Development of a Diagnostic Tool for the Early 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 hematological disorder 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 SM patients is timely diagnosis. This study sought to develop a diagnostic (Dx) algorithm or tool for the early detection of SM

Methods

- The QCCA network real world database was reviewed and 105 SM patients who had presented prior to October 1, 2022 were identified
- A second sample of 104 non-SM patients diagnosed with blood cancers 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 backwards 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 diagnostic (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

Results

- Data were collected from 105 patients with SM and 104 without SM identified within the QCCA real world database
- The group of patients without SM contained individuals with CLL, CML, MDS and MF (n=26 in each group)
- Compared to patients without SM, patients with SM tended to be younger (median age = 56 vs. 70), have fewer comorbidities (median Charlson score = 0 vs. 2), be more symptomatic in terms of diarrhea, flushing, pruritis, rash, skin lesions and weight loss, and tended to have lower WBC, ANC and platelet levels at presentation (**Table 1**)

Table 1. Characteristics of patients with and without SM

Parameter	Patients with SM (n=105)	Patients without SM (n=104)
Median age [range]	56 [24-84]	70 (23-96)
Female sex	48.6% (51)	40.4% (42)
Race		
White	89.5% (94)	82.7% (86)
Other	4.8% (5)	15.4% (16)
Not documented	5.7% (6)	1.9% (2)
Primary Diagnosis		
Indolent SM	47.6% (50)	
Advanced SM	30.5% (32)	
SM Subtype Not Documented	21.9% (23)	
CLL		25.0% (26)
CML		25.0% (26)
MDS		25.0% (26)
MF		25.0% (26)
ECOG Performance Status		
0 or 1	50.5% (53)	63.5% (66)
2	1.9% (2)	4.8% (5)
Not Documented	47.6% (50)	31.7% (33)
Comorbidities and Organ Status		
Median Charlson comorbidity score at diagnosis [range][1]	0 [0-8]	2 [0-6]
Anaphylaxis within 180 days prior to diagnosis	6.7%(7)	0.0% (0)
Spleen enlargement within 30 days of presentation	22.9% (24)	20.2% (21)
Lymph node enlargement within 30 days of presentation	8.6% (9)	15.4% (16)
Symptoms within 30 days of presentation		
Diarrhea	24.8% (26)	3.8% (4)
Fatigue	41.0% (43)	51.0% (53)
Flushing	12.4% (13)	0.0% (0)
Headache	12.4% (13)	11.5% (12)
Hypertension	29.5% (31)	53.8% (56)
Pruritis	27.6% (29)	3.8% (4)
Nausea	12.4% (13)	5.8% (6)
Rash	42.9% (45)	4.8% (5)
Skin Lesions	27.6% (29)	1.9% (2)
Weight Loss	23.8% (25)	11.5% (12)
Baseline hematology/biochemistry (mean, SD)		
Hemoglobin [g/dL]	12.8 (2.5)	11.6 (3.0)
White blood cells [x 10^3/µL]	8.5 (6.2)	17.2 (17.5)
Absolute neutrophil count [x 10^3/µL]	5.0 (3.2)	8.7 (9.1)
Absolute eosinophil count [x 10^3/µL]	0.29 (0.77)	0.42 (0.74)
Platelets [x 10^3/µL]	235 (107)	283 (229)
Serum creatinine [mg/dL]	0.96 (0.43)	1.0 (0.42)

Abbreviations: ECOG = Eastern Oncology Cooperative Group, CLL = Chronic lymphocytic leukemia, CML = Chronic myeloid leukemia, MDS = Myelodysplastic syndrome, MF = Myelofibrosis, SD = Standard deviation.
[1]The weighted comorbidity classes were: Low = 0 points, Median = 1 to 2, High = 3 to 4 and Very high = ≥ 5.

- Following the backwards statistical elimination process, seven factors 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 create an SM diagnostic scoring algorithm (**Tables 3 and 4**)

Table 2. The final predictive model for an SM diagnosis

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

Dependent variable: A positive diagnosis of SM. [1]Statistically significant at p = 0.05 level.

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 WBC 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

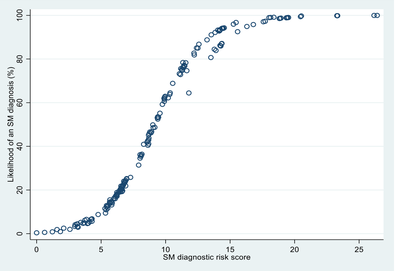
Final score: 14.75
Likelihood of SM: 95.4%
(95%CI: 89% to 98%)

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	91.9%	51.4%	97.1%	74.2%	17.8
> 16	100%	19.0%	100%	59.3%	0.0

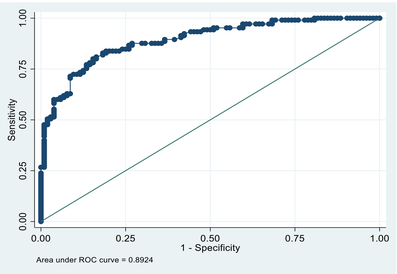
- The total SM diagnostic score for each patient was strongly correlated with the probability of a positive SM diagnosis (**Figure 1**)
- The ROC curve analysis suggested good predictive accuracy (**Figure 2**)
- Patients with a total score > 8 are considered to have a high likelihood of having SM. This 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



Association between the Dx score and likelihood of SM: OR = 1.71, p < 0.001

Figure 2. The area under the ROC curve



AUC of ROC curve for:

- Internal validation (0.89; 95%CI 0.84–0.93)
- A predictive tool with an ROC ≥ 0.70 is considered to have good discrimination

Conclusions

- SM remains a difficult disease to accurately diagnosis in a timely manner
- Through a stepwise statistical process, seven factors associated with an SM diagnosis were identified and quantified
- With these factors, a diagnostic algorithm (or tool) for SM was created
- To our knowledge, this is the first mathematical tool developed in a real-world setting that can assist clinicians in an SM diagnosis
- The tool performed well, was easy to apply and able to discriminate between patients with and without SM
- The application and planned external validation of this diagnostic tool can support the timely diagnosis and treatment of SM patients

Disclosures and Contact Information

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