

Clinical Communications

Characterization of serum biomarkers during anaphylaxis in emergency department patients

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Clinical Implications

- Although common, anaphylaxis might be difficult to diagnose; identification of biomarkers should aid in the improvement of its diagnosis and management.

Anaphylaxis is a serious hypersensitivity reaction that is commonly seen in the emergency department (ED).¹ A multidisciplinary group of experts met in 2005 and created the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for diagnosis. They defined anaphylaxis as "... a serious allergic reaction that is rapid in onset and may cause death" and established 3 sets of criteria for diagnosis.² In 2014, the World Allergy Organization consensus on anaphylaxis reported a series of similar definitions and agreed with the 3 sets of clinical criteria to diagnose anaphylaxis.³ In their reports, both groups identified the need for reliable serum biomarkers to aid the clinical diagnosis. However, there are few if any studies establishing biomarkers in the clinical diagnosis of anaphylaxis in the acute care setting.^{2,3} This study examined an array of biomarkers in the serum of patients presenting to the ED with anaphylaxis.

We enrolled 39 patients with allergic reaction or anaphylaxis who presented to an academic ED from July 2017 to May 2018. Data collection started within 30 minutes of presentation, and a serum sample from an IV line was obtained. Data included a questionnaire for the participant, a clinical form for the practitioner, and a follow-up phone call to the participant 3 days after discharge. Serum samples were used to analyze 26 potential biomarkers. The candidate biomarkers were chosen based on discussion before the study and the availability of a kit at the immunology lab. Participants were stratified into the anaphylaxis group if they met the NIAID/FAAN criteria, and the non-anaphylaxis group if they did not.² The principal investigator (SL), who was blinded to the results of the biomarker testing, verified the diagnoses and resolved any diagnostic disagreements by discussion. A blood sample was collected for biomarker measurement at the time of ED evaluation. After collection, the blood samples were processed and frozen at -80°C for later analysis. Serum markers were measured using a Luminex-based multiplex assay. The mean ratio of each serum biomarker concentrations for the anaphylaxis and non-anaphylaxis groups was calculated along with its 95% confidence interval and *P* value. Using the generalized linear modeling framework and a log link function to account for the right-skewed biomarker distributions, comparisons were made adjusting for the use of epinephrine as a binary response before blood draw.

Of 39 participants, 23 met at least 1 set of anaphylaxis criteria. The median age for the anaphylaxis group was 38.3 (interquartile range [IQR], 18.1) years and for the non-anaphylaxis group 41.9 (IQR, 18.3) years. Food allergy was the most commonly reported precipitating anaphylactic allergen (43.5%, *n* = 10), with other reported inciting events including medication (17.4%, *n* = 4), venom (8.7%, *n* = 2), and contrast media (8.7%, *n* = 2). The inciting trigger was unknown in 5 cases (21.7%). Prior anaphylaxis was more common in the anaphylaxis group (52.2% vs 6.3%; *P* = .005). The remainder of demographics and characteristics are listed in Table I.

Serum biomarker results are shown in Figure 1 (adjusted for epinephrine) and Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org) (not adjusted for epinephrine). When not adjusted for epinephrine use, the following cytokines were decreased: IL-5, IL-16, IL-17, IL-21, IL-31, IL-33, IFN- γ , CINC-1, and CCL1 I-309 (*P* = .020, .004, .006, .004, .014, .005, .001, .026, and .022, respectively). Conversely, IL-10 was increased (*P* = .009). After adjusted for epinephrine use, there was a significant increase for IL-6 and IL-10 (*P* = .047 and .012, respectively) and a significant decrease for IL-5, IL-16, IL-17, IL-21, IL-31, IL-33, IFN- γ , CINC-1, and CCL1 I-309 (*P* = .046, .039, .007, .030, .016, .034, .012, .019, and .046, respectively). Other cytokines tested that showed no significant difference between anaphylaxis and non-anaphylaxis in epinephrine adjusted or unadjusted analysis include C5a, G-CSF, ICAM-1, IL-1RA, IL-4, IL-13, CD40L, IL-1B, IL-2, IL-8, IL-12, IL-18, and TNF α (*P* > .05).

Our study showed several significant serum biomarker relationships that can aid in the clinical diagnosis of anaphylaxis. Currently, serum biomarkers have only a limited role in the clinical setting; these results add to the small but growing body of research. Of particular note, although many of the biomarkers selected were decreased in the anaphylaxis group, IL-6 and IL-10 were elevated.

We identified an increase in IL-6 in anaphylaxis compared with non-anaphylaxis. IL-6 is an important proinflammatory cytokine and hepatic mediator of the acute phase response.⁴ Previous studies have shown increased levels of IL-6 during anaphylaxis and that this increase relates to increased erythema, lower mean arterial blood pressure, and longer duration of symptoms.^{5,6} IL-6 has also been inversely related to histamine levels with its peak in elevation later in the disease course.⁵ Thus, IL-6 may be of use in the ED given the association with symptoms and the duration of its increase.

Similarly, IL-10 was elevated in anaphylaxis compared with non-anaphylaxis, which is also consistent with previous reports.⁶ IL-10 has many important immune regulatory functions, including a known role of helping modulate the progression or resolution of allergic reactions.⁷ As such, elevations in IL-10 may serve as a marker that a systemic reaction has occurred and could be useful in the clinical setting.

This study has several limitations. First, because of logistics, tryptase levels were not measured. The significance of this is unclear as the utility of tryptase testing in the ED setting has been questioned and elevated IL-6 levels have previously been associated with higher tryptase levels.⁵ Other potentially

TABLE I. Participant demographics and reaction characteristics by anaphylaxis and non-anaphylaxis groups

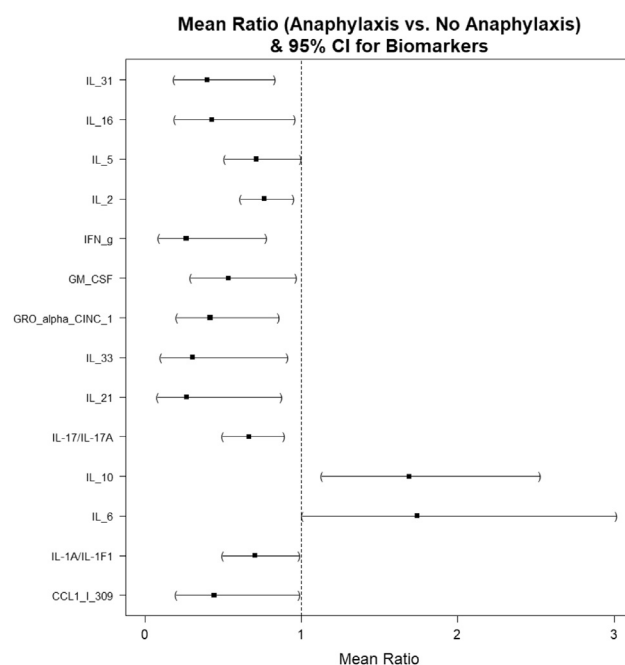
	Variable	Anaphylaxis (N = 23)	Non-anaphylaxis (N = 16)	P value
Patient characteristics	Age	38.3 (18.1)	41.9 (18.3)	.537
	Asthma	43.5%	18.8%	.169
	Food allergy	39.1%	31.3%	.74
	Prior anaphylaxis	52.2%	6.3%	.005
	Male	43.5%	43.8%	>.999
Onset location	Home	13.0%	43.8%	.211
	School	4.4%	6.3%	
	Work	17.4%	6.3%	
	Restaurant	13.0%	0.0%	
	Outdoors	4.4%	6.3%	
	Healthcare facility	21.7%	6.3%	
	Other	31.3%	26.1%	
Precipitating allergen	Food allergy	43.5%	18.8%	.254
	Medication	17.4%	31.3%	
	Venom	8.7%	12.5%	
	Contrast	8.7%	0.0%	
	Other	0.0%	12.5%	
	Unknown	21.7%	25.0%	
Signs/symptoms	Urticaria diffuse	43.5%	25.0%	.317
	Any urticaria	56.5%	37.5%	.333
	Hypoxemia	8.7%	0.0%	.503
	Syncope	8.7%	0.0%	.503
Management	Epinephrine given	82.6%	31.1%	.002
	Home	90.5%	93.8%	>.999
	Observation unit	4.8%	6.3%	
	Inpatient admission	4.8%	0.0%	

important biomarkers, such as bradykinin, were also not evaluated. Second, we have a small sample size so we could not adjust the *P* value for multiple hypothesis testing. This study was exploratory by design, with the main focus being to identify potential biomarkers to be used in the clinical setting. Third, it is possible that the elevated IL-6 was induced by epinephrine and not by the anaphylactic episode. A larger sample is necessary to explore this finding by examining confounders further. Lastly, TH2 cytokines appeared to be decreased in anaphylaxis as were some of the proinflammatory cytokines. It is possible that this is due to the limitation of measuring cytokines in the serum as there may be a sampling bias with the involved cytokines being in the involved organ.

In summary, our study showed that those presenting to the ED with anaphylaxis were found to have elevated IL-6 and IL-10, which could be the unique signature of anaphylaxis. The use of biomarkers can facilitate accurate diagnosis, inform the need for epinephrine prescription, and determine the disposition as the clinical gestalt is not enough to identify anaphylaxis. The next step would be to compare the utility of these biomarkers with tryptase, a common test performed in the allergy practice.

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**FIGURE 1.** Mean ratio and 95% confidence intervals (CI) for serum biomarkers in anaphylaxis versus non-anaphylaxis, adjusted for epinephrine use.

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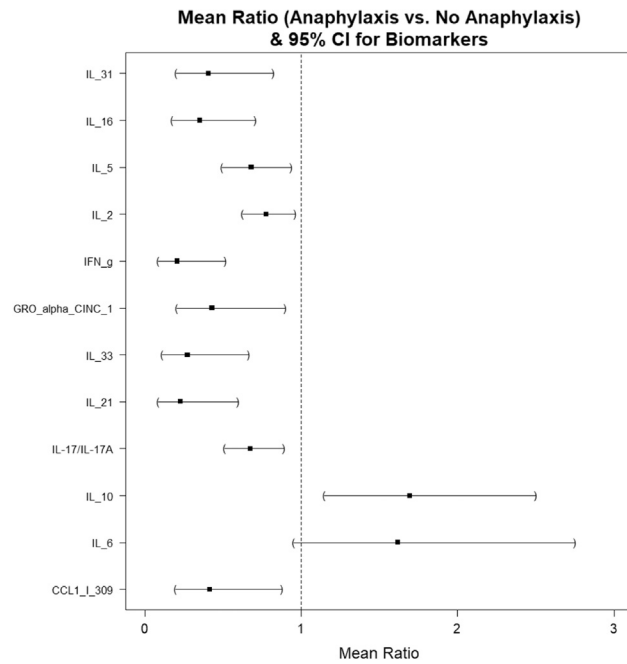


FIGURE E1. Mean ratio and 95% confidence intervals (CI) for serum biomarkers in the anaphylaxis versus non-anaphylaxis groups, not adjusted for epinephrine use.