Development and External Validation of a Diagnostic Tool for the Earlier Detection of Patients with Systemic Mastocytosis Presenting in a Real-World Community Hematology Setting

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Introduction

- Systemic mastocytosis (SM) is a rare, clonal mast cell neoplasm characterized by the accumulation and activation of mast cells in various tissues and organs of the body, including the skin, bone marrow, liver, spleen, and gastrointestinal tract
- The excessive and uncontrolled activation of mast cells can lead to a wide range of symptoms, including skin lesions, flushing, itching, abdominal pain, diarrhea, nausea, and muscle weakness
- Given the heterogeneous clinical presentation, part of the challenge in the effective management of patients with SM is timely diagnosis
  - This study sought to develop a diagnostic (Dx) algorithm or tool to raise clinical suspicion of SM and accelerate SM-specific diagnostic workup and diagnosis

Methods

- The Quality Cancer Care Alliance (QCCA) network real world database was reviewed and 105 patients with SM who had presented prior to October 1, 2022, were identified that met eligibility criteria
- A second sample of 104 patients diagnosed with blood cancers, but not SM, were also identified
- Data collection consisted of patient demographic information, existing comorbidities, symptoms at presentation (including symptoms associated with mast cell activation), performance status, and standard hematologic and biochemistry test outcomes
- General linear models (GLM) with a logit link function and a Bernoulli distribution were then used to measure the association between select risk factors and a diagnosis of SM
- The likelihood ratio test was applied in a backward elimination process (P<0.05 to retain) to select the final set of risk factors for retention in the GLM model
- Nonparametric bootstrapping was applied to test the internal validity of the final Dx model
- From the GLM statistical outputs, the contribution of the individual factor for an SM diagnosis was weighted with the final model coefficients
- To simplify calculations using these weights in a scoring algorithm, the coefficients were transformed by multiplying each by a constant (derived by trial and error) and then rounding to the nearest unit value
- A summary SM Dx score was then assigned to each patient by adding up transformed coefficient values (points) for each risk factor they possessed
- The predictive accuracy of the final SM Dx algorithm was determined by measuring the specificity, sensitivity, and area under the Receiver Operating Characteristic (ROC) curve
- External validation was then performed on a new sample of 162 patients (81 SM and 81 non-SM) who were managed through another community oncology network (National Cancer Care Alliance - NCCA)
- The GLM model and scoring system was applied to the new patient cohort. Odds ratios with 95% confidence interval (CI) for the individual predictive factors were regenerated, as was the specificity, sensitivity, positive predictive value, negative predictive value, and area under the ROC curve for the scoring index
  - Pearson Rho was then used to measure the correlation between patient risk score and probability of a positive SM diagnosis

Results

- The control group of patients without SM contained individuals with chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS) and myelofibrosis (MF), all equally distributed
- Patients with SM in both cohorts were younger, had a lower median Charlson comorbidity score, and tended to have a better overall performance status **(Table 1)**
- Following the backward statistical elimination process, seven predictive clinical characteristics associated with a diagnosis of SM were identified **(Table 2)**
- From the regression outputs, the contribution of the individual factor for an SM diagnosis was weighted with the final model coefficients. To develop a diagnostic scoring algorithm, the coefficients were transformed by multiplying each by a constant and then rounding to the nearest unit value **(Table 3)**
- The total SM diagnostic score for each patient was strongly correlated with the probability of a positive SM diagnosis **(Figure 1)**
- The model development was continued with an ROC analysis on both the derivation and external validation datasets. The findings suggested the area under the ROC in both the derivation and external validation samples was greater than the generally accepted standard for goodness of fit; 0.89 (95% CI: 0.85–0.93) *vs* 0.81 (95% CI: 0.74–0.87), supporting the internal and external validity of the scoring system **(Figures 2 and 3)**
- The analysis identified a diagnostic score threshold of >8 as being the cut point where sensitivity and specificity are optimal and a high proportion (80.4%) of patients were correctly classified as having SM **(Table 4)**

Table 1. Characteristics of patients with and without SM

Parameter	Model development sample		External validation sample	
	Patients with SM (n=105)	Controls (n=104)	Patients with SM (n=81)	Controls (n=81)
Median age (range)	56 (4–84)	70 (23–96)	58 (58–87)	67 (20–89)
Female sex, % (n)	48.6% (51)	40.4 (42)	50.6 (41)	37.0 (30)
Race, % (n)				
White	89.5 (94)	82.7 (86)	84.0 (68)	79.0 (64)
Other	4.8 (5)	15.4 (16)	9.9 (8)	18.5 (15)
Not documented	5.7 (6)	1.9 (2)	6.2 (5)	2.5 (2)
Primary diagnosis, % (n)				
Indolent SM	47.6 (50)		38.8 (31)	
Advanced SM	30.5 (32)		44.4 (36)	
SM subtype not documented	21.9 (23)		17.3 (14)	
CLL		25.0 (26)		24.7 (20)
CML		25.0 (26)		24.7 (20)
MDS		25.0 (26)		25.9 (21)
MF		25.0 (26)		24.7 (20)
ECOG performance status, % (n)				
0 or 1	50.5 (53)	63.5 (66)	59.2 (48)	56.8 (46)
2	1.9 (2)	4.8 (5)	8.6 (7)	11.1 (9)
Not documented	47.6 (50)	31.7 (33)	32.1 (26)	32.1 (26)
Comorbidities and organ status				
Median Charlson comorbidity score at diagnosis (range)[1]	0 (0–8)	2 (0–6)	1 (0–7)	2 (0–7)
Spleen enlargement within 30 days of presentation, % (n)	22.9 (24)	20.2 (21)	23.5 (19)	23.5 (19)
Lymph node enlargement within 30 days of presentation, % (n)	8.6 (9)	15.4 (16)	6.2 (5)	17.3 (14)
Symptoms within 30 days of presentation, %(n)				
Diarrhea	24.8 (26)	3.8 (4)	23.5 (19)	8.6 (7)
Hypertension	29.5 (31)	53.8 (56)	37.0 (30)	45.7 (37)
Pruritis	27.6 (29)	3.8 (4)	21.0 (17)	1.2 (1)
Nausea	12.4 (13)	5.8 (6)	17.3 (14)	9.9 (8)
Rash	42.9 (45)	4.8 (5)	35.8 (29)	4.9 (4)
Skin lesions	27.6 (29)	1.9 (2)	22.2 (18)	0.0 (0)
Weight loss	23.8 (25)	11.5 (12)	9.9 (8)	13.5 (11)
Baseline hematology/biochemistry (mean, SD)				
Hemoglobin [g/dL]	12.8 (2.5)	11.6 (3.0)	12.9 (2.4)	11.7 (2.6)
White blood cells [x 10^3/µL]	8.5 (6.2)	17.2 (17.5)	8.0 (5.0)	16.2 (15.3)
Absolute neutrophil count [x 10^3/µL]	5.0 (3.2)	8.7 (9.1)	4.5 (3.1)	9.2 (9.5)
Platelets [x 10^3/µL]	235 (107)	283 (229)	257 (133)	332 (296)

CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ECOG, eastern cooperative oncology group; MDS, myelodysplastic syndrome; MF, myelofibrosis; SD, standard deviation; SM, systemic mastocytosis.
[1]The weighted comorbidity classes were: Low = 0 points, Median = 1 to 2, High = 3 to 4 and Very high = ≥ 5.

Table 2. The final predictive model for an SM diagnosis

Variable	Odds ratio[a]	95% CI	Likelihood of SM
Age ≥60 years	0.21	(0.08–0.52)	↓ by 79%
Lymph node enlargement	0.22	(0.06–0.85)	↓ by 78%
Diarrhea within 30 days of presentation	7.62	(1.74–33.4)	↑ 7.6 times
Rash within 30 days of presentation	13.6	(4.33–42.8)	↑ 13.6 times
Skin lesions within 30 days of presentation	6.0	(1.19–30.1)	↑ 6.0 times
Weight loss (any) within 30 days of presentation	5.1	(1.67–15.7)	↑ 5.1 times
ANC measured at presentation	0.89	(0.82–0.97)	↓ Likelihood per unit increase
Model adjusted R^2[1]	0.41		

Dependent variable: A positive diagnosis of SM. [1]Statistically significant at P=0.05 level.
ANC, absolute neutrophil count; CI, confidence interval.

Table 3. Transformed diagnostic scoring tool

Diagnostic scoring algorithm for SM

Start at base score of 10

Patient age	If age ≥60 years	– 3
Lymph node status	If lymph nodes enlarged at presentation	– 3
Diarrhea	Diarrhea within 30 days of presentation	+ 4
Rash	Rash within 30 days of presentation	+ 5
Skin lesions	Skin lesions within 30 days of presentation	+ 4
Weight loss	Weight loss (any) within 30 days of presentation	+ 3
Absolute neutrophil count	Measured ANC at presentation	Subtract one quarter of the ANC
Total composite diagnostic score		**?**

Example:
Patient is a 65-year-old female presenting with chronic diarrhea and skin rash for the past 6 weeks. The patient has a white blood count and ANC of 8.5 and 5.0 [x 10^3/µL]. The patient's spleen is normal, and her lymph nodes are not enlarged upon examination.

What is the likelihood this patient has SM?
- Start at a base score of 10 units
- Age is 65, subtract 3 units
- Has diarrhea, add 4 units
- Has a rash, add 5 units
- ANC of 5, subtract (5/4) or 1.25 units

Final score: 14.75
Likelihood of SM: 95.4% (95% CI: 89–98)

Table 4. Accuracy of the SM diagnostic tool

Score cut point	Observed disease prevalence	Sensitivity	Specificity	Correctly classified	Likelihood ratio +
≤6	6.7%	100%	0%	50.2%	1.0
>6 to ≤8	26.0%	97.1%	40.4%	68.9%	1.63
>8 to ≤10	**59.0%**	**84.8%**	**76.0%**	**80.4%**	**3.53**
>10 to ≤12	66.7%	62.9%	91.4%	77.0%	7.26
>12 to ≤16	91.4%	51.4%	97.1%	74.2%	17.8
>16	100%	19.0%	100%	59.3%	0.0

- Patients with a total score >8 are considered to have a high likelihood of having SM. **This is the point where clinicians should be thinking SM and order confirmatory tests**
- Patients who had a positive diagnosis of SM were 3.53 times more likely than patients who did not have SM to have a risk score of at least >8 units

Figure 1. Relationship between the diagnostic score and probability of SM

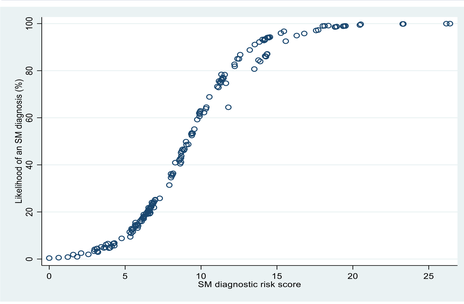


Figure 2. The area under the ROC curve in the model development cohort

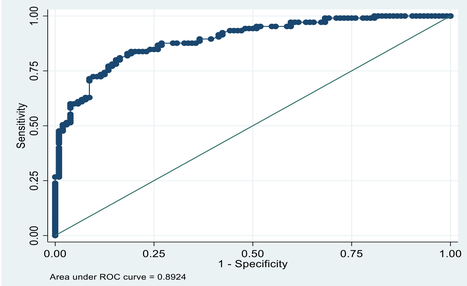
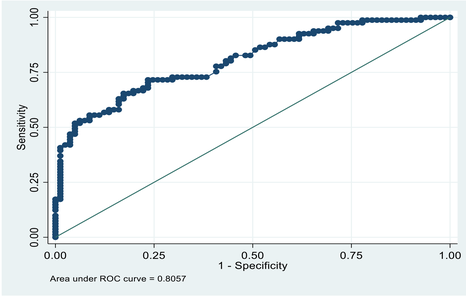


Figure 3. The area under the ROC curve in the external validation cohort



ROC, Receiver Operating Characteristic.

Conclusions

- SM is a rare disorder that may take years to diagnose. The delay in patient diagnosis can have a major impact on patient quality of life and impact overall survival
- To address this need in patient care, we developed and externally validated a diagnostic tool designed to raise clinical suspicion and facilitate the early diagnosis of SM
- The scoring index is easy to apply, able to discriminate between patients with and without SM, and the risk threshold can be varied, depending on the clinical situation
- The diagnostic tool will enhance patient care by accelerating the diagnosis of SM, which would allow the timely initiation of effective targeted therapies

Disclosures and contact information
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