LETTER

HemaSphere ★EHA EUROPEAN HEMATOLOGY ASSOCIATION

Risk stratification models overestimate progression risk in contemporary patients with smoldering multiple myeloma

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Clonal plasma cell disorders represent a spectrum of conditions ranging from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma (MM).[1] In between MGUS and MM, smoldering multiple myeloma (SMM), an asymptomatic precursor state, affects approximately one in two hundred individuals over age 40 years.[2] SMM was historically associated with a 10-fold increase in the risk of progression to MM in the first 5 years after diagnosis when compared to MGUS.[3] However, the clinical landscape of SMM has changed substantially. First, in 2014, the International Myeloma Working Group (IMWG) modified its MM diagnostic criteria to include asymptomatic patients with biomarker-defined (or "SLiM") myeloma that would previously have been classified as SMM.[1] Second, advanced imaging techniques, such as whole-body diffusion-weighted magnetic resonance imaging (MRI) (WB DW-MRI), have allowed physicians to identify bone disease earlier. These developments have led to the "upstaging" of many of the highest-risk patients with SMM to MM.[4,5] Notably, multiple groups have proposed risk-stratification models in SMM: the Spanish/PETHEMA model,[6] Mayo 2008,[7] Mayo 2018 (20/2/20),[8] IMWG SMM,[9] and most recently, PANGEA.[10] Additionally, two randomized trials have raised the question of whether early intervention should be recommended to patients with high-risk SMM.[11–13] However, the models are of differing complexities, use different inputs, and produce discordant results, making it challenging to know which to use in clinical practice. Furthermore, many were validated on cohorts defined by pre-2014 criteria. Hence, we conducted a retrospective cohort study in order to (1) define the baseline characteristics; (2) estimate the risk of progression and closely characterize progression events; and (3) compare the predicted progression risk with different models, for a contemporary cohort of patients with SMM. We hypothesized that the risk of progression to MM in a modern cohort of patients would be substantially lower than historical rates.[3]

We reviewed all patients diagnosed with SMM at Columbia University Irving Medical Center (CUIMC) between January 1, 2014, and January 1, 2022. The primary outcome was the cumulative incidence of progression from SMM to MM or AL amyloidosis. We also estimated the predicted 2-year risk of progression at baseline using risk-stratification models (Mayo Clinic 20/2/20, the IMWG-SMM, and PANGEA).[8–10] For the PANGEA model, based on the personalized 2-year risk of progression, we divided patients into tertiles (low-, intermediate-, and high-risk). We also estimated the cumulative incidence of morbid progression, which was defined as the onset of the following events: lytic bone lesion(s), fracture(s), irreversible renal failure, plasma cell leukemia, and AL amyloidosis. Sankey diagrams were constructed in order to visualize the predicted risk tertiles for patients according to each of the different models.

Among 1466 patients in the database, 108 consecutive patients met diagnostic criteria for SMM after 2014. Of 108 patients, four received treatment, two had monoclonal gammopathy of renal significance, and one had incomplete data. Hence, 101 patients were included in the analysis.

The median age at diagnosis was 68.6 years (range, 44.0–90.6). Baseline demographics and clinical characteristics of the cohort are shown in Appendix SI, which also includes clinical characteristics of patients with SMM from the Olmsted County study[3] and a contemporary screening-detected cohort from the iStopMM study for comparison.[2] Our study cohort was diverse and included 39% of Hispanic ethnicity, 39% Non-Hispanic White, 18% Black, and 5% Asian. The three most common scenarios leading to SMM diagnosis were: workup of anemia/cytopenia(s) (22%), incidentally noted elevated protein or immunoglobulin levels (21%), and workup for renal dysfunction/proteinuria (14%). A detailed breakdown of the context of SMM diagnosis in all patients is summarized in Appendix SII.

The median M-spike at diagnosis was 1.3 g/dL (range, 0–3.3), with the majority (83%) having M-spike ≤2 g/dL. The median serum

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free light chain ratio (sFLCr; involved/uninvolved) was 6.2 (0.6–90.8), with the majority (81%) with sFLCr ≤ 20. A majority of patients (56%) had 11%–20% bone marrow plasma cells (BMPC), and 22% had BMPC > 20%. The most common FISH abnormalities (in decreasing order of prevalence) were del(13q)/monosomy 13 (43%; 29/68 patients), hyperdiploidy (38%; 28/73), gain/amp(1q) (28%; 16/57), and t(11;14) (22%; 15/67). At least one high-risk FISH abnormality (defined as t[4;14], t[14;16], t[14;20], +1q, del[1p], del[17p]) was present in 37.3% (22/59) of patients, with four patients having ≥2 high-risk FISH abnormalities. Baseline bone disease was ruled out by whole-body computed tomography (CT) in 19%, FDG-PET/CT in 49%, WB DW-MRI in 7%, and MRI of the spine/pelvis in 20% (18% with no advanced imaging). The median follow-up was 46.5 months (95% confidence interval [CI], 37.5–53.4). By Mayo 20/2/20 criteria, 12% of patients in our cohort were considered high-risk.

A total of 23/101 patients (22.8%) had progressed to plasma cell dyscrasia, with CRAB myeloma in 19, SLiM-defined myeloma in 1, and systemic AL amyloidosis in three patients. Figure 1 depicts the Kaplan–Meier curve for the cumulative incidence of progression. Cumulative incidence of progression to MM (CRAB or SLiM) or AL amyloidosis at 1, 2, and 3 years was 5.2% (95% CI, 2.2–11.9), 14.8% (95% CI, 8.8–23.4), and 19.1% (95% CI, 11.9–29.1), respectively. Among the 19 patients who progressed to CRAB myeloma, the most common mode of progression was isolated anemia (n = 11), followed by anemia + bone disease (n = 5) and isolated bone disease (n = 3). No patients progressed with new-onset renal impairment or hypercalcemia. The sole patient with SLiM-defined myeloma had an sFLCr >100 as their only myeloma-defining event (MDE). The cumulative incidence of morbid progression at 1, 2, and 3 years was 3.1% (95% CI, 1.0–9.3), 6.8% (95% CI, 3.1–14.4), and 8.2% (95% CI, 4.0–16.4), respectively (Appendix SIII). Notably, the presence of high-risk cytogenetic abnormalities (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 15.4% (95% CI, 7.5–29.1) in those with 0–1 HRCA (p = 0.012).

Of eight patients with bone disease as their MDE, four had >1 lytic lesion on imaging, three had vertebral compression fracture(s) (VCF), and one had a single lytic lesion. Only four patients (4% of the entire cohort) developed symptomatic bony progression (three VCFs and one lytic lesion). Among three patients that progressed with VCF, two had WB DW-MRI 1–3 months prior to disease progression, which showed diffusely increased signal in bone marrow within the spine on DWI sequences. Further details on patients progressing with bone disease are summarized in Appendix SIV.

The mean 2-year predicted risk of progression by 20/2/20 was 14.8%, while it was 8.1% with PANGEA (with BMBx), 6.3% with PANGEA (without BMBx), and 14.1% with the IMWG-SMM model. Figure 2 illustrates risk tertiles for 97 patients according to different models. Notably, 50% of high-risk patients by 20/2/20 (6/12 patients), who may be targeted for early intervention, were re-classified as intermediate risk (2-year risk of progression 8.1%–20%) by the PANGEA-BM model. Of 96 patients with both 20/2/20 and PANGEA with BMBx risk calculations available, 90/96 (94%) had a lower predicted risk with the PANGEA model, 72 (75%) had a decrease of >5% in their 2-year predicted risk, while just 6/96 (6%) had an increased predicted risk of progression to MM with PANGEA.

In summary, our study suggests that contemporary patients with SMM have a lower baseline disease burden than historically, and are overwhelmingly classified as low- or intermediate-risk. The 2-year risk of progression to MM (CRAB/SLiM) or AL amyloidosis was ~15%, substantially lower than historical estimates of 20%. Furthermore, the risk of morbid progression in contemporary patients is low, at approximately 3%/year in the first 3 years. Our SMM cohort shared comparable baseline characteristics to iSTOPMM in terms of disease
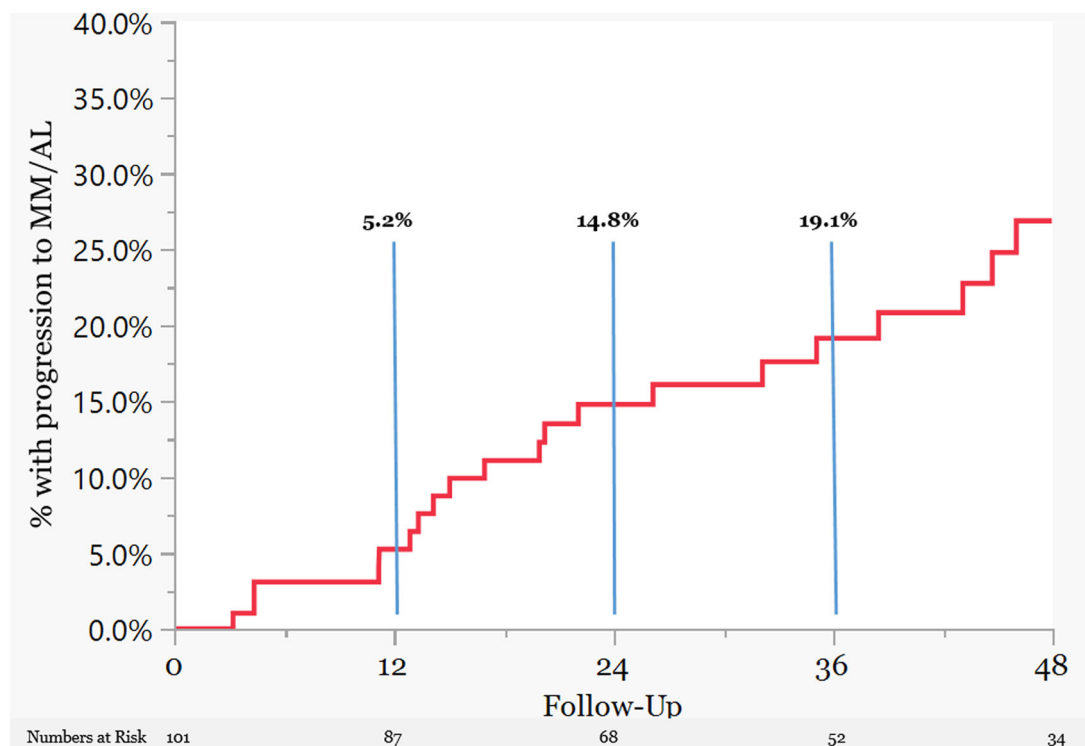

FIGURE 1 Cumulative incidence of progression to multiple myeloma at 1, 2, 3, and 4 years from smoldering multiple myeloma diagnosis.

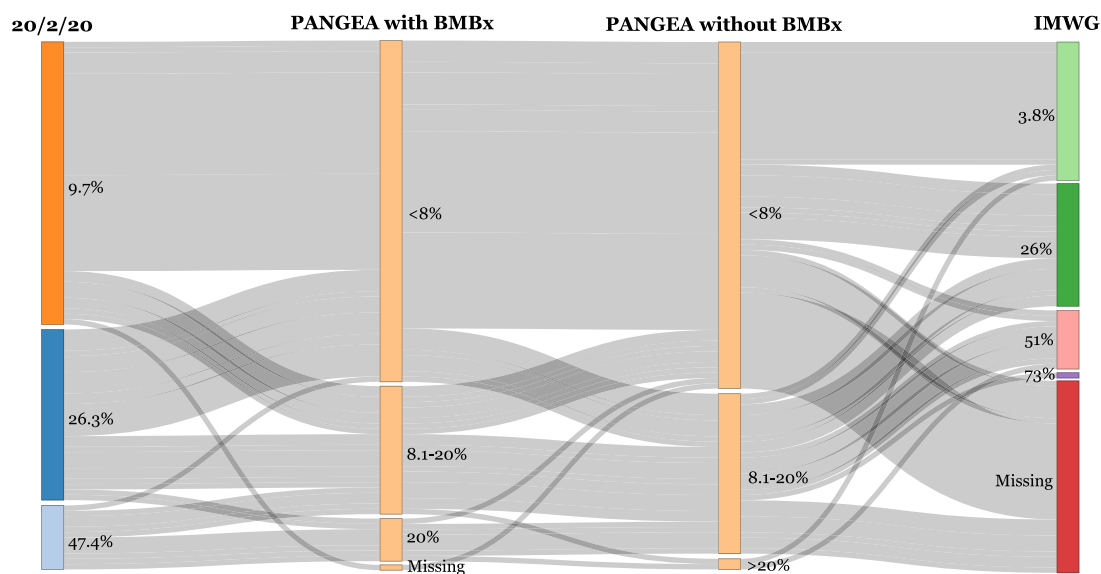**Two year risk of progression to myeloma by various risk-stratification models**

FIGURE 2 Sankey diagrams to visualize the predicted risk tertiles (2-year risk of progression) for patients according to each of the different models (Mayo 20/2/20 Model, PANGEA with Bone Marrow Biopsy, PANGEA model without Bone Marrow Biopsy, and IMWG SMM model).

burden and risk stratification.[2] Virtually none of the patients in our cohort or iSTOPMM had an M-spike >3 g/dL at diagnosis, compared to ~50% of patients in the Olmsted County study.[3] As M-spike ≥3 g/dL is one of the SMM diagnostic criteria,[1] our findings suggest that patients are mostly being diagnosed based on BMPC ≥ 10% in the modern era. Isolated anemia was the most common MDE during progression to MM (50%), followed by bone disease (36%). Since WB DW-MRI can detect focal lesions in advance of lytic lesions or fractures in myeloma, baseline, and longitudinal WB DW-MRI can be employed for active surveillance of patients with SMM who are at a high risk of progression.[14] Importantly, 2/3 of patients who progressed with VCF in our study had evidence of diffuse bone marrow infiltration in the spine on WB DW-MRI. Since diffuse bone marrow infiltration on MRI is not an MDE as per IMWG 2014 criteria, further prospective studies are needed to define the natural history of such patients. In addition, while zoledronic acid was previously shown to not affect disease progression in SMM, such studies might revisit the role of bisphosphonates in preventing bone disease for those patients with diffuse infiltration on WB DW-MRI.[15]

In addition to this study's retrospective nature, limitations include a small sample size, absence of available FISH analyses, and subsequent inability to risk stratify approximately 40% of patients using the IMWG-SMM model. Additionally, long-term follow-up is needed to characterize the risk of progression at later time points. In conclusion, compared to historical cohorts, the modern SMM phenotype (now excluding SLiM-CRAB) is characterized by lower disease burden and risk progression to MM. Therefore, we urge caution regarding whether to treat SMM. Prospective studies evaluating active surveillance in SMM are needed in order to better understand the risk-benefit tradeoff of early intervention in SMM in the modern era.

AUTHOR CONTRIBUTIONS
Rajshekhar Chakraborty, Edward R. Scheffer Cliff, and Ghulam R. Mohyuddin conceived the project and designed the study. George Mellgard, Molly Gilligan, and Rajshekhar Chakraborty performed data collection from electronic medical records, data analysis, and prepared the first draft of the manuscript. Edward R. Scheffer Cliff, Ghulam R. Mohyuddin, Divaya Bhutani, Suzanne Lentzsch, and Andrew Eisenberger critically reviewed the manuscript and provided feedback. All authors approved the final draft of the manuscript.

CONFLICT OF INTEREST STATEMENT
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
Additional supporting information can be found in the online version of this article.

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