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Risk Stratification of Multiple Myeloma Patients in Haematology Department of a Tertiary Medical College Hospital

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Abstract
Introduction: *Multiple myeloma is characterized by malignant proliferation of plasma cells producing monoclonal protein. Accurate detection and interpretation not only assist in counseling patients regarding anticipated outcome but also helps in choice of drugs and in selecting overall therapeutic strategy. Risk stratification is very important for the treatment, therapeutic modalities and probable outcome of patients who are suffering from multiple myeloma*
Aim of the study: *The aim of this study was to evaluate the risk stratification of multiple myeloma patients in haematology department of a tertiary medical college hospital.*
Materials & methodology: *This cross-sectional observational study was carried out in outpatients and indoor patients in the department of Haematology, Dhaka Medical College Hospital, Dhaka from January 2018 to December 2018 for a duration of one year. A total number of 47 patients with multiple myeloma were analyzed cytogenetically by interphase fluorescence in situ hybridization (iFISH).*
Result: *A total 47 study subjects diagnosed as Multiple Myeloma cases were enrolled in this study. The mean age was 56.37±10.38 years and male to female ratio was almost 3:1. Thirty-five (74.47%) of 47 patients were male, rest of 12(25.53%) were female. The risk stratification was done on the basis of serum albumin, LDH, β2 microglobulin and cytogenetic abnormality. Serum albumin >3.5 gm/dl was observed in 28(60.0%) patients and <3.5gm/dl was in 19(40.4%) patients. Elevated serum LDH (>222 U/l) was found in 21(44.5%) patients and 17(36.2%) patients had normal LDH (<222U/l). β2 microglobulin >5.5 µg/mL was detected in 19(40.4%) patients. Eleven (23.4%) patients had β2 microglobulin >3.5to <5.5 µg/mL and rest of 17(36.2%) patients had β2 microglobulin <3.5 (normal). Abnormal cytogenetics detected by FISH were 13(27.7%) and rest of 34(72.3%) cases were found no abnormal cytogenetic by FISH. It was observed that 24(51%) patients belonged to high-risk group, then 13(26.67%) in low risk and 11(23.23%) in intermediate risk according to ISS; also revised international staging system (RISS) respectively.*
Conclusion: *Day after day risk stratification of multiple myeloma is modified. Now a day Revised International Staging System R-ISS is a simple and powerful prognostic staging system, and its use is recommended for future clinical studies to stratify patients with newly diagnosed multiple myeloma effectively with respect to the relative risk to their survival.*

Key words: *Multiple Myeloma; Haematology; Risk Stratification; R-ISS; FISH; Bangladesh.*

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I. Introduction

Multiple myeloma may call as plasma cell myeloma or plasmacytic myeloma or myelomatosis or Kahler's disease, which is a hematological neoplasm characterized by proliferation of a single clone of plasma cells derived from B cells[1]. 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[1]. 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.[2] It is characterized by malignant proliferation of plasma cells producing monoclonal protein. The outcome has drastically improved in the patients of multiple myeloma in last the decade due to a better understanding of the disease biology and evolution of newer therapies[3,4]. Multiple myeloma accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers[1]. 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[5]. Many prognostic factors which define the innate aggressiveness of the disease have been described and attempts have been made to risk stratify the patients using these prognostic factors. A standard myeloma FISH panel will contain probes for the common translocations and structural abnormalities and will detect them regardless of the proliferative rate of the plasma cells. Moreover, FISH provides no information on the proliferative index of the myeloma cells[6]. The importance of the detection and interpretation of cytogenetic abnormalities in multiple myeloma is critical for prognosis and risk stratification of multiple myeloma[7]. The median survival is approximately 6–7 years; in patients eligible for ASCT 4-year survival rates exceed 80%. However, there is major variation in survival depending on host factors, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy[8,9]. Tumor burden in multiple myeloma has traditionally been assessed using the International Staging System (ISS)[10,11]. Disease biology best reflected based on the molecular subtype of multiple myeloma and the presence or absence of secondary cytogenetic abnormalities such as del(17p), gain(1q), or del(1p).21, The Revised International Staging System (RISS) combines elements of tumor burden (ISS) and disease biology (presence of high risk cytogenetic abnormalities or elevated lactate dehydrogenase level)[12]. It is important to note that in order to ensure uniform availability, only 3 widely available cytogenetic markers are used in the RISS;

Revised International Staging System for Myeloma[12]

Stage 1

All of the following:

- Serum albumin ≥3.5 gm/dL
- Serum beta-2-microglobulin <3.5 mg/L
- No high-risk cytogenetics
- Normal serum lactate dehydrogenase level

Stage II

- Not fitting Stage I or III

Stage III

Both of the following:

- Serum beta-2-microglobulin >5.5 mg/L
- High risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated serum lactate dehydrogenase level

The Mayo Clinic mSMART risk stratification has additional detail that is valuable in formulating a therapeutic strategy.23 Mayo stratification for myeloma and risk-adapted therapy (mSMART)

Standard Risk	75%
Trisomies	
t(11;14)	
t(6;14)	
Intermediate Risk	10%
t(4;14)	
Gain(1q)	
High Risk	15%
t(14:16)	
t(14;20)	
del(17p)	

Patients with standard risk multiple myeloma have a median overall survival (OS) of >7 years while those with high-risk disease have a median OS of approximately 3 years despite tandem autologous stem cell transplantation (ASCT)[7]. In addition to cytogenetic risk factors, two other markers that are associated with disease aggressiveness and high-risk disease are elevated serum lactate dehydrogenase and plasma cell leukemia with evidence of circulating plasma cells on routine peripheral smear examination. The high-risk group identified by the ISS is 33.6% which has a median overall survival (OS) of 29 months, while the IMWG has identified a high-risk group of 20% with a 4-year PFS of 12% and OS of 35%. The revised ISS (R-ISS) incorporates the genetic markers t (4;14) and del17p, but not 1q gain or mutational data from TP53 and the high-risk group in this classification comprised only 10% and had a median PFS of 29 months and 5-year OS of 40%. Accurate detection and interpretation not only assist in counseling patients regarding anticipated outcome but also helps in choice of drugs and in selecting overall therapeutic strategy. There is a variable approach to pre-therapy cytogenetic evaluation and risk stratification at different Hematology centers in the country which are often dictated by financial constraints and availability of specialized tests. The aim of this study was to evaluate the risk stratification of multiple myeloma patients in haematology department of a tertiary medical college hospital**.**

II. Objective

The objective of this cross-sectional study was to evaluate the risk stratification of multiple myeloma patients in haematology department of a tertiary medical college hospital**.**

III. Materials & Methodology

This cross-sectional observational study was carried out in outpatients and indoor patients in the department of Haematology, Dhaka Medical College Hospital, Dhaka from January 2018 to December 2018 for a duration of one year. Detailed clinical history, examination findings and investigations were recorded in a pre-designed case record form. Structured questionnaire was prepared in Bangla/English version and was distributed to all the patients and their families. Purposive sampling technique was followed to collect the study subjects. A total number of 47 patients with multiple myeloma were analyzed cytogenetically by interphase fluorescence in situ hybridization (iFISH). The detection and interpretation of cytogenetic abnormalities in MM is of critical importance for prognosis and risk stratification of MM.[7] The median survival is approximately 6–7 years; in patients eligible for ASCT 4-year survival rates exceed 80%. However, there is major variation in survival depending on host factors, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy.[11] Tumor burden in multiple myeloma has traditionally been assessed using the International Staging System (ISS).[10,11] Disease biology best reflected based on the molecular subtype of multiple myeloma and the presence or absence of secondary cytogenetic abnormalities such as del(17p), gain(1q), or del(1p)[13], The Revised International Staging System (RISS) combines elements of tumor burden (ISS) and disease biology (presence of high risk cytogenetic abnormalities or elevated lactate dehydrogenase level)[12]. It is important to note that in order to ensure uniform availability, only 3 widely available cytogenetic markers are used in the RISS.

Inclusion criteria:

All diagnosed cases of multiple myeloma including new and relapsed cases.

Exclusion criteria:

- Patients of Multiple myeloma who were partially treated.
- Patients who have other hematological diseases concomitantly.
- Monoclonal gammopathy of undetermined significance (MGUS) or Smouldering Multiple myeloma SMM.

All information gathered from physical and biochemical findings was documented in a preformed data collection sheet (questionnaire) according to the above-mentioned criteria. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and MS-Excel 2016.

IV. Results

A total 47 patients were selected as study subjects in the Department of Haematology, Dhaka Medical College Hospital, Dhaka. Figure-1 shows the age distribution of the study population. Where we found maximum 19(40.43%) study subjects were 51-59 years of age, then 12(25.53%) were 41-50 years, 9(19.15%) were less than 40 years and 7(14.89%) were found more than 60 years of age respectively. Figure-2 shows the gender distribution of the study subjects. About 35(74.47%) study subjects were found male and 12(25.53%) were female. Male were predominant than female in this study. Table-1 shows the symptoms that found in the study subjects. The most frequent 41(87.23%) symptom was found bone pain (low back pain, shoulder pain, chest pain, generalized pain). Then, the other symptoms were anaemia (fatigue, malaise, palpitation, dizziness)

37(78.72%), fever 23(48.94%), hypercalcaemia 13(27.65%), Spinal cord compression 12(25.53%), renal disease (oliguria, facial puffiness, shortness of breath) 11(23.40%).

Table-2 illustrated the signs of the study subjects. There Anaemia was the dominant clinical sign occurring in 40(84.62%). Then 36(76.92%) had Lytic bone lesions, Vertebral compression had found in 17(36.54%) patients, 8(17.31%) had Pathological fractures. Table-3 shows the variable distribution of the study population. Serum albumin >3.5 gm/dl was observed in 28(60.0%) patients and <3.5gm/dl was in 19(40.4%) patients. The mean serum albumin was 3.17±0.53 gm/dl with range 2.2 to 3.8 gm/dl. Elevated serum LDH (>222 U/I) was found in 21(44.5%) patients and 17(36.2%) patients had normal LDH (<222U/l). The mean serum LDH was 208.87±180.68 U/I with range 26 to 631U/I. β2 microglobulin >5.5 µg/mL was detected in 19(40.4%) patients. Eleven (23.4%) patients had β2 microglobulin >3.5to <5.5 µg/mL and rest of 17(36.2%) patients had β2 microglobulin <3.5 (normal). The mean β2 microglobulin was 5.95±6.77 µg/mL with range 1.6 to 37.28 µg/mL. Table-4 shows the risk stratification of the study population according to cytogenetics detected by FISH. It was observed that 34(72.34%) patients had normal cytogenetics. High risk cytogenetics was found in 5(10.64%) patients, 2(4.25%) patients had intermediate risk cytogenetics and 6(12.77%) patients had standard risk cytogenetics by FISH: Fluorescence in Situ Hybridization. Table-5 shows the risk stratification of the study population. It was observed that 24(51%) patients belonged to high-risk group, then 13(26.67%) in low risk and 11(23.23%) in intermediate risk according to ISS; also revised international staging system (RISS) 24(51%) then 13(26.67%) in low risk and 11(23.23%) in intermediate risk patients belonged to high-risk group respectively.

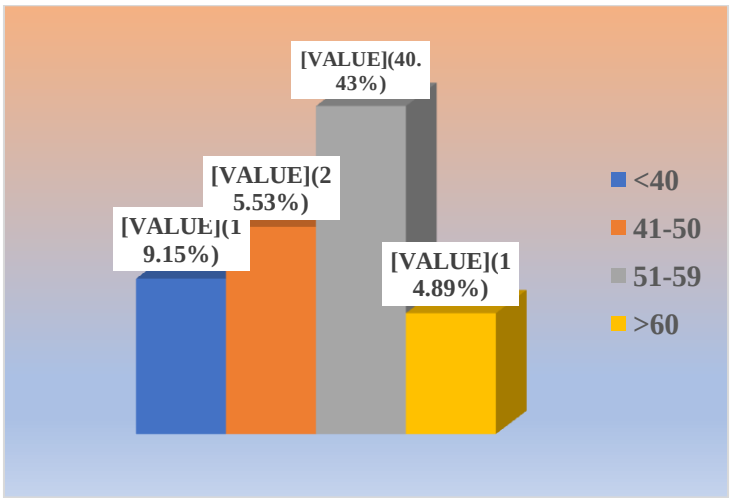

Figure-1: Distribute the study subjects according to age (N=47)

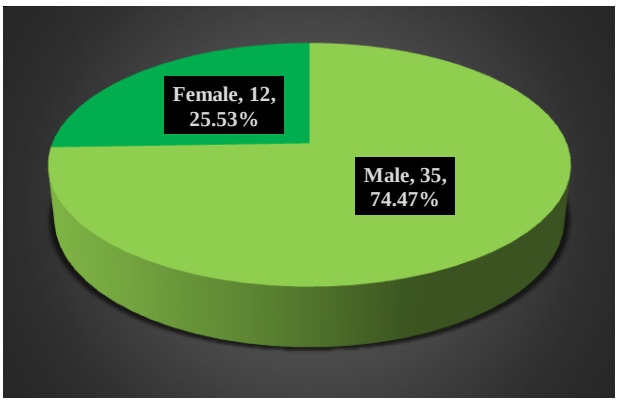

Figure-2: Gender distribution of the study subjects (N=47)

Table-1: Symptoms distribution of the study subjects (N=47)

Symptoms	Yes		No	
	n	%	n	%
Bone pain	41	87.23	6	12.77
Anaemia	37	78.72	10	21.28
Fever	23	48.94	24	51.06
Hypercalcaemia	13	27.65	34	72.34
Renal disease	11	23.40	36	76.60

Spinal cord compression	12	25.53	35	74.47

Table-2: Signs distribution of the study subjects (N=47)

Signs	Yes		No	
	n	%	n	%
Lytic bone lesions	36	76.92	11	23.08
Pathological fractures	8	17.31	39	82.69
Vertebral compression	17	36.54	30	63.46
Anaemia	40	84.62	7	15.38

Table-3: Distribution of the study population by variable (N=47)

Variable	n	%
Serum Albumin (gm/dl)		
<3.5	19	40.4
>3.5 (Normal)	28	60.0
Mean±SD	3.17±0.53	
Range	2.2-3.8	
Serum LDH (U/I)		
<222 (Normal)	26	55.3
>222	21	44.7
Mean±SD	208.87±180.68	
Range	26-631	
β2 microglobulin (µg/mL)		
<3.5 (Normal)	17	36.2
>3.5 to <5.5	11	23.4
>5.5	19	40.4
Mean±SD	5.95±6.77	
Range	1.6-37.28	

Table-4: Risk stratification of the study population according to cytogenetic abnormality detected by FISH (N=47)

FISH	n	%
No abnormal cytogenetics	34	72.34
Standard risk cytogenetics	6	12.77
Inter mediate risk cytogenetics	2	4.25
High risk cytogenetics	5	10.64

Table-5: Risk stratification of the study population by ISS and RISS (N=47)

Variable	n	%
International staging system (ISS)		
Standard risk	13	26.67
Intermediate risk	11	23.33
High risk	24	51.00
Revised International staging system (RISS)		
Standard risk	13	26.67
Intermediate risk	11	23.33
High risk	24	51.00

V. Discussion

Multiple myeloma is an age long hematological malignancy that progresses insidiously but becomes invariably fatal. A total 47 patients were selected as study subjects in the Department of Haematology, Dhaka Medical College Hospital, Dhaka. In this study there found maximum 19(40.43%) study subjects were 51-59 years of age, then 12(25.53%) were 41-50 years, 9(19.15%) were less than 40 years and 7(14.89%) were found more than 60 years of age respectively. As this study multiple myeloma, affects commonly the elderly and middle age groups of population and affects less the young age group. Kyle et al[2] and Kaur P et al[14] have observed that 2% and 3.58% patients were less than 40 years. Besides, Advani et al also reported that majority of patients to be in the age group 50-59 years of age[15].

The gender distribution of the study subjects, about 35(74.47%) study subjects were found male and 12(25.53%) were female. Male were predominant than female in this study. The male female ratio was 3:1 followed. Chowdhury et al reported it 5:2 in Bangladesh[16]. PCM is more common in male to female and the ratio is 1.1:1[17] The variables that affect the ratio are to be considered with importance.

The symptoms that found in our study, Table-1 shows the symptoms that found in the study subjects. The most frequent 41(87.23%) symptom was found bone pain (low back pain, shoulder pain, chest pain, generalized pain). Then, the other symptoms were anaemia (fatigue, malaise, palpitation, dizziness) 37(78.72%),

fever 23(48.94%), hypercalcaemia 13(27.65%), Spinal cord compression 12(25.53%), renal disease (oliguria, facial puffiness, shortness of breath) 11(23.40%). Gupta et al found about 58% patients had bone pains at diagnosis[18]. Sagale MS (2017) found Anemia (85%) was the most common hematological manifestation[19]. Kaushik et al[20] only 0.7% and 16% presented with fever. Partha Pratim Kalita found in his study that, the most frequent presenting feature was bone pain (86.54%) then the other common symptoms were those related to anaemia (78.85%), infection (48.08%) and hypercalcaemia (26.92%)[21]. Moreover, Sultan et al[22] observed fatigability in 81.9% and backache in 80.3% of the patients.

The signs of the study subjects, we found Anaemia was the dominant clinical sign occurring in 40(84.62%). Then 36(76.92%) had Lytic bone lesions, Vertebral compression had found in 17(36.54%) patients, 8(17.31%) had Pathological fractures. Similar results followed in the study of Partha Pratim Kalita (2021), where Anaemia was the dominant clinical sign occurring in 44/52 patients. The radiological hallmark of myeloma is the presence of 'punched out' lytic bone lesions 40/52 patients. Vertebral compression fractures were seen in 29 of 52 patients. Pathological fractures were less common 9 patients [21].

In our study serum albumin >3.5 gm/dl was observed in 28(60.0%) patients and <3.5gm/dl was in 19(40.4%) patients. The mean serum albumin was 3.17±0.53 gm/dl with range 2.2 to 3.8 gm/dl. Low serum albumin is a poor prognostic factor. Jacobson et al[23] was found low serum albumin in 20% of patients. Elevated serum LDH (>222 U/I) was found in 21(44.5%) patients and 17(36.2%) patients had normal LDH (<222U/l). The mean serum LDH was 208.87±180.68 U/I with range 26 to 631U/I. β2 microglobulin >5.5 µg/mL was detected in 19(40.4%) patients. Eleven (23.4%) patients had β2 microglobulin >3.5to <5.5 µg/mL and rest of 17(36.2%) patients had β2 microglobulin <3.5 (normal). The mean β2 microglobulin was 5.95±6.77 µg/mL with range 1.6 to 37.28 µg/mL. Serum β2-microglobulin and albumin are two most important prognostic factors though raised β2-microglobulin level is a poor prognostic sign. Kaur et al[14] showed β2-microglobulin higher in 71.4% subjects. In a study Hu Y et al described increased LDH, increased β2 microglobulin and decreased albumin in 20.8%, 73.3% and 56.7% patients respectively.[24]

The risk stratification of the study population according to cytogenetics detected by FISH, was observed that 34(72.34%) patients had normal cytogenetics. High risk cytogenetics was found in 5(10.64%) patients, 2(4.25%) patients had intermediate risk cytogenetics and 6(12.77%) patients had standard risk cytogenetics by FISH: Fluorescence in Situ Hybridization. It was observed that the risk stratification 24(51.00%) patients belonged to high-risk group according to ISS. According to revised international staging system (RISS) 24(51.00%) patients belonged to high-risk group. Avet-Loiseau Hetal patients with low, intermediate and high-risk disease constituted 51%, 29% and 20% of total respectively[25]. Neben K et al observed 42%, 44% and 14% of their patients had low, inter mediate and high risk disease[26]. Comparing to the other studies high risk patients are preponderant in our study. This may happen, due to the patients that diagnose in our country (Bangladesh) are elderly patients as maximum found 19(40.43%) study subjects were 51-59 years of age, and come for treatment in a difficult moment.

The R-ISS provides prognostic information that is more cogent than that from the original ISS for survival of patients with multiple myeloma. As multiple myeloma is a heterogeneous disease with diverse clinical and laboratory features. It constitutes a significant burden of hematological malignancy at the institution. Hence, we recommend that R-ISS to be used for initial staging in all newly diagnosed MM patients. However, in case cytogenetic evaluation has not been done, ISS should be used for staging. The Asian Myeloma Network recommends the use of R-ISS in the resource limited setting[27].

Limitations of the study

The limitations of this cross-sectional study were, this study was limited in one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country. Besides, small sample size, limited time may not reflect the whole scenario.

VI. Conclusion

In our study an attempt has been made to evaluate the risk stratification of the patients diagnosed to have Multiple Myeloma. Among a total of 47 patients a slight male predominance was seen. we found different signs and symptoms complaints in majority of Multiple Myeloma patients were bone pain, fever, anaemia, hypercalcaemia, Spinal cord compression, renal disease etc. Nearly all patients were evident anaemic about four fifth and lytic bone lesions about three fifth of in the patients. In those patients in whom Fluorescent in situ hybridization (FISH), ISS and R-ISS was done to stratify the risk of patients. Day after day risk stratification of Multiple Myeloma is modified now a day. Revised International Staging System R-ISS is a simple and powerful prognostic staging system, and its use is recommended in future clinical studies to stratify patients with newly diagnosed Multiple Myeloma effectively with respect to the relative risk to their survival. Accurate detection is needed to treat the patients, manage the patients in a proper way. There was no similar study in Bangladesh with

large sample size to compare with this current study. So prospective studies can be undertaken including large number of patients.

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