Evaluating serum free light chain ratio as a biomarker in multiple myeloma

In 2014, the definition of multiple myeloma (MM) was updated to include serum free light chain (FLC) ratio ≥100 as a myeloma defining event (MDE).[1] This biomarker was associated with an imminent risk of progression, defined as a 2-year progression rate of around 80% and a median time to progression (TTP) of 13-15 months.[2-4] As a result, certain patients previously defined as high-risk smoldering MM (SMM) were classified as having MM requiring therapy to prevent development of CRAB criteria (hypercalcemia, renal insufficiency, anemia, or bone lesions). However, recent studies have found lower 2-year progression rates (30-44%), and longer TTP (around 40 months) associated with FLC ratio (FLCr) ≥100.[5-7] Given the disparity in reported progression rates, we aimed to evaluate the risk of progression in patients with SMM and FLCr ≥100 in a large cohort with long follow-up time. We found that patients with FLCr ≥100 as the only MDE had a more moderate risk of progression with a median TTP of 32 months. Furthermore, we found that by stratifying patients with FLCr ≥100 by Mayo-20/2/20 risk factors,[8] we could identify patients who indeed had an imminent risk of progression.

We performed a retrospective analysis of patients with SMM at Memorial Sloan Kettering Cancer Center (MSK) diagnosed 2002-2019 with follow-up until the end of 2021. Diagnosis of SMM and progression to MM or AL amyloidosis was defined according to the International Myeloma Working Group (IMWG) criteria at the time of diagnosis. Date of diagnosis and progression, baseline laboratory data within 3 months of SMM diagnosis, baseline percentage of bone marrow plasma cells (BMPC), and baseline imaging were manually reviewed. Only patients with available FLC levels (Freelite®, Binding Site) at SMM diagnosis were included in the study and only patients with an involved FLC level >10 mg/dL (100 mg/L) were included in the FLCr ≥100 group. All patients in the FLCr ≥100 group had a sustained FLCr ≥100 on at least two occasions. χ^2 test was used to compare categorical values and Mann-Whitney U test to compare continuous variables. Kaplan-Meier method was used to determine TTP, with log-rank tests for comparisons. The MSK Institutional Review Board approved the study. Participant informed consent was waived given the retrospective nature of the project.

We included 466 SMM patients; median age was 64 years and 56% were men. Sixty-five patients (14%) had a FLCr ≥100 and an involved FLC level >10 mg/dL. The median BMPC was 21% in the FLCr ≥100 group compared to 18% in the FLCr <100 group (*P*=0.001). Patients with FLCr ≥100 had a higher degree of immunoparesis and overall Mayo-20/2/20 risk.[8] At baseline, 74% patients were evaluated with advanced imaging (positron emission tomography-computed tomography [PET-CT], whole-body CT, whole-body or total spine magnetic resonance imaging [MRI]), and 26% were evaluated with a skeletal survey, data missing (N=4). Additional baseline characteristics are summarized in Table 1.

During a median follow-up period of 66 months, 42% of patients progressed to MM with a median TTP of 85 months. Among patients with FLCr ≥100, the median TTP was 32 months compared to 108 months in patients with FLCr <100, (*P*<0.001; Figure 1A). At 2 years, 38% of patients with FLCr ≥100 had progressed and at the end of follow-up, 53 patients in the FLCr ≥100 group (82%) had progressed. Among these, 28 (53%) developed bone lesions, 15 (28%) anemia, three (6%) renal insufficiency, seven (13%) had BMPC >60% as the only other MDE, and five (9%) AL amyloidosis. Among patients who progressed with renal insufficiency (CrCl 15-38 mL/min), all had recovery of renal function after initiating MM directed therapy. In total, sixty-five patients were lost to follow-up and censored at the date of last visit. Twenty patients were started on clinical trials and were censored at the date of treatment initiation. Comparing patients enrolled in clinical trials to the remaining cohort, there was no significant difference in baseline risk factors including M-spike, FLCr, or immunoparesis. No SMM patients received myeloma-directed therapy outside of clinical trials.

A sensitivity analysis including only patients diagnosed 2002-2014 prior to the updated IMWG criteria (N=300 patients; 57 patients with FLCr ≥100), yielded similar progression rates as in the whole cohort (median TTP 34 *vs*. 108 months in patients with FLCr ≥100 and FLCr <100, respectively; *P*<0.001). We also identified patients that had FLCr <100 at SMM diagnosis and developed FLCr ≥100 during follow-up (N=22). In these patients, the median TTP from developing FLCr ≥100 to progression to MM was 54 months and the 2-year progression rate was 42%.

To identify patients in the FLCr ≥100 group with an imminent risk of progression, we stratified patients based on number of Mayo-20/2/20 risk factors. Patients with two risk factors in addition to high FLCr (i.e., BMPC >20% and M-spike >2g/dL) had a median TTP of 18 months and 2-year progression rate of 75%, compared to a median TTP of 34 and 72 months, and 2-year progression rates of 50% and 17%, in patients with one or no additional risk factors, respectively (*P*<0.0001; Figure 1B).

To avoid symptomatic disease and potentially life-long consequences for patients, it is important to determine the optimal timing of MM treatment. The 2014 IMWG criteria included three ultra-high risk biomarkers as MDE, enabling treatment initiation before the development of end-organ damage.[1] However, further validation of these biomarkers found that patients with FLCr ≥100 had a considerably lower risk of progression.[5–7,9] Furthermore, several studies have

assessed the risk of progression in relation to the genomic profile and suggested distinct SMM subgroups with higher risk of progression.[10-12] These findings highlight the importance of using additional markers to identify which patients with

Table 1. Baseline patient characteristics.

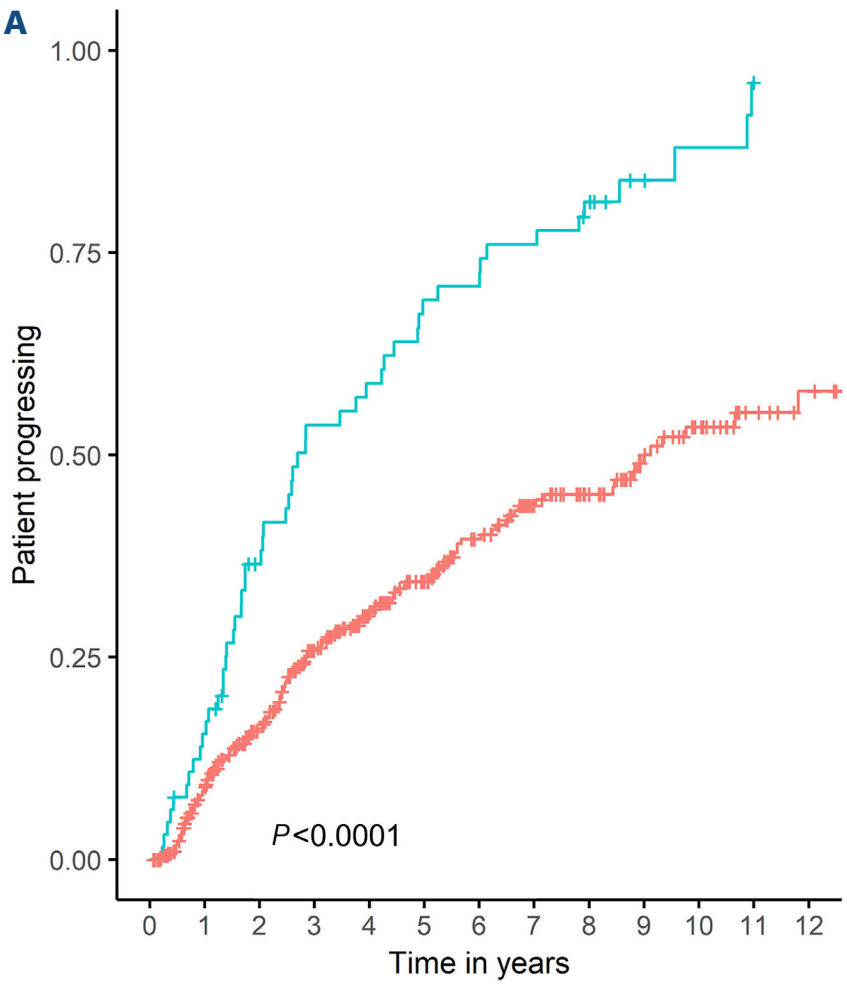
	All patients	FLC ratio <100	FLC ratio ≥100	*P*
Patients, N (%)	466	401 (86)	65 (14)	-
Age in years, median (IQR)	64 (55-72)	64 (55-72)	64 (56-70)	0.527
Sex: male, N (%)	261 (56)	230 (57)	31 (48)	0.186
Race, N (%)				
White	371 (80)	317 (79)	54 (83)	0.071
Black	49 (11)	44 (11)	5 (8.3)	-
Other	46 (9.9)	40 (10)	6 (9.2)	-
Ig heavy chain subtype, N (%)				
IgG	297 (64)	263 (66)	34 (53)	0.054
IgA	90 (19)	80 (20)	10 (15)	0.487
IgM	4 (0.9)	4 (1)	0 (0)	0.933
Biclonal	30 (6.4)	28 (7)	2 (3)	0.359
Light chain only	45 (9.7)	26 (6.5)	19 (29)	<0.001
Involved light chain, N (%)				
κ	302 (65)	266 (66)	36 (55)	0.115
λ	164 (35)	135 (34)	29 (45)	0.115
BMPC				
BMPC %, median (IQR)	18 (13-25)	18 (13-25)	21 (15-40)	0.001
10-20 %, N (%)	296 (64)	264 (67)	32 (54)	0.071
20-60 %, N (%)	156 (34)	129 (33)	27 (45.8)	0.071
>60 %, N (%)	8 (1.7)	3 (0.7)	5 (7.7)	<0.001
Data missing, N (%)	6 (1.3)	-	-	-
Serum monoclonal protein				
M-spike g/dL, median (IQR)	1.3 (0.65-2)	1.3 (0.7-2)	1 (0- 2.2)	0.321
M-spike ≤2 g/dL, N (%)	344 (75)	299 (76)	45 (72)	0.545
M-spike >2 g/dL, N (%)	113 (25)	95 (24)	18 (28)	0.545
Data missing, N (%)	9 (1.9)	-	-	-
Serum FLC, median (IQR)				
Involved FLC, mg/dL	7.5 (2.8-33.4)	5.9 (2.6-17.3)	76 (28.9-169.8)	<0.001
Uninvolved FLC, mg/dL	0.88 (0.55-1.3)	0.96 (0.6-1.4)	0.32 (0.1-0.7)	<0.001
FLC ratio (involved/uninvolved)	10.6 (3.5-44.8)	7.5 (3-22)	208 (142- 400)	<0.001
Number of depressed uninvolved Ig (%)				
0	212 (46)	201 (51)	11 (18)	<0.001
1	126 (28)	110 (28)	16 (25)	<0.001
2	120 (26)	84 (21)	36 (57)	<0.001
Data missing	8 (1.7)	-	-	-
Mayo 2/20/20 risk factors, N (%)				
0	178 (39)	178 (46)	0 (0.0)	<0.001
1	141 (31)	116 (30)	25 (40)	-
2	100 (22)	75 (19)	25 (40)	-
3	33 (7)	21 (5.4)	12 (19)	-
Data missing	14 (3)	-	-	-
Imaging, N (%)				
Advanced imaging	344 (74)	301 (75)	43 (66)	0.173
Skeletal survey	118 (25)	97	21	-
Data missing	4	-	-	-

IQR: interquartile range; Ig: immunoglobulin; FLC: free light chain; BMPC: bone marrow plasma cells; M-spike: monoclonal spike. Advanced imaging was defined as whole-body computed tomography, positron-emission tomography-computed tomography, whole-body and total spine magnetic resonance imaging.

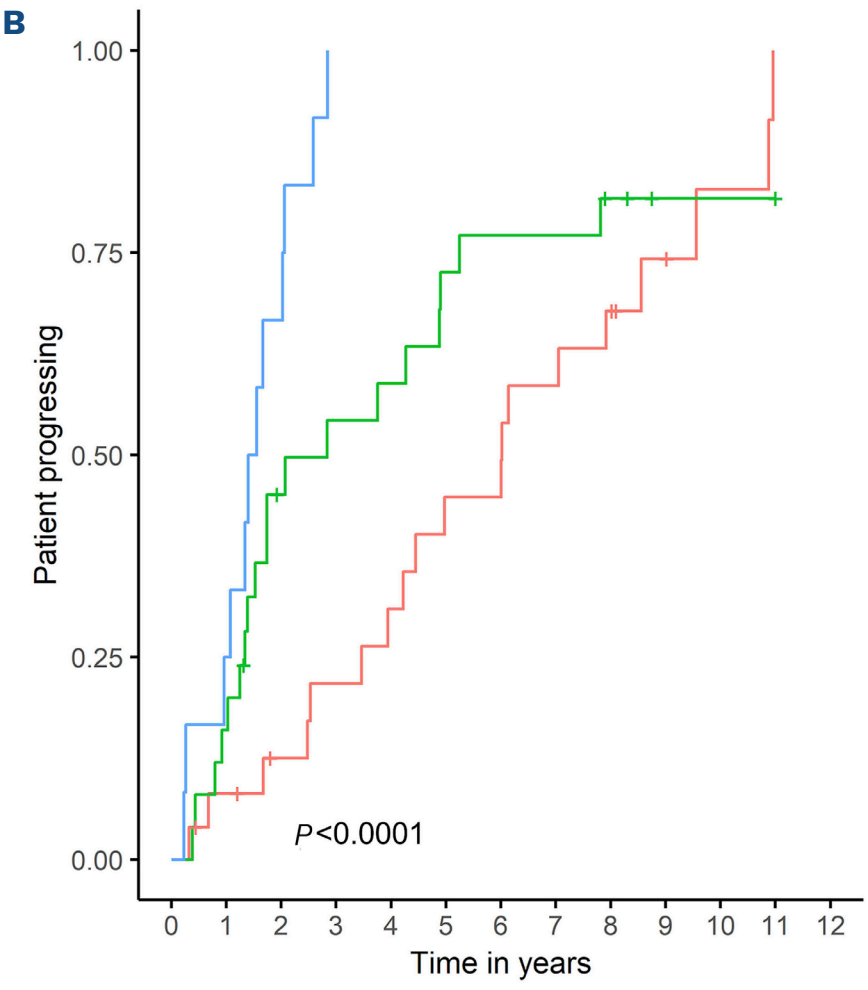
FLCr ≥100 indeed have ultra-high risk of progression, and additional tools are needed to determine which patients have malignant *versus* pre-malignant disease. In this study, we found that by stratifying patients with FLCr ≥100 by Mayo-20/2/20 risk factors, we could identify patients who indeed had an imminent risk of progression.

The median TTP to MM in this study was 85 months for the entire cohort, and 32 months for patients with FLCr ≥100 (N=65), similar to findings from several recent studies. Wu *et al*. reported a median TTP of 78 months overall, and 40 months for patients with FLCr ≥100 in 185 SMM patients diagnosed 2003-2015.[6] In a study by Visram *et al*. including 822 patients diagnosed 2000-2020, the median TTP in patients with FLCr ≥100 was 41 and 95 months, respectively, in those with high and low urine monoclonal protein levels, and 140 months in those with a FLCr <100.[7] These rates are lower than the two initial studies assessing TTP in relation to FLCr.[2,3] These differences are likely attributable to differences in the study periods, some dating back to 1970,[3] and the availability of advanced imaging techniques such as PET-CT and MRI. Notably, 74% of our patients underwent baseline evaluation with advanced imaging, which likely appropriately excluded patients with active MM that may have been included in earlier studies and contributed to the risk beyond the FLCr alone. In the current diagnostic landscape of MM where most patients undergo baseline evaluation with advanced imaging, a FLCr ≥100 alone may be associated with a more moderate risk of progression to MM.

A strength of this study is the large patient cohort with manually curated data. One limitation of the study is that patients with FLCr ≥100 diagnosed after 2014 that were monitored without treatment may have been low-risk by other measures motivating the clinician to manage them observantly. To assess this bias, we performed a sensitivity analysis including only patients diagnosed prior to 2015, and we found a similar progression rate as in the whole cohort. The use of whole-body MRI to assess the MRI biomarker criterium was limited in the earlier years of the



	Median TTP (95% CI)
FLC-ratio ≥100	32 months (25-59)
FLC-ratio <100	108 months (85-118)



	Median TTP (95% CI)
FLC-ratio + M-spike + BMPC	18 months (13-NA)
FLC-ratio + M-spike/BMPC	34 months (18-63)
FLC-ratio only	72 months (51-NA)

Figure 1. Time to progression stratified by free light chain ratio ≥100 and by number of Mayo-2/20/20 risk factors. Panel (A) includes the whole cohort, comparing free light chain (FLC) ratio ≥100 to FLC ratio <100. Panel (B) includes patients with FLC ratio ≥100 only, stratified by number of Mayo-2/20/20 risk factors. TTP: time to progression; M-spike: monoclonal spike; BMPC: bone marrow plasma cells; CI: confidence interval; N/A: not applicable.

study. Further limitations are the lack of genomic data and the lack of serial FLC levels, as studies have demonstrated that evolution of disease biomarkers is a risk factor of progression.[6,13]

To conclude, in this large cohort of SMM patients with long follow-up time we found that most patients with FLCr ≥100 did not have an imminent risk of progression to MM. In our cohort, the median TTP was 32 months, and the 2-year progression rate was 38%. SMM patients with FLCr ≥100 were a heterogenous group with varying disease risk, where those with a high Mayo-20/2/20 score (i.e., both BMPC >20% and M-spike >2g/dL) indeed had an imminent risk of progression with a median TTP of 18 months and a 2-year progression rate of 75%. On the other hand, patients with otherwise low risk by Mayo-20/2/20 (i.e. BMPC ≤20% and M-spike ≤2g/dL), had a substantially lower median TTP of 72 months and 2-year progression rate of 17%. These findings suggest that for patients with FLCr ≥100 as the sole MDE, clinical judgement is warranted and patients who are otherwise low-risk may be considered for close monitoring rather than early treatment. Considering additional markers of high-risk disease such as the Mayo-20/2/20 risk factors or rapid increase in FLCr can help identify patients who are at imminent risk of progression.

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Contributions

TA, OL, and MH designed the study. TA and KM collected the data. TA performed statistical analysis. TA and MH drafted the manuscript.

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Data-sharing statement

The datasets generated and analyzed during the current study are not publicly available as it includes protected health information but are available from the corresponding author on reasonable request.

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