

# C-Reactive Protein and $\beta$ -2 Microglobulin Produce a Simple and Powerful Myeloma Staging System

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Multiple myeloma (MM) staging procedures are still inadequate for detection of the optimal therapeutic procedure for an individual patient. The Durie & Salmon staging system and serum  $\beta$ 2-microglobulin ( $\beta$ 2M) are used worldwide because of their easy clinical application. Other prognostic parameters, such as myeloma cell proliferative activity, are of exceeding importance, but are not as simple as standard methods. Recently, interleukin-6 (IL-6) has been shown to be a major growth factor for MM. IL-6 is a pleiotropic cytokine acting on several cell lineages, and, at the hepatocyte level, stimulates the synthesis of acute phase proteins, such as the well known C-Reactive Protein (CRP). Serum CRP concentration actually reflects the IL-6 activity. A survival analysis

**S**URVIVAL in multiple myeloma (MM) varies from a few months to many years. Currently available staging systems are still inadequate for precise assessment of an individual prognosis. Nevertheless, accurate prognostic evaluation is mandatory for selection of the optimal therapeutic strategy: new aggressive chemotherapy regimens with or without bone marrow transplant or growth factor support have been recently proposed,<sup>1</sup> but they can be most strongly considered only in patients with aggressive disease.

The Durie & Salmon staging system and serum  $\beta$ 2-microglobulin ( $\beta$ 2M), the two worldwide methods used for prognostic classification, mainly reflect tumor burden.<sup>2-6</sup> This is not an absolute criterion. It has been shown, for instance, that proliferative activity of the bone marrow myeloma cells (ie, labeling index, LI) is not related to the tumor burden, but is a powerful independent prognostic factor.<sup>7-10</sup> Other parameters, such as the immunologic phenotype of circulating lymphocytes, also give useful prognostic information.<sup>11</sup> However, these tests are more complex and time-consuming than the Durie & Salmon staging system or serum  $\beta$ 2M determination, which are at present widely used in large cooperative groups.

Recently, interleukin-6 (IL-6) has been shown to be a major growth factor for human myeloma cells.<sup>12-17</sup> IL-6 stimulates *in vitro* and *in vivo* plasma cell growth. Moreover, in MM patients high serum IL-6 levels are related to myeloma cell proliferation and disease severity.<sup>18,19</sup> Anti-IL-6 monoclonal antibodies (MoAbs) block myeloma cell proliferation *in vivo*, this being one type of evidence of the *in vivo* role of IL-6 in myeloma pathogenesis.<sup>20,21</sup>

IL-6 is a pleiotropic cytokine active on B cells and several other cell lineages.<sup>22</sup> For example, it is active on hepatocytes and regulates the major acute phase proteins in liver cells.<sup>23</sup> In particular, it has recently been shown that only IL-6 induces synthesis of C-Reactive Protein (CRP) by human hepatocytes in primary cultures.<sup>24</sup> *In vivo*, a significant correlation between serum IL-6 and CRP levels has been found in rheumatoid arthritis.<sup>25</sup> After infusion of anti-IL-6 MoAbs in MM, serum CRP level decreases to undetectable levels within 10 days, and rapidly increases again at the end of treatment.<sup>20,21</sup> Taken together, all these features show that CRP production is totally dependent on

carried out in 162 MM patients at diagnosis showed that serum CRP level is a highly significant prognostic factor. Moreover, serum CRP was independent of serum  $\beta$ 2M. This feature allowed stratification of MM patients into 3 groups according to CRP and  $\beta$ 2M serum levels: (1) low risk group, CRP and  $\beta$ 2M <6 mg/L (50% of patients); (2) intermediate risk group, CRP or  $\beta$ 2M  $\geq$ 6 mg/L (35% of patients); (3) high risk group, CRP and  $\beta$ 2M  $\geq$ 6 mg/L (15% of patients). Survival was 54, 27, and 6 months, respectively ( $P < .0001$ ). We thus propose a new and powerful myeloma staging system based on simple and reliable laboratory evaluations.

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IL-6, and that serum CRP level actually reflects IL-6 activity.

These observations prompted us to evaluate the serum CRP level in monoclonal gammopathy of undetermined significance (MGUS) subjects and in MM patients. Moreover, serum CRP level was analyzed in MM at diagnosis, during the remission phase, and at relapse. A survival analysis was performed to assess the prognostic value of serum CRP level. Finally, serum CRP was related to other prognostic factors such as the proliferation of bone marrow myeloma cells and serum  $\beta$ 2M levels. Its strong prognostic value, associated with that of serum  $\beta$ 2M level, allowed development of a simple and powerful myeloma staging system.

## PATIENTS AND METHODS

This study was performed on all available frozen sera from MM patients at diagnosis in two hematologic institutions (Department of Immunology and Rheumatology, Montpellier, France, and Department of Medicine and Experimental Oncology, Section of Hematology, University of Torino, Italy) from January 1985 to November 1990. This series almost represents the consecutive patients referred to these institutions. Serum CRP level was

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measured in 52 subjects with MGUS and 162 MM patients at diagnosis. Moreover, in the MM patient group, 49 determinations were performed during remission phase, and 33 at relapse. MGUS and MM were defined as previously reported.<sup>26</sup> In MM at diagnosis, mean age was  $63.8 \pm 10.5$  years; 88:74 was the male/female ratio; 101 patients showed IgG isotype, 42 IgA, and 17 Bence Jones; one was IgD and one nonproducing. Ninety-four MM patients were Durie & Salmon stage III, 43 stage II, and 25 stage I. Patients were treated with alternating VMCP/VBAP (vincristine, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, adriamycin, prednisone) or melphalan and prednisone. Because these treatments showed no statistically significant difference in terms of survival,<sup>27</sup> no distinction was made in the survival analysis. Median survival for MM patients was 36 months; median follow-up for censored patients was 28.7 months (range 2.5 to 120 months); 55% of patients were dead at the time of analysis.

Serum CRP concentrations were evaluated by commercially available enzyme-linked immunosorbent assay (ELISA) kits (Eurogenetics, Tessenderlo, Belgium), or nephelometry (Behring, Mannheim, Germany). These two methods gave very similar results on a series of 48 patient sera (Wilcoxon 2 paired test,  $P = .41$ ). Serum  $\beta$ 2M levels were detected using radio immunoassay (RIA) kits (Pharmacia, France). All sera were stored at  $-20^{\circ}\text{C}$  before measurement.

Plasma cell proliferation was evaluated on fresh samples: isolated bone marrow cells were incubated in vitro with bromodeoxyuridine. The percentage of myeloma cells in S-phase (LI) was evaluated by antibromodeoxyuridine MoAb (Dakopatts, Glostrup, Denmark) and fluorescein-labeled goat antimouse Ig (Becton & Dickinson, Mountain View, CA) as previously described.<sup>28</sup>

CRP values are expressed in terms of the median plus the distribution range, because they were not normally distributed in all groups. Comparison between groups was made by Wilcoxon's test; the Spearman rank sum test was used for correlation analysis. The results of clinical follow-up are expressed in a life-table format according to the Kaplan-Meier method; the log rank test was used to compare survival curves. Multivariate analysis was performed using the Cox model. All data were processed with the SAS statistical software package (SAS Institute Inc, Cary, NC).

## RESULTS

Median serum CRP levels were 0.7 mg/L (range 0 to 89.5) in MGUS, and 3.75 mg/L (range 0 to 121) in MM patients at diagnosis (normal CRP range: 0 to 6 mg/L). However, only 4 of 52 subjects displayed above-normal values in the MGUS group, compared with 60 of 162 in MM patients at diagnosis (Chi square = 15.23;  $P < .0001$ ). Moreover, low values were observed in MM during remission phase (0.9 mg/L, range 0 to 100), and high values again at relapse (3.9 mg/L, range 0 to 79.7) (diagnosis versus remission,  $P < .0001$ ; remission versus relapse,  $P < .008$ ) (Fig 1).

To assess the prognostic value of serum CRP level, a survival analysis was performed in 162 MM patients evaluated at diagnosis. A CRP cutoff of 6 mg/L was chosen because it represents a widely used upper limit for normal subjects. Moreover, using this cutoff, patients were still separated in two well-balanced risk groups: 60 and 102 patients, respectively. Patients with values  $\geq 6$  mg/L showed a reduced survival in comparison with patients with low values (21 v 48 months,  $P < .0001$ ) (Fig 2, Table 1).

The significance of several recognized prognostic factors

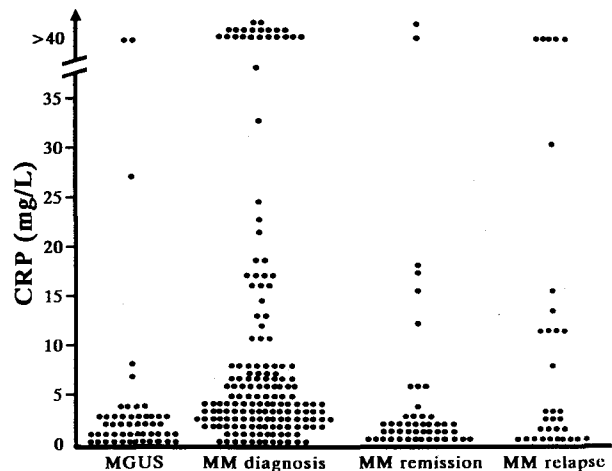


Fig 1. Serum CRP levels in MGUS, and MM at diagnosis, remission, and relapse.

has been tested by univariate analysis in this patient series: serum  $\beta$ 2M, Durie & Salmon stage, serum albumin, LI, and age (Table 1). Serum albumin, using a previously defined cutoff of 30 g/L,<sup>4,5</sup> identified a very poor survival patient subgroup. However, this subgroup represented only 14.1% of the whole series. Serum  $\beta$ 2M level (cutoff of 6 mg/L) separated patients into two groups showing a significantly different survival (14 v 48 months,  $P < .0001$ ; Table 1).

The correlation between serum CRP and other prognostic factors was evaluated. No direct relationship was detected with serum creatinine, serum  $\beta$ 2M, or tumor stage. However, a trend for an inverse relationship between CRP and albumin was observed ( $r = -.44$ ;  $P < .0001$ ). The distribution of clinical parameters according to serum CRP level was evaluated. The 6 mg/L cutoff divided the MM population in two groups showing different stage ( $P < .002$ ), LI ( $P < .008$ ), and albumin ( $P < .0004$ ).  $\beta$ 2M also reached statistical significance ( $P < .01$ ) (Table 2). Other clinical parameters, such as isotype, creatinine, age, and gender were equally distributed in these two groups.

A multivariate analysis was performed using parameters statistically significant in the univariate analysis: CRP,

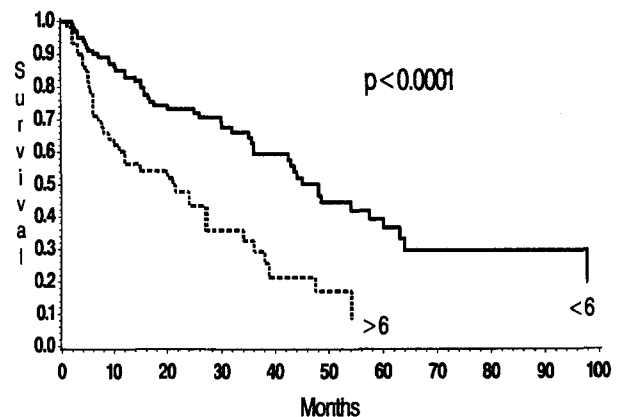


Fig 2. Actuarial survival of 162 MM patients according to serum CRP levels at diagnosis. A CRP cutoff value of 6 mg/L was chosen.

**Table 1. Correlates of Survival: Univariate Analysis**

Variable	Cutoff Value	Median Survival Mo.	No. of Patients	P Value
CRP	<6 mg/L	48.0	102	.0001
	$\geq$ 6 mg/L	21.0	60	
$\beta$ 2M	<6 mg/L	48.0	112	.0001
	$\geq$ 6 mg/L	14.8	50	
LI	<2%	48.4	48	.01
	$\geq$ 2%	16.5	18	
Age	<60	57.3	63	.007
	$\geq$ 60	30.0	99	
Albumin	<30 g/L	7.0	23	.0001
	$\geq$ 30 g/L	42.5	139	
Stage	I	NR*	25	.001
	II	38.8	43	
	III	24.0	94	

\*NR, not reached.

$\beta$ 2M, stage, albumin, age were used as continuous variables (Table 3). LI was available in 66 patients only and excluded from this analysis. The stepwise Cox proportional hazard model contained, first, albumin, followed by  $\beta$ 2M (Table 3). CRP did not enter this model. However, if albumin was excluded, CRP came first because of its mutually exclusive correlation with albumin. CRP was followed by  $\beta$ 2M, and no other parameters entered this model (Table 3).

MM patients were stratified into three groups according to CRP and  $\beta$ 2M serum levels: (1) low-risk group, CRP and  $\beta$ 2M <6 mg/L; (2) intermediate-risk group, CRP or  $\beta$ 2M  $\geq$ 6 mg/L; and (3) high-risk group, CRP and  $\beta$ 2M  $\geq$ 6 mg/L (Fig 3). Eighty-one patients (50%) entered group 1, 56 entered group 2 (34.6%), and 25 entered group 3 (15.4%). Survival was 54, 27, and 6 months, respectively ( $P < .0001$ ) (Table 4).

**DISCUSSION**

IL-6 is a central in vitro growth factor for the malignant plasma cells in MM.<sup>12,13</sup> This is now proved by the ability to reproducibly obtain human myeloma cell lines whose proliferation is totally dependent on the addition of IL-6.<sup>17</sup> Several arguments support the concept that IL-6 is also involved in myeloma cell growth in vivo. (1) A positive correlation exists between the degree of the in vitro myeloma-cell response to IL-6, and the in vivo myeloma cell

**Table 2. Distribution of Prognostic Parameters According to Serum CRP Level**

	CRP <6 mg/L		CRP $\geq$ 6 mg/L		P Value
	No.	%	No.	%	
Stage I	22	21.6	3	5.0	.002
Stage II	31	30.4	12	20.0	
Stage III	49	48.0	45	75.0	
	Mean $\pm$ SD		Mean $\pm$ SD		
$\beta$ 2M (mg/L)	5.4 $\pm$ 7.5		7.2 $\pm$ 9.2		.01
LI (%)	1.1 $\pm$ 1.2		2.3 $\pm$ 2.3		.008
Albumin (g/L)	3.9 $\pm$ 0.6		3.5 $\pm$ 0.8		.0004

**Table 3. Correlates of Survival: Multivariate Analysis**

Variable	Chi Square	P Value
I*		
1† Albumin	17.9	<.0001
2† $\beta$ 2M	4.6	<.03
II‡		
1† CRP	12.7	<.0001
2† $\beta$ 2M	9.1	<.0025

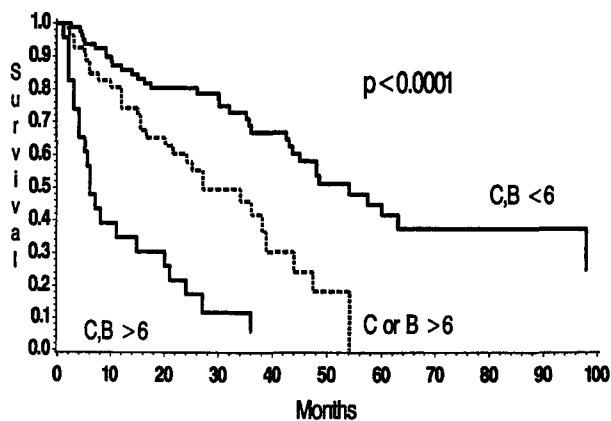
\*CRP,  $\beta$ 2M, tumor mass, creatinine, albumin, age were included in the stepwise Cox proportional hazard model.

†Sequence of entry into equation.

‡Albumin was excluded from this analysis (see text).

proliferative activity.<sup>14,16</sup> (2) Serum IL-6 levels are increased in MM patients and are a reflection of disease severity.<sup>18,19</sup> (3) IL-6 is directly detectable (in terms of mRNA and protein) in the bone marrow from MM patients<sup>15</sup> (4) Anti-IL-6 murine monoclonal antibodies, given to patients with advanced MM, resulted in a strong inhibition of myeloma cell proliferation.<sup>20,21</sup> Of major interest, serum CRP levels were highly increased in these patients with active MM, and became undetectable during the anti-IL-6 therapy.<sup>20</sup> Thus, our data with anti-IL-6 therapy in MM confirmed that CRP synthesis by hepatocytes is totally dependent on IL-6 and serum CRP level actually reflects IL-6 activity in vivo. Taken together, these data prompted us to investigate CRP as a putative prognostic parameter in MM. Incidentally, few studies have ever been devoted to acute phase proteins (not including CRP) in MM.<sup>29</sup>

Our present findings showed that serum CRP level (1) was significantly increased in MM compared with MGUS, (2) reflected MM disease activity, (3) strongly correlated with patient survival, and (4) was a powerful prognostic indicator in MM. Of major interest, the prognostic value of CRP was found to be independent of  $\beta$ 2M, another strong prognostic indicator. Finally, we have shown that simultaneous use of both these parameters constitutes a simple and powerful myeloma staging system.



**Fig 3. Actuarial survival of 162 MM patients according to serum CRP and  $\beta$ 2M levels at diagnosis. C,B <6 = CRP and  $\beta$ 2M <6 mg/L; C or B  $\geq$ 6 = CRP or  $\beta$ 2M  $\geq$ 6 mg/L; C,B  $\geq$ 6 mg/L = CRP and  $\beta$ 2M  $\geq$ 6 mg/L.**

**Table 4. Stratification of Myeloma Patients According to CRP and  $\beta$ 2M**

Risk Categories	Risk Parameters	No. of Patients (%)	No. Alive (%)	Median Survival (mo)
Low	CRP and $< 6$ mg/L	81 (50.0)	45 (55.5)	54
Intermediate	CRP or $\geq 6$ mg/L	56 (34.6)	24 (42.8)	27
High	CRP and $\geq 6$ mg/L	25 (15.4)	2 (8)	6

Serum CRP levels were significantly higher in patients with active MM (diagnosis, relapse) than inactive MM (remission), or MGUS, in complete agreement with previous data showing that serum IL-6 levels reflect disease severity.<sup>18,19</sup> Finally, serum CRP levels were directly related to survival in 162 previously untreated MM patients. These data clearly showed that serum CRP level, by directly reflecting IL-6 production in vivo, is a strong indicator of disease activity in MM. This concept is further supported by serial CRP studies in MM patients showing that (1) induction of remission was associated with a return of serum CRP levels to normal values, and (2) disease progression was associated with increased serum CRP levels (current work and personal data not shown).

Increased serum CRP levels delineated a subset of patients with high cell mass, low serum albumin, but high LI. Actually, a link between CRP and LI was found, and this relation is a strong argument in favour of CRP as a reflection of the effect of IL-6 on plasma cell proliferation. Moreover, no direct correlation between CRP and  $\beta$ 2M

was detected: these data are in agreement with previous observations of a lack of correlation between LI and  $\beta$ 2M.<sup>9,30</sup> A trend for an inverse correlation between CRP and albumin was shown. This is of considerable interest because IL-6 acts on hepatocytes by inhibiting albumin, but stimulating CRP synthesis.<sup>23</sup>

In the stepwise Cox proportional hazard model, excluding LI because of the small number of patients, albumin was the most significant parameter, followed by  $\beta$ 2M. When albumin was removed, CRP came first, followed again by  $\beta$ 2M. These data clearly showed that serum CRP and albumin gave similar prognostic information.

We propose the combination of CRP and  $\beta$ 2M as a strong prognostic staging system for MM. A 6 mg/L cutoff for both these parameters was chosen, and patients were separated into three risk groups (both parameters low, just one high, and both high) with strikingly different median survivals: from 54 months for the low risk to 6 months for the high risk. Although serum albumin and  $\beta$ 2M could also be successfully used, serum CRP and  $\beta$ 2M gave a better balanced stratification of patient groups. Several myeloma staging systems using  $\beta$ 2M associated with other prognostic factors have been proposed. For instance, the combined use of  $\beta$ 2M and albumin, or  $\beta$ 2M and LI have been recently suggested.<sup>4,5,9</sup> Thus, is not surprising to find CRP, which is strongly related to both albumin and LI, as the best partner of  $\beta$ 2M for MM prognosis. Finally, it is critical to remember that CRP and  $\beta$ 2M are highly influenced by infections (via IL-6 overproduction) and renal deficiency. However, this relationship strengthens their prognostic value because infections and renal deficiency are major causes of death in MM.

In conclusion, serum CRP level is shown to be a new and powerful prognostic factor in MM, and, like  $\beta$ 2M, its determination is rapid, simple, reliable, and inexpensive.

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