Scoring the Risk of Having Systemic Mastocytosis in Adult Patients with Mastocytosis in the Skin

Fuchs, David; Kilbertus, Alex; Kofler, Karin; von Bubnoff, Nikolas; Shoumariyeh, Khalid; Zanotti, Roberta; Bonadonna, Patrizia; Scaffidi, Luigi; Doubek, Michael; Elberink, Hanneke Oude

Published in:
Journal of Allergy and Clinical Immunology: In Practice

DOI:
10.1016/j.jaip.2020.12.022

Original Article

Scoring the Risk of Having Systemic Mastocytosis in Adult Patients with Mastocytosis in the Skin

David Fuchs, MD[a,b], Alex Kilbertus, MD[c], Karin Kofler, MD[a], Nikolas von Bubnoff, MD[d,e], Khalid Shoumariyeh, MD[d,f], Roberta Zanotti, MD[g], Patrizia Bonadonna, MD[h], Luigi Scaffidi, MD[g], Michael Doubek, MD[i], Hanneke Oude Elberink, MD[j], Lambert F.R. Span, MD, PhD[k], Olivier Hermine, MD, PhD[l], Chiara Elena, MD[m], Pietro Benvenuti, MD[n], Akif Selim Yavuz, MD[o], Knut Brockow, MD[p], Alexander Zink, PhD[p], Elisabeth Aberer, MD[q], Aleksandra Gorska, MD[r], Jan Romantowski, MD[r], Emir Hadzijusufovic, DVM[s,t,u], Anna Belloni Fortina, MD[v], Francesca Caroppo, MD[v], Cecelia Perkins, MPH[w], Anja Illerhaus, PhD[x], Jens Panse, MD[y], Vladan Vucinic, MD[z], Mohamad Jawhar, MD[aa], Vito Sabato, MD[bb], Massimo Triggiani, MD[cc], Roberta Parente, MD[cc], Anna Bergström, MD[dd], Christine Breynaert, MD, PhD[ee], Jason Gotlib, MD, MS[w], Andreas Reiter, MD[aa], Karin Hartmann, MD[x,ff], Marek Niedoszytko, MD[r], Michel Arock, PharmD, PhD[gg], Hanneke C. Kluin-Nelemans, MD, PhD[k], Wolfgang R. Sperr, MD[s,t], Rosemarie Greul, MD[a], and Peter Valent, MD[s,t] *Linz, Vienna, and Austria; Freiburg, Lübeck, Muncih, Cologne, Aachen, Leipzig, and Mannheim, Germany; Verona, Pavia, Padua, and Salerno, Italy; Brno, Czech Republic; Groningen, The Netherlands; Paris, France; Istanbul, Turkey; Gdańsk, Poland; Stanford, Calif; Antwerpen and Leuven, Belgium; Uppsala, Sweden; and Basel, Switzerland*

What is already known about this topic? Patients with mastocytosis in the skin (MIS) need a bone marrow biopsy to differentiate between cutaneous and systemic mastocytosis. Several parameters may be indicative for systemic involvement in patients with MIS, but no score-based estimation model is available.

What does this article add to our knowledge? Our article is the first to describe a large data set–based risk score for systemic involvement in patients with MIS, ready for application in clinical practice.

How does this study impact current management guidelines? Our score is ready for use to estimate the actual risk of patients with MIS to have systemic mastocytosis, which may in turn support the physician's decision of whether and when to recommend a bone marrow biopsy.

[a]Department for Hematology and Internal Oncology, Kepler University Hospital, Linz, Austria
[b]Johannes Kepler University, Linz, Austria
[c]Department of Dermatology and Venerology, Kepler University Hospital, Johannes Kepler University, Linz, Austria
[d]Department of Medicine I, Medical Center − University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[e]Department of Hematology and Oncology, Medical Center, University of Schleswig Holstein, Campus Lübeck, Lübeck, Germany
[f]German Cancer Consortium (DKTK) Partner site Freiburg, Freiburg, Germany
[g]Section of Hematology, Department of Medicine, Verona University Hospital, Verona, Italy
[h]Allergy Unit, Verona University Hospital, Verona, Italy
[i]University Hospital Brno, Brno, Czech Republic
[j]Department of Internal Medicine, Section of Allergy, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[k]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[l]Imagine Institute Université Paris Descartes, Sorbonne, Paris Cité, Centre national de référence des mastocytoses, Paris, France
[m]Department of Hematology Oncology, IRCCS Policlinico San Matteo Foundation Pavia, Pavia, Italy
[n]Department of Hematology Oncology, School of Hematology, University of Pavia and IRCCS Policlinico San Matteo Foundation, Pavia, Italy
[o]Division of Hematology, Department of Internal Medicine, University of Istanbul, Istanbul, Turkey
[p]Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany
[q]Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria
[r]Department of Allergology, Medical University of Gdańsk, Gdańsk, Poland
[s]Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
[t]Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
[u]Department/Hospital for Companion Animals and Horses, University Clinic for Small Animals, Internal Medicine Small Animals, University of Veterinary Medicine, Vienna, Austria
[v]Pediatric Dermatology Unit, Department of Medicine, University of Padua, Padua, Italy
[w]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, Calif
[x]Department of Dermatology, University of Cologne, Cologne, Germany
[y]Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, Medical Faculty, University Hospital RWTH Aachen, Aachen, Germany
[z]University Hospital of Leipzig, Leipzig, Germany
[aa]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany
[bb]Faculty of Medicine and Health Sciences, Department of Immunology-Allergology-Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerpen, Belgium

Abbreviations used
AUC- Area under the curve
BMB- Bone marrow biopsy
CM- Cutaneous mastocytosis
ECNM- European Competence Network on Mastocytosis
IPSM- International Prognostic Scoring System for Mastocytosis
ISM- Indolent SM
MC- Mast cell
MCL- Mast cell leukemia
MIS- Mastocytosis in the skin
NICAS- National Institute of Health Idiopathic Clonal Anaphylaxis Score
REMA- Red Española de Mastocitosis
ROC- Receiver-operating characteristic
SM- Systemic mastocytosis
SSM- Smoldering SM

BACKGROUND: Mastocytosis in adults often presents with skin lesions. A bone marrow biopsy is necessary to confirm or exclude the presence of systemic mastocytosis (SM) in these cases. When a bone marrow biopsy is not performed, the provisional diagnosis is mastocytosis in the skin (MIS). No generally accepted scoring system has been established to estimate the risk of SM in these patients.

OBJECTIVE: To develop a risk score to predict SM in adults with MIS.

METHODS: We examined 1145 patients with MIS from the European Competence Network on Mastocytosis Registry who underwent a bone marrow biopsy. A total of 944 patients had SM and 201 patients had cutaneous mastocytosis; 63.7% were female, and 36.3% were male. Median age was 44 ± 13.3 years. The median serum tryptase level amounted to 29.3 ± 81.9 ng/mL. We established a multivariate regression model using the whole population of patients as a training and validation set (bootstrapping). A risk score was developed and validated with receiver-operating curves.

RESULTS: In the multivariate model, the tryptase level ($P < .001$), constitutional/cardiovascular symptoms ($P = .014$), and bone symptoms/osteoporosis ($P < .001$) were independent predictors of SM ($P < .001$; sensitivity, 90.7%; specificity, 69.1%). A 6-point risk score was established (risk, 10.7%-98.0%) and validated.

CONCLUSIONS: Using a large data set of the European Competence Network on Mastocytosis Registry, we created a risk score to predict the presence of SM in patients with MIS. Although the score will need further validation in independent cohorts, our score seems to discriminate safely between patients with SM and with pure cutaneous mastocytosis. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:1705-12)

Key words: *Mastocytosis; Mast cell disease; Tryptase; Systemic mastocytosis; Cutaneous mastocytosis; Risk score*

INTRODUCTION

Mastocytosis is a rare and heterogeneous disease characterized by infiltrates of clonal mast cells (MCs) in 1 or more organ system.[1-16] Based on the type and number of organs involved, the World Health Organization differentiates between cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors.[9,17,18] SM can be further divided into indolent SM, smoldering SM (SSM), and more aggressive variants, that is, SM with an associated hematologic neoplasm, aggressive SM, and MC leukemia.[2,10,19,20]

The prognosis in patients with indolent SM or pure CM is excellent, with a 5-year overall survival of 85% to 100%. However, in patients with CM, the survival is even better than that in patients with SM.[21] In patients with advanced SM, the prognosis is dismal despite recent improvements in therapy.[1-11,21-29]

SM is usually diagnosed in adults and often accompanied by skin lesions. Skin involvement is often the first clinical sign detected in these patients. In other words, most adult patients with typical skin lesions of mastocytosis suffer from SM.[1-10] However, the final diagnosis, CM or SM, can be established only by a bone marrow biopsy (BMB).[1-10]

When typical cutaneous lesions of mastocytosis are found in adulthood but no BMB is performed, a final diagnosis of CM or SM cannot be made and these patients receive the provisional diagnosis of mastocytosis in the skin (MIS). It is standard to ask for a BMB in such patients to confirm or rule out the presence of SM.[1-10,30] In contrast, pediatric patients usually suffer from CM, whereas SM is only rarely diagnosed in children. Therefore, in children, a BMB is performed only when clear signs of an advanced systemic disease are found.

[cc]Division of Allergy and Clinical Immunology, Department of Medicine, University of Salerno, Salerno, Italy
[dd]Department of Dermatology and Venereology, Akademiska University Hospital, Uppsala, and Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[ee]Department of General Internal Medicine − Allergy and Clinical Immunology (MASTEL), University Hospitals Leuven and KU Leuven Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, Leuven, Belgium
[ff]Division of Allergy, Department of Dermatology, University of Basel, Basel, Switzerland
[gg]Department of Hematological Biology, Pitié-Salpêtrière Hospital, Paris Sorbonne University, Paris, France

This work was supported by Deutsche Forschungsgemeinschaft (DFG; grant no. RA 2838 to A.I.) and by the Koeln Fortune Program, Faculty of Medicine, University of Cologne (grant no. 216/2016 to A.I.). P.V. and his team were supported by the Austrian Science Fund (Fonds zur Förderung der wissenschaftlichen Forschung; grant nos. F4704-B20 and P32470-B). V.S. is a senior clinical researcher of the Research Foundation Flanders/Fonds Wetenschappelijk Onderzoek (FWO: 1804518N).

Conflicts of interest: D. Fuchs received honoraria from Novartis, outside the submitted work. N. von Bubnoff received honoraria from Amgen, Astra Zeneca, BMS, and Novartis, and research funding from Novartis. J. Panse reports personal fees from Alexion, BMS, Boehringer Ingelheim, Grünenthal, MSD, Novartis, Pfizer, Chugai, Roche, Apellis, and Blueprint medicines, all outside the submitted work. M. Triggiani received fee for Advisory Board from Novartis, Deciphera, and Blueprint Medicines. H. C. Kluin-Nelemans received financial support from Novartis. W. R. Sperr received honoraria from Novartis, Pfizer, AbbVie, Daiichi Sankyo, Amgen, Thermo Fisher, Deciphera, Incyte, Celgene, and Jazz. Valent received honoraria from Deciphera, Blueprint, Celgene, Novartis, Pfizer, and Incyte, all outside the submitted work.

Received for publication July 13, 2020; revised December 5, 2020; accepted for publication December 7, 2020.

Available online December 23, 2020.

Corresponding author: David Fuchs, MD, Department for Hematology and Internal Oncology, Kepler University Hospital, Johannes Kepler University, Med Campus III, Krankenhausstraße 9, 4020 Linz, Austria. E-mail: mail@davidfuchs.at.

2213-2198

https://doi.org/10.1016/j.jaip.2020.12.022

Patients with SM may suffer from various symptoms, including anaphylaxis, cutaneous symptoms (eg, flushing and pruritus), gastrointestinal symptoms (eg, diarrhea and cramping), pain (especially bone pain), osteoporosis (=often cause of pain), and neuropsychiatric problems.[31-40] Although the type and severity of symptoms vary greatly among patients, these symptoms can have a substantial impact on the physical and mental status and the quality of life of these patients.[38,39,41] Serum tryptase levels, which are sometimes related with symptom severity and are a surrogate parameter of the MC burden, vary greatly among patients.

Asymptomatic patients with skin lesions only and normal tryptase levels are often reluctant to undergo a BMB, which, although usually safe, can sometimes be painful and may rarely cause complications such as bleeding, or, extremely rarely, infection.[42-44]

There is no generally accepted recommendation and algorithm in MIS and no defined way to predict an individual patient's risk for SM. Specifically, we currently lack a widely accepted tool to advise physicians and patients when to perform a BMB and in which patients such procedure can be delayed. It is worth noting here that for patients without MIS, but elevated tryptase or symptoms suggestive of systemic MC disease, risk scores have been developed to guide decisions for a full workup including a BMB.[30,45-50]

METHODS

Study population

Data from patients used to develop and validate the risk score were collected in the data registry of the European Competence Network on Mastocytosis (ECNM). The ECNM was established in 2002 as an interdisciplinary cooperative approach to support research and to support management and therapy in patients with mastocytosis in Europe and in the United States (see this article's Online Repository at www.jaci-inpractice.org). The ECNM Registry is the world's largest collection of data on patients with mastocytosis.[51] At the time of analyses performed in this study (2018), the registry had enrolled 2361 patients from 23 centers in Europe and 1 in the United States.[51]

For this study, we included 1145 patients from the ECNM Registry who were at least 18 years old at diagnosis, had cutaneous lesions of mastocytosis, and had a BMB done within 6 months of their first diagnosis. This delay was included to allow time for referral to a hematology center. We excluded all patients with advanced variants of SM (SM with associated hematological neoplasm, aggressive SM, and MC leukemia), localized MC tumors, as well as patients with insufficient data on BMB (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Of the 1145 patients, 944 were diagnosed with SM and 201 with CM after a BMB. Median age was 44 ± 13.3 years (range, 18-81 years), 63.7% were female, and 36.3% were male. Almost all patients had typical (ie, maculopapular) skin lesions (97.6%) and a good performance status (Eastern Cooperative Oncology Group 0-1, 97.6%). Tryptase levels varied greatly among patients (median, 29.3 ± 81.9 ng/mL; range, 1-885 ng/mL).

Most patients (90.7%) suffered from symptoms of their disease (skin symptoms, 81.4% of the total population; other symptoms, 65.5%): 10.9% had headache, 39.0% had gastrointestinal symptoms (diarrhea, cramping, or upper gastrointestinal ulcerative disease), 38.4% had osteoporosis and/or bone pain, and 23.7% had cardiovascular/constitutional symptoms (anaphylactic hypotension). Baseline characteristics and symptoms are summarized in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

The study was approved by the ethics committees of all participating centers. All patients provided written informed consent.

Assessments of mastocytosis at diagnosis and during follow-up

In the ECNM Registry, variables were recorded at the time of diagnosis and at various time points in the follow-up. We used either baseline data at first entry into the registry or—if there was a delay between diagnosis and biopsy—data recorded at the time of BMB. A more detailed description of the registry, its set up, and general aims, as well as a list of all parameters collected, has recently been published.[51]

Statistical analyses and development of the score

We established a risk score in a 3-step procedure. First, we performed univariate analyses and included significant variables in the second step, where we used a multivariate logistic regression model to determine independent prognostic factors for systemic involvement. In a final step, we used the regression coefficients to calculate the relative risk of each variable and to develop a risk score as described for the risk of coronary heart disease in the Framingham Heart Study.[52]

We then validated the predictive power of the risk score by applying receiver-operating characteristic (ROC) area under the curve (AUC, c-statistic). The validation cohorts consisted of 1000 bootstrapped random samples from the study population.[53] We calculated the AUC for each sample and used the SD to determine an optimism-corrected AUC. The same approach was used for the validation of the risk score and the regression model. We accepted significance at P less than .05 and used SPSS 23 (IBM, Armonk, NY) for the analysis. More details can be found in this article's Online Repository at www.jaci-inpractice.org.

RESULTS

Risk factors for SM—Univariate analysis

In univariate analyses, predictors of significance for SM in patients with MIS were the presence of constitutional/cardiovascular symptoms ($P = .002$), bone pain or osteoporosis ($P < .001$), gastrointestinal symptoms ($P = .004$), a higher serum tryptase level ($P < .001$), palpable spleen ($P = .003$), age more than 65 years ($P = .009$), higher lactate dehydrogenase levels ($P = .003$), higher monocyte counts ($P = .001$), and higher beta2-microglobulin levels ($P = .047$) (Table I).

Multivariate regression model

In a multivariate regression model, the tryptase level ($P < .001$), constitutional/cardiovascular symptoms ($P = .014$), and bone pain/osteoporosis ($P < .001$) were identified as independent predictors of SM. This regression model was significant regarding its predictive value (χ^2, $P < .001$) and was well calibrated (Nagelkerke $R^2 = 0.462$, Hosmer-Lemeshow $P = .177$). It correctly classified 88.1% of the cases as SM. Sensitivity was 90.7%, specificity 69.1%, and the model had a positive predictive value of 95.5% and a negative predictive value of 50.3%.

Risk score

Patients with constitutional/cardiovascular symptoms or bone pain/osteoporosis received 1 point for either symptom-group and

TABLE I. Significant predictors for SM and their distribution on univariate analysis

	Univariate analysis				
Predictor	**SM (% or median ± SD)**	**n (n total)**	**CM (% or median ± SD)**	**n (n total)**	***P****
Constitutional/cardiovascular symptoms	25.5%	229 (898)	15.4%	30 (195)	.002
Bone symptoms/osteoporosis	41.7%	347 (831)	21.2%	35 (165)	<.001
GI symptoms	40.1%	373 (912)	29.8%	58 (194)	.004
Tryptase	36.9 ± 86.9	884	9.6 ± 11.7	(184)	<.001
Spleen palpable	6,7%	61 (904)	1.6%	3 (193)	.003
Age ≥65 y	8.8%	83 (944)	3.5%	7 (201)	.009
% Monocytes	6.0% ± 3.9%	816	6.3% ± 5.2%	178	.001
LDH	161.0 ± 58.0	699	180 ± 56.3	111	.003
Beta2-microglobulin	1.7 ± 0.7	189	1.5 ± 0.45	30	.47

GI, Gastrointestinal; *LDH*, lactate dehydrogenase.
*χ^2 for categorical variables, ANOVA for continuous variables.

an additional −1, 0, 1, or 3 points for tryptase levels below 10, 10 to 15, 15 to 20, or more than 20 ng/mL, respectively (Table II). This yielded a 6-point scale (−1 to 5 points), with a risk of SM ranging from 10.7% to 98.0% (Figure 1). To make the score more useful in clinical practice, patients were then classified as either low (−1 and 0 points; 10.7%-24.7% risk of SM), medium (1 and 2 points, 47.1% and 70.7%), or high risk (3-5 points, 86.8%-98.0%) (Figure 2).

KIT D816V mutations in peripheral blood

KIT D816V expression in peripheral blood leukocytes is of special interest in the clinical setting, because, when documented, it indicates a high risk of SM and supports the recommendation to perform a BMB.[30]

Because data on KIT D816V were not included for all patients in the ECNM Registry (available only in 48 patients; 26 with indolent SM [ISM], 13 with MIS without BMB, 4 with SSM, and 3 with maculopapular CM), KIT D816V was not included in our regression model.

In all patients with ISM and all patients with maculopapular CM, in 3 of 4 SSM cases and in 11 of 13 patients with MIS, KIT D816V was identified in peripheral blood leukocytes, did not show a relation to a risk group (low risk, 11of 11 positive; medium risk, 6 of 6 positive; high risk, 26 of 29 positive). Of the 3 high-risk patients with a negative result for KIT D816V, only 1 had a BMB and was diagnosed with SSM.

Validation

The model and risk score were validated with the AUC under the ROC. AUC can take values between 0.5 and 1.0, with higher values indicating better performance of the model or score. An AUC of 0.9 to 1.0 would indicate perfect accuracy, 0.8 to 0.9 good accuracy, and 0.7 to 0.8 poor accuracy. Values close to 0.5 would be considered a failure of the model. In our study, ROC AUC was 0.871 for the model and 0.867 for the risk score. Bootstrap validation uses random samples from the data (in our case, 1000 samples) to correct the ROC AUC ("correction for optimism"). This "optimism-corrected" AUC was 0.853 for the model and 0.849 for the score (see Figures E2 and E3 in this article's Online Repository at www.jaci-inpractice.org).

Risk score distribution

Of all 1145 patients who had a BMB, 17.4% (n = 199) were at low risk (−1 and 0 points, 10.7% and 24.7% risk of SM), 14.5% (n = 166) at medium risk (1 and 2 points, 47.1% and 70.7%), and 68.1% (n = 779) at high risk (3-5 points, 86.8%-98.0%). The 944 patients diagnosed with SM exhibited a lower proportion of low-risk cases (8.0%) when compared with those with CM (64.9%) (Table III). Of patients who had MIS but had not been investigated by BMB (n = 265), 55.9% were at low risk (score −1, 36.2%; 0, 19.7%), 12.7% were at medium risk (1, 10.6%; 2, 2.1%) and 31.4% (3, 21.3%; 4; 7.4%; 5, 2.7%) were at high risk for SM. In the total population with MIS (n = 1410), 24.0% were at low risk, 14.2% at medium risk, and 61.8% at high risk (Table III).

TABLE II. Risk score for SM in patients with MIS

Parameter	**Score**
Tryptase (ng/mL)	
<10.0	−1
≥10.0 and <15.0	0
≥15.0 and <20.0	1
≥20.0	3
Bone symptoms or osteoporosis	1
Constitutional or cardiovascular symptoms	1

Patients are assigned points for serum tryptase and symptoms, and points are added up to get a sum between −1 and 5, with a risk for SM between 10.7% and 98.0% (Figure 1). To make the score useful in clinical practice, patients were classified as low risk (−1 and 0 points; 10.7%-24.7% risk of SM), medium/intermediate risk (1-2 points, 47.1%-70.7%), and high risk (3-5 points, 86.8%-98.0%).

DISCUSSION

For adult patients with MIS, a BMB and a complete staging are standard and mandatory to confirm or exclude the presence of SM and to define the World Health Organization category of SM.[1-10] Moreover, a BMB is important to establish the overall risk profile.[1-10] However, there are certain situations in which a BMB must be delayed, such as in the current virus pandemic, or when the patient refuses an early BMB. For these patients, it is important to offer a tool that predicts the presence of SM with some certainty. We have established a score that can predict the presence of SM in patients with MIS with considerable accuracy. This score is based on independent predictors of SM and divides patients with MIS into major subgroups that greatly differ in their risk to have or develop SM (10.7%-98.0%).

In the group of patients with MIS from the ECNM Registry who did not have a BMB, the proportion of low-risk patients (0-1 points on our risk score) was more than 3 times higher (55.9%

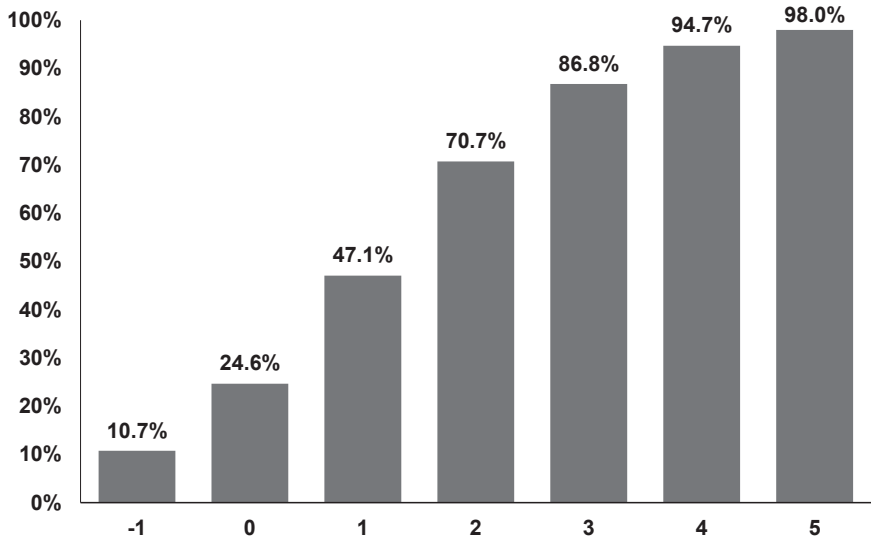

FIGURE 1. Risk of SM in patients with MIS. The calculated sum in the risk score (Table II) yields score results ranging between −1 and 5 (plotted along the x axis) with a clearly divergent risk of SM (plotted along the y axis): score −1, 10.7%; score 0, 24.6%; score 1, 47.1%; score 2, 70.7%; score 3, 86.8%; score 4, 94.7%; score 5, 98.0%.

vs 17.4%) than those who did have the biopsy. This is best explained by the fact that the decision of whether or not to perform a BMB was apparently based on the doctor's opinion or feeling that the patient may not suffer from SM based on clinical and laboratory parameters. In this regard, our scoring model may greatly support the physicians' decision to delay a BMB by providing a solid score model.

Existing risk scores for patients with symptoms suggestive of MC activation or with idiopathic anaphylaxis also use symptoms and serum tryptase to predict the likelihood of an underlying SM (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). However, it is important to bear in mind that these existing scores were established only for patients without skin lesions and have been developed in relatively small data sets. The Spanish Red Española de Mastocitosis (REMA) developed a score that uses sex, serum tryptase, and a set of symptoms including syncope, urticaria, and angioedema to guide decisions for BMB in patients without MIS, but symptoms suggestive of systemic MC activation.[45,46] More recently, the National Institute of Health Idiopathic Clonal Anaphylaxis Score (NICAS) for SM in patients with idiopathic anaphylaxis was published, which uses parameters similar to the REMA score with a slightly different cutoff value of serum tryptase.[49]

The parameters used in the REMA score and NICAS are similar to those we used in our study, except for skin symptoms and sex, both of which did not turn out to be significant predictors of SM in our study. All patients in our data set had, by definition, skin involvement of their mastocytosis, which makes it likely for them to have skin-related symptoms (81.4% had such skin-specific symptoms, eg, pruritus and bullae) and may explain why it did not turn out to be of significant value. A notable addition in the NICAS was the inclusion of peripheral blood screening for the *KIT* D816V mutation, which led to increased sensitivity (62.5% vs 75.0%) and specificity (72.92% vs 100.0%) of the NICAS compared with the REMA score.

Testing of peripheral blood cells for expression of *KIT* D816V may also add substantially to the predictive power of our new score, especially in light of the fact that the mutation is expected to be detectable in most patients with SM.[27,46,54-58] Peripheral screening for *KIT* D816V has also been recommended for patients without MIS and slightly elevated tryptase and also correlates with the serum tryptase level.[47,50,55,59,60] In the ECMN registry, *KIT* D816V mutations in peripheral blood were captured in only a small proportion of cases. This did not allow a formal inclusion of this parameter in the current risk score model, but it might be reasonable to screen patients with MIS at

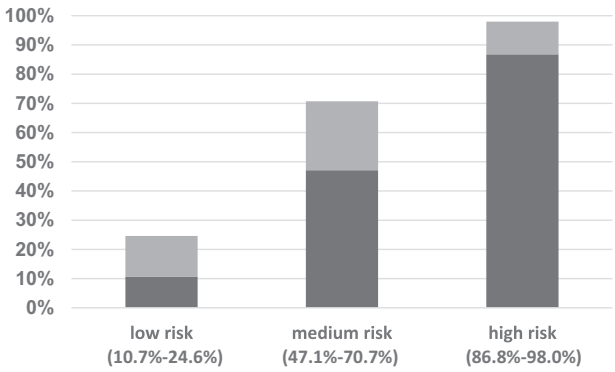

FIGURE 2. Risk for SM in patients with MIS. To enhance clinical usefulness, patients can be grouped into 3 risk groups: low risk (−1 and 0 points in the risk score, risk of SM 10.7%-24.6%), medium risk (score 1-2, risk of SM 47.1%-70.7%), and high risk (score 3-5, risk of SM 86.8%-98.0%). Risk groups are plotted along the x axis, and the risk of SM is plotted along the y axis (dark gray bars, lower boundary of the risk for SM in the group, ie, 10.7% in low-risk patients, 47.1% in medium-risk patients, and 86.8% in high-risk patients; light gray bars, highest boundary of the risk of SM in the group, eg, 24.6% for low-risk patients, 70.7% for medium-risk patients, and 98.0% in high-risk patients).

TABLE III. Distribution of patients according to the MIS risk score

Risk	Total MIS (n = 1410)	MIS with BMB (n = 1145)	MIS without BMB (n = 265)	CM (n = 201)	SM (n = 944)
Low risk	24.0%	17.4%	55.9%	64.9%	8.0%
−1	13.0%	8.2%	36.2%	39.7%	2.0%
0	11.0%	9.2%	19.7%	12.2%	6.0%
Medium risk	14.2%	14.5%	12.7%	21.1%	13.1%
1	10.4%	10.4%	10.6%	18.5%	8.8%
2	3.7%	4.1%	2.1%	2.6%	4.3%
High risk	61.8%	68.1%	31.4%	13.9%	78.8%
3	29.2%	30.9%	21.3%	6.6%	35.7%
4	25.1%	28.7%	7.4%	5.3%	33.3%
5	7.5%	8.5%	2.7%	2.0%	9.8%

Distribution of patients according to risk score in the total population with MIS, in patients in whom a BMB was performed (the group used to build the risk score), and in patients with MIS from the ECNM Registry who were not biopsied.

low or medium risk for SM (ie, who score 1 or 2 points in our score) for the *KIT* D816V mutation before deciding whether or not to perform a BMB. In addition, the ECNM Registry will include more data on the expression of *KIT* D816V in peripheral blood leukocytes. Whether a positive result (KIT D816V+) can improve our current score remains to be determined in future studies. We have indeed the plan to perform these studies in our ECNM Registry.

It is generally accepted that all adult patients with MIS need to have a BMB to establish the correct diagnosis (CM vs SM).[1-10] But the time of the procedure is often considered of less importance. So the real question to answer with our new proposed score may be whether a BMB can be postponed (delayed) without missing important information, or needs to be performed immediately. This question may be regarded to be a rather philosophical question. However, in the current virus pandemic, it may well be of major interest to learn whether an invasive procedure can be delayed safely or needs to be done within the next few weeks or months.

In addition, a BMB is an invasive procedure bearing a low but measurable risk for adverse events.

In the end, however, a BMB will be required for several reasons in all patients. First, only a BMB can exclude an associated hematologic neoplasm, bone marrow fibrosis, or advanced SM. Second, the diagnosis of SM must lead to a full staging at diagnosis and follow-up investigations, including osteodensitometry, to document or exclude osteoporosis, and ultrasound of liver and spleen. Most importantly, however, the prognosis concerning overall survival and progression-free survival is much better in adult patients with CM compared with patients with SM.[19,21] In fact, in patients with CM, progression is usually not seen, whereas patients with ISM, even with low MC burden, may sometimes progress to a high- grade SM. Also, a closer follow-up with respect to bone mineral density as well as prophylactic measures (ie, carrying an adrenaline pen) may be indicated more frequently in patients with ISM compared with patients with CM.

However, no prophylactic or interventional therapy for patients with ISM is known, and disease evolution can thus not be influenced, although patients at a higher risk for disease progression and a worse prognosis could be followed up more closely.

Recently, the ECNM together with REMA published a prognostic scoring system (International Prognostic Scoring System for Mastocytosis [IPSM]) for patients with systemic mastocytosis.[21] Patients older than 60 years, those with elevated alkaline phosphatase more than 100 U/L, or both had a significantly worse prognosis than those without these risk factors.[21] Similar results were seen in a second, smaller, study, which generated a risk score from 580 patients from the Mayo Clinic.[61] In our population, the IPSM was not an independent prognostic factor for SM, although numerically more patients with SM than with CM were in the intermediate-2 risk group (5.6% vs 1.6%; n = 41 vs 2 patients). A higher-risk IPSM (ie, intermediate-2 for nonaggressive mastocytosis) could influence the decision for a BMB because of a need for closer follow-up to detect progression to advanced variants of SM. However, patients with MIS at low risk for SM in our score (−1 and 0 points) are extremely unlikely to have advanced SM or an adverse prognostic profile in the IPSM.

A point of criticism of our study might be the fact that the BMB samples were not centrally reviewed and some of these samples may have been of suboptimal quality. The diagnosis of SM is easily missed if the histologic BMB sample was too short, or the aspirated marrow of insufficient quality to test for major and minor diagnostic criteria.

CONCLUSIONS

Using a large data set from the ECNM Registry, we created a simple and solid risk score for SM in patients with MIS that safely differentiates risk groups using a set of readily available parameters. We could show that there is a relevant proportion of patients at low or medium risk to have or develop SM with an equally low risk of progression, even if SM diagnosis was delayed, and who may not be in need of an immediate BMB. Under certain conditions, such score-derived information may be essential to decide whether and when a BMB should be planned.

Acknowledgments

We thank all centers and experts in the ECNM Registry group for contributing data and patients to the registry. In addition, we thank the scientific advisors of the ECNM for their contribution to the project discussion. Finally, we thank all technicians, study coordinators, study nurses, and colleagues for data entry into the registry system. Our special thanks for data management and data controlling go to Susanne Herndlhofer, Nadja Jaekel,

Bouktit Hassiba, Gabriele Stefanzl, Hana Škabrahová, Gulkan Ozkan, Tarik Tiryaki, Nicole Cabral do O, Deborah Christen, Anne Simonowski, Cecilia Spina, Agnes Bretterklieber, Orsolya Pilikta, Lilla Kurunci, Kerstin Hamberg-Levedahl, Peter Vandenberghe, Dominique Bullens, Toon Ieven, Nele Philips, Stephanie Pulfer, and Didier Ebo.

REFERENCES

1. 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.
2. Valent P, Akin C, Sperr WR, Horny H-P, Arock M, Lechner K, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol 2003; 122:695-717.
3. Horny HP, Sotlar K, Valent P. Mastocytosis: state of the art. Pathobiology 2007; 74:121-32.
4. Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112:946-56.
5. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.
6. Pardanani A. How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage). Blood 2013;121:3085-94.
7. Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. Expert Rev Hematol 2010;3: 497-516.
8. Valent P, Sotlar K, Sperr WR, Escribano L, Yavuz S, Reiter A, et al. Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. Ann Oncol 2014;25: 1691-700.
9. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. Cancer Res 2017;77:1261-70.
10. Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. Blood 2010;116:5812-7.
11. Escribano L, Álvarez-Twose I, Sánchez-Muñoz L, Garcia-Montero A, Núñez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol 2009;124:514-21.
12. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. N Engl J Med 1987;316:1622-6.
13. Akin C, Metcalfe DD. Systemic mastocytosis. Annu Rev Med 2004;55:419-32.
14. Valent P, Arock M, Bonadonna P, Brockow K, Broesby-Olsen S, Escribano L, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. Wien Klin Wochenschr 2012;124: 807-14.
15. Sperr WR, Jordan J-H, Jordan J-H, Fiegl M, Fiegl M, Dirnhofer S, et al. Serum tryptase levels in patients with mastocytosis: correlation with mast cell burden and implication for defining the category of disease. Int Arch Allergy Immunol 2002;128:136-41.
16. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med 2015;373:163-72.
17. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
18. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Álvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol 2016;137:35-45.
19. Sperr WR, Valent P. Diagnosis, progression patterns and prognostication in mastocytosis. Expert Rev Hematol 2012;5:261-74.
20. Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood 2013; 121:2393-401.
21. Sperr WR, Kundi M, Alvarez-Twose I, van Anrooij B, Oude Elberink JNG, Gorska A, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol 2019;6:e638-49.
22. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009;113:5727-36.
23. Ustun C, Reiter A, Scott BL, Nakamura R, Damaj G, Kreil S, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol 2014;32:3264-74.
24. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-41.
25. Jawhar M, Schwaab J, Naumann N, Horny HP, Sotlar K, Haferlach T, et al. Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. Blood 2017;130:137-45.
26. Elena C, Merante S, Ferretti VV, Span LCM, Górska A, Bonifacio M, et al. Selection and efficacy of cytoreductive agents in patients with mastocytosis included in the Registry of the European Competence Network on Mastocytosis (ECNM). Blood 2017;130:1650.
27. Hoermann G, Gleixner KV, Dinu GE, Kundi M, Greiner G, Wimazal F, et al. The KIT D816V allele burden predicts survival in patients with mastocytosis and correlates with the WHO type of the disease. Allergy 2014;69:810-3.
28. Trizuljak J, Sperr WR, Nekvindová L, Elberink HO, Gleixner KV, Gorska A, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy 2020;75:1927-38.
29. Kluin-Nelemans HC, Reiter A, Illerhaus A, van Anrooij B, Hartmann K, Span LFR, et al. Prognostic impact of eosinophils in mastocytosis: analysis of 2350 patients collected in the ECNM Registry. Leukemia 2020;34:1090-101.
30. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 2014; 69:1267-74.
31. González De Olano D, De La Hoz Caballer B, Núñez López R, Sánchez Muñoz L, Cuevas Agustín M, Diéguez MC, 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.
32. Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patient's perceptions of disability in mastocytosis. PLoS One 2008;3:1-14.
33. Rossini M, Zanotti R, Viapiana O, Tripi G, Orsolini G, Idolazzi L, et al. Bone involvement and osteoporosis in mastocytosis. Immunol Allergy Clin North Am 2014;34:383-96.
34. Moura DS, Georgin-Lavialle S, Gaillard R, Hermine O. Neuropsychological features of adult mastocytosis. Immunol Allergy Clin North Am 2014;34: 407-22.
35. Moura DS, Sultan S, Georgin-Lavialle S, Pillet N, Montestruc F, Gineste P, et al. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. PLoS One 2011;6:e26375.
36. Georgin-Lavialle S, Gaillard R, Moura D, Hermine O. Mastocytosis in adulthood and neuropsychiatric disorders. Transl Res 2016;174:77-85.e1.
37. Rossini M, Zanotti R, Bonadonna P, Artuso A, Caruso B, Schena D, et al. Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. Bone 2011;49:880-5.
38. van Anrooij B, Kluin-Nelemans JC, Safy M, Flokstra-de Blok BMJ, Oude Elberink JNG. Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis. Allergy 2016;71:1585-93.
39. Siebenhaar F, Von Tschirnhaus E, Hartmann K, Rabenhorst A, Staubach P, Peveling-Oberhag A, et al. Development and validation of the mastocytosis quality of life questionnaire: MC-QoL. Allergy 2016;71:869-77.
40. Bonadonna P, Rossini M, Zanotti R, Caruso B, Riccio A, Senna G, et al. Bone mineral density of patients affected by clonal mast cell disorders. J Allergy Clin Immunol 2010;125:AB183.
41. Jennings S, Russell N, Jennings B, Slee V, Sterling L. The Mastocytosis Society Survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2013;2:70-6.
42. Tanasale B, Kits J, Kluin PM, Trip A, Kluin-Nelemans HC. Pain and anxiety during bone marrow biopsy. Pain Manag Nurs 2013;14:310-7.
43. Hjortholm N, Jaddini E, Hałaburda K, Snarski E. Strategies of pain reduction during the bone marrow biopsy. Ann Hematol 2013;92:145-9.
44. Sollazzo F, Tendas A, Conte E, Bianchi MP, Niscola P, Cupelli L, et al. Bone marrow aspiration and biopsy-related pain management. Ann Hematol 2014;93: 1061-2.
45. Alvarez-Twose I, González de Olano D, Sánchez Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol 2012;157:275-80.

46. Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López 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.
47. Broesby-Olsen S, Oropeza AR, Bindslev-Jensen C, Vestergaard H, Moller MB, Siebenhaar F, et al. Recognizing mastocytosis in patients with anaphylaxis: value of KIT D816V mutation analysis of peripheral blood. J Allergy Clin Immunol 2015;135:262-4.
48. Doormaal JJ, Veer E, Voorst Vader PC, Kluin PM, Mulder AB, Heide S, et al. Tryptase and histamine metabolites as diagnostic indicators of indolent systemic mastocytosis without skin lesions. Allergy 2012;67:683-90.
49. Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. J Allergy Clin Immunol 2018;141:180-188.e3.
50. Valent P, Aberer E, Aberer E, Beham-Schmid C, Beham-Schmid C, Fellinger C, et al. Guidelines and diagnostic algorithm for patients with suspected systemic mastocytosis: a proposal of the Austrian competence network (AUCNM). Am J Blood Res 2013;3:174-80.
51. Valent P, Oude Elberink JNG, Gorska A, Lange M, Zanotti R, van Anrooij B, et al. The Data Registry of the European Competence Network on Mastocytosis (ECNM): set up, projects, and perspectives. J Allergy Clin Immunol Pract 2019;7:81-7.
52. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. Stat Med 2004;23:1631-60.
53. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci 1986;1:54-77.
54. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 2015;29:1223-32.
55. Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Møller MB. Circulating KIT D816V mutation-positive non-mast cells in peripheral blood are characteristic of indolent systemic mastocytosis. Eur J Haematol 2012;89:42-6.
56. Kristensen T, Vestergaard H, Bindslev-Jensen C, Møller MB, Broesby-Olsen S. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. Am J Hematol 2014;89:493-8.
57. Jara-Acevedo M, Teodosio C, Sanchez-Muñoz L, Álvarez-Twose I, Mayado A, Caldas C, et al. Detection of the KIT D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications. Mod Pathol 2015;28:1138-49.
58. Bai Y, Carter MC, Ruiz-esteves KN, Scott LM, Cantave D, Bolan H, et al. Detection of KIT D816V in peripheral blood of children with manifestations of cutaneous mastocytosis suggests systemic disease. Br J Haematol 2018;183:775-82.
59. Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Moller MB. Serum tryptase correlates with the KIT D816V mutation burden in adults with indolent systemic mastocytosis. Eur J Haematol 2013;91:106-11.
60. Broesby-Olsen S, Kristensen T, Vestergaard H, Brixen K, Møller MB, Bindslev-Jensen C. KIT D816V mutation burden does not correlate to clinical manifestations of indolent systemic mastocytosis. J Allergy Clin Immunol 2013;132:723-8.
61. Pardanani A, Shah S, Mannelli F, Elala YC, Guglielmelli P, Lasho TL, et al. Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. Blood Adv 2018;2:2964-72.

ONLINE REPOSITORY

ECNM AND THE ECNM REGISTRY

Background

The ECNM is a nonprofit, international collaborative group of clinicians and scientists founded in 2002 dedicated to research and treatment of mastocytosis. Its aims are to improve awareness, diagnostics, and, ultimately, treatment for this disease. Specifically, the ECNM wants to provide education for patients and their physicians, to standardize diagnostics and treatment, and to create a network of specialized centers for mastocytosis.

ECNM Centers of Excellence provide a complete spectrum of diagnostics and treatment for all subvariants of mastocytosis, and ECNM Reference Centers specialize in 1 discipline or area of interest and provide guidance for other centers in this regard.[E1,E2]

The ECNM Registry

In 2012, the ECNM established a registry study to collect data on patients with mastocytosis, with the goal of exploring the incidence, pathogenesis, natural course, and treatment response of this disease.

The registry also collects data on disease-related symptoms and their treatment, prognostic factors, and biomarkers potentially related to prognosis or symptoms.

Patients are seen at ECNM centers by the local principal investigator and their teams, and data are collected pseudonymously in a web-based system. Pseudonymization is handled locally; that is, only local investigators have access to personally identifiable patient data. Each center can view its own data but cannot access other centers' data.

The registry is sponsored by the Medical University of Vienna, which provides the IT infrastructure, the core data set, management, and updating.[E3] A central data download can be performed only by the registry coordinator, and this is done once a year. Data are stored at servers of the Austrian Control Bank (OeKB Business Services; https://ecnm-registry.oekb-bs.at), an entity that specializes in IT project management, while the data entry system was created by Asoluto, a communications and digital solutions agency (https://www.asoluto.com).

Participating centers and development of ECNM Registry projects

The ECNM Registry consortium, which consists of the coordinators and local principal investigators, regulates, selects, and distributes projects among individual centers. Based on a contract accepted by all centers, each center, independent of size, but with at least 25 patients included in the registry, can propose a project at the yearly ECNM meeting.

The board of the ECNM, which consists of the previous and current chairs of the ECNM, the ECNM coordinator, and coordinators of the ECNM Registry, prepares the distribution of projects. The decision board panel, which consists of the above board, additional experts who included more than 100 eligible patients in the registry, and members of the scientific advisory board of the ECNM, checks and approves projects. In case of dissent, a decision is reached by voting. Each center can then decide whether to allow inclusion of their patient data in each specific project.

Inclusion and exclusion criteria

Patients must have a World Health Organization–defined variant of mastocytosis to be eligible for inclusion in the registry.[E4-E6]

CM is diagnosed on the basis of published consensus criteria, which require adults with cutaneous involvement to have had a BMB to exclude SM.[E4-E12] Children do not usually require a BMB to be diagnosed with CM.[E7-E9] If, in an adult patient, no BMB was performed, a provisional diagnosis of MIS is established.

SM is diagnosed according to World Health Organization criteria.[E4-E6,E10-E12] When no B- or C-findings are found, ISM is diagnosed. If a patient has at least 2 B-, but no C-findings, the diagnosis is SSM, whereas the presence of at least 1 C-finding constitutes the diagnosis of aggressive SM. Mast cell leukemia is diagnosed when 20% or more mast cells are seen in either peripheral blood or bone marrow.[E4-E6,E10-E12]

When an additional hematological disease is diagnosed and both the criteria for this disease and SM are fulfilled, the diagnosis is SM with an associated hematological neoplasm. In extremely rare patients who do not fulfill criteria for SM, but have localized mast cell tumors with high-grade histology and destructive growth, mast cell sarcoma is diagnosed.

Only those patients who have 1 of the above, World Health Organization–defined variants of mastocytosis are included in the registry.

Ethics committee approval

All patients gave written informed consent. The study was approved by the local ethics committee at each participating center.

Patients

This study's patient cohort uses data from 24 European centers and 1 center from the United States. Patient selection for the study is summarized in a flowchart in Figure E1.

Data on diagnosis and on follow-up

Data on a number of parameters, including age, serum tryptase levels, white blood cell counts, percentage of eosinophils, platelet counts, hemoglobin, serum lactate dehydrogenase, alkaline phosphatase, performance status, presence or absence of urticaria pigmentosa–like skin lesions, presence or absence of osteoporosis (by osteodensitometry), organomegaly, known allergies, and mediator-related symptoms, were collected at diagnosis and follow-up.

At diagnosis, and, optionally, at follow-up, data on bone marrow biopsies, including cytology (Wright-Giemsa–stained smears), histology, immunohistochemistry, cytogenetics, and KIT mutational analysis, were collected.

Quality control

Quality control of the registry data is performed yearly, with checks on completeness, accuracy, and plausibility of information. Queries are then sent out, and the data set is distributed for work on the projects once all queries have been solved.

METHODS

Statistics

We established a risk score in a 3-step procedure. First, we performed a univariate analysis (χ^2 test for categorical, ANOVA for continuous variables) and included significant

variables in the second step, where we used a multivariable logistic regression with manual backwards stepwise elimination to determine the B regression coefficient and *P* values for each variable.

In the last step, we used the regression coefficients to calculate a risk score as previously described in the Framingham Heart Study.[E13] We used the smallest coefficient as a baseline, divided each coefficient by this value, and rounded it to the next lower integer value. The risk of SM was then calculated as previously described in the Framingham Heart Study for the risk of coronary heart disease.[E13]

We validated the model's and risk score's discrimination with ROC AUC (c-statistic). We plotted ROC curves (Figures E2 and E3) with −1 specifity and sensitivity along the x and y axis.

The validation cohorts consisted of 1000 bootstrapped random samples from the study population.[E14] We calculated the AUC for each sample and used the SD to determine an optimism-corrected AUC. We used the same approach for validation of the risk score and the regression model.

Model calibration, or goodness-of-fit, was determined using the Hosmer-Leweshow test. We accepted significance at *P* less than .05 and used SPSS 23 (IBM) for the analysis.

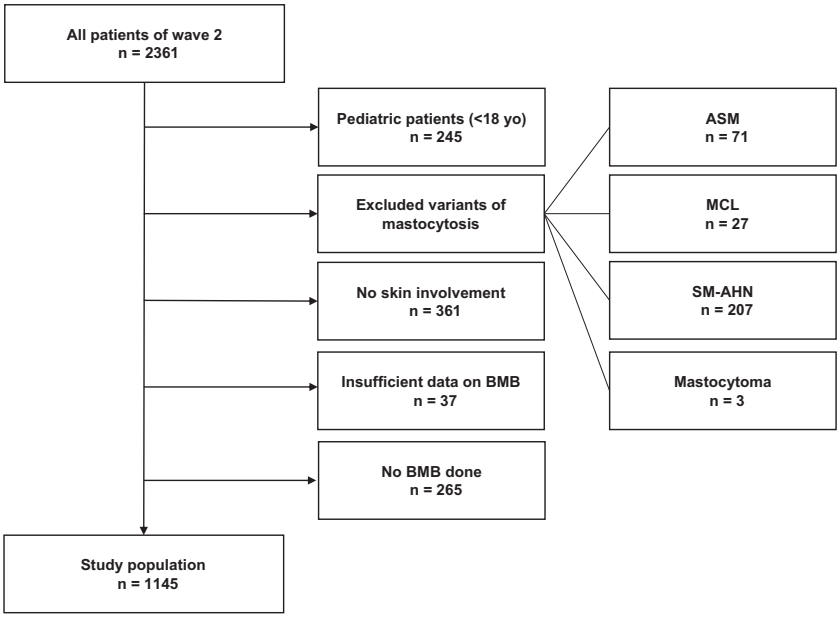

FIGURE E1. Patient groups selected from the ECNM Registry. Adult patients with MIS were included in this project. Pediatric patients (age <18 years at diagnosis), patients with aggressive variants of SM, patients with mastocytoma, patients without skin involvement, and patients who either had no bone marrow biopsy done or had insufficient documented data on their bone marrow biopsy were excluded. *ASM*, Aggressive SM; *SM-AHN*, SM with an associated hematological neoplasm; *yo*, year old.

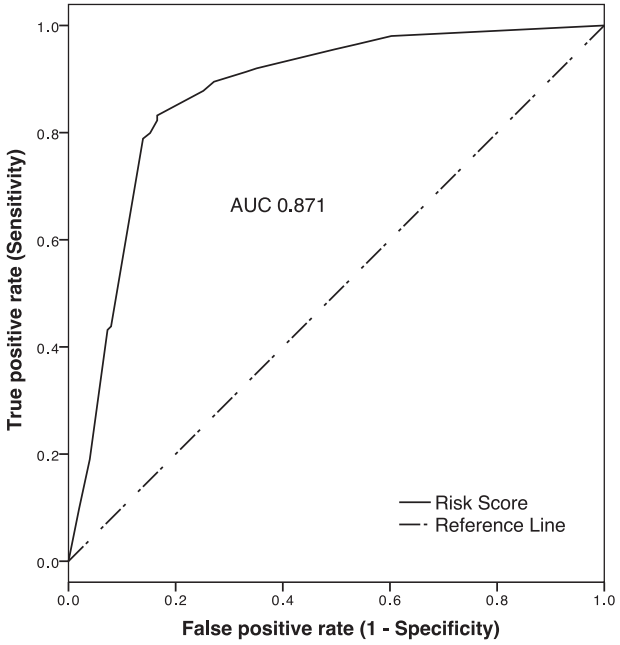

FIGURE E2. ROC curve for regression model. The model's and risk score's ability to correctly classify patients with SM was evaluated with the area under the ROC curve (c-statistic). Shown here is the ROC curve for the regression model with −1 specifity and sensitivity along the x and y axis (AUC = 0.871). AUC can take values between 0.5 and 1.0, in which higher values show a better performance of the model.

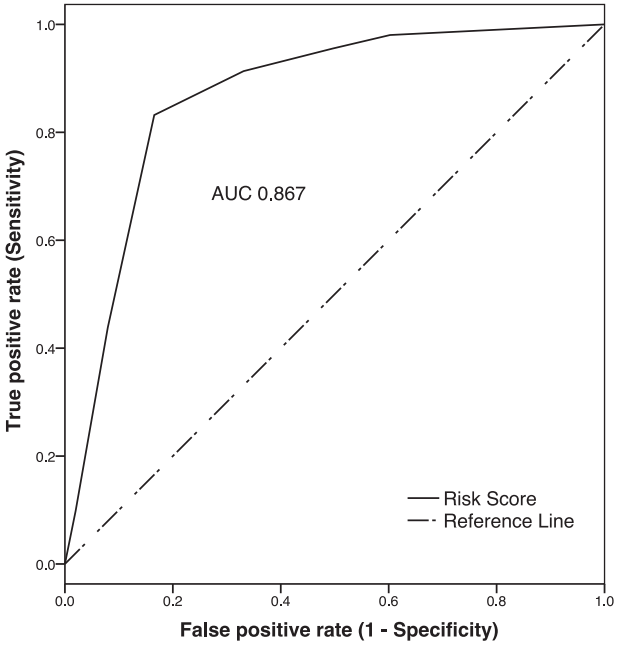

FIGURE E3. ROC curve for risk score. The model's and risk score's ability to correctly classify patients with SM was evaluated with the area under the ROC curve method (c-statistic). Shown here is the ROC curve for the risk score with −1 specifity and sensitivity along the x and y axis (AUC = 0.867). AUC can take values between 0.5 and 1.0, in which higher values show a better performance of the model.

TABLE E1. Baseline characteristics of the study population

Characteristic	%	n	n (total)
Female sex	63.7	729	1145
WHO performance status <2	97.6	1015	1040
Maculopapular skin lesions	97.6	712	790
Darier's sign positive	90.1	712	790
Symptoms: skin	81.4	899	1104
Symptoms: constitutional/ cardiovascular	23.7	259	1093
Symptoms: bone pain/ osteoporosis	38.4%	382	996
Symptoms: gastrointestinal	39.0%	431	1106
Symptoms: headache	10.9%	124	1142
Any symptoms	90.7%	863	951
Any symptoms (nonskin)	65.5%	632	965

	Median ± SD	95% CI	
Age (y)	44.0 ± 13.3 (range, 18-81)	24.0-67.0	1145
Skin involved	50% ± 27.0%	8.0%-90.0%	615
Serum tryptase (ng/mL)	29.3 ± 81.9	5.0-199.6	1068

WHO, World Health Organization.

TABLE E2. Existing risk scores for patients without MIS

Author	Patients	n	Variables	S/S
Alvarez-Twose[E15,E16] (2010, 2012)	Mast cell activation symptoms	83 (+120 validation)	Tryptase <15 and >25, urticaria, angioemeda, (pre)syncope, sex	92%/81%
Carter et al[E17] (2018)	Patients with idiopathic anaphylaxis	56	Tryptase < or >11.4 ng/mL, urticaria, flushing, syncope, angioedma, KIT D816V PCR, sex	75%/100%
Broesby-Olsen et al[E18] (2015)	Anaphylaxis	113	KITD816V PCR	NA
Van Doormaal et al[E19] (2012)	Clinical suspicion of SM	142	Tryptase < or ≥10 ng/mL, urinary histamine metabolites	NA

REFERENCES

E1. Valent P, Arock M, Bischoff SC, Bühring HJ, Brockow K, Escribano L, et al. The European Competence Network on Mastocytosis (ECNM). Wien Klin Wochenschr 2004;116:647-51.
E2. Valent P, Arock M, Bonadonna P, Brockow K, Broesby-Olsen S, Escribano L, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. Wien Klin Wochenschr 2012;124:807-14.
E3. Valent P, Oude Elberink JNG, Gorska A, Lange M, Zanotti R, van Anrooij B, et al. The Data Registry of the European Competence Network on Mastocytosis (ECNM): set up, projects, and perspectives. J Allergy Clin Immunol Pract 2019; 7:81-7.
E4. Valent P, Horny HP, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, et al. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2001. p. 291-302.
E5. Horny HP, Metcalfe DD, Bennett JM, Bain BJ, Akin C, Escribano L, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffee ES, Pileri SA, Stein H, et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 2008. p. 54-63.
E6. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-405.
E7. 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.
E8. Valent P, Akin C, Escribano L, Födinger 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.
E9. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol 2016;137:35-45.
E10. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. J Invest Dermatol 1991;96:2S-4S.
E11. Valent P. Biology, classification and treatment of human mastocytosis. Wien Klin Wochenschr 1996;108:385-97.
E12. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol 2003; 122:695-717.
E13. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. Stat Med 2004;23:1631-60.
E14. Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Stat Sci 1986;1:54-77.
E15. Alvarez-Twose I, González de Olano D, Sánchez Muñoz L, Matito A, Jara-Acevedo M, Teodosio C, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol 2012;157:275-80.
E16. Alvarez-Twose I, de Olano DG, Sánchez-Muñoz L, Matito A, Esteban-López 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.
E17. Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. J Allergy Clin Immunol 2018;141:180-188.e3.
E18. Broesby-Olsen S, Oropeza AR, Bindslev-Jensen C, Vestergaard H, Møller MB, Siebenhaar F, et al. Recognizing mastocytosis in patients with anaphylaxis: value of KIT D816V mutation analysis of peripheral blood. J Allergy Clin Immunol 2015;135:262-4.
E19. Van Doormaal JJ, Van Der Veer E, Van Voorst Vader PC, Kluin PM, Mulder AB, van der Heide S, et al. Tryptase and histamine metabolites as diagnostic indicators of indolent systemic mastocytosis without skin lesions. Allergy 2012;67:683-90.