

## RESEARCH ARTICLE

# International Scoring System in Symptomatic Multiple Myeloma: Experience from a Tertiary Care Center

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### Abstract

**Background:** Symptomatic multiple myeloma (MM) is an acquired B-cell malignant proliferation of antibody secreting plasma cells, characterized by end organ damage due to monoclonal immunoglobulin secretion. The aim of this study was to determine the stage stratification according to an international scoring system in adult Pakistani MM patients at presentation. **Materials and Methods:** This single centre retrospective study extended from January 2012 to December 2015. Data were retrieved from the departmental maintained records. **Results:** A total of 39 patients were diagnosed at our center with MM during the period of the study, 25 males and 14 females. Age ranged between 36 and 81 with a mean of  $54.5 \pm 14.8$  and a median of 57 years. Common presenting complaints included fatigue (80.9%), backache (79.3%) and bone pain (66.2%). Overall, 9 patients were in ISS stage I (23%), 12 were in stage II (30.7%) and 18 were in stage III (46.1%). Out of the total, 29 (74.3%) had kappa immunoglobulin and the remaining 10 (25.6%) had lambda type myelomas. IgG myeloma was commonest, seen in 26 (66.6%) followed by IgA in 11 (28.2%) with non secretory myeloma in one (2.5%) and light chain disease also in one patient (2.5%). **Conclusions:** MM in Pakistani patients is seen in a relatively young population with male predominance. Primarily patients are symptomatic and risk stratification revealed a predominance of advanced stage III disease in our setting.

**Keywords:** Multiple myeloma - international scoring system - stage - Pakistan

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### Introduction

Multiple myeloma is a plasma cell dyscrasia that is characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal band in the blood or urine and an associated end organ dysfunction (Antonio et al., 2011; Diwan et al., 2014). It accounts for approximately 1% of all neoplastic diseases and 13% of hematopoietic malignancies (Rajkumar., 2011; Vincent., 2014). The median age at diagnosis is approximately 70 years with the median survival of 4 years (Sun et al., 2015; Mehdi et al., 2013; Wang et al., 2015).

CRAB, the clinical manifestation comprises of raised calcium, renal impairment, anemia and bone lytic lesions are frequent finding in these symptomatic myeloma patients. Myeloma cells typically release certain factors which activate the osteoclastic activity resulting in bone resorption, hypercalcemia, bony lytic lesions, bone pains and eventually pathological fractures (Sutandyo et al., 2015).

Multiple myeloma is a heterogeneous disease in respect to prognosis, clinical course and response to therapeutic interventions. Previously numerous prognostic factors have been identified however, there was no consensus about the best indicators for survival (Kadar et al.,

2012). Following 2004, International Myeloma Working Group had proposed the new staging system named as International Staging System (ISS). According to this system, albumin and  $\beta_2$  microglobulin are recognized as a new prognostic markers, which predicts the overall survival in myeloma patients. The reported median survival rate of stage 1 is 62 months followed by stage 2 that is 44 months while for stage 3 average survival is 29 months respectively (McKenna et al., 2008).

To the best of authors' knowledge, there was very negligible local data on this entity. This prompts us to review our experience with multiple myeloma in Pakistan. The aim of this study is to ascertain ISS scoring in our patient population at initial disease presentation.

### Materials and Methods

This descriptive study was conducted from January 2012 till December 2015. Thorough information was available for 39 patients were enrolled in the present study. All patients underwent detailed history, general physical and systemic examination.

Patients diagnosis was established as per World Health Organization (WHO) criteria (McKenna et al., 2008). All three criteria must be met for diagnosis: *i*). Presence

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of M-protein in serum or urine; *ii*). Bone marrow clonal plasma cells; *iii*). Related organ or tissue impairment.

Patients with another mature lymphoid neoplasm (both of B-cell or T-cell lineages) were excluded. Patients having history of another associated malignancy or having relapsed or refractory MM were also not included in the analysis.

Venous blood samples were taken for complete blood count and were determined by Automated analyzer (Cell Dyne Ruby, Abbott). Serum calcium and creatinine were detected on HITACHI 912 (Japan) by photometric assay. M-Proteins in blood were determined by serum protein electrophoresis which was done on Interlab Genio-S instrument followed by immunofixation to determine its types.

Serum albumin was detected by Cobas e 501 analyzer (Roche, Japan) and normal range was 3.4 to 5.4 g/dL.  $\beta$ 2-microglobulin levels were determined by chemiluminescence technique. According to ISS system, disease is stratified as stage I:  $\beta$ 2 microglobulin were  $<3.5$  mg/L and albumin  $\geq 3.5$  g/dl; stage II:  $\beta$ 2 microglobulin  $<3.5$  mg/L and albumin  $<3.5$  g/dl or  $\beta$ 2 microglobulin between 3.5-5.5 mg/L irrespective of the albumin; stage III:  $\beta$ 2 microglobulin  $\geq 5.5$  mg/L.

Bone marrow aspirate and trephine biopsy specimen were taken from posterior iliac crest with Jamshidi needle. Each bone marrow aspiration and biopsy was reviewed by consultant hematopathologist.

This study was conducted after approval from Hospital's Institutional Research and Ethical Board.

#### Data analysis

Data was entered and analyzed using SPSS software (Version 21, SPSS Inc, Chicago, Illinois, USA). The results were expressed as mean  $\pm$  SD for quantitative variables. Frequency and percentages was calculated for qualitative variables.

## Results

#### Demographic data

Out of 39 patients, 25 were males (64.1%) and 14 were females (35.8%) with male to female ratio of  $\sim 2:1$ . Median age was 57 years while age ranged between 36 and 81 years with a mean age of  $54.5 \pm 14.8$  years.

#### Clinical findings

The common presenting complaints included fatigue in 80.9% patients, backache in 79.3% patients and bone pain in 66.2% patients. Overall 30.7% patients presented with sign and symptoms of hyperviscosity. Physical examination revealed pallor as a predominant finding detected in 41.2% patients followed by cutaneous rashes in 15.3% of patients.

#### Stage stratification

The mean albumin was  $3.0 \pm 1.9$  g/dl while mean  $\beta$ 2-microglobulin was  $5.4 \pm 4.9$  mg/L. Overall, 9 patients were in ISS stage I (23%), 12 were in stage II (30.7%) and 18 were in stage III (46.1%) respectively.

#### Types of myeloma

Out of total 39 patients, 29 (74.3%) had kappa immunoglobulin and remaining 10 (25.6%) had lambda type myeloma. IgG myeloma was commonest, seen in 26 (66.6%) followed by IgA in 11 (28.2%) and non secretory myeloma in 1 (2.5%) patient and light chain disease also in one patient (2.5%).

#### Laboratory profile

The mean hemoglobin levels were  $8.8 \pm 1.9$  g / dl (3.2-13.3 gm/dl). The mean total leukocyte count of  $8.8 \pm 7.2 \times 10^9/l$  and the mean platelets count were  $181 \pm 141 \times 10^9/l$  ( $11-768 \times 10^9/l$ ).

Of the 39 study patients, 19 (48.7%) had hypercalcemia (S.Ca  $>12$  mg/dl) while renal impairment (serum creatinine  $>1.5$  mg/dl) was noted in 16 (41.0%) patients. Radiological survey showed different levels of skeletal involvement in 31 (79.4%) patients.

## Discussion

Multiple myeloma is a heterogeneous plasma cell dyscrasia, characterized by clonal plasma cells infiltration, presence of M-paraprotein, and an associated end organ failure. MM is incurable disease with varied survival range and an overall median survival of 3-4 years (Sashidharan et al., 2015). A large multicentre study conducted in 2005, provided the base of ISS staging system, showed median survival for patients with ISS stages I, II and III as 62, 44 and 29 months respectively (Greipp et al., 2005). The risk stratification system has made it doable to predict the disease path as well as outcome in such patients with categorization from low to high risk disease.

There is a limited studies reported from our country on this hematopoietic malignancy while only single study reported stage stratification according to ISS (Shaheen et al., 1999; Mansoor et al., 2005; Inamullah et al, 2010; Basit et al., 2014). The researcher reported the international scoring system (ISS) in Pakistani myeloma patients in this study. We determined that MM affected a younger population in our hands; however the male gender dominance was similar to that reported in international and regional studies.

It was noted that the disease stage stratification in our patients had shown advanced disease (stage III- 46.1%) compared with previous local (stage-III- 32%) study reported from Lahore (Basit et al., 2014).

When compared with earlier international reports, our results are in conflict with studies published from Greece and USA, where usually patients presented in stage II of disease (Dimopoulos et al., 2012; Greipp et al., 2005). According to Dimopoulos, 29% patients had ISS-1, 38% patients had ISS-2 and 33% ISS-3 disease while Greipp from USA disclosed stage I, 28.9%; stage II, 37.5%; and stage III, 33.6% (Dimopoulos et al., 2012; Greipp et al., 2005). This difference may be accredited to the aggressive disease course along with concomitant factor of delay in seeking medical attention.

In broad, our patients presented with the more advanced disease with frequent complications. Herein, majority of patients presented with fatigue and backaches.

Comparable presenting complaints were reported by earlier studies, detected fatigue and backaches in 78% and 80% respectively (Shaheen et al., 1999; Kyle et al., 2003). Bones pains and easy fatigability were also the most common symptoms in another study reported from India by Subramanian (Subramanian et al., 2009).

Primarily disease manifestations are due to the infiltration by plasma cells and secretion of M-protein by malignant clones. Predominant type of gammopathy observed in our patients is similar to that in prior Pakistani study (Shaheen et al., 1999). IgG is the commonest (66.6%) monoclonal gammopathy on immunoelectrophoresis. Predominant light chains associated with gamma heavy chains were kappa (74.3%) in the present study. IgA was the second commonest monoclonal protein in our study. In one recent Egyptian study, majority of patients (73%) had an immunoglobulin G monoclonal band and 70 % were Kappa chain-positive (El Husseiny et al., 2014). Similarly another study from Tunisia also reported IgG type in 57%, followed by IgA in 28% of patients (Younes et al., 2014).

Lastly the limitations of present study are its retrospective nature and lack of follow up data to see the disease progression and median survival. Small sample size is another limitation. Despite the limitations; this is the local study which provides essential regional informative data for stratification in our setup.

In conclusion, multiple myeloma is a disease with a varied presentation. Relatively younger age of disease onset is a notable feature of myeloma in Pakistan. The most frequent type is IgG kappa myeloma in our hand. Also, most of our patients have an advanced stage III disease, probably due to late presentation. As lack of public awareness and deprived socioeconomic status are the main hindrances in early diagnosis of this condition leading to poor outcome.

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