

Preliminary findings from a concise emergency department model to predict anaphylaxis and develop a clinical decision support tool

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Clinical Implications

- The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for anaphylaxis may be difficult to use in emergency situations, so we developed a clinical decision support tool. This model, with a cutoff of 9 points, had a sensitivity and specificity of 82.4% and 83.6%, respectively, to diagnose anaphylaxis meeting the NIAID/FAAN criteria.

TO THE EDITOR:

Anaphylaxis is a rapidly progressive systemic allergic reaction, and up to 74% of initial evaluations take place in the emergency department (ED), with a 15% hospitalization rate.¹ Diagnosis of anaphylaxis relies heavily on clinical signs and symptoms, often involving multiple organ systems after exposure to an inciting trigger. Serum biomarker, particularly tryptase, has not always been used in the ED because of low sensitivity. There are inconsistent data on the use of diagnostic criteria in the ED. The high sensitivity but limited specificity of National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria has been demonstrated.² There are a few clinical decision support (CDS) tools for drug allergies,³ but there is no CDS tool for anaphylaxis in the acute care setting to date. There is a critical need to identify the patient population that is actively developing anaphylaxis based on the limited information available in the acute care setting.

To address this need, we aimed to identify the key features of anaphylaxis (International Classification of Diseases, Tenth Revision codes T78.0-T78.2) from our ongoing prospective observational study at a 60,000-visit per year rural Midwest academic medical center ED. Our objective was to develop a prediction model for anaphylaxis in the ED and explore the possibility of developing and validating an anaphylaxis CDS. Our hypothesis is that the combination of clinical signs and symptoms will enable us to identify anaphylaxis meeting the NIAID/FAAN criteria and its related complications better than the clinical impression.

A prospective study was conducted using a convenience sampling of patients presenting to the ED from June 2017 to July 2018 with chief complaints of allergic reaction, food allergy, insect sting, medication reaction, angioedema, or anaphylaxis. After consent, we collected data on patient demographics, inciting allergen, time of onset, signs and symptoms,

medications, ED management, disposition, and follow-up. The chart reviewer (CH) identified anaphylaxis based on the NIAID/FAAN criteria and recorded demographic data, signs and symptoms, and disposition. The PI (SL) verified these data for 20 cases and reported concordance of diagnosis. Any difficult case was resolved by discussion. Logistic regression was conducted to measure the association between exposure to inciting trigger, time of onset, clinical signs and symptoms, and anaphylaxis criteria meeting NIAID/FAAN criteria. Then we selected the prediction model based on c-statistics and simplicity. We used bootstrap resampling to test the internal validity and provided the 95% confidence interval (CI) to the estimate.

A total of 141 patients of all ages were included with a median age of 27 years (interquartile range, 18-48 years), and 79 (56%) patients were female. The inciting trigger, demographic, and outcome information is provided in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). For food-related triggers, 90.5% were within 2 hours (2 subjects were between 2 and 4 hours and 2 subjects had unknown times). For medication-related triggers, 48.4% were within 2 hours (2 subjects were between 2 and 4 hours, 12 subjects were between 6 and 24 hours, and 2 subjects had unknown times). Sixty-eight of the patients (48%) met NIAID/FAAN criteria for anaphylaxis. A total of 47 cases (33.3%) met the first criteria, 31 cases (22.0%) met the second criteria, and 0 cases (0.0%) met the third criteria (10 subjects met both the first and second criteria). The clinician did not diagnose the patient with anaphylaxis when they met NIAID/FAAN criteria in 33 cases and diagnosed anaphylaxis when the patient did not meet NIAID/FAAN criteria in 3 cases. The inter-rater agreement was weak ($\kappa = 0.481$). The concordance between chart reviewer and the expert to diagnose anaphylaxis was κ of 0.79 (0.52-1). Logistic regression demonstrated that the combination of food allergy (odds ratio [OR], 3.67; 95% CI, 1.37-10.5), angioedema (OR, 4.98; 95% CI, 1.81-15.4), shortness of breath (OR, 20.3; 95% CI, 5.62-103), nausea (OR, 10.9; 95% CI, 2.80-49.8), and voice change (OR, 51.1; 95% CI, 8.99-978) was associated with meeting NIAID/FAAN criteria, with a c-statistic of 0.9 (Table I). The Hosmer-Lemeshow goodness-of-fit test was not statistically significant ($P = .91$), indicating that there was no evidence of the model overfitting. The model's performance was evaluated in an internal validation used bootstrapping of 1000 replicates with replacement to predict if a participant would meet the NIAID/FAAN criteria for anaphylaxis, demonstrating the area under the curve of 0.90 (95% CI, 0.90-0.91). Two cutoffs for prediction

TABLE I. Anaphylaxis prediction score generated from model covariates

Variables	Odds ratio	95% CI
Angioedema	5.0	1.73-14.34
Dyspnea	20.35	4.92-84.00
Food allergy	3.67	1.34-10.09
Nausea	10.86	2.61-45.14
Voice change	51.06	6.06-430.36

CI, Confidence interval.

TABLE II. Diagnostic characteristics for using the score cutoff to predict anaphylaxis meeting NIAID/FAAN criteria

Model	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Diagnostic OR (95% CI)	+LR (95% CI)	–LR (95% CI)
Model 1*	82.4 (71.2-90.5)	83.6 (73.1-91.2)	82.4 (73.3-88.8)	83.6 (75.1-89.6)	23.72 (9.85-57.09)	5.01 (2.95-8.50)	0.21 (0.13-0.36)
Model 2†	94.1 (85.6-98.4)	53.4 (41.4-65.2)	65.3 (59.4-70.8)	90.7 (78.6-96.3)	18.35 (6.05-55.67)	2.02 (1.57-2.60)	0.11 (0.0-0.29)

CI, Confidence interval; FAAN, Food Allergy and Anaphylaxis Network; LR, likelihood ratio; NIAID, National Institute of Allergy and Infectious Disease; NPV, negative predictive value; OR, odds ratios; PPV, positive predictive value.

*In model 1, anaphylaxis is defined as having at least one of the following: (1) dyspnea, (2) nausea, (3) voice change, or (4) both angioedema and food allergy.

†In model 2, anaphylaxis is defined as having at least one of the following: (1) dyspnea, (2) nausea, (3) voice change, or (4) angioedema.

models of anaphylaxis were determined. In the first model (model 1), subjects were said to have anaphylaxis if they had at least one of the following: (1) dyspnea, (2) nausea, (3) voice change, or (4) both angioedema and food allergy. Model 1 maintained a specificity of 83.54% (95% CI, 83.26-83.81) and a sensitivity of 82.34% (95% CI, 82.06-82.62), negative likelihood ratio (LR) of 0.21 (95% CI, 0.21-0.22), positive LR of 5.44 (95% CI, 5.33-5.56), and diagnostic OR of 28.89 (95% CI, 27.82-29.96) (Table II). A second model (model 2) used the following definition to predict anaphylaxis: at least one of the following: (1) dyspnea, (2) nausea, (3) voice change, or (4) angioedema. In model 2, a higher sensitivity was observed ($S_n = 94.08\%$; 95% CI, 93.90-94.26) with a lower specificity ($S_p = 53.33\%$; 95% CI, 52.96-53.70), negative LR of 0.11 (95% CI, 0.11-0.12), positive LR of 2.05 (95% CI, 2.03-2.07), and diagnostic OR of 24.19 (95% CI, 23.03-25.35) (Table II).

It has been more than 10 years since NIAID/FAAN criteria were developed from a panel of experts,⁴ and there currently are no validated diagnostic utility screens for anaphylaxis in the ED. The diagnostic characteristics of the criteria were published in the past, showing its high sensitivity of 95.1% but the limited specificity of 71% from the prospective cohort in the ED.^{2,5} The expert criteria remain the gold standard in the literature for research purposes, but access is not always possible. Our research demonstrated that the discrepancy between the clinician's diagnosis of anaphylaxis and NIAID/FAAN diagnosis was substantial due to the insufficient application of criteria in clinical practice, and there was a knowledge gap in the dissemination of the criteria in the emergency medicine practice. Furthermore, a concise prediction model can be used in the prehospital setting by the emergency medical services providers who might lack complete collateral information, extensive scene time, or comprehensive training at the introductory levels of practice (eg, first responders) to take care of any potential allergic reaction or anaphylaxis. Such a concise prediction model might have a role in other settings to identify anaphylaxis and start treatment with epinephrine when the experts are not available. Further study is necessary to examine its utility beyond the ED. Our study has several limitations. First, this study is aimed to derive and validate any potential prediction model and requires external validation. Second, because of the small sample, we were not able to include some of the infrequent but important symptoms, such as hypoxia or syncope, which are a well-known indicator for severe anaphylaxis.

In conclusion, the NIAID/FAAN criteria for anaphylaxis may be difficult to use in emergencies, evidenced by the poor inter-observer agreement in our study, resulting in the underdiagnosis

of anaphylaxis. Our findings are still preliminary and require further validation. The next step would be the external validation of the model, or similar models might be developed and tailored for exploration of potential benefit in various non-ED settings.

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TABLE E1. Clinical features of patients meeting NIAID/FAAN criteria for anaphylaxis and patients who do not meet criteria for anaphylaxis (N = 141)

Variables	Anaphylaxis (n = 68)	Nonanaphylaxis (n = 73)
Demographics	n (%)	n (%)
Age, median* (IQR) (y)	23 (18-42)	29 (17-51)
Female	38 (56)	41 (56)
Race		
African American/Black	5 (7.4)	11 (15.1)
Asian American/Asian	0 (0.0)	1 (1.4)
Caucasian/White	54 (79.4)	54 (74.0)
Hispanic/Latino	4 (5.9)	5 (6.9)
Multiracial	3 (4.4)	1 (1.4)
Other/missing	3 (3.3)	0 (0.0)
History		
Prior anaphylaxis	26 (38)	12 (16)
Angioedema	22 (32)	17 (23)
Seasonal allergies	14 (21)	17 (23)
Asthma or COPD	25 (37)	16 (22)
Trigger		
Food	31 (46)	13 (18)
Medication	9 (13)	21 (29)
Venom	6 (8.8)	5 (6.8)
Latex	2 (2.9)	0 (0)
Contrast	3 (4.4)	2 (2.7)
Other	2 (2.9)	7 (9.6)
Unknown	15 (22)	25 (34)
Symptoms		
Mucocutaneous		
Diffuse urticaria	31 (46)	24 (33)
Angioedema	43 (63)	28 (38)
Throat tightness	30 (44)	18 (25)
Pruritis	35 (51)	34 (47)
Flushing	21 (31)	10 (14)
Respiratory		
Voice change [†]	21 (31)	1 (1.4)
Dyspnea	26 (38)	3 (4.1)
Wheeze	7 (10)	0 (0)
Stridor	1 (1.5)	1 (1.4)
Hypoxemia	3 (4.4)	0 (0)
Gastrointestinal		
Nausea	17 (25.0)	5 (6.9)
Vomiting	9 (13)	2 (2.7)
Diarrhea	1 (1.5)	4 (5.5)
Abdominal pain	10 (15)	5 (6.8)
Cardiovascular		
Dizzy, lightheaded, and/or hypotonia	10 (15)	4 (5.5)
Syncope	4 (5.9)	0 (0)
Treatment		
Any type of steroid [‡]	48 (71)	39 (53)
Epinephrine	42 (76)	16 (22)

COPD, Chronic obstructive pulmonary disease; FAAN, Food Allergy and Anaphylaxis Network; IQR, interquartile range; NIAID, National Institute of Allergy and Infectious Disease.

*The median was reported due to non-normal distribution.

[†]Overall, 21 (30.9%) subjects with anaphylaxis had voice change, and laryngoscope was performed in 5.9% of them, which did not show laryngeal edema in any of the 7 subjects tested.

[‡]Steroid included any oral, intramuscular, or parenteral route.

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