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Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: An observational study

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ABSTRACT

Objectives: To describe the epidemiologic features of out-of-hospital cardiac arrest (OHCA) caused by anaphylaxis and clarify the factors associated with outcomes.

Design: Observational study.

Setting: Data from the Japanese Fire and Disaster Management Agency database.

Participants: Of the 879,057 OHCA events during the period of 2013-2019, 292 patients with OHCA caused by anaphylaxis in whom prehospital resuscitation was attempted were included in the analysis.

Primary and secondary outcome measures: The primary outcome was neurologically favorable 1-month survival, defined as cerebral performance category 1 or 2. The secondary outcome was 1-month survival.

Results: The proportion of OHCAs caused by anaphylaxis was high in non-elderly and male patients, in July–September, and during business hours. Bystander- (adjusted odds ratio [OR] = 4.43; 95% confidence interval [CI] = 1.84–10.7) and emergency medical service-witnessed events (adjusted OR = 3.28; 95% CI = 1.21–8.87) were associated with higher rates of neurologically favorable 1-month survival, as well as better 1-month survival. Shockable initial ECG rhythms were recorded in only 19 patients (6.5%), and prehospital defibrillation was attempted in 16 such patients (84.2%). Neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes. Patients requiring advanced airway
management had poorer neurological outcomes (adjusted OR = 0.28; 95% CI = 0.14–0.58),
and worse 1-month survival (adjusted OR = 0.17; 95% CI = 0.07–0.42).

**Conclusions:** Few cases of OHCA were attributable to anaphylaxis. Witnessed OHCAs,
particularly those witnessed by bystanders, were associated with better neurological
outcomes. Airway complications requiring advanced airway management tended to be
associated with poor outcomes.

(Word count: 256)

**Strengths and limitations of this study**

- This study specifically examined out-of-hospital cardiac arrests (OHCA) caused by
  anaphylaxis.
- The findings highlighted the effects of variables such as the witness status and use of
  prehospitalization defibrillation, epinephrine, and advanced airway management on
  the outcomes of OHCA caused by anaphylaxis.
- It was also emphasized that airway complications can affect the outcomes of OHCA
  caused by anaphylaxis.
- Further analyses are limited because of the small number of OHCA caused by
  anaphylaxis and insufficient information gathering prior to emergency medical service
  (EMS) arrival.
• The present results may not be generalizable to other countries with different EMS systems.

KEYWORDS

out-of-hospital cardiac arrest; anaphylaxis; bystander; emergency medical service; outcome
INTRODUCTION

Anaphylaxis is defined by the World Allergy Organization as “the most serious clinical manifestation of an acute systemic allergic reaction.” Anaphylaxis begins with skin and mucosal symptoms, followed by life-threatening problems involving the airways (pharyngeal or laryngeal edema), breathing (bronchospasm with tachypnea), and the circulation (hypotension, tachycardia). Drug exposure, insect bites, and food consumption are common pathways of exposure to allergens associated with anaphylaxis. Lethal anaphylaxis develops immediately after contact with the trigger, followed by upper airway obstruction attributable to laryngeal edema, circulatory insufficiency attributable to anaphylactic shock, bronchoconstriction leading to asthma-like respiratory insufficiency, and hypoxemia attributable to pulmonary edema leading to cardiac arrest. An unusual form of anaphylactic circulatory collapse known as Kounis syndrome may occur because of coronary spasm or acute coronary syndrome, which may lead to the occurrence of ventricular tachycardia and fibrillation.

A review of anaphylaxis revealed an annual incidence of 1.5–7.9/100,000 people, and estimates suggest that 0.05%–2% of the population will experience anaphylaxis in their lifetimes. In recent years, a combination of genetic and environmental factors has led to greater sensitivity for detecting anaphylactic reactions. However, the mortality rate of anaphylaxis has remained low and stable (0.3%).
Anaphylaxis occurs in both in-hospital and out-of-hospital settings, and little information is available on factors related to epidemiology or outcomes. To our knowledge, few studies used a nationwide out-of-hospital cardiac arrest (OHCA) database to explore the incidence of anaphylaxis-induced OHCA. Of these, a representative study from South Korea reported 196,158 OHCA cases and attributed 233 cases (0.12%) to anaphylaxis.\(^\text{11}\)

To improve the clinical outcomes of patients with anaphylaxis-associated OHCA, correctable factors associated with outcomes should be identified. This study examined the epidemiologic features of OHCA caused by anaphylaxis and the factors associated with outcomes using a large nationwide OHCA database in Japan.

**METHODS**

**Population and setting**

Japan features 47 prefectures, and the country is divided into eight regions from north to south. In 2015, Japan’s population totaled 127 million, and 26.6% of people were \(\geq 65\) years old.\(^\text{12}\) There were 6184 ambulances operating in 750 fire departments throughout the country\(^\text{13}\), and no termination of resuscitation rules exist for prehospital settings. In this situation, unless a patient with OHCA is obviously dead (such as decapitation) or has post-mortem changes, emergency medical service (EMS) personnel continue resuscitation until arrival to the hospital. Paramedics are allowed to use advanced airway adjuncts and start a
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peripheral venous infusion of Ringer’s lactate. Authorized paramedics are permitted to insert
traceal tubes and administer intravenous epinephrine, but they are not allowed to administer
other drugs. To care for patients with OHCA, EMS personnel used a protocol created by their
regional medical control council based on Japan Resuscitation Council Guidelines.14

Data selection

Consent was obtained from the Japanese Fire and Disaster Management Agency
(FDMA) to analyze nationwide OHCA data prospectively collected between Jan 1, 2013 and
Dec 31, 2019. This population-based observational study was approved by the review board
of Ishikawa Medical Control Council.

The All-Japan Utstein Registry of FDMA contains Utstein-style data,15 including
patient sex, age, witness status, initial electrocardiogram (ECG) rhythm, prehospital
defibrillation, prehospital physician involvement, epinephrine administration, advanced
airway management, recorded time of witness, bystander cardiopulmonary resuscitation
(CPR) initiation, emergency call, time to EMS vehicle arrival at the scene and hospital, EMS
contact with patient, EMS CPR initiation, and survival at 1 month with cerebral performance
category (CPC).16

According to the anaphylaxis guidelines of the Japanese Society of Allergology17,
clinical diagnostic criteria for anaphylaxis include changes in vital signs as well as symptoms
such as skin or mucous membranes, respiratory, circulatory, and gastrointestinal tracts.

However, the onset of anaphylaxis or OHCA is rarely witnessed by healthcare personnel. It is difficult for the general public to assess symptoms correctly, let alone measure vital signs. Therefore, physicians collaborate with EMS personnel to clinically assess whether OHCA was caused by anaphylaxis. The physician at discharge from the last hospital to care facilities or home provided information on 1-month survival and CPC to the fire department.

From the cleaned nationwide database of 879,057 patients with OHCA recorded during the study period, we extracted 294 patients (0.03%) with anaphylaxis-associated OHCA. Two patients with no prehospital resuscitation attempts were excluded from consideration, and the remaining 292 patients were analyzed (Figure 1).

For epidemiologic analyses, we obtained detailed information on location, the incidence of epinephrine auto-injection before cardiac arrest from another FDMA database which covered the period of 2015 to 2019. The result of this additional analysis was shown only in the supplemental table.

_Patient involvement_

Patients were not involved in study design, data interpretation, or report writing.

The requirement for informed consent for patients was waived because the data were obtained from an existing anonymous database.
Outcome measures

The primary study outcome was a neurologically favorable 1-month survival, defined as a CPC score of 1 (good recovery) or 2 (moderate disability). The secondary outcome was the 1-month survival.

Statistical analysis

We performed an epidemiological analysis by comparing the incidence by region, month (season), time of day (business time vs. other time), day (weekend vs. weekday), age (elderly [≥70 years] vs. non-elderly), and sex. Considering monthly averages of ambient temperature and the rainy weather in June (commonly called the “plum rain” in Japan), we defined the summer season as July to September. Differences across groups for nominal variables were assessed using the chi-squared test. We reported crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). For each analysis, the null hypothesis was evaluated at a two-sided significance level of $P < 0.05$. Multivariable logistic regression analysis was performed to identify major factors associated with neurologically favorable 1-month survival and 1-month survival. Multivariable logistic regression analysis included the following factors known to be associated with survival: sex, age, witnessed status (unwitnessed, bystander-witnessed, and EMS-witnessed), initial rhythm (shockable or not),
prehospital defibrillation, prehospital epinephrine administration, advanced airway
management (esophageal obstructive or supra-pharyngeal airway and tracheal intubation),
advanced life support by physicians, and the intervals between contact to EMS arrival (EMS
response time) and between EMS arrival and hospital arrival (EMS transportation time). All
statistical analyses were performed using JMP Pro 16 software (SAS Institute, Cary, NC,
USA).

RESULTS

Overview of case selection

Of the included patients, OHCA onset was unwitnessed for 71 patients, witnessed
by a bystander for 161 patients, and witnessed by EMS personnel for 60 patients. Shockable
initial rhythms were recorded in 4.2% (3/71) of unwitnessed cases, 8.1% (13/161) of
bystander-witnessed cases, and 5.0% (3/60) of EMS-witnessed cases. Conversion from
initially non-shockable rhythms to shockable rhythms was recorded in 1.5% (1/68) of
unwitnessed cases, 4.1% (6/148) of bystander-witnessed OHCA, and 8.8% (5/57) of EMS-
witnessed OHCA. Shockable initial rhythms were recorded in 6.5 (19/292) and 7.2% (16/221)
of all OHCAs and witnessed OHCAs, respectively, and conversions to shockable rhythms
were recorded in 4.4 (12/273) and 5.4% (11/205) of these events, respectively. Prehospital
defibrillation was performed in 66.7 (2/3), 84.6 (11/13), and 100% (3/3) of unwitnessed,
bystander-witnessed, and EMS-witnessed OHCAs, respectively. Prehospital defibrillation was performed in 12 of 273 patients with non-shockable initial rhythms after conversion to shockable rhythms (Fig. 1).

**Epidemiologic analyses of OHCA cases caused by anaphylaxis**

The annual incident rate of OCHA was 115.4 per 100000 in the Japanese population, and the proportion caused by anaphylaxis was 0.03%. The epidemiology of OHCA caused by anaphylaxis was analyzed per 1000 cases (Table 1). The proportion was 1.64 in the Shikoku region of Japan, which was significantly higher than the proportions of 0.20–0.65 in the other seven regions. The nationwide proportion was higher in July–September (0.78 vs. 0.22 during other months), during business hours (0.43 vs. 0.26 during other times), and among non-elderly patients (0.57 vs. 0.24 in elderly patients) and male patients (0.39 vs. 0.26 in female patients).

Table 1. Epidemiologic analysis of OHCA cases caused by anaphylaxis

| Variable                  | Incidence rate   | Statistics  |
|---------------------------|------------------|-------------|
|                           | (number/1000 OHCA cases) | (Yates’ chi-square) |
| Region in Japan (north to south) |                   |             |
| Hokkaido                  | 0.23 (9/38,832)  | <0.01       |
| Tohoku                    | 0.32 (24/75,668) |             |
| Kanto                     | 0.20 (58/290,619) |             |
| Chubu                     | 0.36 (57/158,185) |             |
| Location      | Rate (Cases/Population) |
|--------------|-------------------------|
| Kinki        | 0.34 (51/148,042)       |
| Chugoku      | 0.43 (21/49,032)        |
| Shikoku      | **1.64 (46/28,030)**    |
| Kyushu       | 0.65 (59/90,649)        |
| Month (season) | <0.01                 |
| July-September (Summer) | **0.78 (136/174,336)** |
| Other        | 0.22 (158/704,721)      |
| Time of day (emergency call) | <0.01             |
| Business hours (9:00 am-16:59 pm) | **0.43 (169/397,001)** |
| Other        | 0.26 (125/482,056)      |
| Weekday      | 0.80                    |
| Weekend      | 0.33 (84/256,620)       |
| Other        | 0.34 (210/622,437)      |
| Age          | <0.01                   |
| Elderly (>70)| 0.24 (152/631,947)      |
| Other        | **0.57 (142/247,110)**  |
| Sex          | <0.01                   |
| Male         | **0.39 (197/502,059)**  |
| Female       | 0.26 (97/376,998)       |

OHCA, out-of-hospital cardiac arrest.

When detailed locations of OHCA were analyzed for 167 cases from 2015 to 2019, nearly half (44.3%) of cases occurred at home. Medical institutes (25.1%) including medical office, and places for outdoor activities (23.4%) were other major locations of anaphylactic OHCA. Only one case was treated with epinephrine auto-injection before descending into cardiac arrest (Supplemental Table 1).
Factors associated with neurologically favorable 1-month survival

The neurologically favorable 1-month survival rate was 26.7% (78/292). In univariate analysis, bystander- and EMS-witnessed OHCA cases, and shorter EMS response times were associated with better neurological outcomes. Poorer neurological outcomes were associated with male sex, prehospital epinephrine administration, advanced airway management, and with advanced life support by physicians. After adjustment for the confounding factors, bystander- (adjusted OR = 4.33; 95% CI = 1.84–10.7) and EMS-witnessed OHCA (adjusted OR = 3.28; 95% CI = 1.21–8.87) were the predominant factors associated with better neurological outcomes, but the association between shorter EMS response times and favorable neurological outcomes were not significant. Advanced airway management was the sole factor associated with poorer neurological outcomes (adjusted OR = 0.17; 95% CI = 0.07–0.42) in the multivariate-adjusted models. Neither shockable initial rhythms nor prehospital defibrillation was associated with neurological outcomes (Table 2).
Table 2. Factors associated with neurologically favorable 1-month survival

| Characteristics of OHCA | Neurological outcome at 1M | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-------------------------|---------------------------|-------------------|---------------------|
|                         | Favorable (N = 78)        | Unfavorable (N = 214) | or P value | or P value |
| Male patients, % (N)    | 56.4% (44)                | 71.5% (153)        | 0.52 (0.30–0.88) | 0.76 (0.42–1.39) |
| Elderly (≥ 70y) patients, % (N) | 55.1% (43)                | 50.9% (109)        | 1.18 (0.70–1.99) | 1.35 (0.75–2.45) |
| Witness status, % (N)   |                           |                   |                   |                   |
| Unwitnessed             | 10.3% (8)                 | 28.5% (61)         | Reference         | Reference         |
| Bystander-witnessed     | 66.7% (52)                | 51.9% (111)        | 3.57 (1.59–8.01)  | 4.43 (1.84–10.7)  |
| EMS-witnessed           | 23.1% (18)                | 19.6% (42)         | 3.27 (1.30–8.21)  | 3.28 (1.21–8.87)  |
| Shockable initial rhythm, % (N) | 6.4% (5)                 | 6.5% (14)          | 0.98 (0.34–2.81)  | 1.53 (0.27–8.76)  |
| Prehospital defibrillation, % (N) | 7.7% (6)                 | 10.3% (22)         | 0.73 (0.28–1.87)  | 0.57 (0.12–2.71)  |
| Prehospital epinephrine administration, % (N) | 11.5% (9)                | 27.6% (59)         | 0.34 (0.16–0.73)  | 0.51 (0.22–1.20)  |
| Advanced airway management, % (N) | 7.7% (6)                 | 35.5% (76)         | 0.15 (0.06–0.36)  | 0.17 (0.07–0.42)  |
| Advanced life support by physician, % (N) | 14.1% (11)                | 28.5% (61)        | 0.41 (0.20–0.83)  | 0.52 (0.22–1.23)  |
| Physician in ambulance, % (N) | 6.4% (5)                 | 13.1% (28)         | 0.45 (0.17–1.22)  | 0.44 (0.13–1.42)  |
| Time intervals, min, median (IQR) |                   |                   |                   |                   |
OHCA caused by anaphylaxis requiring advanced life support by physicians is likely to have occurred in medical institutions. Despite the higher rate of epinephrine administration (33.3%) and defibrillation (18.1%) in these cases, they were not associated with good outcomes.

### Factors associated with 1-month survival

The 1-month survival rate was 35.3% (103/292). As presented in Supplemental Table 2, both univariate and multivariable regression analyses revealed that bystander- and EMS-witnessed OHCA and shorter EMS response times were associated with better 1-month survival, whereas male sex, prehospital epinephrine administration, and advanced airway management were associated with worse 1-month survival. Advanced life support by physicians was associated with lower survival rates in the univariate analysis, but the association was not significant after adjustment for confounding factors in the multivariate analysis. Notably, neither shockable initial rhythms nor prehospital defibrillation was
associated with 1-month survival.

**Timing of epinephrine administration**

The median interval (interquartile range) between EMS contact and epinephrine administration was 15 (12–20) min. No patients received epinephrine within 6 min of EMS contact (Supplemental Fig. 1).

**DISCUSSION**

This study clarified the epidemiological features of OHCA caused by anaphylaxis and the factors associated with outcomes using a nationwide database from Japan. Although the number of target cases was small, this study is considered meaningful because the analysis is based on large statistical data representing Japan.

Our findings showed that, of 1000 OHCA cases, approximately 0.3 were caused by anaphylaxis, and was much lower than previously reported in South Korea (1.2):\(^{11}\) In this study, the proportion of all OHCA cases in the total population was 115.4 per 100,000 people per year, and OHCA caused by anaphylaxis was 0.039; the South Korean report was 49.0 and 0.058, respectively. In Japan, instances of OHCA caused by anaphylaxis were also low, about two-thirds of that reported in South Korea. In addition to these differences between the countries, the difficulty of generalizing the clinical assessment of anaphylaxis may also be a
factor because the onset of anaphylaxis or cardiac arrest is rarely witnessed by healthcare professionals.

Conversely, as reported in South Korea, our results indicated that the incidence of anaphylaxis-induced OHCA increased during the day and during summer. In addition, non-elderly and male patients had increased rates of anaphylaxis-induced OHCA. In Japan, anaphylaxis is reported to kill 50–80 people each year, and most cases are caused by drugs and bee stings. The high number of insect bites and stings (especially bee stings) in summer might be one of the factors contributing to the increased rate of anaphylaxis-induced OHCA in this season. Physical and environmental factors such as exercise and sunlight were reported to be associated with the risk of anaphylaxis, which may also explain the increased rate of anaphylaxis during summer.

The rate of anaphylaxis-induced OCHA was unusually high in Shikoku, but the proportion of non-elderly people and the number of deaths attributable to bee stings did not differ between Shikoku and other regions. In addition, although “udon” noodles are commonly consumed in Shikoku, the consumption of wheat, one of the typical dietary allergens, is not excessively high. Similarly, no industrial activity has been reported dealing with substances that cause asthma and other allergic diseases, which are peculiar to this region. Although further investigation is needed, it appears that the incidence of anaphylaxis-induced OCHA could vary by region, even in Japan.
OHCA caused by anaphylaxis has been reported to be associated with better outcomes than other types of noncardiogenic OHCA. Bystanders can witness the progression from the initial symptoms of anaphylaxis to worsening, and they were in a position to notice anomalies earlier than EMS and take necessary actions, which could explain why witnessed OHCA was associated with better outcomes. Additionally, based on information from bystanders, EMS personnel potentially suspected anaphylaxis earlier after the onset of OHCA.

The causes of death from anaphylaxis include upper airway obstruction, circulatory insufficiency, bronchoconstriction, and hypoxemia. Respiratory symptoms are more common than cardiovascular symptoms in anaphylaxis, and most cases of lethal anaphylaxis are caused by airway obstruction and severe asthma. In this study, advanced airway management for airway obstruction was the most detrimental factor associated with outcomes. In Japan, advanced airway management is generally performed by authorized paramedics when normal bag-valve-mask ventilation is insufficient. It was reported that the autopsy findings of anaphylactic shock death were predominantly pulmonary congestion/pulmonary edema, upper airway edema, and bronchial mucus plug/severe swelling. Poor outcomes are thus likely to be associated with airway obstruction and bronchoconstriction requiring advanced airway management rather than with advanced airway management itself.

In general cases of OHCA, epinephrine administration is not associated with a good
neurological prognosis\textsuperscript{27}, but administration within 10 minutes has been reported to be associated with a good neurological prognosis.\textsuperscript{28} In circulatory instability and cardiac arrest attributable to anaphylaxis during anesthesia, rapid intravenous administration of epinephrine had been reported to be effective and associated with good neurological outcomes.\textsuperscript{29} However, epinephrine administration was not associated with better outcomes in this study, which may be explained by the prolonged interval between onset and drug administration. In OHCA, immediate administration of epinephrine is difficult because of the time required for EMS personnel to arrive and the need to follow the resuscitation guidelines.\textsuperscript{30} In addition, it is unclear whether delayed intravenous epinephrine administration improves severe respiratory and cardiovascular complications caused by anaphylaxis in patients with OHCA and whether the treatment has side effects.

Kounis syndrome is frequently associated with drugs, and most cases have been easily and successfully resuscitated by defibrillation.\textsuperscript{31, 32} There are fewer reports of Kounis syndrome in OHCA than in in-hospital cardiac arrest. As a factor, Kounis syndrome is not be fully recognized even by medical professionals, and it may have been diagnosed and treated as cardiogenic coronary artery syndrome because of the lack of clear allergen exposure information.

Shockable initial rhythms represent a known major factor associated with better outcomes for OHCA, particularly cardiogenic OHCA.\textsuperscript{16} In this study, the rates of shockable
initial rhythms and conversion to shockable rhythms were lower than reported previously for
general OHCA.33,34 Meanwhile, neither shockable initial rhythms nor prehospital
defibrillation was associated with better outcomes for OHCA caused by anaphylaxis. These
results suggest that respiratory insufficiency is the main pathology of OHCA caused by
anaphylaxis, whereas cardiogenic elements are minor factors. In addition, defibrillation may
be less effective because of noncardiac ventricular fibrillation associated with hypoxemia.

OHCA caused by anaphylaxis requiring advanced life support by physicians is
likely to have occurred in medical institutions (25.1% in 167 cases with detailed information
on location). Despite the higher rate of epinephrine administration and defibrillation in these
cases, they were not associated with good outcomes. Although OHCA caused by anaphylaxis
is a more serious and fatal situation, it also suggests that medical institutions may not be
adequately responding to anaphylaxis. Therefore, it emphasizes the importance of prevention
of anaphylaxis, early detection or notification, and appropriate treatment. Anaphylaxis must
be widely recognized by the general public and healthcare professionals, and the risk of
anaphylaxis should be recognized according to patients’ medical history. Persons at high risk
of anaphylaxis should carry an epinephrine auto-injection kit35 and avoid outdoor activities
alone. Unfortunately, supplemental analysis in this study revealed that auto-injection kit was
applied only in one case during 5 years.
LIMITATIONS

Although this study covered a 6-year period in the community population, the number of patients with OHCA caused by anaphylaxis was small. Information on in-hospital management and treatment, causes of anaphylaxis, or the use of epinephrine auto-injection kits was not collected. Although EMS personal were encouraged to interview the bystanders and identify bystander-related time factors and resuscitation efforts through interview, the records before EMS contact with the patient may be inaccurate. Some cases of anaphylactic circulatory collapse were assessed to be cardiogenic acute coronary syndrome, and it is undeniable that this may have affected patient outcomes. In addition, although all OHCA cases are registered in the FDMA database, the present results may not be generalizable to other countries with different EMS systems. Data in other countries will thus need to be analyzed independently.

CONCLUSIONS

The proportion of cases of OHCA caused by anaphylaxis was extremely low in Japan. Witnessed OHCA, particularly those witnessed by bystanders, were associated with better neurologically favorable outcomes. Compared with common OHCA, there were few examples of shockable initial rhythms and conversion to shockable rhythms. Shockable rhythms, prehospital defibrillation, and epinephrine administration were not associated with
better outcomes. Airway complications requiring advanced airway management appeared to be associated with poor outcomes.

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COMPETING INTERESTS

None

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AUTHORS’ CONTRIBUTIONS
Conception and study design: KM, AY, and HI; data acquisition: KM, AY, and HI; data analyses and/or interpretation: KM, AY, and HI; manuscript drafting: KM, AY, and HI; critical manuscript revision for important intellectual content: AY, HI and YW. KM and AY contributed equally to this article as the first authors. All authors have read and approved the final version of the manuscript.

DATA SHARING STATEMENT

No data are available. The data used in this study are not publicly available. The data are accessible through the Fire and Disaster Management Agency (E-mail: fdma-goiken@ml.soumu.go.jp).

ETHICS STATEMENT

Patient consent for publication

Not applicable.

Ethics approval

This study was approved by the institutional review board of the Ishikawa Medical Control Council (reference number 2012-3). And conducted by the study group comprising of members of the Ishikawa Medical Control Council and their collaborators. Patient consent
was not required for use of the secondary data.

REFERENCES

1. Cardona V, Ansotegui I, Ebisawa M, et al. Anaphylaxis Guidance 2020. World Allergy Organization Journal 2020; doi:10.1016/j.waojou.2020.100472.

2. Anaphylaxis: assessment and referral after emergency treatment. NICE Clinical Guidelines No. 134; 2020 Aug 24. ISBN-13: 978-1-4731-3867-4.

3. Emergency treatment of anaphylaxis. Guidelines for healthcare providers Working Group of Resuscitation Council UK May 2021

4. Anagnostou K, Turner PJ. Myths, facts and controversies in the diagnosis and management of anaphylaxis. Arch Dis Child 2019;104:83–90. doi:10.1136/archdischild-2018-314867.

5. Richard P. Fatal anaphylaxis in the UK, 1992-2001. Novartis Foundation symposium 257:116-28; discussion 128-32, 157-60, 276-85.

6. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol. 2006;110(1):7-14.

7. Panesar SS, Javad S, de Silva D, et al. EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013;68(11):1353-61.

8. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis
9. Ben-Shoshan M, Clarke A. Anaphylaxis: past, present and future. Allergy 2011;66(1):1-
10. doi: 10.1111/j.1398-9995.2010.02422.x
10. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with
anaphylaxis in the United States. J Allergy Clin Immunol 2013;133(4):1075-1083.
DOI: 10.1016/j.jaci.2013.10.029 PMID: 24332862 PMCID: PMC3972293
11. Lee SY, Lee SC, Shin SD, et al. Epidemiology and outcomes of anaphylaxis-associated
out-of-hospital cardiac arrest. PLoS ONE 2018;13(3):e0194921
https://doi.org/10.1371/journal.pone.0194921
12. Statistics Bureau of Japan (Japan). Available from:
https://www.stat.go.jp/data/kokusei/2015/kekka/kihon1/pdf/youyaku.pdf
13. Fire and Disaster Management Agency, Ministry of Internal Affairs and Communications
website. www.fdma.go.jp
14. https://www.japanresuscitationcouncil.org/jrc/
15. Chamberlain DA, Cummins RO, Abramson NS, et al. Recommended Guidelines for
uniform reporting of data from out-of-hospital cardiac arrest: the ‘Utstein style’: Prepared by
a Task Force of Representatives from the European Resuscitation Council, American Heart
Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council.
Resuscitation 1991;22:1-26.
16. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1976;1:480-4.

17. Japanese Society of Allergology (jsaweb.jp)

18. Ministry of Health, Labor and Welfare website. www.mhlw.go.jp

19. Nishi M. Epidemiology of wasp death in Japan. Welfare indicators 2012;59:30-34.

20. CH Kim, A Fifueroa, CH Park, et al. Combined effects of food and exercise on anaphylaxis. Nutr Res Pract. 2013 7(5): 347-351.21.

21. Ministry of Agriculture, Forestry and Fisheries. www.maff.go.jp

22. Ministry of Health, Labour and Welfare. www.mhlw.go.jp

23. Ministry of the Environment, Government of Japan. www.env.go.jp

24. Ota I, Kubota Y, Uejima T, et al. Outcomes after out-of-hospital cardiac arrests by anaphylaxis: A nationwide population-based observational study. Acute Med Surg 2019;7(1):e458. doi: 10.1002/ams2.458. eCollection Jan-Dec 2020

25. Rainbow J, Browne GJ. Fatal asthma or anaphylaxis. Emerg Med J 2002;19:415–417.

26. Xu YS, Kastner M, Harada L, et al. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. Allergy Asthma Clin Immunol 2014;10(1):38.

27. Gavin DP, Chen J, Charles DD, et al. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2018; 379:711-721.

28. Lene HG, Bo B, Morens K, et al. Treatment with epinephrine (adrenaline) in suspected
anaphylaxis during anesthesia in Denmark. Anesthesiology. 2011 Jul;115(1):111-6.

29. Eric JL, Ian RD, Andrea G, et al. Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015; 132(18 Suppl 2): S501-518.

30. Funada A, Tada Y, Shimojima M, et al. Effects of prehospital epinephrine administration on neurologically intact survival in bystander-witnessed out-of-hospital cardiac arrest patients with non-shockable rhythm depend on prehospital cardiopulmonary resuscitation duration required to hospital arrival. Heart and Vessels, 23 Jun 2018, 33(12):1525-1533.

31. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med. 2001;161(1):15-

21. pmid:11146694.

32. Akoz A, Tanboga HI, Emet M, et al. A prospective study of kounis syndrome: Clinical experience and cardiac magnetic resonance imaging findings for 21 patients. Acta Medica Mediterr 2013;9(4):811-816.

33. Wah W, Wai KL, Pek PP. Conversion to shockable rhythms during resuscitation and survival for out-of hospital cardiac arrest. Am J Emerg Med 2017;35(2):206-213.

34. Luo S, Zhang Y, Zhang W, et al. Prognostic significance of spontaneous shockable rhythm conversion in adult out-of-hospital cardiac arrest patients with initial non-shockable
heart rhythms: A systematic review and meta-analysis. Resuscitation. 2017;121:1-8.

35. ASCIA Guidelines for Acute Management of Anaphylaxis. www.allergy.org.au

Figure legends

Figure 1. Overview of case selection.
OHCA: out-of-hospital cardiac arrest; EMS: emergency medical service.

Supplement Fig 1. Timing of epinephrine administration.
Cleaned database for OHCAs transported to hospitals during the period of 2013–2019
N = 879,057

OHCAs caused by anaphylaxis
N = 294

No prehospital resuscitation by bystander or EMS
N = 2

Resuscitation-attempted OHCAs
N = 292

Unwitnessed OHCA
N = 71

Shockable initial rhythms
N = 3 (4.2%)
Non-shockable initial rhythms
N = 68 (95.8%)

Bystander-witnessed OHCA
N = 161

Shockable initial rhythms
N = 13 (8.1%)
Non-shockable initial rhythms
N = 148 (91.9%)

EMS-witnessed OHCA
N = 60

Shockable initial rhythms
N = 3 (5.0%)
Non-shockable initial rhythms
N = 57 (95.0%)

Any prehospital defibrillation
N = 28

N = 2 (66.7%)
N = 1 (1.5%)
N = 11 (84.6%)
N = 6 (4.1%)
N = 3 (100%)
N = 5 (8.8%)
Supplemental Table 1. Additional epidemiologic analysis of OHCA cases during the period of 2015 to 2019

| Location/incidence                                                                 | % (N) in OHCA caused by anaphylaxis (Total number = 167) |
|-------------------------------------------------------------------------------------|----------------------------------------------------------|
| Location                                                                            |                                                          |
| Medical office                                                                       | 18.6 (31)                                                |
| Hospital                                                                            | 1.2 (2)                                                  |
| Care facilities                                                                      | 5.4 (9)                                                  |
| Mountain, forest, field, park, and garden                                           | 11.4 (19)                                                |
| Sidewalk, river, pond, and others for outdoor activities                            | 12.0 (20)                                                |
| Home                                                                                | 44.3 (74)                                                |
| Public                                                                              | 4.8 (8)                                                  |
| Workplace                                                                            | 2.4 (4)                                                  |
| Incidence                                                                            |                                                          |
| Epinephrine auto-injection                                                          | 0.6 (1)                                                  |

OHCA, out-of-hospital cardiac arrest.
### Supplement Table 2. Factors associated with 1-month survival

| Characteristics of OHCA                      | 1M survival | Crude OR (95% CI) for 1M survival | Adjusted OR (95% CI) for 1M survival |
|----------------------------------------------|-------------|-----------------------------------|-------------------------------------|
|                                              | Survivors (N = 103) | Non-survivors (N = 189) | or P value |                                                                 |
| Male patients, % (N)                        | 57.3% (59)  | 73.0% (138) | 0.50 (0.30–0.82) | 0.48 (0.27–0.88) |
| Elderly (≥ 70y) patients, % (N)             | 46.6% (48)  | 55.0% (104) | 0.71 (0.44–1.15) | 0.75 (0.42–1.34) |
| Witness status, % (N)                       |             |                     |            |                                                            |
| Unwitnessed                                  | 9.7% (10)   | 31.2% (59) | Reference | Reference |
| Bystander-witnessed                          | 67.0% (69)  | 49.7% (94) | 4.33 (2.07–9.07) | 4.29 (1.92–9.62) |
| EMS-witnessed                                | 23.3% (24)  | 19.1% (36) | 3.93 (1.69–9.17) | 3.16 (1.25–7.94) |
| Shockable initial rhythm, % (N)             | 9.7% (10)   | 4.8% (9)   | 2.15 (0.84–5.48) | 1.80 (0.42–7.64) |
| Prehospital defibrillation, % (N)           | 13.6% (14)  | 7.4% (14)  | 1.97 (0.90–4.30) | 2.10 (0.61–6.56) |
| Prehospital epinephrine administration, % (N)| 12.6% (13)  | 29.1% (55) | 0.35 (0.18–0.68) | 0.45 (0.21–0.97) |
| Advanced airway management, % (N)           | 11.7% (12)  | 37.0% (70) | 0.22 (0.11–0.44) | 0.28 (0.14–0.58) |
| Advanced life support by physician, % (N)   | 17.5% (18)  | 28.6% (54) | 0.53 (0.29–0.96) | 0.47 (0.21–1.05) |
| Physician in ambulance, % (N)               | 10.7% (11)  | 11.6% (22) | 0.91 (0.42–1.95) | 1.01 (0.36–2.84) |
| Time intervals, min, median (IQR)           |             |                     |            |                                                            |
| EMS response time                            | 8 (7–11)    | 10 (8–14)   | P <0.01    | 0.93 (0.87–0.99) |
| EMS transportation time                      | 24 (17–33)  | 26 (18–34)  | P = 0.09   | 1.06 (0.89–1.24) |

1M, 1-month; CI, confidence interval; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.
STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation | Page No |
|---------|----------------|---------|
| **Title and abstract** | | |
| 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract<br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | |
| 2 | Explain the scientific background and rationale for the investigation being reported | 6-7 |
| **Objectives** | | |
| 3 | State specific objectives, including any prespecified hypotheses | 6-7 |
| **Methods** | | |
| 4 | Present key elements of study design early in the paper | 7-9 |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-9 |
| 6 | (a) **Cohort study**—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>**Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>**Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants<br>(b) **Cohort study**—For matched studies, give matching criteria and number of exposed and unexposed<br>**Case-control study**—For matched studies, give matching criteria and the number of controls per case | 7-9 |
| 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9 |
| 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 10-11 |
| 9 | Describe any efforts to address potential sources of bias | 8-9 |
| 10 | Explain how the study size was arrived at | 9 |
| 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10-11 |
| 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) **Cohort study**—If applicable, explain how loss to follow-up was addressed<br>**Case-control study**—If applicable, explain how matching of cases and controls was addressed<br>**Cross-sectional study**—If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | 10-11 |

Continued on next page
### Results

| Participants | 13+ | 9, 11-12 |
|--------------|-----|----------|
| (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 11-12 |
| (b) Give reasons for non-participation at each stage | 9 |
| (c) Consider use of a flow diagram | 11-12 |

| Descriptive data | 14+ | 11-13 |
|------------------|-----|-------|
| (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | - |
| (b) Indicate number of participants with missing data for each variable of interest | - |
| (c) Cohort study—Summarise follow-up time (eg, average and total amount) | 8 |

| Outcome data | 15+ | 11-17 |
|--------------|-----|-------|
| Cohort study—Report numbers of outcome events or summary measures over time | - |
| Case-control study—Report numbers in each exposure category, or summary measures of exposure | - |
| Cross-sectional study—Report numbers of outcome events or summary measures | - |

| Main results | 16 | 11-17 |
|---------------|----|-------|
| (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | - |
| (b) Report category boundaries when continuous variables were categorized | - |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | - |

| Other analyses | 17 | 13 |
|----------------|----|----|
| Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | - |

### Discussion

| Key results | 18 | 22-23 |
|-------------|----|-------|
| Summarise key results with reference to study objectives | - |

| Limitations | 19 | 22 |
|-------------|----|----|
| Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | - |

| Interpretation | 20 | 17-21 |
|----------------|-----|-------|
| Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | - |

| Generalisability | 21 | 22 |
|-------------------|-----|----|
| Discuss the generalisability (external validity) of the study results | - |

### Other information

| Funding | 22 | 23-24 |
|---------|----|-------|
| Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | - |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
# Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: An observational study

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Original Research

Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: An observational study

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ABSTRACT

Objectives: Describe the epidemiologic features of out-of-hospital cardiac arrest (OHCA) caused by anaphylaxis and identify outcome-associated factors.

Design: Observational study.

Setting: Data from the Japanese Fire and Disaster Management Agency database.

Participants: A total of 292 patients from 879,057 OHCA events between 2013 and 2019 with OHCA caused by anaphylaxis and for whom prehospital resuscitation was attempted were included in the analysis.

Primary and secondary outcome measures: The primary outcome was neurologically favorable 1-month survival, defined as cerebral performance category 1 or 2. The secondary outcome was 1-month survival.

Results: The proportion of OHCA caused by anaphylaxis was high in non-elderly and male patients from July to September and during business hours. Bystander- (adjusted odds ratio [OR] = 4.43; 95% confidence interval [CI] = 1.84–10.7) and emergency medical service-witnessed events (adjusted OR = 3.28; 95% CI = 1.21–8.87) were associated with higher rates of neurologically favorable 1-month survival, as well as better 1-month survival. Shockable initial electrocardiogram rhythms were recorded in only 19 patients (6.5%), and prehospital defibrillation was attempted in 16 such patients (84.2%). Neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes. Patients requiring...
advanced airway management had poor neurological outcomes (adjusted OR = 0.17; 95% CI
= 0.07–0.42), and worse 1-month survival (adjusted OR = 0.28; 95% CI = 0.14–0.58).

**Conclusions:** Few cases of OHCA were attributable to anaphylaxis. Witnessed OHCAs,
particularly those witnessed by bystanders, were associated with better neurological
outcomes. Airway complications requiring advanced airway management were likely
associated with poor outcomes.

(Word count: 254)

**Strengths and limitations of this study**

- This study specifically examined out-of-hospital cardiac arrests caused by anaphylaxis
  using Japan’s nationwide database.

- Diagnosis of anaphylaxis depends on the clinician’s experience based on allergen
  exposure and characteristic clinical symptoms.

- Analyses were limited because of insufficient information gathered before the arrival
  of the emergency medical service.

- The results may not be generalizable to other countries with different emergency
  medical services.

**KEYWORDS**
out-of-hospital cardiac arrest; anaphylaxis; bystander; emergency medical service; outcomes
INTRODUCTION

The World Allergy Organization defines anaphylaxis as “the most serious clinical manifestation of an acute systemic allergic reaction.” Anaphylaxis begins with skin and mucosal symptoms, followed by life-threatening problems involving the airways (pharyngeal or laryngeal edema), breathing (bronchospasm with tachypnea), and circulation (hypotension, tachycardia). Drug exposure, insect bites, and food consumption are common exposure pathways to allergens associated with anaphylaxis. Lethal anaphylaxis develops immediately after contact with the trigger, followed by upper airway obstruction attributable to laryngeal edema, circulatory insufficiency attributable to anaphylactic shock, bronchoconstriction leading to asthma-like respiratory insufficiency, and hypoxemia attributable to pulmonary edema leading to cardiac arrest.

A review of anaphylaxis revealed an annual incidence of 1.5–7.9/100,000 people, and estimates suggest that 0.05%–2% of the population will experience anaphylaxis in their lifetimes. In recent years, a combination of genetic and environmental factors has led to greater sensitivity for detecting anaphylactic reactions. However, the mortality rate of anaphylaxis has remained low and stable (0.3%).

Anaphylaxis occurs in both in-hospital and out-of-hospital settings, and little information is available on factors related to epidemiology or outcomes. To our knowledge, few studies used a nationwide out-of-hospital cardiac arrest (OHCA) database to explore the
incidence of anaphylaxis-induced OHCA. Of these, a representative study from South Korea reported 196,158 OHCA cases and attributed 233 cases (0.12%) to anaphylaxis.\textsuperscript{10}

Correctable factors associated with outcomes should be identified to improve the clinical outcomes of patients with anaphylaxis-associated OHCA. This study examined the epidemiologic features of OHCA caused by anaphylaxis and the factors associated with outcomes using an extensive nationwide OHCA database in Japan.

**METHODS**

*Population and setting*

Japan features 47 prefectures, and the country is divided into eight regions from north to south. In 2015, Japan’s population totaled 127 million, and 26.6% were ≥65 years.\textsuperscript{11} 6184 ambulances were operating in 750 fire departments throughout the country\textsuperscript{12}, and no termination of resuscitation rules exist for prehospital settings. Unless a patient with OHCA is obviously dead (such as decapitated) or has post-mortem changes, emergency medical service (EMS) personnel continue resuscitation until arrival at the hospital. Paramedics are allowed to use advanced airway adjuncts and commence peripheral venous infusion of Ringer’s lactate. Some paramedics are authorized to insert tracheal tubes and administer intravenous epinephrine, but they cannot administer other drugs. To care for patients with OHCA, EMS personnel used a protocol created by their regional medical control council based on Japan
Resuscitation Council Guidelines.\textsuperscript{13}

Data selection

Consent was obtained from the Japanese Fire and Disaster Management Agency (FDMA) to analyze nationwide OHCA data prospectively collected from January 1, 2013 to December 31, 2019. This population-based observational study was approved by the review board of the Ishikawa Medical Control Council.

The All-Japan Utstein Registry of FDMA contains Utstein-style data,\textsuperscript{14} including patient sex, age, witness status, initial electrocardiogram rhythm, prehospital defibrillation, prehospital physician involvement, epinephrine administration, advanced airway management, recorded time of witness, bystander cardiopulmonary resuscitation (CPR) initiation, emergency call, time to EMS vehicle arrival at the scene and hospital, EMS contact with the patient, EMS CPR initiation, and survival at 1 month with cerebral performance category (CPC).\textsuperscript{15} There was missing information in the data finally analyzed in this study.

According to the anaphylaxis guidelines of the Japanese Society of Allergology\textsuperscript{16}, clinical diagnostic criteria for anaphylaxis include changes in vital signs, the skin or mucous membranes, and symptoms of the respiratory, circulatory, and gastrointestinal tracts. However, the onset of anaphylaxis or OHCA is rarely witnessed by healthcare personnel. The untrained public cannot be expected to correctly assess symptoms or measure vital signs.
Therefore, clinicians collaborate with EMS personnel to comprehensively assess whether OHCA was caused by anaphylaxis based on allergen exposure and characteristic clinical symptoms. Biomarker measurements, such as tryptase\textsuperscript{17} may be used in hospitals delivering higher-quality care but have not been included in this study. The clinicians provided information on 1-month survival and CPC to the fire department at the time of discharge, from the last hospital, to care facilities or home.

**Patient involvement**

Patients were not involved in study design, data interpretation, or report writing.

The requirement for informed consent for patients was waived because the data were obtained from an existing anonymous database.

**Outcome measures**

The primary study outcome was a neurologically favorable 1-month survival, defined as a CPC score of 1 (good recovery) or 2 (moderate disability).\textsuperscript{15} The secondary outcome was a 1-month survival.

**Statistical analysis**

We performed an epidemiological analysis by comparing the incidence by region,
month (season), time of day (business time vs. other time), day (weekend vs. weekday), age (elderly [≥70 years] vs. non-elderly), and sex. Considering monthly averages of ambient temperature and the rainy weather in June (commonly termed “plum rain” in Japan), we defined the summer season as July to September. Differences across groups for nominal variables were assessed using the chi-squared test. We reported crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). For each analysis, the null hypothesis was evaluated at a two-sided significance level of P < 0.05. Multivariable logistic regression analysis was performed to identify major factors associated with neurologically favorable 1-month survival and 1-month survival. Multivariable logistic regression analysis included the following factors known to be associated with survival: sex, age, witnessed status (unwitnessed, bystander-witnessed, and EMS-witnessed), initial rhythm (shockable or not), prehospital defibrillation, prehospital epinephrine administration, advanced airway management (esophageal obstructive or supra-pharyngeal airway and tracheal intubation), advanced life support by physicians, and the intervals between contact to EMS arrival (EMS response time) and between EMS arrival and hospital arrival (EMS transportation time).

Information about dispatch locations and epinephrine auto-injection has been available for all emergency transport since 2015. This information was obtained in combination with the FDMA database covering 2015-2019. Therefore, we performed an additional analysis. All statistical analyses were performed using JMP Pro 16 software (SAS
Institute, Cary, NC, USA).

RESULTS

Overview of case selection

From the cleaned nationwide database of 879,057 patients with OHCA recorded during the study period, we extracted 294 patients (0.03%) with anaphylaxis-associated OHCA. Two patients with no prehospital resuscitation attempts were excluded, and the remaining 292 patients were analyzed. Of the 292 patients, the onset of OHCA was not witnessed in 71 (24.3%); was witnessed by bystanders, 161 (55.1%); and was witnessed by EMS personnel, 60 (20.6%). Shockable initial rhythms were recorded in 4.2% (3/71) of unwitnessed cases, 8.1% (13/161) of bystander-witnessed cases, and 5.0% (3/60) of EMS-witnessed cases. Conversion from initially non-shockable rhythms to shockable rhythms was recorded in 1.5% (1/68) of unwitnessed cases, 4.1% (6/148) of bystander-witnessed OHCA, and 8.8% (5/57) of EMS-witnessed OHCA. Shockable initial rhythms were recorded in 6.5 (19/292) and 7.2% (16/221) of all OHCAs and witnessed OHCAs, respectively, and conversions to shockable rhythms were recorded in 4.4 (12/273) and 5.4% (11/205) of these events, respectively. Prehospital defibrillation was performed in 66.7 (2/3), 84.6 (11/13), and 100% (3/3) of unwitnessed, bystander-witnessed, and EMS-witnessed OHCAs, respectively. After conversion to shockable rhythms, prehospital defibrillation was performed in 12 of 273
Epidemiologic analyses of OHCA cases caused by anaphylaxis

The annual incidence of OCHA was 115.4 per 100,000 in the Japanese population, and the proportion caused by anaphylaxis was 0.03%. The epidemiology of OHCA caused by anaphylaxis was analyzed per 1000 cases (Table 1). The proportion was 1.64 in the Shikoku region of Japan, which was significantly higher than the proportions of 0.20–0.65 in the other seven regions. The nationwide proportion was higher in July–September (0.78 vs. 0.22 during other months), during business hours (0.43 vs. 0.26 during other times), and among non-elderly patients (0.57 vs. 0.24 in elderly patients) and male patients (0.39 vs. 0.26 in female patients).

Table 1  Epidemiologic analysis of out-of-hospital cardiac arrest cases caused by anaphylaxis

| Variable       | Incidence rate (number/1000 OHCA cases) | Statistics (Yates’ chi-square) |
|----------------|----------------------------------------|---------------------------------|
| Region in Japan (north to south) |                                        | <0.01                            |
| Hokkaido       | 0.23 (9/38,832)                         |                                 |
| Tohoku         | 0.32 (24/75,668)                        |                                 |
| Kanto          | 0.20 (58/290,619)                       |                                 |
| Chubu          | 0.36 (57/158,185)                       |                                 |
| Kinki          | 0.34 (51/148,042)                       |                                 |
| Chugoku        | 0.43 (21/49,032)                        |                                 |
| Shikoku        | 1.64 (46/28,030)                        |                                 |
| Category                                      | Value    |
|----------------------------------------------|----------|
| Kyushu                                       | 0.65     |
| Month (season)                               | <0.01    |
| July-September (Summer)                      | 0.78     |
| Other                                        | 0.22     |
| Time of day (emergency call)                 | <0.01    |
| Business hours (9:00 am-16:59 pm)            | 0.43     |
| Other                                        | 0.26     |
| Weekday                                      | 0.80     |
| Weekend                                      | 0.33     |
| Other                                        | 0.34     |
| Age                                          | <0.01    |
| Elderly (≥ 70y)                              | 0.24     |
| Other                                        | 0.57     |
| Sex                                          | <0.01    |
| Male                                         | 0.39     |
| Female                                       | 0.26     |

OHCA, out-of-hospital cardiac arrest.

When detailed OHCA locations were analyzed for 167 cases from 2015 to 2019, nearly half (74/167 [44.3%]) occurred at home. Medical institutions (42/167 [25.1%]) including medical offices and places for outdoor activities (39/167 [23.4%]) were other major locations of anaphylactic OHCA. Only one case was treated with epinephrine auto-injection before cardiac arrest (Supplemental Table 1).

**Factors associated with neurologically favorable 1-month survival**

The neurologically favorable 1-month survival rate was 26.7% (78/292). In
univariate analysis, bystander- and EMS-witnessed OHCA cases and shorter EMS response times were associated with better neurological outcomes. Poor neurological outcomes were associated with male sex, prehospital epinephrine administration, advanced airway management, and advanced life support by physicians. After adjustment for confounding factors, bystander- (adjusted OR = 4.33; 95% CI = 1.84–10.7) and EMS-witnessed OHCA (adjusted OR = 3.28; 95% CI = 1.21–8.87) were found to be predominant factors associated with better neurological outcome, but the association between shorter EMS response times and favorable neurological outcome was not significant. In the multivariate-adjusted models, advanced airway management was the sole factor associated with poor neurological outcomes (adjusted OR = 0.17; 95% CI = 0.07–0.42). Neither shockable initial rhythms nor prehospital defibrillation was associated with neurological outcomes (Table 2).
Table 2  Factors associated with neurologically favorable 1-month survival

| Characteristics of OHCA | Neurological outcomes at 1M | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-------------------------|-----------------------------|-------------------|---------------------|
|                         | Favorable (N = 78)          | Unfavorable (N = 214) |                      |                      |
| Male patients, % (N)    | 56.4 (44)                   | 71.5 (153)        | **0.52 (0.30–0.88)**| 0.76 (0.42–1.39)     |
| Elderly patients, % (N) | 55.1 (43)                   | 50.9 (109)        | **1.18 (0.70–1.99)**| 1.35 (0.75–2.45)     |
| Witness status, % (N)   |                             |                   |                     |                      |
| Unwitnessed             | 10.3 (8)                    | 28.5 (61)         | Reference           | Reference            |
| Bystander-witnessed     | 66.7 (52)                   | 51.9 (111)        | **3.57 (1.59–8.01)**| **4.43 (1.84–10.7)**|
| EMS-witnessed           | 23.1 (18)                   | 19.6 (42)         | **3.27 (1.30–8.21)**| **3.28 (1.21–8.87)**|
| Shockable initial rhythm, % (N) | 6.4 (5)                   | 6.5 (14)         | 0.98 (0.34–2.81)    | 1.53 (0.27–8.76)     |
| Prehospital defibrillation, % (N) | 7.7 (6)                   | 10.3 (22)        | 0.73 (0.28–1.87)    | 0.57 (0.12–2.71)     |
| Prehospital epinephrine administration, % (N) | 11.5 (9)                   | 27.6 (59)        | **0.34 (0.16–0.73)**| 0.51 (0.22–1.20)     |
| Advanced airway management, % (N) | 7.7 (6)                   | 35.5 (76)        | **0.15 (0.06–0.36)**| **0.17 (0.07–0.42)**|
| Advanced life support by physician, % (N) | 14.1 (11)                   | 28.5 (61)        | **0.41 (0.20–0.83)**| 0.52 (0.22–1.23)     |
| Physician in ambulance, % (N) | 6.4 (5)                   | 13.1 (28)        | 0.45 (0.17–1.22)    | 0.44 (0.13–1.42)     |
| Time intervals, min, median (IQR) |                         |                   |                     |                      |
| EMS response time       | 8 (7–10)                    | 9 (7–14)         | **P < 0.01**        | 0.94 (0.88–1.01)     |
OHCA caused by anaphylaxis requiring advanced life support by physicians likely occurred in medical institutions. Despite the higher rate of epinephrine administration (33.3%) and defibrillation (18.1%) in these cases, they were not associated with better outcomes.

**Factors associated with 1-month survival**

The 1-month survival rate was 35.3% (103/292). As shown in Supplemental Table 2, both univariate and multivariable regression analyses revealed that bystander- and EMS-witnessed OHCA and shorter EMS response times were associated with better 1-month survival. In contrast, male sex, prehospital epinephrine administration, and advanced airway management were associated with worse 1-month survival. Advanced life support by physicians was associated with lower survival rates in the univariate analysis, but the association was not significant after adjustment for confounding factors in the multivariate analysis. Notably, neither shockable initial rhythms nor prehospital defibrillation was
associated with 1-month survival.

**Timing of epinephrine administration**

The median interval (interquartile range) between EMS contact and epinephrine administration was 15 (12–20) min. No patients received epinephrine within 6 min of EMS contact (Supplemental Fig. 1).

**DISCUSSION**

This study identified the epidemiological features of OHCA caused by anaphylaxis and outcome-associated factors using a nationwide database from Japan. Although the number of target cases was small, this study is meaningful because the analysis is based on extensive statistical data representing Japan.

Our findings showed that, of 1000 OHCA cases, approximately 0.3 were caused by anaphylaxis. This finding was much lower than previously reported in South Korea (1.2).\(^\text{10}\) In this study, the proportion of all OHCA cases in the total population was 115.4 per 100,000 people per year, and OHCA caused by anaphylaxis was 0.039; the South Korean report was 49.0 and 0.058, respectively. In Japan, instances of OHCA caused by anaphylaxis were also low, about two-thirds of that reported in South Korea. Potential differences in incidence rates between countries and regions cannot be ruled out as a factor for low incidence in Japan.
Nevertheless, the diagnosis of anaphylaxis relies on the clinician’s assessment based on allergen exposure and characteristic clinical symptoms. Non-compliance with biomarker measurements may also reduce diagnostic ability. In addition, some patients with Kounis syndrome\textsuperscript{18} may have been diagnosed and treated as pure cardiogenic events.

As reported in South Korea, our results indicate that the incidence of anaphylaxis-induced OHCA increased during the day and summer.\textsuperscript{10} In addition, non-elderly and male patients had increased rates of anaphylaxis-induced OHCA. In Japan, anaphylaxis is reported to kill 50–80 people each year, and drugs and bee stings cause most cases.\textsuperscript{19} The high number of insect bites and stings (especially bee stings) in the summer\textsuperscript{20} might be one of the factors contributing to the increased rate of anaphylaxis-induced OHCA in this season. Physical and environmental factors, such as exercise and sunlight, were associated with the risk of anaphylaxis,\textsuperscript{21} which may also explain the increased rate of anaphylaxis during summer.

OHCA caused by anaphylaxis has been associated with better outcomes than other types of noncardiac OHCA.\textsuperscript{22} In this study, witnessed OHCAs, particularly those witnessed by bystanders, were associated with better outcomes. Bystanders can witness the progression from the initial symptoms of anaphylaxis to worsening, and they were in a position to notice anomalies earlier than EMS and take necessary actions. Additionally, based on information from bystanders, EMS personnel potentially suspected anaphylaxis earlier after the onset of OHCA, which may explain why witnessed OHCA was associated with better outcomes.
The causes of death from anaphylaxis include upper airway obstruction, circulatory insufficiency, bronchoconstriction, and hypoxemia. Respiratory symptoms are more common than cardiovascular symptoms in anaphylaxis, and most cases of lethal anaphylaxis are caused by airway obstruction and severe asthma. In this study, advanced airway management for airway obstruction was the most detrimental factor associated with outcomes. In Japan, advanced airway management is generally performed by authorized paramedics when normal bag-valve-mask ventilation is insufficient. It was reported that the autopsy findings of anaphylactic shock death were predominantly pulmonary congestion/pulmonary edema, upper airway edema, and bronchial mucus plug/severe swelling. Poor outcomes are thus likely to be associated with airway obstruction and bronchoconstriction requiring advanced airway management rather than with advanced airway management itself.

In general cases of OHCA, epinephrine administration is not associated with better neurological outcomes, but administration within 10 minutes has been associated with better neurological outcomes. In circulatory instability and cardiac arrest attributable to anaphylaxis during anesthesia, rapid intravenous administration of epinephrine had been reported to be effective and associated with better neurological outcomes. However, epinephrine administration was not associated with better outcomes in this study, which may be explained by the prolonged interval between onset and drug administration. In OHCA, immediate administration of epinephrine is difficult because of the time required for EMS
personnel to arrive and the need to follow the resuscitation guidelines.\textsuperscript{28} Although the effectiveness of intramuscular injections in anaphylaxis is known, the efficacy of intravenous epinephrine for anaphylactic symptoms is undetermined in the case of cardiac arrest. It has also been reported that intravenous administration of epinephrine has a significantly higher risk of adverse cardiovascular events and overdose than intramuscular injections.\textsuperscript{29}

Shockable initial rhythms represent a known major factor associated with better outcomes for OHCA, particularly cardiogenic OHCA.\textsuperscript{15} In this study, the rates of shockable initial rhythms and conversion to shockable rhythms were lower than reported previously for general OHCA.\textsuperscript{30,31} Meanwhile, neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes for OHCA caused by anaphylaxis. These results suggest that respiratory insufficiency is the primary pathology of OHCA caused by anaphylaxis, whereas cardiogenic elements are minor factors. In addition, defibrillation may be less effective because shockable rhythm is of noncardiac origin.\textsuperscript{32}

OHCA caused by anaphylaxis requiring advanced life support by physicians is likely to have occurred in a medical institution (25.1% in 167 cases with detailed location information). Despite the higher rate of epinephrine administration and defibrillation in these cases, they were not associated with better outcomes. Although OHCA caused by anaphylaxis is a more serious and fatal situation, medical institutions may not be adequately responding to anaphylaxis. These findings emphasize the importance of prevention, early detection or
notification, and appropriate treatment of anaphylaxis. Anaphylaxis must be widely
recognized by the general public and healthcare professionals, and the risk of anaphylaxis
should be recognized according to patients’ medical history. Persons at high risk of
anaphylaxis should carry an epinephrine auto-injection kit and avoid outdoor activities
alone. Unfortunately, supplemental analysis in this study revealed that an auto-injection kit
was applied only in one case in five years. In one report in Japan, only 449 (0.87%) were used
in seven years, despite the prescription of 51,447 auto-injection kits mainly for children with
food allergies. Caregivers inject more than half. Self-injection may be difficult in some
situations. In Japan, being used by anyone other than the prescribed person is legally
prohibited; hence, it will not be used in patients who suffer anaphylaxis for the first time. It is
necessary to increase the number of prescriptions and usage to prevent OHCA caused by
anaphylaxis by disseminating information about auto-injection kits. It is also desirable that
unassigned auto-injection kits be used for non-specific patients in the future.

Additional research is needed to improve the diagnosis of anaphylaxis through tests,
such as biomarker measurements. We also hope that similar studies in regions other than East
Asia would allow accurate diagnosis.

LIMITATIONS

Although this study covered a 6-year period in the community population, the
number of patients with OHCA caused by anaphylaxis was small. Information on in-hospital
management and treatment and causes of anaphylaxis was not collected. Although EMS
personnel were encouraged to interview the bystanders and identify bystander-related time
factors and resuscitation efforts, the records before EMS contact with the patient may be
inaccurate. Except in cases of obvious death or post-mortem change, resuscitation is
mandated for OHCA, but careful decisions must be made to reduce its impact on outcomes.

Although all OHCA cases are registered in the FDMA database, the present results
may not be generalizable to other countries with different EMS systems. Data in other
countries will thus need to be analyzed independently.

CONCLUSIONS

The proportion of cases of OHCA caused by anaphylaxis was extremely low in
Japan. Witnessed OHCAs, particularly those witnessed by bystanders, were associated with
better neurologically favorable outcomes. Compared with common OHCA, there were few
elements of shockable initial rhythms and conversion to shockable rhythms. Shockable
rhythms, prehospital defibrillation, and epinephrine administration were not associated with
better outcomes. Airway complications requiring advanced airway management appeared to
be associated with poor outcomes.

The person at high risk of anaphylaxis should carry an epinephrine auto-injection
kit and avoid outdoor activities alone; the general public and healthcare professionals must widely recognize first aid for anaphylaxis.

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COMPETING INTERESTS

None

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AUTHORS’ CONTRIBUTIONS
Conception and study design: KM, AY, and HI; data acquisition: KM, AY, and HI; data analyses and/or interpretation: KM, AY, and HI; manuscript drafting: KM, AY, and HI; critical manuscript revision for important intellectual content: AY, HI, and YW. KM and AY contributed equally to this article as the first authors. All authors have read and approved the final version of the manuscript.

FIGURE LEGENDS

Figure 1. Data selection

EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

REFERENCES

1. Cardona V, Ansotegui I, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472. doi: 10.1016/j.waojou.2020.100472

2. Anaphylaxis: assessment and referral after emergency treatment. NICE Guidelines, 2021. Available: https://www.nice.org.uk/guidance/cg134/chapter/1-recommendations [Accessed 13 Sept 2021].

3. Emergency treatment of anaphylaxis Guidelines for healthcare providers. Working Group of Resuscitation Council UK, 2021. Available: https://www.resus.org.uk/library/additionalguidance/guidance-anaphylaxis/emergency-
4. Anagnostou K, Turner PJ. Myths, facts and controversies in the diagnosis and management of anaphylaxis. *Arch Dis Child* 2019;104:83-90. doi:10.1136/archdischild-2018-314867

5. Richard P. Fatal anaphylaxis in the UK, 1992-2001. *Novartis Found Symp* 2004;257:116-28; discussion 128-32, 157-60, 276-85.

6. Panesar SS, Javad S, de Silva D, *et al.* The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy* 2013;68:1353-61. doi: 10.1111/all.12272

7. Lieberman P, Camargo CA Jr, Bohlke K, *et al.* Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596-602. doi:10.1016/S1081-1206(10)61086-1

8. Ben-Shoshan M, Clarke A. Anaphylaxis: past, present and future. *Allergy* 2011;66:1-14. doi: 10.1111/j.1398-9995.2010.02422.x

9. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;133:1075-83. doi: 10.1016/j.jaci.2013.10.029

10. Lee SY, Lee SC, Shin SD, *et al.* Epidemiology and outcomes of anaphylaxis-associated out-of-hospital cardiac arrest. *PLoS ONE* 2018;13:e0194921. doi: 10.1371/journal.pone.0194921
11. Statistics Bureau of Japan (Japan), 2021. Available: https://www.stat.go.jp/data/kokusei/2015/kekka/kihon1/pdf/youyaku.pdf [Accessed 13 Sept 2021].

12. Fire and Disaster Management Agency (Japan), 2015. Available: http://www.fdma.go.jp/publication/hakusho/h27/2/1/398.html [Accessed 13 Sept 2021].

13. JRC Resuscitation Guidelines. Japan Resuscitation Council, 2021. Available: https://www.japanresuscitationcouncil.org/jrc-g2015/ [Accessed 13 Sept 2021].

14. Chamberlain DA, Cummins RO, Abramson NS, et al. Recommended Guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the ‘Utstein style’: Prepared by a Task Force of Representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. Resuscitation 1991;22:1-26.

15. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480-4. doi:10.1016/s0140-6736(75)92830-5

16. Japanese Society of Allergology, 2019. Available: http://www.jsaweb.jp/uploads/images/guideline/JAGL2019_9.jpg [Accessed 13 Sept 2021].

17. Melissa MW, Anne MD. Anaphylaxis. Allergy Asthma Proc 2019;40:453-6. doi: 10.2500/aap.2019.40.4270

18. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a
natural paradigm? *Int J Cardiol* 2006;110:7-14. doi: 10.1016/j.ijcard.2005.08.007

19. e-Stat (Portal Site of Official Statistics of Japan) website, 2021. Available: https://www.e-stat.go.jp/dbview?sid=0003411698 [Accessed 13 Sept 2021].

20. Nishi M. Epidemiology of wasp death in Japan. *Welfare indicators* 2012;59:30-4.

21. Kim CW, Figueroa A, Park CH, *et al*. Combined effects of food and exercise on anaphylaxis. *Nutr Res Pract* 2013;7:347-51. doi: 10.4162/nrp.2013.7.5.347

22. Ota I, Kubota Y, Uejima T, *et al*. Outcomes after out-of-hospital cardiac arrests by anaphylaxis: A nationwide population-based observational study. *Acute Med Surg* 2019;7:e458. doi:10.1002/ams2.458

23. Rainbow J, Browne GJ. Fatal asthma or anaphylaxis. *Emerg Med J* 2002;19:415-17. doi:10.1136/emj.19.5.415

24. Xu YS, Kastner M, Harada L, *et al*. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. *Allergy Asthma Clin Immunol* 2014;10:38. doi:10.1186/1710-1492-10-38

25. Gavin DP, Chen J, Charles DD, *et al*. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2018;379:711-21. doi:10.1056/NEJMoa1806842

26. Lene HG, Bo B, Morens K, *et al*. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology* 2011;115:111-6. doi:10.1097/ALN.0b013e318218119d
27. Eric JL, Ian RD, Andrea G, et al. Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S501-18. doi: 10.1161/CIR.0000000000000264

28. Funada A, Tada Y, Shimojima M, et al. Effects of prehospital epinephrine administration on neurologically intact survival in bystander-witnessed out-of-hospital cardiac arrest patients with non-shockable rhythm depend on prehospital cardiopulmonary resuscitation duration required to hospital arrival. *Heart Vessels* 2018;33:1525-33. doi: 10.1007/s00380-018-1205-6

29. Campbell RL, Bellolio MF, Knutson BD, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 2015;3:76-80. doi: 10.1016/j.jaip.2014.06.007

30. Wah W, Wai KL, Pek PP. Conversion to shockable rhythms during resuscitation and survival for out-of-hospital cardiac arrest. *Am J Emerg Med* 2017;35:206-13. doi: 10.1016/j.ajem.2016.10.042

31. Luo S, Zhang Y, Zhang W, et al. Prognostic significance of spontaneous shockable rhythm conversion in adult out-of-hospital cardiac arrest patients with initial non-shockable heart rhythms: A systematic review and meta-analysis. *Resuscitation* 2017;121:1-8. doi:
32. Hess FP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. *Resuscitation* 2007;72:200-6. doi: 10.1016/j.resuscitation.2006.06.040

33. ASCIA Guidelines for Acute Management of Anaphylaxis, 2021. Available: https://allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines/ [Accessed 13 Sept 2021].

34. Ito K, Ono M, Kando K, *et al.* Surveillance of the use of adrenaline auto-injectors in Japanese children. *Allergol Int* 2018;67:195-200. doi: 10.1016/j.alit.2017.07.002
Cleaned database for OHCAs transported to hospitals during the period of 2013–2019
N = 879,057

OHCAs caused by anaphylaxis
N = 294

No prehospital resuscitation by bystander or EMS
N = 2

Resuscitation-attempted OHCAs
N = 292

Unwitnessed OHCA
N = 71

Bystander-witnessed OHCA
N = 161

EMS-witnessed OHCA
N = 60

Shockable initial rhythms
N = 3 (4.2%)

Non-shockable initial rhythms
N = 68 (95.8%)

Shockable initial rhythms
N = 13 (8.1%)

Non-shockable initial rhythms
N = 148 (91.9%)

Shockable initial rhythms
N = 3 (5.0%)

Non-shockable initial rhythms
N = 57 (95.0%)

Any prehospital defibrillation
N = 28

N = 2 (66.7%)

N = 1 (1.5%)

N = 11 (84.6%)

N = 6 (4.1%)

N = 3 (100%)

N = 5 (8.8%)
Supplemental Table 1  Additional epidemiologic analysis of OHCA cases during the period of 2015 to 2019

| Location/incidence                          | % (N) in OHCA caused by anaphylaxis (Total number = 167) |
|---------------------------------------------|----------------------------------------------------------|
| **Location**                                |                                                          |
| Medical office                              | 18.6 (31)                                                |
| Hospital                                    | 1.2 (2)                                                  |
| Care facilities                             | 5.4 (9)                                                  |
| Mountain, forest, field, park, and garden   | 11.4 (19)                                                |
| Sidewalk, river, pond, and others for outdoor activities | 12.0 (20)                                                |
| Home                                        | 44.3 (74)                                                |
| Public                                      | 4.8 (8)                                                  |
| Workplace                                   | 2.4 (4)                                                  |
| **Incidence**                               |                                                          |
| Epinephrine auto-injection                  | 0.6 (1)                                                  |

OHCA, out-of-hospital cardiac arrest.
Supplemental Table 2  Factors associated with 1-month survival

| Characteristics of OHCA                        | IM survival | Crude OR (95% CI) | Adjusted OR (95% CI) |
|------------------------------------------------|-------------|-------------------|----------------------|
|                                                | Survivors   | Non-survivors     | for 1M survival      | for 1M survival       |
|                                                | (N = 103)   | (N = 189)         | or P value           | or P value            |
| Male patients, % (N)                           | 57.3 (59)   | 73.0 (138)        | 0.50 (0.30–0.82)     | 0.48 (0.27–0.88)      |
| Elderly patients, % (N)                        | 46.6 (48)   | 55.0 (104)        | 0.71 (0.44–1.15)     | 0.75 (0.42–1.34)      |
| Witness status, % (N)                          |             |                   |                      |                      |
| Unwitnessed                                    | 9.7 (10)    | 31.2 (59)         | Reference            | Reference             |
| Bystander-witnessed                            | 67.0 (69)   | 49.7 (94)         | 4.33 (2.07–9.07)     | 4.29 (1.92–9.62)      |
| EMS-witnessed                                  | 23.3 (24)   | 19.1 (36)         | 3.93 (1.69–9.17)     | 3.16 (1.25–7.94)      |
| Shockable initial rhythm, % (N)                | 9.7 (10)    | 4.8 (9)           | 2.15 (0.84–5.48)     | 1.80 (0.42–7.64)      |
| Prehospital defibrillation, % (N)              | 13.6 (14)   | 7.4 (14)          | 1.97 (0.90–4.30)     | 2.10 (0.61–6.56)      |
| Prehospital epinephrine administration, % (N)  | 12.6 (13)   | 29.1 (55)         | 0.35 (0.18–0.68)     | 0.45 (0.21–0.97)      |
| Advanced airway management, % (N)              | 11.7 (12)   | 37.0 (70)         | 0.22 (0.11–0.44)     | 0.28 (0.14–0.58)      |
| Advanced life support by physician, % (N)      | 17.5 (18)   | 28.6 (54)         | 0.53 (0.29–0.96)     | 0.47 (0.21–1.05)      |
| Physician in ambulance, % (N)                  | 10.7 (11)   | 11.6 (22)         | 0.91 (0.42–1.95)     | 1.01 (0.36–2.84)      |
| Time intervals, min, median (IQR)              |             |                   |                      |                      |
| EMS response time                              | 8 (7–11)    | 10 (8–14)         | P <0.01              | 0.93 (0.87–0.99)      |
| EMS transportation time                        | 24 (17–33)  | 26 (18–34)        | P = 0.09             | 1.06 (0.89–1.24)      |

1M, 1-month; CI, confidence interval; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.
N = 68

Time interval between EMS contact to patient and epinephrine administration
STROBE Statement—checklist of items that should be included in reports of observational studies

| Item | No | Recommendation | Page No |
|------|----|----------------|---------|
| Title and abstract | 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 2 |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4 |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 6-7 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 6-7 |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the paper | 7-9 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-9 |
| Participants | 6 | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants | 7-9 |
| | | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9 |
| Data sources/measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 10-11 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8-9 |
| Study size | 10 | Explain how the study size was arrived at | 9 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | 9-11 |
| | | (b) Describe any methods used to examine subgroups and interactions | - |
| | | (c) Explain how missing data were addressed | - |
| | | (d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy | - |
| | | (e) Describe any sensitivity analyses | - |

Continued on next page
Results

Participants 13*  
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 9, 11
(b) Give reasons for non-participation at each stage 9
(c) Consider use of a flow diagram 11

Descriptive data 14*  
(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 9-11
(b) Indicate number of participants with missing data for each variable of interest -
(c) Cohort study—Summarise follow-up time (eg, average and total amount) 8

Outcome data 15*  
Cohort study—Report numbers of outcome events or summary measures over time 11-17
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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: An observational study

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Original Research

Epidemiology of out-of-hospital cardiac arrests caused by anaphylaxis and factors associated with outcomes: An observational study

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ABSTRACT

Objectives: Describe the epidemiologic features of out-of-hospital cardiac arrest (OHCA) caused by anaphylaxis and identify outcome-associated factors.

Design: Observational study.

Setting: Data from the Japanese Fire and Disaster Management Agency database.

Participants: A total of 292 patients from 879,057 OHCA events between 2013 and 2019 with OHCA caused by anaphylaxis and for whom prehospital resuscitation was attempted were included in the analysis.

Outcome measures: The incidence of anaphylaxis-induced OHCA, neurologically favorable 1-month survival, defined as cerebral performance category 1 or 2, and 1-month survival.

Results: The proportion of OHCA caused by anaphylaxis was high in non-elderly and male patients from July to September and during business hours. Bystander- (adjusted odds ratio [OR] = 4.43; 95% confidence interval [CI] = 1.84–10.7) and emergency medical service-witnessed events (adjusted OR = 3.28; 95% CI = 1.21–8.87) were associated with higher rates of neurologically favorable 1-month survival, as well as better 1-month survival. Shockable initial electrocardiogram rhythms were recorded in only 19 patients (6.5%), and prehospital defibrillation was attempted in 16 such patients (84.2%). Neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes. Patients requiring advanced airway management had poor neurological outcomes (adjusted OR = 0.17; 95% CI
= 0.07–0.42), and worse 1-month survival (adjusted OR = 0.28; 95% CI = 0.14–0.58).

**Conclusions**: Few cases of OHCA were attributable to anaphylaxis. Witnessed OHCAs, particularly those witnessed by bystanders, were associated with better neurological outcomes. Airway complications requiring advanced airway management were likely associated with poor outcomes.

(Word count: 249)

**Strengths and limitations of this study**

- This study specifically examined out-of-hospital cardiac arrests caused by anaphylaxis using Japan’s nationwide database.
- Diagnosis of anaphylaxis depends on the clinician’s experience based on allergen exposure and characteristic clinical symptoms.
- Analyses were limited because of insufficient information gathered before the arrival of the emergency medical service.
- The results may not be generalizable to other countries with different emergency medical services.

**KEYWORDS**

out-of-hospital cardiac arrest; anaphylaxis; bystander; emergency medical service; outcomes
INTRODUCTION

The World Allergy Organization defines anaphylaxis as “the most serious clinical manifestation of an acute systemic allergic reaction” [1]. Anaphylaxis begins with skin and mucosal symptoms, followed by life-threatening problems involving the airways (pharyngeal or laryngeal edema), breathing (bronchospasm with tachypnea), and circulation (hypotension, tachycardia) [1], [2], [3]. Drug exposure, insect bites, and food consumption are common exposure pathways to allergens associated with anaphylaxis. Lethal anaphylaxis develops immediately after contact with the trigger [3], [4], [5], followed by upper airway obstruction attributable to laryngeal edema, circulatory insufficiency attributable to anaphylactic shock, bronchoconstriction leading to asthma-like respiratory insufficiency, and hypoxemia attributable to pulmonary edema leading to cardiac arrest [3].

A review of anaphylaxis revealed an annual incidence of 1.5–7.9/100,000 people, and estimates suggest that 0.05%–2% of the population will experience anaphylaxis in their lifetimes [4], [6], [7]. In recent years, a combination of genetic and environmental factors has led to greater sensitivity for detecting anaphylactic reactions [8], [9]. However, the mortality rate of anaphylaxis has remained low and stable (0.3%) [9].

Anaphylaxis occurs in both in-hospital and out-of-hospital settings, and little information is available on factors related to epidemiology or outcomes. To our knowledge, few studies used a nationwide out-of-hospital cardiac arrest (OHCA) database to explore the
incidence of anaphylaxis-induced OHCA. Of these, a representative study from South Korea reported 196,158 OHCA cases and attributed 233 cases (0.12%) to anaphylaxis [10].

Correctable factors associated with outcomes should be identified to improve the clinical outcomes of patients with anaphylaxis-associated OHCA. This study examined the epidemiologic features of OHCA caused by anaphylaxis and the factors associated with outcomes using an extensive nationwide OHCA database in Japan.

METHODS

Population and setting

Japan features 47 prefectures, and the country is divided into eight regions from north to south. In 2015, Japan's population totaled 127 million, and 26.6% were ≥65 years [11]. 6184 ambulances were operating in 750 fire departments throughout the country [12], and no termination of resuscitation rules exist for prehospital settings. Unless a patient with OHCA is obviously dead (such as decapitated) or has post-mortem changes, emergency medical service (EMS) personnel continue resuscitation until arrival at the hospital. Paramedics are allowed to use advanced airway adjuncts and commence peripheral venous infusion of Ringer's lactate. Some paramedics are authorized to insert tracheal tubes and administer intravenous epinephrine, but they cannot administer other drugs. To care for patients with OHCA, EMS personnel used a protocol created by their regional medical control
council based on Japan Resuscitation Council Guidelines [13].

**Data selection**

Consent was obtained from the Japanese Fire and Disaster Management Agency (FDMA) to analyze nationwide OHCA data prospectively collected from January 1, 2013, to December 31, 2019. This population-based observational study was approved by the review board of the Ishikawa Medical Control Council.

The All-Japan Utstein Registry of FDMA contains Utstein-style data [14], including patient sex, age, witness status, initial electrocardiogram rhythm, prehospital defibrillation, prehospital physician involvement, epinephrine administration, advanced airway management, recorded time of witness, bystander cardiopulmonary resuscitation (CPR) initiation, emergency call, time to EMS vehicle arrived at the scene and hospital, EMS contact with the patient, EMS CPR initiation, and survival at 1 month with cerebral performance category (CPC) [15]. There was no missing information in the final data used in this study.

According to the anaphylaxis guidelines of the Japanese Society of Allergology [16], clinical diagnostic criteria for anaphylaxis include changes in vital signs, the skin or mucous membranes, and symptoms of the respiratory, circulatory, and gastrointestinal tracts. However, the onset of anaphylaxis or OHCA is rarely witnessed by healthcare personnel. The untrained public cannot be expected to correctly assess symptoms or measure vital signs.
Therefore, clinicians collaborate with EMS personnel to comprehensively assess whether OHCA was caused by anaphylaxis based on allergen exposure and characteristic clinical symptoms. Biomarker measurements, such as tryptase [17] may be used in hospitals delivering higher-quality care but have not been included in this study. The clinicians provided information on 1-month survival and CPC to the fire department at the time of discharge, from the last hospital to care facilities or home.

Patient involvement

Patients were not involved in study design, data interpretation, or report writing. The requirement for informed consent for patients was waived because the data were obtained from an existing anonymous database.

Outcome measures

First, we investigated the incidence of anaphylaxis-induced OHCA based on the population. Then, we investigated neurologically favorable 1-month survival, defined as a CPC score of 1 (good recovery) or 2 (moderate disability) [15], and 1-month survival.

Statistical analysis

We performed an epidemiological analysis by comparing the incidence by region,
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month (season), time of day (business time vs. other time), day (weekend vs. weekday), age (elderly [≥70 years] vs. non-elderly), and sex. Considering monthly averages of ambient temperature and the rainy weather in June (commonly termed “plum rain” in Japan), we defined the summer season as July to September. Differences across groups for nominal variables were assessed using the chi-squared test. We reported crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). For each analysis, the null hypothesis was evaluated at a two-sided significance level of P < 0.05. Multivariable logistic regression analysis was performed to identify major factors associated with neurologically favorable 1-month survival and 1-month survival. Multivariable logistic regression analysis included the following factors known to be associated with survival [14]: sex, age, witnessed status (unwitnessed, bystander-witnessed, and EMS-witnessed), initial rhythm (shockable or not), prehospital defibrillation, prehospital epinephrine administration, advanced airway management (esophageal obstructive or supra-pharyngeal airway and tracheal intubation), advanced life support by physicians, and the intervals between contact to EMS arrival (EMS response time) and between EMS arrival and hospital arrival (EMS transportation time).

Information about dispatch locations and epinephrine auto-injection has been available for all emergency transport since 2015. This information was obtained in combination with the FDMA database covering 2015-2019. Therefore, we performed an additional analysis. All statistical analyses were performed using JMP Pro 16 software (SAS...
RESULTS

Overview of case selection

From the cleaned nationwide database of 879,057 patients with OHCA recorded during the study period, we extracted 294 patients (0.03%) with anaphylaxis-associated OHCA. Two patients with no prehospital resuscitation attempts were excluded, and the remaining 292 patients were analyzed. Of the 292 patients, the onset of OHCA was not witnessed in 71 (24.3%); was witnessed by bystanders, 161 (55.1%); and was witnessed by EMS personnel, 60 (20.6%). Shockable initial rhythms were recorded in 4.2% (3/71) of unwitnessed cases, 8.1% (13/161) of bystander-witnessed cases, and 5.0% (3/60) of EMS-witnessed cases. Conversion from initially non-shockable rhythms to shockable rhythms was recorded in 1.5% (1/68) of unwitnessed cases, 4.1% (6/148) of bystander-witnessed OHCA, and 8.8% (5/57) of EMS-witnessed OHCA. Shockable initial rhythms were recorded in 6.5 (19/292) and 7.2% (16/221) of all OHCA and witnessed OHCA, respectively, and conversions to shockable rhythms were recorded in 4.4 (12/273) and 5.4% (11/205) of these events, respectively. Prehospital defibrillation was performed in 66.7 (2/3), 84.6 (11/13), and 100% (3/3) of unwitnessed, bystander-witnessed, and EMS-witnessed OHCA, respectively. After conversion to shockable rhythms, prehospital defibrillation was performed in 12 of 273
patients with non-shockable initial rhythms (Fig. 1).

**Epidemiologic analyses of OHCA cases caused by anaphylaxis**

The annual incidence of OHCA was 115.4 per 100,000 in the Japanese population, and the proportion caused by anaphylaxis was 0.03%. The epidemiology of OHCA caused by anaphylaxis was analyzed per 1000 cases (Table 1). The proportion was 1.64 in the Shikoku region of Japan, which was significantly higher than the proportions of 0.20–0.65 in the other seven regions. The nationwide proportion was higher in July–September (0.78 vs. 0.22 during other months), during business hours (0.43 vs. 0.26 during other times), and among non-elderly patients (0.57 vs. 0.24 in elderly patients) and male patients (0.39 vs. 0.26 in female patients).

**Table 1  Epidemiologic analysis of out-of-hospital cardiac arrest cases caused by anaphylaxis**

| Variable         | Incidence rate (number/1000 OHCA cases) | Statistics (Yates’ chi-square) |
|------------------|----------------------------------------|-------------------------------|
| Region in Japan  |                                        |                               |
| north to south   |                                        |                               |
| Hokkaido         | 0.23 (9/38,832)                        |                               |
| Tohoku           | 0.32 (24/75,668)                       |                               |
| Kanto            | 0.20 (58/290,619)                      |                               |
| Chubu            | 0.36 (57/158,185)                      |                               |
| Kinki            | 0.34 (51/148,042)                      |                               |
| Chugoku          | 0.43 (21/49,032)                       |                               |
| Shikoku          | **1.64 (46/28,030)**                   |                               |
When detailed OHCA locations were analyzed for 167 cases from 2015 to 2019, nearly half (74/167 [44.3%]) occurred at home. Medical institutions (42/167 [25.1%]) including medical offices and places for outdoor activities (39/167 [23.4%]) were other major locations of anaphylactic OHCA. Only one case was treated with epinephrine auto-injection before cardiac arrest (Supplemental Table 1).

**Factors associated with neurologically favorable 1-month survival**

The neurologically favorable 1-month survival rate was 26.7% (78/292). In
univariate analysis, bystander- and EMS-witnessed OHCA cases and shorter EMS response times were associated with better neurological outcomes. Poor neurological outcomes were associated with male sex, prehospital epinephrine administration, advanced airway management, and advanced life support by physicians. After adjustment for confounding factors, bystander- (adjusted OR = 4.33; 95% CI = 1.84–10.7) and EMS-witnessed OHCA (adjusted OR = 3.28; 95% CI = 1.21–8.87) were found to be predominant factors associated with better neurological outcome, but the association between shorter EMS response times and favorable neurological outcome was not significant. In the multivariate-adjusted models, advanced airway management was the sole factor associated with poor neurological outcomes (adjusted OR = 0.17; 95% CI = 0.07–0.42). Neither shockable initial rhythms nor prehospital defibrillation was associated with neurological outcomes (Table 2).
Table 2  Factors associated with neurologically favorable 1-month survival

| Characteristics of OHCA | Neurological outcomes at 1M | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-------------------------|-----------------------------|-------------------|----------------------|
|                         | Favorable (N = 78)          | Unfavorable (N = 214) | for favorable outcomes | for favorable outcomes |
| Male patients, % (N)    | 56.4 (44)                   | 71.5 (153)         | 0.52 (0.30–0.88)     | 0.76 (0.42–1.39)       |
| Elderly patients, % (N)| 55.1 (43)                   | 50.9 (109)         | 1.18 (0.70–1.99)     | 1.35 (0.75–2.45)       |
| Witness status, % (N)   |                            |                   |                      |                      |
| Unwitnessed             | 10.3 (8)                    | 28.5 (61)          | Reference            | Reference            |
| Bystander-witnessed     | 66.7 (52)                   | 51.9 (111)         | 3.57 (1.59–8.01)     | 4.43 (1.84–10.7)      |
| EMS-witnessed           | 23.1 (18)                   | 19.6 (42)          | 3.27 (1.30–8.21)     | 3.28 (1.21–8.87)      |
| Shockable initial rhythm, % (N) | 6.4 (5)             | 6.5 (14)          | 0.98 (0.34–2.81)     | 1.53 (0.27–8.76)      |
| Prehospital defibrillation, % (N) | 7.7 (6)             | 10.3 (22)         | 0.73 (0.28–1.87)     | 0.57 (0.12–2.71)      |
| Prehospital epinephrine administration, % (N) | 11.5 (9)            | 27.6 (59)         | 0.34 (0.16–0.73)     | 0.51 (0.22–1.20)      |
| Advanced airway management, % (N) | 7.7 (6)             | 35.5 (76)         | 0.15 (0.06–0.36)     | 0.17 (0.07–0.42)      |
| Advanced life support by physician, % (N) | 14.1 (11)            | 28.5 (61)         | 0.41 (0.20–0.83)     | 0.52 (0.22–1.23)      |
| Physician in ambulance, % (N) | 6.4 (5)             | 13.1 (28)         | 0.45 (0.17–1.22)     | 0.44 (0.13–1.42)      |
| Time intervals, min, median (IQR) |                    |                   |                      |                      |
| EMS response time       | 8 (7–10)                  | 9 (7–14)          | P < 0.01             | 0.94 (0.88–1.01)      |
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1M, 1-month; CI, confidence interval; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.

OHCA caused by anaphylaxis requiring advanced life support by physicians likely occurred in medical institutions. Despite the higher rate of epinephrine administration (33.3%) and defibrillation (18.1%) in these cases, they were not associated with better outcomes.

Factors associated with 1-month survival

The 1-month survival rate was 35.3% (103/292). As shown in Supplemental Table 2, both univariate and multivariable regression analyses revealed that bystander- and EMS-witnessed OHCA and shorter EMS response times were associated with better 1-month survival. In contrast, male sex, prehospital epinephrine administration, and advanced airway management were associated with worse 1-month survival. Advanced life support by physicians was associated with lower survival rates in the univariate analysis, but the association was not significant after adjustment for confounding factors in the multivariate analysis. Notably, neither shockable initial rhythms nor prehospital defibrillation was

| EMS transportation time | 25 (16–33) | 26 (18–34) | P =0.06 | 1.03 (0.84–1.21) |
|-------------------------|------------|------------|---------|------------------|
| /1 min                  |            |            |         |                  |
| /10 min                 |            |            |         |                  |
associated with 1-month survival.

**Timing of epinephrine administration**

The median interval (interquartile range) between EMS contact and epinephrine administration was 15 (12–20) min. No patients received epinephrine within 6 min of EMS contact (Supplemental Fig. 1).

**DISCUSSION**

This study identified the epidemiological features of OHCA caused by anaphylaxis and outcome-associated factors using a nationwide database from Japan. Witnessed OHCAs were associated with better neurologically favorable outcomes than unwitnessed OHCAs. Airway complications requiring advanced airway management were associated with poor outcomes. Although the number of target cases was small, this study is meaningful because the analysis is based on extensive statistical data representing Japan.

Our findings showed that, of 1000 OHCA cases, approximately 0.3 were caused by anaphylaxis. This finding was much lower than previously reported in South Korea (1.2) [10]. In this study, the proportion of all OHCA cases in the total population was 115.4 per 100,000 people per year, and OHCA caused by anaphylaxis was 0.039; the South Korean report was 49.0 and 0.058, respectively. In Japan, instances of OHCA caused by anaphylaxis were also
low, about two-thirds of that reported in South Korea. Potential differences in incidence rates
between countries and regions cannot be ruled out as a factor for low incidence in Japan.

Nevertheless, the diagnosis of anaphylaxis relies on the clinician’s assessment based on
allergen exposure and characteristic clinical symptoms. Non-compliance with biomarker
measurements may also reduce diagnostic ability. In addition, some patients with Kounis
syndrome [18] may have been diagnosed and treated as pure cardiogenic events.

As reported in South Korea, our results indicate that the incidence of anaphylaxis-
induced OHCA increased during the day and summer [10]. In addition, non-elderly and male
patients had increased rates of anaphylaxis-induced OHCA. In Japan, anaphylaxis is reported
to kill 50–80 people each year, and drugs and bee stings cause most cases [19]. The high
number of insect bites and stings (especially bee stings) in the summer [20] might be one of
the factors contributing to the increased rate of anaphylaxis-induced OHCA in this season.

Physical and environmental factors, such as exercise and sunlight, were associated with the
risk of anaphylaxis [21], which may also explain the increased rate of anaphylaxis during
summer.

OHCA caused by anaphylaxis has been associated with better outcomes than other
types of noncardiac OHCA [22]. In this study, witnessed OHCAs, particularly those
witnessed by bystanders, were associated with better outcomes. Bystanders can witness the
progression from the initial symptoms of anaphylaxis to worsening, and they were in a
position to notice anomalies earlier than EMS and take necessary actions. Additionally, based on information from bystanders, EMS personnel potentially suspected anaphylaxis earlier after the onset of OHCA, which may explain why witnessed OHCA was associated with better outcomes.

The causes of death from anaphylaxis include upper airway obstruction, circulatory insufficiency, bronchoconstriction, and hypoxemia [3]. Respiratory symptoms are more common than cardiovascular symptoms in anaphylaxis, and most cases of lethal anaphylaxis are caused by airway obstruction and severe asthma [4], [23]. In this study, advanced airway management for airway obstruction was the most detrimental factor associated with outcomes. In Japan, advanced airway management is generally performed by authorized paramedics when normal bag-valve-mask ventilation is insufficient. It was reported that the autopsy findings of anaphylactic shock death were predominantly pulmonary congestion/pulmonary edema, upper airway edema, and bronchial mucus plug/severe swelling [24]. Poor outcomes are thus likely to be associated with airway obstruction and bronchoconstriction requiring advanced airway management rather than with advanced airway management itself.

In general cases of OHCA, epinephrine administration is not associated with better neurological outcomes [25], but administration within 10 minutes has been associated with better neurological outcomes [26]. In circulatory instability and cardiac arrest attributable to
anaphylaxis during anesthesia, rapid intravenous administration of epinephrine had been reported to be effective and associated with better neurological outcomes [27]. However, epinephrine administration was not associated with better outcomes in this study, which may be explained by the prolonged interval between onset and drug administration. In OHCA, immediate administration of epinephrine is difficult because of the time required for EMS personnel to arrive and the need to follow the resuscitation guidelines [28]. Although the effectiveness of intramuscular injections in anaphylaxis is known, the efficacy of intravenous epinephrine for anaphylactic symptoms is undetermined in the case of cardiac arrest. It has also been reported that intravenous administration of epinephrine has a significantly higher risk of adverse cardiovascular events and overdose than intramuscular injections [29].

Shockable initial rhythms represent a known major factor associated with better outcomes for OHCA, particularly cardiogenic OHCA [15]. In this study, the rates of shockable initial rhythms and conversion to shockable rhythms were lower than reported previously for general OHCA [30], [31]. Meanwhile, neither shockable initial rhythms nor prehospital defibrillation was associated with better outcomes for OHCA caused by anaphylaxis. These results suggest that respiratory insufficiency is the primary pathology of OHCA caused by anaphylaxis, whereas cardiogenic elements are minor factors. In addition, defibrillation may be less effective because shockable rhythm is of noncardiac origin [32].

OHCA caused by anaphylaxis requiring advanced life support by physicians is
likely to have occurred in a medical institution (25.1% in 167 cases with detailed location information). Despite the higher rate of epinephrine administration and defibrillation in these cases, they were not associated with better outcomes. Although OHCA caused by anaphylaxis is a more serious and fatal situation, medical institutions may not be adequately responding to anaphylaxis. These findings emphasize the importance of prevention, early detection or notification, and appropriate treatment of anaphylaxis. Anaphylaxis must be widely recognized by the general public and healthcare professionals, and the risk of anaphylaxis should be recognized according to patients’ medical history. Persons at high risk of anaphylaxis should carry an epinephrine auto-injection kit [33] and avoid outdoor activities alone. Unfortunately, supplemental analysis in this study revealed that an auto-injection kit was applied only in one case in five years. In one report in Japan, only 449 (0.87%) were used in seven years, despite the prescription of 51,447 auto-injection kits mainly for children with food allergies [34]. Caregivers inject more than half. Self-injection may be difficult in some situations [34]. In Japan, being used by anyone other than the prescribed person is legally prohibited; hence, it will not be used in patients who suffer anaphylaxis for the first time. It is necessary to increase the number of prescriptions and usage to prevent OHCA caused by anaphylaxis by disseminating information about auto-injection kits. It is also desirable that unassigned auto-injection kits be used for non-specific patients in the future.

Additional research is needed to improve the diagnosis of anaphylaxis through tests,
such as biomarker measurements. We also hope that similar studies in regions other than East Asia would allow for accurate diagnosis.

LIMITATIONS

Although this study covered a 6-year period in the community population, the number of patients with OHCA caused by anaphylaxis was small. Information on in-hospital management and treatment and causes of anaphylaxis was not collected. Although EMS personnel were encouraged to interview the bystanders and identify bystander-related time factors and resuscitation efforts, the records before EMS contact with the patient may be inaccurate. Except in cases of obvious death or post-mortem change, resuscitation is mandated for OHCA, but careful decisions must be made to reduce its impact on outcomes.

Although all OHCA cases are registered in the FDMA database, the present results may not be generalizable to other countries with different EMS systems. Data in other countries will thus need to be analyzed independently.

CONCLUSIONS

The proportion of cases of OHCA caused by anaphylaxis was extremely low in Japan. Witnessed OHCA, particularly those witnessed by bystanders, were associated with better neurologically favorable outcomes. Compared with common OHCA, there were few
examples of shockable initial rhythms and conversion to shockable rhythms. Shockable rhythms, prehospital defibrillation, and epinephrine administration were not associated with better outcomes. Airway complications requiring advanced airway management appeared to be associated with poor outcomes.

The person at high risk of anaphylaxis should carry an epinephrine auto-injection kit and avoid outdoor activities alone; the general public and healthcare professionals must widely recognize first aid for anaphylaxis.

**FIGURE LEGENDS**

Figure 1. Data selection

EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest.

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CONTRIBUTORSHIP

Conception and study design: KM, AY, and HI; data acquisition: KM, AY, and HI; data analyses and/or interpretation: KM, AY, and HI; manuscript drafting: KM, AY, and HI; critical manuscript revision for important intellectual content: AY, HI, and YW. KM and AY contributed equally to this article as the first authors. All authors have read and approved the final version of the manuscript.

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COMPETING INTERESTS

No, there are no competing interests for any author.

ETHICS APPROVAL

This study involved human participants and was approved by the institutional review board of Ishikawa Medical Control Council. The requirement for informed consent for patients was waived because the data were obtained from an existing anonymous database.
DATA SHARING

No data are available.

REFERENCES

1. Cardona V, Ansotegui I, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J* 2020;13:100472. doi: 10.1016/j.waojou.2020.100472

2. Anaphylaxis: assessment and referral after emergency treatment. NICE Guidelines, 2021. Available: https://www.nice.org.uk/guidance/cg134/chapter/1-recommendations [Accessed 13 Sept 2021].

3. Emergency treatment of anaphylaxis Guidelines for healthcare providers. Working Group of Resuscitation Council UK, 2021. Available: https://www.resus.org.uk/library/additionalguidance/guidance-anaphylaxis/emergency-treatment [Accessed 13 Sept 2021].

4. Anagnostou K, Turner PJ. Myths, facts and controversies in the diagnosis and management of anaphylaxis. *Arch Dis Child* 2019;104:83-90. doi:10.1136/archdischild-2018-314867

5. Richard P. Fatal anaphylaxis in the UK, 1992-2001. *Novartis Found Symp* 2004;257:116-28; discussion 128-32, 157-60, 276-85.

6. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a
systematic review. *Allergy* 2013;68:1353-61. doi: 10.1111/all.12272

7. Lieberman P, Camargo CA Jr, Bohlke K, *et al.* Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596-602. doi:10.1016/S1081-1206(10)61086-1

8. Ben-Shoshan M, Clarke A. Anaphylaxis: past, present and future. *Allergy* 2011;66:1-14. doi: 10.1111/j.1398-9995.2010.02422.x

9. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;133:1075-83. doi: 10.1016/j.jaci.2013.10.029

10. Lee SY, Lee SC, Shin SD, *et al.* Epidemiology and outcomes of anaphylaxis-associated out-of-hospital cardiac arrest. *PLoS ONE* 2018;13:e0194921. doi: 10.1371/journal.pone.0194921

11. Statistics Bureau of Japan (Japan), 2021. Available: https://www.stat.go.jp/data/kokusei/2015/kekka/kihon1/pdf/youyaku.pdf [Accessed 13 Sept 2021].

12. Fire and Disaster Management Agency (Japan), 2015. Available: http: https://www.fdma.go.jp/publication/hakusho/h27/2/1/398.html [Accessed 13 Sept 2021].

13. JRC Resuscitation Guidelines. Japan Resuscitation Council, 2021. Available:
https://www.japanresuscitationcouncil.org/jrc-g2015/ [Accessed 13 Sept 2021].

14. Chamberlain DA, Cummins RO, Abramson NS, et al. Recommended Guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the ‘Utstein style’: Prepared by a Task Force of Representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. *Resuscitation* 1991;22:1-26.

15. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;1:480-4. doi:10.1016/s0140-6736(75)92830-5

16. Japanese Society of Allergology, 2019. Available: http://www.jsaweb.jp/uploads/images/guideline/JAGL2019_9.jpg [Accessed 13 Sept 2021].

17. Melissa MW, Anne MD. Anaphylaxis. *Allergy Asthma Proc* 2019;40:453-6. doi: 10.2500/aap.2019.40.4270

18. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7-14. doi: 10.1016/j.ijcard.2005.08.007

19. e-Stat (Portal Site of Official Statistics of Japan) website, 2021. Available: https://www.e-stat.go.jp/dbview?sid=0003411698 [Accessed 13 Sept 2021].

20. Nishi M. Epidemiology of wasp death in Japan. *Welfare indicators* 2012;59:30-4.

21. Kim CW, Figueroa A, Park CH, et al. Combined effects of food and exercise on anaphylaxis. *Nutr Res Pract* 2013;7:347-51. doi: 10.4162/nrp.2013.7.5.347
22. Ota I, Kubota Y, Uejima T, et al. Outcomes after out-of-hospital cardiac arrests by anaphylaxis: A nationwide population-based observational study. *Acute Med Surg* 2019;7:e458. doi:10.1002/ams2.458

23. Rainbow J, Browne GJ. Fatal asthma or anaphylaxis. *Emerg Med J* 2002;19:415-17. doi: 10.1136/emj.19.5.415

24. Xu YS, Kastner M, Harada L, et al. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. *Allergy Asthma Clin Immunol* 2014;10:38. doi: 10.1186/1710-1492-10-38

25. Gavin DP, Chen J, Charles DD, et al. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2018;379:711-21. doi:10.1056/NEJMoa1806842

26. Lene HG, Bo B, Morens K, et al. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology* 2011;115:111-6. doi: 10.1097/ALN.0b013e318218119d

27. Eric JL, Ian RD, Andrea G, et al. Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S501-18. doi: 10.1161/CIR.0000000000000264

28. Funada A, Tada Y, Shimojima M, et al. Effects of prehospital epinephrine administration on neurologically intact survival in bystander-witnessed out-of-hospital
cardiac arrest patients with non-shockable rhythm depend on prehospital cardiopulmonary resuscitation duration required to hospital arrival. *Heart Vessels* 2018;33:1525-33. doi: 10.1007/s00380-018-1205-6

29. Campbell RL, Bellolio MF, Knutson BD, *et al*. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 2015;3:76-80. doi: 10.1016/j.jaip.2014.06.007

30. Wah W, Wai KL, Pek PP. Conversion to shockable rhythms during resuscitation and survival for out-of-hospital cardiac arrest. *Am J Emerg Med* 2017;35:206-13. doi: 10.1016/j.ajem.2016.10.042

31. Luo S, Zhang Y, Zhang W, *et al*. Prognostic significance of spontaneous shockable rhythm conversion in adult out-of-hospital cardiac arrest patients with initial non-shockable heart rhythms: A systematic review and meta-analysis. *Resuscitation* 2017;121:1-8. doi: 10.1016/j.resuscitation.2017.09.014

32. Hess FP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. *Resuscitation* 2007;72:200-6. doi: 10.1016/j.resuscitation.2006.06.040
33. ASCIA Guidelines for Acute Management of Anaphylaxis, 2021. Available: https://allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines/ [Accessed 13 Sept 2021].

34. Ito K, Ono M, Kando K, et al. Surveillance of the use of adrenaline auto-injectors in Japanese children. *Allergol Int* 2018;67:195-200. doi: 10.1016/j.alit.2017.07.002
Cleaned database for OHCAs transported to hospitals during the period of 2013–2019
N = 879,057

OHCAs caused by anaphylaxis
N = 294

No prehospital resuscitation by bystander or EMS
N = 2

Resuscitation-attempted OHCAs
N = 292

Unwitnessed OHCA
N = 71

Bystander-witnessed OHCA
N = 161

EMS-witnessed OHCA
N = 60

Shockable initial rhythms
N = 3
(4.2%)

Non-shockable initial rhythms
N = 68
(95.8%)

Shockable initial rhythms
N = 13
(8.1%)

Non-shockable initial rhythms
N = 148
(91.9%)

Shockable initial rhythms
N = 3
(5.0%)

Non-shockable initial rhythms
N = 57
(95.0%)

Any prehospital defibrillation
N = 28

N = 2
(66.7%)

N = 1
(1.5%)

N = 11
(84.6%)

N = 6
(4.1%)

N = 3
(100%)

N = 5
(8.8%)
Cumulative probability

Time interval between EMS contact to patient and epinephrine administration

N = 68
Supplemental Table 1  Additional epidemiologic analysis of OHCA cases during the period of 2015 to 2019

| Location/incidence                  | % (N) in OHCA caused by anaphylaxis |
|-------------------------------------|-------------------------------------|
| Location                            |                                     |
| Medical office                      | 18.6 (31)                           |
| Hospital                            | 1.2 (2)                             |
| Care facilities                     | 5.4 (9)                             |
| Mountain, forest, field, park, and garden | 11.4 (19)                   |
| Sidewalk, river, pond, and others for outdoor activities | 12.0 (20)                   |
| Home                                | 44.3 (74)                           |
| Public                              | 4.8 (8)                             |
| Workplace                           | 2.4 (4)                             |
| Incidence                           |                                     |
| Epinephrine auto-injection          | 0.6 (1)                             |

OHCA, out-of-hospital cardiac arrest.
Supplemental Table 2  Factors associated with 1-month survival

| Characteristics of OHCA | IM survival | Crude OR (95% CI) for 1M survival or P value | Adjusted OR (95% CI) for 1M survival |
|------------------------|-------------|-------------------------------------------|-------------------------------------|
|                        | Survivors (N = 103) | Non-survivors (N = 189) |                                    |                                     |
| Male patients, % (N)   | 57.3 (59) | 73.0 (138) | 0.50 (0.30–0.82) | 0.48 (0.27–0.88) |
| Elderly patients, % (N)| 46.6 (48) | 55.0 (104) | 0.71 (0.44–1.15) | 0.75 (0.42–1.34) |
| Witness status, % (N)  |            |            |                                    |                                     |
| Unwitnessed            | 9.7 (10) | 31.2 (59) | Reference | Reference |
| Bystander-witnessed    | 67.0 (69) | 49.7 (94) | 4.33 (2.07–9.07) | 4.29 (1.92–9.62) |
| EMS-witnessed          | 23.3 (24) | 19.1 (36) | 3.93 (1.69–9.17) | 3.16 (1.25–7.94) |
| Shockable initial rhythm, % (N) | 9.7 (10) | 4.8 (9) | 2.15 (0.84–5.48) | 1.80 (0.42–7.64) |
| Prehospital defibrillation, % (N) | 13.6 (14) | 7.4 (14) | 1.97 (0.90–4.30) | 2.10 (0.61–6.56) |
| Prehospital epinephrine administration, % (N) | 12.6 (13) | 29.1 (55) | 0.35 (0.18–0.68) | 0.45 (0.21–0.97) |
| Advanced airway management, % (N) | 11.7 (12) | 37.0 (70) | 0.22 (0.11–0.44) | 0.28 (0.14–0.58) |
| Advanced life support by physician, % (N) | 17.5 (18) | 28.6 (54) | 0.53 (0.29–0.96) | 0.47 (0.21–1.05) |
| Physician in ambulance, % (N) | 10.7 (11) | 11.6 (22) | 0.91 (0.42–1.95) | 1.01 (0.36–2.84) |
| Time intervals, min, median (IQR) |            |            |                                    |                                     |
| EMS response time      | 8 (7–11) | 10 (8–14) | P < 0.01 | 0.93 (0.87–0.99) |
| EMS transportation time | 24 (17–33) | 26 (18–34) | P = 0.09 | 1.06 (0.89–1.24) |

1M, 1-month; CI, confidence interval; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; OR, odds ratio.
STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation                                                                 | Page No |
|--------|---------------------------------------------------------------------------------|---------|
| 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 2       |
| 1      | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3-4     |
| 2      | Explain the scientific background and rationale for the investigation being reported | 6-7     |
| 3      | State specific objectives, including any prespecified hypotheses                | 6-7     |
| 4      | Present key elements of study design early in the paper                         | 7-9     |
| 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-9     |
| 6      | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants | 7-9     |
| 6      | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case | 7-9     |
| 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9     |
| 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 10-11    |
| 9      | Describe any efforts to address potential sources of bias                       | 8-9     |
| 10     | Explain how the study size was arrived at                                        | 9       |
| 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-11    |
| 12     | (a) Describe all statistical methods, including those used to control for confounding | 9 -11   |
|        | (b) Describe any methods used to examine subgroups and interactions             | -       |
|        | (c) Explain how missing data were addressed                                     | -       |
|        | (d) Cohort study—If applicable, explain how loss to follow-up was addressed     | -       |
|        | Case-control study—If applicable, explain how matching of cases and controls was addressed | -       |
|        | Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy | -       |
|        | (e) Describe any sensitivity analyses                                           | -       |

Continued on next page
### Results

**Participants**

13*

- (a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
- (b) Give reasons for non-participation at each stage
- (c) Consider use of a flow diagram

| 9, 11 |

**Descriptive data**

14*

- (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders
- (b) Indicate number of participants with missing data for each variable of interest
- (c) *Cohort study*—Summarise follow-up time (e.g., average and total amount)

| 9-11 |

**Outcome data**

15*

- *Cohort study*—Report numbers of outcome events or summary measures over time
- *Case-control study*—Report numbers in each exposure category, or summary measures of exposure
- *Cross-sectional study*—Report numbers of outcome events or summary measures

| 11-17 |

**Main results**

16

- (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included
- (b) Report category boundaries when continuous variables were categorized
- (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

| 11-17 |

**Other analyses**

17

- Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses

| 13 |

### Discussion

**Key results**

18

Discuss key results with reference to study objectives

| 22-23 |

**Limitations**

19

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

| 21-22 |

**Interpretation**

20

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

| 17-21 |

**Generalisability**

21

Discuss the generalisability (external validity) of the study results

| 22 |

### Other information

**Funding**

22

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

| 23 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.