ELSEVIER

Blood 142 (2023) 4768–4769

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

654.MGUS, AMYLOIDOSIS AND OTHER NON-MYELOMA PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL

Risk Stratification Models Overestimate Progression Risk in Contemporary Patients with Smoldering Multiple Myeloma (SMM)

George Mellgard[1], *Molly Gilligan*[1], *Edward R Scheffer Cliff, MBBS,MPH*[2], *Divaya Bhutani, MD*[3], *Ghulam Rehman Mohyuddin, MD*[4], *Andrew Eisenberger, MD*[3], *Suzanne Lentzsch, MD PhD*[5], *Rajshekhar Chakraborty*[1]

[1] Columbia University Irving Medical Center, New York, NY
[2] Austin Health, Brooklyn, MA
[3] Columbia University Medical Center, New York, NY
[4] Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
[5] Division of Hematology & Oncology, Columbia University Medical Center, New York, NY

Introduction: SMM is an asymptomatic precursor of multiple myeloma (MM), affecting ~1 in 200 people aged >40 years. Historically, risk of progression from SMM to MM was 10% per year in the first 5 years. However, since then, the definition and characteristics of the SMM patient population have changed substantially. First, IMWG diagnostic criteria for MM in 2014 changed to include biomarker-only myeloma (SLiM), reclassifying asymptomatic patients previously considered SMM. Second, incorporation of advanced imaging (CT, PET/CT, MRI) identified bone disease with greater sensitivity. Hence, we hypothesized that in the contemporary era, the risk of progression from SMM to MM would be markedly lower than historically.
Methods: We performed a retrospective cohort study of consecutive patients with SMM at Columbia University Irving Medical Center from 2014-2022 and observed without therapeutic intervention. Our primary objective was to measure cumulative incidence of progression to MM and to characterize progression events. We also calculated predicted 2-year risk of progression by different risk-stratification models (Mayo 20/2/20, PANGEA, IMWG SMM model) in our cohort.
Results: 102 consecutive patients with SMM were included. Median year of diagnosis was 2019 (range, 2014-2022). Baseline clinical and demographic characteristics of the cohort are shown in Table 1. The three most common scenarios that led to SMM diagnosis were workup of anemia/cytopenias(s) (n=22; 21.8%), incidental protein gap or elevated immunoglobulin level (n=20; 19.8%), and renal dysfunction (n=16; 15.8%). The racial/ethnic makeup of our study cohort was 38% Hispanic/Latino, 38% Non-Hispanic White, 19% Black/African-American, and 5% Asian. Bone disease was ruled out by advanced imaging (whole body CT, PET/CT, WB-MRI, and/or MRI spine+ pelvis) in 81.2% of patients. The most common abnormality on FISH was hyperdiploidy (39.2%), followed by t(11;14) (22.1%), with ≥1 high-risk cytogenetic abnormality (HRCA) in 35% of patients. Median follow-up was 45 months (95% CI, 34-52). 22/102 patients (21.6%) progressed to symptomatic plasma cell dyscrasia: CRAB myeloma in 18, SLiM myeloma in 1, systemic AL amyloidosis in 3 patients. The cumulative incidence of progression to MM (CRAB/SLiM) at 1, 2, 3, and 4 years from SMM diagnosis was 3.1% (95% CI, 0.99-9.1), 7.7% (95% CI, 3.7-15.3), 13.9% (95% CI, 8.1-23.1), and 17.1% (95% CI, 10.3-27.1) respectively [Figure 1]. Notably, presence of HRCA by FISH had a dose-dependent increase in risk of progression, with the 2-year risk being 75% (95% CI, 24-97%) in patients with ≥2 HRCA vs 13.0% (95% CI, 5.9-26.3) in those with 0-1 HRCA respectively (p=0.0049). Among 18 patients who progressed to CRAB myeloma, the myeloma-defining event/s (MDEs) were anemia in 11, anemia + bone disease in 4, and bone disease in 3 patients. Among patients with a bone disease MDE, 4/7 had >1 lytic lesions on imaging and 3 had vertebral compression fracture(s). No patient had renal insufficiency or hypercalcemia as MDE. The sole patient with SLiM had a serum free light chain ratio>100 as the only MDE. 13/102 patients (12.75%) died, with 4/13 deaths attributed to myeloma after disease progression.
The predicted median 2-year risk of progression to MM with different risk-stratification models were as follows: PANGEA with Bone Marrow (BM): 5.75% (range, 1.2-42); PANGEA without BM: 4.6% (0.7-26.6); Mayo 20/2/20: 9.7% (9.7-47.4); IMWG SMM: 26% (3.8-73). Figure 2 shows Sankey diagram of predicted risk tertiles for patients at SMM diagnosis by different models. Notably, a substantial proportion of high-risk patients by 20/2/20, who are currently considered for therapeutic intervention, were re-assigned to intermediate risk (2-year risk of progression 8.1-20%) by PANGEA-BM.
Conclusion: The risk of progression to MM among this cohort of contemporary patients with SMM is <5% per year for the 1 st 4 years, which is substantially lower than the historical rate of 10% per year. Morbid progression such as renal failure or fractures

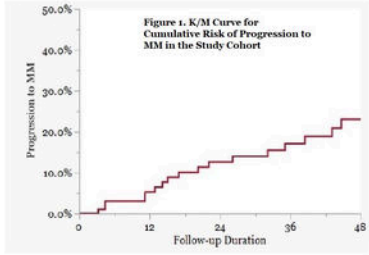
are very infrequent, with anemia being the most common MDE. Prospective studies testing active surveillance strategies are needed in contemporary SMM cohorts to determine the optimal approach to these patients and ensure balancing of potential risks and benefits of treatment.

Disclosures Bhutani: *Sanofi:* Consultancy, Research Funding. **Lentzsch:** *Pfizer:* Consultancy; *Regeneron:* Honoraria; *Alexion Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol Meyers Squibb:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Research Funding; *Celgene:* Research Funding; *Adaptive Biotechnologies:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Caelum Biosciences:* Membership on an entity's Board of Directors or advisory committees, Patents & Royalties: January 1, 2041; *Clinical Care Options:* Honoraria; *Oncopeptide:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees. **Chakraborty:** *AbbVie:* Research Funding; *Genentech:* Research Funding; *Adaptive Biotech:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria.

Table 1. Baseline Clinical and Demographic Characteristics of the Study Cohort (n=102)

Median age, years (range)	68.8 (44.0-90.6)
Male sex (n; %)	53 (51.9)
Hispanic ethnicity (n; %)	39 (38.2)
Race (n; %): White Black Asian/Pacific Islander Mixed Other	 39 (38.2) 19 (18.6) 5 (4.9) 1 (0.98) 38 (37.3)
Median hemoglobin, range (g/dl)	12.5 (7.7-17.2)
Median M-protein, range (g/dl) M-protein>2 g/dl (%)	1.3 (0-3.3) 21.8
Median sFLC ratio (involved/uninvolved), range sFLCr>20 (%)	6.15 (0.56-90.78) 18.8
Median Bone Marrow Plasma Cells (%), range*	20 (9-50)
Mayo 20/2/20 Risk Model Low-Risk (%) Intermediate-Risk (%) High-Risk (%)	 53.5 33.3 13.1

sFLC: Serum Free Light Chain; BMPC: Bone Marrow Plasma Cells; CT: Computed Tomography; PET/CT: Positron Emission Tomography-CT; DW-MRI: Diffusion Weighted Magnetic Resonance Imaging
* Bone marrow biopsy was not performed at diagnosis in 2 patients



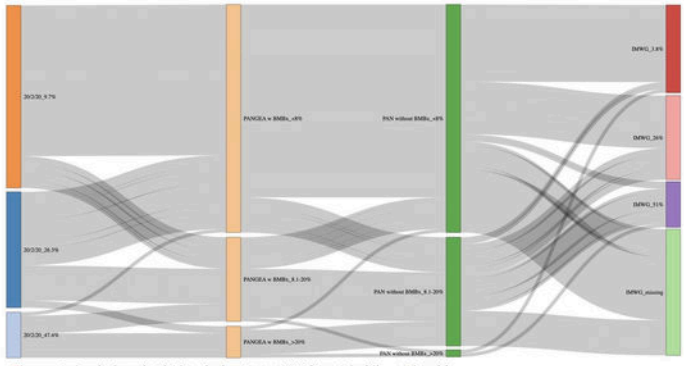


Figure 2. Sankey plot for predicted risk tertiles for patients at SMM diagnosis by different risk models.
The first verticle bar represents Mayo 20/2/20 model, with the 3 tertiles being low-risk, intermeidate-risk, and high-risk. The second verticle bar represents PANGEA model with bone marrow biopsy and the third verticle bar represents PANGEA model without bone marrow biopsy. Based on the individualized predicted risk of progression at 2 years, the risk estimates were divided into 3 tertiles for both.
The fourth verticle bar represents IMWG SMM model. Notably, a substantial proportion of patients had missing data on IMWG SMM model due to lack of FISH cytogenetics at diagnosis.

Figure 1

https://doi.org/10.1182/blood-2023-174908