

Improvement of the Elevated Tryptase Criterion to Discriminate IgE- From Non-IgE-Mediated Allergic Reactions

Gabriel Gastaminza, MD, PhD,* Alberto Lafuente, MD, PhD,† Maria Jose Goikoetxea, MD, PhD,* Carmen M. D'Amelio, MD, PhD,* Amalia Bernad-Alonso, MD,* Olga Vega, MD,* Juan Ambrosio Martinez-Molina, MD,† Marta Ferrer, MD, PhD,* and Jorge M. Nuñez-Cordoba, MD, PhD‡

BACKGROUND: Differentiating between immunoglobulin E (IgE)-dependent and IgE-independent hypersensitivity reactions may improve the etiologic orientation and clinical management of patients with allergic reactions in the anesthesia setting. Serum tryptase levels may be useful to discriminate the immune mechanism of allergic reactions, but the diagnostic accuracy and optimal cutpoint remain unclear.

We aimed to compare the diagnostic accuracy of tryptase during reaction (TDR) alone and the TDR/basal tryptase (TDR/BT) ratio for discriminating IgE- from non-IgE-mediated allergic reactions, and to estimate the best cut point for these indicators.

METHODS: We included 111 patients (45% men; aged 3–99 years) who had experienced an allergic reaction, even though the allergic reaction could be nonanaphylactic. Allergy tests were performed to classify the reaction as an IgE- or non-IgE-mediated one. The area under the curve (AUC) of the receiver operating characteristic analysis was performed to estimate the discriminative ability of TDR and TDR/BT ratio.

RESULTS: An IgE-mediated reaction was diagnosed in 49.5% of patients, of whom 56% met anaphylaxis criteria. The median (quartiles) TDR for the IgE-mediated reactions was 8.0 (4.9–19.6) and 5.1 (3.5–8.1) for the non-IgE-mediated ($P = .022$). The median (quartiles) TDR/BT ratio was 2.7 (1.7–4.5) in IgE-mediated and 1.1 (1.0–1.6) in non-IgE-mediated reactions ($P < .001$). The TDR/BT ratio showed the greatest ability to discriminate IgE- from non-IgE-mediated reactions compared to TDR (AUC TDR/BT = 0.79 [95% confidence interval (CI), 1.1–2.2] and AUC TDR = 0.66 [95% CI, 1.1–2.2]; $P = .003$). The optimal cut point for TDR/BT (maximization of the sum of the sensitivity and specificity) was 1.66 (95% CI, 1.1–2.2).

CONCLUSIONS: The TDR/BT ratio showed a significantly better discriminative ability than TDR to discriminate IgE- from non-IgE-mediated allergic reactions. An optimal TDR/BT ratio threshold of approximately 1.66 may be useful in clinical practice to classify allergic reactions as IgE- or non-IgE-mediated. (Anesth Analg 2017;XXX:00–00)

KEY POINTS

- **Question:** The ability of tryptase during reaction (TDR) to discriminate between immunoglobulin E (IgE)- and non-IgE-mediated reactions could improve using also basal tryptase (BT).
- **Findings:** The TDR/BT ratio showed the greatest ability discriminating IgE- and non-IgE-mediated reactions.
- **Meaning:** The optimal cut point for TDR/BT was 1.66.

The diagnosis of severe or life-threatening allergic reactions continues to be quite challenging, especially under certain circumstances where many different drugs administrations and other clinical procedures are performed in rapid succession, such as in anesthesia settings. In these contexts, knowing the immune mechanism

(immunoglobulin E [IgE] dependent or IgE independent) of the hypersensitivity reaction may orient the clinician to the wide variety of potential etiologies that can cause the allergic reaction and, consequently, improve the clinical management of patients.

IgE receptors are present on the mast cell membranes, and when IgE-coated antigens bind to these surface receptors, mast cell degranulation occurs. Tryptase, a 134-kDa serine esterase present in mast cells granules, is released during anaphylactic reactions.¹ Tryptase levels in basophils correspond to <1% of those found in tissue mast cells.² For this reason, increases in tryptase concentrations are considered to be indicative of mast cell degranulation.³ Tryptase is released from mast cells in a protease–proteoglycan complex, which diffuses slowly, peaking 15–120 minutes after its release, with a half-life time of approximately 2 hours.⁴ This time interval makes it easy to obtain a serum sample to test tryptase levels once the acute reaction has been treated and the patient is fully recovered.

From the Departments of *Allergology and Clinical Immunology, †Anaesthesia, and ‡Research Support Service, Central Clinical Trials Unit, Clínica Universidad de Navarra, Pamplona, Spain.

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Address correspondence to Gabriel Gastaminza, MD, PhD, Departamento de Alergología e Inmunología Clínica, Clínica Universidad de Navarra, 31008 Pamplona, Spain. Address e-mail to Gastaminza@unav.es.

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Despite the promising characteristics of tryptase levels to guide clinicians in the diagnosis of allergic reactions, there is still no clear consensus on the cut point that should be used to consider tryptase levels as elevated.

In many studies, a fixed cut point in the tryptase levels during the reactions (TDR) is used, disregarding the patient's basal tryptase (BT) values.^{5,6} Some authors have pointed out the importance of considering the BT values, but different criteria to do it have been suggested.⁶⁻⁹ In a previous study performed in patients who suffered an allergic reaction in an anesthesia setting, our group found that the cut point that best discriminated between IgE- and non-IgE-mediated hypersensitivity reactions was a ratio between the TDR and the BT of ≥ 2 .⁹

The hypothesis of this study is that, since the main mechanism of mast cell activation (and of tryptase release) is IgE dependent, considering the patient's BT values improves the usefulness of the TDR values to diagnose an IgE-dependent mechanism. In particular, our hypothesis is that the TDR/BT ratio is better than any cut point possibly used in the TDR to diagnose an IgE-mediated reaction.

We primarily aimed to evaluate the diagnostic accuracy for discriminating IgE- from non-IgE-mediated reactions of TDR/BT ratio, in comparison with considering only TDR, and with TDR – BT (Δ). The second objective was to estimate the best cut point for TDR/BT and compare its discriminative ability with a cut point defined in literature as TDR $\geq 20\%$ plus 2 $\mu\text{g/L}$ over the BT.⁸

METHODS

The study was approved by the Local Ethics Research Committee. Not all the patients signed the informed consent, but since this is a retrospective study, this requirement was waived by the institutional review board.

Subjects

The study was performed retrospectively in a single center from Spain (Clínica Universidad de Navarra). All participants suffered an immediate allergic reaction (skin or mucosal involvement, respiratory symptoms, gastrointestinal, neurological, or cardiac symptoms) of rapid onset after being exposed to a trigger, which occurred perioperatively, during hospitalization or was treated in the emergency room from 2009 to 2015.

We reviewed the medical records of patients who had undergone a determination of serum tryptase in real life in our hospital. Of the 248 medical records reviewed, 137 were excluded due to the following reasons: 53 patients had tryptase level determinations for a reason different than an immediate allergic reaction; 40 patients did not have a baseline tryptase value despite the fact that the patients underwent an allergy study; 28 patients did not complete the allergy study; and 16 patients did not have a tryptase determination during the reaction or this determination was obtained >2 hours after the start of the reaction. After these exclusions, 111 patients remained available for the analysis.

All patients had also been studied for BT and had undergone allergy tests to determine the cause of their reaction 4–8 weeks after its onset. TDR was determined by different physicians according to their clinical suspicion of an immediate allergic reaction, following a protocol that was started

some years ago by agreement between different departments of our hospital. Reactions were clinically classified as anaphylaxis or nonanaphylaxis, following the criteria established by the World Allergy Organization Guidelines for the assessment and management of anaphylaxis.¹⁰

Two different authors (G.G., O.V.) revised all clinical records and classified the reactions as anaphylactic or not, and as IgE-mediated or not, whereas they were blinded to results of tryptase levels.

Measurement of Serum Tryptase Levels

Serum tryptase levels were determined using a tryptase fluoroenzyme immunoassay performed in accordance with the manufacturer's instructions (ImmunoCAP, Thermo Fisher, Uppsala, Sweden).⁶

TDR was measured when the patient received medical assistance. In some patients, another sample for TDR was obtained 2 hours after the onset of the reaction. In the case of patients with 2 determinations for TDR, the TDR considered for this study was that corresponding to the highest tryptase level registered for both samples, having in mind that the highest increase of serum tryptase is usually observed within 30–120 minutes from the onset of symptoms.^{4,11,12}

BT was measured at least 24 hours after the total recovery of the reaction⁸ or observed in a blood sample obtained during the previous month to its onset (usually in patients with a perioperative reaction).

Allergy Testing

Allergy tests were performed 4–8 weeks after the onset of the reaction. Skin prick tests, intradermal tests, blood-specific IgE determinations, and drug or food challenge tests were used to establish the diagnosis of an IgE- or non-IgE-mediated reaction, as well as to determine the cause of the reaction.

When the reaction occurred in an anesthesia setting, all drugs and products used before the onset of the reaction (including latex, chlorhexidine, iodine povidone) were tested. In the case of other locations, allergy studies were performed for all foods, drugs, or other possible causes suspected to have triggered the reaction in each patient.

An IgE-mediated reaction was defined as a positive result in the skin tests (ST), prick or intradermal, to the allergen suspected to have caused the reaction. We considered a reaction to be non-IgE-mediated (ie, we could not demonstrate an IgE-mediated mechanism in the reaction) when all STs were negative. When serum-specific IgE resulted positive and STs negative, we performed a challenge test to establish whether the reaction was due to this cause (eg, penicillin or a food).

Statistical Analysis

Initially, data were screened for missing data and outliers. All missing data were collected from the patients' medical records. Appropriate descriptive statistics were computed for all variables based on the level of measurement and the empirical data distribution. The area under the curve (AUC) of a nonparametric receiver operating characteristic (ROC) analysis was calculated using the trapezoidal rule to determine the global discriminative ability of each index test. The AUC can be interpreted as the probability that the result of the

index test value of a randomly selected IgE-mediated reaction will be greater than the result of the same index test value from a randomly selected non-IgE-mediated reaction. The AUC ranged from 0.5 (no discriminative ability) to 1 (perfect discriminative ability). The comparison between both AUCs was performed using the nonparametric approach described by DeLong et al.¹³ Overall, accuracy was defined as the probability of the allergic reaction having been correctly classified using a specific cut point for the predictor. Sensitivity (probability of patients with an IgE-mediated allergic reaction testing positive), specificity (probability of patients without an IgE-mediated allergic reaction testing negative), positive predictive value (probability of patients with a positive test truly having an IgE-mediated allergic reaction), and negative predictive value (probability of patients with a negative test truly not having an IgE-mediated allergic reaction) were also calculated. The Youden index was used to estimate the empirical cut point for maximized discriminative ability. This approach estimates the threshold value for which sensitivity + specificity – 1 is maximized.¹⁴ The bootstrapped 95% confidence interval (95% CI) for the cut point was based on 200 replications. A type I error rate of 0.05 was assumed. All analyses were performed using Stata 14 (StataCorp, College Station, TX). The minimum required sample size was determined based on the comparison between AUC of TDR/BT ratio and AUC of only TDR, which was the principal aim of this study. Assuming a 2-sided α level of .05, a rank correlation between the 2 index tests of 0.8 in both IgE- and non-IgE-mediated reactions cases, 94 patients (47 cases in both IgE- and non-IgE-mediated reactions groups) were necessary to detect a difference of 10 percentage points between index tests with a power of 80% (hypothesized AUC of TDR/BT ratio and only TDR: 0.8 and 0.7, respectively).

RESULTS

A total of 111 patients were included in the study. Forty-seven patients (42%) suffered from the hypersensitivity reaction in an anesthesia setting, 30 patients (27%) went to the emergency department to be treated for the allergic reaction, 15 patients suffered the reaction during their hospitalization (14%), and 19 patients (17%) experienced it in other areas of the hospital (radiology, endoscopy, external consultations, etc). The triggers of these reactions were drugs in 61 patients (55%), foods in 21 (19%), iodinated contrast media

in 10 (9%), other causes (hymenoptera venom allergy, natural rubber latex, or physical urticaria) in 9 patients (8%), and unknown in 10 patients (9%).

The demographic and clinical characteristics of the 111 participants (45.1% men; aged 3–99 years) with allergic reactions are shown in Table 1. As expected, patients with IgE-mediated allergic reactions (49.5%) were more likely to experience anaphylaxis and showed a higher mean level of TDR and a greater mean TDR/BT ratio. The remaining characteristics were relatively balanced between both groups. Both the IgE- and non-IgE-mediated allergic reaction groups reported drugs as the most frequent known cause of their allergic reaction (55% and 39%, respectively), and the perioperative setting presented the highest frequency in terms of location for both groups (49% and 36% for IgE- and non-IgE-mediated allergic reactions, respectively).

The symptoms suffered by the patients affected the skin (82%), respiratory system (28%), cardiovascular system (26%), digestive system (23%), upper airways (14%), and neurologic system (11%), whereas other symptoms appeared in 11% of the patients. Sixty-two patients (56%) suffered an anaphylactic reaction. The median TDR was 9.1 $\mu\text{g/L}$ for patients experiencing anaphylaxis and 4.9 $\mu\text{g/L}$ for patients not experiencing anaphylaxis ($P < .001$).

The median (quartiles) TDR value was 8 $\mu\text{g/L}$ (4.9, 19.6) for the IgE-mediated reactions and 5.1 $\mu\text{g/L}$ (3.5, 8.1) for the non-IgE-mediated reactions ($P = .022$). The median (quartiles) TDR/BT ratio was 2.7 (1.7, 4.5) in IgE-mediated reactions and 1.1 (1, 1.6) in non-IgE-mediated reactions ($P < .001$). The ROC curves for TDR and TDR/BT ratio are shown in Figure A. The TDR/BT ratio showed a statistically significant higher ability to discriminate IgE- from non-IgE-mediated allergic reactions compared with TDR alone (AUC [95% CI]: 0.79 [0.70–0.88], and AUC [95% CI]: 0.66 [0.56–0.76], respectively; $P = .001$). The difference between AUC of TDR/BT ratio and AUC of TDR was 0.13 (95% CI, 0.05–0.20). The Figure B shows the ROC curves for TDR/BT ratio and for TDR – BT (Δ in the figure), the indicator described by Brown et al.⁷ The TDR/BT ratio showed a slightly greater ability to discriminate IgE- from non-IgE-mediated allergic reactions in comparison with TDR – BT (AUC [95% CI] for TDR – BT: 0.76 [0.67–0.85]). The difference between AUC of TDR/BT ratio and AUC of TDR – BT was 0.03 (95% CI, 0.003–0.06).

Table 1. Demographic and Clinical Characteristics of Patients With Allergic Reactions (n = 111)

	Allergic Reaction		P Value
	Non-IgE-Mediated	IgE-Mediated	
N	56	55	
Age, y	52.9 (17.5)	48.1 (21.2)	.197
Men, n (%)	29 (51.8)	21 (38.2)	.150
Location, n (%)			
Perioperative	20 (35.7)	27 (49.1)	.121
Emergency room	13 (23.2)	17 (30.9)	
Hospitalization	10 (17.9)	5 (9.1)	
Other hospital areas	13 (23.2)	6 (10.9)	
Anaphylaxis, n (%)	23 (41.1)	39 (70.9)	.002
Basal tryptase levels, $\mu\text{g/L}$	5.4 (3.8)	4.3 (3.1)	.108
Tryptase levels during the reaction, $\mu\text{g/L}$, median (percentile 25, percentile 75)	5.1 (3.5, 8.1)	8.0 (4.9, 19.6)	.022
Tryptase ratio (during reaction/basal), median (percentile 25, percentile 75)	1.1 (1, 1.6)	2.7 (1.7, 4.5)	<.001

Unless otherwise specified, all values are reported as mean (standard deviation).

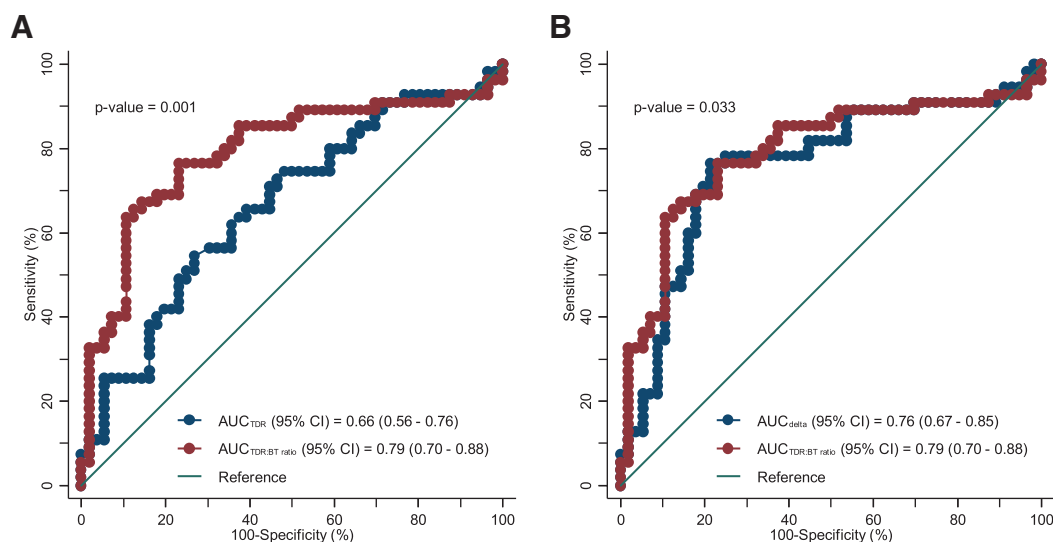


Figure. Receiver operating characteristic curves for discriminating immunoglobulin E (IgE)- from non-IgE-mediated allergic reactions. A, Tryptase during reaction (TDR) versus TDR/basal tryptase (BT) ratio. B, TDR/BT ratio versus TDR - BT (Δ). Difference between area under the curve (AUC) of the TDR/BT ratio and AUC of TDR (95% confidence interval [CI]): 0.13 (0.05–0.20). Difference between AUC of the TDR/BT ratio and AUC of Δ (95% CI): 0.03 (0.003–0.06).

The Youden index method was used to estimate an optimal TDR/BT ratio cut point value for IgE-mediated reactions. The optimal threshold for the TDR/BT ratio value for diagnosing IgE-mediated reactions was 1.66 (95% CI, 1.07–2.25). The sensitivity, specificity, and predictive values of the estimated optimal TDR/BT ratio cut point, several other TDR/BT ratio cut points, and a consensual cut point for mast cells activation (TDR $\geq 20\%$ + 2 $\mu\text{g/L}$ over the BT)⁸ are shown in Table 2. The sensitivity, specificity, and positive and negative predictive values associated with a TDR/BT ratio cut point of 1.66 were 76.4%, 76.8%, 76.4%, and 76.8%, respectively. The overall accuracy was slightly higher compared with the result of the cut point for mast cells activation.

When we restricted the evaluation of the discriminative ability of TDR/BT ratio and the estimation of its optimal threshold to patients with anaphylaxis, results did not differ substantially to those obtained with the whole sample of patients. The diagnostic accuracy did not vary substantially when the estimated optimal TDR/BT ratio cut point was applied to patients in the anesthesia group.

DISCUSSION

Tryptase is a serum protease present in mast cells. Thus, elevation of serum tryptase levels during an allergic reaction has been considered to be indicative of mast cell activation.³

In some patients, mainly during surgical procedures, it is difficult to diagnose an allergic reaction due to the fact that some symptoms could be related to another heart or respiratory condition (eg, intubation or cardiac ischemic disease). Serum tryptase and plasma histamine determinations are useful laboratory tests for the diagnosis of patients suffering these reactions.¹⁵

However, there is no consensus on which cut point should be used to consider tryptase levels as elevated.⁹ The Thermo Fisher Company recommends a cut point of 11.4 $\mu\text{g/L}$ for its technique due to the fact that it constituted the

95th percentile of its 129 control subjects. Other authors used cut points as different as 5 $\mu\text{g/L}$,¹⁶ 8.23 $\mu\text{g/L}$,⁵ 10.5 $\mu\text{g/L}$,⁶ 14 $\mu\text{g/L}$,¹⁷ and so on. In recent years, some studies have demonstrated that a significantly high number of patients diagnosed with systemic mastocytosis or mast cell activation had tryptase levels as low as 5 $\mu\text{g/L}$.^{18,19}

Moreover, BT levels have some variability within a normal population: 7% of normal subjects had BT levels >10 $\mu\text{g/L}$, and 4.3% of subjects had BT levels >11.4 $\mu\text{g/L}$.²⁰ In this study, the main factor associated with increased BT levels was patient age. An increase in BT levels can also be seen in the myelodysplastic syndrome, acute myeloid leukemia, and chronic kidney disease.²¹

More than 2 decades ago, Schwartz et al⁶ found that double basal levels of tryptase during the reaction correctly classified most individuals as allergic or nonallergic. Brown et al⁷ found that a deviation of 2.0 $\mu\text{g/L}$ between high and low values of tryptase was significantly more discriminatory than a single consensus on the cut point and had a sensitivity of 0.73 and a specificity of 0.98 to diagnose anaphylaxis.

More recently, a consensus of experts defined the minimal increase in serum tryptase to be accepted as evidence for systemic mast cell activation, establishing that the TDR should be $\geq 20\%$ + 2 $\mu\text{g/L}$ over baseline level.⁸

Despite the evidence showing the potential importance of accounting BT levels for the proper interpretation of TDR, some authors do not consider BT levels^{22,23} or simply recommend considering BT levels during an anaphylaxis diagnosis without explaining how this should be done.^{24,25}

Because the main mast cell activation mechanism is dependent on IgE antibodies, we tried to study whether an increase in TDR could be a marker, not only for mast cell activation but also to discriminate between IgE- and non-IgE-mediated allergic reactions. In a previous study including only patients who suffered allergic reactions after receiving anesthesia, an ROC analysis revealed a TDR/BT ratio of ≥ 2 as the best value⁹ to differentiate between IgE- and

Table 2. Sensitivity, Specificity, and Predictive Values of the TDR/BT Ratio Cut Points for the Prediction of IgE-Mediated Allergic Reactions

TDR/BT ratio	Sensitivity (n = 55)			Specificity (n = 56)			Positive Predictive Value			Negative Predictive Value			Overall Accuracy (n = 111)		
	% (TP/[TP + FN])	95% CI		% (TN/[TN + FP])	95% CI		% (TP/[TP + FP])	95% CI		% (TN/[TN + FN])	95% CI		%(TP+TN)/[TP + TN + FP + FN])	95% CI	
1.5	76.4 (42/55)	63.0–86.8		67.9 (38/56)	54.0–79.7		70.0 (42/60)	56.8–81.2		74.5 (38/51)	60.4–85.7		72.1 (80/111)	62.8–80.2	
1.66 ^a	76.4 (42/55)	63.0–86.8		76.8 (43/56)	63.6–87.0		76.4 (42/55)	63.0–86.8		76.8 (43/56)	63.6–87.0		76.6 (85/111)	67.6–84.1	
2	65.5 (36/55)	51.4–77.8		85.7 (48/56)	73.8–93.6		81.8 (36/44)	67.3–91.8		71.6 (48/67)	59.3–82.0		75.7 (84/111)	66.6–83.3	
2.5	52.7 (29/55)	38.8–66.3		89.3 (50/56)	78.1–96.0		82.9 (29/35)	66.4–93.4		65.8 (50/76)	54.0–76.3		71.2 (79/111)	61.8–79.4	
3	47.3 (26/55)	33.7–61.2		89.3 (50/56)	78.1–96.0		81.3 (26/32)	63.6–92.8		63.3 (50/79)	51.7–73.9		68.5 (76/111)	59.0–77.0	
TDR ≥20% + 2 µg/L over the BT ^{ts}	69.1 (38/55)	55.2–80.9		80.4 (45/56)	67.6–89.8		77.6 (38/49)	63.4–88.2		72.6 (45/62)	59.8–83.1		74.8 (83/111)	65.6–82.5	

Abbreviations: 95% CI, 95% confidence interval; BT, basal tryptase; FN, false negatives; FP, false positives; IgE, immunoglobulin E; TDR, tryptase during reaction; TN, true negatives; TP, true positives.
^aEstimated optimal cut point (value for which sensitivity + specificity – 1 is maximized¹⁴).

non-IgE-mediated reactions. The present study included a greater number of patients who had suffered an allergic reaction in different settings of the hospital, including the emergency department, not only after receiving anesthesia. The TDR/BT ratio showed a better discrimination capacity than TDR alone and slightly superior than the indicator described by Brown et al⁷ (TDR – BT). In a real-life environment to discriminate IgE- from non-IgE-mediated allergic reactions, the overall accuracy of the estimated optimal cut point of TDR/BT ratio (1.66) was slightly better than that obtained applying the cut point described by Valent et al.⁸ It is important that our results be confirmed in patient series performed by other groups. However, we believe that anaphylaxis and anesthesia allergic reaction guides must recommend the use of the TDR/BT ratio, not only of acute tryptase levels.

In our study, we included patients with anaphylaxis but also patients who suffered a milder allergic reaction but did not fulfill clinical anaphylaxis criteria. Because the level of TDR is dependent on the severity of the reaction,^{12,26} in most mild reactions, TDR levels will not reach the most used cut point described above. However, the TDR/BT ratio and other cut points that compare TDR with BT will also be useful to discriminate the IgE-mediated reactions in these patients not suffering anaphylaxis.

A limitation of our study could be that peak TDR was considered in different patients at different times. However, this coincides with the fact that in different patients, peak tryptase is observed at different times.⁶ Moreover, this is a real-life study; during an allergic reaction, it is difficult to obtain samples at the same time in all patients. Another limitation of our study is that, using our criteria to considering an allergic reaction as IgE-mediated, it could be some patients in which the IgE mechanism was not found due to the low sensitivity of STs with some allergens. However, our patients were studied in the correct time interval after the reaction to obtain the best results in allergic study.²⁷ Potential limitations associated with the retrospective study design, population characteristics (eg, genetic predispositions or age of the patients), sample size, or skewness of the indexes tested compel us to be cautious in terms of generalization of results and highlight the need for further studies in other specific and larger populations. The present study may be a useful starting point given the current and relative limited information on this topic.

In conclusion, this study provides new insight on the diagnostic role of tryptase levels in an allergic reaction that may improve the clinical criteria to differentiate between IgE- and non-IgE-mediated reactions. In this clinical observational study, the TDR/BT ratio showed a greater capacity than TDR alone to discriminate between IgE- and non-IgE-mediated reactions, not only in anaphylactic reactions but also in mild immediate allergic reactions. The estimated optimal cut point for the TDR/BT ratio to discriminate between IgE- and non-IgE-mediated reactions was 1.66. External validation studies assessing the performance of this indicator in independent samples from different health care settings and with diverse patient cases are warranted. ■■

DISCLOSURES

Name: Gabriel Gastaminza, MD, PhD.

Contribution: This author helped in study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript, obtaining funding, and study supervision.

Name: Alberto Lafuente, MD, PhD.

Contribution: This author helped in acquisition of the data, drafting of the manuscript, and obtaining funding.

Name: Maria Jose Goikoetxea, MD, PhD.

Contribution: This author helped in acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and administrative, technical, and material support.

Name: Carmen M. D'Amelio, MD, PhD.

Contribution: This author helped in acquisition of the data, drafting of the manuscript, and administrative, technical, and material support.

Name: Amalia Bernad-Alonso, MD.

Contribution: This author helped in acquisition of the data and drafting of the manuscript.

Name: Olga Vega, MD.

Contribution: This author helped in acquisition of the data, analysis and interpretation of the data, and drafting of the manuscript.

Name: Juan Ambrosio Martinez-Molina, MD.

Contribution: This author helped in acquisition of the data and drafting of the manuscript.

Name: Marta Ferrer, MD, PhD.

Contribution: This author helped in acquisition of the data, drafting of the manuscript, and critical revision of the manuscript.

Name: Jorge M. Nuñez-Cordoba, MD, PhD.

Contribution: This author helped in study concept and design, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript, and statistical expertise.

This manuscript was handled by: Richard C. Prielipp, MD.

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