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**Letter to the Editor**

# 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

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**Running title: Serum BCMA in MGUS and SMM**

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**To the Editor,**

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 gamma-secretase complex releases called serum BCMA (sBCMA) 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. All the included patients underwent BM examination, and most patients with SMM (81.5%) received both CT and MRI. Frozen serum samples at -40°C from these patients were used for analysis. Of these, 40 patients with AL 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 Table S1. The median follow-up time was 32.5 (9.25–64.75) and 51 (26–109) months for MGUS and SMM, respectively. 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, United States).

Figure 1, A 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 and interquartile range of 41.4 (37.1–46.3), 64.0 (53.8–80.6), 88.1 (71.5–124.4), and 282.5 (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 1, B) Patients with immunoparesis exhibited elevated sBCMA levels (Figure 1, C). 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 IgG, IgA, and involved free light chain (FLC) (Pearson $r = 0.746$, 0.741, and 0.669, respectively, $p < 0.001$) (Figure 1S, A–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 (Figure 2S). 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 cut-off for differentiating MM from SMM was 187.8 ng/mL (sensitivity, 95.8%; specificity, 74.3%). However, the optimal cut-off 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, 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 cut-off of 100 ng/mL and the other based on the 2/20/20 model (Figure 2, A-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% 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 AUCs (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 multiple myeloma (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 gamma-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 cut-off 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 MRI, 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 gamma-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 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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Table

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

| Risk factor | Univariate model | | Multivariate model (Cox | | |
|---|---|---|---|---|---|
| | Hazard ratio (95% CI) | p-value | | Hazard ratio (95% CI) | p-value |
| **BMPC percentage** | | | **sBCMA > 100** | 22.19 (4.903–100.4) | **< 0.0001** |
| **> 20% (n = 29)** | 2.459 (1.021–5.923) | **0.0378** | **BMPC% > 20** | 0.9397 (0.3645–2.422) | 0.8976 |
| **≤ 20% (n = 66)** | | | **sFLCr > 20** | 1.799 (0.6603–4.902) | 0.2508 |
| **serum M-protein** | | | | | |
| **> 2 g/dL (n = 51)** | 4.376 (1.638–11.69) | **0.00733** | **sBCMA > 100** | 19.72 (4.327–89.89) | **0.00012** |
| **≤ 2 g/dL (n = 44)** | | | **SMP > 2** | 2.069 (0.7823–5.47) | 0.1429 |
| **serum FLC ratio** | | | **sFLCr > 20** | 1.576 (0.6117–4.061) | 0.3461 |
| **> 20 (n = 12)** | 4.975 (1.961–12.62) | **0.00018** | | | |
| **≤ 20 (n = 83)** | | | **sBCMA > 100** | 22.61 (5.059–101.1) | **< 0.0001** |
| **Immunoparesis** | | | **SMP > 2** | 0.9615 (0.39–2.37) | 0.932 |
| **Present (n = 45)** | 3.615 (1.312–9.965) | **0.00778** | **BMPC% > 20** | 2.213 (0.8311–5.894) | 0.1119 |
| **Absent (n = 50)** | | | | | |
| **soluble BCMA** | | | **sBCMA > 100** | 22.4 (5.089–98.61) | **< 0.0001** |
| **> 100 ng/mL (n = 31)** | 28.1 (6.473–122) | **< 0.00001** | **SMP > 2** | 2.195 (0.8389–5.745) | 0.1091 |
| **≤ 100 ng/mL (n = 64)** | | | | | |
| **Cytogenetic abnormalities** | | | **sBCMA > 100** | 24.96 (5.657–110.1) | **< 0.0001** |
| **Del(13q) (n = 22)** | 1.573 (0.5374–4.604) | | **BMPC% > 20** | 1.129 (0.4671–2.728) | 0.788 |
| **t(4;14) (n = 5)** | 2.621 (0.3402–20.19) | | | | |
| **t(14;16) (n = 3)** | 2.488 (0.5635–10.98) | | **sBCMA > 100** | 22 (4.89–99.01) | **< 0.0001** |

| | | | | | |
|---|---|---|---|---|---|
| **t(11;14) (n = 27)** | 0.853 (0.2801–2.599) | | **sFLCr > 20** | 1.758 (0.6888–4.486) | 0.238 |
| **1q+ (n = 22)** | 1.968 (0.7621–5.083) | | | | |
| **Del(17p) (n = 2)** | <0.001 | | **sBCMA > 100** | 19.63 (4.319–89.22) | **0.00012** |
| **High-risk CAs (n = 28)** | 2.832 (1.147–6.993) | **0.018** | **Immunoparesis** | 2.169 (0.7023–6.696) | 0.1784 |
| | | | **sBCMA > 100** | 33.36 (4.351–255.8) | **< 0.001** |
| | | | **High-risk CAs** | 2.001 (0.7865–5.091) | 0.1454 |

Abbreviation: *BMPC;* bone marrow plasma cell, *BMPC%*; bone marrow plasma cell percent, *SMP*; serum M-protein, *FLC*; free light chain, *sFLCr*; involved / uninvolved serum free light chain ratio, *BCMA;* B-cell maturation antigen, *CAs;* cytogenetic abnormalities

## Figures

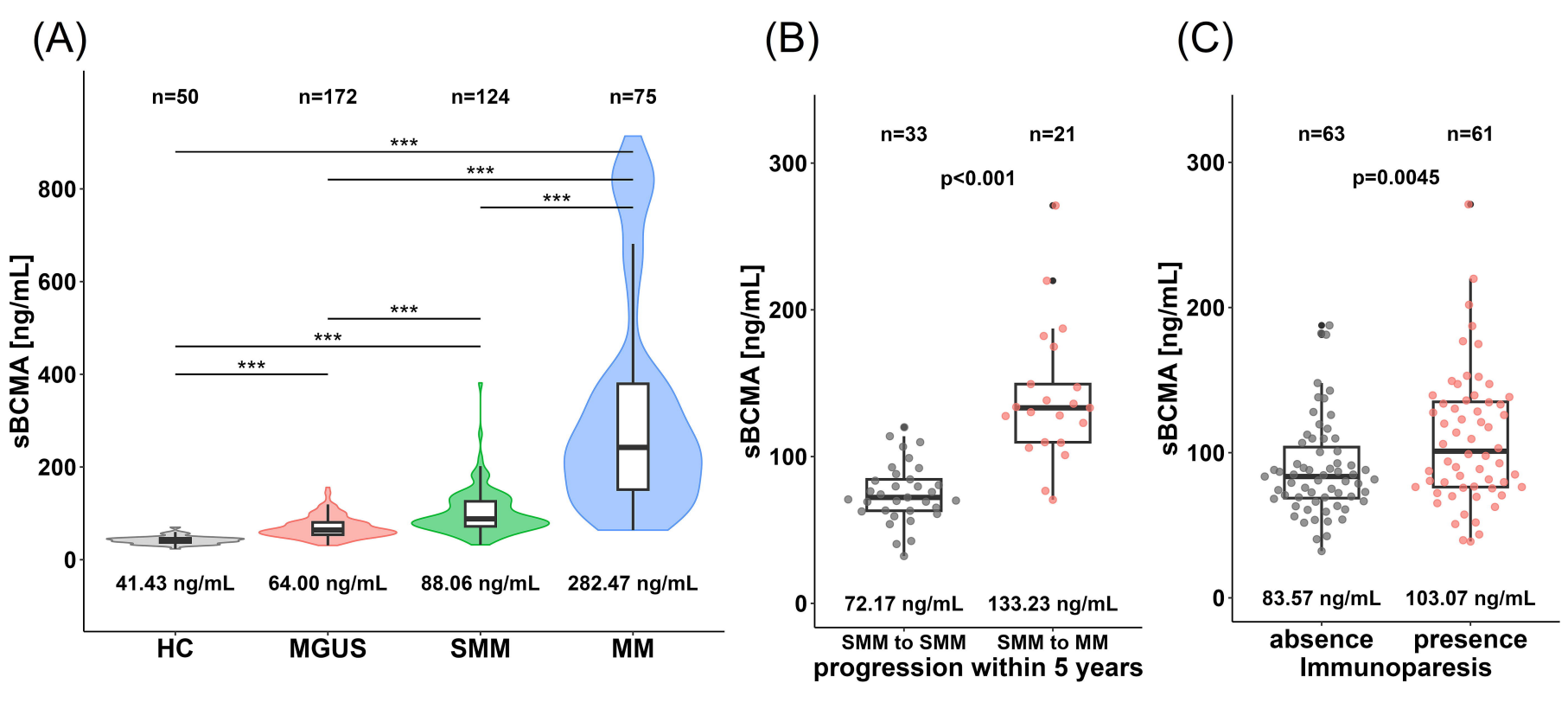
### Figure legends

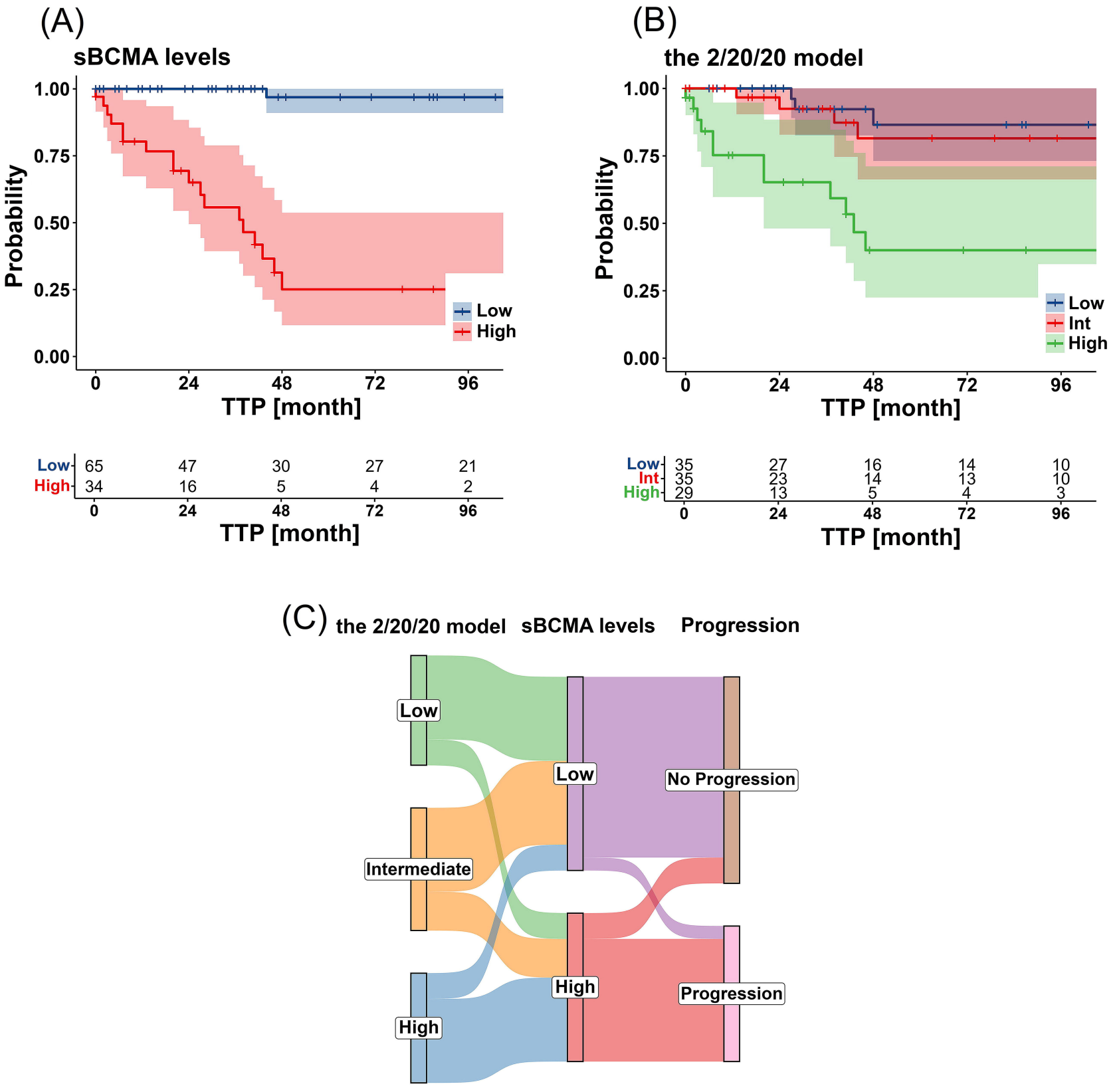
**Figure 1.** The violin plot and box-and-whisker plot demonstrate the distribution of sBCMA levels. (A) sBCMA levels increased with disease progression, reaching their highest levels in patients with active MM. (B) Patients who progressed to active MM within 5-years exhibited higher sBCMA levels in SMM. (C) Patients with immunoparesis demonstrated higher sBCMA levels compared to those without.

Abbreviations: *HC*; healthy control, *MGUS*; monoclonal gammopathy of undetermined significance, *SMM*; smoldering multiple myeloma, *MM*; multiple myeloma, *sBCMA*; serum B-cell maturation antigen

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

Abbreviations: *SMM*; smoldering multiple myeloma, *MM*; multiple myeloma, *sBCMA*; serum B-cell maturation antigen, *TTP*; time to progression, *Int*; Intermediate


(A)
n=50
n=172
n=124
n=75
***
***
***
***
***
***
sBCMA [ng/mL]
800
600
400
200
0
41.43 ng/mL
64.00 ng/mL
88.06 ng/mL
282.47 ng/mL
HC
MGUS
SMM
MM
(B)
n=33
n=21
p<0.001
sBCMA [ng/mL]
300
200
100
0
72.17 ng/mL
133.23 ng/mL
SMM to SMM
SMM to MM
progression within 5 years
(C)
n=63
n=61
p=0.0045
sBCMA [ng/mL]
300
200
100
0
83.57 ng/mL
103.07 ng/mL
absence
presence
Immunoparesis


(A)
sBCMA levels
Probability
1.00
0.75
0.50
0.25
0.00
0
24
48
72
96
TTP [month]
Low
High
Low 65 47 30 27 21
High 34 16 5 4 2
0
24
48
72
96
TTP [month]
(B)
the 2/20/20 model
Probability
1.00
0.75
0.50
0.25
0.00
0
24
48
72
96
TTP [month]
Low
Int
High
Low 35 27 16 14 10
Int 35 23 14 13 10
High 29 13 5 4 3
0
24
48
72
96
TTP [month]
(C)
the 2/20/20 model
sBCMA levels
Progression
Low
Intermediate
High
Low
High
No Progression
Progression

**Supplemental material**

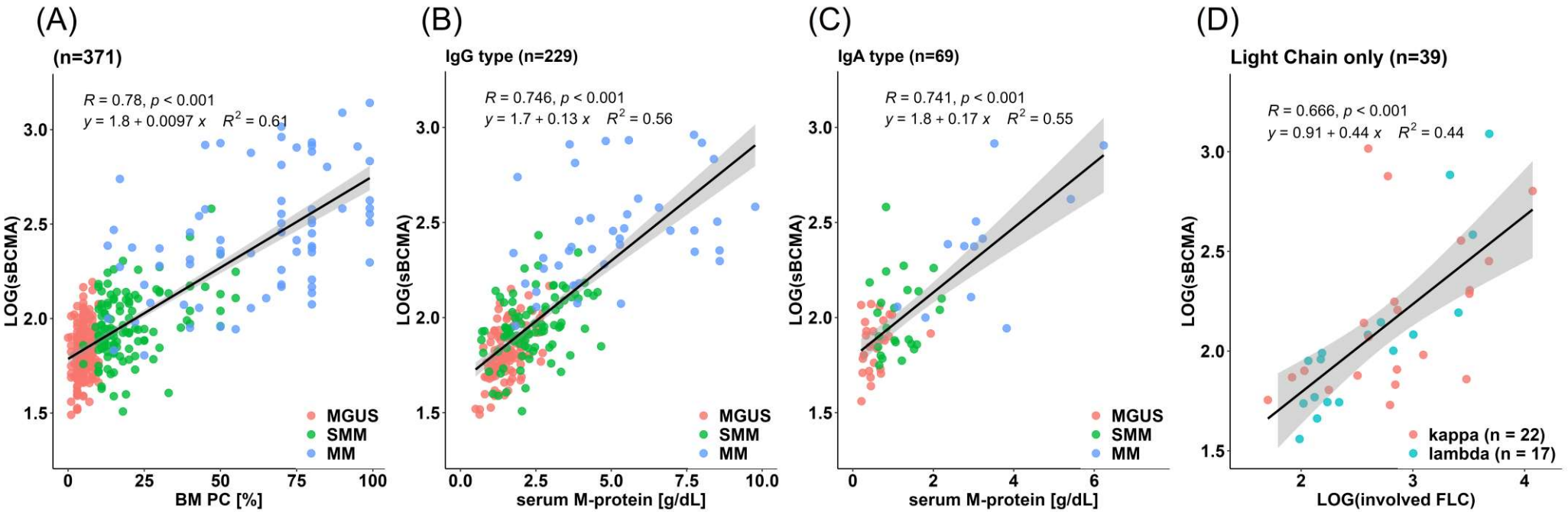
**Table 1S. Patient characteristics of MGUS, SMM, and MM**

| | MGUS | SMM | MM |
|---|---|---|---|
| **Total number of patients** | 202 | 138 | 75 |
| **Number of patients for final analysis (%)** | 172 (85.2) | 124 (89.8) | 75 (100) |
| | | | |
| **Age at diagnosis (years), median (IQR)** | 72 (64–79) | 71 (63.5–79) | 74 (67–80.5) |
| **Female - n (%)** | 66 (38.4) | 56 (45.2) | 26 (34.7) |
| **Male - n (%)** | 106 (61.6) | 68 (54.4) | 49 (65.3) |
| | | | |
| **Immunoglobulin type - n (%)** | | | |
| **IgG type** | 106 (61.6) | 88 (71.0) | 41 (54.7) |
| **IgA type** | 29 (16.9) | 25 (20.2) | 16 (21.3) |
| **IgM type** | 23 (13.4) | 0 | 0 |
| **IgD type** | 0 | 1 (0.8) | 3 (4) |
| **Light Chain only** | 14 (8.1) | 10 (8.1) | 14 (18.7) |
| **Non-secretary** | 0 | 0 | 1 (1.3) |
| | | | |
| **Bone marrow plasma cell (%), median (IQR)** | 5.0 (3.0–7.0) | 15.0 (11.71–22.48) | 70.0 (40.0–80.0) |
| **Serum M-protein (g/dL), median (IQR)** | 1.19 (0.69–1.69) | 1.99 (1.36–2.82) | 4.12 (3.05–5.66) |
| **Hemoglobin (g/dL), median (IQR)** | 12.2 (10.5–14.1) | 12.4 (11.1–13.9) | 9.4 (8.43–11.8) |
| **Calcium (mg/dL), median (IQR)** | 9.4 (9.1–9.6) | 9.4 (9.2–9.8) | 9.65 (9.3–10) |
| **Creatinine (mg/dL), median (IQR)** | 0.95 (0.68–1.43) | 0.8 (0.64–1.07) | 1.01 (0.74–1.45) |
| **Creatinine Clearance (mL/min), median (IQR)** | 85.51 (51.01–108.38) | 89.22 (70.22–110.27) | 70.7 (41.7–103.6) |
| **Serum FLC ratio, median (IQR)** | 1.67 (1.10–2.78) | 3.71 (1.70- 11.61) | 34.67 (9.35–108.16) |

| | | | |
|---|---|---|---|
| **Immunoparesis - n (%)** | 51 (29.7) | 61 (49.2) | 68 (90.7) |
| **Circulating plasma cells - n (%)** | 70 (40.7) | 72 (58.1) | 69 (92) |
| **(x 10^-5), median (IQR)** | 2.104 (0–29.88) | 16.47 (0.72–100.0) | 551.0 (53.32–7003) |
| **Bone marrow plasma-cell FISH - positive/all (%)** | | | |
| **Del(13q)** | 11/84 (13.1) | 24/83 (28.9) | 33/74 (44.6) |
| **t(4;14)** | 2/91 (2.2) | 6/100 (6) | 13/74 (17.6) |
| **t(14;16)** | 0/88 (0) | 3/95 (3.2) | 3/74 (4.1) |
| **t(11;14)** | 19/98 (19.4) | 28/93 (30.1) | 20/74 (27) |
| **1q+** | 6/101 (5.9) | 22/95 (23.2) | 29/73 (39.7) |
| **Del(17p)** | 0/111 (0) | 2/101 (2.0) | 5/75 (6.7) |
| **Imaging - n (%)** | | | |
| **Xray** | 172 (100) | 124 (100) | 75 (100) |
| **CT** | 157 (91.3) | 120 (96.8) | 75 (100) |
| **MRI** | 75 (43.6) | 104 (83.9) | 74 (98.7) |
| **PET-CT** | 32 (18.6) | 72 (58.1) | 75 (100) |
| **CT and MRI** | 73 (42.4) | 101 (81.5) | 74 (98.7) |

Abbreviation: *MGUS*; monoclonal gammopathy of undetermined significance, *SMM*; smoldering multiple myeloma, *MM*; multiple myeloma, *IQR*; interquartile range, *Ig*; immunoglobulin, *FLC*; free light chain, *FISH*; fluorescence in situ hybridization, *CT*; computed tomography, *MRI*; magnetic resonance imaging, *PET*; positron emission tomography

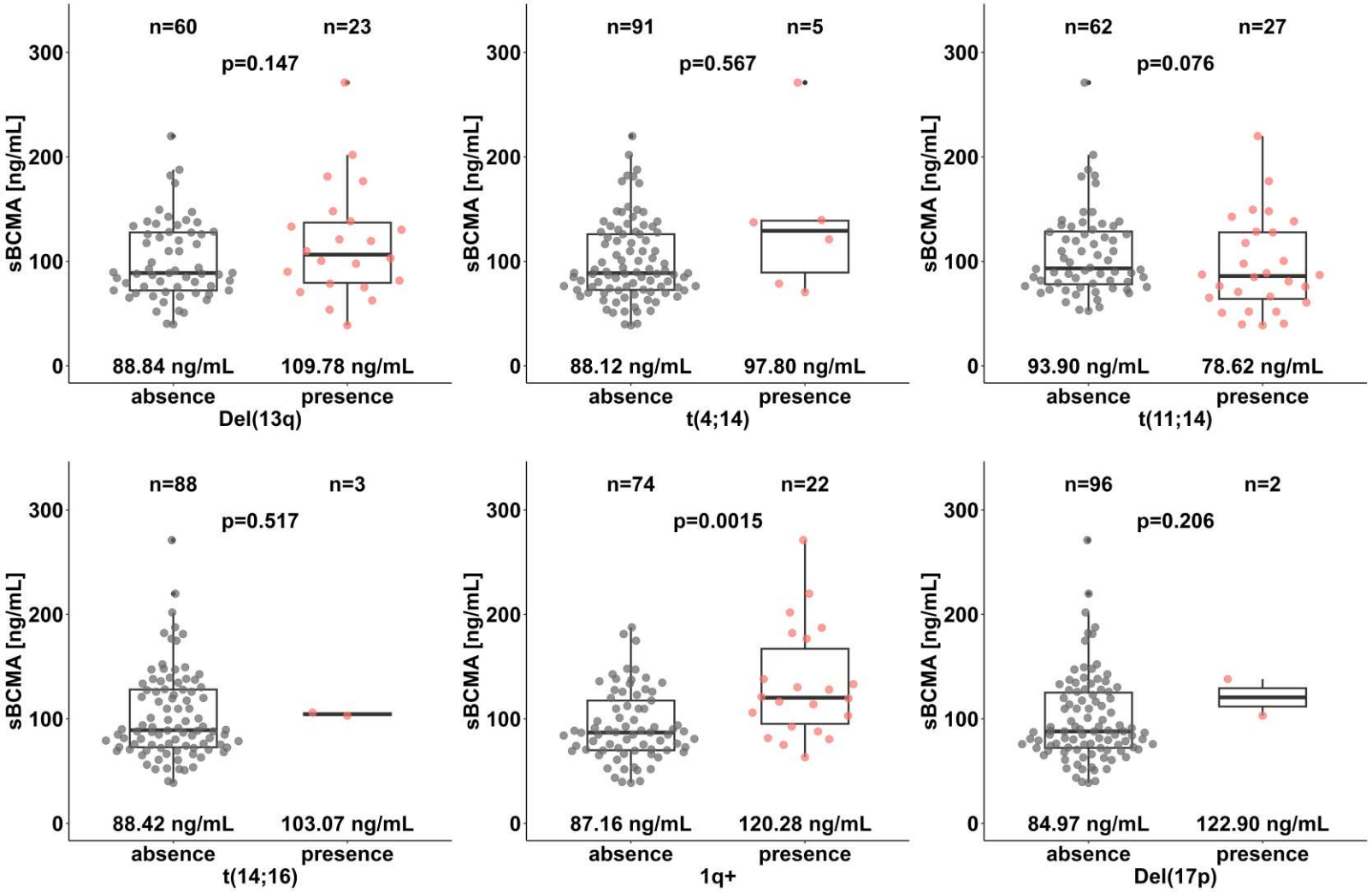
**Figure 1S. Correlations between % of bone marrow plasma cell and involved paraprotein levels.**




Abbreviation: MGUS; monoclonal gammopathy of undetermined significance, SMM; smoldering multiple myeloma, MM; multiple myeloma, Ig; immunoglobulin, FLC; free light chain, BM PC%; bone marrow plasma cell percent

**Figure 2S. Association between sBCMA levels and FISH abnormalities, including Del(13q), t(4;14), t(14;16), t(11;14), Del(17p), and 1q+ in SMM.**

**No significant differences in sBCMA levels were observed for abnormalities other than 1q+. However, sBCMA levels were significantly higher in patients with 1q+.**




Abbreviation: *sBCMA*; serum B-cell maturation antigen, *SMM*; smoldering multiple myeloma, *FISH*; fluorescence in situ hybridization