*Original Article*

# A Clinical and Laboratory Profile of Multiple Myeloma

Md. Rezaul Karim Chowdhury[1]

## *Abstract*

***Background****: Myeloma, the most common malignant disease of bone, is incurable and occurring with increasing frequency in elderly population. Typical clinical features are weakness, fatigability, bone pain, anemia, renal insufficiency and hypercalcemia. Incidental discovery on comprehensive laboratory panels is common. Serum or urine protein electrophoresis or immunofixation and bone marrow aspirate analysis help the diagnosis of multiple myeloma.* **Objective***: The aim of this study was to define and evaluate the clinico-laboratory features of newly diagnosed adult multiple myeloma (MM) patients in the context of Bangladesh.* **Materials and Methods***: This study was carried out in two centers, from October 2005 to January 2010 in Bangabandhu Sheikh Mujib Medical University (BSMMU) and July 2012 to June 2017 in Enam Medical College and Hospital (EMCH). Thirty two diagnosed valid cases of multiple myeloma were included in this study. Clinical history, physical and relevant laboratory findings were carefully recorded and analyzed.* **Results***: In this study among 32 patients, 29 were males and 3 were females with mean age 51.94 ± 10.09 years. The common complaints were bone pain, weakness and fatigue. The common clinical findings were bone tenderness, pallor and high ESR (ESR of all the study patients was more than 100 mm in 1st hour). Hemoglobin level was <8.5 gm/dL in 13 patients, serum creatinine ≥2 mg/dL in seven patients, serum albumin <30 mg/L in 14 patients and serum β2 microglobulin >5.5 mg/L in 15 patients. Three patients were hypercalcemic. Lytic lesions were the most common radiological finding in the study.* **Conclusion***: This study showed that multiple myeloma is a disease of the middle and elderly aged population with male preponderance, with high male female ratio. Multivenued studies are needed to view the real picture of multiple myeloma in the context of Bangladesh.*

***Key words****: Multiple myeloma; Clinical profile; Laboratory profile; Bangladesh*

J Enam Med Col 2018; 8(3): 159−164

## Introduction

Multiple myeloma (plasma cell myeloma or plasmacytic myeloma or myelomatosis or Kahler disease) is a hematological neoplasm characterized by proliferation of a single clone of plasma cells derived from B cells. This clone of plasma cells proliferates in the bone marrow and frequently invades the adjacent bone, producing skeletal destruction that results in bone pain and fractures. Occasionally, plasma cells infiltrate multiple organs and produce other symptoms. The excessive production of a monoclonal protein (M-protein) may lead to renal failure from Bence Jones protein or hyperviscosity from excessive amounts of M-protein in the blood. The diagnosis depends on identification of abnormal monoclonal plasma cells in the bone marrow, M-protein in the serum or urine, osteolytic lesions, and a clinical picture consistent with multiple myeloma.[1]

Multiple myeloma accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers. In Western countries, the annual age-adjusted incidence is 5.6 cases per 100,000 persons. The median age at diagnosis is approximately 70 years; 37% of patients are younger than 65 years, 26% are

1. Rezaul Karim Chowdhury, Associate Professor, Department of Haematology, Enam Medical College & Hospital, Savar, Dhaka
   **Correspondence** Rezaul Karim Chowdhury, Email: rkchow71@gmail.com

between the ages of 65 and 74 years, and 37% are 75 years of age or older.[2,3] In India, the incidence varies from 0.3−1.9/100000 for male and 0.04−1.3/100000 for female.[4]

In most patients with this disease no clear risk factor can be identified. Exposure to ionizing radiation, farming pesticides, or possibly petrochemicals increase the risk. There is an increased incidence of multiple myeloma in persons with rheumatoid arthritis or obesity (body mass index of more than 30 kg per m[2]).[5]

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal center B cells. Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm. Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (usually known as MGUS) that progresses to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities that occur in tumor plasma cells play major roles in the pathogenesis of myeloma.[6,7] The adhesion of myeloma cells to hematopoietic and stromal cells induces the secretion of cytokines and growth factors, including interleukin-6, vascular endothelial growth factor (VEGF), insulin-like growth factor 1, members of the superfamily of tumor necrosis factor, transforming growth factor β1, and interleukin-10.[8] These cytokines play an important role in myeloma cell proliferation.

Myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction, including hypercalcemia, renal insufficiency, anemia, and bone disease.[9] It is important to note that 34% of patients are asymptomatic at presentation with incidental abnormalities on total protein, creatinine, calcium or hemoglobin laboratory panels.[10] Anemia, which is present in about 73% of patients at diagnosis, is generally related to myeloma marrow infiltration or renal dysfunction.[11] Bony lesions develop in almost 80% of patients with newly diagnosed disease; in one study, 58% of patients reported bone pain.[1] Renal impairment occurs in 20 to 40% of patients with newly diagnosed disease[1,12] mainly as a result of direct tubular damage from excess protein load, dehydration, hypercalcemia, and the use of

nephrotoxic medications.[13] The risk of infection is increased with active disease but decreases with response to therapy.[14] Hypercalcemia is uncommon.[1]

Serum β2-microglobulin and albumin are two most important prognostic factors. The International Staging System defines three risk groups on the basis of these two.[15] Myeloma is usually incurable. In recent years, the introduction of autologous stem-cell transplantation and the availability of agents such as thalidomide, lenalidomide, and bortezomib have changed the management of myeloma and extended overall survival. In patients presenting at an age under 60 years, 10-year survival is approximately 30%.[16] Therefore, the purpose of this study which determines the spectrum of clinical, hematological and biochemical changes in the patients of multiple myeloma in the context of Bangladesh is obviously appropriate and timely as there was no such study conducted in our country previously.

**Materials and Methods**

This study was carried out in two centers − from October 2005 to January 2010 in Bangabandhu Sheikh Mujib Medical University and from July 2012 to June 2017 in Enam Medical College and Hospital. In this study the total number of cases was 32. Diagnosis was based on serum protein electrophoresis, bone marrow examination and FNAC from plasmacytoma. Relevant clinical history, physical findings, complete blood count and ESR, bio-chemical tests like serum albumin, serum calcium, serum creatinine, serum β2 microglobulin and radiological survey were recorded for further analyses.

**Results**

Total 32 patients diagnosed as multiple myeloma were included in this study. Out of them 29 (90.63%) were males and 3 (9.27%) were females with male female ratio 9.67:1. Age range of patients was 36−71 years with mean 51.94 ± 10.09 years and median 53 years. Table I shows the distribution of patients according to age.

Table I: Distribution of subjects according to age

| Age groups (years) | Number | Percentage |
|---|---|---|
| <40 | 5 | 15.63 |
| 40− 60 | 20 | 62.50 |
| >60 | 7 | 21.87 |

Bone pain, weakness and fatigue were the most commonly presented complaints. Bone tenderness and anemia were the common clinical findings. No organomegaly or lymphadenopathy was found.

Table II: Clinical features of multiple myeloma subjects

| Clinical features | Number | Percentage |
|---|---|---|
| Weakness and fatigability | 28 | 87.50 |
| Bone pain | | |
|    low back pain | 23 | 71.88 |
|    shoulder pain | 2 | 6.25 |
|    chest pain | 3 | 9.38 |
|    generalized pain | 4 | 12.50 |
| Fever | 10 | 31.25 |
| Impaired consciousness | 1 | 3.13 |
| Headache | 5 | 15.63 |
| Anaemia | 29 | 90.63 |
| Bone tenderness | 32 | 100 |
| Paraplegia | 1 | 3.13 |

*Some subjects presented with more than one complaints

Investigations revealed that Hb level was <8.5 gm/dL in 13 (40.62%) patients, 8.5−10 gm/dL in 7 (21.88%) patients and >10 gm/dL in 12 (37.50%) patients. ESR was more than 100 mm in 1st hour in all patients. Total WBC count was <4000/cu mm in 5 (15.63%) patients, 4000–11000/cu mm in 23 (71.87%) patients and in 4 (12.5%) patients it was >11000/cu mm. Platelet count was <100000/cu mm in 6 (18.75%) patients and in 26 (81.25%) patients it was >100000/cu mm.

The calcium level was <11 mg/dL in 29 (90.62%) patients and in 3 (9.38%) patients it was ≥11 mg/dL. S. creatinine was <1.4 mg/dL in 5 (15.63%) patients, 1.5 −1.9 mg/dL in 20 (62.5%) patients and in 7 (21.87%) patients it was >2 mg/dL.

S. albumin level was >30 gm/L in 18 (56.25%) patients and in 14 (43.75%) patients it was <30 gm/dL. None of the patients showed $\beta_2$ microglobulin level <2 mg/L, in 5 (15.63%) patients the level was 2−3.4 mg/L, 3.5−5.5 mg/L in 12 (37.50%) patients and in 15 (46.87%) patients the level was >5.5 mg/L accordingly.

Radiography showed that 17 (53.12%) patients had lytic lesion, 7 (21.88%) had vertebral compression fracture and 4 (12.50%) patients had osteoporosis and 4 (12.50%) showed no skeletal changes.

According to the international prognostic index of multiple myeloma 3 (9.37%) patients were stratified as in the stage I, 14 (43.75%) patients in the stage II and 15 (46.88) patients in the stage III.

## Discussion

Diagnostic criteria of multiple myeloma were fulfilled by all 32 patients in this study. Multiple myeloma, as this study shows, affects commonly the elderly and middle age groups of population and affects less the young age group. Kyle et al[1] and Kaur P et al[17] have observed that 2% and 3.58% patients were less than 40 years. We observed that 15.63% patients were younger than 40 years which is comparable with the study of Sultan et al[18] who found it 13.1%. The mean age of patients was 55.4, 51, 58.8 and 56 years in the studies of Wadhwa et al[19], Kaur et al[17] and Sultan et al[18]. In our study the mean age was 52 years whereas in another study[20] in Bangladesh it was 63 years.

In this study the male-female ratio was 9.67:1. But Chowdhury et al[20] reported it 5:2 in Bangladesh. The variables that affect the ratio are to be considered with importance. As most of the females in our country are housewives, they are conservatives and have less exposure to the outside community. Moreover in our study the sample size was small.

In our study most of the patients presented with later stage of disease with various clinical presentations. Weakness and fatigability (87.50%) and low backache (71.88%) were the commonly presented complaints. Sultan et al[18] observed fatigability in 81.9% and backache in 80.3% of the patients. Kaur et al[17] observed weakness and fatigability in 46.4% cases and bone pain in 50% cases. Kyle et al[1] observed weakness and fatigability in 32% and bone pain in 58% cases. In our observation this percentages were found higher possibly because of the advanced stage at presentation. In our study 31.25% of patients presented with fever but in the studies of Kyle et al[1] and Kaushik et al[20] only 0.7% and 16% presented with fever. But Diwan et al[22] found that 35% presented with fever which is comparable with our study.

Pallor (90.63%) and bone tenderness (100%) were the

most common physical findings in this study. In the study of Kaushik et al[21] pallor was seen in 94% of the patients which is similar to this study. But it was 44.2% patients in the study of Sultan et al.[18] Bone tenderness was in 47% cases observed by Kaushik et al.[21] It was lower than the findings in this study possibly due to late stage of presentation in our study.

Anemia in myeloma is caused due to replacement of marrow by myeloma cells and decreased production of erythropoietin due to accompanying renal involvement. In some cases it may be associated with cytokine mediated bone marrow suppression. Hemoglobin value ≤10 gm/dL was seen in 63.9% of the patients in Sultan et al[18] study and in the study of Wadhwa[19] it was in 59% of the patients. These are similar to the present study (62.5%). But these are less than Kaur et al[17] study (92.8%) and more than Kyle et al[1] study (35%). Moderate to severe anemia (<8.5 gm/dL) was seen in 40.62% of patients in the present study. It is lower in comparison to the studies of Kaur et al[17] (75%) and Subramanian et al[23] (71%) and higher than the studies of Kalita et al[24] (33%) and Diwan et al[22] (25%) studies. But it is nearly similar to studies of Gupta et al[25] (40%) and Kaushik et al[21] (45%) studies. The anemia was normochromic normocytic in most of our patients.

ESR is high in multiple myeloma due to increased paraproteins and anemia. ESR >100 mm in 1st hour was reported in different series from 33−100%.[1,17,22,23] This is similar to the present study (100%).

Leukopenia and leucocytosis were found in 15.63% and 12.5% in patients of the present study. In the study of Kyle et al[1] these were 20% and 8%. Low platelet count is uncommon in early phases of myeloma. Thrombocytopenia may be due to infiltration of the marrow by plasma cells or intravascular destruction of platelets or thrombopoietic activity of IL-6. In our study thrombocytopenia was in 18.75% cases, but in the study of Kaur et al[17] it was higher (25%) and in the studies of Diwan et al[22] and Kyle et al[1] it was in 10% and 5% of the patients respectively.,

In multiple myeloma, the main causes of renal failure are cast nephropathy due to light chain excretion and glomerular deposition of immunoglobulin. In the current study, raised serum creatinine was found in 84.38% of the patients, which is similar to the findings in the study of Kaur et al[17] (86.4%), but it is higher than the studies of Kyle et al[1] (55%) and Sultan et al[18] (40.9%). In our study serum creatinine was ≥2mg/dL in 21.87% patients which is similar to Kyle et al[1] (19%).

Hypercalcemia remains the most frequent metabolic complication of myeloma patients and excessive osteolysis plays a major contributory role in its pathogenesis. In our study 9.38% patients were hypercalcemic which is comparable to Kyle et al[1] (13%) but it is lower than the findings in Sultan et al[18] (47.5%) study.

Serum β2-microglobulin and albumin are two most important prognostic factors though raised β2-microglobulin level is a poor prognostic sign. In our study 84.37% patients had their serum β2-microglobulin ≥3.5 mg/dL. Kaur et al[17] showed it higher in 71.4% subjects and Kyle et al[1] showed it in 75% of their patients. Low serum albumin is also a poor prognostic factor. In 43.75% of our patients serum albumin level was <30 gm/dL, but in the study of Jacobson et al[26] it was in 20% of patients. Our study shows a higher rate because of late stage of presentation and the enrollment of a limited number of patients.

Lytic lesions, compression fractures and osteoporosis are the most common bone lesions in multiple myeloma. In this study lytic lesions were seen in 53.12% of the patients. This is consistent with some other studies in the literature.[1,21,24] In our study compression fracture was observed in 21.88% of the patients, which is similar to Kyle et al[1] (22%) study. In our study osteoporosis was found in 12.5% cases. It was found in 23%, 20%, 52% patients in the studies of Kyle et al[1], Kaushik et al[21] and Kalita et al[24] respectively. In 12.5% of our patients radiological findings were normal, but in the study of Kyle et al[1] radiological findings were found normal in 21% cases.

According to International Staging System (based on Serum β2 microglobulin and serum albumin), 9.37% patients were stratified in stage I, 43.75% patients in stage II and 46.88 patients in stage III. In the study of Rahman et al[27] 22% patients were in the stage I, 26% patients were in the stage II and 52% in stage III. The International Staging System has better reliability, simplicity and predictability for survival of patients

with multiple myeloma.

Multiple myeloma is a disease of middle age and elderly with male preponderance. The presentation of multiple myeloma can range from asymptomatic to severely symptomatic with complications. Our clinico-laboratory findings were comparable to other studies with some variations. It may be due to small number of patients included in this study. Our study can be considered as an important step towards studying multiple myeloma. Nonetheless, further such multicenter studies would enrich our views to determine the actual picture of multiple myeloma in the context of Bangladesh.

## References

1.  Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78: 21−23.

2.  Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W et al. SEER cancer statistics review, 1975−2007. Bethesda, MD: National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2007/index.html. Accessed September 2017.

3.  Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bj. rkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol 2007; 25: 1993−1999.

4.  Cancer incidence in five continents. In: Waternonse J, Munir C, m Mack T, Fowell J, Wn clan SL (eds). Lyon IARC Scientific Publications (Vol 5, No 88); 1987: 779−785.

5.  Sirohi B, Powles R. Epidemiology and outcomes research for MGUS, myeloma and amyloidosis. Eur J Cancer 2006; 42(11): 1671−1683.

6.  Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. Nat Rev Cancer 2002; 2: 175−187.

7.  Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. Blood 2007; 109: 3489−3495.

8.  Podar K, Tai YT, Lin BK, Narsimhan RP, Sattler M, Kijima T et al. Vascular endothelial growth factor-induced migration of multiple myeloma cells is associated with beta 1 integrin- and phosphatidylinositol 3-kinase-dependent PKC alpha activation. J Biol Chem 2002; 277: 7875−7881.

9.  Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364: 1046−1060.

10. Nau KC, Lewis WD. Multiple myeloma: diagnosis and treatment. Am Fam Physician 2008; 78(7): 853−860.

11. Birgegard G, Gascón P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European Cancer Anaemia Survey. Eur J Haematol 2006; 77: 378−386.

12. Eleutherakis-Papaiakovou V, Bamias A, Gika D, Simeonidis A, Pouli A, Anagnostopoulos A et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. Leuk Lymphoma 2007; 48: 337−341.

13. Dimopoulos MA, Kastritis E, Rosinol L, Bladé J, Ludwig H. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia 2008; 22: 1485−1493.

14. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 2009; 49: 1211−1225.

15. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J et al. International staging system for multiple myeloma. J Clin Oncol 2005; 23: 3412−3420.

16. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008; 111: 2521−2526.

17. Kaur P, Shah BS, Baja P. Multiple myeloma: a clinical and pathological profile. Gulf J Oncolog 2014; 1(16): 14−20.

18. Sultan S, Ifran SM, Parveen S, Ali H, Basharat M. Multiple myeloma: a retrospective analysis of 61 patients from a tertiary care center. Asian Pac J Cancer Prev 2016; 17(4): 1833−1835.

19. Wadhwa J. Multiple myeloma: a retrospective analysis of 534 patients. DM Dissertation. Department of Medical oncology, All India Institute of Medical Sciences. New Delhi. December 1999.

20. Chowdhury S, Sultana T, Islam MS, Islam MA, Khanam PA. Multiple myeloma: a hospital based based cross sectional study in Bangladesh. J Asiat Soc Bangladesh Sci 2012; 38(2): 189−198.

21. Kaushik R, Thakur RK, Gulati A, Sharma SK. Multiple myeloma: clinico-hematological profile in a tertiary care hospital: a three years study. Annals of Pathology and Laboratory Medicine 2017; 4(5): 270−275.

22. Diwan AG, Gandhi SA, Krishna K, Shinde VP. Clinical profile of the spectrum of multiple myeloma in a teaching hospital. Medical Jr of Dr DY. Patil University 2014; 7(2): 185−188.

23. Subramanian R, Basu D, Dutta TK. Prognostic significance of bone marrow histology in multiple myeloma. Indian J Cancer 2009; 46(1): 40−45.

24. Kalita LK, Kalita C, Gogoi PK, Sarma UC. A clinico-epidemiological study of multiple myeloma−a hospital based study at Gauhati Medical College and Hospital, Guwahati, Assam. J Evid Based Med Health 2016; 3(36): 1788−1794.

25. Gupta P, Kochupillai V, Singh S, Berry M, Kumar L, Sundaram KR. A twelve year study of multiple myeloma at the All India Institute of Medical Sciences, New Delhi. Ind J Med & Ped Oncol 1995; 16(2): 108−114.

26. Jacobson JL, Hussein MA, Barlogie B, Brian GM. Durie BGM, Crowley JJ. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. British Journal of Haematology 2003; 122: 441−450.

27. Rahman AAU, Shah SZA, Devrajani BR, Rajput S, Baloch ZAQ, Das T. International Staging System: a tool to predict survival in patients with multiple myeloma. World Applied Sciences Journal 2012; 16(7): 1004−1008.