

## Original Research Article

# Study of prognostic factors in multiple myeloma

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### ABSTRACT

**Background:** Multiple myeloma (MM) is cancer of the plasma cell characterized by interpatient heterogeneity, in most of the cases it is incurable. It is the second most common hematological malignancy. Overall survival of patients has significantly increased recently. Lot of research is going on for prognostic factors, which can predict disease and response to therapy. During the past decades, biomarkers: M protein and  $\beta_2$  microglobulin have shaped the knowledge about MM. This study was undertaken to evaluate the role of prognostic factors in newly diagnosed and few follow up patients of MM before, during and after the treatment in Indian population.

**Methods:** We analyzed 177 samples (90 MM patients and 87 healthy control) for creatinine, calcium, phosphorus, LDH, total protein, albumin, globulin,  $\beta_2$ M, Immunoglobulines (Igs), IgG, IgA, IgM, Kappa light chain and Lambda light chains, serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE).

**Results:** The result of our study are significant at  $p < 0.0001$  for creatinine,  $\beta_2$ M, LDH, albumin, globulin and immunoglobulins whereas for calcium and phosphorus results are not significant at  $p < 0.005$ . We observed that the levels of  $\beta_2$ m, creatinine, LDH and M band concentration declined during the treatment (chemotherapy).

**Conclusions:** We conclude that these results will help the clinicians to tailor-made the chemotherapy doses for betterment of patients and improve survival rate in MM patients.

**Keywords:** Multiple myeloma,  $\beta_2$  microglobulin, LDH, Calcium, Immunoglobulins, SPE and IFE

### INTRODUCTION

Multiple myeloma (MM) is a cancer of plasma cells (also known as plasma cell myeloma) responsible for producing antibodies, initially no symptoms are noticed. These myeloma cells deposit at multiple joints of the bone, hence it is called Multiple Myeloma. It is the second most common hematological malignancy affecting elderly women (age more than 65 years) slightly more than men.<sup>1</sup> It is characterized by  $>30\%$  plasma cells, in bone marrow.<sup>2</sup> Patients with heavy proteinuria ( $>1$  g/2h) usually have myeloma.<sup>3</sup> Many symptoms of disease are produced by nonfunctional Igs produced in large quantity by these myeloma cell. which burdens organs like kidneys, nerves and immune system which affects normal body functions.

Initially, often no symptoms are noticed. When disease is advanced, bone pain, frequent infections, bleeding and anemia may occur. Complications may include amyloidosis.<sup>4</sup> 0.7% of people are affected by MM at some point in their life.<sup>5</sup> Survival is seven months, Without treatment. With current treatments, survival is usually 4–5 years.<sup>6</sup> This gives a five-year survival rate of about 49%.<sup>5</sup> MM is not curable unless treated. High dose therapy followed by bone marrow transplantation is being used to improve response to therapy and survival. Diagnostic profile for MM includes blood tests, urine tests and bone X-ray or bone marrow aspiration test for number of plasma cells present. CRAB symptoms (C=Calcium (elevated), R=Renal failure, A=Anemia, B=Bone lesions.) and proliferation of monoclonal plasma cells in the bone

marrow are part of the diagnostic criteria.<sup>7</sup> However, there are cases of MM with absence of CRAB features.

The biochemical tests include most useful laboratory tests such as quantitative measurement of IgA, IgG, IgM to look for SPE and IFE, along with levels of albumin (Alb), calcium (Ca), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), beta2-microglobulin ( $\beta$ 2m) and creatinine(Cr) in the blood.

Prognostic factors play important role in cancer management. Determining the prognosis in MM requires the knowledge of tumor stage classification with the use of International Staging System (ISS).<sup>8</sup> Higher levels of  $\beta$ 2m, LDH, and CRP and lower levels of Alb are associated with a poorer prognosis generally. Serum  $\beta$ 2m <4 mcg/mL is a good prognostic factor in patients with MM. It is believed that serum  $\beta$ 2m rise due to renal failure in MM patient and hence in some cases it was found that due to the deposition of  $\beta$ 2m in joint spaces leads to synovitis. a poor prognosis is associated with increased levels of serum  $\beta$ 2m in patients with MM.<sup>9</sup> Serum  $\beta$ 2m is used in the follow-up of patients with plasma cell tumors. This marker highly correlates with the total mass of myeloma cells.<sup>10</sup> Igs are overproduced by myeloma cells. Presence or absence of MM depends on levels of IgG or IgA antibodies in the blood. Most patients with symptomatic MM have increased M protein levels (more than 3g/dL) on SPE (Figure 1). 80% has elevated urine excretion of light chains ( $\kappa$  or  $\lambda$ ), which is often called Bence Jones myeloma.<sup>11</sup> IFE (Figure 2) can identify the type of abnormal antibody proteins present in the blood, and aids in classification of the disease.

Light chains (also called Bence Jones proteins: BJP) are classified as kappa or lambda. Presence of MM or a related disease can be determined by abnormal levels and/or ratio of FLCs.<sup>12</sup> Proteinuria-induced renal failure is a major cause of morbidity and mortality in patients with MM.<sup>13</sup> In symptomatic MM, serum albumin level is a significant prognostic factor reflecting severity of disease.<sup>14</sup> Hypercalcemia is commonly observed in patients with MM. Serum LDH can be used as an important biomarker in diagnosis and prognosis of hematological malignancies, because it is a general indicator of the existence and severity of acute/chronic tissue damage.<sup>15</sup> serum LDH levels are as useful markers as  $\beta$ 2m and monoclonal Igs for follow-up of MM disease.

Multiple myeloma is characterized by several features, including

Monoclonal gammopathy indicates many copies of the same antibody. Not everyone with monoclonal gammopathy has MM, although people with MM have a monoclonal gammopathy. It can also occur in other diseases, such as Waldenstrom macroglobulinemia and some lymphomas. It can also occur in a disorder known as MGUS (monoclonal gammopathy of undetermined

significance), which does not cause problems like MM does.<sup>11</sup>

Light chain amyloidosis occurs when too many light chains are made by abnormal plasma cells. These light chains can deposit in tissues, where they build up. This can lead to an abnormal protein in tissues known as amyloid. Amyloid in the kidneys can cause them to work poorly. The poor kidney function may be found on blood tests, even though this may not cause early symptoms. Amyloid in the kidney can lead to kidney failure, if it gets worse.<sup>11</sup>

In MGUS, abnormal plasma cells produce many copies of the same antibody (a monoclonal antibody protein). However, these plasma cells do not cause any of the other problems seen in MM. When a routine blood test finds a high level of protein in the blood and the protein is a monoclonal antibody, it indicates MGUS. Some of MGUS patients eventually develop MM, lymphoma, or amyloidosis. (about 1% of people with MGUS develops one of these diseases, every year).<sup>11</sup>

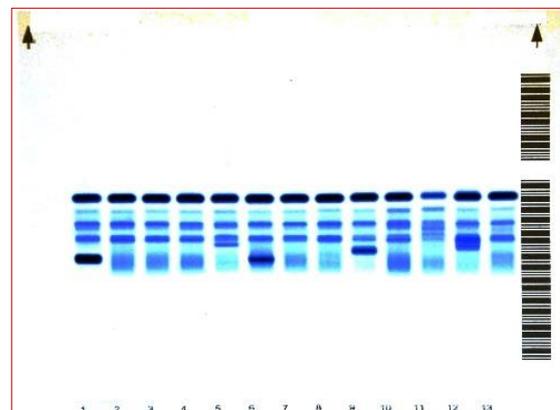


Figure 1: SPE.

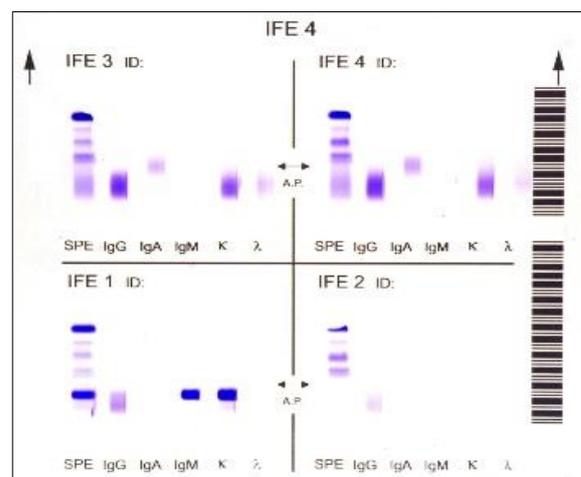


Figure 2: IFE.

Solitary plasmacytomas, as the name suggests, there is only one tumor, instead of many tumors in different

locations as in MM. Most often, it develops in a bone, and may be called an isolated plasmacytoma of bone.<sup>11</sup>

**Objective of the study**

Lot of research is going on for prognostic factors, which can predict disease and response to therapy. Quantitative measurement of IgA, IgG, IgM, kappa light chain, lambda light chains, to look for SPE and IFE, along with levels of albumin, calcium, LDH, BUN,  $\beta$ 2m and creatinine in the blood play an important role in prognosis in MM. Hence, this study was undertaken to evaluate the role of these prognostic factors in newly diagnosed and few follow up patients of MM before, after and during treatment. In Tata memorial Hospital approx. 200-250 new MM patients are registered every year.

**METHODS**

**Study type**

The study type was retrospective.

**Study place**

The study was conducted at Department of Biochemistry, Tata Memorial Hospital.

**Period of study**

The study was conducted for a period of January 2017 to March 2020.

**Selection of criteria of patients**

Patients having MM with no prior treatment and no other disease/disorders, ascertained from clinical records were selected for the study. All these cases were registered in Tata Memorial Hospital, Parel, India and were histologically or cytological proven malignant. Normal controls did not show any malignancy.

**Group I**

87 Normal Controls (25 Females and 62 males with the age group of 30-58 years). This served as reference group.

**Group II**

90 newly diagnosed MM patients (22 Females and 68 males with the age group of 47-77 years) in our hospital with no prior treatment. The International Staging System (ISS) for MM was used to classify the stage of Multiple myeloma.

MM stage I (MM SSI); No. of patients 26.

MM stage II (MM SSII); No. of patients 27.

MM stage III (MM SSIII); No. of patients 37.

**Procedure**

From all the patients as well as control groups, 5 ml blood was collected in a plain tube (SS tubes) and 24 hrs urine samples was collected. Serum was separated from blood by centrifuging at 4000 rpm for 10 minutes, and analyzed for all the tests: Quantitative measurement of IgA, IgG, IgM, kappa light chain, lambda light chains, albumin, calcium, LDH, BUN,  $\beta$ 2m and creatinine along with SPE and IFE.

All the parameters were investigated as mentioned in Table 1.

Ethical approval was taken from Ethics committee for the present study.

**Table 1: Blood investigations and method name.**

Blood investigations (serum/plasma)	Method
Creatinine, Calcium, Phosphorous, LDH, Albumin	Spectrophotometry
$\beta$ 2-microglobuline	Immuno-turbidimetry
IgA, IgG, IgM, kappa light chain and lambda light chain	Rate nephelometry
Serum Protein Electrophoresis (SPE) Immunofixation (IFE)	Gel electrophoresis
Urine Investigations	
Kappa Light Chain, Lambda Light Chain	Rate nephelometry

**Statistical analysis**

The dataset in patient groups did not follow a normal distribution for any of the parameters that were analyzed as they did not pass tests for normality distribution (Shapiro-Wilk normality test). Thus, data were depicted as median and range (with interquartile range) and comparison between groups were done using Mann-Whitney U test. A receiver operating characteristic (ROC) curve was plotted for different cut off points and the ideal cut off level for each parameter was determined to differentiate Group I from Group II. Positive predictive value (PPV) and Negative predictive value (NPV) were calculated as follows:

Sensitivity =  $a \div a+c$  = Probability of being test positive when disease present.

Specificity =  $d \div b+d$  = Probability of being test negative when disease absent.

PPV =  $a \div a+b$  = Probability (patient having disease when test is positive)

NPV: =  $d \div c + d$  = Probability (patient not having disease when test is negative)

Where: a = true positive,

b = true negative,

c = false negative and

d = false positive.<sup>16</sup>

**RESULTS**

Analysis of serum Cr, Ca, Phos, LDH, Total Pr, Alb, Globulin,  $\beta$ 2M, Immunoglobulines; IgG, IgA, IgM, Kappa light chain and Lambda light chains were done for MM cases (before, during and after the treatment) and normal healthy controls and statistical data was analyzed. Table 2, 3 predict the statistical data.

**Table 2: Statistical data of various biochemical parameters.**

Parameters units	Creatinine mg/dl		Calcium mg/dl		Phosphorus mg/dl		$\beta$ 2M mg/l		LDH U/l		Albumin gm/dl		Globulin gm/dl	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II
<b>Group</b>	I	II	I	II	I	II	I	II	I	II	I	II	I	II
<b>Median</b>	0.9	1.2	9.4	9.05	3.6	3.6	2.14	5.16	169	166	4.3	3.55	3.2	4.75
<b>Minimum</b>	0.6	0.6	7.9	6.9	2.7	1.1	1.33	0.97	85	54	2.2	1.6	2.5	1.9
<b>Maximum</b>	1.4	11.7	10.3	13.2	5.4	8.1	5.32	67	281	411	4.8	5.0	4.7	11.6
<b>Interquartile range</b>	0.8	0.9	9.1	8.4	3.3	2.88	1.83	3.44	150	117.5	4.1	2.8	3.0	3.2
	1.0	1.63	9.7	9.93	4.1	4.03	2.51	9.63	190	214.8	4.5	4.1	3.5	7.43
<b>P value</b>	<0.00001*		0.163256**		0.380308**		<0.00001*		0.049959*		<0.00001*		<0.00001*	

**Table 3: Statistical data of Total Protein, Immunoglobulins and free light chains.**

Parameters units	Total Protein gm/dl		IgA mg/dl		IgM mg/dl		IgG mg/dl		Kappa Mg/dl		Lambda mg/dl		Kapp/Lambda Ratio %	
	I	II	I	II	I	II	I	I	I	II	I	II	I	II
<b>Group</b>	I	II	I	II	I	II	I	I	I	II	I	II	I	II
<b>Median</b>	7.5	9.0	213	64	101	26.95	3.2	3.2	1000	2770	575	296.5	1.83	4.63
<b>Minimum</b>	6.4	5.1	71.2	7.86	27.3	4.17	2.5	2.5	95	70.4	230	30	0.471	0.0219
<b>Maximum</b>	8.8	13.8	394	8410	348	4430	4.7	4.7	1330	15600	1240	14400	4.16	363.3
<b>Interquartile range</b>	7.3	8.1	135	39.18	64	15.53	3.0	3.0	844	593.5	456	147.8	1.53	0.763
	7.8	10.9	279	194.8	129	44.85	3.5	3.5	1120	5702.5	667	1600	2.09	37.3
<b>P value</b>	<0.00001*		<0.00001*		<0.00001*		<0.00001*		<0.00001*		<0.00001*		<0.00001*	

\*The result is significant at p <0.0001 for creatinine,  $\beta$ 2M, LDH, albumin, globulin and immunoglobulins where as \*\*the result is not significant at p <0.005 for calcium and phosphorus.

Figure 3 indicates sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for all the parameters studied. Sensitivity and specificity was calculated at different cutoffs levels. Cutoff value selected was with maximum sensitivity and a stable level of specificity.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at cut off levels

The result of our study are significant at p<0.0001 for creatinine,  $\beta$ 2M, LDH, albumin, globulin and immunoglobulins whereas for calcium and phosphorus results are not significant at p<0.005. This is in agreement with Choo-Kang and Campbell, who proposed that hypercalcemia, hyperphosphatemia, occurred in about one-third of patients in their study group.<sup>17</sup> In the present study 27 out of 90 showed elevated calcium levels and 22 out of 90 patients showed elevated phosphorus levels.

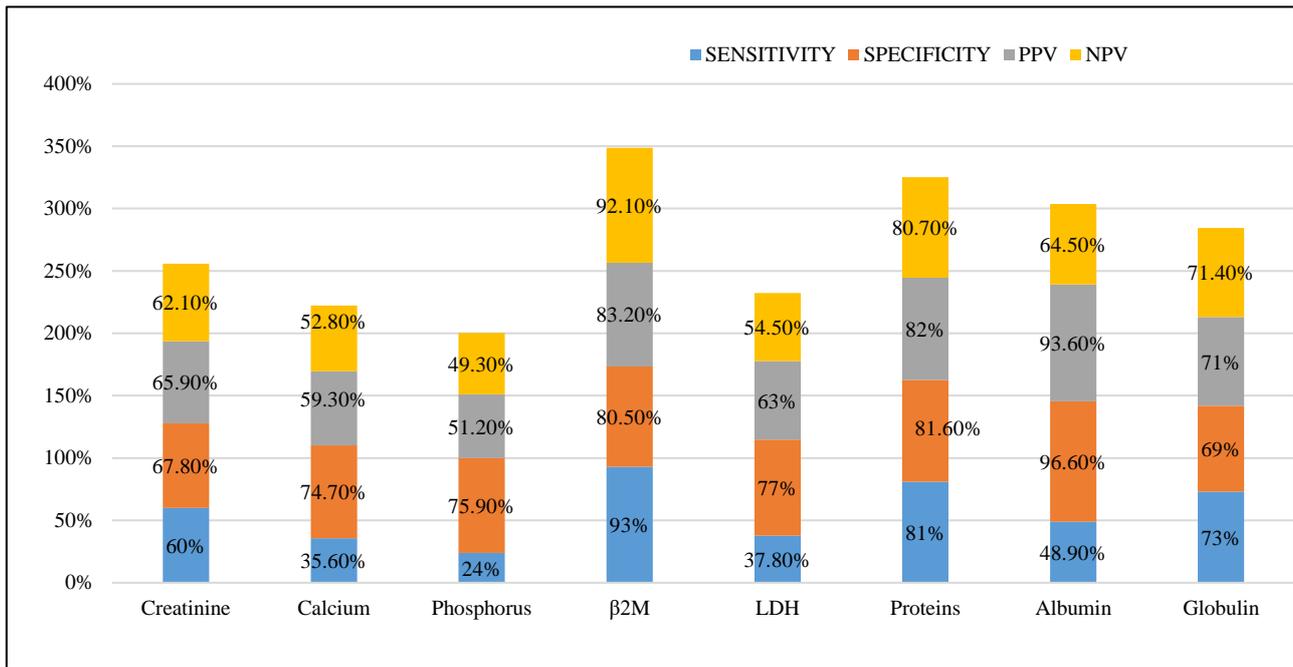


Figure 3: Sensitivity, specificity, PPV and NPV for all the biochemical parameters.

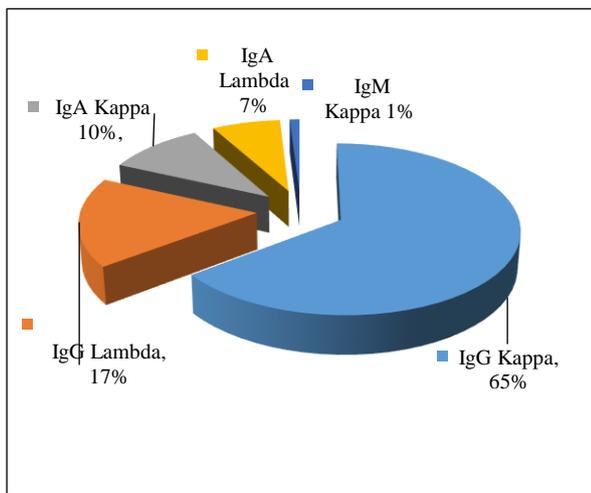


Figure 4: Share of IFE findings percentage wise.

To measure the strength of correlation between Kappa/Lambda ratio and all the studied parameters a Pearson correlation coefficient was used. When Kappa/Lambda ratio is compared with all the parameters, it is noted that the R value for Cr, Ca, Phos, LDH is less than 0.5, although technically it is positive correlation but not strong correlation. TP and Alb Showed weak negative correlation with R value less than 0.5. For β2M the value for R is 0.8482. This is a strong positive correlation. The value for R<sup>2</sup>, the coefficient of determination is 0.7194.

When we studied all the mentioned parameters before, during and after the treatment was completed we observed that all these 15 patient's K/L ratio were well correlating with the clinical findings. These findings of ours will surely help the clinicians to tailor-made the chemotherapy

doses for betterment of patients and improve survival rate in MM patients.

### DISCUSSION

The prognosis of patients with MM who develop acute renal failure is poor stated by defronzo and associates.<sup>18</sup> In the present study 54 out of 90 patient showed renal insufficiency. In defronzo's study on 35 patients with MM, they suggested that BJP exert a direct nephrotoxic effect at the tubular level with resultant tubular dysfunction and tubular atrophy.<sup>19</sup> In our study 55 of 90 patients had BJP positive with kappa (43 out of 55) or Lambda (12 out of 55) excretion rate. Prakash and associates stated that Dialysis support was needed in 77% of the patients because of severe renal failure in MM cases.<sup>20</sup> Our results of creatinine are in agreement with Michels et al and other researchers, who showed elevated creatinine in about 48% of MM.<sup>21-24</sup> Goldschmidt and associates stated that 15% to 30% of patients of MM present with acute renal failure at the time of diagnosis and approximately 20% of the patient develops progressive renal failure during the course of the disease.<sup>25</sup> According to International Myeloma Working Group (IMWG), renal impairment caused by light chain cast nephropathy is considered as an event defining myeloma.<sup>26,27</sup> LDH plays an important role as the disease progresses and has a major impact on the survival of MM patients. It is a readily available and inexpensive test. 34 of 90 patients showed elevated LDH levels which is in agreement with the study conducted by Teropos et al, and Krina et al.<sup>28-30</sup>

In patients with MM, the increased levels of serum β2M have been associated with a poor prognosis. Avils et al estimated serum β2M in 70 untreated patients with MM

and reported it as the most significant prognostic factors.<sup>9</sup> Our results for  $\beta$ 2M are in agreement with their studies and also with the study conducted by Rossi D and coworkers.<sup>31</sup> Chelazzi et al proved that serum  $\beta$ 2M is highly correlated with the total mass of myeloma cells and suggested that it can be used in the follow-up of patients with plasma cell tumors.<sup>32</sup> According to Chelazzi, in the clinical management of monoclonal gammopathies, serum  $\beta$ 2M is a useful test. IgG accounts for about 60% to 70% of all MM cases, and IgA accounts for about 20% of cases.

Patients are likely to relapse with recurrent disease, after initial therapy, transplant, and even after maintenance therapy. At this point in their course they can be treated with further therapy. Approved therapies for this include dexamethasone, bortezomib, carfilzomib, lenalidomide, pegylated liposomal doxorubicin (with bortezomib), thalidomide, pomalidomide, panobinostat, alkylating agents, daratumumab, elotuzumab, ixazomib and all combinations of these drugs. Prognostic indicators may also help to determine when treatment for MM should begin, and which treatment is best according to a person's individual risk for relapse.

In our study the predominant immunoglobulin found was IgG Kappa type with 65% followed by IgG Lambda 17% IgA Kappa 10% and IgA Lambda 7% (fig IV) which is in agreement with the findings reported by MM research foundation.<sup>30</sup>

On follow up some patients (60%) showed decline in the levels of prognostic indicators that is they were responding to the treatment, 20% showed decline and again relapse and remaining 20% cases either did not respond to therapy or very slow prognosis who needed change in therapy.

## CONCLUSION

We conclude that Immunoglobulin levels with SPE and IFE along with  $\beta$ 2m play a very important role as prognostic indicator for MM. In our multivariate analysis, serum  $\beta$ 2m levels was found the most significant prognostic factor. Serum creatinine, albumin and LDH levels were also found significant at a  $p < 0.05$ . We conclude that  $\beta$ 2m level is one of the most useful prognostic factors in patients with multiple myeloma. Levels of  $\beta$ 2m, creatinine, LDH and M band concentration declined during the treatment (chemotherapy), hence these results can help the clinicians to tailor-made the chemotherapy doses for betterment of patients and improve survival rate in MM patients.

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Ethical approval was taken from Ethics committee for the present study.

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