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SUPPORTING INFORMATION

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Anisakis is a major cause of anaphylaxis in seaside areas: An epidemiological study in Japan

To the Editor,

Anaphylaxis is a common condition observed in emergency departments and is sometimes associated with a fatal outcome. Following the establishment of standard criteria for anaphylaxis, several epidemiological studies have reported increasing incidence rates ranging from 50 to 112 per 100 000.¹

We undertook this retrospective case-based study by identifying cases of anaphylaxis among the residents of two cities (Tateyama and Minami-Boso) in the Awa region of the southernmost part of Boso Peninsula, Japan (Figure S1). We identified patients who had been diagnosed with anaphylaxis at two hospitals, namely the Kameda Medical Center (KMC) and Awa Regional Medical Center (ARMEC), between September 2010 and August 2015. Most emergency patients in the Awa region attend these emergency departments as there are few emergency hospitals within this rural area (these two hospitals accepted 78.4% of all emergency patients in the region; in-house data). Episodes of anaphylaxis were identified by searching electronic medical records using diagnostic anaphylaxis-related codes. In all cases, the diagnosis of anaphylaxis was confirmed based on the World Allergy Organization anaphylaxis criteria.² In patients with two or more events, each anaphylactic event was counted separately. We excluded all patients with drug hypersensitivity-related anaphylaxis because of incomplete data collection. The inciting factors were determined in each case, based on patient history and examinations mainly involving in vitro-specific immunoglobulin E (IgE) testing. We report the age-adjusted incidence of anaphylaxis and its causes. Incidence rates were calculated according to the number of residents in the two cities. The World Health Organization³ standard population distribution was used for age adjustment. A Fisher's test of variance was used to compare values between multiple groups. The study was approved by the KMC (approval number: 15-081) and ARMEC (approval number: 14) review boards according to the

Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Japanese Ministry of Health, Labor, and Welfare. The requirement to obtain informed consent from each participant was waived by the ethics committee in favor of posting an opt-out document on the hospital website (Method S1).

A total of 232 cases of anaphylaxis were identified in 203 patients. The total age-adjusted incidence rate was calculated as 56.0 cases (95% confidence interval [CI], 45.1-66.9) per 100 000 person-years. Of 203 patients, 67.2% were male. The incidence associated with each culprit is shown in Table 1. The age distribution (Figure 1) exhibits two peaks at 0-4 and 55-69 years of age. Most cases occurring in the sixth and seventh decades were due to ingested fish.

In 93 (45.8%) patients, specific IgE antibodies to putative allergens were investigated. As shown in Table 1 and Figure S2, ingested fish was the most frequent allergen ($n = 128$, 55.2%). Specific IgE antibodies were tested in 45 of 128 (35.2%) of cases involving ingested fish, and of these, 41 (91%) were positive for *Anisakis*-specific IgE antibodies, while specific IgE antibody tests for fish types (including mackerel, salmon, tuna, moth, and sardine) were negative.

A detailed list of symptoms categorized by presumed cause is provided in the Table S1. Gastrointestinal symptoms were markedly more frequent with ingested fish-related anaphylaxis compared with other food-related anaphylaxis ($P = .029$). The average time from ingestion to anaphylaxis onset was longer in cases of ingested fish-related anaphylaxis (Table 1). A biphasic reaction was identified in only five patients (2.2%). There were no cases of fatal anaphylaxis.

The estimated incidence rate in our study (56.0 per 100 000 person-years) may have been underestimated because we excluded drug-hypersensitivity cases. The large number of patients with ingested fish-related anaphylaxis was a distinctive feature of this study.

TABLE 1 Summary of demographic characteristics, hospital visit behavior, therapy, and comorbidities

	Overall		Ingested fish-related		Ingested food other than fish		Hymenoptera sting		Non-Hymenoptera sting		Other or unidentified	
n	232		128		50		22		11		21	
Age-adjusted incidence (/100 000)	56.0		23.0		18.6		3.51		3.58		5.47	
Male sex	156	67.2	83	64.8	26	52	19	86.4	10	90.9	13	61.9
Age	47.8 (44.7-55.9)		56.4 (54.3-58.4)		24.5 (17.6-31.5)		60.0 (51.6-68.3)		30.9 (16.7 to 45.1)		41.4 (34.2-48.7)	
Ambulance call	28	12.1	17	13.2	10	20.0	3	13.6	5	45.5	1	4.8
T1	117.2 (102.5-131.9)		165.8 (151.8-179.8)		56.5 (37.9-75.2)		13.3 (4.3-22.2)		15.6 (5.4 to 25.7)		124.0 (91.1-157.0)	
T2	90.9 (76.9-104.9)		103.8 (88.6-118.9)		80.3 (47.4-113.2)		47.5 (33.9-61.0)		61.1 (40.3 to 81.9)		91.5 (71.3-111.7)	
T3	20.6 (17.1-24.0)		21.4 (18.4-24.5)		27.7 (19.1-36.1)		14.2 (8.5-20.0)		-4.0 (-24.8 to 16.8)		19.4 (15.3-23.5)	
Therapy												
Adrenaline ^a	157	67.7	84	65.6	39	78	17	77.2	9	81.8	8	38.1
H1	225	97.0	128	100	46	92	21	95.5	11	100	19	90.5
H2	213	91.8	123	96.0	41	82	21	95.5	11	100	17	81.0
CS	206	88.8	113	88.3	43	86	21	95.5	11	100	18	85.7
Admission	134	57.8	73	57.0	38	76.0	16	72.7	8	72.7	7	33.3
Adrenaline autoinjector	94	40.5	43	33.6	22	44	17	77.3	8	72.7	4	19.0
Recurrence within study period	33	14.2	19	14.8	5	10.0	0	0	10	30.30	9	42.9
Comorbidities												
Urticaria	15	6.5	10	7.8	1	2.0	0	0.0	1	9.1	3	14.3
Previous anaphylaxis	37	15.9	19	14.8	6	12.0	3	13.6	4	36.4	5	23.8
Bronchial asthma	11	4.7	3	2.3	4	8.0	0	0.0	2	18.2	2	9.5
Atopic dermatitis	6	2.6	0	0.0	4	8.0	0	0.0	1	9.1	1	4.8

Abbreviations: CS, corticosteroids; H1, histamine H1 receptor inhibitor; H2, histamine H2 receptor inhibitor; T1, time from exposure to onset; T2, time from onset to hospital visit; T3, time from hospital visit to epinephrine administration.

^aIncluding pre-hospital use of adrenaline autoinjector

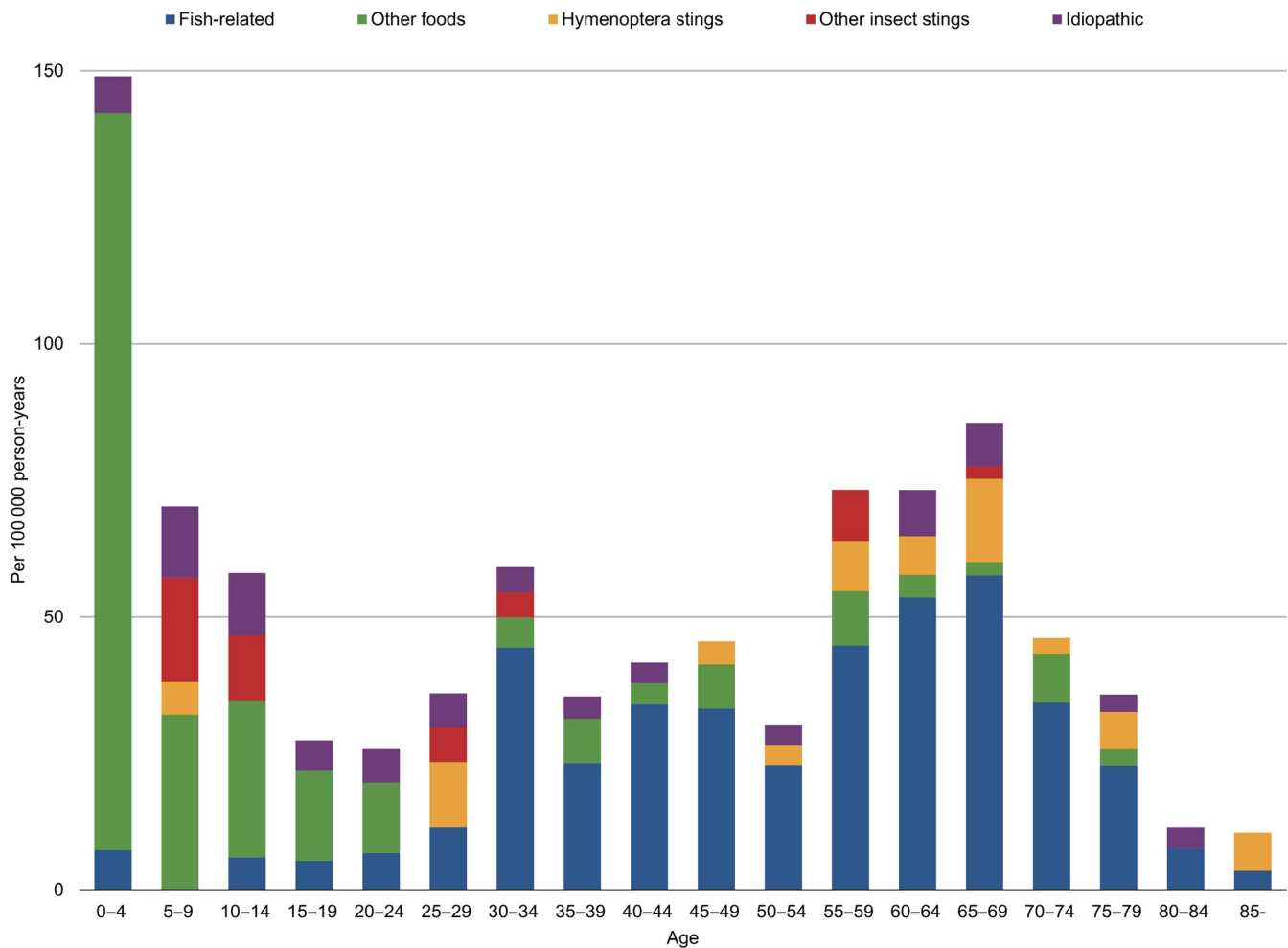


FIGURE 1 Age-specific anaphylaxis incidence rates (per 100 000 person-years) in Minami-Boso, 2010-2015. Age was adjusted according to the World Health Organization³ standard population distribution. There were 50 cases of "other food-related anaphylaxis," among which 21 cases involved patients older than 15 y; of these, 6, 5, 5, and 4 involved meat, shrimp, wheat (including two cases of wheat-dependent exercise-induced anaphylaxis), and unknown cause, respectively. Among the 29 cases involving children (age ≤ 15 y), 8, 6, 5, 5, and 3 involved eggs, milk, wheat, nuts, and shrimp, respectively, with some overlaps

Most cases of ingested fish-related anaphylaxis may be associated with *Anisakis*, as 91% of cases subjected to IgE antibody testing were positive for *Anisakis*-specific IgE antibodies. Histamine intoxication (ie, scombroid poisoning), a differential diagnosis of this condition, is otherwise considerably rare in Japan nowadays as hygiene management has improved. *Anisakis* has been reported as a common cause of anaphylaxis in areas where raw fish intake is popular, such as the Awa region. *Anisakis* is killed by exposure to temperatures at or below -20°C for more than 24 hours. This may be a good way to prevent *Anisakis* allergy.^{4,5} Although previous studies conducted in Spain reported *Anisakis* allergy incidences of 10.8%-11.1%,^{6,7} *Anisakis*-related anaphylaxis has rarely been reported in other areas.^{1,8} The consumption of a raw fish diet in Japan may have contributed to this epidemiological difference.

The higher incidence of anaphylaxis among males in our study findings is noteworthy. The underlying cause of such differences remains unclear, although differences in lifestyles and outdoor

behavior patterns between the sexes may contribute, as most of the insect sting cases in our study involved males.

In our study, two incidence peaks were observed at 0-4 and 55-69 years of age, and the latter peak is an unusual result. Our data showed that ingested fish-related anaphylaxis was the cause of the second incidence peak (55-69 years). Animal meat anaphylaxis was also identified in this age-group. These two allergens commonly have longer intervals from ingestion to anaphylaxis onset, presumably because of slow digestion and absorption. It is unclear why the distribution of inciting allergens differed from those in the younger age-group. There are several possible explanations, namely: (a) IgE antibody production may be more readily induced in elderly patients due to an increase in type 2 helper T cells (Th2)⁹; (b) *Anisakis* larval protein may have characteristics similar to Th2-adjuvant and common characteristics of parasites; (c) younger people have less exposure to raw fish; and (d) the use of acid suppressant medication may alter the digestion kinetics of ingested food.

The study limitations include the retrospective nature of the study design. Investigations regarding the cause of the allergy were insufficient in some cases. Nevertheless, this study showed that the age-adjusted incidence was greater than that identified in previous reports, most likely due to the significantly higher incidence of ingested fish-related allergies related to *Anisakis* in the Awa region.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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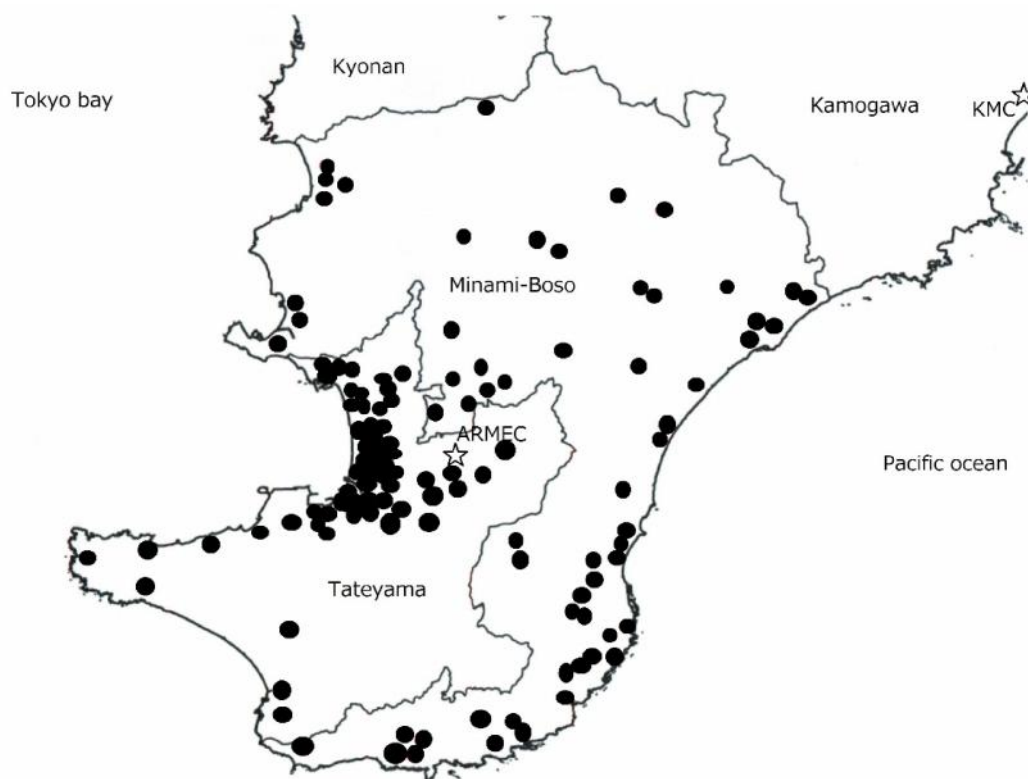
Severe asthma, biologicals, and auto-injection: Yes, no, may be!

To the Editor,

WHO defines empowerment as “a process through which people gain greater control over decisions and actions affecting their health” and should be seen as both an individual and a community-based process.¹ The main components reported as essential into the process of patients' empowerment are principally the following: (a) understanding

by the patient of his/her role; (b) acquisition by patients of a sufficient knowledge of the disease(s) to actively cooperate with their healthcare provider; (c) patient skills; and (d) the presence of a facilitating environment.² Therefore, empowerment can be defined a process in which patients understand their role, are given the knowledge and skills by their healthcare provider to perform a task in an environment that

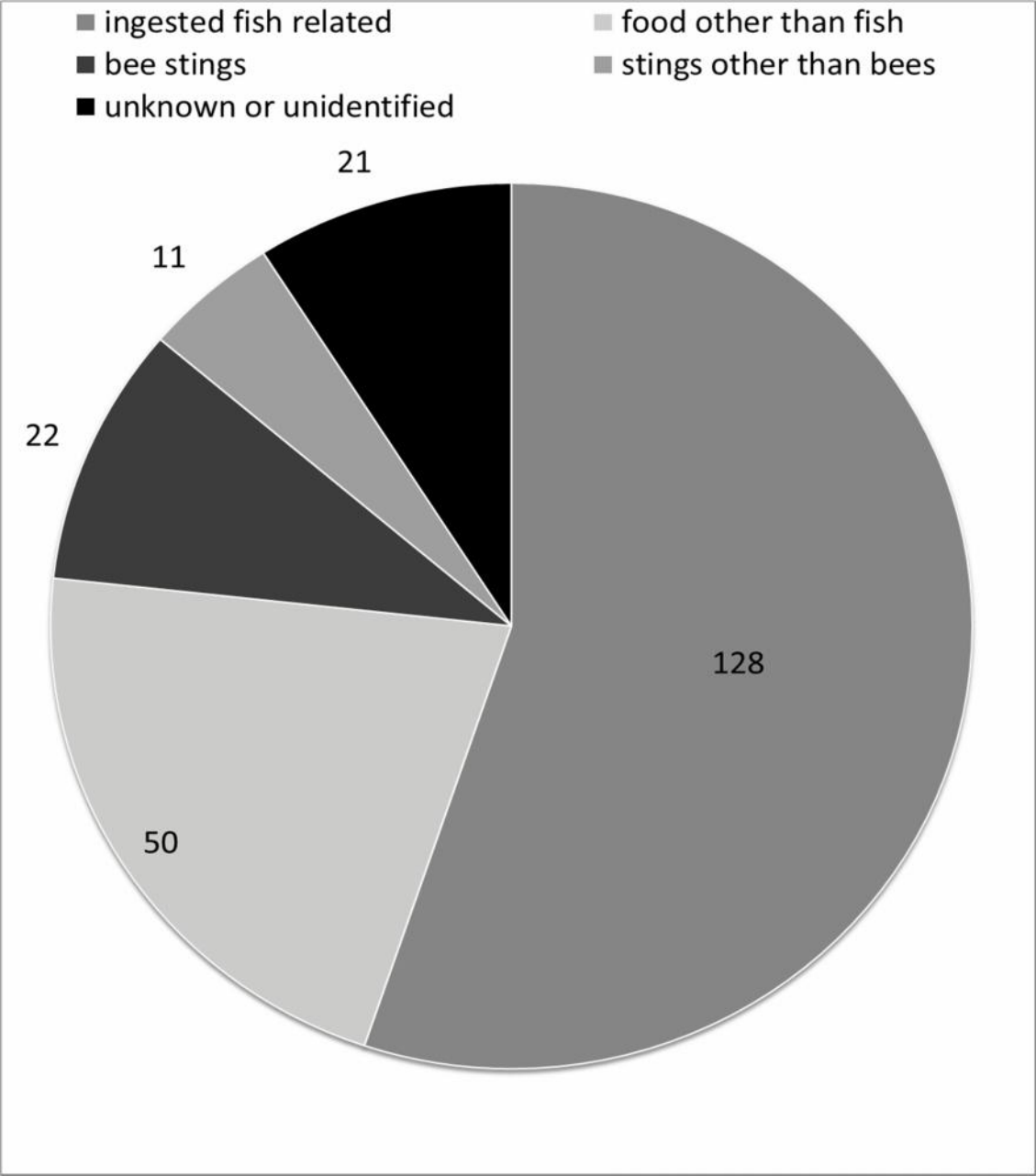
Figure S1: Geographical features of the Awa area.



☆: location of the medical institution, ●: locations of residences of patients with anaphylaxis induced by ingesting fish. This distribution of fish-related anaphylaxis was shown to correlate with the overall distribution of residents.

Abbreviations: ARMEC, Awa Regional Medical Center; KMC, Kameda Medical Center

1 Figure S2: Inciting agents.



2

3

4 The type of fish ingested in each case varied, but included mackerel, pike, sardine,
5 salmon, tuna, and bonito. "Foods other than fish" that induced allergies included eggs,
6 milk, nuts, wheat, shrimp, animal meat, and food-dependent, exercise-induced
7 anaphylaxis. "Stings other than bees" included 5 cases of centipede stings, 4 cases of ant
8 stings, 1 case of rabbitfish stings, and 1 case of caterpillar stings.

Supplementary Table. Signs and symptoms on presentation (n = 232)

Factor	overall		ingested fish-related		ingested food other than fish		<u>p value between fish and other foods</u>
	No	(%)	No	(%)	No	(%)	
Mucocutaneous symptoms	227	97.8%	125	97.7%	50	100.0%	<u>0.56</u>
diffuse urticaria	173	74.6%	97	75.8%	35	70.0%	<u>0.45</u>
itching	105	45.3%	60	46.9%	19	38.0%	<u>0.31</u>
flushing	55	23.7%	25	19.5%	16	32.0%	<u>0.11</u>
angioedema	26	11.2%	10	7.8%	10	20.0%	<u>0.032</u>
<u>conjunctival erythema</u>	21	9.1%	9	7.0%	6	12.0%	<u>0.37</u>
oropharyngeal edema	8	3.4%	0	0.0%	0	0.0%	<u>1</u>
tear	1	0.4%	1	0.8%	0	0.0%	<u>1</u>
Respiratory symptoms	186	80.2%	97	75.8%	39	78.0%	<u>0.85</u>
wheezes	50	21.6%	26	20.3%	16	32.0%	<u>0.11</u>
shortness of breath	114	49.1%	65	50.8%	18	36.0%	<u>0.095</u>
rhinorrhea	8	3.4%	1	0.8%	6	12.0%	<u><0.01</u>
cough	13	5.6%	3	2.3%	8	16.0%	<u><0.01</u>
desaturation	60	25.9%	36	28.1%	7	14.0%	<u>0.052</u>
tachypnea	47	20.3%	33	25.8%	4	8.0%	<u><0.01</u>
snooze	4	1.7%	1	0.8%	3	6.0%	<u>0.068</u>
stridor	2	0.9%	2	1.6%	0	0.0%	<u>1</u>
respiratory arrest	1	0.4%	1	0.8%	0	0.0%	<u>1</u>
chest discomfort	2	0.9%	2	1.6%	0	0.0%	<u>1</u>
<u>Throat tightness</u>	11	4.7%	9	7.0%	1	2.0%	<u>0.29</u>
<u>Throat itching</u>	26	11.2%	13	10.2%	5	10.0%	<u>1</u>
hoarseness	4	1.7%	2	1.6%	1	2.0%	<u>1</u>
rhinitis	4	1.7%	1	0.8%	1	2.0%	<u>0.48</u>
Gastrointestinal tract symptoms	115	49.6%	78	60.9%	21	42.0%	<u>0.029</u>
abdominal pain	31	13.4%	23	18.0%	6	12.0%	<u>0.38</u>
nausea	55	23.7%	39	30.5%	8	16.0%	<u>0.039</u>
vomiting	59	25.4%	42	32.8%	11	22.0%	<u>0.20</u>
diarrhea	39	16.8%	34	26.6%	2	4.0%	<u><0.01</u>
<u>dysphagia</u>	2	0.9%	1	0.8%	0	0.0%	<u>1</u>
heartburn	1	0.4%	1	0.8%	0	0.0%	<u>1</u>
Cardiovascular symptoms	107	46.1%	62	48.4%	16	32.0%	<u>0.064</u>
hypotension	38	16.4%	22	17.2%	6	12.0%	<u>0.50</u>
syncope	19	8.2%	8	6.3%	7	14.0%	<u>0.13</u>
tachycardia	63	27.2%	38	29.7%	8	16.0%	<u>0.085</u>
chest pain	4	1.7%	3	2.3%	0	0.0%	<u>0.56</u>
palpitation	9	3.9%	4	3.1%	1	2.0%	<u>1</u>
shock	4	1.7%	1	0.8%	0	0.0%	<u>1</u>
Total	232		128		50		

Methods

Setting and participants

We undertook this retrospective case-based study by identifying cases of anaphylaxis among residents in two cities in the Awa region, which is surrounded geographically by the sea and mountains (**Figure 1**). We identified patients who had been newly diagnosed with anaphylaxis at two hospitals, namely the Kameda Medical Center (KMC) and Awa Regional Medical Center (ARMEC), between September 2010 and August 2015. KMC is a referral hospital, while ARMEC is a community-based regional hospital. These medical centers form an integrated healthcare system and provide emergency care 24 hours per day, 7 days per week. Throughout the study period, these two hospitals accepted 78.4% of all patients transported by ambulance in this area (in-house data). In Japan, emergency medical services are available to any resident at no additional cost. We searched the medical records of these two hospitals using the diagnostic codes “anaphylaxis,” “anaphylactic shock,” “food-dependent exercise-induced anaphylaxis,” and “food allergy”. These diagnostic codes were created using a minor modification of the International Classification of Diseases, 10th revision. For each patient, the diagnosis was made by the attending physician who performed the initial examination and was confirmed according to the WAO anaphylaxis criteria.

Variables in defining a case of anaphylaxis

Anaphylaxis is diagnosed clinically on the basis of symptoms involving the mucocutaneous, gastrointestinal, respiratory, and/or cardiovascular systems. Three criteria are used to classify a clinical event as anaphylaxis²: (i) acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both, and respiratory compromise and/or cardiovascular symptoms; (ii) two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours), namely, mucocutaneous symptoms, respiratory compromise, cardiovascular symptoms, or persistent gastrointestinal symptoms, and; (iii) reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours). The following symptoms pertain to each of the involved organ systems:

1. Mucocutaneous symptoms: flushing; pruritus or tingling of the lips, axilla, hand, or feet; general pruritus; urticaria or angioedema; lip tingling; and conjunctival erythema or chemosis.

2. Gastrointestinal tract symptoms: oral mucosal pruritus; intraoral angioedema of the buccal mucosa, tongue, palate, or oropharynx; nausea, emesis, dysphagia, abdominal cramps, or diarrhea.
3. Respiratory tract symptoms: rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnea, wheezing, hypopharyngeal or laryngeal edema, and cyanosis.
4. Cardiovascular system symptoms: chest pain, arrhythmia, hypotension, pre-syncope, syncope, tachycardia, bradycardia, orthostasis, seizures, and shock.

Data collection, exclusion, and bias

Medical records were reviewed to determine whether each diagnosis satisfied the diagnostic criteria. Patients attending the study hospitals from other areas and patients who declined to consent to the use of their medical records for research purposes were excluded. In patients with two or more events, each anaphylactic event was counted separately. We excluded all patients with drug hypersensitivity-related anaphylaxis. Two researchers independently reviewed the complete inpatient and outpatient medical records of each study patient to confirm each episode of anaphylaxis. Demographic data, presenting symptoms, inciting allergens, treatment, and the outcome of the anaphylactic episode were also collected. The inciting factors in each case were determined based on the history of illness and in vitro-specific immunoglobulin-E (IgE) testing (ImmunoCAP fluorescent enzyme immunoassay), skin tests, and challenge tests in some cases.

Statistical analysis

We reported the age-adjusted incidence of anaphylaxis and its causes. Incidence rates were calculated according to the number of residents in two cities within the Awa region, namely Tateyama city and Minami-Boso city. Information about the numbers of residents was obtained from the population census data of the Statistics Bureau, Japanese Ministry of Internal Affairs and Communications. The World Health Organization (WHO) 2001 standard population distribution was used for age adjustment. A Fisher's test of variance was used to compare values between multiple groups. A p-value <0.05 was considered statistically significant.