Serum B-cell maturation antigen could be a simple and accurate biomarker to identify and prognosticate monoclonal gammopathy of undetermined significance and smoldering multiple myeloma

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are plasma cell (PC) disorders. Both conditions vary in their risk of progressing to symptomatic multiple myeloma (MM). Several prognostic models have been proposed,[1,2] and the 2/20/20 model is a commonly used risk stratification system based on three factors: serum M protein (SMP) ≥2 g/dL, serum free light chain ratio (sFLCr) ≥20, and bone marrow PC percentage (BMPC%) ≥20.[1] Risk is classified as low, intermediate or high based on the presence of 0, 1 or 2 or more of these factors. Additionally, the presence of certain cytogenetic abnormalities determined by fluorescence *in situ* hybridization (FISH) may also influence risk stratification.

B-cell maturation antigen (BCMA) is an important biomarker involved in the development and survival of B cells and is primarily expressed on the surface of mature B lymphocytes and PC.[3] Cleavage of BCMA by γ-secretase complex called serum BCMA (sBCMA) releases ssBCMA into circulation and may reflect the change of disease activity in MM.[4,5] However, only a few studies to date have integrated sBCMA values into risk models for disease progression.[6,7] This study aims to evaluate sBCMA levels in patients with MGUS, SMM, and MM and investigate the correlation between sBCMA and other biomarkers, including cytogenetic abnormalities. Additionally, it assesses whether sBCMA can serve as a marker of disease progression in patients with MGUS and SMM. This study was approved by the Ethics Committee of Kameda Medical Center.

A total of 296 patients (172 patients with MGUS and 124 with SMM) identified between 2006 and 2022 at Kameda Medica Center, Kamogawa, Japan were included in the study. All the included patients underwent bone marrow examination, and most patients with SMM (81.5%) received both computed tomography (CT) and magnetic resonance imaging (MRI). Frozen serum samples at -40°C from these patients were used for analysis. Of these, 40 patients with amyloid light-chain amyloidosis were included in the group of 28 patients with MGUS and 12 with SMM. For comparison, we included 75 patients newly diagnosed with MM between January 2021 and 50 healthy individuals at our center. The baseline demographics and laboratory characteristics are shown in *Online*

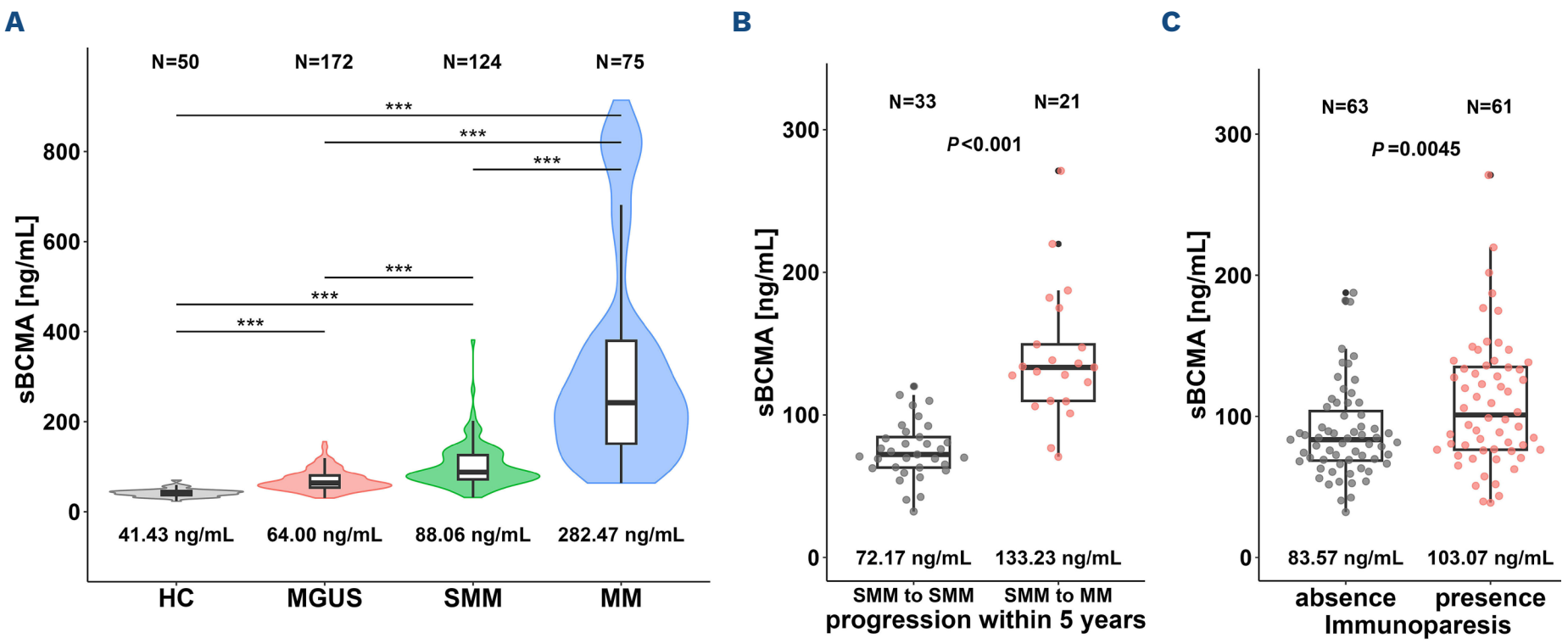

Figure 1. The violin plot and box-and-whisker plot demonstrate the distribution of serum B-cell maturation antigen levels. (A) Serum B-cell maturation antigen (sBCMA) levels increased with disease progression, reaching their highest levels in patients with active multiple myeloma (MM). (B) Patients who progressed to active MM within 5-years exhibited higher sBCMA levels in smoldering multiple myeloma (SMM). (C) Patients with immunoparesis demonstrated higher sBCMA levels compared to those without. HC: healthy control; MGUS: monoclonal gammopathy of undetermined significance.

Supplementary Table S1. The median follow-up time was 32.5 months with (interquartile range [IQR], 9.25-64.75) for MGUS and 51 (interquartile range [IQR], 26.0-109.0) months for SMM. Among the patients with SMM, the percentage of patients who progressed to MM at 3 and 5 years was 23.2% (13/56) and 38.9% (21/54), respectively. The diagnostic and response criteria were in accordance with the revised International Myeloma Working Group 2014 criteria. Seven patients with MGUS progressed to SMM, three to MM, and one to Waldenström macroglobulinemia. sBCMA was measured by enzyme-linked immunosorbent assay with a polyclonal anti-BCMA antibody (Human BCMA/TNFRSF17 DuoSet ELISA DY193 - R&D Systems, Minneapolis, MN, USA).

Figure 1A compares sBCMA levels in healthy control (HC) with MGUS, SMM, and MM. Significant increases in sBCMA levels were observed with disease progression from HC to MGUS, SMM, and MM, with median values of 41.4 (IQR, 37.1- 46.3), 64.0 (IQR, 53.8-80.6), 88.1 (IQR, 71.5-124.4), and 282.5 (IQR, 170.8-591.7) ng/mL, respectively (P<0.001). The median values for HC, MGUS, and SMM groups were comparable to those previously reported.[5-8]

The patients with SMM who progressed had significantly higher baseline sBCMA levels compared to those who did not (133.2 ng/mL *vs*. 72.27 ng/mL; P<0.001) (Figure 1B) Patients with immunoparesis exhibited elevated sBCMA levels (Figure 1C). A strong correlation between sBCMA levels and BMPC% was observed (Pearson r=0.78; P<0.001), which was also seen between sBCMA and the paraprotein levels of immunoglobulin (Ig)G, IgA, and involved free light chain (FLC) (Pearson r=0.746, 0.741, and 0.669, respectively; P<0.001) (*Online Supplementary Figure S1A-D*). Cytogenetic abnormalities, including Del(13q), t(4;14), t(14;16), t(11;14), and Del(17p), as detected by FISH, were not associated with sBCMA levels (*Online Supplementary Figure S2*). However, patients with 1q+ exhibited significantly higher sBCMA levels than those without (1q+ *vs*. no 1q+: 120.3 ng/mL *vs*. 87.2 ng/mL; P=0.0015).

Based on the Youden index, the optimal sBCMA cut-off used to differentiate healthy individuals from patients with plasma cell dyscrasia was 50.10 ng/mL (sensitivity, 90.0%; specificity, 89.5%). The optimal cutoff for differentiating MM from SMM was 187.8 ng/mL (sensitivity, 95.8%; specificity, 74.3%). However, the optimal cutoff for MGUS and SMM was not determined due to the overlapping sBCMA levels. Over the 5-year follow-up, 21 patients with SMM progressed to active MM, and 33 patients did not. The ROC curve analysis to detect the progression of SMM within a 5-year period yielded a cut-off value of 101.00 ng/mL, exhibiting a sensitivity of 83.8% and a specificity of 90.0%. For convenience and simplicity, we set the 100 ng/mL as the cut-off level for sBCMA to detect the progression high-risk group.

To predict progression from SMM to MM, BMPC%, SMP level, involved and uninvolved sFLCr, presence or absence of immunoparesis, and presence or absence of any of the cytogenetic abnormalities and a high sBCMA level was examined (Table 1). Univariate analysis revealed that all of the above factors were associated with progression of symptomatic MM. Combinations of two or three variables,

Table 1. Univariate and multivariate analysis with Cox proportional hazards model for risk factors for progression in smoldering multiple myeloma.

Risk factor	Univariate model	
	Hazard ratio (95% CI)	*P*
BMPC% >20, N=29 ≤20, N=66	2.459 (1.021-5.923)	0.0378
serum M-protein g/dL >2, N=51 ≤2, N=44	4.376 (1.638-11.69)	0.00733
serum FLC ratio >20, N=12 ≤20, N=83	4.975 (1.961-12.62)	0.00018
Immunoparesis Present, N=45 Absent, N=50	3.615 (1.312-9.965)	0.00778
soluble BCMA ng/mL >100, N=31 ≤100, N=64	28.1 (6.473-122)	< 0.00001
Cytogenetic abnormalities Del(13q), N=22 t(4;14), N=5 t(14;16), N=3 t(11;14), N=27 1q+, N=22 Del(17p), N=2 High-riskCA, N=28	 1.573 (0.5374-4.604) 2.621 (0.3402-20.19) 2.488 (0.5635-10.98) 0.853 (0.2801-2.599) 1.968 (0.7621-5.083) <0.001 2.832 (1.147-6.993)	0.018
	Multivariate model (Cox)	
	Hazard ratio (95% CI)	***P***
sBCMA >100 BMPC% >20 sFLCr >20	22.19 (4.903-100.4) 0.9397 (0.3645-2.422) 1.799 (0.6603-4.902)	<0.0001 0.8976 0.2508
sBCMA >100 SMP >2 sFLCr >20	19.72 (4.327-89.89) 2.069 (0.7823-5.47) 1.576 (0.6117-4.061)	0.00012 0.1429 0.3461
sBCMA >100 SMP >2 BMPC% >20	22.61 (5.059-101.1) 0.9615 (0.39-2.37) 2.213 (0.8311-5.894)	<0.0001 0.932 0.1119
sBCMA >100 SMP >2	22.4 (5.089-98.61) 2.195 (0.8389-5.745)	<0.0001 0.1091
sBCMA >100 BMPC% >20	24.96 (5.657-110.1) 1.129 (0.4671-2.728)	<0.0001 0.788
sBCMA >100 sFLCr >20	22 (4.89-99.01) 1.758 (0.6888-4.486)	<0.0001 0.238
sBCMA >100 Immunoparesis	19.63 (4.319-89.22) 2.169 (0.7023-6.696)	0.00012 0.1784
sBCMA > 100 High-risk CA	33.36 (4.351-255.8) 2.001 (0.7865-5.091)	<0.001 0.1454

CI: confidence interval; BMPC: bone marrow plasma cell; SMP: serum M-protein; FLC: free light chain; sFLCr: involved/uninvolved serum free light chain ratio; BCMA: B-cell maturation antigen; sBCMA: serum BCMA; CA: cytogenetic abnormalities.

including sBCMA levels, were considered, and multivariate analysis identified sBCMA levels higher than 100 ng/mL as an independent predictor of prognosis in all combinations (Table 1). A comparison of 5-year progression rates to symptomatic MM was made in the SMM cohort using two models: one based on an sBCMA cutoff of 100 ng/mL and the other based on the 2/20/20 model (Figure 2A-C). The patients with sBCMA levels below 100 ng/mL showed significantly reduced likelihood of progression to MM. The progression risk to MM at 5 years was 74.9% (95% confidence interval [CI]: 55.0-90.9) for patients with sBCMA levels >100 ng/mL. In the 2/20/20 model, the progression risks at 5 years in low-intermediate and high-risk groups were 14.1% (95% CI: 4.6-38.7), 26.3% (95% CI: 13.0-48.6), and 65.4% (95% CI: 45.1-84.6), respectively. ROC curve analysis revealed that sBCMA >100ng/mL provided superior prognostic accuracy compared to the high-risk groups identified in the 2/20/20 model with an area under the ROC curve [AUC]) of 0.89 (95% CI: 0.803-0.977) compared to 0.78 (95% CI: 0.582-0.834) for the 2/20/20 high-risk group. DeLong's test confirmed the significant difference between the two AUC (*P*=0.0068), supporting the superior predictive performance of the sBCMA-based classification.

Our study examined the relationship between sBCMA and various factors related to the prognosis of MM. We observed that sBCMA increased as the disease progressed and demonstrated a strong correlation with the BMPC%. Additionally, sBCMA correlated with paraprotein levels, irrespective of the type of MM, and elevated in patients with immunoparesis. Our findings were similar to Berenson *et al.*,[6] but Visram *et al.*[7] reported slightly higher sBCMA levels. These differences may result from variations in patient selection, as many MGUS patients lacked bone marrow examinations, and some SMM patients were diagnosed without adequate imaging. Other than 1q+, sBCMA showed no correlation with chromosomal anomalies detectable by FISH, consistent with our previous findings in symptomatic MM.[9] One potential explanation is that the gene encoding anterior pharynx 1A (APH1A), a component of the γ-secretase complex, is located at 1q21.[10]

The 2/20/20 model aims to predict the progression of myeloma-defining lesions in patients with SMM by detecting them through routine laboratory testing. However, recent observations indicate that even with such active surveillance, end-organ damage at the time of progression cannot always be prevented, and in a quarter of patients who progressed to MM, it could not be diagnosed with routine surveillance testing.[11] In this study, we examined whether sBCMA stratification is more effective than the 2/20/20 model for prognostication in SMM. We divided the SMM cohort into two groups using an sBCMA cutoff of 100 ng/mL and compared the results with the 2/20/20 model. sBCMA stratification was found to predict progression with greater accuracy than the 2/20/20 model. It predicts progression solely from blood test data without requiring bone marrow examination, FISH, diffusion magnetic resonance imaging, and whole-body CT.

This study has some limitations, including a relatively small number of patients, its single-center retrospective design, the lack of external validation, and the inclusion of patients with short follow-up periods. Moreover, it is possible that sBCMA levels may differ in relation to γ-secretase activity or BCMA expression in tumor cells,[10,12,13] and this aspect has not been investigated in the present study. However, this is one of the largest comprehensive studies of sBCMA using stored sera from patients with MGUS and SMM.

In conclusion, this study demonstrates that sBCMA levels

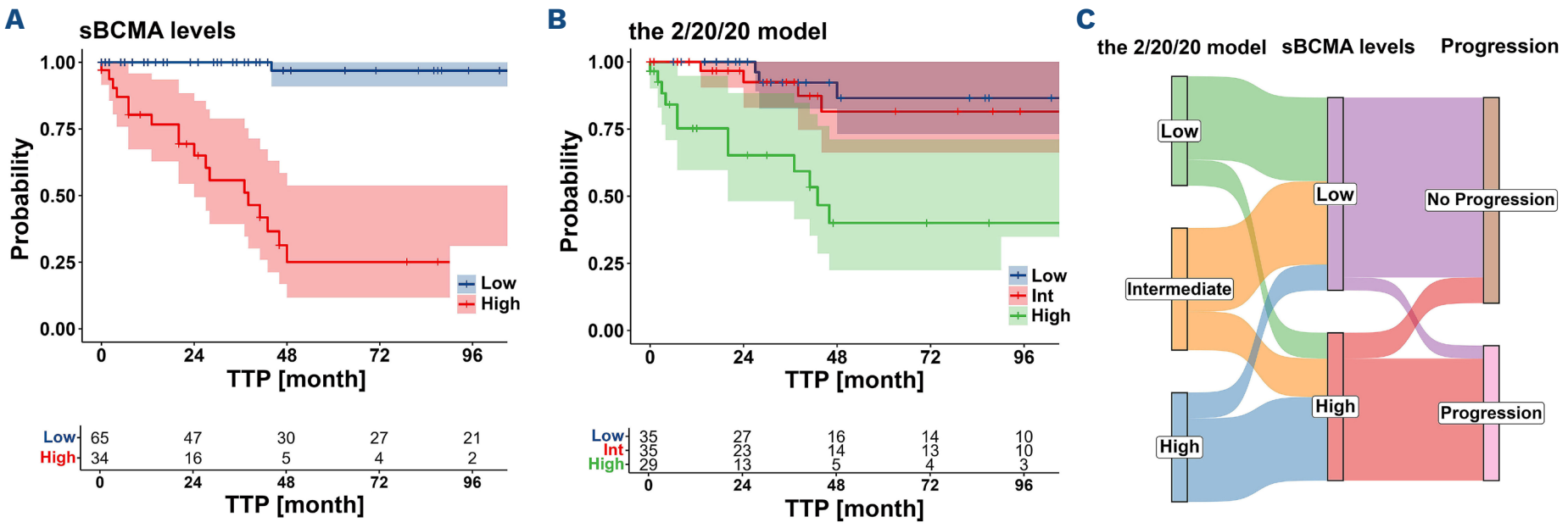

Figure 2. Progression of smoldering multiple myeloma to symptomatic multiple myeloma within a 5-year period according to the serum B-cell maturation antigen level and the 2/20/20 model. (A) Kaplan-Meier curve representing time to progression (TTP) to symptomatic multiple myeloma (MM) within 5 years for each classification based on a cutoff of 100 ng/mL of serum B-cell maturation antigen (sBCMA) levels in patients with smoldering MM (SMM). (B) Kaplan-Meier curve representing TTP to symptomatic multiple myeloma (MM) within 5 years for each classification based on the 2/20/20 model in SMM patients. (C) The Sankey diagram illustrates the SMM classification by the 2/20/20 model and how these changes when stratified by the sBCMA levels. Int: intermediate.

serve as a valuable biomarker to distinguish SMM from active MM and predicting disease progression in SMM patients. Elevated sBCMA levels correlate strongly with BMPC% and paraprotein levels, highlighting its role in assessing tumor burden. Additionally, sBCMA levels >100 ng/mL were an accurate predictor of disease progression from SMM to MM within 5 years. To further confirm our findings, future studies with larger cohorts and external validation are needed.

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Disclosures

No conflicts of interest to disclose.

Contributions

MToho, DI and KM designed the study, interpreted the data, performed the statistical analysis, provided patient care, and wrote the manuscript. MO, FF, HS, AU, RT, KN, and MTakeuchi provided the patient care. SA, CM, TW and YO measured sBCMA levels. All authors critically reviewed and approved the manuscript.

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Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable request.

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