



# Anaphylaxis in a country where Asia and Europe meet: Evaluation according to World Allergy Organization (WAO) and European Academy of Allergy and Clinical Immunology (EAACI) diagnostic criteria

İsmet Bulut<sup>a</sup>, Zeynep Yegin Katran<sup>a\*</sup> and Dilek Yavuz<sup>b</sup>

## ABSTRACT

**Background:** Anaphylaxis is an acute-onset, life-threatening clinical emergency involving more than one system. The World Allergy Organization (WAO) published anaphylaxis guidelines in 2020. The European Academy of Allergy and Clinical Immunology (EAACI) published anaphylaxis guidelines in 2021 and reviewed the diagnosis of anaphylaxis, risk factors, comorbid diseases, treatment management, and prevention studies.

In this study, clinical features, demographic characteristics, risk factors, treatment management, and evaluations according to EAACI and WAO diagnostic criteria were analysed in patients diagnosed with anaphylaxis. In this way, it was aimed to provide a perspective on the diagnosis, etiology, and treatment management in patients with anaphylaxis and to open a window for new studies.

**Methods:** We retrospectively analysed the data recording system of patients who were evaluated with a history of systemic allergic reaction in the Allergy and Immunology outpatient clinic of our tertiary referral hospital in a ninety-month period between January 2016 and June 2023. The total number of patients admitted to our Allergy and Immunology Clinic between January 2016 and June 2023 was 14,9425. Among these patients, 1032 patients were evaluated in the outpatient clinic according to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) coding system and diagnosed as T78.2 Anaphylaxis by Allergy and Immunology Specialist. Each patient file was re-evaluated by the authors of the study and 689 eligible patients were included.

**Results:** Included in the study were 689 patients. The mean age of the patients was  $46.2 \pm 14.2$  (35–57) years. 64.4% ( $n = 444$ ) of the patients were female. Venom, drugs, and food were the 3 leading causes of anaphylaxis. In our study, younger age was determined as a statistically significant risk factor for food-induced anaphylaxis, female gender for drug-induced anaphylaxis and male gender for venom-induced anaphylaxis. ( $p < 0.001$ ) If the cause of anaphylaxis can be

<sup>a</sup>University of Health Sciences, Süreyyapaşa Training and Research Hospital, Department of Allergy and Immunology, Turkey

\*Corresponding author. E-mail: [zynpyegin@hotmail.com](mailto:zynpyegin@hotmail.com)

Full list of author information is available at the end of the article

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identified, such as venom, drug or food, the frequency of anaphylaxis decreases statistically significantly compared to idiopathic anaphylaxis. ( $p < 0.001$ ) The rate of acute hypotension, bronchospasm, or laryngeal involvement without skin involvement according to WAO and the rate of WAO severity classification grade 5 were significantly higher in patients who developed anaphylaxis due to venom compared to other patients ( $p < 0.001$ ). The rate of Grade 3 in the EAACI classification was significantly higher in patients who developed anaphylaxis due to venom compared to other cases ( $p < 0.001$ ).

**Conclusion:** Our study was conducted in a city such as Istanbul, which connects both Asian and European continents. Moreover, it is important because it was conducted in a centre with the highest number of Allergy and Immunology outpatients per year in our country. It is important because it gives the prevalence of anaphylaxis and emphasises the risk factors for each allergen separately.

**Keywords:** Anaphylaxis, Venom, Idiopathic anaphylaxis, Drug, Tryptase

## INTRODUCTION

Anaphylaxis is an acute-onset, life-threatening clinical emergency involving more than one system.<sup>1</sup> Although the mortality rate due to anaphylaxis is decreasing,<sup>2</sup> hospital admission rates are increasing due to drug- and food-induced anaphylaxis.<sup>3</sup> Food, drugs, and hymenoptera are the most common causes of anaphylaxis.<sup>1,4,5</sup> Among hymenoptera, both honeybee and vespula may cause anaphylaxis. All drugs may potentially cause anaphylaxis. However, nonsteroidal anti-inflammatory agents and betalactam antibiotics are frequently seen.<sup>6,7</sup> When the cause cannot be determined despite all investigations, it is called idiopathic anaphylaxis. Clinical diagnostic criteria are used for the diagnosis. Of particular importance in the diagnosis is that anaphylaxis can present with one organ, such as when there is World Allergy Organization (WAO) 2 or European Academy of Allergy and Clinical Immunology (EAACI) 3 with shock in the setting of a known allergen.<sup>1</sup> If possible, tryptase should be measured within the first half hour to two hours or up to 6 h from onset of anaphylaxis and repeated after 24 h.<sup>1,8,9</sup> The first recommended treatment is intramuscular adrenaline administration in the vastus lateralis. The patient should be taught to carry an identification card at discharge. The patient should be informed in detail about allergens and allergen sources causing

anaphylaxis. An adrenaline autoinjector for emergency use should be prescribed and its use should be taught.<sup>1</sup> Patients with a history of anaphylaxis are at risk for future anaphylaxis attack. Identification of the trigger, scratching from the trigger, and specific immunotherapy reduce this risk.<sup>10</sup> WAO published anaphylaxis guidelines in 2020.<sup>11</sup> EAACI published anaphylaxis guidelines in 2021 and reviewed the diagnosis of anaphylaxis, risk factors, comorbid diseases, treatment management, and prevention studies.<sup>1</sup>

In this retrospective study, clinical features, demographic characteristics, risk factors, treatment management, and evaluations according to EAACI and WAO diagnostic criteria were analysed in patients diagnosed with anaphylaxis. Starting from the treatment of patients in the emergency department, it is aimed to examine diagnostic tests and allergic treatments and to share long-term follow-up details. In this way, it was aimed to provide a perspective on the diagnosis, etiology, and treatment management in patients with anaphylaxis and to open a window for new studies. Are new diagnostic criteria required for the diagnosis of anaphylaxis? Are new laboratory markers required for diagnosis? What are the deficiencies of healthcare professionals in treatment management? These are the new areas of research that come to the fore.

## METHODS

### Study design

We retrospectively analysed the data recording system of patients who were evaluated with a history of systemic allergic reaction in the Allergy and Immunology outpatient clinic of our tertiary referral hospital in a ninety-month period between January 2016 and June 2023. A total of 689 patients were included.<sup>1</sup>

Patients were analysed according to WAO 2020 and EAACI 2021 diagnostic criteria (Table 1).<sup>1,11</sup> The severity of anaphylaxis reactions was grouped according to the WAO grading system (Table 2).

Ethics Committee approval was obtained prior to the study at University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital (116.2017.R-302). Written informed consent was obtained from all participants.

### Patient selection

The total number of patients evaluated to our Allergy and Immunology Clinic between January 2016 and June 2023 was 14,9425. Among these patients, 1032 patients were evaluated in the outpatient clinic according to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) coding system and diagnosed as T78.2 Anaphylaxis by Allergy and Immunology Specialist. Each patient file was re-evaluated by the authors of the study and 689 eligible patients were included. A standardised patient record form was created for each patient. The questionnaire form was analysed under five different headings.

1. Characteristics of the patients: age, gender, allergic diseases, and atopy status were analysed.
2. Diagnostic tests for the cause responsible for anaphylaxis (clinical history, skin prick test, serum specific IgE level)

| WAO 2020 <sup>11</sup>   |  | EAACI2021 <sup>1</sup>   |  |  |
|--|--|--|--|--|
| Diagnostic Criteria 1  | Diagnostic Criteria 2  | Diagnostic Criteria 1  | Diagnostic Criteria 2  | Diagnostic Criteria 3  |
| Acute onset (minutes to several hours) of a disease involving the skin, mucosal tissue or both at the same time                                | Acute onset of hypotension(a) or bronchospasm or laryngeal involvement   | Acute onset of illness (minutes to several hours) with involvement of skin, mucosal tissue or both                                       | Two or more of the following that occur rapidly after exposure to a likely allergen for that patient   | Reduced BP after exposure to known allergen for that patient (minutes to several hours): |
| And at least one of the following  | after exposure to a known or probable allergen for that patient (minutes to several hours), even without typical skin involvement. | And at least one of the following  | a. Involvement of the skin–mucosal tissue (eg generalized hives, itch–flush, swollen lips–tongue–uvula | systolic BP of <90 mmHg or >30% decrease from that person’s baseline                     |
| a. Respiratory failure (e.g. dyspnoea, wheezing–bronchospasm, stridor, decreased PEF, hypoxaemia)  |  | a. Respiratory failure (e.g. dyspnoea, wheezing–bronchospasm, stridor, decreased PEF and hypoxaemia)                                     | b. Respiratory compromise (eg dyspnoea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)          |  |
| b. Decreased blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope–dizziness, incontinence)       |  | b. Decreased blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope–dizziness, incontinence) | c. Reduced BP or associated symptoms (eg hypotonia, syncope–dizziness, incontinence)                   |  |
| c. severe gastrointestinal symptoms (e.g. severe cramping abdominal pain, recurrent vomiting), especially after exposure to non-food allergens |  |  | d. Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting)                           |  |

**Table 1.** WAO 2020<sup>11</sup> and EAACI 2021<sup>1</sup> Diagnostic Criteria (a Hypotension defined as a decrease in systolic BP greater than 30% from that person’s baseline) BP: Blood Pressure

|                                       |                |  |  |                 |   |                 |   |
|---------------------------------------|----------------|--|--|-----------------|---|-----------------|---|
| <b>WAO ANAPHYLAXIS GRADING SYSTEM</b> | <b>Grade 3</b> | <b>Any 1 (or more) of the following symptom / signs:</b> | <b>Lower airway</b><br>Mild bronchospasm, e.g., cough, wheezing, shortness of breath which responds to treatment | <b>And / Or</b> | <b>Gastrointestinal</b><br>Abdominal cramps and/or Vomiting/ diarrhea | <b>And / Or</b> | <b>Uterine</b><br>cramps +/- uterine bleeding |
|                                       | <b>Grade 4</b> |  | <b>Lower airway</b><br>Severe bronchospasm e.g., not responding or worsening in spite of treatment               |                 | <b>Upper airway</b><br>Laryngeal edema with stridor                   |                 |   |
|                                       | <b>Grade 5</b> |  | <b>Lower or upper airway</b><br>Respiratory failure  |                 | <b>Cardiovascular</b><br>Collapse/ hypotension                        |                 | <b>Uterine</b>                                |

**Table 2.** WAO anaphylaxis grading system<sup>11</sup>

3. Serum total IgE level, eosinophil count and percentage, tryptase level, DV 816 gene mutation (c kit) result, venom specific IgE results in peripheral blood,
4. WAO 2020 and EAACI 2021 criteria for the diagnosis of anaphylaxis; system involvement separately skin, respiratory system, cardiovascular system, gastrointestinal system findings; WAO anaphylaxis grading system
5. Early treatment and long-term treatment: In case of anaphylaxis, emergency department admission status, treatment administered in the emergency department, prescription of adrenaline autoinjectors after evaluation in the allergy clinic, alternative drug tests, food elimination, allergen immunotherapy applications, and mastocytosis investigations were examined.

### Statistical analysis

The data obtained as a result of the study were transferred to the computer environment and analysed with SPSS (Statistical Package for Social Sciences) 18.0 package programme. In descriptive analyses, frequency data were presented as number (n) and percentage (%) and numerical data were presented as arithmetic mean ± standard deviation (Interquartile Range (IQR)). Chi-square (χ<sup>2</sup>) test was used to compare categorical data.

The compatibility of the numerical data with normal distribution was analysed by Shapiro Wilk test. One way ANOVA test was used to compare normally distributed numerical data in more than two independent groups. Homogeneity of variances was evaluated by Levene’s test. Welch test was used for non-homogenous variances. In the post hoc analysis of the data with significant difference between the groups, Bonferoni test was used if the variances were homogeneous and Tamhane test was used if the variances were not homogeneous. Statistical significance level was accepted as p < 0.05 for all tests.

### RESULTS

Included in the study were 689 patients. Demographic and clinical characteristics of the patients are presented in Table 3. The mean age of the patients was 46.2 ± 14.2 (35-57) years; 64.4% (n = 444) of the patients were female. Venoma, drug, and food-induced anaphylaxis developed in 37.6%, 32.7%, and 17.9% of the patients, respectively. Allergic diseases were present in 41.5% (n = 286) of the patients. Anaphylaxis developed once in 55.2% and twice in 28.3% of all patients. Asthma was present in 19.3% (n = 133) of the patients. Skin prick test with respiratory allergens was performed in a total of 451 patients and was positive in 46.8% of these patients.

| Variables   | Results                 |
|---|-------------------------|
| Age (years); (mean $\pm$ SD (IQR))                                      | 46.2 $\pm$ 14.2 (35-57) |
| Gender; n (%)   |                         |
| Female  | 444 (64.4)              |
| How many years before first anaphylaxis (years); (mean $\pm$ SD; (IQR)) | 6.8 $\pm$ 6.7 (3-8)     |
| Cause of Anaphylaxis; n (%)   |                         |
| Venom   | 259 (37.6)              |
| Drug  | 225 (32.7)              |
| Food  | 123 (17.9)              |
| Idiopathic  | 46 (6.7)                |
| Latex   | 18 (2.6)                |
| Cold  | 11 (1.6)                |
| Alpha gal   | 3 (0.4)                 |
| Allergen Immunotherapy  | 2 (0.3)                 |
| Exercise Associated   | 1 (0.1)                 |
| Cat Epithelium  | 1 (0.1)                 |
| Venom Type (n = 259)  |                         |
| Honeybee  | 148 (57.2)              |
| Vespula   | 98 (37.8)               |
| Both of them  | 13 (5)                  |
| Venom Test (n = 259); n (%)   |                         |
| Specific IgE Positive   | 247 (95.4)              |
| Prick Positive  | 12 (4.6)                |
| Venom Specific Class (n = 247); n (%)                                   |                         |
| Grade 1 (0.35-0.69)   | 56 (22.7)               |
| Grade 2 (0.7-3.49)  | 121 (49)                |
| Grade 3 (3.5-17.49)   | 50 (20.2)               |
| Grade 4 (17.5-49.99)  | 15 (6.1)                |
| Grade 5 (>49.99)  | 5 (2)                   |
| Type of drug (n = 225); n (%)   |                         |
| NSAIDs  | 62 (27.6)               |
| Antibiotic  | 57 (25.3)               |
| Chemotherapeutic  | 54 (24)                 |
| General Anaesthetic   | 16 (7.1)                |
| Radiocontrast Media   | 14 (6.2)                |
| Local Anaesthetic   | 8 (3.6)                 |
| PPI   | 6 (2.7)                 |
| NSAIDs + Antibiotic   | 6 (2.7)                 |
| Antihistamines  | 1 (0.4)                 |
| Iron  | 1 (0.4)                 |
| Food Type (n = 123); n (%)  |                         |
| Nuts  | 35 (28.5)               |
| Fruit   | 21 (17.1)               |
| Egg   | 19 (15.4)               |
| Fish  | 14 (11.4)               |
| Red meat  | 10 (8.1)                |
| Milk and dairy product  | 8 (6.5)                 |
| Vegetable   | 5 (4.1)                 |
| Chicken   | 4 (3.3)                 |

(continued)

| Variables  | Results    |
|--|------------|
| Sesame   | 3 (2.4)    |
| Legumes  | 2 (1.6)    |
| Shellfish products   | 2 (1.6)    |
| Allergic Disease; n (%)  | 286 (41.5) |
| Anaphylaxis Frequency; n (%)   |            |
| Total 1 times  | 380 (55.2) |
| Total 2 times  | 195 (28.3) |
| Total 3-5 times  | 78 (11.3)  |
| 6 attacks per year or at least 2 attacks in the last 2 years           | 36 (5.2)   |
| Asthma; n (%)  | 133 (19.3) |
| Skin Prick Test Positive with Respiratory Allergens (n = 451); n (%)   | 211 (46.8) |
| Prick to prick in food-induced anaphylaxis (n = 139); n (%)            | 115 (82.7) |
| Prick to prick positivity in food-induced anaphylaxis (n = 115); n (%) | 108 (93.9) |
| Latex Prick Positivity (n = 99); n (%)                                 | 27 (27.3)  |

**Table 3. (Continued)** Demographic and disease characteristics of patients. NSAIDs: Nonsteroidal anti-inflammatory drugs.

The distribution of laboratory parameters, WAO classification of symptoms, severity and EAACI classification of anaphylaxis patients included in the study are presented in Table 4. IgE concentration was  $252 \pm 482$  (37-268), lymphocyte count distribution was  $2169 \pm 738$  (1730-2520) and tryptase distribution was  $6.95 \pm 7.15$ .<sup>3-8</sup> Dyspnea was recorded in 644 patients (93.5%), syncope dizziness in 312 patients (45.3%) and hypotension in 285 patients (41.4%). According to the WAO Anaphylaxis Guidance, 71.5% (n = 493) were classified as grade 3. According to EAACI classification, 69.1% (n = 476) of the patients were in the class 1 group.

The distribution of data according to the causes of anaphylaxis is given in Tables 5 and 6. There was a statistical difference in the distribution of age according to the causes of anaphylaxis ( $p < 0.001$ ). This difference was due to the fact that the age of patients with food-induced anaphylaxis was significantly lower than that of patients with venom-induced anaphylaxis ( $p < 0.001$ ). There was a statistical difference in gender distribution according to the causes of anaphylaxis ( $p < 0.001$ ). While 80.4% of patients with drug-induced anaphylaxis were female, 49.0% of patients with venom-induced anaphylaxis were male. A statistically significant difference was found in the distribution of the frequency of anaphylaxis according to the causes of anaphylaxis

( $p < 0.001$ ). This difference was due to the lower frequency of anaphylaxis in patients with anaphylaxis due to venom, drug, food, and latex compared to other causes of anaphylaxis. Skin prick test was more frequently positive in patients who developed anaphylaxis due to food than in other patients ( $p = 0.005$ ). The rate of acute hypotension, bronchospasm or laryngeal involvement without skin involvement according to WAO and the rate of WAO severity classification grade 5 were significantly higher in patients who developed anaphylaxis due to venom compared to other patients ( $p < 0.001$ ). The rate of grade 3 in EAACI classification was significantly higher in patients who developed anaphylaxis due to venom compared to other cases ( $p < 0.001$ ).

There was a statistical difference in IgE concentration according to the causes of anaphylaxis ( $p = 0.024$ ). This difference was due to the fact that IgE level was significantly higher in patients with food-induced anaphylaxis than in patients with latex-induced anaphylaxis ( $p = 0.049$ ). The distribution of other laboratory parameters was statistically similar ( $p > 0.05$ ). The rate of dyspnoea was found to be significantly lower in patients with venom-induced anaphylaxis and lower in patients with latex-induced anaphylaxis ( $p = 0.008$ ). The rate of development of syncope-dizziness and hypotension was found to be higher in patients who developed venom-induced anaphylaxis compared



| Variables  | Results                    |
|--|----------------------------|
| IgE concentration; (mean $\pm$ SD (IQR))                               | 252 $\pm$ 482 (37-268)     |
| Lymphocyte Count; (mean $\pm$ SD (IQR))                                | 2169 $\pm$ 738 (1730-2520) |
| Lymphocyte Percentage; (mean $\pm$ SD (IQR))                           | 29 $\pm$ 8 (25-34)         |
| Eosinophil Count; (mean $\pm$ SD (IQR))                                | 177 $\pm$ 227 (60-210)     |
| Eosinophil Percentage; (mean $\pm$ SD (IQR))                           | 2 $\pm$ 2 (1-3)            |
| Tryptase; (mean $\pm$ SD (IQR))  | 6.9 $\pm$ 7.1 (3-8)        |
| D816 V mutation positivity (n = 30); n (%)                             | 2 (6.7)                    |
| Latex Specific IgE positivity (n = 90); n (%)                          | 16 (17.8)                  |
| Alpha Gal positivity (n = 12); n (%)                                   | 8 (66.7)                   |
| Presence of urticaria and angioedema at the time of anaphylaxis; n (%) | 618 (89.7)                 |
| Dyspnoea; n (%)  | 644 (93.5)                 |
| Syncope, dizziness; n (%)  | 312 (45.3)                 |
| Hypotension; n (%)   | 285 (41.4)                 |
| Flushing; n (%)  | 236 (34.3)                 |
| Chest pain; n (%)  | 124 (18)                   |
| Nausea, vomiting; n (%)  | 106 (15.4)                 |
| Abdominal pain, diarrhoea; n (%)                                       | 97 (14.1)                  |
| Rhinitis; n (%)  | 54 (7.8)                   |
| Change in mood; n (%)  | 47 (6.8)                   |
| WAO 2020; n (%)  |                            |
| Diagnostic Criteria 1  | 556 (80.7)                 |
| Diagnostic Criteria 2  | 133 (19.3)                 |
| WAO anaphylaxis grading; n (%)   |                            |
| Grade 3  | 493 (71.5)                 |
| Grade 4  | 53 (7.7)                   |
| Grade 5  | 143 (20.8)                 |
| EAACI 2021; n (%)  |                            |
| 1  | 476 (69.1)                 |
| 2  | 90 (13.1)                  |
| 3  | 123 (17.8)                 |

**Table 4.** Distribution of laboratory parameters, symptoms and classifications

to other patients, and lower in patients who developed food-induced anaphylaxis ( $p < 0.001$ ). The rate of flushing was significantly lower in patients with drug-induced anaphylaxis compared to

other patients ( $p = 0.005$ ). The rate of nausea and vomiting was significantly lower in patients with venom-induced anaphylaxis and lower in patients with food-induced anaphylaxis ( $p < 0.001$ ). The

|  | Causes of Anaphylaxis |            |            |           |           | p                   |
|--|-----------------------|------------|------------|-----------|-----------|---------------------|
|  | Venom                 | Drugs      | Food       | Latex     | Others    |                     |
| Age (year)   | 50 ± 13               | 48 ± 14    | 39 ± 12    | 42 ± 9    | 38 ± 11   | <0.001 <sup>a</sup> |
| Gender   |                       |            |            |           |           |                     |
| Female   | 132 (51)              | 181 (80.4) | 78 (63.4)  | 13 (72.2) | 40 (62.5) | <0.001 <sup>b</sup> |
| Male   | 127 (49)              | 44 (19.6)  | 45 (36.6)  | 5 (27.8)  | 24 (37.5) |                     |
| Frequency  |                       |            |            |           |           |                     |
| Total 1 times  | 128 (49.4)            | 161 (71.6) | 56 (45.5)  | 3 (16.7)  | 32 (50)   |                     |
| Total 2 times  | 91 (35.1)             | 47 (20.9)  | 38 (30.9)  | 10 (55.6) | 9 (14.1)  | <0.001 <sup>b</sup> |
| Total 3-5 times  | 31 (12)               | 14 (6.2)   | 21 (17.1)  | 4 (22.2)  | 8 (12.5)  |                     |
| 6 attacks per year or at least 2 attacks in the last 2 years | 9 (3.5)               | 3 (1.3)    | 8 (6.5)    | 1 (5.6)   | 15 (23.4) |                     |
| Skin Prick Test Positive with Respiratory Allergens          |                       |            |            |           |           |                     |
| Positive   | 64 (43.8)             | 53 (38.1)  | 63 (61.8)  | 9 (60)    | 22 (44.9) | 0.005 <sup>b</sup>  |
| Negative   | 82 (56.2)             | 86 (61.9)  | 39 (38.2)  | 6 (40)    | 27 (55.1) |                     |
| WAO 2020   |                       |            |            |           |           |                     |
| Diagnostic Criteria 1  | 163 (62.9)            | 207 (92)   | 114 (92.7) | 16 (88.9) | 56 (87.5) | <0.001 <sup>a</sup> |
| Diagnostic Criteria 2  | 96 (37.1)             | 18 (8)     | 9 (7.3)    | 2 (11.1)  | 8 (12.5)  |                     |
| WAO grading  |                       |            |            |           |           |                     |
| Grade 3  | 143 (55.2)            | 190 (84.4) | 97 (78.9)  | 16 (88.9) | 47 (73.4) |                     |
| Grade 4  | 17 (6.6)              | 15 (6.7)   | 14 (11.4)  | 2 (11.1)  | 5 (7.8)   | <0.001 <sup>b</sup> |
| Grade 5  | 99 (38.2)             | 20 (8.9)   | 12 (9.8)   | 0 (0)     | 12 (18.8) |                     |
| EAACI 2021   |                       |            |            |           |           |                     |
| 1  | 144 (55.6)            | 183 (81.3) | 82 (66.7)  | 16 (88.9) | 51 (79.7) |                     |
| 2  | 17 (6.6)              | 28 (12.4)  | 37 (30.1)  | 2 (11.1)  | 6 (9.4)   | <0.001 <sup>b</sup> |
| 3  | 98 (37.8)             | 14 (6.2)   | 4 (3.2)    | 0 (0)     | 7 (10.9)  |                     |

**Table 5.** Distribution of data according to causes of anaphylaxis. Mean ± SD (IQR); n (%). <sup>a</sup>Welch Testi. <sup>b</sup>Pearson Ki-kare Testi.



|                          | Causes of Anaphylaxis |            |            |            | Others     | p                   |
|--------------------------|-----------------------|------------|------------|------------|------------|---------------------|
|                          | Venom                 | Drug       | Food       | Latex      |            |                     |
| Total IgE                | 215 ± 348             | 216 ± 488  | 342 ± 630  | 139 ± 127  | 348 ± 596  | 0.024 <sup>a</sup>  |
| Lymphocyte Count         | 2191 ± 623            | 2082 ± 878 | 2249 ± 714 | 2088 ± 513 | 2252 ± 692 | 0.362 <sup>a</sup>  |
| Lymphocyte Percentage    | 30 ± 6                | 27 ± 9     | 29 ± 7     | 30 ± 6     | 28 ± 8     | 0.057 <sup>a</sup>  |
| Eosinophil Count         | 168 ± 147             | 173 ± 308  | 208 ± 235  | 166 ± 83   | 174 ± 158  | 0.684 <sup>b</sup>  |
| Eosinophil Percentage    | 2.3 ± 1.9             | 2.1 ± 2.7  | 2.9 ± 3.7  | 2.3 ± 1.2  | 2.4 ± 2.5  | 0.465 <sup>a</sup>  |
| Triptase                 | 7.4 ± 8.5             | 6.8 ± 5.9  | 5.6 ± 4.5  | 4 ± 2      | 7.9 ± 7.4  | 0.495 <sup>b</sup>  |
| Dyspnoea                 |                       |            |            |            |            |                     |
| Yes                      | 231 (89.2)            | 218 (96.9) | 116 (94.3) | 18 (100)   | 61 (95.3)  | 0.008 <sup>c</sup>  |
| No                       | 28 (10.8)             | 7 (3.1)    | 7 (5.7)    | 0 (0)      | 3 (4.7)    |                     |
| Syncope, dizziness; n(%) |                       |            |            |            |            |                     |
| Yes                      | 168 (64.9)            | 73 (32.4)  | 31 (25.2)  | 5 (27.8)   | 35 (54.7)  | <0.001 <sup>c</sup> |
| No                       | 91 (35.1)             | 152 (67.6) | 92 (74.8)  | 13 (72.2)  | 29 (45.3)  |                     |
| Hypotension              |                       |            |            |            |            |                     |
| Yes                      | 160 (61.8)            | 57 (25.4)  | 31 (25.2)  | 6 (33.3)   | 31 (48.4)  | <0.001 <sup>c</sup> |
| No                       | 99 (38.2)             | 167 (74.6) | 92 (74.8)  | 12 (66.7)  | 33 (51.6)  |                     |
| Flushing                 |                       |            |            |            |            |                     |
| Yes                      | 97 (37.5)             | 59 (26.2)  | 42 (34.1)  | 6 (33.3)   | 32 (50)    | 0.005 <sup>c</sup>  |
| No                       | 162 (62.5)            | 166 (73.8) | 81 (65.9)  | 12 (66.7)  | 32 (50)    |                     |
| Chest pain               |                       |            |            |            |            |                     |
| Yes                      | 47 (18.1)             | 40 (17.8)  | 17 (13.8)  | 3 (16.7)   | 17 (26.6)  | 0.323 <sup>c</sup>  |
| No                       | 212 (81.9)            | 185 (82.2) | 106 (86.2) | 15 (83.3)  | 47 (73.4)  |                     |
| Nausea, vomiting         |                       |            |            |            |            |                     |
| Yes                      | 28 (10.8)             | 29 (12.9)  | 35 (28.5)  | 2 (11.1)   | 12 (18.8)  | <0.001 <sup>c</sup> |

(continued)

|                           | Causes of Anaphylaxis |            |            |           | Others    | p                   |
|---------------------------|-----------------------|------------|------------|-----------|-----------|---------------------|
|                           | Venom                 | Drug       | Food       | Latex     |           |                     |
| No                        | 231 (89.2)            | 196 (87.1) | 88 (71.5)  | 16 (88.9) | 52 (81.2) |                     |
| Abdominal pain. diarrhoea |                       |            |            |           |           |                     |
| Yes                       | 24 (9.3)              | 21 (9.3)   | 36 (29.3)  | 1 (5.6)   | 15 (23.4) | <0.001 <sup>c</sup> |
| No                        | 235 (90.7)            | 204 (90.7) | 87 (70.7)  | 17 (94.4) | 49 (76.6) |                     |
| Rhinitis                  |                       |            |            |           |           |                     |
| Yes                       | 21 (8.1)              | 9 (4)      | 14 (11.4)  | 2 (11.1)  | 8 (12.5)  | 0.062 <sup>c</sup>  |
| No                        | 238 (91.9)            | 216 (96)   | 109 (88.6) | 16 (88.9) | 56 (87.5) |                     |
| Change in mood            |                       |            |            |           |           |                     |
| Yes                       | 23 (8.9)              | 7 (3.1)    | 10 (8.1)   | 1 (5.6)   | 6 (9.4)   | 0.106 <sup>c</sup>  |
| No                        | 236 (91.1)            | 218 (96.9) | 113 (91.9) | 17 (94.4) | 58 (90.6) |                     |

**Table 6. (Continued)** Distribution of laboratory parameters and symptoms according to causes of anaphylaxis. Mean  $\pm$  SD; n (%). <sup>a</sup>Welch Testi. <sup>b</sup>One Way ANOVA Testi. <sup>c</sup>Pearson Ki-kare Testi.

rate of abdominal pain-diarrhoea was significantly lower in patients with latex-induced anaphylaxis and higher in patients with food-induced anaphylaxis ( $p < 0.001$ ).

Among all patients, 235 (34.1%) presented to the emergency department. Adrenaline treatment was administered to 124 (52.7%) of the patients evaluated in the emergency department. Although anaphylaxis developed, adrenaline was administered in 17.9% of the patients. After evaluation in the Allergy and Immunology outpatient clinic, 451 (65.4%) received adrenaline auto-injectors. In 259 patients who developed venom-induced anaphylaxis, 83 (32%) patients were started venom immunotherapy. Elimination was recommended in all patients who developed food-induced anaphylaxis. All patients who developed drug-induced anaphylaxis were tested for alternative drugs and given an identification card. When further investigated for mast cell activation syndrome and mastocytosis, mastocytosis was diagnosed in 2 patients.

## DISCUSSION

Our study is one of the real-life studies with the largest number of patients evaluated with a single centre diagnosis of anaphylaxis. Patients from all over the country apply to our reference hospital and it is the centre with the highest number of Allergy and Immunology outpatients per year in our country. In addition, it is very important because it is a detailed investigation study requiring long-term follow-up, starting from the treatment of patients in the emergency department, examining diagnostic tests and allergic treatments.

During the 90-month period, the total number of patients admitted was 149,425 and the number of patients who were considered compatible with anaphylaxis was 689, ie, the prevalence of anaphylaxis was calculated as 0.46%. This percentage is high compared to the literature,<sup>12</sup> but this is due to the fact that we are a reference hospital and patients with suspected anaphylaxis are referred to our centre. In our study, the incidence of anaphylaxis was higher in women than in men. Considering the average age of our patients, anaphylaxis is more common in women

up to the fifth decade, as also reported in the literature.<sup>13</sup>

The causes of anaphylaxis vary according to age and geographical regions. The 3 most common causes were found to be venom, drug, and food in our study, which was similar to the studies conducted in our region.<sup>14-16</sup> The leading causes of food-induced anaphylaxis in adults were found to be similar to those found in a study conducted in a completely different geographical region.<sup>17</sup> Our study grouped the triggers of anaphylaxis according to age, gender, and frequency of anaphylaxis reaching statistical significance. The mean age of patients with venom-induced anaphylaxis was statistically significantly higher in patients with food-induced anaphylaxis. Venoma-induced anaphylaxis was more common in males and drug-induced anaphylaxis was more common in females. In all Pharmacovigilance Database analyses conducted nationwide in China, Poland and Russia, drug-induced anaphylaxis was more common in the female gender.<sup>18-20</sup> The incidence of anaphylaxis due to causes other than drugs, food, latex and venom, including idiopathic anaphylaxis, was higher in women. It has been suggested that the hormone estradiol is a factor potentiating sex differences in anaphylaxis and may potentiate mast cell releasability.<sup>16,21,22</sup>

In anaphylaxis, knowing the trigger reduces the possibility of recurrence. In our study, the frequency of anaphylaxis was statistically significantly higher in idiopathic anaphylaxis. It was thought that the frequency of anaphylaxis decreased with measures such as applying immunotherapy in venom-induced anaphylaxis and avoiding food or drug in drug- or food-induced anaphylaxis. Recently, it has been emphasised that a group of patients with idiopathic anaphylaxis due to changes in dietary habits may actually be due to a food that is not consumed frequently.<sup>23</sup>

According to Jerschow et al, the presence of hypotension in drug-induced anaphylaxis reached statistical significance.<sup>24</sup> In our study, hypotension in venom-induced anaphylaxis was statistically significant. It was thought that this may be related with the high number of honey production as an occupation in our country. The high number of patients with venom-induced anaphylaxis also supports this situation.

If patients presenting with anaphylaxis are evaluated by an allergist, triggering factors are further investigated; immunotherapy is applied for venom and comorbidities such as mastocytosis are investigated.<sup>25</sup> The compliance of our centre with these recommendations is very high. In particular, the use of adrenaline autoinjectors is reviewed at each hospital admission of the patients and their knowledge about its use is examined. The global rate of adrenaline administration in the management of anaphylaxis is low.<sup>26</sup> The rate of adrenaline administration in our patients admitted to the emergency department was 17.9%. More education is needed for the recognition of anaphylaxis by health authorities and the administration of adrenaline.<sup>1,10</sup> The 2023 anaphylaxis update recommends administration of adrenaline even if not all diagnostic criteria for anaphylaxis are met.<sup>27</sup>

The most important limitation of our study is that it is retrospective. Our hospital is a centre to which patients are referred from all over the country. During the study period, a total of 149,425 patients were examined in our Allergy and Immunology outpatient clinic. The diversity and high number of patients are also strengths. This situation is intended to guide future studies.

#### Abbreviations

EAACI: The European Academy of Allergy and Clinical Immunology; ICD-10: International Statistical Classification of Diseases and Related Health Problems; WAO: World Allergy Organization.

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#### Authors' contributions

All authors took part of Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

#### Ethics approval and consent to participate

Ethics committee approval of the University of Health Sciences, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital was obtained for this study (116.2017.R-302).

#### Author's consent for publication

We, the undersigned, give my consent for the publication of identifiable details, which can include photograph(s) and/or videos and/or case history and/or details within the text ("Material") to be published in World Allergy Organization Journal.

#### Declaration of competing interest

The authors have no conflicts of interest to declare.

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#### Author details

<sup>a</sup>University of Health Sciences, Süreyyapaşa Training and Research Hospital, Department of Allergy and Immunology, Turkey. <sup>b</sup>University of Health Sciences, Yedikule Training and Research Hospital, Department of Allergy and Immunology, Turkey.

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