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doi.org/10.58931/cait.2025.5179

Use of the REMA Score to Distinguish Individuals with Systemic Mastocytosis From Those with Hereditary Alpha-tryptasemia

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Background: Systemic mastocytosis (SM) and hereditary alpha-tryptasemia (HαT) may present with overlapping clinical manifestations of mast cell activation, making them difficult to distinguish on clinical grounds. Diagnosing SM requires a bone marrow or tissue biopsy whereas HαT can be diagnosed with a buccal swab for genetic testing. Another potential method to differentiate SM from HαT is through a validated scoring system. For example, the Spanish Network on Mastocytosis, Red Española de Mastocitosis (REMA) score has been validated as a predictor of mast cell clonality in SM by using basal serum tryptase levels, clinical symptoms, and sex. This study aims to determine whether REMA scores can differentiate sufficiently between individuals with SM and HαT, thereby confidently ruling in or out the need for more invasive investigations such as bone marrow or tissue biopsy.

Methods: A retrospective chart review was conducted on 39 patients with SM and 24 patients with HαT to calculate their individual REMA scores. A two-sample Wilcoxon test was conducted to assess the difference in median REMA scores between patients with SM and those with HαT. Within the SM cohort, subgroup analysis was performed to compare REMA scores based on the *KIT* D816V mutation and SM subtype. The area under the curve was calculated to evaluate the discriminatory property of the REMA score.

Results: The Median REMA score within the SM cohort was 2 (0.50, 4.00) compared to -1 (-1.50 0.00) within the HαT cohort ($p < 0.001$). REMA scores in patients with SM did not differ based on the *KIT* mutation status. A REMA score cut-off of 0.5 was able to distinguish SM and HαT with a specificity of 83.3% (67%,96%).

Conclusion: This novel comparison of REMA scores in patients with SM and HαT highlights a potential role for the calculated REMA score in informing decisions about the need for invasive testing for patients presenting with symptoms of mast cell activation. However, larger comparative studies are needed before incorporating REMA scoring into routine care.

Introduction

Tryptases are trypsin-like proteases derived from mast cells and are expressed by allergic effector cells, tissue mast cells, and basophils.[1-3] The genes *TPSB2* and *TPSAB1* encode alpha and beta-tryptases, respectively. The frequency of alleles containing alpha-tryptase isoforms encoded at *TPSAB1* varies significantly based on an individual's race and ethnicity.[1] Basal serum tryptase levels, with an upper limit of normal at 11.4 ng/mL, reflect the total alpha and beta tryptase in the absence of acute mast cell activation.[1,4] Elevated basal serum tryptase levels, found in approximately 4–6% of the Western population,[5] can be caused by rare hematologic disorders such as systemic mastocytosis (SM) and myelodysplastic syndrome, reactive conditions such as allergic disorders and chronic urticaria, and other conditions such as kidney failure and hereditary alpha-tryptasemia.[6]

Amongst the conditions associated with elevated basal serum tryptase levels, SM, and hereditary alpha-tryptasemia (HαT) often exhibit overlapping clinical manifestations of mast cell activation, and are often difficult to distinguish on clinical grounds.[4,7] Diagnosing SM requires a bone marrow or tissue biopsy.[8] In contrast, HαT, an autosomal dominant trait defined by germline replications of the *TPSAB1* gene encoding alpha tryptase, can be diagnosed non-invasively with a buccal swab for genetic testing.[7] The prevalence of these conditions varies significantly, with SM estimated to affect 1 in 10,000–20,000 individuals while HαT is estimated to occur in 5% of the general population.[4,7]

The Spanish Network on Mastocytosis (Red Española de Mastocitosis) has developed a highly sensitive and simple clinical score known as the Red Española de Mastocitosis (REMA) score. This score has been validated as a predictor of mast cell clonality and SM by using a combination of basal serum tryptase levels, clinical symptoms, and sex.[9] A REMA score of 2 or higher is associated with a high probability of mast cell clonality and SM, whereas a score below 2 is associated with a low probability of mast cell clonality and SM.[9] To our knowledge, no published studies have compared REMA scores between individuals with SM and HαT. We hypothesize that individuals with HαT would have lower REMA scores compared to those with SM, and that using REMA scoring to differentiate these conditions would lead to more informed and targeted investigations for patients presenting with symptoms of mast cell activation.

Methods

All patients were assessed at a tertiary care teaching hospital and identified by retrospective chart review as approved by the St. Michael's Hospital Research Ethics board. Patients of all ages were included if they had been formally diagnosed with either SM (according to WHO diagnostic criteria) or HαT via buccal swab genetic testing.[10] Patients were excluded if there were no investigations confirming either their diagnosis or if they had not undergone basal tryptase testing.

The REMA score was calculated for all patients.[9] For those with multiple basal serum tryptase measurements, the highest basal serum tryptase level was used. Patients with SM were further stratified according to the presence of the *KIT* D816V mutation and the WHO subtype of systemic mastocytosis.[11]

A two-sample Wilcoxon test was conducted to assess the statistical significance of differences in median REMA scores between patients with SM and those with HαT. Additionally, subgroup analysis within the SM cohort was conducted to assess the statistical significance of differences in median REMA scores between patients with and without the *KIT* D816V mutation, as well as among patients with different WHO subtypes of SM.

The optimal cut-off values of the REMA score for distinguishing between SM and HαT were calculated using receiver operator characteristic (ROC) curves. Chi-squared and Fisher Exact tests were performed to determine which REMA score variables were most strongly associated with predicting a diagnosis of SM or HαT. P-values ≤0.05 were considered statistically significant. All statistical analyses were performed with R 3.6.3 statistical software (R Foundation for Statistical Computing, Vienna, Austria) and R studio 1.2.5033 statistical software (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA).[12,13]

Results

The study included 39 patients with SM and 24 patients with HαT. **Tables 1 and 2** provide details on each patient's sex, age, tryptase levels, REMA score, and where applicable, SM subtype, and c-KIT mutation status. The median REMA score within the SM cohort was 2 (0.50, 4.00)

Age	Sex	Serum Tryptase (*mcg/L*)	REMA Score
56	Female	12.8	-1
52	Female	16	-3
52	Male	20.2	-1
39	Female	13.6	0
13	Male	13.9	1
69	Female	12.4	-4
1	Female	13.4	-4
31	Female	21.9	-3
59	Female	19.2	0
33	Female	11.3	-1
48	Female	14	-1
34	Female	13	-1
7	Female	11.4	-4
46	Female	28	2
25	Female	11.9	-1
40	Female	11.4	-1
36	Female	11.9	-1
67	Female	15	0
25	Female	14.5	-1
51	Male	12.1	1
39	Female	12.2	-1
31	Female	12.2	-4
52	Male	16	2
33	Female	11.4	-1

Table 1. Patient demographics, serum tryptase, and Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score of patients with hereditary alpha-tryptasemia; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

Age	Sex	Serum Tryptase (*mcg/L*)	REMA Score	SM Subtype	c-KIT Mutation Status
42	Female	60.1	5	Indolent	C-kit mutation + D816V
42	Female	50.1	2	Indolent	C-kit mutation + D816V
44	Female	23.5	0	Indolent	C-kit mutation + D816V
33	Male	42.2	4	Indolent	C-kit mutation + D816V
23	Female	65.1	2	Indolent	C-kit mutation + D816V
47	Female	11.4	1	Indolent	C-kit mutation + D816V
76	Male	166	4	Smoldering	C-kit mutation + D816V
37	Male	424	1	Mast cell leukemia	C-kit mutation + D816V
39	Female	10.8	-1	Indolent	C-kit mutation + D816V
53	Female	32	2	Indolent	C-kit mutation -
65	Female	81.1	5	Indolent	C-kit mutation + D816V
42	Female	63.1	2	With associated hematologic neoplasm	C-kit mutation -
37	Male	11.3	5	Indolent	C-kit mutation -
39	Female	55.2	2	Indolent	C-kit mutation + D816V
72	Female	44.5	2	Indolent	C-kit mutation + D816V
42	Female	50.1	2	Indolent	C-kit mutation + D816V
50	Male	16.8	2	Indolent	C-kit mutation + D816V
67	Male	39	4	Indolent	C-kit mutation + D816V
56	Female	21.3	-3	Indolent	C-kit mutation -
34	Male	20	2	Indolent	C-kit mutation + D816V
35	Female	16.6	0	Indolent	C-kit mutation -
38	Female	29.4	-1	Indolent	C-kit mutation -

27	Female	26	2	Indolent	C-kit mutation + D816V
38	Female	193	2	Indolent	C-kit mutation + D816V
68	Male	180	4	Smoldering	C-kit mutation + D816V
52	Female	59.3	2	Indolent	C-kit mutation + D816V
57	Female	38.8	5	Indolent	C-kit mutation + D816V
34	Male	25.4	4	Indolent	C-kit mutation + D816V
29	Female	35.3	-1	Indolent	C-kit mutation + D816V
66	Male	21.3	2	Indolent	C-kit mutation + D816V
65	Male	36.5	4	Indolent	C-kit mutation + D816V
44	Female	20.5	0	Indolent	C-kit mutation + D816V
27	Female	9.5	-1	Indolent	C-kit mutation -
51	Female	22.4	0	Indolent	C-kit mutation + D816V
43	Male	60.8	4	Indolent	C-kit mutation -
58	Male	33.3	4	Indolent	C-kit mutation -
47	Female	199	5	Aggressive	C-kit mutation + D816V
38	Male	59.2	4	Indolent	C-kit mutation + D816V
52	Female	13.9	-1	Indolent	C-kit mutation + D816V

Table 2. Patient demographics, serum tryptase, Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score, systemic mastocytosis (SM) subtype, and c-KIT mutation status of patients with SM; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP*.

compared to -1 (-1.50, 0.00) in the HαT cohort (p<0.001). Within the SM cohort, 28 patients had the *KIT* D816V mutation whereas the remaining 11 patients did not. The REMA scores for patients with the *KIT* D816V mutation (2, interquartile range [IQR] 1-4) did not differ significantly from those without the mutation (2, IQR -0.5-4; p=0.56). The variation in REMA scores between the different SM subtypes could not be accurately assessed, as the majority of patients in the SM cohort were classified as having indolent SM. **Table 3** provides the distribution of SM subtypes.

Table 4 presents the sensitivities, specificities, positive predictive values, and negative predictive values for various REMA score thresholds in differentiating SM from HαT. The area under the curve was 0.869 (0.786, 0.953). **Figure 1** shows the ROC curve with 85% confidence intervals. Overall, a REMA score cut-off of 0.5 distinguished between SM and HαT with a sensitivity of 74.4% and a specificity of 83.3%.

Chi-squared and Fisher Exact tests revealed that serum tryptase was the variable in the REMA score most strongly associated with a diagnosis of SM or HαT (p<0.001).

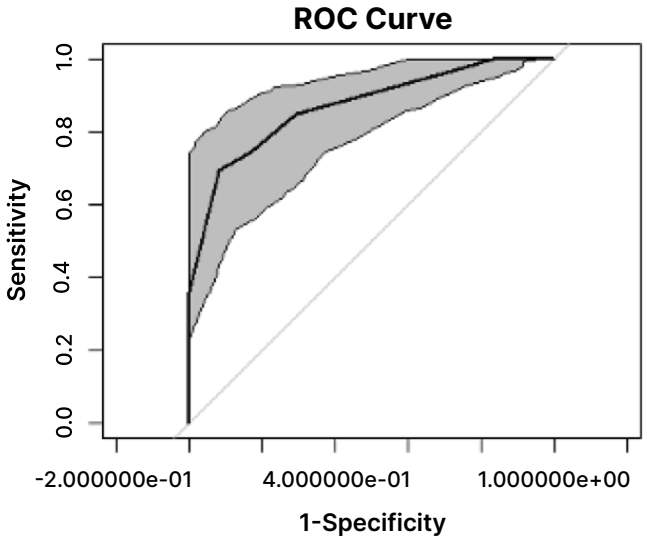

Figure 1. Receiver operator characteristic curve with 85% confidence intervals; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

Abbreviations: ROC: receiver operator characteristic

Discussion

The diagnostic work up and appropriate classification of patients with symptoms of mast cell activation can be challenging given the heterogeneity of patient presentations. Distinguishing between SM and HαT can be particularly difficult without invasive tests such as bone marrow or tissue biopsies. Our study used a retrospective chart review to investigate the role of the previously validated REMA score in guiding the decisions about whether to proceed with invasive investigations, such as bone marrow or tissue biopsies. The findings suggest that REMA scoring could be a valuable tool to guide decision making in the diagnostic work up of patients with symptoms of mast cell activation, as patients with SM and HαT had significantly different REMA scores. Our results suggest that a REMA score of 0 or lower (below the 0.5 cut-off identified above) may be used by clinicians to support the decision to start with genetic testing for HαT as opposed to invasive testing with bone marrow or tissue biopsies in the diagnostic work up for SM. This has important implications for reducing potentially unnecessary health care expenditures and avoiding potentially unnecessary and uncomfortable testing for patients. This is especially important given that HαT is approximately 500 times more prevalent than SM.[4,7]

Our study has limitations that may affect its generalizability. Our patient population was extracted from one tertiary care teaching hospital in Toronto, Ontario, Canada and may not adequately reflect the heterogeneous global population of patients with SM and HαT. The indolent subtype of SM was disproportionately represented within the SM cohort. Finally, our study did not examine REMA scoring in patients with both SM and HαT, an overlap increasingly recognized within the literature, with an estimated 12-17% of SM patients found to have concurrent HαT in two studies.[14,15] Ultimately, these limitations highlight further areas for additional investigation. Future studies should apply REMA scoring to larger cohorts of patients with SM and HαT, especially those with different WHO subtypes of SM, and those diagnosed with both SM and HαT.

World Health Association Subtype	# (% of Total Systemic Mastocytosis Cohort)
n	39
Indolent	34 (87.2%)
Smoldering	2 (5.1%)
Aggressive	1 (2.5%)
Mast Cell Leukemia	1 (2.5%)
With Associated Hematologic Neoplasm	1 (2.5%)

Table 3. Distribution of systemic mastocytosis subtypes according to the World Health Association classification[11]; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

Threshold	Specificity	Sensitivity	PPV	NPV
-Inf	0.000	1.000	0.619	NaN
-3.5	0.167	1.000	0.661	1.000
-2.0	0.250	0.974	0.679	0.857
-0.5	0.708	0.846	0.825	0.739
0.5	0.833	0.744	0.879	0.667
1.5	0.917	0.692	0.931	0.647
3.0	1.000	0.359	1.000	0.490
4.5	1.000	0.128	1.000	0.414
Inf	1.000	0.000	NaN	0.381

Table 4. Sensitivities, specificities, positive predictive values, and negative predictive values of the different Spanish Network on Mastocytosis, (Red Española de Mastocitosis [REMA]) score thresholds in differentiating systemic mastocytosis and hereditary alpha-tryptasemia; *courtesy of Maggie Jiang, MD and Peter Vadas, MD, PhD, FRCPC, FACP.*

For this dataset, the area under the curve was 0.869 and the 95% confidence interval was 0.786, 0.953.

Abbreviations: PPV: positive predictive values, **NPV:** negative predictive values, **NaN:** Not able to calculate

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Financial Disclosures

P.V.: None declared.
M.J.: None declared.

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