

CLINICAL AND DEMOGRAPHIC PROFILE OF MULTIPLE MYELOMA IN NORTH INDIAN POPULATION

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ABSTRACT:

BACKGROUND and OBJECTIVE: The incidence of multiple myeloma varies among different ethnic group and among different countries but from past few years its incidence is increasing in Asian countries. In India due to financial constraints, lack of adequate health infrastructure and lack of knowledge among people lead to delay in the treatment of Multiple Myeloma and it became a challenge to medical field in India. The objective of the study is to study the various parameters and its incidence in Multiple Myeloma patients.

METHODS: This is a cross sectional study conducted in the department of medicine and oncology of tertiary care hospital of north India. Data was taken from 2015-2022, 102 cases of multiple myeloma was diagnosed out of which 2 were excluded. The diagnosis was made based on the International Myeloma Working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorder. The demographic profile, clinical symptoms and laboratory parameters were studied.

RESULTS: Multiple Myeloma was most common in 5th decade with male predominance and more common in urban population. Most common symptom was bone pain 63 (63%) and weight loss (9%) least common. 65% had anaemia, 18% had renal insufficiency and 34% had hypercalcaemia. All of the patients had M-band in gamma globulin region with 48% had ISS stage 1. 70(70%) had lytic lesions in the skull.

INTERPRETATION AND CONCLUSION: To conclude majority of the patients of Multiple Myeloma were males and majority were farmers. Majority of patients were from urban area.

Bone pain being the most common symptom followed by the fatigue. Anaemia and Hypercalcemia were less common in our study population. Most of the patients had ISS stage 1. The presentation of MM varies among patients and with adequate health infrastructure better outcome and early diagnosis of multiple myeloma will be there.

KEYWORDS: Beta 2 microglobulin, Hypoalbuminemia, Hypercalcemia, Multiple Myeloma, Plasma cells, Renal insufficiency

BACKGROUND:

Multiple Myeloma (plasma cell myeloma, plasmacytoma, myelomatosis, Kahler disease) represents a malignant proliferation of plasma cells derived from B cell¹. It is more commonly seen in farmers, wood workers and leather workers. Incidence of MM is lowest in Asian countries than African American and European countries but it is increasing rapidly². According to 2017 data, the Age Standardised Rate for MM incidence in India is 0.7/1 lakh population amounting to about 6800 new cases a year. Its median age of diagnosis is 52-61 years but is less common under 40 years. Male are affected more than females³.

Diagnostic criteria for Multiple Myeloma:

- 1) Clonal bone marrow plasma cells or biopsy proven bony or extramedullary plasmacytoma and any one of the following myeloma defining events.
- 2) Evidence of one or more end organ damage that can be attributed to the underlying plasma cell proliferative disorder specifically:
 - Hypercalcemia: serum calcium $> 0.25\text{mmol/l}$ ($>1\text{ mg /dl}$) higher than the upper limit of normal or $> 2.75\text{mmol/l}$ ($>11\text{mg/dl}$).
 - Renal insufficiency: creatinine clearance $<40\text{ ml per min}$ or serum creatinine $>177\text{mcmol/l}$ ($>2\text{ mg/dl}$)
 - Anaemia : haemoglobin value of $>20\text{g/l}$ below the lower limit of normal or haemoglobin value $<100\text{g/l}$
 - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET CT
 - Any one or more of the following biomarkers of malignancy:
 - Clonal bone marrow plasma cells percentage $>_{60}\%$
 - Involved : uninvolved serum free light chain ratio $>_{100}$
 - >1 focal lesions on MRI studies².

It causes many organ dysfunction and symptoms such as renal failure, bony pains or fracture, anaemia, susceptibility to infection, hypercalcemia, neurologic symptoms and manifestation of hyperviscosity. It is more commonly seen in farmers, wood workers and leather workers². It is characterised by the development of osteolytic lesion in the bone and involves the activation of osteoclasts with simultaneous suppression of new bone formation of osteoblast inhibition⁴. Bone pain is the most common symptom. Other presentation is anaemia, hypercalcemia, renal failure, weight loss. Rare features are cord compression, CNS involvement⁵. Immunomodulatory agents like thalidomide, lenalidomide and protease

inhibitor like bortezomib along with dexamethasone is a good induction therapy and has good response rate. Autologous stem cell transplant is good option in selected patients after induction therapy⁶. This study aims at demographic and clinical profile of multiple myeloma patients in north part of India.

METHODS:

This cross sectional study included multiple myeloma patients visiting our tertiary care hospital for management. The patients were from 2015-2022. Patients and their attendants were explained about the purpose of this study and informed consent was taken from them excluding terminally ill patient. A total of 102 patients on treatment were taken out of which 2 died. Data on demographic profile such as age, religion, sex, and address along with occupation was collected. Clinical features such as bone pain, weight loss and fatigue along with biochemical findings were also considered such as number of plasma cells in bone marrow, serum calcium levels, serum creatinine levels, serum haemoglobin levels, peripheral blood smear, hypoalbuminemia, serum protein electrophoresis (presence of M spike), bence jones protein in urine and beta 2microglobulin levels. Skeletal survey (xray skull and spine) were performed. Staging of MM done based on 3 stage International Staging System (ISS). Bone marrow biopsy and peripheral blood film were reported by pathologists. Data was collected, analysed and presented as frequency tables, pie charts and figures.

RESULTS: In our study we consider data of total 100 patients and study it accordingly. The majority of the Multiple Myeloma was in 5th decade as 48% of the patients were 51-60 years of age and only 2% below 41 years. The distribution parameters are presented in figure 1.

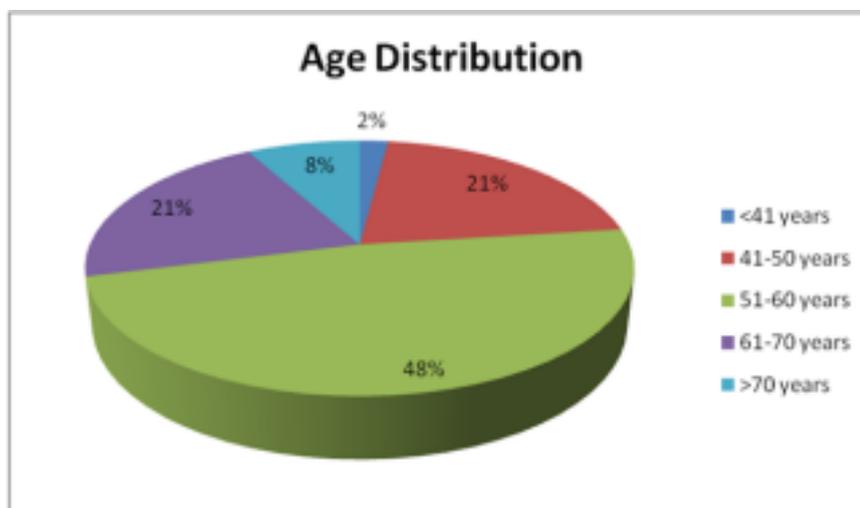


Fig. 1 Age Distribution

The demographic profile shows that majority of our patients were Sikhs (73%) as shown in figure 2. It is predominant in males i.e 54% (n=54) of the patients were males and 46% (n=46) were female and majority were from rural area. 58% of the patients were from rural area as shown in figure 3. All the females were housewives i.e. 46% of the patients. In males majority were farmers (28%) as in figure 4.

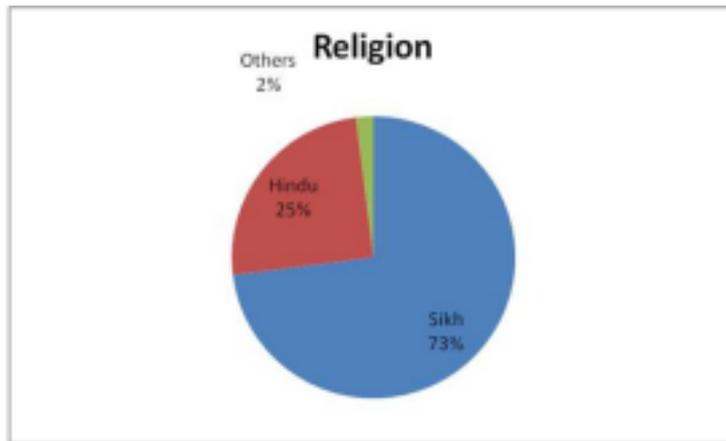


Fig. 2 Demographic Profile

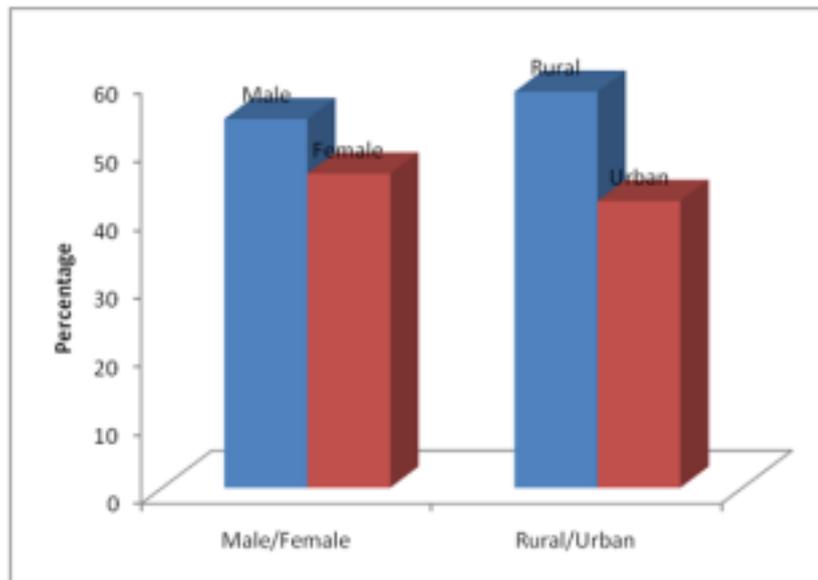


Fig. 3 Distribution of patients according to their gender and background

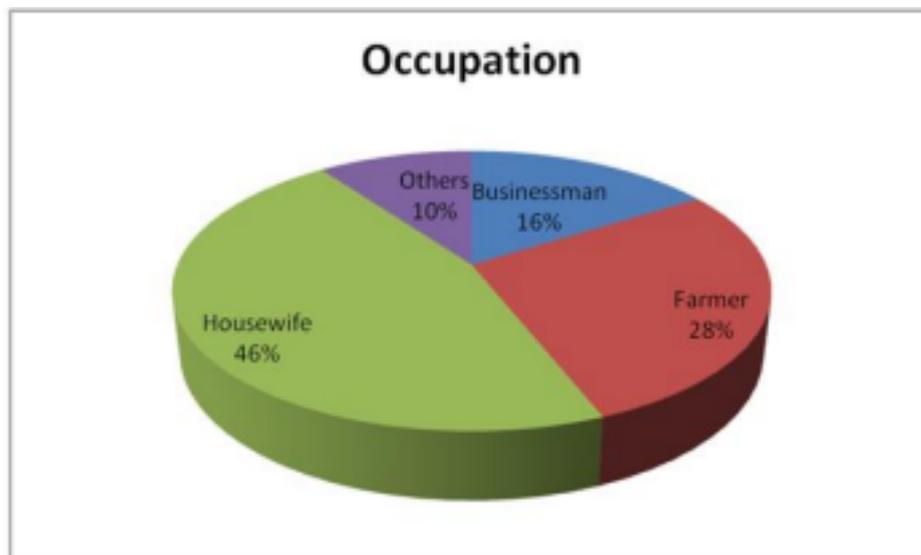


Fig. 4 Patient distribution as per occupation

The most common symptoms were bone pain 63% followed by fatigue 31% and weight loss 9% as clinical features were depicted in figure 5.

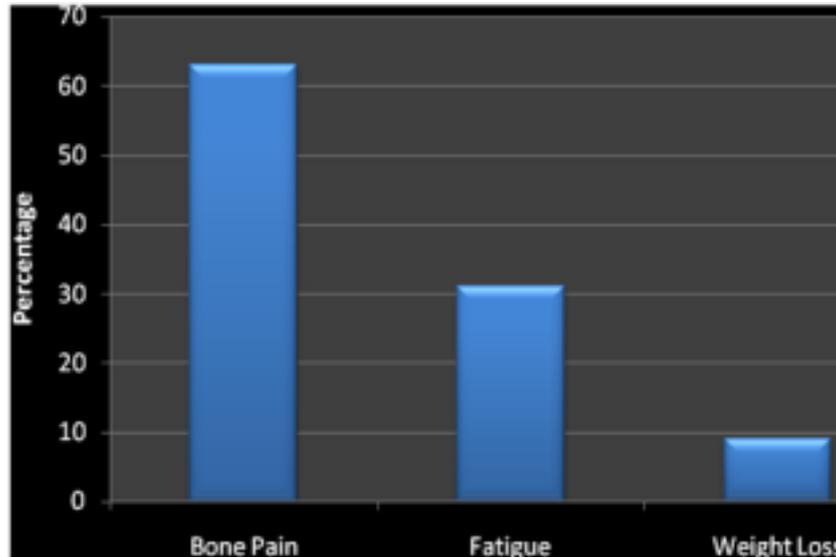


Fig. 5 Clinical Features

Clonal bone marrow plasma cell percentage were calculated with 63% (n=63) of the patients had <60% of the plasma cells and 37% (n=37) had >60% plasma cells as shown in figure 6.

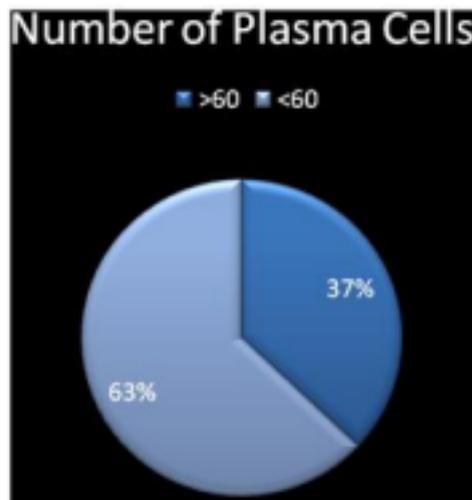


Fig. 6 Percentage of Plasma Cells

The 65% of the patients were having anaemia with serum haemoglobin <10 g/dl, only 34% of the patients had hypercalcemia with serum calcium >11mg/dl and 18% of the patients were having serum creatinine >2mg/dl as shown in figure 7. 76% of the patients had normocytic normochromic smear, 22 % having iron deficiency anaemia and only 2% with dimorphic smear as depicted in figure 8.

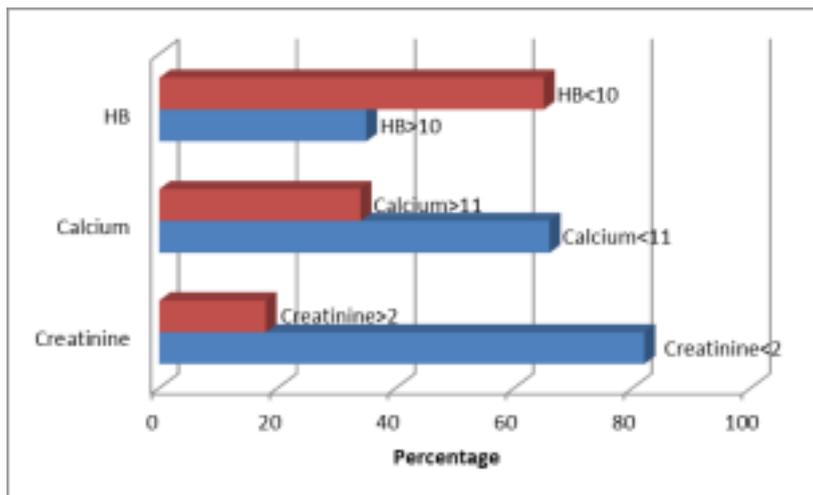


Fig. 7 Lab parameters

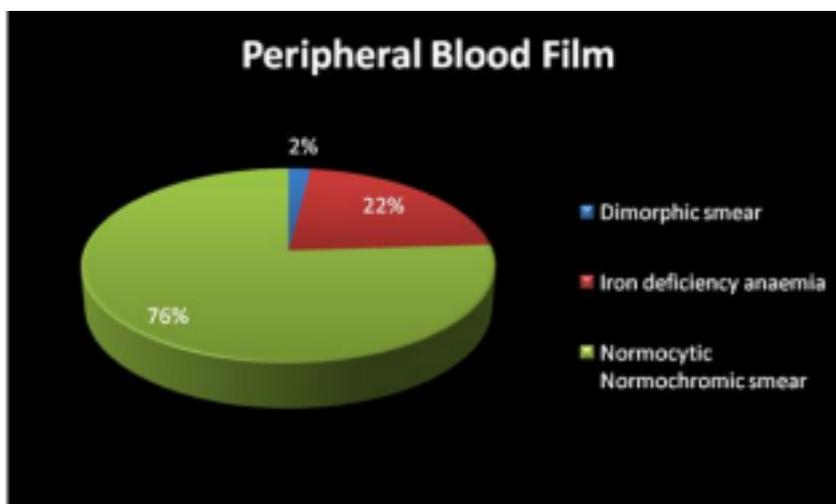


Fig. 8 Peripheral Blood Film

In our patients 46 % of the patients had hypoalbuminemia with serum albumin <3.5 g/dl and 54% having serum albumin >3.5 g /dl as shown in figure 9.

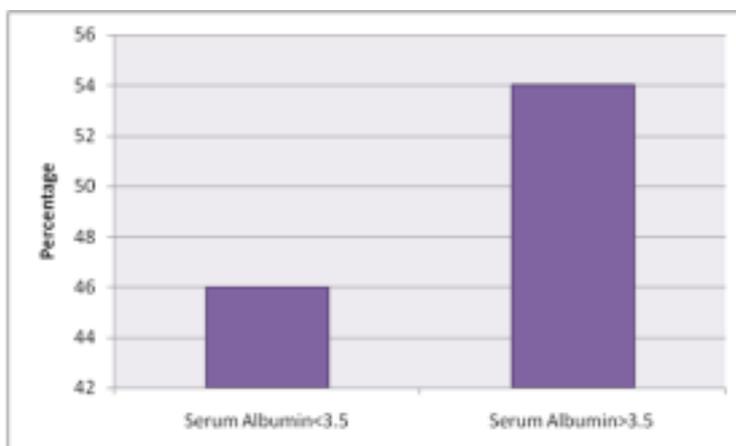


Fig. 9 Percentage of Serum Albumin

All the patients show presence of M band on serum protein electrophoresis. As shown in figure 10, 48%(n=48) of the patients had beta 2 microglobulin<3.5 mg/l, 40%(n=40) had beta 2 microglobulin between 3.5-5.5 mg/l and 12% (n=12) had beta 2 microglobulin>5.5 mg/l.

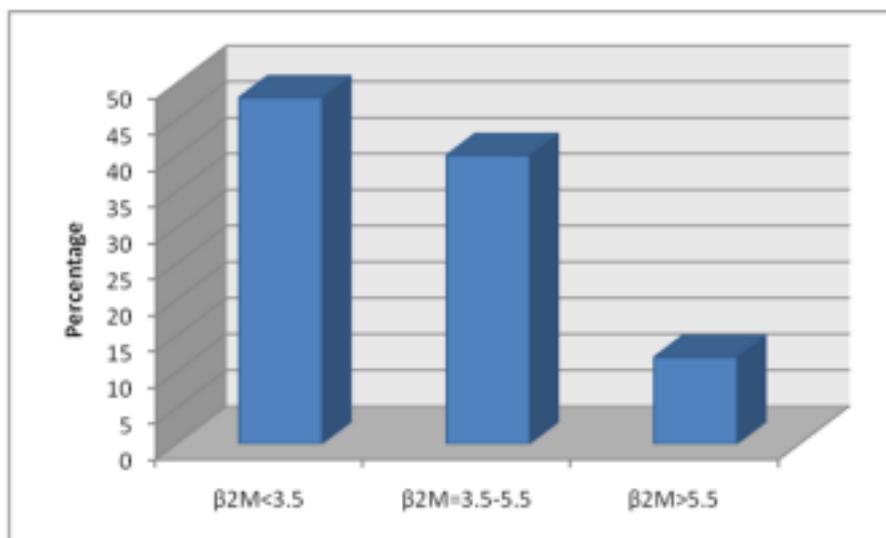


Fig. 10 Beta 2 microglobulin levels

Bence jones protein was detected in the urine. Only 15% of the patients had bence jones proteins in the urine and 85% had no bence jones protein in the urine as depicted in figure 11.

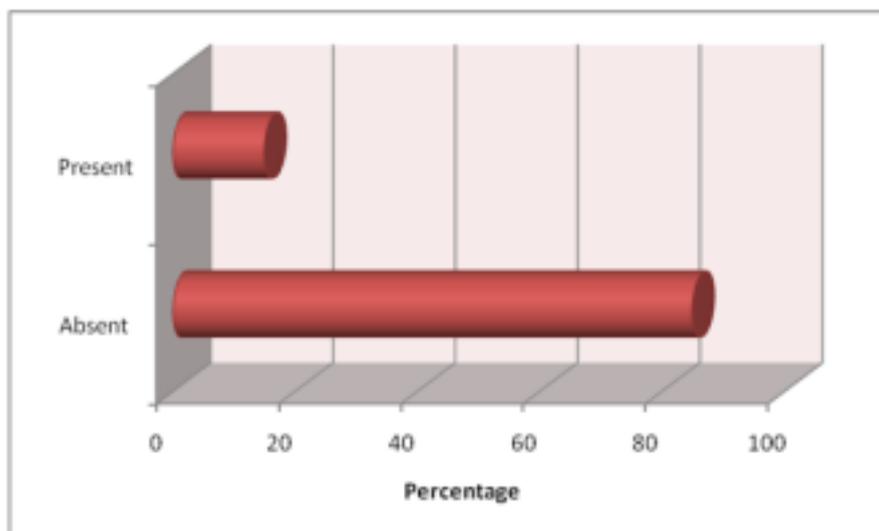


Fig. 11 Bence jones protein

International staging system (ISS) is depicted in the figure 12 maximum of 48%(n=48) had ISS 1 , 40% (n=40) had ISS 2 and 12% (n=12) shows ISS 3. 70% (n=70) of the patients shows lytic lesions in the x ray skull and 30% (n=30) of the patients had no lytic lesions in the skull as shown in figure 13.

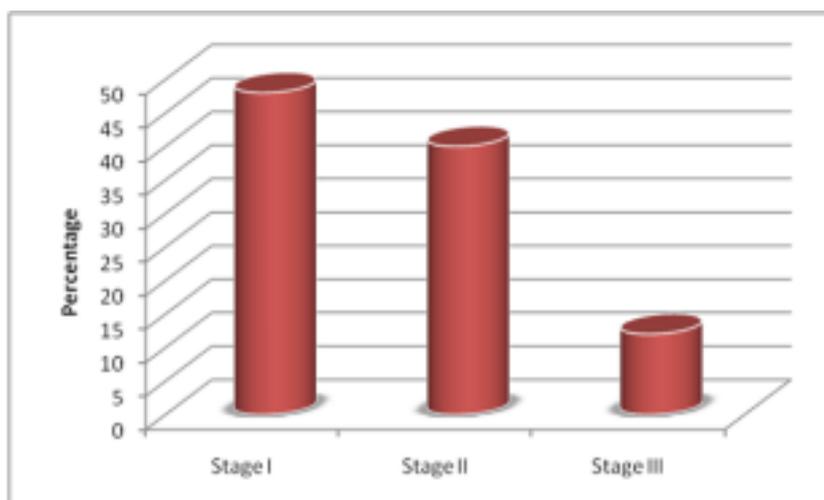


Fig. 12 ISS Profile

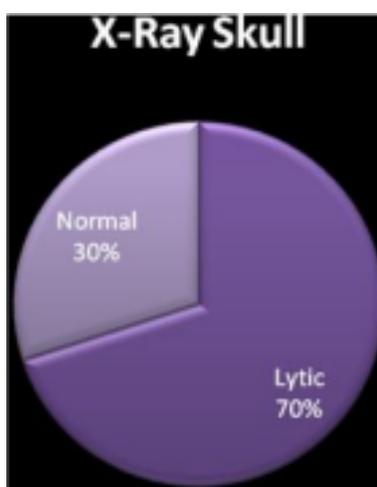


Fig. 13 Lytic lesions in the X-ray skull

DISSCUSSION: In our study, multiple myeloma was maximum in 5th decade between age group 51-60 year with median age of 56 year. Worldwide median age of Multiple Myeloma was 70 years⁷ and in Asian countries median age was 62 years⁸. 73% of the affected patients were sikh. In male population maximum number of the patients 52% were farmers which was also the most affected population as per text in Harrison's principles of internal medicine². Majority of our patients 63% presented with bony pain associated with spine tenderness, bony swelling, 31% had fatigue and only 9% presented had weight loss. A study in kerala by Fousadet *al.*⁶ 32% of the patients presented with fatigue and 31% presented with bone pain. A study from Mayo clinic in Rochester by Kyle *et al.*¹ reported bone pain (68%) as predominant symptom.

Clonal plasma cells in the bone marrow $\geq 10\%$ is the mandatory criteria for the diagnosis of Multiple Myeloma, but the clonal plasma cells in the bone marrow $\geq 60\%$ is one of the to be chosen criteria. In our study, 63% of the patients had plasma cells $<60\%$ and only 37% of the patients had plasma cells $\geq 60\%$. A study by Kyle *et al.*¹ shows 66% of the patients had

plasma cells <60% and 34% of the patients had plasma cells ≥60% which is almost equivalent to our study.

CRAB (hypercalcemia, renal insufficiency, anaemia, bone lesions) criteria is one of the criteria for diagnosis of multiple myeloma, presence of any one of the following represent the end organ damage due to multiple myeloma². In our study, 65% of the patients had anaemia with Hemoglobin <10g/dl with 22% having iron deficiency anaemia and 76% having normocytic normochromic smear. Anaemia can be due to renal impairment causing relative erythropoietin deficiency or due to bone marrow infiltration by myeloma cells⁹. Anaemia commonly result in fatigue and pallor and our 31% of the patient complained of fatigue.

Our 34% of the patient had hypercalcemia with serum calcium levels of >11 mg/dl. It was one of the most important diagnostic criteria in CRAB symptoms and 66% had serum calcium <11 mg/dl. Hypercalcemia can occur due to widespread tumour induced bone destruction. It is primarily due to increased osteoclastic bone resorption caused by potent cytokines expressed or secreted locally by the myeloma cells or overexpressed by other cells in the local microenvironment¹⁰. In study by Fousad *et al.* 18% had hypercalcemia.

Our only 18% of the patients had renal impairment with serum creatinine >2 mg/dl. Studies by Kyle *et al.*¹ and Kaur *et al.*⁹ showed 55% and 86.4% of patients had renal impairment. Most common cause of renal impairment was hypercalcemia. Other cause of renal impairment is light chain cast nephropathy (also called as myeloma kidney). Glomerular deposits of amyloid, hyperuricemia, recurrent infections, frequent use of Non steroidal anti-inflammatory agents for pain control, use of iodinated contrast dye for imaging, bisphosphonate use and occasional infiltration of kidney by the myeloma cells all may contribute to renal dysfunction. Tubular damage associated with excretion of light chain is almost always present².

X ray skull was important radiological investigation to look for lytic and punched out lesions in the bone¹¹. In our study 70% of the patients had lytic lesion in the brain and 30% of the patients had normal x ray skull.

All the patients in our study had presence of M- band in serum protein electrophoresis and in gamma globulin region. Study by Kyle *et al.*¹ 82% had M-band and by Fousad *et al.*⁶ 94% of the patient had M-band. Combination of serum beta 2 microglobulin and serum albumin levels forms the basis of International Staging System (ISS)². Hypoalbuminemia with serum albumin <3.5g/dl was present in 46% of the patients while remaining 54% had normal serum albumin levels. Hypoalbuminemia was primarily related to extent of myeloma proliferation and was therefore having prognostic and diagnostic importance^{12,13}. Serum beta 2 microglobulin was single most powerful predictor of survival and can substitute for staging. It was the light chain of class 1 major histocompatibility antigen (HLA-A, -B, -C) on the surface of every cell². 48% of the patients had beta 2 microglobulin <3.5mg/l, 40% had between 3.5-5.5 mg/l and 12% had beta 2 microglobulin >5.5 mg/l. With 48% of the patients had Stage 1 of ISS with median survival months of 62, 40% had Stage 2 ISS with median survival months of 44 and 12% had Stage 3 ISS with median survival months of 29.

International Staging System (ISS) was used to predict the survival of multiple myeloma patients.

Bence Jones proteinuria test is done in those patients when plasma cell disorders multiple myeloma is suspected. It is the detection of monoclonal light chains in the urine by the Bence Jones heat test¹⁴. In our study 15% of the patients had bence jones protein positive and 85% were negative for bence jones protein. It was not mandatory that all multiple myeloma patients are positive for bence jones protein.

Majority of the patients of our hospitals were on Bortezomib, Dexamethasone and Lenalidomide combination therapy with good response rates^{15,16}. Serum free light chain assay could not be done of all the patients because of financial constraints thus not included in the study.

CONCLUSION: To conclude, multiple myeloma was more common in 5th decade and less common in age group above 70 years of age with male predominance and more common in urban population and all females were housewife and among males majority were farmers. Bone pain was the most common presenting feature in our patients followed by fatigue. All the patients had M- band in gamma globulin region in serum protein electrophoresis. Majority of the patients had plasma cells <60%. Hypercalcemia is although the most important criteria but present in few patients, with majority patients had normal levels of serum albumin. Maximum patients had stage 1 ISS. The presentation of MM varies among patient to patient. Staging of MM can be reduced with earlier diagnosis and adequate treatment.

DECLARATIONS:

Author Contributions: All the authors have equally contributed in the preparation of manuscript.

Conflicts of Interest: Authors do not have any conflict of interest.

Ethical Approval: Not Applicable

Consent to participate: Informed consent to participate in the study was obtained from all participants.

Consent to publication: Informed consent to publication was obtained from relevant participants.

Availability of data and materials: Not Applicable

Funding: Not Applicable

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