

Letter to the Editor

Serum levels of 9 α ,11 β -PGF₂ and cysteinyl leukotrienes are useful biomarkers of anaphylaxis

To the Editor:

Anaphylaxis is a life-threatening hypersensitivity reaction.¹ Mast cell (MC) activation results in the release of multiple mediators,² but their relation to the outcome of an anaphylactic episode remains poorly defined, and systematic analyses concurrently investigating several mediators are sparse. Tryptase and histamine levels reportedly increase during anaphylaxis³ but are inadequate to unambiguously identify all anaphylactic responses.⁴ More reliable markers to support the clinical diagnosis of anaphylaxis are currently needed.

In this study serum levels of molecules potentially produced by several cell sources but released in large amounts on MC activation² were examined as biomarkers of anaphylaxis. A prior comparison of mediator levels in serum versus plasma revealed no discernable difference between the 2 blood-derived fluids (data not shown). Our cohort consisted of 18 patients sampled 2 or less hours after an anaphylactic reaction (ie, the postanaphylaxis group). Control groups comprised 27 patients sampled outside of an acute reaction but with a history of anaphylaxis (ie, the anaphylaxis-prone group) and 12 patients with acute cardiovascular or febrile reactions (ie, the other diseases group). The clinical reaction patterns of the cohorts are specified in Tables E1-E3 in this article's Online Repository at www.jacionline.org.

For this study, we analyzed sera collected from patients with anaphylactic symptoms on arrival in emergency departments in 2010-2011 (blood sampled maximally 2 hours after onset of the reaction; the postanaphylaxis group, $n = 18$). Anaphylaxis was established clinically by routine patient evaluation. Patients were stratified into 4 severity groups according to Ring and Messmer⁵ based on clinical reaction patterns (see Table E1). Control groups consisted of patients with a history of anaphylaxis but without symptoms at the time of blood sampling (the anaphylaxis-prone group, $n = 27$; see Table E2) and a group with acute cardiovascular or febrile reactions (the other diseases group, $n = 12$, see Table E3).

Baseline serum samples were available for 9 of 18 patients from the postanaphylaxis group and served to compare basal mediator levels with corresponding levels during acute anaphylaxis in the same patients. Levels of histamine (LDN, Nordhorn, Germany), cys-LTs (LTC₄, LTD₄, and LTE₄), and 9 α ,11 β -PGF₂ (both from Cayman Chemical, Ann Arbor, Mich) were measured by means of ELISA, according to the manufacturer's instructions. Tryptase levels were quantified by Thermo Fisher Scientific (Freiburg, Germany) using the UniCAP-Tryptase fluoroimmunoassay technique. According to the manufacturer, tryptase levels greater than 11.4 μ g/L can be regarded as increased.

Statistical analyses were performed with Prism 5.0 software (GraphPad Software, La Jolla, Calif) by using nonparametric ANOVA with the Dunn posttest. Pairwise comparisons were conducted with the Wilcoxon matched pairs test. Correlations were analyzed by using the Spearman rank correlation test.

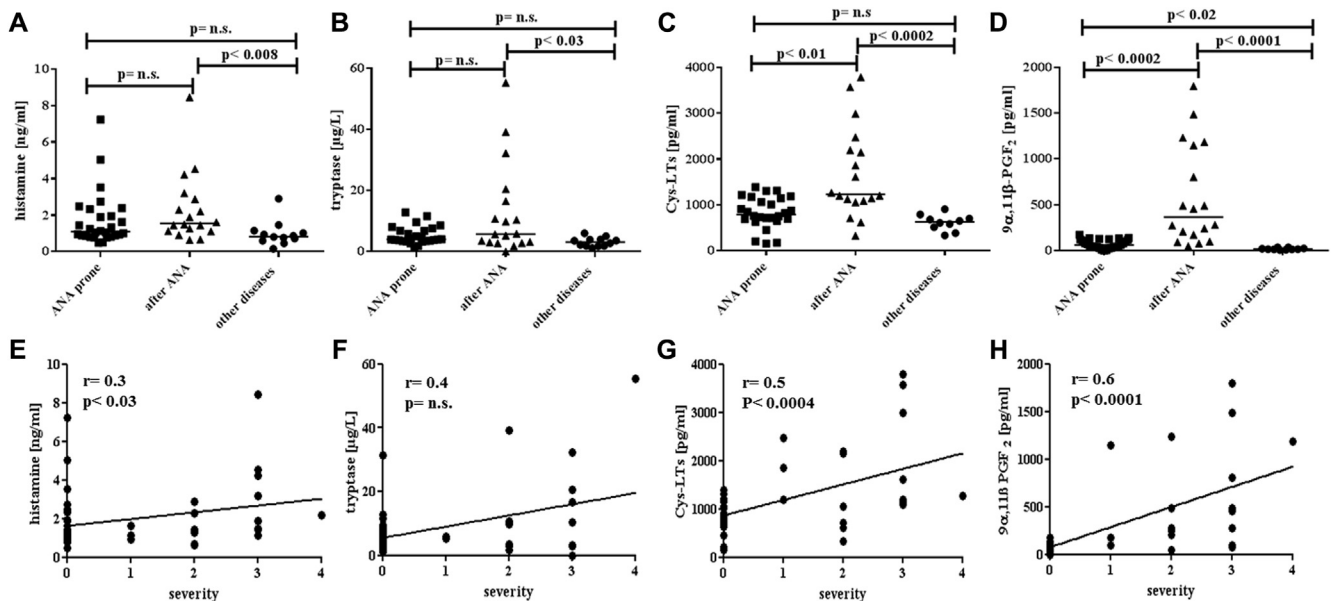


FIG 1. A-D, Serum levels of histamine (Fig 1, A), tryptase (Fig 1, B), cys-LTs (Fig 1, C), and 9 α ,11 β -PGF₂ (Fig 1, D) in sera of patients with acute anaphylaxis: relation to anaphylaxis severity. Serum levels of mediators in the active anaphylaxis group (after ANA; blood obtained maximally 2 hours after the precipitating event) compared with the control group (ANA prone) who had experienced anaphylaxis in the past but did not experience an anaphylactic reaction at the time of blood withdrawal and a group with acute cardiovascular and febrile reactions (other diseases) are shown. The cohorts are specified in Tables E1-E3. Mediators were measured by using ELISA (histamine, cys-LTs, and 9 α ,11 β -PGF₂) or the UniCAP system (tryptase). E-H, Mediators are shown as a function of anaphylaxis severity. *n.s.*, Not significant.

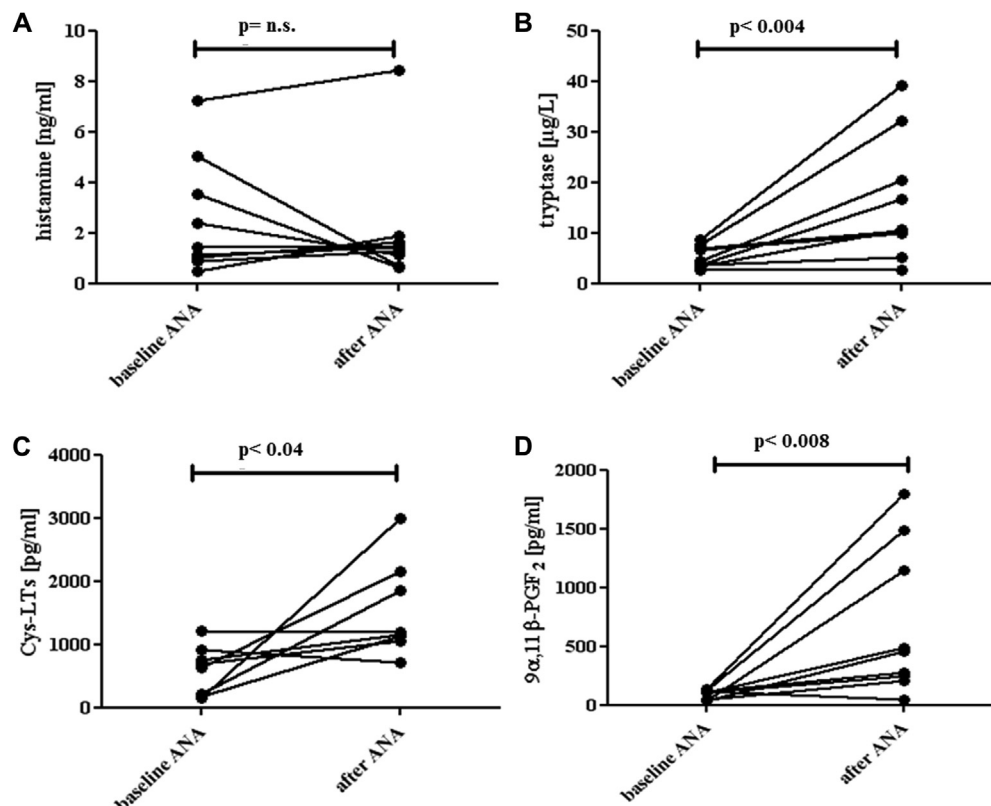


FIG 2. Mast cell mediator concentrations during anaphylaxis in a paired setting. The utility of tryptase as a biomarker of anaphylaxis depends on comparison with matched nonanaphylaxis values. Nine of 18 patients of the postanaphylaxis group (*after ANA*; Fig 1) provided sera outside of an anaphylactic episode. Mediator concentrations were assessed as in Fig 1. Dots corresponding to the same patient are interconnected. *n.s.*, Not significant.

Receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) was calculated to establish the predictive power of single mediators as standalone diagnostic tools and compared with mediator combinations in an adjunctive setting. An AUC equal to 1.0 indicates that the diagnostic test discriminates perfectly between anaphylactic and nonanaphylactic responses; that is, there are no false-positive or false-negative results. An AUC equal to 0.5 indicates that the results of the diagnostic test are purely random. A *P* value of less than .05 was considered statistically significant.

Focusing on histamine first, we found no difference between the anaphylaxis-prone and the postanaphylaxis groups (Fig 1, A), which is consistent with the short biological half-life of histamine.³ Anaphylactic episodes can occur anywhere, and a considerable period of time typically passes before the patient with anaphylaxis is actually seen by an emergency physician. Time seems decisive in the case of histamine because patients with food allergy (*n* = 11) undergoing controlled challenges show slight yet significant (*P* = .005) increases (maximum increase, 35%) in serum histamine levels after approximately 15 minutes, despite their mild symptoms (unpublished results).

Tryptase is less labile and most sensitively detected at 0.5 to 2 hours after anaphylaxis.^{3,4} Baseline tryptase levels vary from 1 to 11 ng/mL in most healthy subjects but can be increased in patients with various other conditions, including mastocytosis.^{3,6} In our postanaphylaxis group the median tryptase level was

unaltered compared with that of the anaphylaxis-prone group (Fig 1, B), although single values were increased (>11.4 µg/L).

MCs also quickly generate arachidonic acid metabolites on stimulation, in particular prostaglandin (PG) D₂ and leukotriene (LT) C₄,² which are rapidly metabolized *in vivo* to 9α,11β-PGF₂ and LTE₄, respectively, with these metabolites being more stable in body fluids. Their measurements in the context of allergic conditions, such as anaphylaxis and asthma, typically have been reported in urine. When measured in sera, we found significant increases in levels of cysteinyl leukotrienes (cys-LTs; Fig 1, C) and 9α,11β-PGF₂ (Fig 1, D), implying their suitability for the detection of anaphylaxis in serum up to 2 hours after onset of the acute event. Differences between the postanaphylaxis and other diseases groups were equal or more pronounced if compared with the differences between the anaphylaxis-prone and postanaphylaxis groups, indicating that their increase was specific for anaphylaxis and not found in patients with other acute conditions (Fig 1).

Previous evidence suggested a correlation between histamine⁷ or tryptase^{4,8} levels and anaphylaxis severity. To examine whether this was true for our cohort, patients were stratified by severity grade,⁵ and mediator levels were plotted in relation to the severity of anaphylaxis (Fig 1, E-H). Histamine and tryptase levels showed little correlation with severity (Fig 1, E and F), and both turned out to be poor biomarkers of anaphylaxis by using ROC curve analysis with the postanaphylaxis and anaphylaxis-

prone groups as positive and negative samples, respectively (see Fig E1 and Table E4 in this article's Online Repository at www.jacionline.org). Conversely, levels of cys-LTs and $9\alpha,11\beta$ -PGF₂ showed significant correlation with severity (Fig 1, G and H) and were associated with a higher sensitivity/specificity, as measured by AUC values (see Fig E1 and Table E4). The preceding analyses concentrated on a comparison between groups of unrelated patients to derive anaphylaxis-related mediator profiles, even without knowledge of their baseline levels in the patient, because such information might not be available in emergency settings. We wondered whether the above conclusions would prove reproducible if only anaphylaxis-triggered changes in the same patient were considered. Matched data sets were available for 9 patients. As shown in Fig 2, median concentrations of histamine in the baseline and acute anaphylaxis groups were not significantly different, whereas concentrations of acute tryptase, cys-LTs, and $9\alpha,11\beta$ -PGF₂ were significantly higher than baseline values (see Table E5), supporting their use as biomarkers of anaphylaxis.

In conclusion, our data revealed that the assessed mediators vary in their utility as serum biomarkers of anaphylaxis. An appropriate timing of blood withdrawal might increase the sensitivity of each mediator. Histamine seems inadequate under most circumstances because of its short half-life and might only be able to detect anaphylaxis when assessed early after anaphylaxis onset. Tryptase is more stable³ and can be used to detect anaphylaxis in subgroups of patients, but it is crucial to know the baseline level of the patient in accordance with previous observations.^{3,9} Metabolites of LTC₄ and in particular PGD₂ seemed most useful: while the parent mediators are rapidly degraded, cys-LTs and $9\alpha,11\beta$ -PGF₂ are more stable, and increased levels are detectable in serum up to 2 hours after onset of anaphylaxis. The particular advantages of $9\alpha,11\beta$ -PGF₂ are (1) its very low baseline level, (2) little variability in the basal concentration among patients, (3) its profound increase after anaphylaxis (approximately 8-fold), (4) its relative stability and persistence in the circulation, and (5) its correlation with severity, making it a robust candidate biomarker. Cys-LTs seem to constitute a supportive marker, but they correlate less well with severity and show more heterogeneous baseline levels. However, because levels of $9\alpha,11\beta$ -PGF₂ and cys-LTs are not correlated (pairwise comparisons revealed no significant correlation among the mediators investigated, see Fig E2 in this article's Online Repository at www.jacionline.org), we assumed that their combination could result in superior sensitivity/specificity compared with each

molecule alone. ROC curve calculations and associated AUC values revealed that a combination of cys-LTs with $9\alpha,11\beta$ -PGF₂ improved the diagnostic power of $9\alpha,11\beta$ -PGF₂ (see Fig E1). Further investigations are needed to verify the generalizability of these findings because only a small cohort could be considered by this study. However, the clear increase in serum cys-LT and $9\alpha,11\beta$ -PGF₂ levels during anaphylaxis, combined with their relation to anaphylaxis severity and predictive power, imply that these molecules might prove to be highly suitable serum markers to assist in the diagnosis of anaphylaxis.

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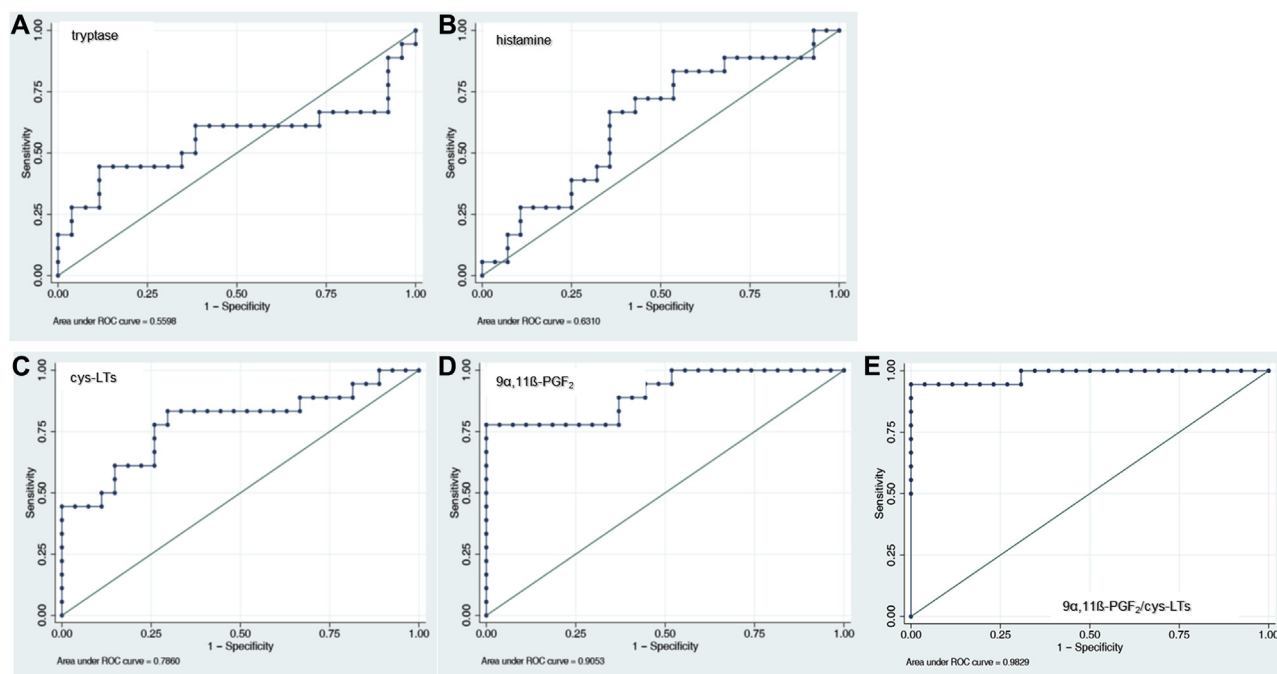


FIG E1. Predictive power of mediators to serve as biomarkers for anaphylaxis. ROC curves and AUC values are given for tryptase (A), histamine (B), cys-LTs (C), $9\alpha,11\beta$ -PGF₂ (D), and the combination of $9\alpha,11\beta$ -PGF₂ and cys-LTs (E).

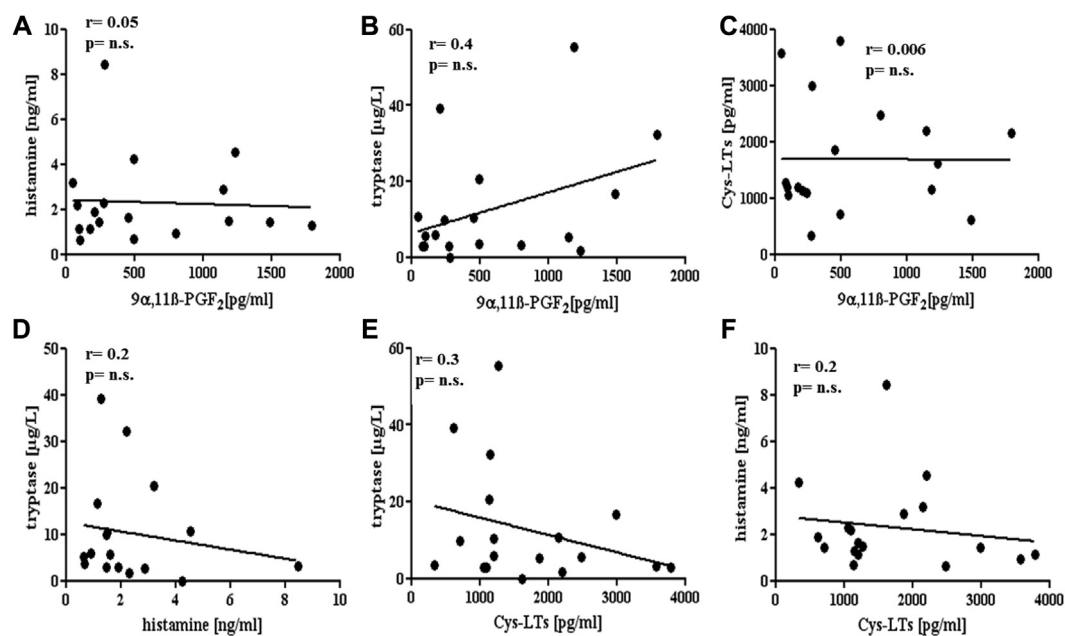


FIG E2. Pairwise correlations between mast cell mediators during anaphylaxis. Correlation coefficients and associated P values for all possible mediator combinations were calculated by using the Spearman test. No significant correlations could be detected.

TABLE E1. Definition of the postanaphylaxis group and their clinical reaction patterns

Elicitor	Sex	Clinical manifestation	Anaphylaxis severity	Mediator			
				Histamine (ng/mL)	Tryptase (μg/L)	Cys-LTs (pg/mL)	9α,11β-PGF ₂ (pg/mL)
Insect	Female	Skin	I	1.112	5.860	1203.026	172.504
Insect	Female	Respiratory symptoms, cardiovascular symptoms	III	8.455	16.590	2991.307	1487.829
Insect	Female	Respiratory symptoms, skin	III	1.126	10.430	1198.554	455.371
Insect	Male	Cardiovascular symptoms	IV	2.203	55.370	1265.882	1183.984
Insect	Male	Skin	II	0.667	9.870	710.396	241.913
		gastrointestinal symptoms					
Insect	Male	Skin, cardiovascular symptoms	II	1.453	39.200	618.005	208.658
Insect	Male	Skin	I	1.609	5.290	186.218	1148.530
Insect	Male	Skin, cardiovascular symptoms	III	1.492	32.270	1143.555	1794.455
Food	Female	Skin, cardiovascular symptoms	III	4.530	0.00	1612.247	281.029
Food	Female	Cardiovascular symptoms, gastrointestinal symptoms	III	4.218	2.82	3789.607	91.712
Food	Female	Skin, cardiovascular symptoms	III	1.887	20.50	1127.916	490.787
Drugs	Female	Skin, cardiovascular symptoms	II	0.650	2.77	1057.900	275.765
Drugs	Female	Skin, respiratory symptoms	II	2.880	1.75	329.087	490.848
Drugs	Female	Skin	I	0.909	5.66	2479.089	99.369
Idiopathic	Female	Skin, cardiovascular symptoms	II	2.880	1.75	2193.698	1233.296
Idiopathic	Male	Skin, respiratory symptoms	III	1.452	3.00	1092.026	77.193
Idiopathic	Female	Skin, respiratory symptoms	III	3.204	3.16	3571.286	803.100
Idiopathic	Female	Skin, cardiovascular symptoms	II	1.272	10.76	2148.403	49.673

The study compared 3 groups of patients. [Table E1](#) shows the postanaphylaxis cohort, which comprised 18 patients admitted to the emergency department in the years 2010-2011 shortly (maximum 2 hours) after an anaphylactic reaction. [Table E2](#) shows the control group, which consisted of 27 patients outside of an acute reaction but who had at least 1 anaphylactic episode in the past. The clinical manifestations and severity grades for the latter group refer to that previous anaphylactic episode. The culprit elicitor (if known), sex, manifestation profile, and anaphylaxis grades according to Ring and Messmer⁵ and the amount of assessed mediators in sera are given for each patient. [Table E3](#) shows the other diseases cohort, which included 12 patients with acute cardiovascular symptoms (n = 6) or fever of unknown origin (n = 6).

TABLE E2. Definition of the anaphylaxis-prone group and their clinical reaction patterns

Elicitor	Sex	Clinical manifestation	Anaphylaxis severity	Mediator			
				Histamine (ng/mL)	Tryptase (μg/L)	Cys-LTs (pg/mL)	9α,11β-PGF ₂ (pg/mL)
Insect	Female	Skin, cardiovascular symptoms	II	1.897	5.010	1387.000	40.394
Insect	Female	Skin, cardiovascular symptoms	II	0.895	3.360	1306.867	79.571
Insect	Female	Skin, gastrointestinal symptoms	III	0.777	3.860	821.093	24.624
Insect	Male	Skin, cardiovascular symptoms respiratory symptoms	III	1.060	3.990	728.859	67.592
Insect	Male	Skin, cardiovascular symptoms	II	1.014	3.730	1184.310	ND
Insect	Male	Skin, cardiovascular symptoms	II	0.496	1.200	711.431	44.853
Insect	Male	Skin, cardiovascular symptoms, respiratory symptoms	III	0.868	3.960	1172.289	81.66
Insect	Male	Skin, cardiovascular symptoms	II	0.780	3.250	879.616	139.434
Insect	Female	Skin, respiratory symptoms	II	0.804	3.480	760.769	5.264
Insect	Female	Skin, respiratory symptoms	II	1.949	4.100	1146.250	133.701
Insect	Male	Cardiovascular symptoms, respiratory symptoms	II	2.325	11.600	712.862	45.300
Insect	Male	Cardiovascular symptoms, respiratory symptoms	II	1.338	8.000	1061.175	26.906
Insect	Female	Skin, cardiovascular symptoms	II	1.626	12.900	688.621	9.902
Insect	Male	Gastrointestinal symptoms, cardiovascular symptoms, respiratory symptoms	III	2.749	9.600	1007.161	127.322
Insect	Male	Skin, respiratory symptoms	II	2.487	4.500	848.779	61.276
Insect	Male	Skin, cardiovascular symptoms, respiratory symptoms	III	1.248	1.900	651.540	172.058
Insect	Female	Skin, respiratory symptoms	II	0.822	5.800	1312.411	36.916
Insect	Female	Skin, respiratory symptoms, gastrointestinal symptoms	III	0.955	ND	455.874	30.957
Insect	Female	Respiratory symptoms, cardiovascular symptoms	III	3.517	2.740	695.991	119.145
Insect	Male	Skin, cardiovascular symptoms	III	0.500	4.310	175.298	102.802
Food	Female	Cardiovascular symptoms, gastrointestinal symptoms	III	7.230	3.780	155.447	123.520
Food	Female	Skin, cardiovascular symptoms	III	2.390	6.890	1217.910	39.542
Drugs	Female	Skin, respiratory symptoms	II	5.040	6.770	911.958	107.594
Idiopathic	Female	Skin, cardiovascular symptoms	II	1.130	8.560	ND	44.454
Idiopathic	Male	Skin, respiratory symptoms	III	1.050	3.560	203.970	41.125
Idiopathic	Female	Skin, respiratory symptoms	III	0.900	3.450	632.255	120.838
Idiopathic	Female	Skin, cardiovascular symptoms	II	1.44	7.680	756.509	131.791

The study compared 3 groups of patients. [Table E1](#) shows the postanaphylaxis cohort, which comprised 18 patients admitted to the emergency department in the years 2010-2011 shortly (maximum 2 hours) after an anaphylactic reaction. [Table E2](#) shows the control group, which consisted of 27 patients outside of an acute reaction but who had at least 1 anaphylactic episode in the past. The clinical manifestations and severity grades for the latter group refer to that previous anaphylactic episode. The culprit elicitor (if known), sex, manifestation profile, and anaphylaxis grades according to Ring and Messmer⁵ and the amount of assessed mediators in sera are given for each patient. [Table E3](#) shows the other diseases cohort, which included 12 patients with acute cardiovascular symptoms (n = 6) or fever of unknown origin (n = 6).

ND, Not detectable.

TABLE E3. Definition of the other diseases group and their clinical reaction patterns

Elicitor	Sex	Clinical manifestation	Mediator			
			Histamine (ng/mL)	Tryptase (μ g/L)	Cys-LTs (pg/mL)	9 α ,11 β -PGF ₂ (pg/mL)
Unknown	Female	Acute cardiovascular symptoms	0.722	3.91	386.557	24.796
Unknown	Male	Acute cardiovascular symptoms	0.162	4.01	584.497	ND
Unknown	Female	Acute cardiovascular symptoms	1.465	2.22	609.904	21.658
Unknown	Male	Acute cardiovascular symptoms	2.906	2.77	682.282	13.673
Unknown	Male	Acute cardiovascular symptoms	0.771	6.01	333.551	14.711
Unknown	Male	Acute cardiovascular symptoms	0.871	5.1	516.491	8.79
Unknown	Female	Fever	1.02	1.76	ND	15.645
Unknown	Male	Fever	0.463	3.57	909.616	15.725
Unknown	Female	Fever	1.158	3.63	791.213	36.172
Unknown	Male	Fever	0.603	1.87	702.595	ND
Unknown	Female	Fever	0.946	1.19	ND	5.545
Unknown	Male	Fever	0.81	1.88	651.415	36.353

The study compared 3 groups of patients. [Table E1](#) shows the postanaphylaxis cohort, which comprised 18 patients admitted to the emergency department in the years 2010-2011 shortly (maximum 2 hours) after an anaphylactic reaction. [Table E2](#) shows the control group, which consisted of 27 patients outside of an acute reaction but who had at least 1 anaphylactic episode in the past. The clinical manifestations and severity grades for the latter group refer to that previous anaphylactic episode. The culprit elicitor (if known), sex, manifestation profile, and anaphylaxis grades according to Ring and Messmer⁵ and the amount of assessed mediators in sera are given for each patient. [Table E3](#) shows the other diseases cohort, which included 12 patients with acute cardiovascular symptoms (n = 6) or fever of unknown origin (n = 6).

ND, Not detectable.

TABLE E4. Predictive power of mediators to serve as biomarkers for anaphylaxis

Mediator	No.	AUC	SE	Lower 95% CI	Upper 95% CI
Tryptase	44	0.5598	0.1020	0.3599	0.7597
Histamine	46	0.6310	0.0859	0.4626	0.7993
Cys-LTs	45	0.7860	0.0758	0.6374	0.9346
9 α ,11 β -PGF ₂	45	0.9053	0.0479	0.8114	0.9993
9 α ,11 β -PGF ₂ /cys-LTs	44	0.9829	0.0178	0.9479	1.0000
9 α ,11 β -PGF ₂ /cys-LTs/tryptase	42	0.9815	0.0193	0.9436	1.0000
9 α ,11 β -PGF ₂ /cys-LTs/histamine	44	0.9829	0.0178	0.9479	1.0000
9 α ,11 β -PGF ₂ /cys-LTs/histamine/ tryptase	42	0.9815	0.0193	0.9436	1.0000

AUCs for combinations of mediators were calculated from ROC curves derived by using logistic regression analysis. An AUC equal to 1.0 indicates that the diagnostic test discriminates perfectly between anaphylactic and nonanaphylactic responses.

TABLE E5. Comparison between baseline and acute serum levels within the same patients

Patients (n = 9)	Histamine	Tryptase	Cys-LTs	9 α ,11 β -PGF ₂	Elicitor	Anaphylaxis severity
1. Baseline	3.52	2.74	659.91	119.15	Insect	III
1. Acute	0.65	2.77	1057.9	275.77		
1. Change (%)	-441.5	+1.1	+60.3	+131.4		
2. Baseline	0.5	4.31	175.29	102.80	Insect	III
2. Acute	1.89	20.5	1127.92	490.79		
2. Change (%)	+278	+375.6	+543.5	+377.4		
3. Baseline	7.23	3.78	155.45	123.52	Food	III
3. Acute	8.46	16.59	2991.31	1487.83		
3. Change (%)	+7.23	+338.9	+1824.3	+1104.5		
4. Baseline	2.39	6.89	1217.91	39.54	Food	III
4. Acute	1.13	10.43	1198.55	455.37		
4. Change (%)	-111.5	+51.4	-1.6	+1051.6		
5. Baseline	5.04	6.77	911.96	107.59	Drug	II
5. Acute	0.67	9.87	710.39	241.91		
5. Change (%)	-652.2	+45.8	-28.4	+124.8		
6. Baseline	1.13	8.56	ND	44.45	Idiopathic	II
6. Acute	1.45	39.2	618.01	208.66		
6. Change (%)	+28.3	+358		+369.4		
7. Baseline	1.05	3.56	203.97	41.13	Idiopathic	III
7. Acute	1.61	5.29	1863.22	1148.53		
7. Change (%)	+53.3	+48.6	+813.5	+2692.4		
8. Baseline	0.9	3.45	632.26	120.84	Idiopathic	III
8. Acute	1.27	10.76	2148.41	49.67		
8. Change (%)	+41.1	+211.9	+239.8	-143.3		
9. Baseline	1.44	7.68	756.51	131.79	Idiopathic	II
9. Acute	1.49	32.27	1143.56	1794.46		
9. Change (%)	+3.5	+320.2	+51.2	+1261.6		

Levels of histamine, tryptase, cys-LTs, and 9 α ,11 β -PGF₂ were detected in basal and acute sera (maximum 2 of hours after an anaphylactic reaction) in the same patient. The amounts detected are followed by a row showing the percentage change versus baseline. The culprit elicitor (if known) and anaphylaxis severity grades based on Ring and Messmer⁵ are provided for each patient. The percentage increase in each mediator in acute versus baseline levels is indicated in boldface. ND, Not detectable.