

Original Article

Risk Factor Analysis of Anaphylactic Reactions in Patients With Systemic Mastocytosis

Theo Gülen, MD, PhD^{a,b,c}, Christopher Ljung, BSc^{a,b}, Gunnar Nilsson, PhD^{b,c,d}, and Cem Akin, MD, PhD^e *Stockholm, Sweden; and Boston, Mass*

What is already known about this subject? Anaphylaxis is a common feature in patients with mastocytosis; however, not all patients with mastocytosis experience anaphylaxis. Presently, there are no predictive markers to discriminate patients with mastocytosis at high risk of anaphylaxis from those at low risk.

What does this article add to our knowledge? This is the first study to demonstrate that patients with mastocytosis with anaphylaxis display unique clinical and biological features. A risk analysis model for anaphylaxis was developed and translated into a clinical scoring system.

How does this study impact current management guidelines? The risk assessment tool described here may provide a simple method of identifying and alerting patients with mastocytosis at high risk of anaphylaxis who would benefit from self-injectable epinephrine.

BACKGROUND: Systemic mastocytosis (SM) is a rare disorder of abnormal mast cells in at least 1 extracutaneous organ/tissue. Anaphylaxis is an acute, severe systemic hypersensitivity reaction, and a strong association between SM and anaphylaxis has been shown. However, not all patients with SM experience anaphylaxis. Presently, there are no predictive markers to

discriminate patients with SM at high risk of anaphylaxis from those at low risk.

OBJECTIVE: This study sought to determine risk factors for the occurrence of anaphylaxis in patients with SM.

METHODS: A cross-sectional study was conducted in 122 consecutive adult patients with SM admitted to the Mastocytosis Center at Karolinska University Hospital. All patients underwent medical evaluation, including bone marrow biopsy and a thorough allergy workup. To determine risk factors, study subjects were categorized into 2 groups according to the presence ($n = 55$) or absence ($n = 67$) of anaphylaxis and compared for their demographic, clinical, and biochemical characteristics.

RESULTS: Patients with SM with anaphylaxis had less frequent presence of mastocytosis in the skin ($P < .001$), more atopic predisposition ($P = .021$), higher total IgE levels ($P < .001$), and lower baseline tryptase levels (27 ng/mL vs 42 ng/mL; $P = .024$) compared with patients with SM without anaphylaxis.

CONCLUSIONS: Patients with SM with anaphylaxis display unique clinical and laboratory features. Hence, a risk analysis tool that is capable of discriminating patients with SM at high risk of anaphylaxis from those at low risk with 86% sensitivity was developed by using the variables male sex, absence of mastocytosis in the skin, presence of atopy, IgE levels of 15 kU/L or more, and baseline tryptase levels of less than 40 ng/mL. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Mastocytosis; Anaphylaxis; Risk factors; Tryptase; IgE; Atopy; Venom; Risk assessment tool

^aDepartment of Respiratory Medicine and Allergy, Karolinska University Hospital Huddinge, Stockholm, Sweden

^bDepartment of Medicine Solna, Immunology and Allergy unit, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden

^cMastocytosis Centre Karolinska, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden

^dDepartment of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital Solna, Stockholm, Sweden

^eMastocytosis Centre at Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

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Corresponding author: Theo Gülen, MD, PhD, Department of Respiratory Medicine and Allergy, C177, Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden. E-mail: Theo.Gulen@karolinska.se.

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Anaphylaxis is a sudden, severe systemic hypersensitivity reaction resulting from excessive release of mast cell (MC) mediators. Patients can present with a broad array of symptoms and signs, often including skin manifestation, and death may occur because of airway obstruction or cardiovascular collapse.¹

Abbreviations used

ISM- Indolent systemic mastocytosis
MC- Mast cell
MIS- Mastocytosis in the skin
sBT- Serum baseline tryptase
SM- Systemic mastocytosis
VIA- Venom-induced anaphylaxis

Mastocytosis is a heterogeneous disorder characterized by accumulation and activation of clonal MCs in the skin and/or internal organs.^{2,3} In cutaneous mastocytosis, MC accumulation is by definition limited to the skin, whereas in systemic mastocytosis (SM), at least 1 extracutaneous organ/tissue, most often the bone marrow, is involved.³ According to the World Health Organization criteria, patients with SM can be further classified into 4 major subvariants: indolent systemic mastocytosis (ISM), SM with associated clonal hematological non-MC-lineage disease, aggressive SM, and MC leukemia.^{4,5} In adults, the vast majority of patients have ISM.⁶ The clinical manifestations of ISM are protean and range from relatively asymptomatic to frequent episodes of MC mediator symptoms and even life-threatening anaphylaxis.³

The existing evidence indicates a strong association between anaphylaxis and mastocytosis.⁶⁻⁹ The prevalence has been reported to be 20% to 56% in adult patients with various forms of mastocytosis, which represents a 100- to 1000-fold increased risk compared with the general population.¹⁰ The most common elicitors of anaphylaxis in ISM appear to be wasp sting (hymenoptera venom), 53%, followed by reactions without clear trigger, that is, idiopathic, 39%.⁶ Although rare, drugs and food can also be elicitors in patients with SM.^{11,12} The clinical course of anaphylactic reactions in patients with SM is often severe and presents with cardiovascular features including hypotensive syncope.^{6,8,9,13}

Although anaphylaxis is a common feature in patients with SM, some patients with SM never experience anaphylactic episodes and consequently would not need self-injectable adrenaline. While the risk of having underlying clonal MC disease, that is, mastocytosis, in patients presenting with anaphylaxis has been studied, there are presently no predictive markers to discriminate patients with SM at high risk of anaphylaxis from those at low risk. This, in turn, creates a challenge for the clinician to make an adequate risk assessment for the patient who has already been diagnosed with SM. Previous observational studies on patients with anaphylaxis and SM suggest that anaphylaxis occurs more often in patients with SM lacking cutaneous engagement^{6,9} and in those with atopic predisposition.^{6,8} A male predominance has also been observed in patients with SM with anaphylaxis.⁸ In contrast, the levels of baseline tryptase have been controversial to assess the risk of anaphylaxis in these patients, and both higher⁹ and lower⁶ tryptase levels have been reported in patients with SM with anaphylaxis compared with those without anaphylaxis.

A risk predicting model that can be used to foresee the occurrence of anaphylaxis in anaphylaxis-naïve patients with SM would therefore be of immense clinical importance. This study sought to validate previously suggested risk factors and to explore new potential ones to predict anaphylaxis in patients with SM. The ultimate aim was to generate a risk predictive model.

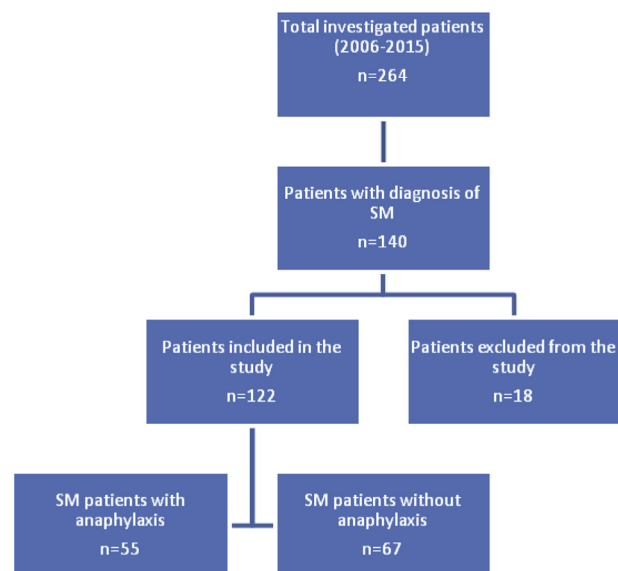


FIGURE 1. Flowchart showing study population and the process of selecting study subjects. Ultimately, study subjects were divided into 2 groups according to presence/absence of anaphylaxis.

METHODS

Study subjects and procedures

The Mastocytosis Center Karolinska was established in 2006 at Karolinska University Hospital and Karolinska Institute in Stockholm, Sweden, and receives referrals from the entire country. As of December 1, 2015, 264 consecutive adult patients (≥ 18 years) had been referred to the center. In accordance with World Health Organization criteria, the diagnostic workup included histopathological evaluation of bone marrow, flow cytometry, *KIT* D816V mutation analysis, and measurement of serum baseline tryptase (sBT) levels. Accordingly, 140 of the investigated patients met the criteria for the diagnosis of SM.

A cross-sectional study was conducted among 122 patients diagnosed with SM after excluding 18 patients with SM because of either inadequate investigation (lack of allergy workup) or lack of consent (Figure 1). Ethical approval was obtained from Regional Ethical Review Board, Stockholm, Sweden (approval no. 2011/1750-31/3). All 122 patients provided their written consent to participate.

All enrolled patients underwent comprehensive allergy workup including detailed medical history and allergy tests at Karolinska University Hospital Huddinge, Department of Respiratory Medicine and Allergy, as previously described.⁶ The clinical relevance of aeroallergens, foods, drugs, and insects was recorded and evaluated by skin prick test and/or specific IgE antibody test (ImmunoCAP Phadiatop, ThermoFisher, Uppsala, Sweden) in relation to patient's medical history. The total IgE level was measured for all patients, always together with the sBT level. The possible effect of general triggers, such as physical exertion, heat, cold, friction, emotional stress, alcohol, or histamine-containing food, was carefully evaluated.

Diagnostic criteria

Diagnosis of SM was made using current World Health Organization criteria, and on the basis of bone marrow investigations to

confirm the presence/absence of major criterion and/or minor criteria.^{2,4} All patients with SM obtained the final diagnosis after staging investigations by computerized tomography of the chest and abdomen, and the measurement of bone density. Involvement with mastocytosis in skin (MIS) was verified after skin biopsy or on the basis of typical morphologic appearance of the skin lesions assessed by an experienced dermatologist or allergist. In this study, patients with MIS who did not have bone marrow engagement, that is, patients with diagnosis of cutaneous mastocytosis, were not included.

Anaphylaxis was diagnosed according to National Institutes of Health criteria.¹⁴ All anaphylactic reactions were assessed by an allergist and the diagnosis was based on patient's history and review of records including those from an acute attack. In this study, in the absence of emergency department reports, to ascertain the diagnosis of anaphylaxis, only patients reacting with syncope after exposure to known or probable allergen were considered to have had anaphylaxis. Hereditary angioedema, pheochromocytoma, and carcinoid tumors were ruled out with appropriate studies.

Atopic predisposition was defined as having at least 1 positive reaction to skin prick test and/or ImmunoCAP against aeroallergens.

Data collection

The data of enrolled patients were extracted from electronic patient charts to an Excel file. To ensure anonymity, patients were given a study ID. The potential risk factors for anaphylaxis including age, sex, atopic predisposition, total IgE levels, baseline tryptase levels, skin involvement with mastocytosis, and bone marrow findings were evaluated. Furthermore, these patients were categorized for the presence or absence of anaphylaxis; thereby, 55 patients who had experienced at least 1 episode of anaphylaxis were assigned to the group of patients with anaphylaxis. The remaining 67 patients had experienced no anaphylactic episodes at the time of this study and therefore were categorized as patients with SM without anaphylaxis.

Statistical analyses

The statistical analyses were performed using SPSS 23.0 for Windows (SPSS, Inc, Chicago, Ill). Frequencies were reported for categorical variables, and group differences were analyzed by using the chi-square test. Data were presented as median values and ranges, and because the distribution of the data was not normal according to Shapiro Wilks test, group differences were analyzed by using Mann-Whitney *U* test and Spearman correlation test using rank-ordered values. *P* value of .05 or less was considered to be significant.

To reveal factors associated with increased risk of anaphylaxis, univariate and multivariate logistic regression analyses were performed, in which the presence of anaphylaxis was defined as the dependent variable. First, the potential risk factors/variables were individually assessed in univariate analysis and correlations between variables were determined by using Pearson and Spearman correlation coefficients. Afterward, the relevant variables in the univariate analysis were selected as potential risk factors and assessed together in a multivariate logistic regression model. The accuracy of the final multivariate regression model, in terms of discriminating patients with SM with anaphylaxis from patients with SM without anaphylaxis, was determined by calculating the area under the receiving operating characteristic curve (*c*-statistic). Finally, a risk scoring model, requiring a high sensitivity of association with anaphylaxis in patients with SM was developed on the basis of variables with independent predictive roles in multivariate logistic regression analysis and variables with clinical relevance.

RESULTS

Characteristics of study subjects

The most common subvariant of SM was ISM (92%), followed by SM associated with hematological non-MC-lineage disease (5%) and aggressive SM (3%). Concurrent occurrence of MIS was found in 68% of patients with SM, of whom the majority (86%) had biopsy-verified skin involvement and the remaining had a diagnosis based on clinical features. The overall rate of atopic predisposition was 30% (36 of 122), and 45% (55 of 122) of the patients were males. Demographic data and characteristics of study subjects are presented in Table I.

Comparison between patients with SM with anaphylaxis and patients with SM without anaphylaxis

We observed significant differences between the group of patients with SM with anaphylaxis (*n* = 55) compared with the group of patients with SM without anaphylaxis (*n* = 67) in relation to the presence/absence of MIS (*P* < .001), the presence/absence of atopic predisposition (*P* = .021), total IgE levels (*P* < .001), and baseline tryptase levels (*P* = .024). There was an inverse correlation between total IgE levels and baseline tryptase levels (*P* < .02), calculated by using rank-ordered values by Spearman rank correlation test. We did not observe any significant difference between the groups regarding sex (*P* = .057) although there were more males among patients with SM with anaphylaxis. The list of all variables compared between the groups is presented in Table II.

Patients with SM with anaphylaxis

A total of 114 anaphylactic episodes were recorded in 55 patients for an indefinite period of time, that is, not only during data collection time (2006-2015). Twenty-eight of 55 patients suffered from more than 1 anaphylaxis episode. In this study, the main elicitor of anaphylaxis was wasp sting (62%; 34 of 55), followed by idiopathic anaphylaxis (31%; 17 of 55) and food and drug (7%; 4 of 55). Remarkably, all patients who had multiple (≥ 2) anaphylactic episodes maintained the same elicitor throughout their episodes and the frequency of males was significantly higher among these patients (*P* = .043, calculated by χ^2 test). However, there was no substantial evidence to suggest that anaphylaxis may have been caused alone by general triggers such as heat, cold, or physical exercise.

We also compared patients with SM with anaphylaxis on the basis of elicitors to determine whether there were internal differences among the groups. Interestingly, when comparing venom-induced anaphylaxis (VIA) with non-VIA (including idiopathic anaphylaxis or food/drug-induced anaphylaxis), no statistically significant differences were obtained between anaphylaxis groups regarding sex, atopic predisposition, presence of MIS, baseline tryptase levels, and total IgE levels.

Univariate and multivariate analyses of risk factors of anaphylaxis

Univariate regression analysis of the data of 122 patients with SM showed that the following variables had significant odds ratios (*P* < .05): absence of MIS, presence of atopy, and baseline tryptase levels. Before we further tested these risk factors in a multivariate logistic regression model, we explored baseline tryptase and total IgE levels in detail and assigned appropriate cutoff values.

TABLE I. Demographic, clinical, and biological characteristics of patients with SM

Characteristic	SM (n = 122; 100%)	ISM (n = 113; 92.6%)	SM-AHNMD (n = 6; 4.9%)	Aggressive SM (n = 3; 2.5%)
Sex, male, n (%)	55 of 122 (45%)	51 of 113 (45%)	3 of 6 (50%)	1 of 3 (33%)
Age as of BM biopsy, median (range)	55 (20-84)	52 (20-83)	69 (53-82)	73 (61-84)
Presence of multifocal MC clusters in BM, n (%)	73 of 122 (59.8)	64 of 113 (56.6)	6 of 6 (100)	3 of 3 (100)
Atypical MC morphology, n (%)	117 of 122 (95.9)	109 of 113 (96.5)	5 of 6 (83.3)	3 of 3 (100)
CD2/CD25, n (%)	121 of 122 (99.2)	113 of 113 (100)	6 of 6 (100)	2 of 3 (66.7)
<i>KIT</i> mutation D816V, n (%)	85 of 101 (84.2) (21 ND)	76 of 92 (82.6) (21 ND)	6 of 6 (100)	3 of 3 (100)
Presence of MIS, n (%)	83 of 122 (68)	81 of 113 (71.7)	2 of 6 (33.3)	0 of 3 (0)
Occurrence of anaphylaxis, n (%)	55 of 122 (45.1)	53 of 113 (46.9)	2 of 6 (33.3)	0 of 3 (0)
Atopic predisposition, n (%)	36 of 122 (29.5)	35 of 113 (31)	1 of 6 (16.7)	0 of 3 (0)
sBT levels (ng/mL), median (range)	31.5 (5.9-650)	29 (5.9-650)	190 (94-620)	110 (80-200)
Total IgE (kU/L), median (range)	13 (1-1600)	13 (1-1600)	12 (7.7-140)	76 (5.8-240)

BM, Bone marrow; ND, not done; SM-AHNMD, systemic mastocytosis associated with hematological non-mast cell-lineage disease.

TABLE II. Comparison between patients with SM with anaphylaxis and patients with SM without anaphylaxis

Characteristic	Patients with SM with anaphylaxis (n = 55)	Patients with SM without anaphylaxis (n = 67)	P
Sex, male, n (%)	30 of 55 (55)	25 of 67 (37)	.057*
Age as of BM biopsy (y), median (range)	56 (22-80)	52 (20-84)	.582†
Presence of multifocal MC clusters in BM, n (%)	28 of 55 (51)	45 of 67 (67)	.068*
<i>KIT</i> mutation D816V, n (%)	35 of 45 (78) (10 ND)	50 of 56 (89) (11ND)	.115*
Presence of MIS, n (%)	28 of 55 (51)	55 of 67 (82)	<.001*
sBT levels (ng/mL), median (range)	27 (7-200)	42 (5.9-650)	.024†
Atopic predisposition, n (%)	22 of 55 (40)	14 of 67 (21)	.021*
Total IgE (kU/L), median (range)	18 (2.6-1600)	8.7 (1-240)	<.001†

BM, Bone marrow; ND, not done.

Bold indicates statistical significance ($P < .05$).

* P values were calculated using a chi-square test.

† P values were calculated using a 2-tailed Mann-Whitney U test.

Cutoff less than 40 ng/mL for baseline tryptase in scoring system

The risk of anaphylaxis decreased with higher levels of baseline tryptase. The cutoff of less than 40 ng/mL for baseline tryptase was selected after careful examination of anaphylaxis prevalence per interval of tryptase (interval range, 10 ng/mL), as illustrated in [Figure 2, A](#).

Cutoff 15 kU/L or more for total IgE in scoring system

Likewise, the risk of anaphylaxis increased with higher levels of total IgE, as illustrated in [Figure 2, B](#). The cutoff IgE level of 15 kU/L or more was selected after careful examination of anaphylaxis prevalence per interval of total IgE (interval range, 10 kU/L).

Therefore, the final multivariate logistic regression model included these variables with defined cutoff levels as risk factors for anaphylaxis, in addition to statistically significant variables (ie, absence of MIS and the atopic predisposition). Finally, we forced male sex into the multivariate logistic regression analyses because of its clinical relevance. We were also concerned about a

potential confounding by sex because this variable associates both with the MIS and anaphylaxis. Furthermore, Spearman correlation analysis of sex and MIS revealed an association between these variables ($P = .035$). With stratification analysis, however, we determined that the risk for developing anaphylaxis can increase independently from sex with lack of MIS. Consequently, it seemed unlikely that sex would be a confounder. The results of the univariate and multivariate analyses are presented in [Table III](#). The accuracy of the final multivariate model was good, as demonstrated by the c -statistic of 0.806 (95% CI, 0.725-0.887; $P < .001$), as shown in [Figure 3](#).

Scoring system to assess the risk of anaphylaxis in patients with SM

A risk predicting tool was developed by using variables from the final multivariate model for the occurrence of anaphylaxis in patients with SM ([Table IV](#)). Using this model, we obtained a sensitivity of 86% and a specificity of 54%. In our cohort, the ability of detecting patients with VIA was 85%, whereas 86% of patients with SM with idiopathic/food/drug-induced anaphylaxis were detected by this risk predicting tool.

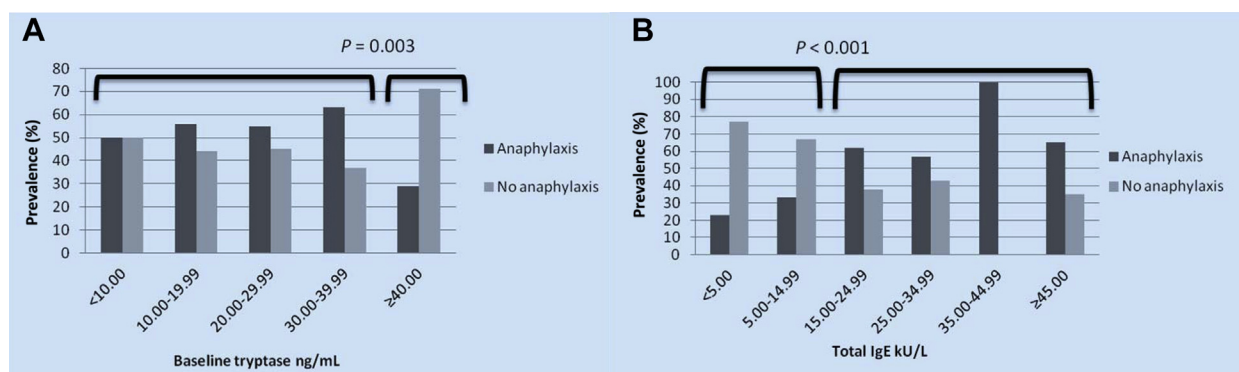


FIGURE 2. Role of baseline tryptase and total IgE levels in relation to prevalence of anaphylaxis. P values were calculated using a 2-tailed Mann-Whitney U test. **A**, Prevalence of anaphylaxis per interval of baseline tryptase. Interval range is 10 ng/mL for the first 4 intervals, and the last interval ranges from 40 ng/mL to 650 ng/mL. Prevalence of anaphylaxis was decreasing with higher levels of baseline tryptase. **B**, Prevalence of anaphylaxis per interval of total IgE. Interval range is 10 kU/L except the first interval (<5 kU/L) and the last interval (ranges from 45 kU/L to 1600 kU/L). Prevalence of anaphylaxis was increasing with higher levels of total IgE.

TABLE III. Results of univariate and multivariate logistic regression analyses for predictors of anaphylaxis in 122 adult patients with SM

Predictor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Male sex	2.016 (0.976-4.166)	.058	2.186 (0.891-5.363)	.088
Age as of BM	1.006 (0.983-1.030)	.606		*
Lack of MC clusters in BM	1.972 (0.946-4.111)	.070		*
Lack of MIS	4.420 (1.950-10.017)	<.001	4.752 (1.794-12.589)	.002
Atopic predisposition	2.524 (1.136-5.609)	.023	2.370 (0.890-6.308)	.084
Baseline tryptase level <40 ng/mL	3.203 (1.478-6.940)	.003	4.582 (1.779-11.804)	.002
Total IgE level ≥15 kU/L	4.407 (2.048-9.487)	<.001	2.600 (1.071-6.312)	.035

BM, Bone marrow; OR, odds ratio.

For multivariate analysis, variables with significant P (<.05) values and in addition, because of its clinical relevance, male sex were tested. Values are expressed as OR with 95% CI. Bold indicates statistical significance (P < .05).

*The variable was not tested in multivariate regression analysis because of a P value of greater than .05 in the univariate regression analysis and no known clinical importance.

DISCUSSION

This is the first detailed analysis of clinical and biological features and risk assessment for anaphylaxis in patients with SM. In contrast to previous studies in which risk factors were proposed only individually, we analyzed potential risk factors at group levels in 122 thoroughly investigated patients with SM from a single center using univariate and multivariate analyses. A risk assessment model for anaphylaxis was proposed and translated into an arbitrary scoring system consisting of the following variables: sex, skin involvement of SM, presence/absence of atopic predisposition, total IgE levels, and baseline tryptase levels.

The overall prevalence of anaphylaxis in our SM cohort was 45%. This is comparable to previous studies reporting anaphylaxis prevalence from 20% to 56% in adult patients with various forms of mastocytosis.⁶⁻⁹ The predominantly high proportion of VIA (62%) is also in line with previous reports on anaphylaxis in patients with SM.^{6,8,9} Thereby, the overall prevalence of VIA in this SM cohort was 28% (34 of 122), which is approximately 10-fold higher risk than that in the general population (about 3%).

It would be tempting to speculate that higher MC load reflected by higher sBT levels would be at least partially responsible for the higher prevalence of anaphylaxis in patients with SM. To support this notion, higher tryptase levels in patients with

mastocytosis with anaphylaxis were previously reported by Brockow et al.⁹ However, the median sBT levels in the present study were significantly lower in patients with SM with anaphylaxis compared with patients with SM without anaphylaxis (27 ng/mL vs 42 ng/mL; $P = .024$). A possible explanation for this discrepancy between the 2 studies could be due to heterogeneity of study subjects in the former report. Indeed, in the study by Brockow et al,⁹ patients with cutaneous mastocytosis without proven systemic involvement were included, whereas in our study all patients had SM. In addition, the association between baseline tryptase levels and anaphylaxis was obvious when examining the prevalence of anaphylaxis per interval of tryptase (interval range, 10 ng/mL), as the prevalence of anaphylaxis decreased with higher levels of baseline tryptase. The study by Brockow et al did not analyze this association in detail; however, these results were consistent with a later study by van Anrooij et al¹⁵ on VIA in patients with mastocytosis. Accordingly, the correlation between higher sBT levels and the prevalence of anaphylaxis in patients with mastocytosis does not appear to be linear but shows rather a bell-shaped association where the risk is indeed lower with very high levels of sBT. In this study, we determined that tryptase levels of 40 ng/mL or more were associated with a lower risk of anaphylaxis compared with

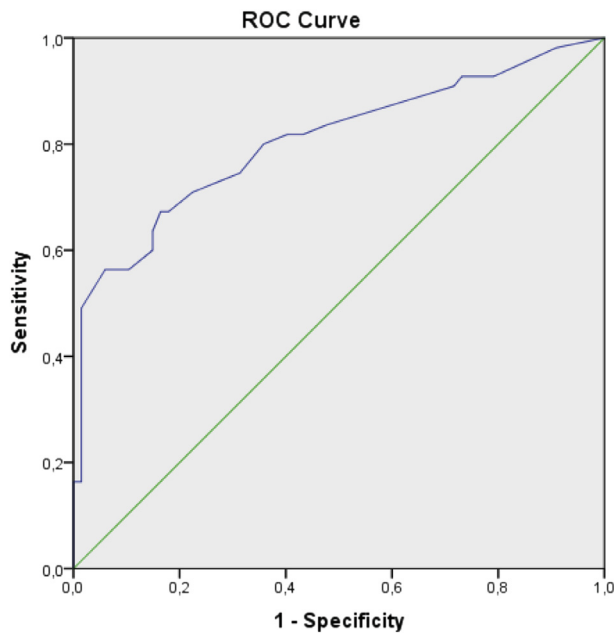


FIGURE 3. The accuracy of the final multivariate regression model. The accuracy of the model was measured by the area under the receiving operating characteristic (ROC) curve using the variables male sex, presence of atopy, absence of MIS, baseline tryptase level of less than 40 ng/mL, and total IgE level of 15 kU/L or more. The *c*-statistic is 0.806 (95% CI, 0.725-0.887; $P < .001$).

TABLE IV. Scoring system proposed as risk assessment tool for anaphylaxis

Variables		Score	
Sex	Male	1	
	Female	0	
Skin engagement	Lack of MIS	3	
	Presence of MIS	0	
Baseline tryptase level	<40 ng/mL	2	
	≥40 ng/mL	0	
Atopic predisposition	Presence of atopy	1	
	Absence of atopy	0	
Total IgE level	≥15 kU/L	3	
	<15 kU/L	0	
Score <3	Low probability of anaphylaxis		
Score ≥3	High probability of anaphylaxis		
Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)
86% (74.6-93.1)	54% (41.8-65.4)	81.8% (68.8-91.2)	60.3% (49.2-70.7)

MIS, Mastocytosis in the skin.

tryptase levels of less than 40 ng/mL ($P = .003$). Thus, very high levels of sBT appear to protect against anaphylaxis. The protection could be a result of MCs' ability to modulate the adaptive immune system through the release of mediators, degradation of allergens or IgE,^{16,17} costimulation of B or T cells,^{18,19} or alterations in IgE receptor or bound specific IgE density per MC.

In general, higher prevalence of atopic predisposition, that is, IgE sensitization against aeroallergens, has been shown in patients with anaphylaxis compared with the healthy population.^{20,21} In this study, we have also shown that atopic predisposition was more frequent in patients with SM with anaphylaxis compared with patients with SM without anaphylaxis, although it did not reach statistical significance in multivariate analysis. In addition, total IgE levels were significantly higher in patients with SM with anaphylaxis when compared with patients with SM without anaphylaxis. Interestingly, when we analyzed patients with anaphylaxis separately according to elicitor groups, atopy was not a predictive marker in patients with SM with VIA, although IgE levels were significantly higher in these patients (data not shown). Furthermore, careful analysis of the data exposed that IgE level of 15 kU/L or higher was a general risk factor for the occurrence of anaphylaxis compared with IgE level of less than 15 kU/L ($P < .001$). We also determined an inverse correlation between total IgE levels and baseline tryptase levels in this study as previously shown.^{22,23}

In addition, the presence of MIS was less frequent among patients with anaphylaxis than among patients without anaphylaxis in congruence with a previous study.⁹ The reason for this association is not entirely clear but may reflect a selection bias because these patients would not have been readily recognized as having mastocytosis if they had not had anaphylaxis. Furthermore, although we observed a male predominance among patients with SM with anaphylaxis, this did not reach statistical significance. Nevertheless, it is noteworthy that the male predominance was statistically significant when we separately analyzed patients with SM with VIA ($P = .04$). Interestingly, however, when we compared the characteristics of patients with SM with VIA to the characteristics of patients with SM with idiopathic/food/drug-induced anaphylaxis, there were no statistically significant differences regarding sex, atopic predisposition, presence of MIS, baseline tryptase levels, and total IgE levels. This supports the concept of a general anaphylaxis-SM phenotype and provides the opportunity to develop a predictive model not only for VIA but also for anaphylaxis irrespective of elicitor in patients with SM.

In multivariate logistic regression analysis we confirmed that variables with statistically significant odds ratios in univariate analysis could be used together in a model to identify patients with anaphylaxis. After this analysis, positive predictors of anaphylaxis were shown to be absence of MIS, higher levels of total IgE (≥15 kU/L), and presence of atopic predisposition, whereas negative predictor was higher baseline tryptase levels (≥40 ng/mL). Because we wanted to develop a universal model of risk assessment for anaphylaxis covering both VIA and non-VIA, we included a clinically relevant variable, male sex, as a positive risk factor, although overall it did not reach statistical significance in regression analysis. Using above-mentioned variables, the accuracy of the final multivariate model was good (the *c*-statistic, 0.806), when calculated by the receiving operating characteristic curve.

Taking the above-mentioned aspects into consideration, the multivariate model was gradually transformed into a scoring system to develop a risk assessment tool. In addition, a higher sensitivity was the absolute requirement in the development of such a scoring tool, because the consequence of not equipping patients at high risk of anaphylaxis with autoinjector of adrenaline can be fatal. Afterward, the arbitrary scores were given for

sex, absence/presence of MIS, atopic status, IgE level of more than 15 kU/L, and tryptase level of less than 40 ng/mL. We determined the best cutoff value as 3 or more to predict the risk for anaphylaxis with a sensitivity and specificity of 86% and 54%, respectively. The overall sensitivity was well balanced even when we applied the scoring tool to the patients with SM with different elicitors of anaphylaxis because the sensitivities were 85% and 86% in VIA and idiopathic/food/drug-induced anaphylaxis, respectively.

We believe one of the strengths in this study was that we had a cohort consisting of 122 consecutive adult patients with SM investigated at a single center by the same experienced allergy group. In addition, we were able to create a highly efficient model on the basis of differences between patients with anaphylaxis and patients without anaphylaxis. Nevertheless, several limitations may have affected these results. First, because mastocytosis is a rare disease, the study time frame was not plausible to collect adequate sample size to develop a fully powered predictive model. In addition, some information loss is inevitable, when translating a logistic regression model into a linear scoring model. Therefore, the true accuracy of our predictive model cannot be assessed in this study on our material because of the risk of overfitting. Furthermore, statistically significant difference between anaphylaxis and nonanaphylaxis groups could be a result of selection or referral bias. However, the inclusion criterion was an SM diagnosis irrespective of the presence/absence of anaphylaxis and our patients were equally recruited from dermatology and allergy referrals. In addition, because it is impossible to personally examine each patient during anaphylaxis, emergency room reports and patient's history were used to determine anaphylaxis. In the absence of emergency room reports when diagnosis of anaphylaxis was based only on patient's history, there might be a risk of recall bias.

In conclusion, patients with SM with anaphylaxis display a characteristic pattern of clinical and biochemical features different from patients with SM without anaphylaxis. These observations may suggest the existence of a distinct SM anaphylaxis phenotype. In the present study, male sex, presence of atopy, IgE levels of 15 kU/L or more, baseline tryptase levels of less than 40 ng/mL, and absence of MIS appeared to be risk factors of anaphylaxis in patients with SM. Hence, a preliminary scoring tool (86% sensitivity and 54% specificity) capable of discriminating patients with SM at high risk of anaphylaxis from those at low risk is proposed by using these variables. The risk predicting tool proposed may improve the care of patients with SM by enabling the physician to make more adequate risk assessment and determine individual patient's need, for instance, to prescribe lifesaving self-injectable adrenaline for appropriate patients. This would ultimately improve quality of life for patients. In addition, the new approach may provide cost-effective long-term care for the caretakers. Nevertheless, caution should be exercised in the use of this prediction model until validation is performed by prospective, ideally multicenter, studies with larger SM cohorts.

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REFERENCES

- Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144-50.
- Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-53.
- Gulen T, Hagglund H, Dahlen B, Nilsson G. Mastocytosis: the puzzling clinical spectrum and challenging diagnostic aspects of an enigmatic disease. *J Intern Med* 2016;279:211-28.
- Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-25.
- Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. *Immunol Allergy Clin North Am* 2014;34:207-18.
- Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis—a single-centre experience. *Clin Exp Allergy* 2014;44:121-9.
- Florian S, Krauth MT, Simonitsch-Klupp I, Sperr WR, Fritsche-Polanz R, Sonneck K, et al. Indolent systemic mastocytosis with elevated serum tryptase, absence of skin lesions, and recurrent severe anaphylactoid episodes. *Int Arch Allergy Immunol* 2005;136:273-80.
- de Olano DG, Caballer BD, Lopezz RN, Munoz LS, Agustin MC, Dieguez M, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007;37:1547-55.
- Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-32.
- Akin C. Anaphylaxis and mast cell disease: what is the risk? *Curr Allergy Asthma Rep* 2010;10:34-8.
- Brockow K, Bonadonna P. Drug allergy in mast cell disease. *Curr Opin Allergy Clin Immunol* 2012;12:354-60.
- Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, et al. How much specific is the association between hymenoptera venom allergy and mastocytosis? *Allergy* 2009;64:1379-82.
- Alvarez-Twose I, Gonzalez de Olano D, Sanchez-Munoz L, Matito A, Esteban-Lopez MI, Vega A, et al. Clinical, biological, and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol* 2010;125:1269-1278.e2.
- Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;47:373-80.
- van Anrooij B, van der Veer E, de Monchy JG, van der Heide S, Kluin-Nelemans JC, van Voorst Vader PC, et al. Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. *J Allergy Clin Immunol* 2013;132:125-30.
- Rauter I, Krauth MT, Flicker S, Gieras A, Westritschnig K, Vrtala S, et al. Allergen cleavage by effector cell-derived proteases regulates allergic inflammation. *FASEB J* 2006;20:967-9.
- Rauter I, Krauth MT, Westritschnig K, Horak F, Flicker S, Gieras A, et al. Mast cell-derived proteases control allergic inflammation through cleavage of IgE. *J Allergy Clin Immunol* 2008;121:197-202.
- Frossi B, Gri G, Tripodo C, Pucillo C. Exploring a regulatory role for mast cells: 'Mcregs'? *Trends Immunol* 2010;31:97-102.
- Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. *Nat Rev Immunol* 2008;8:478-86.
- Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol* 1996;77:285-91.

21. Tejedor Alonso MA, Sastre DJ, Sanchez-Hernandez JJ, Perez FC, de la Hoz Caballer B. Idiopathic anaphylaxis: a descriptive study of 81 patients in Spain. *Ann Allergy Asthma Immunol* 2002;88:313-8.
22. Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with “idiopathic” anaphylaxis. *Blood* 2007;110:2331-3.
23. Gulen T, Hagglund H, Sander B, Dahlen B, Nilsson G. The presence of mast cell clonality in patients with unexplained anaphylaxis. *Clin Exp Allergy* 2014;44:1179-87.