INTRODUCTION

Anaphylaxis is a serious, life-threatening generalized or systemic hypersensitivity reaction. Most anaphylaxis symptoms present acutely and worsen in a short period of time. For this reason, most anaphylactic patients report to the emergency department. Therefore, it is important for the medical staff of emergency department who first face anaphylactic patients to make an accurate diagnosis and provide an immediate and appropriate treatment. The incidence of anaphylaxis has been continuously rising worldwide over the past 20 years. The prevalence of anaphylaxis in the general population is at least 1.6% higher in the United States and ranged from 1.5 to 7.9 per 100,000 person-years in Europe. There has been active research on anaphylaxis, but many study subjects are limited to patients registered with anaphylaxis codes. However, anaphylaxis codes tend to be underused. The aim of this study was to investigate the accuracy of anaphylaxis code registration and the clinical characteristics of accurate and inaccurate anaphylaxis registration in anaphylactic patients. Methods: This retrospective study evaluated the medical records of adult patients who visited the university hospital emergency department between 2012 and 2016. The study subjects were divided into the groups with accurate and inaccurate anaphylaxis codes registered under anaphylaxis and other allergy-related codes and symptom-related codes, respectively. Results: Among 211,486 patients, 618 (0.29%) had anaphylaxis. Of these, 161 and 457 were assigned to the accurate and inaccurate coding groups, respectively. The average age, transportation to the emergency department, past anaphylaxis history, cancer history, and the cause of anaphylaxis differed between the 2 groups. Cutaneous symptom manifested more frequently in the inaccurate coding group, while cardiovascular and neurologic symptoms were more frequently observed in the accurate group. Severe symptoms and non-alert consciousness were more common in the accurate group. Oxygen supply, intubation, and epinephrine were more commonly used as treatments for anaphylaxis in the accurate group. Anaphylactic patients with cardiovascular symptoms, severe symptoms, and epinephrine use were more likely to be accurately registered with anaphylaxis disease codes. Conclusions: In case of anaphylaxis, more patients were registered inaccurately under other allergy-related codes and symptom-related codes rather than accurately under anaphylaxis disease codes. Cardiovascular symptoms, severe symptoms, and epinephrine treatment were factors associated with accurate registration with anaphylaxis disease codes in patients with anaphylaxis.

Key Words: Anaphylaxis; international classification of disease codes; emergency department
idence of anaphylactic patients registered under other codes than anaphylaxis. Therefore, this study determined the frequency and clinical characteristics of anaphylactic patients who met diagnostic criteria but were not registered under anaphylaxis codes in the emergency department by comparing them with those of patients who were accurately diagnosed with anaphylaxis.

MATERIALS AND METHODS

Study population

The subjects of this study included adult patients with anaphylaxis aged over 16 years who had presented to the emergency department of a tertiary hospital for 5 years between January 2012 and December 2016. Anaphylactic patients were defined based on a review of anaphylaxis frequency and characteristics and allergy-related codes.11,12 To identify the omitted anaphylactic patients, disease codes related to symptoms and signs suggested in the clinical diagnostic criteria of anaphylaxis were also collected (Table 1).13 During the survey period, all medical records of the adult patients who were registered under the disease codes were reviewed retrospectively in order to re-evaluate whether they were actually diagnosed with anaphylaxis. Subjects were excluded if they did not meet the diagnostic criteria of anaphylaxis (as defined by the 2011 World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis) after reviewing all medical records for anaphylaxis, allergy-related, and symptom-related codes. The study subjects were divided into the accurate group which was registered under T78.2B, T78.2C, T78.0, T80.5, T88.6 codes with the direct specification of anaphylaxis and into the inaccurate coding group which was registered under allergy-related codes and symptom and sign related codes.

As the diagnostic criteria of anaphylaxis, the clinical criteria for diagnosing anaphylaxis suggested by 2011 World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis was applied.13

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled.

1. Acute onset of an illness with involvement of the skin, mucosal tissue, or both and at least one of the following:
   A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   B. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) or
   2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient
   A. Involvement of the skin-mucosal tissue (e.g., generalized urticarial, itch-flush, swollen lips-tongue-uvula)
   B. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, hypoxemia)

Table 1. International Statistical Classification of Diseases 10th Revision (ICD-10) codes associated with anaphylaxis

| Codes                        | ICD-10 codes       |
|------------------------------|--------------------|
| Anaphylaxis codes            |                    |
| Anaphylaxis                  | T78.2B, T78.2C     |
| Anaphylactic shock           | T78.0, T78.2, T80.5, T88.6 |
| Allergy-related codes        |                    |
| Asthma                       | J45.0, J45.1, J45.8, J45.9, J46 |
| Urticaria                    | L28.2C, L50.0, L50.1, L50.8, L50.9 |
| Angioedema                   | T78.3              |
| Food allergy                 | T78.1              |
| Allergy                      | T78.4, T78.4A, T78.4B |
| Drug allergy                 | T88.7, T88.7B, T88.7C, T88.7D, T88.7E, Z88 |
| Insect stings                | S-codes, T00.9F, T14.00, T14.1A, T63.4, T63.4A, W57, X23 |

Symptom and sign codes

| Skin and mucosal             |                    |
| Laryngeal edema              | J38.48, J38.49     |
| Itch                         | L29.9              |
| Rash, flushing               | R21, R23.2         |
| Edema                        | R60.0, R60.1, R60.9 |
| Respiratory                  |                    |
| Cough                        | R05                |
| Dyspnea, cyanosis            | R06.0, R23.0       |
| Stridor, wheezing            | R06.1, R06.2       |
| Cardiovascular               |                    |
| Cardiac arrest               | I46.0, I46.9       |
| Hypotension                  | I95.0, I95.1, I95.2, I95.8, I95.9 |
| Chest pain                   | R07.1, R07.3, R07.4 |
| Syncope                      | R55.0, R55.8       |
| Shock                        | R57.8, R57.9       |
| Gastrointestinal             |                    |
| Abdominal pain               | R10.1, R10.3, R10.4 |
| Nausea, vomiting             | R11.1, R11.2, R11.3 |
| Incontinence                 | R15, R32           |
| Neurologic                   |                    |
| Confusion                    | R41.0              |
| Dizziness                    | R42                |
| Headache                     | R51                |
| Seizure                      | R56.8              |
Data collection

Relevant materials were surveyed to evaluate the patients’ general characteristics, causes of anaphylaxis, clinical characteristics, and treatments. We also collected demographic data including patient age, gender, transportation to the emergency department, elapsed time from exposure to symptom onset, elapsed time from symptom onset to emergency department arrival, history of allergic diseases, comorbidities, smoking status, and drinking status. Transportation to the emergency department was classified into public ambulance, transfer from another medical facility, and individual transportation. History of allergic diseases was classified into anaphylaxis, asthma, rhinitis, atopy, drugs, and foods. The causes of anaphylaxis were classified into drugs, radiocontrast media, insect stings, food, exercise, and idiopathic factors. For more detailed causes, drugs were categorized into nonsteroidal anti-inflammatory drugs, penicillin, cephalosporin, vaccines, and acetaminophen; insect stings were categorized into bee, ant, and other insects. Foods were classified into seafood, wheat, buckwheat, nuts, egg, and pork. Aside from those, exercise-induced causes, food-dependent exercise-induced causes, and idiopathic causes were also investigated. Regarding clinical manifestations, the patient symptoms were classified into skin and mucosal, respiratory, cardiovascular, gastrointestinal, and neurologic symptoms. In addition, the severity of hypersensitivity reactions, blood pressure at the time of emergency department arrival, and consciousness were surveyed. On the basis of the method reported by Brown,\textsuperscript{14} the severity of the hypersensitivity reactions was classified into severe and non-severe grades depending on hypoxia (SpO$_2$ $\leq$ 92%), hypotension (systolic blood pressure < 90 mmHg), and neurologic symptoms. Regarding prehospital treatment, the oxygen supply, fluid administration, and epinephrine administration were investigated. With regard to treatment in the emergency department, the oxygen supply, endotracheal intubation, fluid administration, steroid administration, epinephrine administration, bronchodilator administration, and cardiopulmonary resuscitation were investigated.

**Figure.** The numbers of accurately and inaccurately registered anaphylaxis patients. We excluded patients (a) without ICD-10 codes that are associated with anaphylaxis (anaphylaxis, anaphylaxis-related, and symptom-related codes). We further excluded (b) patients with allergy- and symptom-related codes who did not satisfy the diagnostic criteria of anaphylaxis patients among those with ICD-10 codes associated with anaphylaxis.
Table 2. General characteristics of accurate and inaccurate anaphylaxis registration

| Variables                        | Accurate (n=161) | Inaccurate coding (n=457) | P  |
|----------------------------------|------------------|---------------------------|----|
| Average age (year)               | 48.0 ± 13.3      | 44.2 ± 14.2               | 0.003* |
| Sex, male                        | 89 (55.3)        | 229 (50.1)                | 0.259 |
| Transportation to ED             |                  |                           | 0.000 |
| Public ambulance                 | 32 (19.9)        | 37 (8.1)                  |     |
| Other medical facility           | 19 (11.8)        | 14 (3.1)                  |     |
| Individual transportation        | 110 (68.3)       | 406 (88.8)                |     |
| Elapsed time from (minute)       |                  |                           |     |
| Exposure to symptom onset        | 10 (0-30)        | 30 (1-95)                 | 0.010' |
| Symptom onset to ED arrival      | 60 (30-120)      | 60 (40-300)               | 0.000' |
| Past history of allergy          | 71 (44.1)        | 199 (43.5)                | 0.273 |
| Anaphylaxis                      | 12 (7.5)         | 16 (3.5)                  | 0.038 |
| Asthma                           | 7 (4.3)          | 10 (2.2)                  | 0.1644 |
| Allergic rhinitis                | 4 (2.5)          | 19 (4.2)                  | 0.335 |
| Atopic dermatitis                | 2 (1.2)          | 10 (2.2)                  | 0.740 |
| Drug                             | 19 (11.8)        | 56 (12.3)                 | 0.880 |
| Food                             | 27 (16.8)        | 73 (16.0)                 | 0.813 |
| Comorbid diseases                |                  |                           |     |
| DM                               | 13 (8.1)         | 29 (6.3)                  | 0.454 |
| Hypertension                     | 27 (16.8)        | 54 (11.8)                 | 0.109 |
| Ischemic heart disease           | 7 (4.3)          | 12 (2.6)                  | 0.276 |
| Cancer                           | 16 (9.9)         | 17 (3.7)                  | 0.003 |
| Alcohol ingestion, case No./total No. | 8/112 (7.1) | 18/235 (7.7)              | 0.864 |
| Smoking, case No./total No.      | 21/72 (29.2)     | 27/142 (19.0)             | 0.212 |

Values are presented as mean±standard deviation, median (interquartile range), or number (%).

ED, emergency department; DM, diabetes mellitus.

Univariate comparison analysis was performed using *Student’s t test; †Mann-Whitney U test; ‡Fisher’s exact test.

RESULTS

During the 5-year study period, of 211,486 total adult patients who presented to the emergency department, we reviewed all medical records of 63,826 with International Statistical Classification of Diseases 10th Revision (ICD-10) codes that were associated with anaphylaxis, including anaphylaxis, allergy-related, and symptom-related codes. After excluding cases that did not meet the diagnostic criteria of anaphylaxis in each group, of 618 anaphylaxis patients, 161 (26.1%) and 457 (73.9%) were assigned to the accurate and inaccurate coding groups, respectively; 365 patients had allergy-related codes and 92 had symptom codes (Figure). The average ages were 48.0 ± 13.3 and 44.2 ± 14.2 years in the accurate and inaccurate coding groups, respectively. The 2 groups had no difference in gender. Regarding transportation to the emergency department, 68.3% of the accurate group and 88.8% of the inaccurate coding group had individual transportation. The inaccurate coding group had longer elapsed times from exposure to symptom onset and from symptom onset to emergency department arrival. With regard to past history of allergy, 7.5% of the accurate and 3.5% of the inaccurate coding groups had anaphylaxis history. Regarding comorbid diseases, 9.9% of the accurate and 3.7% of the inaccurate coding group had cancer history. The 2 groups had no differences in smoking history and alcohol consumption at the time of symptom onset (Table 2). Drugs were the cause of anaphylaxis, in 47.8% and 33.9% of the accurate and inaccurate coding groups, respectively. Analysis of the detailed causes revealed the differences between the 2 groups in cephalosporin (8.7% vs 4.4%), acetylsalicylic acid (5.0% vs 1.8%), and radiocontrast media (13.7% vs 2.0%). Insect stings accounted for 18.0% of the accurate group and 9.0% of the inaccurate coding group. Foods accounted for 26.1% and 42.5% of the accurate and inaccurate coding groups, respectively. The 2 groups had no difference in exercise. Idiopathic cases accounted for 6.8% of the accurate group and 12.5% of the inaccurate coding group (Table 3).

Among anaphylaxis symptoms, the accurate group had more cardiovascular (77.0% vs 34.8%) and neurologic (29.8% vs 9.8%) symptoms than the inaccurate coding group, whereas the inaccurate coding group had more cutaneous symptoms (92.3%) than the accurate group (74.5%). Severe symptoms occurred in 57.1% of the accurate group and 9.8% of the inaccurate coding group. Non-alert consciousness was present in 14.3% and 0.9% of the patients in the accurate and inaccurate coding groups, respectively. Regarding prehospital treatment, the accurate group more often had oxygen supply (4.3% vs 1.1%) and epinephrine use compared to the inaccurate coding group (2.5% and 0%). Regarding emergency department treatment, the accurate group had more oxygen supply (34.8% vs 9.8%), endo-
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Table 3. Causes of accurate and inaccurate anaphylaxis registration

| Variables       | Accurate (n=161) | Inaccurate coding (n=457) | P     |
|-----------------|------------------|---------------------------|-------|
| Drug            | 55 (34.2)        | 146 (31.9)                | 0.093 |
| NSAIDs          | 27 (16.8)        | 53 (11.6)                 | 1.000*|
| Penicillin      | 4 (2.5)          | 12 (2.6)                  | 0.039 |
| Cephalosporin   | 14 (8.7)         | 20 (4.4)                  | 0.040*|
| Acetaminophen   | 8 (5.0)          | 8 (1.8)                   | 0.000 |
| Radiographic    | 22 (13.7)        | 9 (2.0)                   | 0.000 |
| Insect sting    | 29 (18.0)        | 41 (9.0)                  | 0.000 |
| Bee             | 28 (17.4)        | 34 (7.4)                  | 0.000 |
| Food            | 42 (26.1)        | 194 (42.5)                | 0.000 |
| Sea food        | 13 (8.1)         | 89 (19.5)                 | 0.001 |
| Wheat           | 2 (1.2)          | 9 (2.0)                   | 0.737*|
| Peanut          | 1 (0.6)          | 7 (1.5)                   | 0.687*|
| Pork            | 2 (1.2)          | 14 (3.1)                  | 0.262*|
| Exercise without| 3 (1.9)          | 0 (0.0)                   | 0.185*|
| Exercise with    | 0 (0.0)          | 3 (0.7)                   | 0.571*|
| Idiopathic      | 11 (6.8)         | 57 (12.5)                 | 0.049 |

Values are presented as number (%).
NSAID, nonsteroidal anti-inflammatory drug.
*Fisher’s exact test.

Table 4. Clinical characteristics of accurate and inaccurate anaphylaxis registration

| Characteristics       | Accurate (n=161) | Inaccurate coding (n=457) | P     |
|-----------------------|------------------|---------------------------|-------|
| Symptoms              |                  |                           |       |
| Cutaneous             | 120 (74.5)       | 422 (92.3)                | 0.000 |
| Respiratory           | 114 (70.8)       | 312 (68.3)                | 0.550 |
| Cardiovascular        | 124 (77.0)       | 159 (34.8)                | 0.000 |
| Gastrointestinal      | 27 (16.8)        | 128 (28.0)                | 0.005 |
| Neurologic            | 48 (29.3)        | 45 (9.8)                  | 0.000 |
| Blood pressure (mmHg) |                  |                           |       |
| Systolic blood pressure| 120.0 (89-142)  | 134.0 (119-149)           | 0.000 |
| Diastolic blood pressure| 70.0 (66.5-85.0)| 80.0 (71.5-92.0)          | 0.000 |
| Severe symptoms       | 92 (57.1)        | 45 (9.8)                  | 0.000 |
| Non-alert consciousness| 23 (14.3)        | 4 (0.9)                   | 0.000 |
| Pre-hospital treatment|                 |                           |       |
| Oxygen supply         | 7 (4.3)          | 5 (1.1)                   | 0.017*|
| Epinephrine use       | 4 (2.5)          | 0 (0.0)                   | 0.004*|
| ED treatment          |                  |                           |       |
| Oxygen supply         | 56 (34.8)        | 45 (9.8)                  | 0.000 |
| Endotracheal intubation| 7 (4.3)          | 0 (0.0)                   | 0.000*|
| Fluid administration  | 159 (98.8)       | 440 (95.4)                | 0.053 |
| Steroid use           | 150 (93.2)       | 407 (89.1)                | 0.133 |
| Epinephrine use       | 93 (57.8)        | 67 (14.7)                 | 0.000 |
| Bronchodilator use    | 29 (18.0)        | 63 (13.8)                 | 0.195 |
| Cardiopulmonary resuscitation| 3 (1.9) | 0 (0.0) | 0.017*|

Values are presented as median (interquartile range) or number (%).
ED, emergency department.
*Fisher’s exact test.

Table 5. Factors associated with disease codes for accurate anaphylaxis registration

| Characteristics       | Odds ratio | 95% confidence interval | P     |
|-----------------------|------------|-------------------------|-------|
| Cardiovascular symptom| 2.705      | 1.667-4.390             | 0.000 |
| Severe symptom        | 5.481      | 3.335-9.007             | 0.000 |
| Epinephrine use in ED | 4.334      | 2.737-6.864             | 0.000 |

ED, emergency department.

DISCUSSION

Anaphylaxis is a hypersensitivity reaction, ranging from urticaria to fatal systemic cardiovascular compromise. Its symptoms and signs vary and its causal relation with allergens is not clear. For this reason, relevant patients may be registered using other codes related to the symptoms and signs rather than anaphylaxis codes. Although anaphylaxis patients are registered under urticaria or angioedema symptom-related codes rather than anaphylaxis codes, any appropriate patient treatment is not incorrect. Nevertheless, registration of patients under other codes rather than anaphylaxis codes makes it difficult to accurately determine the anaphylaxis incidence. To our knowledge, there is no research on anaphylactic patients registered under other related codes. Therefore, future research on anaphylaxis should also consider inaccurately registered anaphylactic patients, as shown in this study.

In this study of patients who had presented to the emergency department for 5 years, 618 patients met the diagnostic criteria for anaphylaxis; of these, in the inaccurate coding group were registered under other codes than anaphylaxis codes, a number greater than that in the accurate group (161 patients). In the inaccurate coding group, the most common registered code was urticaria (173 patients), followed by angioedema (130 patients) (Figure). This finding indicates that skin features arising in urticaria and angioedema are easily observed with the naked eye. Additionally, compared to objective symptoms, subjective symptoms such as abdominal pain and shortness of breath are...
unclear or mild; therefore, patients meeting the diagnostic criteria were likely to be registered as having the subjective symptoms or angioedema, which are relatively clearer than anaphylaxis. In particular, if patients had clear skin features but other mild symptoms, they were often registered under urticaria. Patients with clear mucosal edema accompanied by respiratory symptoms were often registered under angioedema. In the inaccurate coding group, 92 patients (14.9%) were registered under the codes in which the symptoms and signs are directly specified. The patient group registered under their respiratory symptoms was the largest (31 patients), followed by skin and mucosal symptoms (29 patients). This is most likely because the medical staff was unable to accurately understand diagnostic criteria of anaphylaxis and to make a diagnosis; thus, the patients were registered under their chief complaint as a symptom code. Therefore, to accurately survey the anaphylaxis incidence rate, it is necessary to educate the medical staff of emergency departments to accurately understand the anaphylaxis diagnostic criteria.

Previous studies reported the principal triggers of anaphylaxis to include foods, insect stings, and drugs; however, there were differences depending on the study population, study design, and geographic area. In this study, the causes of anaphylaxis in the accurate group included drugs, foods, and insect stings in this order of prevalence, compared to foods, drugs, and idiopathic anaphylaxis in the inaccurate coding group. This result was similar to those of previous studies. In the accurate group, radiocontrast media were significantly large. That was because the administration of radiocontrast media in the course of examination in the emergency department triggered anaphylaxis and consequently there was a clear causal relation. In the inaccurate coding group, idiopathic anaphylaxis was significantly large.

Skin signs are the most characteristic symptoms and signs of anaphylaxis, frequently accompanied by respiratory, gastrointestinal, and cardiovascular symptoms. In this study, cardiovascular signs, such as hypotension, were most common in the accurate group, followed by skin signs; in the inaccurate coding group, skin signs were most common, followed by respiratory symptoms. The reason for these differences was that the medical staff recognized patients with severe reactions like hypotension or hypoxia. As described earlier, the medical staff clearly recognized these severe reactions as anaphylaxis and registered the patients with anaphylaxis codes. Medical practitioners in the emergency department tend to focus on patients with severe anaphylaxis who present with specific symptoms and treatment, as shown in this study. However, anaphylaxis can present with a wide range of symptom severity, from mild to fatal. No case of anaphylaxis should be overlooked, as anaphylaxis has a high probability of worsening within a short period. Therefore, it is important to continuously educate the medical staff in the emergency department about the manifestations and management of anaphylaxis. To accurately diagnose patients with mild symptoms and signs as anaphylactic patients, the medical staffs in the emergency department need to understand the diagnostic criteria of anaphylaxis and accurately register anaphylaxis codes. As shown in this study, there are cases where patients who met the diagnostic criteria of anaphylaxis were registered under other codes. Therefore, to identify anaphylactic patients, it is necessary to search for study patients including those registered with anaphylaxis-related codes.

The results of this study cannot be generalized as this was a retrospective study that was conducted at a single university hospital. Further prospective multicenter studies will be needed to overcome this limitation. The study subjects were only those patients who had reported to the hospital emergency department and did not include outpatients or patients who were hospitalized and had anaphylaxis. Given that anaphylaxis occurs acutely, the initial treatment is likely to be provided to the patients in the Emergency Department rather than outpatients, except for those who are hospitalized and have anaphylaxis. To search for anaphylactic patients, this study collected the disease codes used in previous works and symptom codes that satisfied the diagnostic criteria of anaphylaxis. Therefore, it is likely to have excluded anaphylactic patients who were registered with different disease codes. This study focused on the registered disease codes for anaphylactic patients in the emergency department of a single university hospital. The emergency department of a research hospital may have high or low registered disease codes for anaphylaxis, making it difficult to generalize the results of this study. Nevertheless, this study shows the potential for the underestimation of the anaphylaxis frequency and incidence rates reported in previous studies on anaphylaxis.

This study revealed that among adult anaphylactic patients who reported to the emergency department, those registered...
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Inaccurately outnumbered those registered accurately and that they were sometimes registered not only under allergy-related codes but also under symptom-related codes. Patients with cardiovascular symptoms, severe symptoms, and epinephrine use in the emergency department were highly likely to be accurately registered with anaphylaxis codes.

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