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Optimizing Prognostic Assessment in De Novo Myelodysplastic Syndromes: Using WHO classification and IPSS-R Criteria in focus: A Single-Centre Study

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ABSTRACT

OBJECTIVE: To assess clinicopathological, morphological and molecular characterization in De Novo Myelodysplastic patients (MDS).

METHODOLOGY: This prospective observational study was conducted at NIBD between December 2022 and March 2025. A study involving 100 adult patients diagnosed with de novo MDS, according to the WHO 2017 criteria. Demographic and clinical variables, as well as laboratory indices, were collected, alongwith bone marrow evaluation and karyotyping. Patients were classified according to the WHO 2017 subtypes and assigned to IPSS-R risk groups. Survival was estimated using the Kaplan–Meier method, and differences in overall survival among MDS subtypes were compared using the log-rank test. Statistical significance was set at $p < 0.05$.

RESULTS: Median patient age was 54 years (IQR 40–65), with male predominance (64%). The most prevalent WHO subtype MDS-unclassifiable(38%), followed MDS-EB1-EB1 (21%) and MDS-EB2-EB2 (20%). Regarding IPSS-R, 14% of patients were classified as low risk, 54% as intermediate risk, and the remainder as high/very high risk. The cohort's median overall survival, calculated from the time of diagnosis to death or last follow-up, was approximately 24 months. Notably, severe cytopenias were linked with survival: patients with haemoglobin levels between 8–<10 g/dL exhibited a median survival of 8 months, while those with platelet counts $< 50 \times 10^9$/L or absolute neutrophil count ($< 0.8 \times 10^9$/L) survived approximately 16 months. IPSS-R risk categories demonstrated significant associations with hematologic parameters (all $p \leq 0.02$).

CONCLUSION: In de novo MDS, WHO 2017 subtypes and IPSS-R jointly refine prognosis. Younger-onset cases and frequent unclassifiable cases highlight the value of integrated morphologic–cytogenetic assessment.

KEYWORDS: Cytopenia, Epidemiology, Myelodysplastic Syndromes, Prognosis, Risk Assessment

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders defined by ineffective hematopoiesis, persistent peripheral blood cytopenias, morphologic dysplasia in one or more myeloid lineages, and an elevated risk of progression to acute myeloid leukemia (AML)[1,2]. These abnormalities arise from a complex interplay of genetic and epigenetic perturbations that disrupt normal hematopoietic differentiation and promote clonal expansion[3,4].

Cumulative evidence suggests substantial geographic variability in Incidence and age at diagnosis. Systematic meta-analysis indicates that the pooled crude Incidence in Asia is 1.6 per 100,000 residents yearly (95% CI: 1.5–1.7), which is less than in Europe (3.6 per 100,000, 95% CI: 1.3–6.3) and in America (4.0 per 100,000, 95% CI: 2.8–5.3). Age-specific incidence rates also show the same pattern, with isolated Asian reports of 1.13–1.51 per 100,000 compared to 2.26–7 per 100,000 in Western populations. The age of diagnosis is also considerably younger in Asians. Median ages in China and Japan are 62–76 years, compared to higher medians in Western countries. Within a single Chinese cohort, the median age was as low as 57 years, with 61.9% of patients diagnosed below the age of 60. It has been demonstrated through epidemiological studies that the Incidence of MDS subtypes is highly heterogeneous between Western and Asian populations. According to a large meta-analysis, subtypes such as MDS with isolated del(5q), MDS with ring sideroblasts (MDS-RS), and MDS-U (Unclassifiable) are more frequent in Western than in Asian cohorts[5,6]. Specifically, isolated del(5q) is observed in about 2.67% of Western cases, compared to just 1.12% in Asian populations; MDS-RS shows a similar disparity (7.83% vs 0.97%); and MDS-U is reported in 55.80% of Western cases versus 5.62% in Asian studies. Conversely, MDS with excess blasts (MDS-EB) and MDS with multilineage dysplasia (MDS-MLD) are more prevalent in Asian populations (41.46% vs. 15.52% for MDS-EB; 36.56% vs. 7.35% for MDS-MLD)[5]. In terms of cytogenetic profiles, Chinese cohorts exhibit lower frequencies of del(5q), normal karyotypes, and loss of the Y chromosome, but higher rates of complex karyotypes, trisomy 8, and del(20q) compared to the Western cohorts[7].

Prognosis in myelodysplastic syndromes is most accurately assessed using established risk-stratification systems that integrate clinical and cytogenetic variables. IPSS-R is widely accepted. It incorporates bone marrow blast count, cytogenetic abnormalities, and severity of cytopenias to stratify patients into five risk categories: very low, low, intermediate, high, and very high, which correlate closely with overall survival (OS) and risk of progression to acute leukemia. The IPSS-R has demonstrated superior predictive power for survival and leukaemia-free survival compared with earlier systems, such as the original IPSS and the WHO-based WPSS, across multiple international and multicenter cohorts[8-11]. At the same time, the WHO 2017 classification remains crucial for providing a biological and prognostic perspective, categorizing patients based on morphological and genetic features, including excess blasts, ring sideroblasts, or del(5q), which inform treatment decisions and eligibility for clinical trials. This study addresses a gap in region-specific prognostic data by evaluating the applicability of the WHO 2017 classification and the IPSS-R risk stratification in a Pakistani cohort of de novo MDS patients.

The present study aimed to evaluate the prognostic relevance of the WHO 2017 and Revised IPSS-R in de novo MDS patients from our local population, examining their correlation with OS and key hematologic parameters to determine their value for routine clinical risk stratification.

METHODOLOGY

A prospective observational study was conducted on 100 consecutive adult patients diagnosed with de novo MDS at the National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan, between December 2022 and March 2025. Primary data were collected prospectively from the time of diagnosis until death or last follow-up. The study was approved by the Ethical Review Committee (ERC) of Ziauddin University (**Reference No. 5780722SKPAT)**. All procedures were in accordance with the Declaration of Helsinki and institutional ethical guidelines, and informed consent was obtained from the study participants.

Inclusion criteria: adult patients diagnosed with newly diagnosed de-novo MDS according to the WHO 2017 criteria.

Exclusion criteria: therapy-related or secondary MDS cases.

Non-probability consecutive sampling was employed for selecting patients. The target population comprised all adult patients diagnosed with de novo MDS, and the final sample consisted of 100 consecutive patients who met all criteria. The sample size calculation was performed using OpenEpi version 3, an open-source calculator, to ensure adequate power for a clinically significant correlation. Diagnosis was confirmed based on bone marrow morphology and cytogenetics. Data were collected prospectively for both clinical and laboratory information using structured case records. Baseline variables included age, sex, and comorbidities (HTN: hypertension; DM: diabetes mellitus; IHD: ischemic heart disease). Complete blood counts and bone marrow morphology for blast count and dysplastic cells were performed in all patients. Cytogenetic analysis was performed to detect chromosomal abnormalities, and molecular tests were performed when necessary. The subtyping of MDS based on bone marrow morphology, cytogenetics, and molecular studies was performed according to the WHO 2017 criteria.

Patients were followed at regular outpatient visits until death or last documented contact. The time from diagnosis to death from any cause, or to the last known follow-up, was termed overall survival. Follow-up information from the study database was used to estimate OS time. Patients alive at final follow-up were censored. Risk groups and various hematologic variables were used to estimate median OS using Kaplan-Meier methods.

The statistical analysis was carried out using SPSS version 27. Results of the cytogenetic groups, blood counts, and percentage of bone marrow blasts were used to derive IPSS-R risk categories and scores (very low, low, intermediate, high, and very high). Continuous variables such as age, hemoglobin level, leukocyte count, platelet count, and bone marrow blast percentage were presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data, based on assessment of normality using the Shapiro–Wilk test. Categorical variables were presented as frequency and percentage. The chi-square or Fisher's exact test was used to compare MDS groups with categorical data. In contrast, where appropriate, one-way ANOVA or the Kruskal-Wallis test was used in the case of continuous variables. A p-value < 0.05 was considered statistically significant.

RESULTS

The study population comprised 100 adult patients with de novo MDS, with a median age of 54 years (IQR: 40–65 years). The cohort comprised 64 men (64%) and 36 women (36%), with a 1.78:1 ratio of men to women. The median age of males was 55 years (IQR: 41-70), whereas that of females was 53 years (IQR: 34-60). This was not a statistically significant difference ($p = 0.914$). Among the studied patients, most (69%) had no known comorbidities (NKCM). The most common single comorbidities were HTN (11%), DM (6%), and IHD (4%). Combinations were less frequent: HTN+DM (7%) and DM+HTN+IHD (3%). Due to small numbers in each category, no statistical associations of comorbidities with MDS subtypes were assessed.

Based on the WHO 2017 classification, the most common subtype was MDS-unclassifiable (MDS-U), observed in 38 patients (38%). MDS with excess blasts-1 (MDS-EB1) and MDS with excess blasts-2 (MDS-EB2) were seen in 21 (21%) and 20 (20%) patients, respectively. Other subtypes included MDS with single-lineage dysplasia (MDS-SLD) in 7 patients (7%), MDS with multilineage dysplasia (MDS-MLD) in 11 patients (11%), and MDS with isolated del(5q) in 3 patients (3%).

According to IPSS-R, 54% of patients were at intermediate risk, 24% at high risk, 14% at low risk, and 8% at very high risk; no patients were classified as very low risk (**Table I**). The remaining patients were distributed across very low-, high-, and very high-risk categories.

Table I: Characteristics of MDS patients based on the WHO 2017 classification

Characteristics	MDS-U	MDS EB-1	MDS EB-2	Isolated del(5q)	MDS–SLD	MDS-MLD	p-value
Patients n(%)	38 (38%)	21 (21%)	20 (20%)	3 (3%)	7 (7%)	11(11%)	-
Female n(%)	15 (41.67)	4 (11.11)	5 (13.89)	2 (5.56)	3 (8.33)	7 (19.44)	0.099[a]
Male n(%)	23 (35.94)	17 (26.56)	15 (23.44)	1 (1.56)	4 (6.25)	4 (6.25)	
Age, years	54.0 (43.0–64.3)	56.0 (33.5–73.0)	53.5 (30.5–60.0)	62.0 (40.0)	54.0 (52.0–73.0)	60.0 (43.0–70.0)	0.748[b]
Hb, g/dL mean ± SD	7.82 ± 2.11	8.35 ± 2.00	8.35 ± 1.68	7.17 ± 2.61	7.99 ± 2.56	7.70 ± 1.53	0.800[c]
WBC ×10⁹/L, median (IQR)	3.73 (2.15–6.56)	3.40 (2.17–5.89)	2.69 (1.84–4.78)	5.60 (5.19)	4.10 (1.70–6.09)	2.58 (1.80–4.65)	0.28[b]
ANC ×10⁹/L, median (IQR)	1.68 (0.65–4.98)	0.96 (0.28–2.25)	0.66 (0.29–1.47)	2.30 (1.79)	0.69 (0.10–3.29)	1.26 (0.25–2.01)	0.300[b]
Plt ×10⁹/L, median (IQR)	54 (29–147)	34 (24–82)	35.5 (19–75)	353 (179)	96 (76–246)	66 (25–202)	0.020[b]*
Abnormal karyotype	8 (30.8%)	6 (23.1%)	7(26.9%)	2 (7.7%)	0	3 (11%)	0.255[a]
Normal karyotype	30 (40%)	15 (20.3%)	13(17.6%)	1 (1.4%)	7 (9.5%)	8 (10.8%)	
IPSS-R low	8 (57.1%)	1 (7.1%)	0	1 (7.1%)	2 (14.3%)	2 (14.3%)	0.050[a]
IPSS-R intermediate	23 (42.6%)	10 (18.5%)	10 (18.5%)	2 (3.7%)	3 (5.6%)	6 (11.1%)	
IPSS-R high	7 (29.2%)	8 (33.3%)	5 (20.8%)	0	2 (8.3%)	2 (8.3%)	
IPSS-R very high	0	2 (25%)	5 (62.5%)	0	0	1 (12.5%)	

***Abbreviations**: Hb, Hemoglobin; WBC, White Blood Cells; ANC, Absolute Neutrophil Count; Plt, Platelet; IPSS-R, Revised International Prognostic Scoring System*

*a: Fisher-Freeman-Halton Exact test, b: Kruskal-Wallis test, c: ANOVA, * Statistically significant*

No statistically significant associations were found between WHO subtype classification and various laboratory parameters. These included lactate dehydrogenase (LDH) levels (n = 41; p = 0.063), C-reactive protein (CRP) levels (n = 37; p = 0.676), mean platelet volume (MPV; n = 76; p = 0.174), and absolute lymphocyte count (ALC; n = 60; p = 0.908). The median IPSS-R score was 4.5 (IQR: 3.5–5.0). Age distribution did not differ significantly across IPSS-R categories (p = 0.399). However, significant associations were observed between IPSS-R and total leukocyte count (p = 0.006), hemoglobin (p < 0.001), platelet count (p = 0.019), and absolute neutrophil count (p = 0.002). **Figure 1** illustrates the median values and interquartile ranges of key hematologic parameters across the various IPSS-R risk categories.

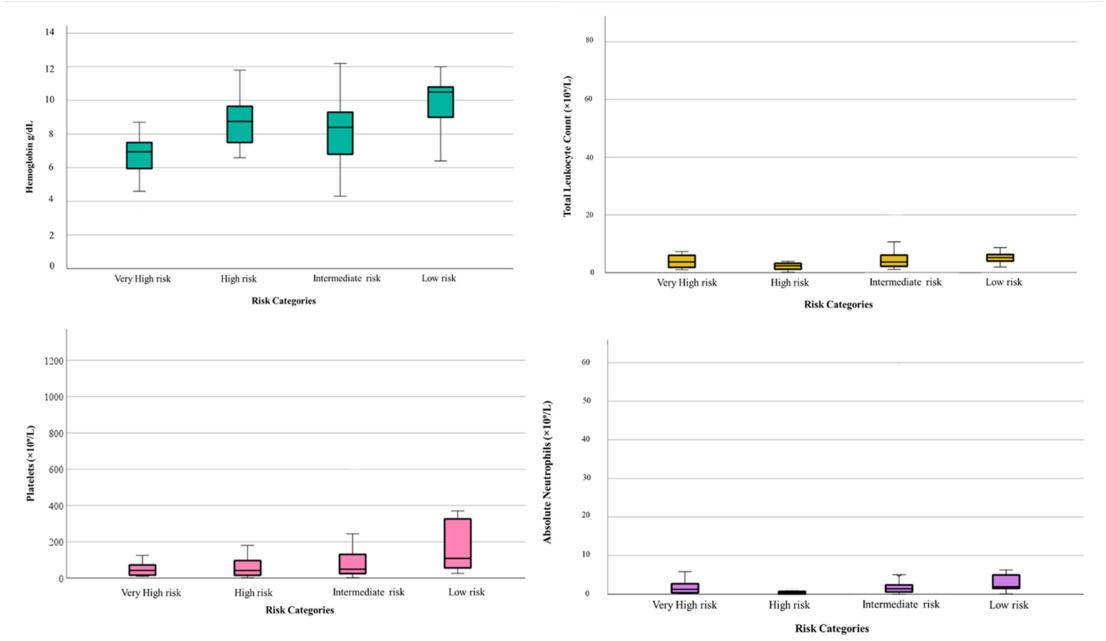

Figure 1: The median and interquartile ranges of blood parameters across risk categories.

Other laboratory parameters showed no significant association with IPSS-R. LDH (p = 0.770), CRP (p = 0.416), MCV (p = 0.881), and ALC (p = 0.658) did not correlate significantly with risk category. For example, among high-risk patients, 14 had LDH > 220 U/L, and 4 had LDH < 220 U/L; 10 had CRP > 5 mg/L, and 3 had CRP < 5 mg/L. Similarly, 5 patients in the high-risk group had MCV >100fL, and 20 had MCV <100fL. ALC >1.2 x 10^9/L was found in 14 high-risk patients, while 10 had ALC <1.2 x 10^9/L. The median overall survival in this MDS cohort was 24 months. Kaplan-Meier analysis (**Figure 2**) was used to assess OS by MDS subtype. Among 100 patients, 34 deaths occurred, and 66 patients remained alive till last follow-up. Median OS could be reliably estimated only for disease subtypes with a sufficient number of events. The median OS of patients with EB-2 was 13.2 months, whereas that of patients with SLD was markedly longer at 50.4 months. For the remaining subtypes (MDS-U, EB-1, MLD, and del(5q)), less than 50% of patients had an event during follow-up; thus, the median OS was not reached (NR). Overall survival was significantly different across subtypes (log-rank p = 0.003). These data suggest that EB-2 has the worst survival, whereas lower-risk subtypes such as SLD have better outcomes. However, this data needs to be interpreted cautiously in light of the limited number of events available within smaller subgroups.

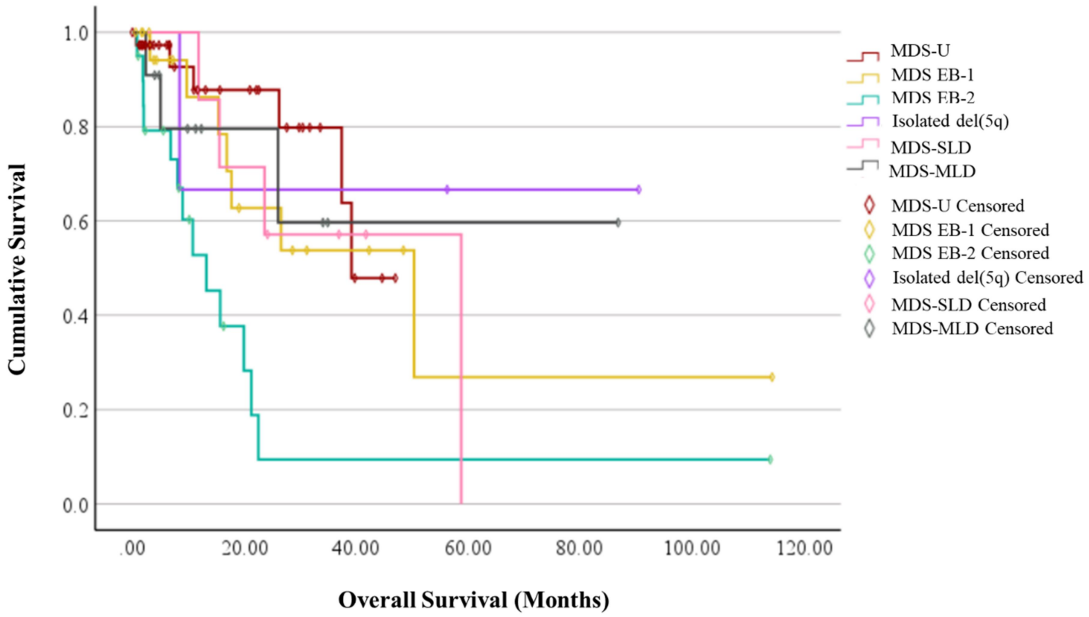

Figure 2: Kaplan–Meier curves depicting overall survival of patients stratified by WHO-defined MDS subtypes. Overall survival is shown in months, with censoring events indicated by diamond-shaped markers

Furthermore, stratified analysis showed that specific haematological parameters were important prognostic factors, particularly in the high-risk IPSS-R group. The median survival of patients who had platelets count less than 50 x 10^9/L and ANC less than 0.8 x 10^9/L had a median survival of 16 months. It is worth noting that those patients whose hemoglobin levels were 8 to less than 10 g/dL recorded the lowest outcomes, as they died within 8 months.

DISCUSSION

The present work investigating 100 de novo MDS cases highlighted that the combination of IPSS-R scoring with WHO 2017 classification was effective in the stratification of clinical characteristics and outcomes. The demographic trend, i.e., a median age of 54 years, indicates a slightly earlier starting age than most Western series (median age ~70 years)[12]. Epidemiological investigations further support that the median age of MDS onset is approximately 76 years, with more than 80% of cases being diagnosed at the age of 60 years and above[12,13], while others report a median of about 70 years[14,15]. The median age of diagnosis in another cohort, under 50 years, was estimated at 43 years[16,17].

Our study findings are notable regarding the distribution of WHO subtypes. MDS with MLD, which is typically the largest single category in large series, accounted for only 11% in our cohort, with MDS U (unclassifiable) unusually high at 38%. Comparisons with other populations often reveal only approximately 6–7% MDS U[18]. This difference may result from more common borderline dysplasia at our centre or referral bias. The review notes the low frequency of MDS-U and hypothesizes several contributing factors, including differences in diagnosis and classification. Of most significance, variability in diagnosis within institutions results in misclassification of borderline or doubtful cases, where these are classified as MDS-U rather than clearer subtypes. Such misclassification may lead to an overestimation of MDS-U case prevalence.

In addition, variations in the diagnostic criteria applied in MLD are likely to influence the occurrence of subtypes profoundly. MDS-MLD is likely to be identified as one of such categories. Nevertheless, cut-offs for classifying dysplasia in MLD are likely to be non-conformant and may require less stringent criteria for at least two lineages. These stringent criteria reduce the number of cases classifiable as MLD, so more of these cases are likely to be considered unclassifiable. This interplay between the diagnostic criteria is pivotal in the classification and prevalence of MDS-U. This divergence in classification thresholds most likely explains the increased Incidence described. Furthermore, MDS-U might include a heterogeneous range of cases of unknown biological and genetic features, especially if cases with recently recognized genetic or epigenetic alterations whose implications have not yet been entirely explained or classified are included.

Examination of these factors may shed light on the aetiology of the over-representation of MDS U in our series and whether any change in diagnostic practice, population demographics, or classification systems could account for the observation. The subtype of distinct biology also conformed to the anticipated pattern: pure del(5q) MDS was rare (3%), and all such individuals (a few) were transfusion-dependent but did not transform during follow-up. Notably, del(5q) MDS is recognized as a favorable prognosis subtype in the WHO system, often responding well to lenalidomide[19,20]. It was observed herein that the few del(5q) cases had relatively stable disease (median survival > 24 months). By IPSS-R, the cohort skewed toward intermediate and higher risk: 54% intermediate, 32% high/very-high. This contrasts with some Western countries where lower-risk categories predominate.

In line with the patterns of cytogenetic abnormalities outlined by Jiang and colleagues, patients of Asian origin with MDS are more often represented in higher-risk IPSS-R categories and have different cytogenetic abnormalities, which include fewer del(5q), TET2, SF3B1 mutations characteristic of Western tissues and more trisomy 8, del(20q), U2AF1, and ETV6 abnormalities[5]. The same trends are evident in the study of Chinese and Western patients. Chinese patients possessed significantly more isolated del(20q), trisomy 8, and complex karyotypes, and fewer normal karyotypes, del(5q), and -Y abnormalities[7].

In our cohort, the predominance of intermediate- and high/very-high-risk IPSS-R groups mirrored a higher representation of poor-risk cytogenetics and a relative scarcity of favorable-

risk profiles, closely resembling the cytogenetic profile reported in Asian populations rather than Western series. This observation suggests potential regional genetic, environmental, or healthcare system influences, reinforcing the need for larger regional studies to understand these distinctions better.

Furthermore, the recent MENA review reported ~45.8% in the very-low/low group and only ~36% in the high/very-high group, whereas our study reported only 14% in the lowest group. The higher-risk profile likely explains our relatively short median survival of ~2 years. We confirmed that higher IPSS-R risk strongly correlated with shorter survival ($p < 0.001$) and with worse cytopenias (p-values ranging from 0.002 to 0.019 for various blood counts). These findings are consistent with the established prognostic power of the IPSS-R. Our survival results align with known MDS outcomes: lower-risk MDS patients typically have a median survival of several years, whereas high-risk patients often have <3 years survival[14]. In our study, severe anemia and thrombocytopenia were poor prognostic signs.

In prior studies, thrombocytopenia, including severe cases with platelet counts $<30 \times 10^9$/L (present in about 7.1% of patients), has been associated with a significantly worse prognosis[21,22]. Furthermore, Severe thrombocytopenia (platelet count $< 30 \times 10^9$/L), observed in approximately 7% of patients, was associated with markedly reduced survival (median OS: 16 vs 71 months; HR = 4.66; $P < 0.0001$)[23]. Broader thresholds (platelets $<100 \times 10^9$/L) have also been linked to median survival of approximately 9 months[24]. Similarly, severe neutropenia (ANC $< 0.5 \times 10^9$/L), present in 4% of low/intermediate-1 IPSS-stratified patients, was associated with significantly worse outcomes (OS: 28 vs 66 months; HR = 2.19; $P < 0.0001$)[25]. The second outcome, which was also an intermediate neutropenia (ANC $< 0.8 \times 10^9$/L), is a predictor of poor survival and suggests that multilineage cytopenia compounds risk.

This research presents necessary regional data that validate the high prevalence of MDS-U and its early onset, and that require region-specific epidemiological models and harmonized diagnostic criteria. It also stresses that, even in the absence of access to molecular testing, IPSS-R, alongside conventional cytopenic indices, remains an acceptable method of risk stratification and clinical decision-making. In the future, classification based on molecular data using the IPSS-M is more prognostically informative and better suited for reclassification in mixed patient populations[26-28]. Serial follow-up over time of patients with MDS-U also accounts for their diagnostic course, and dynamical modelling of time-evolving cytopenias, such as the initial platelet course, can improve prognostic performance[29,30]. Lastly, multicenter South Asian studies would confirm genetic or environmental regional determinants of heterogeneity of MDS subtypes and early onset and increased statistical power.

This research has limitations, including its single-site context and a restricted sample size, which could significantly affect external validity. However, by applying WHO categories and citing modern literature, this research provides a balanced, contextually appropriate evaluation of prognostication in MDS. While next-generation studies based on molecular risk stratification models, such as the IPSS-M, are likely to improve anticipated accuracy, the IPSS-R and WHO systems remain the current gold standard for daily clinical use.

CONCLUSION

This 100 de novo MDS patient examination confirms again that the integration of WHO-classified morphological classification and IPSS-R risk stratification provides a strong foundation for clinical assessment. For our centre, the younger age at presentation and exceedingly high proportion of MDS-U cases highlight the importance of region-specific epidemiologic patterns. Despite these geographically different variations and possible cohort-specific characteristics that may affect absolute survival outcomes, the prognostic hierarchy tested remained valid; higher IPSS-R risk categories and higher levels of cytopenias were associated with significantly worse survival, consistent with the literature. Detection of favorable-prognosis subgroups, such as single del(5q), and routine application of IPSS-R guidance informed therapeutic decision and counseling of patients. While molecular-integrated tools such as IPSS-M may become useful to enhance risk stratification in the future, our findings establish the continued utility and practicality of the WHO classification and IPSS-R in routine MDS practice. Potential confounding factors, including age, disease subtype, and comorbidities, should be considered when interpreting survival outcomes.

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AUTHOR CONTRIBUTION

Shaikh S: Substantial contributions to the conception or design of the work, manuscript title and manuscript writing.
Anwar N: Drafting the work, sample collection, data analysis and final approval of the version to be published.
Mushtaq S: Substantial contributions to the conception or design of the work, drafting the work, manuscript title, manuscript writing, critical review and final approval of the version to be published.
Fatima N: Data analysis and SPSS statistics.
Jammal Q: Critical review of the article and final approval of the version to be published.

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