxia. Third, we obtained information on whether dispatcher instruction was performed but could not obtain information on its content. In our study, the EMS removed the foreign body in all cases, and it is possible that bystander removal was not performed or was unsuccessful even in cases where dispatcher instruction was performed and bystander CPR was performed. Fourth, there is a lack of detailed information on AAM. We have no information about the initial success rate or the number of times AAM

was attempted. Also, the choice of device for airway management varies by region and ELST preference. Previous studies have reported that initial intubation failure is associated with increased chest compression interruption time and that ETI performed by less experienced technicians has a lower success rate than SGA.<sup>36,37,38</sup> In the case of out-of-hospital cardiac arrest, it is also known that there is a difference in favorable neurological outcome between prehospital SGA and ETI.<sup>39,40</sup> Our study was unable to distinguish between the two because of the use of PSM. When we checked, there was no difference between the ETI and SGA groups in terms of favorable neurological outcomes in our dataset (before and after PSM,  $p = 1.000$ ). Fifth, treatment in the hospital to which the patient was transported has an impact on the neurological outcome of non-cardiogenic OHCA. However, data regarding this factor were not available.<sup>41</sup>

## Conclusions

The rate of favorable neurological outcomes was significantly lower when ELSTs used AAMs than when they did not following OHCA due to FBAO. Although we have not demonstrated the benefit of AAM for patients with OHCA due to FBAO, further study will be required to confirm the efficacy of AAM for those patients.

## Author contributions

Kanako Otomune and Toru Hifumi were responsible for the conception of the study, and they drafted and revised the manuscript. Kanako Otomune and Toru Hifumi established the study design and drafted the manuscript. Keisuke Jinno, Kentaro Nakamura, Tomoya Okazaki, Akihiko Inoue, Kenya Kawakita, and Yasuhiro Kuroda revised the manuscript. All authors read and approved the final manuscript.

## Conflict of interest

The authors declare that they have no competing interests.

## Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

## Acknowledgements

We thank all of the members of the all emergency transportation data of Japan and the All-Japan Utstein Registry. We thank the Medical Informatic division of Kagawa Prefectural Central Hospital.

## 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.resplu.2021.100140>.

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