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Slim-Crab Diagnostic Features And Their Association With Msmart 3.0 Risk In Multiple Myeloma: A Real-World Healthtree Cure Hub Registry Study

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Background

While the SLiM-CRAB criteria define disease onset in newly diagnosed multiple myeloma (NDMM), therapeutic decisions increasingly depend on cytogenetic risk stratification. Among available stratification tools,, the mSMART 3.0 model—though not without limitations—remains one of the few tools routinely used in clinical practice to capture genetic risk and guide frontline treatment choices. Despite its widespread adoption, little is known about how the clinical features that define SLiM-CRAB relate to mSMART-defined risk. Understanding how diagnostic features align—or fail to align—with cytogenetic risk could offer a pragmatic approach to triage, especially when molecular testing is delayed or unavailable.

Purpose

To evaluate how individual SLiM-CRAB features correlate with mSMART 3.0 cytogenetic risk in NDMM, and whether specific clinical presentations may serve as early indicators of high- or low-risk disease.

Methods

We conducted a retrospective analysis of NDMM patients enrolled in the HealthTree Cure Hub Registry, a real-world, patient-reported and EHR-validated platform capturing longitudinal clinical data across diverse care settings. Patients were included if they had sufficient structured and unstructured data to assign both mSMART 3.0 cytogenetic risk and SLiM-CRAB diagnostic status at presentation. Cytogenetic risk classification followed mSMART 3.0 criteria, categorizing patients into standard-, double-, or triple-hit groups based on presence of high-risk features, including del(17p), t(4;14), t(14;16), gain/amp 1q, and other established markers.

SLiM-CRAB features were derived from structured EHR inputs and laboratory values. Bone marrow plasma cell percentage, serum free light chain (FLC) ratio, renal function (creatinine), calcium, hemoglobin, and skeletal involvement were assessed. Notably, radiographic bone involvement and MRI data—frequently embedded in unstructured reports—were extracted using a GPT-o1-based few-shot prompting model, which had been internally validated against manual abstraction with a classification accuracy of 98%. Patients were stratified into three diagnostic subgroups: SLiM-only, CRAB-only, and SLiM+CRAB, reflecting their presenting clinical phenotype.

To evaluate the relationship between diagnostic phenotype and cytogenetic risk, we performed univariate linear regression treating mSMART risk as an ordinal variable (0=standard risk, 1=double-hit, 2–3=triple-hit). Each SLiM-CRAB feature was tested as an independent variable. Regression coefficients (β), directionality, and p-values were reported; statistical significance was defined as $p<0.05$. This analytic approach allowed us to quantify the individual contribution of each diagnostic feature to the likelihood of harboring high-risk cytogenetics.

Results

Of the 381 patients, 158 (41%) presented with both SLiM and CRAB features, 112 (29%) with CRAB-only, and 111 (29%) with SLiM-only. Higher bone marrow plasma cell percentages were significantly associated with higher mSMART risk ($\beta=+0.28$; $p<0.05$), with median plasma cell infiltration rising from 16% in standard-risk to 44% in triple-hit patients. Conversely, bone lesions were more frequent in lower-risk patients and inversely associated with cytogenetic risk ($\beta=-0.25$; $p<0.01$), observed in 55% of standard-risk vs 28% of double-hit cases. No other SLiM-CRAB features showed significant associations.

Table 1. SLiM/CRAB Feature Prevalence by mSMART Risk Group

Feature	Standard (n = 180)	High (n =140)	Double Hit (n = 43)	Triple Hit (n = 18)	Total (n=381)	Risk change Estimate	Direction	p-value
(S) Plasma	28 (15.6%)	40 (28.6%)	13 (30.2%)	8 (44.4%)	89 (23.4%)	0.28	↑ Higher Risk	**p < 0.05**
(Li) Light Chains	61 (33.9%)	40 (28.6%)	13 (30.2%)	6 (33.3%)	120 (31.5%)	-0.04	↓ Lower Risk	p = 0.67
(M) MRI	63 (35.0%)	44 (31.4%)	11 (25.6%)	6 (33.3%)	124 (32.5%)	-0.09	↓ Lower Risk	p = 0.35
(C) Calcium	16 (8.9%)	11 (7.9%)	3 (7.0%)	1 (5.6%)	31 (8.1%)	-0.1	↓ Lower Risk	p = 0.53
(R) Renal	21 (11.7%)	18 (12.9%)	7 (16.3%)	3 (16.7%)	49 (12.8%)	0.14	↑ Higher Risk	p = 0.29
(A) Anemia	41 (22.8%)	41 (29.3%)	13 (30.2%)	7 (38.9%)	102 (26.77%)	0.16	↑ Higher Risk	p = 0.12
(B) Bone Lesions	99 (55.0%)	67 (47.9%)	12 (27.9%)	7 (38.9%)	185 (48.6%)	-0.25	↓ Lower Risk	**p < 0.01**

This table summarizes the distribution of SLiM and CRAB features across mSMART risk categories in newly diagnosed multiple myeloma patients. For each feature, we report the absolute count and relative prevalence (%) per risk group (Standard, High, Double, Triple), the linear regression coefficients (β) in risk change (estimate), the direction of association, and p-value. Risk was modeled as an ordinal score from 0 (Standard) to 3 (Triple Hit), and directionality was estimated using univariate linear regression. Features with significant associations are highlighted as potential markers of higher- or lower-risk disease stratification. Positive effect estimates indicate positive correlation. P values <0.05 are considered statistically significant.

Conclusion

Most SLiM-CRAB features showed no significant correlation with mSMART-risk. However, elevated plasma cells and bone lesions may serve as early indicators of higher and lower mSMART-risk, respectively. These findings support the potential role of diagnostic feature profiling in prioritizing genetic testing or triaging NDMM patients. The lack of association with other features likely reflects disease heterogeneity or limited power. Larger, multivariate studies are needed to further explore SLiM-CRAB phenotype and risk genotype links in NDMM.