Original Articles

Clinico-Pathological Spectrum and Novel Karyotypic Findings in Myelodysplastic Syndrome: Experience of Tertiary Care Center in India

Ruchi Gupta, Khaliqur Rahman, Manish Kumar Singh, Surabhi Kumari, Geeta Yadav and Soniya Nityanand

Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

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Abstract. *Background*: Myelodysplastic syndrome (MDS) is a heterogeneous disorder characterized clinically by the presence of cytopenia/s. Limited data are available about the morphological spectrum and cytogenetic profile of Indian MDS patients. The aim of the study was to ascertain the clinico-pathological, morphological and cytogenetic spectrum of Indian MDS patients.

Material and methods: A retrospective analysis of all patients diagnosed with MDS from June 2012 to December 2016 was performed. Their clinical and laboratory data were collated and reviewed.

Results: A total of 150 patients with primary MDS were evaluated with M: F ratio of 1.6:1 and the median age of 55.5 years. 64% patients presented with pancytopenia and 31% with bicytopenia. Morphologically they included MDS-MLD [63 (42%)], MDS-EB 2, [33 (22%)], MDS-EB 1 [32 (21.3%)], MDS-SLD [13 (8.6%)] and two cases (1.4%) each of MDS-SLD-RS, MDS-MLD-RS, and RCC. An abnormal cytogenetic profile was detected in 50% patients. Complex karyotype was observed to be the commonest abnormality (32.5%), and chromosome 7 was the most frequently involved chromosome. Isolated deletion 5q was seen in 6.9 % cases. Novel translocations like t(9;22)(q11.2;q34.2), t(1;5)(p22;q33), t(1;12)(p34;p11.2) and t(5;7;9)(q13;q32;p22) were observed in addition to other complex abnormalities. The majority of the patients belonged to the high risk IPSS-R prognostic groups (31.4%); followed by intermediate and very high-risk groups, 29% and 24.4% respectively.

Conclusion: The median age of patients in India is a decade younger than the western population. Complex karyotype was observed to be the commonest cytogenetic abnormality, while the frequency of deletion 5q and trisomy 8 was much lower as compared to the west. The majority of the patients were in high to very high IPSS-R risk categories and seventy percent individuals below 40 years showed abnormal karyotype, indicating that Indian MDS patients have high disease burden at a young age and thus more likelihood for leukemic transformation.

Keywords: MDS, cytogenetic, IPSS-R, India.

Correspondence to: Ruchi Gupta. E-mail: ruchipgi@yahoo.co.in

Introduction. Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal hematopoietic stem cell disorder characterized by morphological dysplasia and ineffective erythropoiesis secondary to immunological dysregulation and apoptosis.[1] The most frequently seen chromosomal

abnormalities in MDS include the deletion 5q (5q−), trisomy 8 (+8), the deletion 20q (20q−), monosomy of chromosome 7 (−7), the deletion 7q (7q−), monosomy of chromosome 5 (−5) and loss of sex chromosome (-Y).[2] Though these cytogenetic abnormalities are detected in approximately 30-70% individuals, they are one of the most important independent prognostic parameters and have been incorporated into the risk stratification models for predicting prognosis. Risk stratification is traditionally carried out by using international prognostic scoring systems (IPSS) and WHO prognostic system.[3] IPSS is based on the blast percentage, number of cytopenias and cytogenetic subgroups as the most significant independent variables for overall survival (OS) and disease progression, whereas WPSS model incorporated the WHO subgroups, IPSS karyotype, and transfusion requirement. However, none of these scoring systems considered the severity of cytopenias nor did they offer prognostic information for patients with treated or secondary MDS.[3] The impact of cytogenetic on survival in a large dataset of patients with MDS suggested that a distinction into five cytogenetic risk groups provided a more precise prognostication. This lead to the formulation of revised international prognostic scoring system, (IPSS-R) which stratifies MDS into five risk groups based on their depth of cytopenias and inclusion of newer cytogenetic risk stratification for MDS.[4,5] IPSS-R is based on five different categories of cytogenetics, bone marrow blast percentage (≤ 2, 3-4, 5-10, and >10%), hemoglobin (≥ 10, 8-<10, and <8g/dl), platelet count (≥ 100, 50-99, and <50,000/mm^3) and absolute neutrophil count (≥ 0.8 and <0.8/mm^3). Though the newer cytogenetic classification takes into account into the majority of the clonal cytogenetic abnormalities, yet approximately 15% patient's exhibit abnormalities of unknown significance.[5] A recent breakthrough has been DNA sequencing that has helped to find out mutations in nearly 50 genes related to signal transduction, DNA methylation, transcriptional regulation, and RNA splicing.[6] This information has been helpful in the therapeutic management of MDS. Despite the recent advances in the molecular landscape of MDS[7,8] which help in understanding the disease biology and heterogeneity, the importance of conventional cytogenetic cannot be over-emphasized for the screening and risk stratification of MDS patients in clinical practice.

There are a limited number of studies describing the cytogenetic profile of MDS from India,[9-13] and hence this highlights the importance of the present study. It has been previously observed that the disease biology among Indian subcontinent is distinct when compared to the Western population. In this study, we describe the clinico-pathological profile and cytogenetic abnormalities in patients with MDS and categorize them according to the IPSS-R scoring system to assess the disease burden in our cohort of patients.

Materials and Methods.
Patients. This was a retrospective observational study over a period of 4.5 years (June 2012 to December 2016). All cases with a diagnosis of primary untreated cases of MDS were included in the study. Most of the patients were evaluated for refractory cytopenia/s, which was defined as per IPSS-R recommendations. The detailed clinical and investigation profile was traced from patient medical records. The study was approved by the institutional ethics committee.

Morphological examination. May-Grunwald Giemsa (MGG) stained bone marrow aspirate smears were reviewed by two independent pathologists (RG and KR) and diagnosis of MDS was made according to WHO 2016 classification. Perl's staining for iron stores was also carried out in all the cases to assess for the presence of ring sideroblasts.

Cytogenetic analysis. Heparinized bone marrow samples were collected for conventional karyotyping. The G-banding technique was used, and a minimum of 20 metaphases was analyzed. Karyotypes were described with reference to the International System of Human Cytogenetic Nomenclature (ISCN) 2009 & 2013. The cytogenetic abnormalities were then scored according to IPSS-R cytogenetic categories. Complex karyotype was defined as the presence of three or more structural defects or monosomies[5]. Monosomal karyotype was defined as the presence of at least two autosomal monosomies or a single monosomy associated with at least one additional structural abnormality.[14]

Statistical analysis. Statistical analysis was performed using SPSS version 16.0. The difference among groups and correlation studies were analyzed by analysis of variance and Pearson correlation. The level of significance was assigned at p-value <0.05.

Results.

Patient characteristics. A total of 150 patients were analyzed of which 93 were males and 57 females (M: F=1.6:1). The median age was 55.5 (range 2-87 years). Sixty-seven percent patients were below the age of 60 years at presentation. The majority of the patients were being evaluated for unexplained refractory cytopenia/s which included pancytopenia at the presentation in 64% (n=96) patients, bicytopenia in 31.3% (n=47) and isolated anemia and thrombocytopenia in only 3.3 % (n=5) and 1.3% (n=2) patients respectively. The baseline characteristic of the patients is shown in **Table 1**.

Morphology. The patients were classified according to WHO 2016 into single lineage dysplasia (MDS-SLD, n=13), multilineage dysplasia (MDS-MLD, n = 63), single lineage dysplasia with ring sideroblasts (MDS-SLD-RS, n = 2), multilineage dysplasia with ring sideroblasts (MDS-MLD-RS, n = 2), excess of blast 1 (MDS - EB 1, n = 32), excess of blast 2 (n = 33), two cases of refractory cytopenia of childhood (RCC) and 3 cases of 5q – MDS. Morphologically, 16 patients showed hypoplastic marrow, and the majority of them had excess blasts (57%); with a median blast count of 5%. Clonal abnormalities were detected in 62.5% cases of MDS-SLD, 48.7% cases of MDS-MLD, 44.4% cases of MDS-EB-1, 50% cases of MDS-EB-2 and 78% cases of hypoplastic MDS.

Cytogenetic and risk stratification. Cytogenetic analysis by conventional karyotyping was available in 86/150 (57.3%) cases (**Supplementary Table S1**). An abnormal karyotype was detected in 43 cases (50%). According to the IPSS-R cytogenetic risk stratification, a significant number of patients exhibited high-risk cytogenetic abnormalities (56.9%). Age adjusted analysis showed an abnormal cytogenetic profile in 70.5% patients aged less than 40 years, in 42.5% patients in the 40-60 years sub-group and 44.8% patients above

Table 1.

Total Patients (n)	150 (%)
Gender	
Male	93
Female	57
Age (years)	
Median (Range)	55.5 (2-87)
Age group	
<40 years	27 (18%)
40-60 years	71 (47.3%)
>60 years	52 (34.7 %)
Hemoglobin (g/dl)	
Median (Range)	6.9 (3-12)
Total Leukocyte counts/ TLC (x10⁹/ l)	
Median (Range)	3.1 (1.1-45)
Platelet counts (x10⁹/ l)	
Median (Range)	41.0 (5-558)
S. LDH levels (U/L)	
Median (Range)	533 (195-5055)
WHO diagnosis	
MDS-SLD	13 (8.7)
MDS-RS	02 (1.3)
MDS-MLD	63 (42)
MDS-MLD-RS	02 (1.3)
MDS-EB I	32 (21.4)
MDS-EB II	33 (22)
Refractory cytopenia of childhood	02 (1.3)
MDS with isolated del(5q)	03 (2)
Ringed Sideroblasts	
Present	26 (17.3)
Absent	124 (82.7)
Karyotyping Available	**N = 86**
Normal karyotype	43 (50)
Abnormal karyotype	43 (50)
Cytogenetics group (R-IPSS)	**N = 86**
Very good	1(1.1)
Good	49 (56.9)
Intermediate	10 (11.6)
Poor	12 (13.9)
Very poor	14 (16.2)
R-IPSS prognostic risk stratification	**N = 86 (%)**
Very Low	2(2.3)
Low	11(12.8)
Intermediate	25 (29)
High	27 (31.4)
Very High	21 (24.4)

60 years old.

The presence of a complex karyotype was found to be the most common cytogenetic abnormality and detected in 32.5% patients. Isolated chromosomal abnormalities were detected in 39.5% (17/43) patients and double abnormalities were present in 16.2% cases. A monosomal karyotype was identified in 15/43 patients (34.9%) patients, of which 73% cases (11/15) had a complex karyotype. Chromosome 7 was the most frequently [32.5% (14/43)] involved chromosome, in the form of monosomy and interstitial deletions and occasional translocation. Isolated monosomy seven was seen in only 6.9%

(3/43) cases. Deletion 20q (del 20q) and deletion 5q (del 5q), in isolation or combination with other chromosomal aberrations, were present in 9.3% and 6.9% patients respectively. The incidence of trisomy 8 was found to be very low (2.3%, 1/43). Interestingly, the presence of t(9;22)(q34;q11.2) was noted in three cases (6.9%), one each of MDS-SLD, MDS-MLD and MDS-EB 2. None of them had any clinical or morphological features suggestive chronic myeloid leukemia (CML). Four patients revealed the presence of chromosomal translocation, unusually reported in MDS, which were 46,XY,t(1;5)(p22;q33), in MDS-SLD, t(1;12)(p34;p11.2) and t(5;7;9;)(q13;q32;p22) in a case of MDS-EB 1, and t(1;2)(p36.1;q21) in MDS-EB 2.

The majority of the patients were assigned to the high risk IPSS-R prognostic group (31.4%); followed by intermediate and very high-risk groups, 29% and 24.4% respectively. Only 2.3% patients belonged to the very low-risk category. Age adjusted IPSS-R revealed that 70% patients aged less than <40 years were in the very high and high-risk categories as compared to 51% in the high-risk groups (**Supplementary Table S2**).

There was no statistically significant correlation between the complex cytogenetic abnormalities and the WHO sub groups and age. The complex karyotype was also detected with equal frequency in both low risk and high-risk morphological categories of MDS and across all age groups.

Discussion. Myelodysplastic syndromes are a heterogeneous group of hematological disorders, regarding morphology, cytogenetics and clinical outcome. In comparison to the western countries it has been observed that the median age for MDS is almost a decade lower in India and other Asian countries.[9-13,14,15,16] This corroborates with the available demographic profile of Chinese patients with MDS and earlier reports published from Japan.[17,18] However, the recent reports from Japan and the Western literature show a preponderance of the disease in old age groups, with the median age being 65-72 years.[4,8,19,20] In a multi-institutional study[4] of 7012 MDS patients, by Greenberg et al, the average age was found to be 71 years with only 23% patients aged less than 60 years old. This is in contrast to our observation, where more than 67% patients were younger than 60 years.

Clinically, the majority of the patients in our population presented with 2 or 3 lineage cytopenias rather than isolated ones. Morphologically, the incidence of low-risk categories, RA and RARS was only 10%, while high-grade MDS (EB-1 and EB-2) was observed to be 43.4%. The frequency of high-risk MDS is comparable to the data from other Asian countries; however, it is significantly higher (30-40% vs 10-30%) as compared to the western literature.[8,19,20] In an attempt to delineate the difference in MDS in the eastern and western countries, a comparative analysis was performed by Matsuda et al in 2005.[21] They compared the Japanese and German FAB – RA (refractory anemia) categories, and found that Japanese patients were significantly younger (57 vs 71 years) and had more severe cytopenias than the German patients. An abnormal karyotype was detected in 29% Japanese patients and 53% patients of the German cohort in this subgroup. In our study, the median age of patients in FAB-RA was 52 years, which is comparable to the Japanese cohort, however, the incidence of cytogenetic alterations was very high (62.5 %). The high incidence of cytogenetic abnormalities in RA has also been reported previously from India, where they observed clonal abnormalities in 63.6% patients.[9] Another morphological variation worth discussion is the hypoplastic MDS group. The frequency of hypoplastic MDS documented in literature is 8-20%.[22,23] In a recent study of 100 hypoplastic MDS patients, it was observed that these patients have statistically significant lower peripheral blood counts, bone marrow blast percentages and a lower incidence of poor-risk cytogenetic abnormalities, as compared to the non hypoplastic groups.[24] On the contrary, in our cohort of 9.3% (14/150) patients with hypoplastic MDS, the median blast count was 5% and 78% (7/9) of these patients were found to harbor abnormal karyotype (**Supplementary table 2**).

Clonal abnormalities were found in 50% cases in our study, which is in concordance with the documented western and Indian literature.[9-13,19,20] Importantly, a significantly higher incidence of complex abnormalities and monosomal karyotype was noted in our population (**Figure 1**) as compared to other published Indian, Chinese[14] and western data (32.5% vs 6.5-11%, and 34.5% vs 8.1-15%),[19,20,25] while the frequency of 5q deletion and trisomy 8 were much lower (6.9 vs 26-30% and 2.3 vs 15-31%, respectively). In recent

Frequency (%) of cytogenetic abnormalities reported in different studies
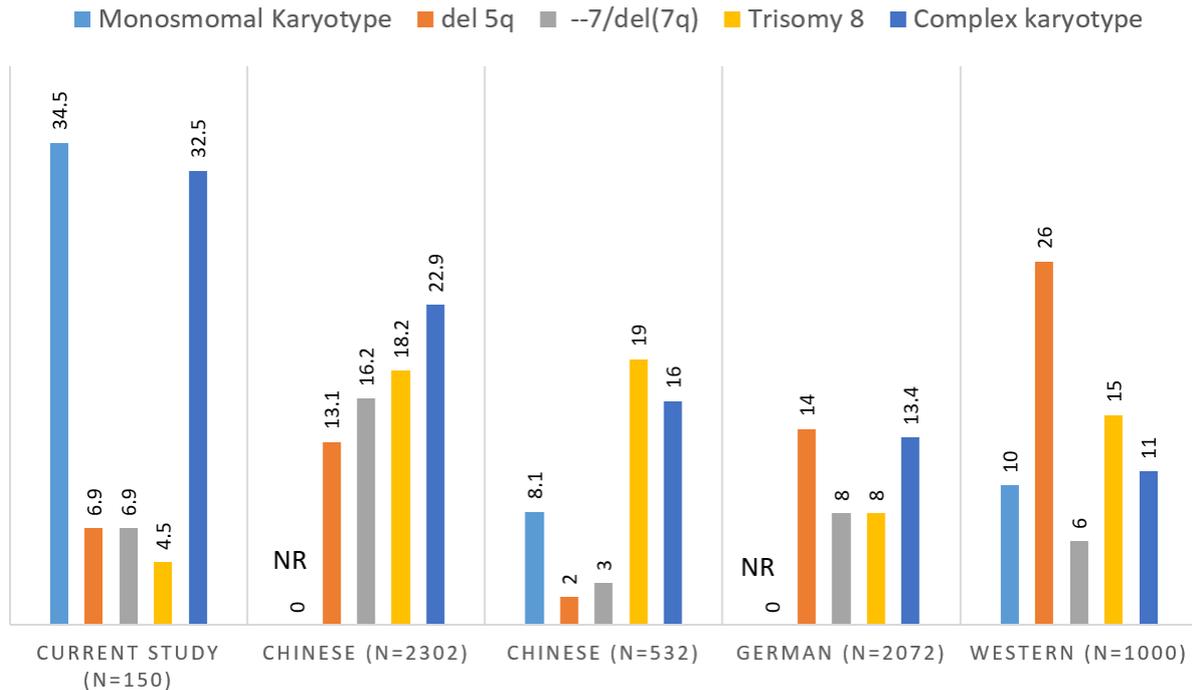

Figure 1. Comparative bar diagram highlighting the difference between the common cytogenetic abnormalities reported in different parts of the world.[16,19,20,29] The incidence of complex karyotype, monosomal karyotype and isolated del 5q, monosomy 7/del 7q, trisomy 8 is compared.[8] The incidence of complex and monosomal karyotype is much higher in our study while that of del 5q, monosomy 7/del 7q, trisomy is low.

studies, monosomal karyotype has also been proposed to be a predictor of bad prognosis. Patients with a monosomal karyotype, invariably belong to poor or very poor cytogenetic risk groups and it has been observed the rate of overall mortality and relapse was significantly higher among patients with monosomal karyotype than in those without it.[14, 25] We also detected a few novel cytogenetic abnormalities, mostly in association with complex karyotype. It has been previously observed too, that these rare translocations are usually found in association with other chromosomal alterations and thus their role in disease pathogenesis is unclear.[5] Other rarely reported abnormality includes the presence of Philadelphia chromosome in MDS. Keung MB et al, retrospectively screened 148 Philadelphia positive patients and observed 2% cases of MDS to harbor this mutation.[26] Three patients in our study group showed presence of Philadelphia chromosome or t(9;22)(q34;q11.2) in addition to other cytogenetic alterations. It is intriguing that Armas et al. in their recent review of Philadelphia positive de novo MDS cases have shown that, t(9;22) was the sole abnormality in 50% cases. Additionally, trisomy 8 has been reported in

approximately 40% cases along with other complex cytogenetic abnormalities.[27] In our series, all three patients had presented with complaints of cytopenias and past history of packed RBC/platelet transfusion. None of these patients had organomegaly or lymphadenopathy. Morphologically, two of these patients had a normocellular to mildly hypocellular marrow, with evidence of dyspoiesis. The absence of organomegaly, leukocytosis or hypercellular bone marrow and presence of cytopenias with significant dyspoiesis and a complex karyotype favored the diagnosis of MDS over chronic myeloid leukemia in these patients.

As per the IPSS-R prognostic risk stratification, 55.8% of our patients belonged to the high and very high risk categories and only 2.3% and 12.8% of our patients belonged to the very low-risk category and low risk categories respectively. Seventy percent of the individuals aged below 40 years, belonged to the high and very high risk prognostic risk categories. This is in contrast to the available Indian data from southern India and the western data, where IPSS-R risk stratification has been performed (**Figure 2**).[4,13,16,19,20] Narayanan S, in their study cohort of 60 patients from southern

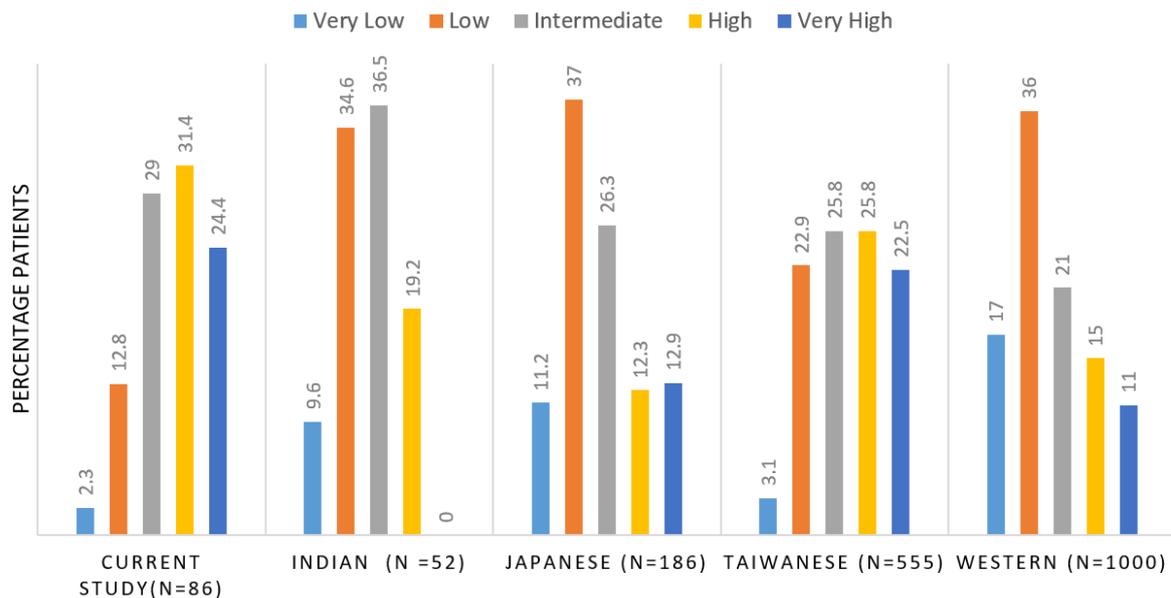## Distribution of IPSS-R risk categories in various studies

Figure 2. Comparative bar diagram highlighting the difference between the IPSS-R risk groups in different studies.[8,13,20,30]

India, observed majority (73%) of their patients to be aged above 70 years and only 19.2% patients in high risk IPSS-R category.[13] In a multi centric study by Greenberg P et al, data for 7012 primary untreated MDS patients, from multiple international institutions including Spanish, French, Piemonte (Italy) and Brazilian MDS Registries and the International MDS Risk Analysis Workshop (IMRAW), was compiled and evaluated. IPSS-R stratification revealed 57% patients in very low/low risk and 23% patients in the high/very high risk categories,[4] Similarly, in a report from the European LeukemiaNet MDS registry, 71.5% and 3.5% patients were assigned in the very low/low risk and high/very high risk categories respectively. These studies clearly highlight the differences in the disease burden in Indian and Western population.[28]

The inclusion of FISH in the diagnostic armamentarium would aid in identifying additional patients with cryptic abnormalities of chromosome 5 and 7 which might be missed in conventional cytogenetics.[29] This has been confirmed by Lai et al in a large multi centric

study of 2032 chinese patients, where they observed clonal abnormalities by FISH in 23.6% cases with apparently normal cytogenetics. Further, abnormalities detected by FISH were more frequently observed among patients with <5% bone marrow blasts.

In conclusion, the average age of MDS in our country is about a decade less than that reported in western literature. The cytogenetic profile is largely distinct, though there is significant overall heterogeneity in the Indian data, from different parts of the country. Overall, we observed a very high incidence of complex karyotypes and the incidence of isolated del 5q, appears to be much lower as compared to the western data. The majority of our patients belong to high IPSS-R risk categories; indicating the need for early intervention and counseling for stem cell transplantation. A larger population and gene expression profiling based studies with follow up data are required to understand the reasons for the regional variations, genetic mechanism of MDS in our part of the world and their therapeutic implications.

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Supplementary Files.

Supplementary Table 1: Cytogenetic profile of MDS patients in different sub groups.

MDS SUBGROUP N=86	KARYOTYPE	NO. OF PATIENTS	% ABNORMAL	% COMPLEX KARYOTYPE (N)
MDS-SLD N=8	46XX[20]	2	62.5	40% (2/5)
	46XY[20]	1		
	41~47,XX,+2,-8,-9,-14,-15,+16,-17,+19,+22 [cp10]	1		
	46,XY,del(20q) [20]	1		
	45,XX,-21[20]	1		
	46,XX,del(11)(q23)[4]/46,XX[16]	1		
	46,XY,t(1;5)(p22;q33),-8,t(9;22) (q34;q11.2), +22[15]	1		
MDS-MLD N=39	46 XY [20]	12	48.7	14.2 (3/21)
	46XX [20]	6		
	46,XY,-5,del 7(q11.2),-13,+17,-18[20]	1		
	46, XX, add (19)(q33.3) [20]	1		
	47,XY,+10,del(20)(q11.2)[04]/46,XY,del(20)(q11.2) [06]	1		
	45,XX,-7 [20]	4		
	45,XX,-7,inv(14)[20]	1		
	46,XY,del(3)(q23)[08]/46,XY[12]	1		
	46,XY,del(20q)(q12) [20]	1		
	44~46,XX,-18,-19[cp3]/46,XX[17]	1		
	47,XY,+9[20]	1		
	45,XY,-9[20]	1		
	45,XY,-7[12]/46,XY,-7,+21[8]	1		
	47XY, -7, +21, +22 [20]	1		
	45,XX,-4,t(9;22)(q34;q11.2) [20]	1		
	45,XY,-7,del(20)(q12)[10]/45,XY,-7[10]	1		
	45,XX,-7[15]; 46,XX,-7,+22[05]	1		
	44~45/46,XY,-15,-16,-19,-20[cp08]/46,XY[12]	1		
MDS-RS N=1	46, XY[20]	1		
MDS MLD-RS N=2	45,XY,-9[20]	1		
	46XY [20]	1		
MDS -EB 1 N=18	46XY [20]	6	44.4	62.5 (5/8)
	46XX [20]	4		
	47,XY,del(1)(p34),t(1;12)(p34;p11.2),der(5)add(5)(p15.1),t(5;7;9;)(q13;q32;p22),del(12)(p11.2),+14,+mar1,+mar2,+mar3[20]	1		
	Monosomy 5,9, 12,14,16,18,20,21[20]	1		
	46,XX,del(20)(q12)	1		
	45,XY,-7[06]/46,XY[14]	1		
	41-43,XY,-7,-13,-16,-17,-18,-19,-20,-21,+mar1,+mar2 , [cp20]	1		
	45XY, -9[08]; 46XY [02]	1		
	42,XX,-9,-16,-17,-19,-21,-22[20]	1		
	50,XY,+13,+19,+21,+21[20]	1		
MDS-EB 2 N=12	46XX[20]	4	50	50 (3/6)
	46XY [20]	2		
	43~48,XX,-1,+1,-5,-6,-7,-9,-10,-12,-13,-15,-17,+19,+20,+21, +mar1 ,+mar2 [cp20]	1		
	45XY, -7[20]	1		
	92<4n>,XXYY[02]/46,XY[18]	1		
	44~45,XY,der(4),-5,der(7),-7,-8,t(9;22)(q34;q11.2),-15,+22	1		
	44~47,XY,t(1;2)(p36.1;q21),-2,-4,-5,-6,+13,+18,+mar [20]	1		
	47,XY, +8[20]	1		
RCC N=2	40 ~46,XY,-4,-5,-6,-7,-12,-20,-21,-22,+mar [20]	1		
	46XY [20]	1		
5Q- N=3	46,XY,del(5)(q11.2q13)[02]/46,XY[08]	1		
	46,XY,del(5)(q22)[12]	1		
	92 <4N>,XXXX,DEL (5) (Q22) X2 [03] / 46, XX ,DEL (5) (Q22)[09]/46 ,XX[08]	**1**		
HYPOPLASTI	**46,XY**	**2**	**78%**	**42.8 (3/7)**

C MDS* N=9		
	45XY, -9[08]; 46XY [02]	1
	45,XX,-4,t(9;22)(q34;q11.2)	1
	42,XX,-9,-16,-17,-19,-21,-22	1
	45,XY,-7,del(20)(q12)[10]/45,XY,-7[10]	1
	45,XX,-7[15]; 46,XX,-7,+22[05]	1
	50,XY,+13,+19,+21,+21[20]	1
	44~45/46,XY,-15,-16,-19,-20[cp08]/46,XY[12]	1

*Cytogenetics listed again, of cases with hypoplastic MDS

Supplementary Table 2: Age related IPSS-R

Age (N)	Very high risk	High risk	Intermediate risk	Low risk	Very low risk
<40 yrs (20)	7 (35%)	7 (35%)	5 (25%)	1(5%)	-
40-60 yrs (37)	8 (21.6%)	11 (29.7%)	13 (35.1%)	5 (13.5%)	-
> 60 yrs (29)	6 (20.6%)	9 (31.0%)	7 (24.1%)	5 (17.2%)	2 (6.8%)