

ORIGINAL ARTICLE

Skin and Eye Allergy

Development and validation of the mastocytosis activity score

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Abstract

Background: Mastocytosis is a heterogeneous disease characterized by a clonal expansion of mast cells in various organs. The vast majority of patients suffer from signs and symptoms caused by mediator release from mast cells. Although the disease burden is high, there is currently no specific and validated instrument to measure and monitor signs and symptoms in patients with mastocytosis.

Objective: To develop and validate a disease-specific tool to measure and monitor the activity of signs and symptoms in patients with mastocytosis, the Mastocytosis Activity Score (MAS).

Methods: Nineteen potential MAS items were developed in a combined approach consisting of semi-structured patient interviews, expert input and literature research. Item selection was performed by impact analysis with 76 patients followed by a review for face validity. The resulting MAS was tested for validity, reliability and influence factors. In parallel, a US American English version of the MAS was developed.

Results: A total of 68 mastocytosis patients took part in the MAS validation study. The final 9-item MAS was found to have a three-domain structure ("skin," "gastrointestinal tract" and "other"), a valid total score and an excellent test-retest reliability. Multiple regression analysis revealed that disease duration, age or gender is not a significant determinant of the MAS results.

Conclusions: The MAS is a disease-specific, valid and reliable patient-reported outcome measure for adult patients with cutaneous and indolent systemic mastocytosis. It may serve as a valuable tool to measure and monitor mastocytosis activity, both, in clinical trials and in routine care.

KEYWORDS

disease activity, mastocytosis, patient-reported outcome, questionnaire, symptoms

1 | INTRODUCTION

Mastocytosis is characterized by an excessive increase in the number of mast cells (MCs) in different tissues. Most often, the skin and the

bone marrow are involved, but MC infiltrates may also be found in other organs, for example the spleen, liver, lymph nodes and the gastrointestinal tract.^{1,2} Signs and symptoms result either from organ infiltration or, more frequently, from the release of pro-inflammatory MC mediators, including histamine, platelet activating factor (PAF), prostaglandins, leukotrienes and cytokines.³⁻⁷ Whereas in cutaneous mastocytosis (CM), the increase in MC numbers is limited to the skin, systemic mastocytosis is characterized by the accumulation of

Abbreviations: CM, Cutaneous mastocytosis; HRQoL, Health-related quality of life; ISM, Indolent systemic mastocytosis; MAS, Mastocytosis Activity Score; MIS, Mastocytosis of the skin; PRO, Patient-reported outcome; SSM, Smouldering systemic mastocytosis.

neoplastic MCs in the bone marrow and/or other extracutaneous organs.^{1,8,9} The majority of adult patients presents with indolent systemic mastocytosis (ISM) and commonly shows symptoms resulting from MC mediator release, including pruritus, flushing, headaches, muscle/joint pain, gastrointestinal symptoms and anaphylaxis.¹⁰⁻¹⁵ Accordingly, many mastocytosis patients experience a major impairment of their quality of life¹⁶ and require continuous treatment, aimed at the prevention of MC mediator-induced signs and symptoms.

Symptom control is an important goal in the management of patients with mastocytosis, and validated patient-reported outcome (PRO) instruments such as symptom scores are becoming increasingly important in, both, clinical trials and routine care. Patient-reported outcome tools determine the unfiltered patient perspective on diseases and their impact and prevent a loss of useful information that may occur in the case of isolated clinician evaluations.¹⁷ Therefore, it is strongly recommended by leading health authorities to include PRO instruments into the study design of randomized controlled trials.^{17,18}

Here, we report the development and validation of a disease-specific tool for use in adult patients with cutaneous and ISM, the Mastocytosis Activity Score (MAS).

2 | METHODS

The development of the MAS consisted of three major phases: (i) item generation, (ii) item selection and (iii) MAS validation.

2.1 | MAS item generation

Mastocytosis Activity Score item generation was performed following current recommendations for the development of PRO instruments.^{19,20} In the first step, mastocytosis-related symptoms that should be assessed by the MAS were specified and criterion measures of mastocytosis symptoms and impact (anchors) to be used for the evaluation of the MAS performance were defined. To identify and generate potential items for the MAS, a combined approach of three strategies was applied as follows: (i) exploratory semi-structured interviews with 10 patients suffering from CM ($n = 3$) or ISM ($n = 7$). Interviews also served for the item generation of the Mastocytosis Quality of Life Questionnaire MC-QoL, which was developed and validated in a parallel study.²¹ (ii) A literature search for published data on mastocytosis-related symptoms and (iii) mastocytosis expert opinions on potentially relevant items. Item responses were designed as 5-point Likert scales with the answer options "not at all," "mild," "moderate," "severe" and "very severe." Mastocytosis Activity Score was designed as a single level item tool on intensity of signs and symptoms. To prove that this single level approach is sufficient, we expanded the levels of items to explore the impact of frequency and duration of signs and symptoms, each on a 4-point Likert scale for signs and symptoms that reached a score on the intensity level with the answer

Highlights

- Mastocytosis Activity Score is a valid and reliable instrument to assess the activity of disease in mastocytosis patients.
- Mastocytosis Activity Score helps to improve the quality and performance of future clinical trials.
- Mastocytosis Activity Score allows to determine and monitor the level and profile of disease activity in individual mastocytosis patients.

options "1-2," "3-4," "5-6," ">6" times for frequency and "<1 hour," "1-6 hours," "7-12 hours," ">12 hours" within the last 24 hours assessed over 7 days.

2.2 | MAS item selection

Item selection (reduction) was performed by impact analysis in combination with a review of its results for face validity (content validity). As for the development of MC-QoL, all signs and symptoms identified in the item generation phase were administered to 76 mastocytosis patients (55 females; mean age $\pm$ SD: 51.6 $\pm$ 13.5 years, median: 52.5, range: 20-77) recruited from the outpatient clinic at the Department of Dermatology and Allergy, Charité — Universitätsmedizin Berlin, Germany.²¹ The patients completed all potential MAS items and subsequently evaluated their relevance and importance (impact analysis).

2.2.1 | Impact analysis

An impact analysis was performed to exclude all potential MAS items with a low impact score. To this end, the participating patients evaluated the importance of each potential item (response options: 1 = not important to 5 = extremely important) and specified whether they had experienced the item content during the last year (response options: yes or no). Each item's "importance" and "frequency" were computed as the mean of all response values and the proportion of patients who experienced the item content divided by 100, respectively. The "impact" score of each item was calculated by multiplication of its "frequency" and "importance."

2.2.2 | Expert review for face validity and regression analysis

As a final step of item selection, the impact analysis was complemented by a review of the expert working group. The face validity assessment suggested an "impact" score of 1.6 points as the best suitable cut-off value for item selection. All items that reached this score were included in the final MAS, unless they were redundant to other selected items or the face validity assessment clearly argued against an inclusion.

2.3 | MAS validation

A total of 68 patients with mastocytosis recruited by the Mastocytosis outpatient clinic were included in the MAS validation phase (Table 1). Ethics committee approved the study and all patients provided written informed consent (EA1/187/12). All participating patients were asked to complete the validation study survey twice in an interval of 6 weeks. Patients answered the MAS items on a daily basis over a 7-day period. The survey consisted of all final MAS items, a patient global assessment of patients' disease severity (PGA disease severity), mastocytosis-related QoL impairment (PGA-QoL) during the previous 2 weeks (4-point Likert scales), the MC-QoL, the 12-item Short Form Survey (SF-12) and questions on patient characteristics, that is age, gender and disease duration.

2.3.1 | MAS computation

The five answer options of each MAS item were scored from 0 to 4 points. For the validation study, total and domain raw values of the MAS were calculated by summing all relevant item values over 7 consecutive days (total score range 0-252 points). Subsequently, all raw values were linearly transformed to a 0-100 scale, with higher values indicating a higher burden and activity of symptoms. In the case of missing items, the total of the items in each domain was

TABLE 1 Patient sample characteristics of Mastocytosis Activity Score validation study

	n	%
Gender		
Female	51	75.0
Male	17	25.0
Age		
18-30 y	5	7.4
31-50 y	19	27.9
51-70 y	37	54.4
>70 y	7	10.3
Diagnosis		
Cutaneous mastocytosis (CM)	17	25.0
Prediagnosis mastocytosis in the skin (Mastocytosis of the skin)	13	19.1
Indolent systemic mastocytosis + cutaneous manifestation (ISMs ⁺)	28	41.2
Indolent systemic mastocytosis without cutaneous manifestation (ISMs ⁻)	7	10.3
Smouldering systemic mastocytosis (SSM)	1	1.5
Systemic mastocytosis with associated neoplasm (SM-AHN)	2	2.9
Duration of mastocytosis		
<5 y	13	19.1
5-10 y	28	41.2
11-20 y	18	26.5
>20 y	9	13.2

related to the number of nonmissing items. A total value was not computed when >25% of items were missing. More than 25% missing items were identified in 3 cases during the first assessment and in 12 cases during the second (retest) assessment.

2.3.2 | Exploratory factor analysis

To determine the domain structure of the MAS, we performed an exploratory factor analysis. The approach chosen was a principal component analysis with Promax rotation.²²⁻²⁵ The criterion chosen to determine factors (domains) was an eigenvalue ≥ 0.5 . Items were assigned to the domains for which they showed the highest factor loading.

2.3.3 | Internal consistency reliability

Internal consistency measures the homogeneity of total and domain scores. The internal consistency reliability of the MAS total value and its domain values were assessed by computing Cronbach's α coefficient. A commonly suggested interpretation of Cronbach's α coefficient values is: <0.60: unacceptable; 0.60-0.65: undesirable; 0.65-0.70: minimally acceptable; 0.70-0.80: respectable; 0.80-0.90: excellent; >0.90: excessive consistency.²⁶

2.3.4 | Convergent validity

To assess the convergent validity of MAS, we correlated its total and domain values (Pearson correlation) with different anchors for disease severity and health-related quality of life (HRQoL), that is PGA disease severity, PGA-QoL, the MC-QoL and the 12-item Short Form Survey (SF-12). The SF-12 is a generic tool to assess disease burden.²⁷ It is a short form of the 36-item Short Form Survey (SF-36), and its results are expressed as a physical component summary (PCS) and a mental component summary (MCS), each ranging from 0 to 100 points, with higher scores indicating a higher self-reported health. PGA disease severity and PGA-QoL were assessed on 4-point Likert scales. MC-QoL is a mastocytosis-specific QoL instrument consisting of 27 items in 4 domains ("symptoms," "functioning/social life," "emotions" and "skin") with a recall period of 2 weeks. MC-QoL can be computed as domain scores or total score, each ranging from 0 to 100 points, with higher scores indicating a higher impairment of life quality.²¹

2.3.5 | Known-groups validity

The known-groups validity of the MAS was determined by calculating and comparing the total value and its distribution in patients with different levels of disease severity (PGA disease severity).

2.3.6 | Test-retest reliability

The test-retest reliability of the MAS was examined in a subgroup of patients, who completed all items twice in an interval of not less

than 6 weeks. The mean values of the first and second assessments were compared. In addition, the intraclass correlation coefficient (ICC) was computed. An ICC of 0.5–0.7 was considered to indicate moderate-to-good reproducibility, and an ICC of greater than 0.7 was considered to demonstrate excellent reproducibility.²⁴

2.3.7 | Multiple linear regression analysis

Multiple linear regression was used to detect factors that influence MAS values. Age (in years), gender and duration of disease (in months) were included as independent variables, the MAS total value was set as dependent variable.

2.3.8 | Development of an US American English version

Two independent forward translations of the original German MAS version to US American English (AE) were performed by native AE speakers bilingual in German. The two forward translations were reconciled by national US American experts and subsequently back-translated by a German native speaker bilingual in AE. The backward translation was then reviewed against the original German version and the German team and the US American experts agreed on a final US AE consensus version.

2.4 | Statistical analysis

All statistical analyses were performed using SPSS (IBM SPSS Statistics version 22, IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | MAS development

The item generation phase resulted in 19 items possibly relevant to patients with mastocytosis. For item selection, the impact of each item was computed (Table S1). Ten items with an impact score < 1.6 were excluded. An exception was made for the item p7 ("abdominal cramps") that failed the cut-off but covers relevant symptoms. After discussions in the expert working group, item p7 was not removed for reasons of face (content) validity. In addition, the expert group recommended to exclude the item p10 ("sweating attacks") despite an impact score > 1.6 due to an overlap with p2 ("flushing episodes"). Subsequently, 9 items remained in the final MAS.

To evaluate the impact of the frequency and duration of signs and symptoms occurring over the day, additional exploratory items on frequency and duration were included during MAS development and validation. Pearson's correlation and testing of exploratory items on frequency and duration of signs and symptoms revealed very high correlation to the intensity item alone. Thus, answers on frequency and duration in addition to intensity were found to be redundant and confirmed that the single level of items on intensity is sufficient (Table S4).

3.2 | MAS validation and first results

The final 9-item MAS was used in the validation study that included 68 adult patients with mastocytosis. Table 1 shows the demographic and clinical data of this population.

3.2.1 | Exploratory factor analysis

Exploratory factor analysis identified a three-domain structure of the questionnaire (Table 2) that explained 78.8% of its variance. According to the content of the domains, these received the headings "skin," "gastrointestinal tract" and "other." All items could be clearly assigned to one domain. In a final review of the domain structures, the expert working group regarded no further changes as necessary. The final German version and US American English version of MAS can be found as supporting information (Figures S1 and S2).

3.2.2 | Internal consistency reliability

The internal consistency of the MAS total value and each MAS domain was tested by computing Cronbach's α coefficient (Table 3). Its value was > 0.8 for all domains, indicating their excellent internal consistency. The Cronbach's α coefficient for the whole instrument was 0.85, which indicates that it is appropriate to calculate a total value in addition to the domain values.

3.2.3 | MAS results

The distribution of MAS total and domain values of the mastocytosis population investigated in the validation study are shown in Figure 1. The domains "skin," "gastrointestinal tract" and "other" showed well-balanced mean values (Figure 1A). The exact mean MAS values $\pm$ SD were 19.5 ± 14.5 (total score), 19.5 ± 17.9 (domain "skin"), 14.1 ± 16.7

TABLE 2 Exploratory Factor analysis

Item	Factor 1 (Skin)	Factor 2 (Gastrointestinal tract)	Factor 3 (Other)
Itching	0.936	−0.103	−0.017
Wheals	0.822	0.020	−0.108
Flush episodes	0.561	0.071	0.224
Diarrhoea	−0.060	0.946	−0.073
Abdominal cramps	0.030	0.817	0.065
Muscle or joint pain	0.245	0.134	0.539
Fatigue	−0.071	0.021	0.922
Headache	0.040	0.031	0.669
Difficulty in concentrating	−0.084	−0.124	0.994

The 3-domain structure, skin, gastrointestinal tract and other of the final 9-item Mastocytosis Activity Score, was identified by exploratory factor analysis. Items were assigned to the domains for which they showed the highest factor loading. Items with a factor loading > 0.5 are printed in bold.

TABLE 3 Item overview and internal consistency of the Mastocytosis Activity Score

Domain	Item	Cronbach's α
Skin	Itching	0.83
	Wheals	
	Flush episodes	
Gastrointestinal tract	Diarrhoea	0.86
	Abdominal cramps	
Other	Muscle or joint pain	0.86
	Fatigue	
	Headache	
	Difficulty in concentrating	
Total instrument		0.85

(domain "gastrointestinal tract") and 22.2 ± 20.1 (domain "other"). The distributions of the total and domain values were broad. When comparing the different mastocytosis subtypes, the total mean values also were well-balanced. However, significant differences between the groups were detected during the first assessment (Figure 1B; ANOVA $P = 0.02$) but not the second (retest) assessment (Figure 1C).

3.2.4 | Convergent validity

To test for the convergent validity of the MAS, we correlated the MAS total and domain values with the results of the anchor instruments PGA disease severity, PGA-QoL, MC-QoL, and SF-12 PCS and MCS, (Table 4). All correlations were significant and in the expected direction. The correlations between the MAS total value and the total values of the applied anchors were all good ($r > 0.5$).

3.2.5 | Known-groups validity

The MAS total values were found to well discriminate between patients with different levels of disease severity (Table 5). The MAS

total values increased with increasing disease severity (PGA disease severity). In addition, the MAS total values of the interquartile range of the different levels of disease severity did not significantly overlap.

3.2.6 | Test-retest reliability

Data of 55 patients were available for the computation of the test-retest reliability. The mean MAS values of the first and second assessment, which showed well-balanced results, are depicted in Table S2. Figure 1B,C shows the distribution of MAS values between different mastocytosis subtypes. Whereas a statistically significant difference between the groups was found in the initial assessment ($n = 63$, ANOVA $P = 0.02$), the retest analysis did not reveal statistical difference ($n = 55$, ANOVA $P = 0.16$). The intraclass correlation coefficient (ICC) was 0.91 for the MAS total value and >0.8 for the MAS domains "gastrointestinal tract" and "other," indicating excellent reproducibility. Only the ICC of the "skin" domain was slightly lower (0.75), but still indicated excellent reproducibility.

3.2.7 | Influence factors of the MAS total value

In multiple linear regression analyses, neither age, gender nor duration of disease was found to significantly influence the MAS total value (Table S3).

4 | DISCUSSION

Many patients with mastocytosis have a high burden of signs and symptoms and severely impaired QoL.¹⁶ Research in this field is currently hampered by the lack of appropriate and validated PRO instruments.^{3,28} We recently reported the development and validation of the Mastocytosis Quality of Life questionnaire (MC-QoL), a

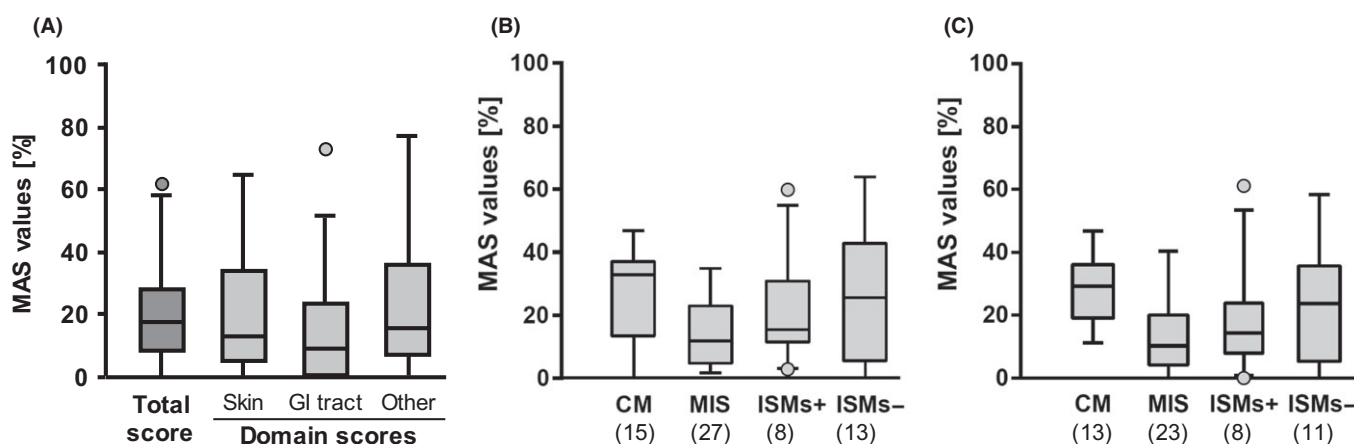


FIGURE 1 Mastocytosis Activity Score results. The domains "skin," "gastrointestinal tract" and "other" showed well-balanced mean values (A). When comparing the different mastocytosis subtypes (CM, Mastocytosis of the skin, ISMs+, ISMs-), the total mean values also were well-balanced. However, significant differences between the groups were detected during the first (B, $n = 63$, ANOVA $P = 0.02$) but not the retest (C, $n = 55$, ANOVA $P = 0.16$) assessment. The total patient numbers of each subtype are displayed in brackets. Patients with SM-AHD and Smouldering systemic mastocytosis were not included in this analysis

TABLE 4 Mastocytosis Activity Score values correlated significantly with other instruments assessing mastocytosis severity and impairment of quality of life: PGA, MC-QoL, SF12

	MAS values			
	Total score	Skin	Gastrointestinal tract	Other
PGA				
Disease severity	0.751**	0.615**	0.390**	0.642**
QoL impairment	0.676**	0.495**	0.340**	0.622**
MC-QoL				
Total score	0.876**	0.581**	0.462**	0.837**
Symptoms	0.824**	0.433**	0.423**	0.868**
Emotions	0.568**	0.373**	0.344**	0.527**
Social life/Functioning	0.774**	0.489**	0.450**	0.739**
Skin	0.711**	0.896**	0.196	0.470**
SF12 ^a				
MCS	−0.524**	−0.283*	−0.365**	−0.512**
PCS	−0.645**	−0.419**	−0.281*	−0.652**

PGA, patients global assessment; MCS, mental component summary; PCS, physical component summary; MAS, Mastocytosis Activity Score.

Correlations were computed between the MAS values and the PGA disease severity, PGA-QoL, MC-QoL scores and the SF12 (12-Item Short Form Survey) component scores. The results are expressed as Pearson's correlation coefficients.

^aCorrelations with the SF-12 are negative, because, in contrast to MAS, lower scores in this instrument represent a stronger QoL impairment.

* $P < 0.05$; ** $P < 0.01$.

TABLE 5 The Mastocytosis Activity Score (MAS) total values were found to well discriminate between patients with different levels of disease severity

Patients global assessment ^a	n	MAS total value mean $\pm$ SD (median)	1st quartile	3rd quartile
Disease severity				
None	3	2.9 $\pm$ 5.0 (0)	0	4.4
Mild	34	11.0 $\pm$ 6.9 (10.3)	5.7	16.4
Moderate	20	28.1 $\pm$ 8.8 (26.6)	21.7	34.7
Severe	8	42.4 $\pm$ 12.8 (41.3)	33.3	49.7

The results are expressed as MAS total values in relation to the patients self-rated disease severity.

^awith regard to the previous 2 wk.

disease-specific tool to measure HRQoL impairment in patients with CM and ISM.²¹ Here, we report the development and validation of the MAS, a 9 item PRO instrument for the assessment of disease activity in patients with mastocytosis. Use of the MAS allows for an overall assessment of disease activity, reflected by the total score value, and it yields domain-specific information on gastrointestinal, cutaneous and other signs and symptoms. The validation study demonstrates high levels of validity and reliability for the MAS. In addition, the MAS is easy to administer and fast to complete.

The MAS was found to have a valid total value as well as 3 domain values ("skin," "gastrointestinal tract" and "other"), all characterized by high levels of internal consistency. The "other symptom" domain, including the symptoms "muscle or joint pain," "fatigue/exhaustion," "headache" and "difficulty concentrating," was not further subdividable. Accordingly, the MAS can be used as an instrument to measure overall activity of mastocytosis signs and symptoms by assessing the total value, but may also be used to assess the profile of activity by determining the three domain scores.

Our results obtained in the MAS validation study suggest that its three domains are quite homogeneously affected in patients with mastocytosis, because the differences between the mean domain values were rather small (between 14.1 and 22.9 points). The distributions of the MAS total and domain values were broad, demonstrating that a considerable variation of the disease activity exists in mastocytosis patients. In addition, it shows that the patient population included in the study consisted of patients with different levels of disease sign and symptom activity, well-corresponding to the real-life clinical situation.

The convergent validity of the MAS was found to be good. The MAS values strongly and significantly correlated with the results of all anchor tools. This indicates that the MAS indeed measures what it intends to measure.

Important criteria for the validity and reliability of a PRO instrument are its ability to distinguish different patient groups (known-groups validity) as well as to yield stable results when applied twice in short intervals (test-retest reliability), that is in stable patients. Notably, the mean MAS total values were found to be clearly different in patients with mastocytosis exhibiting different levels of disease severity and mastocytosis-related QoL impairment. Mean MAS total scores of 11.0, 28.1 and 42.4 points are found in patients who self-rated their overall disease severity "mild," "moderate" and "severe," respectively. This may help to interpret the MAS results in individual patients. Mastocytosis Activity Score total values of the interquartile range of the different levels of disease severity did not overlap, which further stresses the good discriminative ability of the MAS. The test-retest reliability of the MAS was generally excellent. All MAS domains showed a high level of reproducibility within the minimum interval of 6 weeks between the first and second assessment during the validation study.

Multiple linear regression analysis identified neither age, gender nor disease duration as important influence factor of the MAS total score values. This indicates that the MAS is able to measure the activity of mastocytosis signs and symptoms independently of these factors.

Limitations of this work include that our study was performed in one specialized centre in Germany but not in populations of other cultural and ethnic backgrounds and different levels of medical care, which may have led to a selection bias. However, this may affect the absolute values of the MAS, but should be of minor impact on the results on the levels of validity and reliability of the instrument. The MAS applied in this study was developed and validated in patients with CM or ISM, but not in patients with advanced categories of mastocytosis such as ASM or MCL. Only one patient with

Smouldering systemic mastocytosis (SSM) or two SM-AHN took part in the MAS validation. Therefore, it is currently unclear how well the MAS works in patients with ASM, MCL, SSM or SM-AHN. Particularly, signs and symptoms may significantly differ in these types of mastocytosis as compared to CM, Mastocytosis of the skin (MIS) and ISM. It should also be noted that the selected study population did not include children and adolescents. Therefore, it is currently unclear if the results of this work could be transferred to minors. Finally, the MAS responsiveness and minimal clinically important difference have not yet been assessed. Projects to assess these properties of the MAS are ongoing.

In conclusion, the MAS is a valid and reliable instrument to assess the activity of disease in mastocytosis patients. It may help to improve the quality and performance of future clinical studies, but may also help to determine and monitor the extent and profile of disease activity in individual patients. As of yet, only German and US American English versions of the MAS are available. A linguistic validation and cross-cultural adaptation for other countries and languages are encouraged to make it a multi-national tool for the conduction of international, multicentre clinical trials and for the use in clinical practice.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors provided significant contribution to the manuscript by collecting data and providing scientific input. All authors gave significant input and were involved in developing the instrument and writing the manuscript. F.S., B.S. and L.H. collected the data. A.E., F.S. and K.W. performed statistical analyses.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Supplemental Figure 1. German version of MAS.

Mastozytose-Aktivitäts-Score – MAS

Anleitung: Bitte schätzen Sie einmal täglich abends die Schwere Ihrer mit der Mastozytose-Beschwerden über die vergangenen 24 Stunden an 7 aufeinander folgenden Tagen ein. Bitte geben Sie für jede der Beschwerden nur eine Antwort pro Tag an.

		Wie schätzen Sie die Schwere ihrer heutigen Beschwerden ein?							
	Tag	1	2	3	4	5	6	7	
Juckreiz	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Rötungen und Schwellungen der Haut (Quaddeln)	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Erröten des Gesichtes mit Hitzegefühl (Flush-Episoden)	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Diarrhoe (Durchfall)	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Bauchschmerzen	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Gliederschmerzen (Muskel- oder Gelenkschmerzen)	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Müdigkeit/Abgeschlagenheit	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Kopfschmerzen	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
Konzentrationsschwierigkeiten	gar nicht	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderat	☐	☐	☐	☐	☐	☐	☐	
	stark	☐	☐	☐	☐	☐	☐	☐	
	sehr stark	☐	☐	☐	☐	☐	☐	☐	
									Total MAS (0-252)

Supplementary Figure 2. American-English version of MAS

Mastocytosis Activity Score – MAS

Instructions: Please assess the severity of your symptoms associated with mastocytosis once daily in the evening over the last 24 hours on 7 consecutive days. Please select one of the five answers for each symptom per day.

		How do you assess the severity of your today's symptoms?							
	Day	1	2	3	4	5	6	7	
Itching	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Skin redness/swelling (wheals)	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Sudden feeling of warmth and reddening of the face (Flush episodes)	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Diarrhea/loose stools	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Abdominal cramps	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Muscle or joint pain	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Fatigue/exhaustion	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Headache	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
Difficulty concentrating	not at all	☐	☐	☐	☐	☐	☐	☐	(0-28)
	mild	☐	☐	☐	☐	☐	☐	☐	
	moderate	☐	☐	☐	☐	☐	☐	☐	
	severe	☐	☐	☐	☐	☐	☐	☐	
	very severe	☐	☐	☐	☐	☐	☐	☐	
									Total MAS (0-252)

Supplement Table 1. Impact analysis of potential MAS items. Impact analysis and face validity by the expert group selected 9 final MAS items (*italic*) from 19 potential items (high impact scores (>1.6, **bold**) from 68 patients.

Item no.*	Item	Frequency	Importance (mean)	Impact
<i>p1</i>	<i>Itching</i>	0.778	3.33	2.59
<i>p2</i>	<i>Skin redness</i>	0.883	3.51	3.10
<i>p3</i>	<i>Flush episodes</i>	0.559	3.02	1.69
<i>p4</i>	<i>Diarrhoea</i>	0.583	2.76	1.61
p5	Nausea	0.458	2.50	1.15
p6	Flatulence	0.525	2.62	1.38
<i>p7</i>	<i>Abdominal cramps</i>	0.517	2.48	1.28
<i>p8</i>	<i>Fatigue</i>	0.770	3.05	2.35
p9	Palpitation	0.559	2.82	1.58
p10	Sweating attacks	0.614	2.64	1.62
p11	Dyspnoea	0.475	2.58	1.23
p12	Dizziness	0.508	2.73	1.39
<i>p13</i>	<i>Headache</i>	0.600	2.74	1.64
<i>p14</i>	<i>Muscle or joint pain</i>	0.705	2.97	2.09
<i>p15</i>	<i>Difficulty in concentrating</i>	0.593	2.88	1.71
p16	Hot flushes	0.576	2.54	1.46
p17	Forgetfulness	0.550	2.52	1.39
p18	Mood swings	0.607	2.47	1.50
p19	Hypertension	0.534	2.61	1.39

*The p in the item number indicates that these items are potential MAS items

Supplement Table 2. Test-retest reliability of the MAS. A subsample of 64 mastocytosis patients completed the MAS twice in an interval of 6 weeks. The intraclass correlation coefficient (ICC) >0.7 corresponds to excellent reproducibility.

MAS	Mean score ± SD (median) 1st assessment	Mean score ± SD (median) 2nd assessment	ICC
Total score	19.8 ± 14.4 (17.9)	21.0 ± 15.2 (18.9)	0.912
Skin	19.4 ± 17.7 (13.7)	20.4 ± 16.0 (19.1)	0.749
Gastrointestinal tract	14.1 ± 16.6 (8.0)	15.7 ± 18.1 (12.5)	0.866
Other	22.9 ± 20.2 (18.7)	24.1 ± 20.7 (19.6)	0.942

Supplement Table 3. Influence factors of the MAS. Multiple linear regression analysis identified duration of disease, age and gender not as significant influence factors of the MAS total value.

	Unstandardized Coefficient B	Standard Error	<i>p</i>-value
Age (in years)	-0.024	0.142	0.864
Gender	-7.366	4.301	0.093
Disease duration (in month)	0.003	0.019	0.876

Supplementary Table 4. Frequency and duration of symptoms were excluded from MAS due to high correlation and redundancy to intensity. Based on Pearson's correlation and testing the additional questions on frequency and duration of symptoms were found to be redundant. The p-values were consistently smaller than 0.001 and therefore highly significant. The table shows the correlation values of the symptom intensity with their according frequency and duration.

Intensity	Frequency	Duration
Itching	0.91	0.92
Wheals	0.89	0.86
Flush episodes	0.92	0.92
Diarrhoea	0.94	0.89
Abdominal cramps	0.94	0.93
Muscle or joint pain	0.91	0.92
Fatigue	0.90	0.91
Headache	0.89	0.89
Difficulty in concentrating	0.89	0.92

Supplementary Figure 3. Flow diagram of MAS development.

