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Original Research Article

Risk stratification of newly diagnosed multiple myeloma patients

Ismat Ara Islam[1]*, Mohsin Hasan Samarat[2], Nishat Mahzabin[3], Nusrat Jahan[4], M. Akhlak-Ul-Islam[4], M. Salahuddin Shah[1], Sharup Chandra Poddar[5], M. Maruf Reza Kabir[3], Papri Nasrin[6], M. Aminur Rahman[7], Nasrin Akhter[8], Nowreen Afroz Chowdhury[9], M. Rafiquzzaman Khan[1]

[1]Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Department of Orthopaedic, National Institute of Traumatology and Orthopaedic Rehabilitation, Dhaka, Bangladesh
[3]Department of Pediatric Haematology and Oncology, Dhaka Medical College Hospital, Dhaka, Bangladesh
[4]Department of Haematology, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh
[5]Mongla Upazilla Health Complex, Khulna, Bangladesh
[6]Department of Haematology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh
[7]Department of Medicine, Sheikh Hasina Medical College Hospital, Tangail, Bangladesh
[8]Department of Haematology, Dhaka Medical College Hospital, Dhaka, Bangladesh
[9]Directorate General of Health Services, Dhaka, Bangladesh

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***Correspondence:**
Dr. Ismat Ara Islam,
E-mail: iaislambsmmu@gmail.com

ABSTRACT

Background: Multiple Myeloma is a neoplastic proliferation of plasma cells, associated with an M (monoclonal) protein in serum and/or urine and evidence of organ damage. Despite advances in treatment, the disease remains heterogeneous, necessitating a comprehensive understanding of its risk stratification. Risk-adapted initial therapy, maintenance therapy, refractory disease management and prognosis varies according to risk group. The aim of our study is to categorize the newly diagnosed MM patients according to their risk groups.
Methods: This cross-sectional observational study was conducted at the Department of Haematology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from August 2019 to July 2020. A total of 31 newly diagnosed MM patients were enrolled based on specific inclusion and exclusion criteria. Risk stratification was performed using ISS, R-ISS, mSMART criteria and Avets risk group categorization.
Result: The majority of the patients were male (64.52%) and aged between 55-64 years (45.16%). Clinical features predominantly included low back pain (74.19%) and general weakness (38.71%). Cytogenetic abnormalities were noted in 38.7% of the patients, with del (13q) being the most common (32.30%). Most patients were in ISS Stage III (70.97%) and R-ISS Stage II (48.39%). According to mSMART criteria, 80.65% were at standard risk while Avet's risk stratification identifies 58.06% were at intermediate risk.
Conclusion: The study reveals a high prevalence of patients in advanced ISS stages and intermediate to high-risk categories, emphasizing the need for early and personalized intervention strategies.

Keywords: Myeloma, Risk stratification, Cytogenetic, ISS, R-ISS, mSMART

INTRODUCTION

Multiple Myeloma (MM) is a complex hematological malignancy that accounts for approximately 10% of all hematological cancers.[1] It is characterized by the clonal proliferation of plasma cells in the bone marrow. Despite significant advancements in diagnostic and therapeutic strategies, MM exhibits considerable heterogeneity in survival outcomes, emphasizing the critical need for effective risk stratification methodologies. The complexity of MM is further highlighted by its genetic heterogeneity. Various cytogenetic abnormalities contribute to the disease's multifaceted nature, complicating its prognosis.[2,3] Traditional staging systems like the Durie-Salmon Staging (DSS) and the International Staging System (ISS) have been employed to gauge tumor burden but often fall short in capturing the full scope of risk factors.[4,5] Recent advancements have led to the development of more comprehensive risk stratification systems. The Revised international staging system (RISS) Mayo Clinic mSMART and Avet et al categorization has incorporated both tumor burden and disease biology into their frameworks.[6,7] These systems utilize a combination of serum markers and cytogenetic findings from fluorescent in situ hybridization (FISH) to delineate risk groups more accurately. However, there is a noticeable gap in data, particularly in specific populations like Bangladesh, where MM has a median diagnosis age of 55 years.[8] Bangladesh faces a rising burden of cancer, with approximately 200,000 new cases diagnosed each year.[9] With the increasing prevalence of multiple myeloma and the presence of unique demographic and genetic factors within the Bangladeshi population, there is an urgent call for localized studies that focus on refining risk stratification. The implications of risk stratification in multiple myeloma are extensive, ranging from tailoring initial therapy and maintenance strategies to managing refractory disease and forecasting prognosis. However, despite these profound implications, adequate data regarding risk stratification in our country is still lacking.

Therefore, the primary objective of this study is to observe and analyze the distribution of risk strata among newly diagnosed multiple myeloma patients in accordance with the ISS, R-ISS, mSMART, and Avet et al models.[6,7]

METHODS

This cross-sectional observational study was conducted at the department of haematology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from August 2019 to July 2020. A total of 31 diagnosed cases of multiple myeloma patients aged 18 or older, of both genders, and willing to provide informed consent were included in the study. Patients with other hematological malignancies were excluded. Data collection utilized a purposive sampling technique. Variables in the study were categorized into independent and dependent variables. Independent variables included demographic factors like age and gender, and disease-related variables such as clinical presentation, percentage of plasma cells in bone marrow, types of monoclonal protein, serum albumin and beta-2 microglobulin concentration, and cytogenetic risk groups determined by fluorescence-in-situ hybridization (FISH).[10] The dependent or outcome variable was the risk categories of newly diagnosed MM patients, which were classified into, stage I,II,II according to ISS staging and Revised International Staging System (R-ISS) staging system. Standard and High risk according to Mayo stratification for myeloma and risk-adapted therapy (mSMART) and low-risk, intermediate-risk, and high-risk based on criteria from Avet et al.[6,7,11] After obtaining ethical clearance and informed consent, data were collected using semi-structured questionnaires and analyzed using SPSS version 20.0.

RESULTS

In the study, a total of 31 patients were analyzed to assess the baseline characteristics. The gender distribution showed a male predominance, with 20 male patients (64.52%) compared to 11 female patients (35.48%). Regarding age distribution, the majority of the patients fell within the 55-64 age group, accounting for 45.16% (N=14) of the total sample.

Table 1: Baseline characteristics of the patients (n=31).

Characteristics	N	%
Gender		
Male	20	64.52
Female	11	35.48
Age (years)		
35-44	3	9.68
45-54	6	19.35
55-64	14	45.16
≥65	8	25.81

Table 2: Distribution of the participants by S. Albumin, S. β2 microglobulin.

Cut-Off value	N	%
Serum albumin (gm/dl)		
≥3.5	13	58.10
<3.5	18	41.90
Serum β2 microglobulin (mg/l)		
<3.5	7	22.60
3.5-5.4	2	6.50
≥5.5	22	71.00

This was followed by the ≥65 age group, which comprised 25.81% (N=8) of the patients. The 45-54 age group made up 19.35% (N=6), while the least represented age group was 35-44, accounting for only 9.68% (N=3) of the study population. The participants were divided by

normal and abnormal values of serum albumin, β2 microglobulin. Among them, 41.90% had abnormal serum albumin levels. 6.50% had above normal serum β2 microglobulin, while 71% had very high β2 microglobulin levels. The cytogenetic findings obtained through fluorescence in situ hybridization (FISH) revealed a diverse distribution among the 31 participants. The most common cytogenetic abnormality was deletion 13q (del 13q), observed in 32.30% (N=10) of the patients. This was followed by the presence of more than one cytogenetic finding in 19.40% (N=6) of the participants. Gain 1q was noted in 12.90% (N=4) of the patients. Translocations t (11,14) and t (4,14) were relatively rare, each found in 3.20% (N=1) and 6.40% (N=2) of the study population, respectively.

Table 3: Distribution of participants by cytogenetics by FISH.

Cytogenetics findings	N	%
T (11,14)	1	3.20
T (4, 14)	2	6.40
Del (13q)	10	32.30
Del (17p)	1	3.20
Gain 1q	4	12.90
More than 1 cytogenetic findings	6	19.40
All negative	19	61.30

Table 4: Distribution of participants by R-ISS staging.

R-ISS staging	N	%
R-ISS I	4	12.90
R-ISS II	15	48.39
R-ISS III	12	38.71

Table 5: Distribution of participants by mSMART risk criteria.

mSMART risk criteria	N	%
Standard risk	25	80.65
High risk	6	19.35

Deletion 17p (del 17p) was also uncommon, observed in only 3.20% (N=1) of the participants. Interestingly, a majority of the patients, 61.30% (N=19), showed no cytogenetic abnormalities, indicating an "All Negative" result in the FISH test. The distribution of participants by ISS (International Staging System) staging revealed that a significant majority of the patients were classified under ISS Stage III, accounting for 70.97% (N=22) of the total study population. This was followed by ISS Stage II, which comprised 19.35% (N=6) of the participants. ISS Stage I was the least represented, with only 9.68% (N=3) of the patients falling into this category.

The distribution of participants according to the revised international staging system (R-ISS) revealed a more balanced spread across the three stages. R-ISS II was the most common stage, accounting for 48.39% (N=15) of the study population. This was followed by R-ISS III, which comprised 38.71% (N=12) of the participants. The least represented was R-ISS I, making up 12.90% (N=4) of the study cohort. The distribution of participants based on the mSMART (Mayo stratification for myeloma and risk-adapted therapy) risk criteria showed that a substantial majority of the patients were categorized as Standard Risk, making up 80.65% (N=25) of the study cohort. In contrast, the High-Risk group accounted for 19.35% (N=6) of the participants.

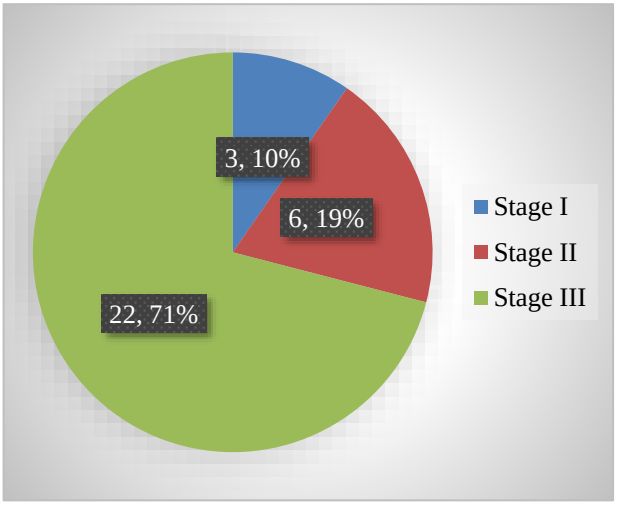

Figure 1: Distribution of participants by ISS staging.

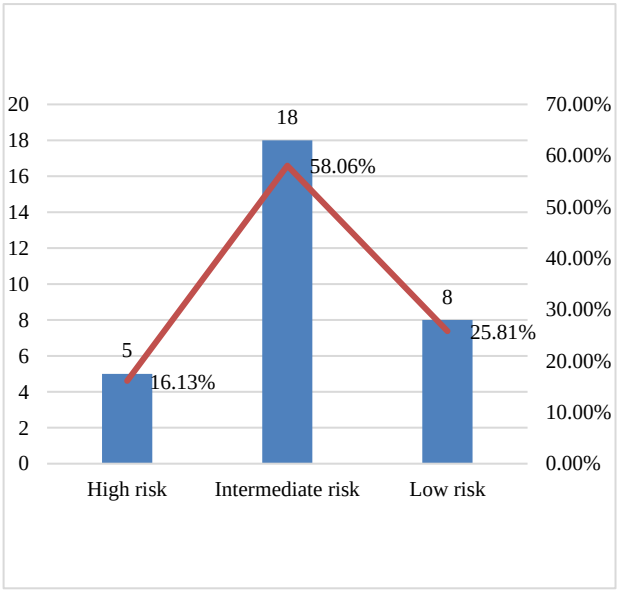

Figure 2: Distribution of the participants by Avet's risk category.

The risk stratification of the 31 participants, according to Avet's risk stratification criteria, showed a predominance of patients in the Intermediate Risk category, comprising 58.06% (N=18) of the study population. This was followed by the Low-Risk group, which accounted for 25.81% (N=8) of the participants. The High-Risk category was the least represented, with 16.13% (N=5) of the patients falling into this risk stratum.

DISCUSSION

We had conducted this cross-sectional study in Department of Haematology, BSMMU from August 2021 to July 2022. Total 31 patients were enrolled following inclusion criteria to understand the risk of each participating patient following ISS staging, R-ISS staging, mSMART model and risk stratification model proposed by Avet et al.[6,7]

The majority of the patients in our study were male (64.52%), which is consistent with existing literature indicating a male predominance in Multiple Myeloma cases.[11] The age group most affected was 55-64 years (45.16%), corroborating the notion that Multiple Myeloma is predominantly a disease of older adults.[11] These demographic findings could guide targeted screening and awareness programs. In several studies like that of Kim et al it was found that low albumin level was common among the patients with MM.[12]

In our study, the difference in serum albumin value from the normal range was prominent as compared to the previously mentioned ones. On the other hand, we had got that the mean β2 microglobulin value was much higher compared to the normal range of the participants, ranging from 0.08 mg/l to 19 mg/l. Some studies have recognized β2 microglobulin as an independent predictor of progression among patients suffering from MM patients.[13] MM is a cytogenetically heterogenous plasma cell malignancy.

Cytogenetic abnormalities in MM affect every aspect of the disease, from evolution of the malignancy to clinical presentation, response to therapy and prognosis the interpretation of cytogenetic abnormalities MM is often a challenging task. In our study we had found the commonest cytogenetics by FISH marker of the participants was del 13q, observed in 32.30% of the participants, while 6.40% had t (4;14) marker, and 3.20% had t (11;14) marker.

19.40% of the participants had multiple cytogenetic findings. A study conducted in Chennai in 2019 also found that del 13 q was the commonest in their region.[14] But other studies outside this subcontinent did not match with this finding. Some authors showed in their studies that the most common subtypes of MM patients are t (11;14), t (4;14), gain 1q.[15,16] This finding also gives us a clue regarding genetic heterogenicity among different ethnic background warranting further research.

The ISS is generally applied for its usefulness in providing a better understanding of the disease severity and median survival of the patients.[5] It combines two important biochemical markers S. albumin and beta 2 microglobulin.

According to criteria of ISS staging, very few participants in our study were from ISS stage I (10 %) or II (19%), while about 71% of the participants belonged to ISS stage III. In the 2019 study of Govindasamy et al it was found that around 67% patients in ISS stage III.[14] This data was also supported by another study by Du et al.[17]

But this finding did not correspond with few others studies, like that of Shaikh et al who showed that they found 33.75% patients in ISS stage I, 28.75% patients in ISS stage II and 37.5% participants in ISS stage III disease.[18] This gives us a clue of diversity of risk patterns among patients of MM in different parts of the globe. The revised ISS stage Revised International staging system (RISS) was developed by pooling data from 4445 patients with NDMM enrolled on 11 international trials. It combines the ISS with high-risk CA; del (17p), t (4; 14) (p16; q32) or t (14; 16) (q32; q23 and serum LDH to classify patients into three risk groups. The 5-year overall survival (OS) of patients with stage I, II and III RISS was 82, 62 and 40, while the 5-year progression-free survival (PFS) was 55%, 36% and 24% respectively.

According to our study we had found most of the patients were in R-ISS stage II that is 48.39%. Next common is R-ISS III 38.71%. The least was R-ISS I 12.9%. This is in correlation with the study of Tandon et al., 2017, who also got most of the NDMM in RISS stage II.[19] The mSMART criteria classified 80.65% of patients as Standard Risk. This is consistent with international studies and suggests that the majority of patients may respond well to standard treatment protocols.

The present study employed Avet's Risk Stratification Criteria and found that a significant proportion (58.06%) of patients were categorized as Intermediate Risk. This aligns with Avet et al own findings and suggests that a considerable number of patients may require more aggressive treatment than those in the low-risk category.[7] In terms of ISS staging, a striking 70.97% of patients were in ISS Stage III. This high percentage could be indicative of late-stage diagnosis, which is particularly concerning in resource-limited settings like Bangladesh. R-ISS staging showed that 48.39% of patients were in R-ISS II, aligning with studies that found R-ISS to be a more discriminatory tool than ISS alone.[20]

A notable observation was the high percentage of patients classified as Intermediate Risk (58.06%) according to Avet's criteria, compared to 70.97% in ISS Stage III. This discrepancy suggests that ISS staging may be identifying a higher-risk population, which is further supported by the mSMART criteria where 80.65% were classified as Standard Risk. The R-ISS staging, which is considered a more refined tool, showed a more balanced distribution with 48.39% in R-ISS II. These variations in risk stratification underscore the complexity of Multiple Myeloma and highlight the importance of using multiple criteria for a more nuanced understanding of patient risk. This multi-criteria approach can guide clinicians in tailoring treatment plans and could be particularly

beneficial in resource-limited settings where optimizing treatment efficacy is crucial.

The findings of this study have several implications for both clinical practice and future research. The high prevalence of ISS Stage III and Intermediate Risk according to Avet's criteria suggests that a significant proportion of newly diagnosed Multiple Myeloma patients in Bangladesh may require aggressive treatment regimens. This is in line with the need for early intervention strategies, as highlighted by studies like those of Greipp et al and Avet et al.[5,7] The variations in risk stratification also indicate that a one-size-fits-all approach may not be effective for treatment and that personalized medicine, guided by multiple risk stratification criteria, could be the way forward.

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

Risk stratification of MM patients at diagnosis has critical role in disease management. According to our risk stratification study most of the patients were ISS stage III R-ISS stage II mSMART standard risk group and according to Avet et al in intermediate risk group. Our study had shown significant relationship with previously established studies and revealed the fact that the patient's age of presentation and nature of genetic complexity are different in our country. Risk stratification assists in choice of drugs, minimize toxicity and maximize outcome. It also helps us to select overall therapeutic strategy including maintenance therapy and decision about autologous stem cell transplant (ASCT). Prognostic information can also be gathered from risk stratification.

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