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# Profile of patients with Myelodysplastic syndrome: A report from a tertiary care teaching hospital from Eastern India

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## ABSTRACT

**Objectives:** Myelodysplastic syndrome (MDS) is a group of myeloid neoplasms. The clinical manifestations and treatments vary depending on the subtype and risk stratification of the disease. There is a paucity of data on Indian patients with MDS. This study was undertaken to understand MDS with regard to their clinical presentation, pathological, cytogenetic profiles and also to assess their therapeutic outcomes and prognosis from our center in Eastern India.

**Materials and Methods:** This is a prospective observational study conducted in the department of hematology at a tertiary care teaching hospital from eastern part of India. The diagnosis of MDS was made from the peripheral blood examination, bone marrow aspirate examination, cytogenetics, and Fluorescence *in situ* hybridization results, according to the WHO guidelines. Patients were risk stratified using Revised International Prognostic Scoring System (R-IPSS) and subsequent therapeutic planning was done, with either supportive therapy in the form of recombinant human erythropoiesis stimulating agents, colony stimulating factors, packed red blood cell support as needed for low risk MDS patients. High risk patients were treated with hypomethylating agents such as Azacytidine, Decitabine, or Lenalidomide.

**Results:** The mean duration of follow-up of patients with MDS from the point of diagnosis was 1.8 years (range 4 months–6 years). The median OS was 1.33 years. The median OS in the analysis of our patient cohort with low, intermediate, high, and very high R-IPSS was 1.67 years, 1.33 years, 1.67 years, and 1.67 years, respectively. No patients of very low risk group were identified in our study.

**Conclusion:** Our findings reflect that MDS-MLD with low or intermediate R-IPSS risk groups is the most common types of MDS. Although supportive therapy was used to treat patients irrespective of other therapy given (depending on the risk group of the patient), it was used alone even in higher risk groups due to logistic reasons in some cases. Those patients who received supportive care alone also had a good survival duration. However, a longer follow-up duration is required to firmly establish this outcome. The median age of patients (55 years) was also lower than established studies with a median overall survival of 1.67 years.

**Keywords:** Myelodysplastic syndrome, Revised international prognostic scoring system, Hypomethylating agents, Lenalidomide

## INTRODUCTION

Myelodysplastic syndrome (MDS) is a group of myeloid neoplasms, which are characterized by a clonal group of cells with dysplasia and ineffective hematopoiesis.[1] The disease is predominantly seen in elderly patients. The clinical manifestations and treatment vary depending on the

subtype and risk stratification of the disease.[1,2] There is a paucity of data on Indian patients with MDS.[3] This study was undertaken to understand MDS with regard to clinical presentation, pathological as well as cytogenetic profiles and also the therapeutic outcomes and prognosis of MDS patients from Eastern India.

## MATERIALS AND METHODS

This is a prospective observational study conducted in department of hematology at a tertiary care teaching hospital from eastern part of India. The study commenced on January 1, 2018, till June 30, 2020, patient enrolment was done till June 2019 and subsequently followed for another 1 year, and the total duration of study is 2 years and 6 months.

### Inclusion criteria

All patients with age more than 18 years and sex with cytopenia as defined by hemoglobin (Hb), <10 g/dL (100 g/L); absolute neutrophil count (ANC), $<1.8 \times 10^9$/L (<1800/μL), and platelets, $<150 \times 10^9$/L (<150,000/μL) were included in the study.

### Exclusion criteria

All patients with secondary cause of dysplasia, pregnant females, and age <18 years were not included in the study.

After obtaining informed consent from each patient, in detail clinical history was collected, and physical examination was performed. The primary investigations undertaken for the diagnosis of MDS include complete hemogram, peripheral smear, bone marrow aspiration, imprint, and trephine biopsy. Cytogenetic profile was determined in all cases by karyotyping or fluorescence *in situ* hybridization (FISH). Other investigations that were done for patients were folic acid, Vitamin B12 estimation, autoimmune markers if necessary, hepatitis B surface antigen, anti-hepatitis C virus antibody, and HIV by enzyme-linked immunosorbent assay.

Bone marrow morphology: Leishman Giemsa stained bone marrow aspirate smears were reviewed by two independent pathologists in our laboratory and diagnosis of MDS was established according to the WHO 2016 classification.[1] Perl's staining for iron stores was also carried out in all the cases to assess for the presence of ring sideroblasts.

The demographic details of patients, including their age, sex, clinical presentation, complete hemogram, bone marrow aspiration and biopsy reports, cytogenetic, and molecular reports were recorded in detail. The diagnosis of MDS was made from these investigations, according to the WHO guidelines.[1]

The patients were further risk stratified according to their conventional cytogenetics or FISH studies (sent from bone marrow aspirate) and molecular analysis (sent from peripheral blood).

### Ethics

Institutional Ethics Committee of our institution approved the concerned study.

### Patient consent

Written informed consent was obtained from all patients who had participated in this study before procedure and also before therapy. For patients who were of unsound mind, written informed consent was obtained from their guardians.

### Study design

All patients were risk stratified using revised International Prognostic Scoring System (R-IPSS) and subsequent therapeutic planning was done, with either supportive therapy in the form of recombinant human erythropoiesis stimulating agents, colony stimulating factors, and packed red blood cell (PRBC) support as needed. High risk patients were treated with hypomethylating agents such as Azacytidine (Aza) and Decitabine (Dec). For few patients of High risk MDS, who could not receive injectable chemotherapy due to logistic issues, oral Lenalidomide (Len) was administered. Therapeutic selection was planned taking age, performance status, and family support of each patient into consideration. As our hospital is a State Government owned teaching hospital, almost all drugs were provided free for patient care, no particular manufacturer of any therapeutic agents was stressed on. There was no internal control in this study and neither there was any comparison done among individual therapeutic agents. Relapsed patients were re-stratified and received therapy based on the current risk group and tailored according to the previous therapy received.

The median overall survival (OS) was calculated from the point of first detection of the disease and inclusion in the analysis up to the end point of analysis. The final analysis was done till June 30, 2020.

### Statistical analysis

The data have been analyzed after digitization with the help of R Software (R 3.5.1 Software) in graphical fashion. The frequency of patients with their mean, median, and range variables was analyzed in nominal fashion and subsequently percentages were calculated.

## RESULTS

In our analysis, 29 patients were diagnosed to have MDS, with a male: female ratio of 1.4:1. The median age of the

study population was 55 years, (range 19–86.5 years). Three patients were <40 years and the youngest patient was 19-years-old.

Most patients were referred to hematology department both in outpatient department and also from indoor referrals, the most common reason being cytopenias in one or more cell lineages and it was found in all patients. Fever was present in 8 (27.6%), mild bleeding symptoms were present in 5 (17.2%) and generalized weakness and fatigue in 10 (34.5%) patients. However, the most common initial presentation was pallor in 15 (51.7%) of patients, and it progressed to transfusion requirement in form of PRBC and platelets in 28 (96.6%) of patients. Another interesting symptom was diffuse pain abdomen and pain in digits in few patients 5 (17.2%). There was presence of pleural effusion in one patient. Several patients had combination of symptoms at presentation [Table 1].

The mean Hb, total leukocyte count, ANC, and platelet counts were 7.45g/dl (range 4.8–10.6 g/dl), 4095/dl (range 370–16,400/dl), 1753.3/dl (range 168–3,348/dl), and 54,384.6/dl (range 5,000–259,000/dl), respectively. There were 3 (10.3%) patients with a platelet count >1.5 lakhs/dl. Bone marrow aspiration was used for diagnosis of MDS. MDS with Multilineage dysplasia (MDS-MLD) was the most common subtype among our patients 11 (37.9%), followed by MDS with excess blasts 2 (MDS-EB2) and MDS-single lineage dysplasia (SLD) with 5 (17.2%) of patients in each group. The other subtypes were hypoplastic MDS in 3 (10.3%) of patients, MDS-EB1 in 3 (10.3%) and MDS with ring sideroblasts (MDS-RS) in 2 (6.9%) of patients [Figure 1]. The reports of cytogenetics and/or FISH were normal XX/XY in 14 (48.3%) of patients, Monosomy 7 with deletion 5q- in 2 (6.9%) of patients, deletion Y and 20q- in 2 (6.9%) of patients, ring chromosome 7 in 1 (3.4%), no metaphase detected in 1 (3.4%), and test not done in 1 (3.4%) of patients. Reports were unavailable in 8 (27.6%) of patients [Table 1].

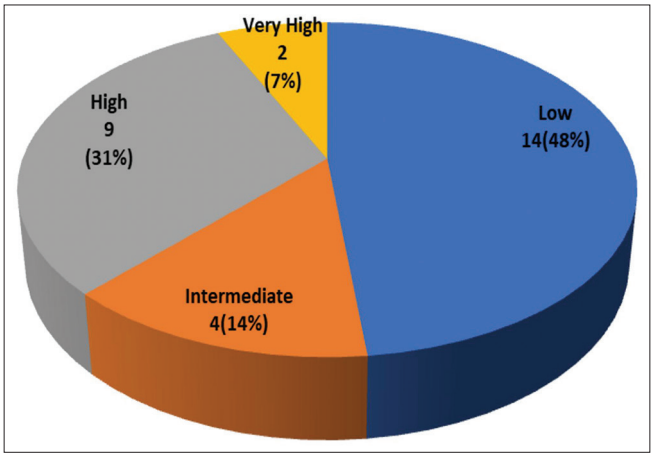


**Figure 1:** Distribution of patients according revised international prognostic scoring system (*n*=29).

The risk stratification was done according to the R-IPSS. Risk stratification wise was low 14/29(48%), intermediate 4/29 (14%), high 9/29 (31%), and very high 2/29 (7%), respectively [Figure 1].

All patients with low or intermediate R-IPSS risk groups (MDS-SLD and many patients of MDS-MLD) were treated with supportive therapy in the form of PRBC or Random donor platelets (RDP) transfusions 86.2% ($n$ = 25). Other forms of supportive therapy in the form of folic acid, deferasirox, erythropoietin or GCSF were given in 68.96% ($n$ = 20) patients. Some form of supportive therapy was also used to treat high risk MDS patients. However, in addition to supportive therapy, intermediate and high risk patients also received chemotherapy based on their molecular profile and risk stratification. Few patients of Intermediate risk, all high risk and very high risk group patients (MDS-MLD or MDS-EB1) were treated with Aza or Len. Len though not a standard therapy in the high risk group, was used in patients who were unable to come to the institute for injectable chemotherapy due to logistics. All patients with deletion 5q were administered Len. Most patients with MDS-EB2 received Aza. One patient with MDS-EB2 was planned for 3+7 chemotherapy. Hypomethylating agents, such as Aza or Dec, were given to 37.9% ($n$ = 11) patients. Len was administered to 13.8% ($n$ = 4) patients [Figure 2].

There were 13.8% ($n$ = 4) patients who were refractory to the first line therapy and were then were given a second line of therapy. The second line of therapy varied between a hypomethylating agent if supportive therapy was initiated or, changing the type of hypomethylating agent if already started with a hypomethylating agent. Among our study cohort, no patients were taken up for allogeneic transplant.

The mean duration of MDS from the point of diagnosis was 1.8 years (range 4 months–6 years). The median OS was 1.33 years. The median OS in the analysis of our patient cohort with low, intermediate, high, and very high R-IPSS was 1.67 years, 1.33 years, 1.67 years, and 1.67 years, respectively.

## DISCUSSION

MDS is a relatively rare group of myeloid neoplasms. In our study, over a span of 2.5 years, 29 patients were detected to have MDS, with a median age of 55 years. About 31% patients were above the age of 60 years. In published literature from different countries the incidence of MDS is found to vary between 4 and 4.9/lakh/year and prevalence is found to be 7/lakh/year.[2,4,5] It has been seen in these published literature that incidence of MDS increases with age, with increasing incidence above the age of 60 or 80 years.[2,5] In a study conducted in the southern part of the Indian subcontinent, 60 patients were diagnosed with MDS, of whom 73% patients were aged >60 years age and

**Table 1:** Demographic features and symptoms of patients with MDS, including the distribution of MDS subtypes, their risk stratification, and treatment modalities (*n*=29).

| | | |
|---|---|---|
| Patient characteristics (***n***=29) | | |
| Median age (range) | | 55 years (19–86.5years) |
| Number of patients >60 years age | | 9 (31.03%) |
| Number of patients <40 years | | 3 (10.3%) |
| Sex (male:female) | | 17:12 (1.4:1) |
| Mean duration of disease (range) | | 1.8 years (0.33–6 years) |
| Symptoms | | |
| One or more cytopenias | | 28 (96.6%) |
| Transfusion requirement (regular or occasional) | | 28 (96.6%) |
| Pallor | | 15 (51.7%) |
| Bleeding | | 5 (17.2%) |
| Generalized weakness and lethargy | | 10 (34.5%) |
| Fever | | 8 (27.6%) |
| Pain abdomen or digits | | 5 (17.2%) |
| Pleural effusion | | 1 (3.4%) |
| Mean hemoglobin (range) | | 7.45 g/dl (4.8–10.6 g/dl) |
| Mean TLC (range) | | 4095/cumm (370–16,400/cumm) |
| Mean ANC (range) | | 1753.3/cumm (168–3348/cumm) |
| Mean platelet count (range) | | 54,384.6/cumm (5,000–259,000/cumm) |
| Number of patients with platelet count >1.5 lakhs/dl | | 3 (10.3%) |
| MDS subtypes based on Bone marrow aspirate | | |
| MDS-MLD | | 11 (37.9%) |
| MDS-EB2 | | 5 (17.2%) |
| MDS-SLD | | 5 (17.2%) |
| Hypoplastic MDS | | 3 (10.3%) |
| MDS-EB1 | | 3 (10.3%) |
| MDS-RS | | 2 (6.9%) |
| Cytogenetics/FISH | | |
| Normal | | 14 (48.3%) |
| Monosomy 7 with deletion 5q | | 2 (6.9%) |
| Deletion Y and 20q | | 2 (6.9%) |
| Ring chromosome 7 | | 1 (3.4%) |
| Not done | | 1 (3.4%) |
| No metaphase | | 1 (3.4%) |
| Report unavailable | | 8 (27.6%) |
| **Response** | | |
| **Risk stratification (R-IPSS)** | | **Median overall survival (range)** |
| Low | 14 (48.3%) | 1.67 years (1–6 years) |
| Intermediate | 4 (13.8%) | 1.33 years (1.33–1.67 years) |
| High | 9 (31%) | 1.67 years (0.75–4 years) |
| Very high | 2 (6.9%) | 1.67 years (0.33–1.67 years) |
| Refractory disease | | 4 (13.8%) |

MDS: Myelodysplastic syndrome, TLC: Total leukocyte count, ANC: Absolute neutrophil count, MDS-MLD: MDS with multilineage dysplasia, MDS-SLD: MDS with single lineage dysplasia, MDS-EB: MDS with excess blasts, MDS-RS: MDS with ring sideroblasts, FISH: Fluorescent in situ hybridization, g/dl: gram/deciliter, cumm: Cubic millimeter

only 3.3% patients were <40 years age.[3]Another study had found 30 patients of MDS patients over a span of 8 years, and the median age was 55 years (8–73 years).[6] In literature from western countries also it has been stated that the incidence of MDS <50 years age is approximately 10%.[7] In a study by Zeidan *et al*., incidence of MDS in those aged <40 years is only 0.1/lakh person years.[8] However, we have found 10.3% (3/29) patients in the <40 years age group. Published literature has found the male: female ratio to be 1.67.[8] Similarly, there was a slight male preponderance in our study (1.7:1). In another Indian study also, there was a male predominance (male: female = 7:3).[3]

Most patients in our study presented with incidental findings of cytopenias (96.6%) when they were evaluated for fever,

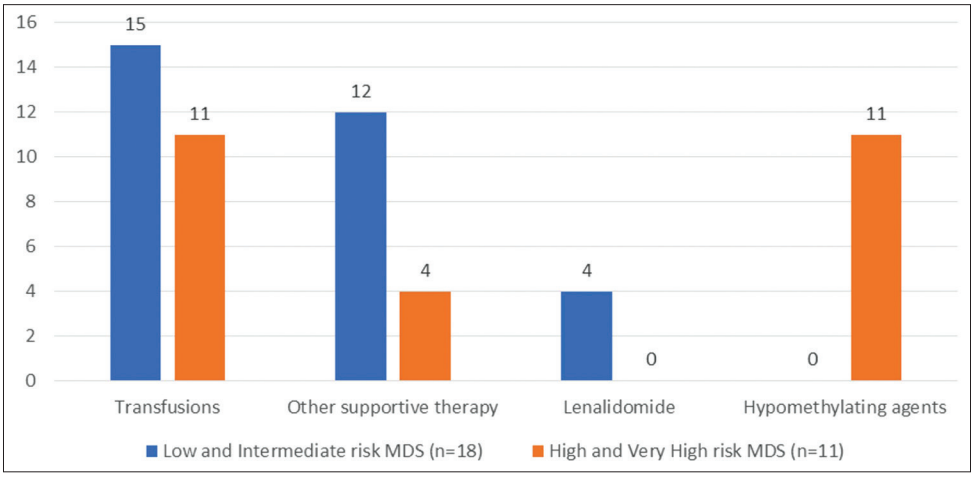


**Figure 2:** Treatment history of MDS patients. Many patients received more than one type of treatment measure. Transfusions included: PRBC and/or RDP; Supportive therapy included: FA, GCSF, EPO, Dsx; Hypomethylating agents: Azacytidine or Decitabine. MDS: Myelodysplastic syndrome, PRBC: Packed red blood cells, RDP: Random donor platelets, FA: Folic acid, GCSF: Granulocyte colony stimulating factor, EPO: Erythropoietin, Dsx: Deferasirox

progressive weakness, or bleeding. Majority of the patients required transfusions of PRBC or RDP. The most common clinical manifestation was anemia and bleeding was relatively rare.[1] Germing *et al.* have pointed out how most patients were detected incidentally during evaluation of other diseases or a routine examination.[5] In the study conducted in India, fatigue was most common (90%), along with other symptoms of exertional dyspnea (66.7%), palpitation (53.3%), fever (31.7%), or bleeding (33.3%).[3]

Diagnosis of MDS requires one or more cytopenias in the blood (Hb <10 g/dl, ANC <1800/dl, and platelet count <100,000/dl), along with dysplasia (>10%), and presence of blasts <20% in the blood and/or bone marrow.[1] In our study, the mean Hb (7.45 g/dl), ANC (1753.3/dl) and platelet counts (54,384.6/dl) conformed to the established WHO criteria of cytopenias in MDS diagnosis. In a study by Narayanan the mean Hb was 5.5 g/dL, nearly 28% patients had a platelet count <20,000/dl and 21.6% patients had a platelet count >1.5 lakhs/dl.[3] We have found 10.3% patients with a platelet count >1.5 lakhs/dl.

In the SEER registry, nearly 60% new MDS cases had an unspecified MDS sub-type.[9] Many studies have depicted the prevalence of subtypes of MDS as follows: MDS-MLD (25–40%), MDS-RS (5–8%), and MDS with deletion 5q (2–5%).[10,11] It is also noted that the incidence of MDS-unclassified has greatly reduced in recent years as compared to earlier times.[11] In our study, MDS-MLD (37.9%) was the most common, followed by MDS-EB2 (17.2%). Zeidan *et al.* have described how in the recent literature MDS-EB is the most common sub-type.[8]

In MDS aneuploidy rather than translocations are more common and the most frequently observed ones are deletion 5q, deletion 7q, trisomy 8, and deletion 20q.[12] The cytogenetic report was available in 72.4% ($n$ = 21) patients. Most had normal cytogenetics (48.3%), followed by Monosomy 7 with deletion 5q (6.9%), deletion Y and 20q (6.9%), and ring chromosome 7 (3.4%). Similarly, in another study, though cytogenetic reports of eight patients were unavailable, majority patients 56.7% (34/60) had a normal karyotype, 18.3% (11/60) patients had deletion 5q, and 6.7% (4/60) patients had deletion 7q.[3] Gangat *et al.* have shown in their study on cytogenetic profile in MDS, 52.5% (21/40) patients had a normal karyotype, similar to our findings.[11] About 90% MDS patients usually have a median of three somatic mutations.[8] In one study, patients with deletion 5q have increased platelet counts.[3] Similarly, in our study two patients with deletion 5q have platelet count >1.5 lakhs/dl.

The MDS patients are treated with supportive therapy, low intensity treatment with systemic agents, or high intensity treatment with stem cell transplant.[2] Therapy is selected based on the risk profile.[13] In our study, patients were risk stratified according to the R-IPSS score. R-IPSS is a scoring system for classification of patients with MDS, which helps to predict the prognosis.[1] In our study, the most common prognostic score was low risk group (48.3%). In a similar study conducted on Indian patients, 34.6% patients (18/52) had low risk and 36.5% (19/52) patients had intermediate disease.[3] The patients with low or intermediate risk, irrespective of the MDS (WHO) subtypes were treated with supportive care, occasionally observation. Few MDS high risk patients were treated with supportive therapy and/or hypomethylating agents such as Aza or Dec. Patients with deletion 5q were administered Len. It is known that patients with deletion 5q have a good response to Len.[13]

Patients with very high risk MDS and low risk MDS have a median OS of 0.8 years and 8.8 years, respectively.[14] Deletion

5q is considered a good prognostic marker, and a study has described the 5-year survival of 40% without treatment and 54% with treatment.[15] MDS-RS or MDS-SLD have a good survival with a median OS ranging from 3 to 12 months.[16] The median OS in our study was 1.33 years. The median OS in the analysis of our patient cohort with low, intermediate, high, and very high R-IPSS was 1.67 years, 1.33 years, 1.67 years, and 1.67 years, respectively, different from the established literature. The OS is not representative of the entire population because, this is a retrospective study and the follow-up period is not too long to accurately reflect the disease characteristics. Knowing the epidemiologic profile of MDS in a specific population is helpful to understand the specific disease characteristics, which may be different from the established characteristics in a different patient population. This, in turn, will help in correct prognostication and treatment of the disease. A prospective study conducted over a longer time span and with a larger patient population will help in better understanding the nuances of MDS. This will greatly aid in planning therapy, especially in refractory cases of MDS.

## CONCLUSION

Our findings reflect that MDS-MLD with low or intermediate R-IPSS risk groups are the most common types of MDS, and in many cases, supportive therapy alone leads to a good OS. The median age of patients (55 years) was also lower than established studies with a median OS of 1.67 years. A prospective study is required in future to better understand the disease characteristics in our patient population.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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