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ORIGINAL ARTICLE

Bence Jones proteinuria in smoldering multiple myeloma as a predictor marker of progression to symptomatic multiple myeloma

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The diagnosis of smoldering multiple myeloma (SMM) includes patients with a heterogeneous risk of progression to active multiple myeloma (MM): some patients will never progress, whereas others will have a high risk of progression within the first 2 years. Therefore, it is important to improve risk assessment at diagnosis. We conducted a retrospective study in a large cohort of SMM patients, in order to investigate the role of Bence Jones (BJ) proteinuria at diagnosis in the progression to active MM. We found that SMM patients presenting with BJ proteinuria had a significantly shorter median time to progression (TTP) to MM compared with patients without BJ proteinuria (22 vs 88 months, respectively; hazard ratio = 2.3, 95% confidence interval = 1.4–3.9, $P = 0.002$). We also identified risk subgroups based on the amount of BJ proteinuria: $\geqslant 500$ mg/24 h, < 500 mg/24 h and without it, with a significantly different median TTP (13, 37 and 88 months, $P < 0.001$). Thus, BJ proteinuria at diagnosis is an independent variable of progression to MM that identifies a subgroup of high-risk SMM patients (51% risk of progression at 2 years) and $\geqslant 500$ mg of BJ proteinuria may allow, if validated in another series, to reclassify these patients to MM requiring therapy before the end-organ damage development.

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INTRODUCTION

Smoldering multiple myeloma (SMM) is a plasma cell disorder characterized by the presence of one or both of the features of $\geqslant 3$ g/dl serum M-protein[1] and 10–60% bone marrow plasma cells (BMPCs), but with no evidence of myeloma-related symptomatology (hypercalcemia, renal insufficiency, anemia or bone lesions (CRAB)) or any other myeloma-defining event.[2]

SMM represents an intermediate stage between monoclonal gammopathy of undetermined significance and multiple myeloma (MM), with a risk of progression to MM that is not uniform. In order to predict the probability of developing active disease at the moment of SMM diagnosis, several risk models have been developed; most of them include factors related to tumor burden. Two risk models, one proposed by the Mayo Clinic group[3] and the other by the Spanish Myeloma group,[4] have been thoroughly studied and validated in a prospective trial. The fist one is based on the proportion of BMPCs and the serum M-protein level at diagnosis and identified a high-risk SMM group (serum M-protein $\geqslant 3$ g/dl and BMPCs $\geqslant 10\%$) with a median time to progression (TTP) of 2 years. Similarly, the Spanish Group based on two parameters, the presence of $> 95\%$ phenotypically aberrant plasma cells by flow cytometry and the occurrence of immunoparesis identified a high-risk SMM group with a TTP of ~2 years.

In addition, several independent studies showed that patients with any other of recently defined myeloma-defining event ($\geqslant 60\%$ BMPCs, a serum free light chains (FLCs) ratio of $\geqslant 100$ or the presence of two or more focal lesions of the skeleton as revealed by magnetic resonance imaging) are at ultra-high risk of progression to MM (80–90% at 2 years) and therefore they should be considered and treated as active MM patients, instead of therapeutic abstention.[2]

Bence Jones (BJ) proteinuria is a myeloma feature defined by the presence of monoclonal immunoglobulin light chains in the urine. The kidney regulates light-chain balance by a poorly understood mechanism,[5] in which monoclonal light chains are freely filtered across the glomerulus and then reabsorbed at the proximal tubules. However, the reabsorptive function is compromised when there is overproduction, resulting in monoclonal light-chain excretion and detectable BJ proteinuria. Based on this, we hypothesized that BJ proteinuria is related with tumor burden[6] and could predict transformation to symptomatic MM, similar to other myeloma features mentioned above.

The purpose of this study was to examine the impact of BJ proteinuria on the risk of progression to MM in a well-defined cohort of patients with SMM. We show in this study that the presence of BJ proteinuria in SMM identifies a subgroup at high risk of progression to MM.

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PATIENTS AND METHODS

Study cohort

Patients were identified by searching a regional database from Castilla-León, a western region of Spain, and reviewing the medical records of all patients diagnosed with SMM between 1986 and 2013, according to the International Myeloma Working Group criteria established in 2003,[1] in whom BJ proteinuria was available at the time of diagnosis. All patients had ⩾10% BMPCs and/or ⩾3 g/dl of serum M-protein, but did not have CRAB symptoms. Patients with SMM included in the database and allocated to the experimental arm (lenalidomide plus low-dose dexamethasone) in the phase 3 trial conducted by the Spanish Myeloma Group were excluded.[7] The study was approved by the Institutional Review Board at University Hospital of Salamanca and in accordance with the Declaration of Helsinki.

Clinical and biological data were collected at diagnosis and at the time of progression to MM, or last monitoring if progression to MM had not occurred.

Methodology

BJ proteinuria was analyzed at diagnosis by capillary electrophoresis and immunotyping a 24-h collection sample and a concentrated urine sample. This process involves quantifying total urinary proteins by a nephelometric method and protein separation by capillary electrophoresis. When a monoclonal spike was detected in the urine protein electrophoresis, the sample was overlaid with two monospecific antibodies, anti-κ and anti-λ in the immunotyping assay to identify the κ-or λ-chain. The UV absorption method was then used to determine its concentration and to calculate the amount of BJ excreted in a 24-h period. The measurement of monoclonal BJ proteinuria has been considered for our analysis.

Immunophenotypic analysis was performed by highly trained specialists. Percentage of aberrant plasma cells is the total number of clonal plasma cells within the total plasma cell compartment and it was evaluated as described in Pérez-Persona *et al.*[4]

Fluorescence *in situ* hybridization analysis was performed in some BM samples at diagnosis for clinical or investigational purposes. Fluorescence *in situ* hybridization studies included the detection of the *IGH* rearrangements t(4;14)(p16;q32) and t(14;16)(q32;q23) with the corresponding dual-color, dual-fusion translocation probes and 17p deletions (LSI p53, 17p13.1) (Abbott Molecular/Vysis, Des Plaines, IL, USA).

The serum FLC assay (Freelite, Binding Site, Birmingham, UK) was performed following the principles of turbidimetry. Absolute FLC κ (normal range, 0.33–1.94 mg/dl) and FLC λ (normal range, 0.57–2.63 mg/dl) were measured and clonality was assessed as FLC κ/λ. A FLC ratio <0.26 or >1.65 was considered abnormal.

End points and statistical analyses

TTP was taken as the time from diagnosis until progression to MM, defined by the presence of CRAB symptoms.TTP and overall survival were considered the primary and secondary end points of the study, respectively. The χ^2-, Student's *t*- and Mann–Whitney *U*-tests were used to estimate the statistical significance of group differences. Survival curves were plotted according to the Kaplan–Meier method, using the log-rank test to determine the statistical significance of differences between the curves. Values of $P<0.05$ were considered statistically significant. Effects of potential risk factors of progression were analyzed in a Cox proportional hazards model. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp..

RESULTS

Patient characteristics

A total of 152 SMM patients were included in the study. The baseline characteristics are summarized in Table 1. There were 72 (47%) men and 80 (53%) women. The median age at diagnosis was 70 years (range, 35–90 years). The concentration of serum M-protein at diagnosis ranged from 0.1 to 6.6 g/dl (median, 2.5 g/dl); 56 patients (37%) had concentrations higher than 3 g/dl. The heavy chain isotype was IgG in 105 patients (69%) and IgA in 31%. The proportion of BMPCs ranged from 1 to 55% (median, 14%);124 patients (83%) had ⩾10% plasma cell bone marrow infiltration.

BJ proteinuria, the monoclonal part, was evaluated in all patients at diagnosis and detected in 41 patients (27%). The median level was 100 mg/24 h in patients with positive proteinuria. Of those patients, 24 (58%) and 17 (42%) featured a κ and a λ light chain, respectively. Seven patients (17%) had at least 500 mg/24 h. One of them did not express serum heavy–light chain, which is considered as light-chain smoldering myeloma κ.

Table 1. Baseline characteristics SMM patients

Baseline patient characteristics	*SMM (n = 152)*	*SMM BJ+ (n = 41)*	*SMM BJ − (n = 111)*	P-*values*
Male/ female, no. (%)	80 (53)/72 (47)	21 (51)/20 (49)	51 (46)/60 (54)	NS
Age, median year (range)	70 (35–90)	71 (43–89)	69 (35–90)	NS
Heavy chain type				
IgG, no. (%)	105 (69)	21 (53)	85 (76)	0.005
IgA, no. (%)	46 (31)	19 (46)	26 (24)	
Light chain type				
κ, no. (%)	92 (61)	25 (61)	67 (60)	NS
λ, no. (%)	60 (39)	16 (39)	44 (40)	
Serum M-protein, median g/dl (range)	2.5 (0.1–6.6)	2.4 (0.3–6.6)	2.6 (0.1–5.0)	NS
Serum M-protein ⩾3 g/dl, no. (%)	56 (37)	14 (34)	42 (38)	NS
Presence of BJ proteinuria, no. (%)	41 (27)	—	—	—
BJ protein g/24 h, median (range)	0 (0–2.60)	0.1 (0.006–2.6)	—	—
% BMPC by morphology, mean (s.d.)	17 (10)	23 (12)	14 (8)	0.001
⩾ 10% BMPC, no. (%)	124 (82.7)	37 (90)	87 (80)	NS
Immunoparesis, no. (%)[a]	72 (49.7)	24 (63)	48 (45)	0.05
⩾95% aPC, no. (%)[b]	99 (69.7)	27 (73)	72 (68.6)	NS
High-risk Mayo Clinic Criteria, no. (%)	36 (24)	12 (29)	24 (22)	NS
High-risk Spanish Criteria, no. (%)	58 (38)	19 (47.5)	37 (33)	0.04
Abnormal serum FLC ratio (<0.26 or >1.65), no. (%)[c]	15 (83)	7 (100)	8 (72)	NS

Abbreviations: aPC, aberrant plasma cells by flow cytometry; BJ+, SMM patients who had BJ proteinuria at diagnosis; BJ −, SMM patients without BJ proteinuria at diagnosis; BMPC, bone marrow plasma cell; FLC, serum free light chain; High-risk Mayo Clinic Criteria, serum M-protein ⩾3 g/dl+BMPC ⩾10%; High-risk Spanish Criteria: aPC ⩾95%+immunoparesis; NA, not available; NS, not significant; SMM, smoldering multiple myeloma; [a]Immunoglobulins not available in seven patients. [b]Not available in 10 patients. [c]FLCs available in 18 patients.

Bone marrow aspirate was performed in all patients but none had a plasma cell infiltration higher than 60%. Serum FLC ratio was done in 18 patients and it was abnormal (<0.26 or >1.65) in 15 (83%) of them, only 3 cases over 100. Magnetic resonance imaging was not performed in our patients, so it is not possible to exclude patients at ultra-high risk of progression according to the presence of focal lesions.

Three patients had a normal serum FLC ratio, none of whom had BJ proteinuria. Among the patients with an abnormal FLC ratio, 47% had BJ proteinuria and 53% did not ($P=0.13$). As we mentioned above, the FLC ratio was >100 in three patients: 2 of them had BJ proteinuria, both of which were κ-type and with <0.100 g/24 h; BJ proteinuria was not present in the other patient.

Fluorescence *in situ* hybridization results at diagnosis were available for 41 patients, 4 of whom (9.8%) were thereby classified as having high-risk cytogenetic abnormalities: 3 had *t(4;14)* and only one had *del 17p*.

One hundred and fifty and 145 patients were evaluated according to the Mayo Clinic and Spanish model, respectively. Applying the first risk model, we identified 36 (24%) high-risk SMM patients with serum M-protein >3 g/dl and $>10\%$ of BMPCs, whereas 58 patients (40%) were considered high-risk SMM according to the Spanish criteria.

Outcome

The median follow-up for survivors was 65 months (range, 0.4–199.8 months). Seventy-three patients (48%) progressed to MM during this period with a median TTP of 68 months (95% confidence interval (95% CI) = 42.0–93.6 months). The probability of progression to MM at 5 years was 49%. Half of the SMM patients died during this period. The median overall survival in the whole series was 7.6 years (95% CI = 6.7–8.5years), but it was significantly shorter for SMM patients who had progressed to MM (6.3 years; 95% CI = 5.4–7.2 years), in comparison with those who remained free of progression (15.6 years; 95% CI = 6.7–24.5years) ($P<0.0001$). In the group of SMM patients who progressed to MM and died, MM was the most frequent cause of death (60%), followed by disease-related events, such as infection (15%) or toxicity(10%).There were 29 patients (19%) who died before progression, due to causes unrelated to the disease (cardiac and respiratory disease, thrombosis, stroke, traffic accident and so on).

Interestingly, 24 out of 41 patients (58.8%) with SMM and BJ proteinuria (BJ+ group) progressed to MM, with a significantly higher probability of progression than patients without BJ proteinuria (BJ− group), with a median TTP of 21.7 versus 88.3 months, respectively (hazard ratio (HR) = 2.3, 95% CI = 1.4–3.9, $P=0.002$) (Figure 1). The probability of progression to MM at 2 years in the BJ+ and BJ− groups was 51% and 22%, respectively. Although there were higher levels of SMM IgA and immunoparesis in the BJ+ group, there were no significant differences in baseline characteristics between these two groups (Table 1). BJ proteinuria was significantly associated with BMPC infiltration ($P=0.001$). Anemia was the most common CRAB feature at the time of progression in the BJ+ group, being present in 38 patients (52%). Only one patient progressed with renal impairment (RI) that had >500 mg/24 h of κ-light chain proteinuria.

During the period studied, 21 of the 41 patients in the BJ+ group (51%) and 57 of the 111 patients in the BJ− group (51%) had died ($P=0.89$); the median overall survival was longer for the BJ− than the BJ+ group (8 vs 6 years; $P=0.053$) (HR = 1.64, 95% CI = 0.99–2.73, $P=0.055$) (Figure 2).

To determine whether the amount of BJ proteinuria could enable SMM patients to be categorized into risk subgroups, we investigated several cutoff values. Interestingly, the 500 mg/24 h cutoff value identified three risk subgroups, with a significantly different probability of progression to symptomatic myeloma: 111 patients did not have BJ proteinuria, 34 had <500 mg/24 h and 7 had >500 mg/24 h, with median TTP of 88, 37 and 13 months, respectively (HR = 2.4, 95% CI = 1.6–3.6, $P<0.001$) (Figure 3). The probability of progression to MM at 18 months in those patients with >500 mg/24 h of BJ proteinuria was 80%.

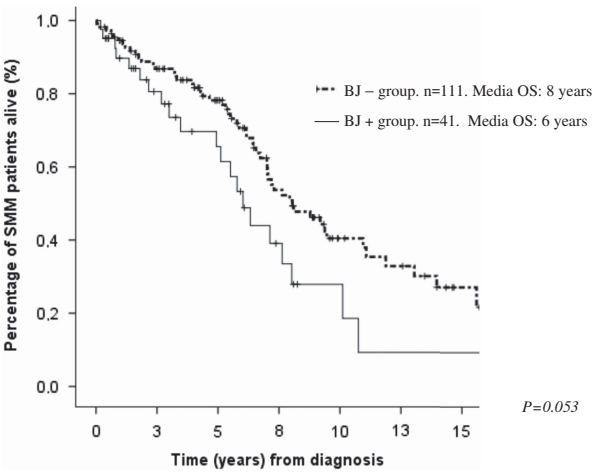

Figure 2. Overall survival in years since diagnosis of SMM according to the presence or absence of BJ proteinuria.

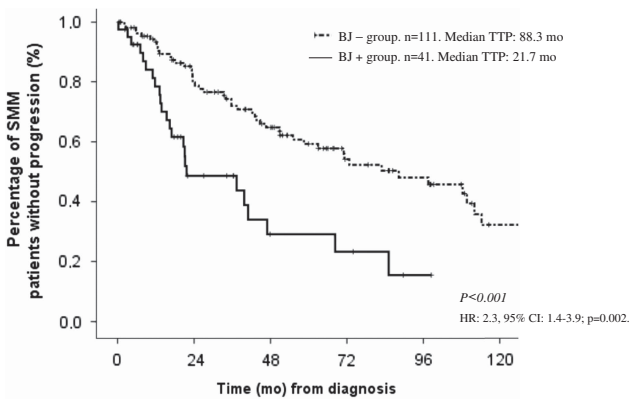

Figure 1. TTP in months from diagnosis of SMM, according to the presence or absence of BJ proteinuria.

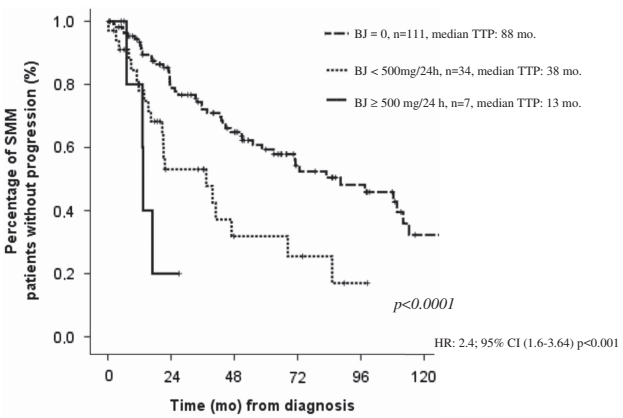

Figure 3. TTP in months from diagnosis of SMM; comparison of BJ groups by amount of BJ proteinuria.

Table 2. Univariate and multivariate analysis

Variable	*n (%)*	*TTP*				*OS*	
		Median (months)	*Univ.*	*Multivariate*		*Median (years)*	*Univ.*
			P-*value*	*HR (95%)*	P-*value*		P-*value*
Sex							
Male	72 (47)	71	NS	—	—	7.0	NS
Female	80 (53)	68				8.0	
Age (years)							
⩾65	106 (70)	83	NS	—	—	9.5	0.01
<65	46 (30)	47				7.1	
Isotype							
IgA	46 (31)	68	NS	—	—	7.1	NS
IgG	105 (69)	71				7.9	
Light chain							
κ	92 (61)	51	0.03	1.60 (0.97–2.63)	0.07	7.9	NS
λ	60 (39)	88				7.0	
Serum M-protein							
⩾3 g/dl	56 (37)	36	0.005	—	—	7.1	NS
<3 g/dl	96 (63)	88				7.6	
BJ proteinuria							
Yes	41 (27)	22	<0.001	2.3 (1.38–3.94)	0.002	6.0	0.05
No	111 (73)	88				8.1	
BMPC							
⩾10%	124 (83)	55	0.03	—	—	7.3	NS
<10%	26 (17)	150				7.0	
NA	2						
Immunoparesis							
Yes	72 (50)	51	0.004	—	—	7.0	NS
No	73 (50)	98				9.2	
NA	7						
aPC							
⩾95%	99 (70)	47	0.004	—	—	7.2	NS
<95%	43 (30)	98				7.9	
NA	10						
High-risk Mayo Clinic Criteria							
Yes	36 (24)	23	<0.001	3.36 (2.04–5.52)	<0.001	7.0	NS
No	114 (75)	108				7.6	
NA	2						
High-risk Spanish Criteria							
Yes	58 (42)	36	<0.001	1.87 (1.15–3.03)	0.012	7.0	NS
No	88 (58)	85				8.0	
NA	7						
sFLC ratio							
Abnormal	15 (83)	24	0.19	—	—	NR	NS
Normal	3 (17)	NR				3.3	
NA	134						
Cytogenetic risk							
High	4 (10)	15	0.79	—	—	6.0	NS
Standard	37 (90)	33				7.0	
NA	111						

Abbreviations: aPC, aberrant plasma cells by flow cytometry; BJ, Bence Jones; BMPC, bone marrow plasma cell; FLC, serum free light chains; High-risk Mayo Clinic Criteria, serum M-protein ⩾3 g/dl+BMPC ⩾10%; High-risk Spanish Criteria, aPC ⩾95%+immunoparesis; HR, hazard ratio; mo, months; NA, not available; NR, not reached; NS, not significant; OS, overall survival; SMM, smoldering multiple myeloma; TTP, time to progression; Univ., univariate analysis. Markers of progression and survival among 152 patients with SMM.

Additional risk factors for progression to MM were identified in the univariate analysis (Table 2): serum M-protein concentration >3 g/dl ($P=0.005$); BMPCs $\geqslant 10\%$ ($P=0.03$), κ-light chain ($P=0.03$); and the Mayo Clinic and Spanish criteria of high-risk SMM (both $P<0.001$). Sex, IgA subtype, International Staging System, abnormal FLC ratio and high-risk cytogenetics were not significantly associated with progression.

One hundred and forty-two patients were included in the multivariate analysis and BJ proteinuria at diagnosis was selected as an independently significant variable for progression to MM (HR = 2.33, 95% CI = 1.39–3.94, $P=0.002$). The features evaluated in the Mayo Clinic and Spanish risk models were both validated as independent risk factors for progression. Of the Mayo Clinic criteria for high-risk SMM, the median TTP was 23 months, with a HR of progression of 3.36 (95% CI = 2.13–5.34, $P<0.001$), whereas the median TTP in patients with $\geqslant 95\%$ aberrant plasma cells plus immunoparesis was 36 months (HR = 1.87, 95% CI = 1.15–3.03, $P=0.012$) (Table 2).

DISCUSSION

We report that BJ proteinuria in SMM can be useful for defining the risk of progression to MM and can identify a subgroup of high risk of progression to active disease.The study was conducted in a large and representative series of 152 smoldering myeloma patients. The proportion of high-risk patients, using Mayo Clinic criteria, was similar to the 29% found in the Swedish Myeloma Registry.[8] Moreover, the risk of transformation of SMM to symptomatic MM at 5 years was 50%, the same level reported by the Mayo Clinic in 2007.[3]

BJ proteinuria could be considered as a tumor burden marker, which is significantly associated with BMPC infiltration in our series and allowed the two SMM groups to be discriminated with significantly different risks of progression to symptomatic myeloma. Patients with BJ proteinuria had twice the risk of progression as those without it, with a <2-year median TTP compared with 7 years in the BJ− group. The cumulative probability of progression to active MM was 51% at 2 years; thus, compared with the aforementioned studies, SMM patients with BJ proteinuria should also be considered as a high-risk SMM group. In our study, the detection of >500 mg/24 h of BJ proteinuria also identified patients with a higher risk of progression, that is, 80% at 18 months,which means that they can be classified as ultra-high risk SMM patients, even though they could be considered as having active MM. To the best of our knowledge, this is the first study to evaluate BJ proteinuria in the setting; therefore, these results need to be validated and confirmed in other independent studies.

BJ proteinuria may not have been evaluated in SMM, because this can be done by the FLC assay instead. However, according to the International Myeloma Working Group guidelines, 24-h urine protein electrophoresis and immunofixation should not be replaced by the serum FLC assay for the diagnosis of monoclonal gammopathies. Even in the recently updated MM diagnostic criteria,[2] BJ evaluation is still recommended for diagnosing light-chain smoldering myeloma defined by monoclonal light-chain excretion of $\geqslant 0.5$ g/24 h without immunoglobulin heavy-chain expression and/or $>10\%$ BMPCs in the absence of CRAB symptoms, with slower clinical course and progression than SMM.[9] In addition, we consider it necessary to perform both analyses at diagnosis for several reasons: to avoid misdiagnosing other important disorders such as nephrotic syndrome as a consequence of primary amyloidosis; to ensure adequate monitoring;[10] due to the power of the level of proteinuria to predict the development of RI;[11] and finally, as the correlations between serum FLC and BJ proteinuria are not concordant among studies. Some of them[12–14] have shown that the urine BJ protein screening test is no longer necessary, because the FLC assay plus serum immunofixation has a sensitivity of up to 99%, although almost 15% of BJ proteinuria cases had a normal serum FLC ratio in the Mayo Clinic[12] and British studies.[13] In a prospective study,[15] 7% of patients with BJ proteinuria at diagnosis had a normal serum FLC ratio ($P<0.0001$). In a European study,[16] BJ proteinuria was detected in 34 out of 483 patients, 25% of whom had normal serum FLC ratio. Moreover, in a different study,[17] 30% of patients with small amounts of BJ proteinuria had normal ratios and 40% of patients with $\geqslant 500$ mg urine protein/24 h had normal FLC ratios, suggesting that replacement of the 24-h urine collection would have overlooked clinically significant proteinuria in those cases.

The presence of a high FLC ratio has been included in the new definition of MM, supported by two studies. However, a recent Danish population-based cohort study of 321 newly diagnosed SMM patients was unable to confirm the association with the high FLC ratio[17], whereas Waxman *et al.*[18] found that a high FLC ratio was associated with a low (64%) risk of progression to MM.

In addition, although the FLC assay makes a great contribution at diagnosis, monitoring and prognosis, because of its greater specificity, technical limitations have also been identified, such as: variable immunoreactivity of individual FLC, with a coefficient of variability up to 20% due to variation between antisera sera,[19] underestimation of κ-FLC if there is an excess of antigen,[20] FLC levels depend on renal function and so on.

Moreover, urine protein analysis is a cheap and easily available procedure in most of biochemistry laboratories. Its sensitivity is influenced by the methods of urine collection, protein quantification and separation, the concentration of urine, interferences caused by salts and other compounds, and the immunotyping method used. In spite of the problems with the urine protein analysis, the procedure is well standardized in most hospitals and patients are trained in how to collect 24-h urine samples.To increase the sensitivity, concentration and dialysis are performed to eliminate salts from urine. Despite this, we could not avoid inter-laboratory and historical differences.

Another consideration is that 27% of smoldering myeloma patients in our series had BJ proteinuria at diagnosis, with no RI, and only one case had RI at progression, which corresponds to one patient with >500 mg of *k* BJ proteinuria at diagnosis.The explanation for these results could be that the risk of cast nephropathy seems to be directly related not only to the amount of urinary light chain but also with the type (κ or λ) and biochemical characteristics conferred by variable nephrotoxic potential.[21] In addition, the incidence of RI at the time of progression in our series was very low (6%). There is no data about the presence of specific features in SMM predicting RI as myeloma-related symptomatology and in another series in which proteinuria or serum FLC were evaluated[22,23] there was no relationship reported. One possible explanation is the closer follow-up for these patients contributing to detect progression to MM in earlier stages before RI is established.

In conclusion, the presence of BJ proteinuria at diagnosis of SMM patients is associated with a significantly higher probability of progression to symptomatic MM. Detection of BJ proteinuria may help identify high-risk patients, as they had a 51% probability of progression at 2 years. Moreover, the presence of $\geqslant 500$ mg/24h of BJ proteinuria can be considered to be a marker for the identification of ultra-high-risk SMM; even if these results were confirmed in other studies, this may allow to reclassify these patients to MM requiring therapy before the end-organ damage development.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

MVM conceived the idea and together with VGC designed the study. VGC, JD, FE, AGC, CA, RL, AB, JMA, RH, JMH and PF provided the data acquisition. VGC and MVM developed the analysis and interpretation of data. VGC drafted the article under the supervision of MVM. MVM, NP, EMO, NG and RGS revised it critically and gave final approval of the version to be submitted. All authors of this paper have read and approved the final version submitted.

REFERENCES

1 Kyle RA, Child JA, Anderson K, Barlogie B, Bataille R, Bensinger W *et al.* Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003; **121**: 749–757.
2 Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV *et al.* International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014; **15**: 538–548.
3 Kyle RA, Remstein ED, Therneu TM, Dispenzieri A, Kurtin PJ, Hodnefield JM *et al.* Clinical course and prognosis of smoldering multiple myeloma. *N Engl J Med* 2007; **356**: 2582–2590.
4 Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, de Coca AG *et al.* New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood* 2007; **110**: 2586–2592.
5 Leung N, Behrens J. Current approach to diagnosis and management of acute renal failure in myeloma patients. *Adv Chron Kidney Dis* 2012; **19**: 297–302.
6 Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer* 1975; **36**: 842–854.
7 Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, López Corral L *et al.* Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med* 2013; **369**: 438–447.
8 Kristinsson SY, Holmberg E, Blimark C. Treatment for high-risk smoldering myeloma. *N Engl J Med* 2013; **369**: 1762–1765.
9 Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Melton LJ, Benson JT *et al.* Clinical course of light-chain smouldering multiple myeloma (idiopathic Bence Jones proteinuria): a retrospective cohort study. *Lancet Haematol* 2014; **1**: 28–36.
10 López-Corral L, García-Sanz R, San Miguel JF. Value of serum free light chains assay in plasma cell disorders. *Med Clin (Barc)* 2010; **135**: 368–374.
11 Singhal S, Stein R, Vickrey E, Mehta J. The serum-free light chain assay cannot replace 24-hour urine protein estimation in patients with plasma cell dyscrasias. *Blood* 2007; **109**: 3611–3612.
12 Katzmann JA, Dispenzieri A, Kyle RA, Snyder MR, Plevak MF, Larson DR *et al.* Elimination of the need for urine studies in the screening algorithm for monoclonal gammopathies by using serum immunofixation and free light chain assays. *Mayo Clin Proc* 2006; **81**: 1575–1578.
13 Hill PG, Forsyth JM, Rai B, Mayne S. Serum free light chains: an alternative to the urine Bence Jones proteins screening test for monoclonal gammopathies. *Clin Chem* 2006; **52**: 1743–1748.
14 Abraham RS, Clark RJ, Bryant SC, Lymp JF, Larson T, Kyle RA *et al.* Correlation of serum immunoglobulin free light chain quantification with urinary Bence Jones protein in light chain myeloma. *Clin Chem* 2002; **48**: 655–657.
15 Nowrousian MR, Brandhorst D, Sammet C, Kellert M, Daniels R, Schuett P *et al.* Serum free light chain analysis and urine immunofixation electrophoresis in patients with multiple myeloma. *Clin Cancer Res* 2005; **11**: 8706–8714.
16 Beetham R, Wassell J, Wallage MJ, Whiteway AJ, James JA. Can serum free light chains replace urine electrophoresis in the detection of monoclonal gammopathies? *Ann Clin Biochem* 2007; **44**: 516–522.
17 Sørrig R, Klausen TW, Salomo M, Vangsted AJ, Østergaard B, Gregersen H *et al.* Smoldering multiple myeloma risk factors for progression: a Danish population-based cohort study. *Eur J Haematol* 2015; e-pub ahead of print 29 December 2015; doi:10.1111/ejh.12728.
18 Waxman AJ, Mick R, Garfall AL, Cohen A, Vogl DT, Stadtmauer EA *et al.* Classifying ultra-high risk smoldering myeloma. *Leukemia* 2015; **29**: 751–753.
19 Tate JR, Mollee P, Dimeski G, Carter AC, Gill D. Analytical performance of serum free light-chain assay during monitoring of patients with monoclonal light-chain diseases. *Clin Chim Acta* 2007; **376**: 30–36.
20 Tate Daval S, Tridon A, Mazeron N, Ristori JM, Evrard B. Risk of antigen excess in serum free light chain measurements. *Clin Chem* 2007; **53**: 1985–1986.
21 Solomon A, Weiss DT, Kattine AA. Nephrotoxic potential of Bence Jones proteins. *N Engl J Med* 1991; **324**: 1845–1851.
22 Weber DM, Dimopoulos MA, Moulopoulos LA, Delasalle KB, Smith T, Alexanian R. Prognostic features of asymptomatic multiple myeloma. *Br J Haematol* 1997; **97**: 810–814.
23 Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J *et al.* Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood* **111**: 785–789.