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Clinical outcomes of WHO 2022 and ICC MDS entities with risk stratification by IPSS-R and IPSS-M

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Running heads: WHO 2022/ICC MDS outcomes with IPSS-R/-M

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Data availability statement

The deidentified datasets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

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Author contributions

Conceptualization and design: YK, Y-JK and MK. Patient data and samples: DK, SYP, SP and Y-JK. Review pathologic and genetic analysis: JJ, HSK, J-ML, AA, YK and MK. Review clinical data: SP and Y-JK. Experiments, collections, and assembly of data: DK, BB, JJ, HSK, J-ML, AA, JSY and SYP. Data analysis and interpretation: DK, BB, YK, Y-JK and MK. Manuscript writing and editing: DK, BB, Y-JK and MK. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

The classification and prognostic stratification of myelodysplastic neoplasms (MDS) are undergoing substantial refinement, driven by the integration of molecular genetic data with established morphologic assessment. In 2022, two major diagnostic frameworks were introduced: the 5th edition of the World Health Organization classification (WHO2022) and the International Consensus Classification (ICC)(1, 2). Both are designed to provide globally applicable, evidence-based definitions of MDS entities, facilitating a shared diagnostic language for clinical care and research. Apart from the above disease classification, there has been a significant shift in the risk stratification model predicting survival and leukemia progression in MDS, which also emerged in 2022. The Molecular International Prognostic Scoring System (IPSS-M) was introduced(3), with its enhanced predictive capabilities over the previous revised IPSS (IPSS-R) primarily attributed to the incorporation of molecular genetic alterations(4). To explore how these frameworks function in practice, we retrospectively reclassified a large single-center cohort of Korean patients with MDS−originally diagnosed according to WHO2016−under both WHO2022 and ICC criteria. We then examined how outcomes varied within each classification and assessed the prognostic performance of IPSS-R and IPSS-M when applied within those diagnostic categories.

The study included 639 adult MDS patients per WHO2016 criteria aged 18 years or older who were treated at Seoul St. Mary's Hospital, a national tertiary referral and transplant center, between 2007 and 2022. Patients were enrolled if they had available next-generation sequencing (NGS) data from untreated samples and complete clinical, pathologic, and cytogenetic information. The Institutional Review Board of the Catholic Medical Center approved this study (KC18TESE0700). The analyses were conducted in accordance with the guidelines of the Institutional Review Board and followed the ethical principles outlined in the Declaration of Helsinki. The diagnosis was independently re-reviewed by five experienced hematopathologists and reclassified into new classifications considering additional genetic information. The baseline characteristics of the patients are summarized in Table 1. The median age was 58 years (range 18–88), and 380 (59.5%) were male. Patients with therapy-related MDS were included; this subgroup comprised 5.3% of the cohort. Disease-modifying therapy−including lenalidomide, hypomethylating agents, or allogeneic hematopoietic stem cell

transplantation (HSCT)−was given to 388 patients (60.7%). Cytogenetic analysis was performed using conventional G-banding techniques, with abnormalities reported according to the 2024 International System for Human Cytogenetic Nomenclature(5). Fluorescence in situ hybridization assays targeted common recurrent alterations, including del(5q), del(20q), chromosome 7 abnormalities, *MECOM* rearrangement, and *TP53* deletion. NGS used the St. Mary's customized 87-gene myeloid panel, and variants were classified in accordance with the Association for Molecular Pathology guidelines and somatic oncogenicity criteria(6). Variants with at least 20 supporting reads and variant allele frequency (VAF) ≥5% were considered pathogenic; known driver hotspot mutations were included even if below this VAF threshold. All detected *DDX41* mutations underwent germline confirmation via buccal DNA testing(7). Multiplex ligation-dependent probe amplification was used to identify *KMT2A* partial tandem duplications.

Among the 639 enrolled patients, 25 subjects(3.9%) were classified as AML by WHO2022 due to *KMT2A*, *MECOM*, and *NUP98* rearrangements or an *NPM1* mutation. Six(0.9%) were classified as clonal cytopenia of undetermined significance (CCUS) and 17(2.7%) as chronic myelomonocytic leukemia (CMML). The remaining 592(92.6%) had MDS, including 80(13.5%) as 'MDS with defining genetic abnormalities' and 512(86.5%) as 'morphologically-defined MDS' (Figure 1). By ICC, 5 patients(0.8%) were classified as AML, 7(1.1%) as CCUS, and 17(2.7%) as CMML. Of the 610(95.5%) defined as MDS, 81(13.3%) were assigned to the distinct subgroup MDS/AML. In direct comparison, WHO2022 classified 19 additional cases as AML due to low blast counts. Except for cases with *TP53* mutation, most patients in the ICC-defined MDS/AML category were classified as MDS with increased blasts-2 (MDS-IB2) under WHO2022 (n=68, 95.9%). Another key difference lies in the definition of MDS with BM blast <5%: WHO2022 applies BM cellularity, whereas ICC relies on the number of dysplastic lineages. The proportion of hMDS within MDS, not otherwise specified, with single lineage dysplasia (MDS-NOS-SLD) and with multilineage dysplasia (MDS-NOS-MLD) did not differ significantly (18/77, 23.4% vs. 55/251, 21.2%). In our cohort, the distribution of MDS subtypes was largely consistent with previous large unselected series including hypoplastic MDS (hMDS)(8-10).

Of all 639 enrolled patients, pathogenic mutations were detected in 446(69.8). These included 153(23.9%) with one mutation, 129(20.2%) with two mutations, and 164 subjects(25.7%) with three or more mutations. Nine genes were mutated in more than 5% of patients: *ASXL1* (n=120), *U2AF1* (n=114), *DDX41* (n=58), *TP53* (n=56), *RUNX1* (n=55), *SF3B1* (n=47), *DNMT3A* (n=45), *TET2* (n=43), and *STAG2* (n=31). Among the 193 patients without a detectable mutation, 105 had karyotypic abnormalities, resulting in 551(86.2%) with at least one genetic abnormality. Among the 592 patients with MDS classified by WHO2022, 410(69.3%) had at least one mutation. Of the 182 without a detectable mutation, 96 had karyotypic abnormalities, giving a total of 506(85.5%) with genetic abnormalities. Of the 610 MDS cases classified by ICC, mutations were detected in 425(69.7%), and 524(85.9%) had either mutations or karyotypic abnormalities. This frequency is somewhat lower than the 80–90% reported in Western cohorts(11) but is comparable to other Asian series, where overall mutation rates are 60–70% and *SF3B1* mutations are notably less frequent(12). Conversely, *ASXL1* and *U2AF1* were among the most common drivers, consistent with prior Asian reports(13).

After excluding patients classified as CCUS, CMML, or AML within each system, survival analysis was conducted in 592 patients by WHO2022 and 610 by ICC. Both classifications significantly discriminated overall survival (OS) and leukemia-free survival (LFS) (Supplementary Figures S1A–D). The worst outcomes were seen in MDS-bi*TP53 (*median OS 1.0 year) and MDS with increased blasts and fibrosis (MDS-F)(1.0 year) by WHO2022, and MDS/AML-*TP53* (0.9 year) and MDS-*TP53* (1.0 year) by ICC. The most favorable outcomes were observed in MDS with low blasts (MDS-LB) (median not reached [NR]) and hMDS (14.6 years) in WHO2022, and MDS-NOS-SLD (median NR) in ICC. Consistently, MDS-*SF3B1* (9.8 years) and MDS-5q (9.3 years) showed prolonged survival in both systems. LFS showed similar patterns to OS. Also, when we assessed IPSS-R and IPSS-M in 592 WHO2022-defined MDS patients, both systems showed effective discrimination against survival (Supplementary Figures S1E–H). However, IPSS-M demonstrated superior predictive ability, with a statistically higher Harrell's C-index (0.751 vs 0.713, $p<0.001$)(14), and further stratified prognosis within the same IPSS-R groups (Supplementary Figures S1I-M).

To further clarify prognostic capabilities of diagnostic classifications, we integrated WHO2022 with IPSS-R and IPSS-M. When analyzing the distribution of IPSS-M-based risk groups within each WHO2022 category, the ‘very low’ and ‘low’ risk groups constituted the majority of the MDS-5q, MDS-*SF3B1*, hMDS, and MDS-LB subsets (Figures 2A-D). Conversely, MDS-bi*TP53* and MDS-F were classified as ‘very high’ risk by the IPSS-M (Figures 2E-H). The prognostic utility of IPSS-M was more pronounced in MDS-LB, MDS-IB1, and MDS-*SF3B1* categories. For other MDS categories, the discriminatory power of IPSS-M seemed to largely be limited by an inadequate number of patients. Supplementary Figure S2 displays the IPSS-R/IPSS-M risk categories by WHO2022 classification.

In addition, we assessed the survival impact of newly defined subcategories within WHO2022 and ICC by Cox models adjusted for sex, IPSS-M, and HSCT (Supplementary Table S1). In WHO2022, newly defined category MDS-F showed poorer median OS (1.0 year) than MDS-IB1 (6.1 years) and MDS-IB2 (3.2 years) (Supplementary Figure S1A), but fibrosis was not an independent prognostic factor in multivariable model (adjusted HRs vs. MDS-IB1: MDS-IB2, 1.12 [95% CI 0.69–1.85]; MDS-F, 1.44 [95% CI 0.64–3.23]). In patients with lower blast counts, no significant difference was observed in hMDS, a recently identified entity, compared to MDS-LB (adjusted HR 1.24 [95% CI 0.74–2.08]). In ICC, survival did not differ between MDS-NOS-SLD and MDS-NOS-MLD (adjusted HR 1.17 [95% CI 0.67–2.04]). Similarly, no differences were observed among MDS/AML subcategories (MDS/AML with MDS-related cytogenetic abnormalities and MDS/AML-NOS vs. MDS/AML with MDS-related gene mutations: adjusted HR 2.08 [95% CI 0.77–5.65] and 1.38 [95% CI 0.56–3.37], respectively). Finally, within the *TP53*-mutated subsets, survival was comparable between MDS-*TP53* and MDS/AML-*TP53*(adjusted HR of MDS/AML-*TP53* vs. MDS-*TP53*: 0.81 [95% CI 0.29–2.29]).

This study clarified the role of contemporary MDS classifications in clinical practice and highlights the complementary but distinct functions of diagnostic classification and prognostic scoring. Both WHO2022 and ICC provided meaningful population-level outcome discrimination, while IPSS-M demonstrated superior prognostic accuracy across morphologically defined subgroups(9). Importantly, *TP53*-mutated categories consistently showed the poorest outcomes, reaffirming their distinct

significance. After adjustment for IPSS-M (and HSCT where applicable), morphologic features such as hypocellularity, fibrosis, and the number of dysplastic lineages did not retain independent prognostic value. Although morphology-defined entities such as hMDS and MDS-F retain value beyond prognosis—clarifying the differential diagnosis with related mimics (e.g., aplastic anemia and primary myelofibrosis) and, in selected patients, informing entity-aligned management (e.g., immunosuppression in hMDS), our findings underscore the need to refine the interface between diagnostic classification and prognostic scoring models(15).

This retrospective, single-center analysis spans a long accrual period and has a relatively short follow-up. Our cohort skews older with a high proportion of HSCT recipients and small numbers in several subgroups. Nevertheless, our results offer actionable guidance: WHO2022/ICC remain indispensable for disease definition and biologic categorization, whereas IPSS-M provides the most reliable patient-level survival prediction—including within diagnostic entities. Moreover, morphology-defined features contribute little independent prognostic information once IPSS-M is considered. Taken together, further refinements should integrate molecularly defined categories, more closely with prognostic modeling to improve risk stratification and ultimately guide therapeutic strategies.

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Table 1. Baseline characteristics

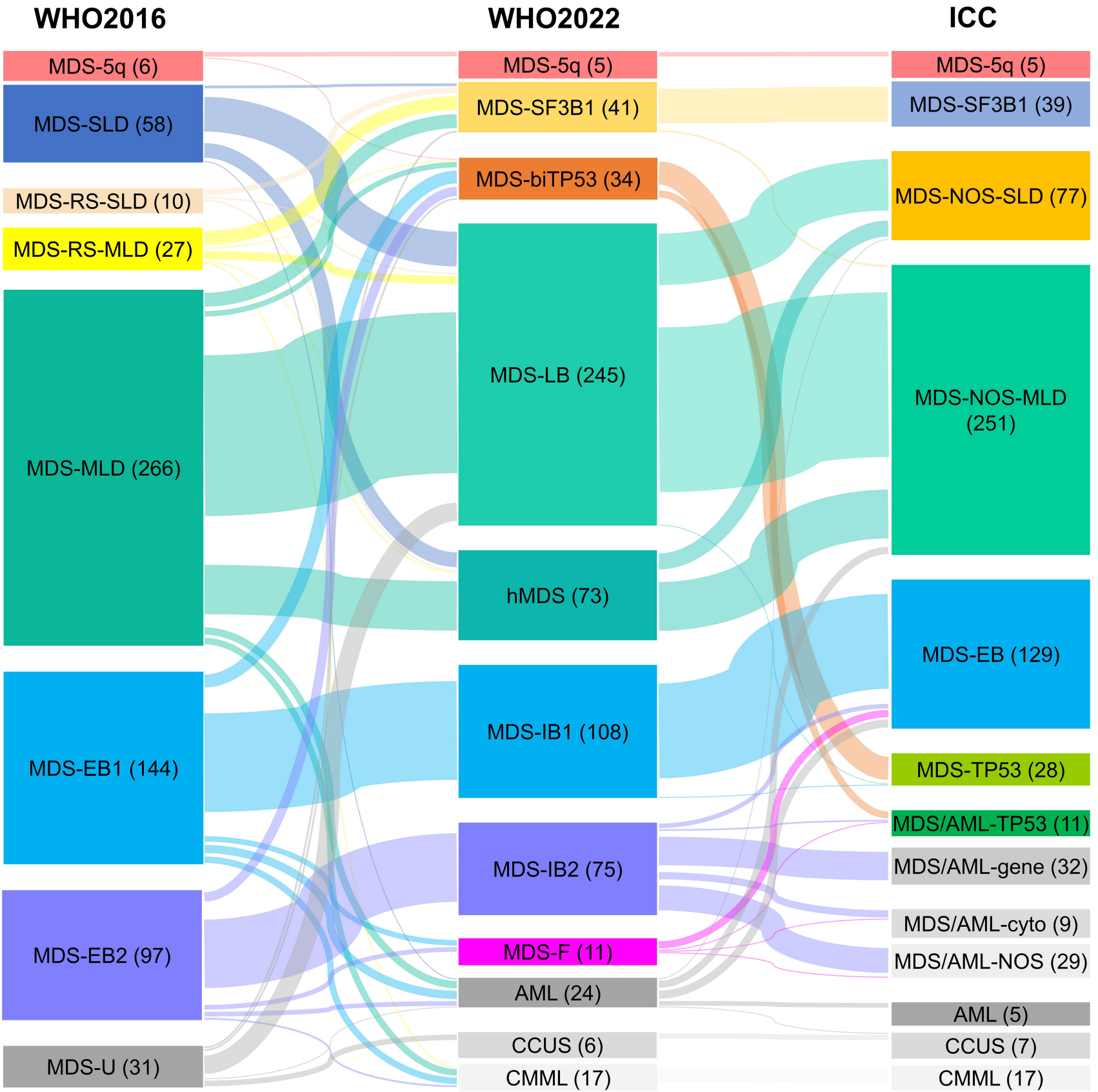
Characteristics	Total, n=639
Median age, years (range)	58 (18-88)
Male sex, n (%)	380 (59.5)
Cytogenetic risk groups by IPSS-R, n (%)	
Very good	19 (3.0)
Good	360 (56.3)
Intermediate	162 (25.4)
Poor	38 (5.9)
Very poor	60 (9.4)
IPSS-R category, n (%)	
Risk groups	
Very low	47 (7.4)
Low	189 (29.6)
Intermediate	188 (29.4)
High	113 (17.7)
Very high	102 (16.0)
Risk score	
< 4	314 (49.1)
≥ 4	325 (50.9)
IPSS-M category, n (%)	
Risk groups	
Very low	28 (4.4)
Low	151 (23.6)
Moderate low	99 (15.5)
Moderate high	89 (13.9)
High	115 (18.0)
Very high	117 (18.3)
Risk score	
≤ 0	278 (43.5)
> 0	321 (50.2)
Undetermined	40 (6.3)
RBC Transfusion dependency, n (%)	213 (33.3)
Treatment modalities, n (%)	
Supportive care	251 (39.3)
Lenalidomide	2 (0.3)
HMA	214 (33.5)
Allogeneic HSCT	308 (38.2)
Leukemic transformation, n (%)	115 (18.0)
Survivors, n (%)	380 (59.5)
Median follow-up duration*, years (95% confidence interval)	4.5 (4.2-4.9)

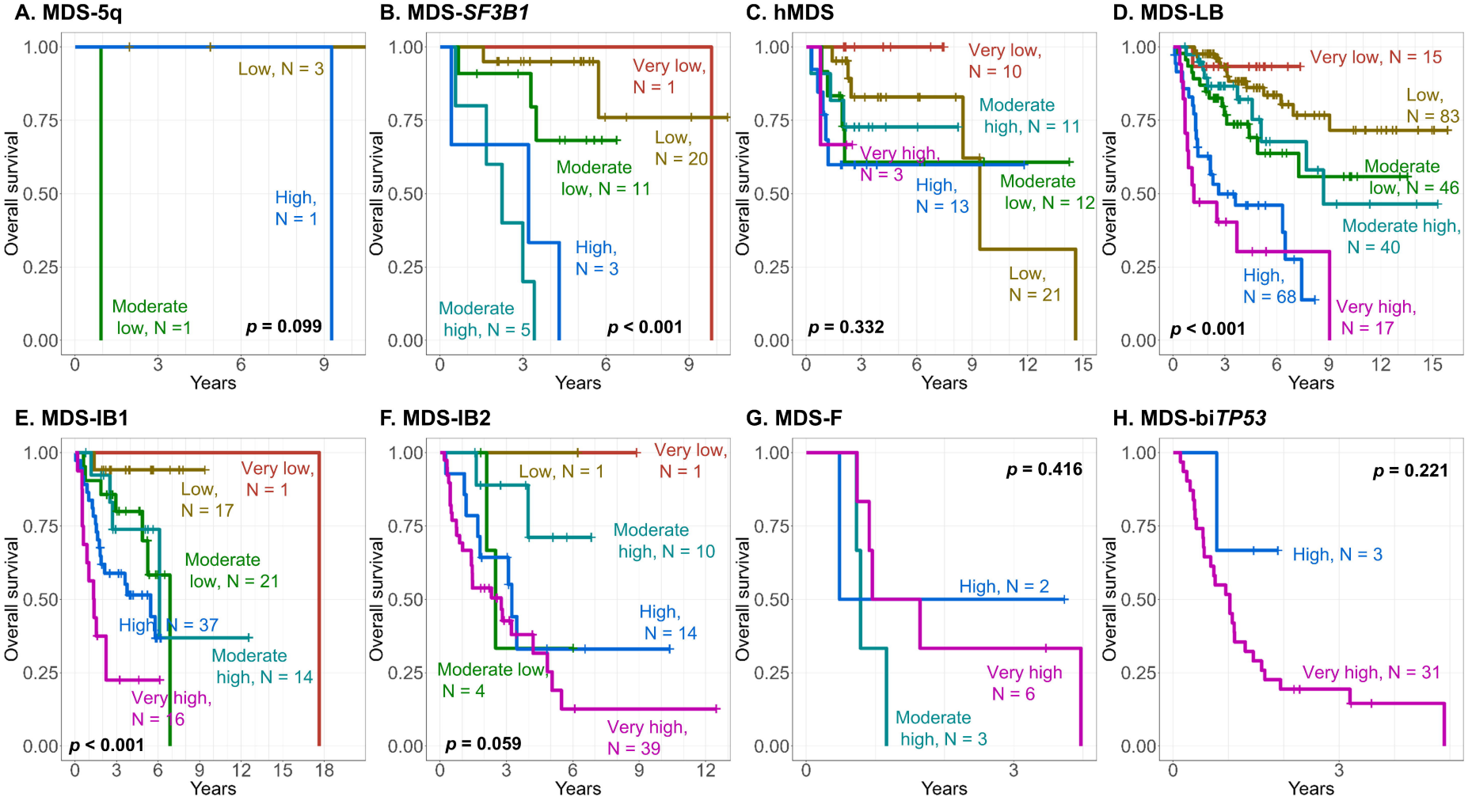
*Estimated by reverse Kaplan-Meier method.
IPSS-R Revised International Prognostic Scoring System, HMA Hypomethylating agent, HSCT hematopoietic stem cell transplantation. RBC Red blood cell

Figure legends

Figure 1. Redistribution of MDS patients according to WHO2016, WHO2022 and ICC classifications. MDS myelodysplastic neoplasm, WHO World Health Organization classification, ICC International Consensus Classification, MDS-5q MDS with low blasts and 5q deletion, MDS-SLD MDS with single-lineage dysplasia, MDS-RS MDS with ring sideroblasts, MDS-MLD MDS with multilineage dysplasia, MDS-EB1 MDS with excess blasts-1, MDS-EB2 MDS with excess blasts-2, MDS-U MDS, unclassifiable, MDS-SF3B1 MDS with low blasts and *SF3B1* mutation, MDS-biTP53 MDS with biallelic *TP53* inactivation, MDS-LB MDS with low blasts, hMDS MDS, hypoplastic, MDS-IB1 MDS with increased blasts-1, MDS-IB2 MDS with increased blasts-2, MDS-F MDS with increased blasts and fibrosis, AML acute myeloid leukemia, CCUS clonal cytopenia of undetermined significance, CMML chronic myelomonocytic leukemia, NOS not otherwise specified, MDS-TP53 MDS with mutated *TP53*, MDS/AML-gene MDS/AML with myelodysplasia-related gene mutations, MDS/AML-cyto MDS/AML with myelodysplasia-related cytogenetic abnormalities.

Figure 2. Overall survival according to IPSS-M within each WHO2022 category. IPSS-M Molecular International Prognostic Scoring System, MDS myelodysplastic neoplasm, WHO World Health Organization classification, MDS-5q MDS with low blasts and 5q deletion, MDS-SF3B1 MDS with low blasts and SF3B1 mutation, MDS-biTP53 MDS with biallelic TP53 inactivation, MDS-LB MDS with low blasts, hMDS MDS, hypoplastic, MDS-IB1 MDS with increased blasts-1, MDS-IB2 MDS with increased blasts-2, MDS-F MDS with increased blasts and fibrosis.


WHO2016
WHO2022
ICC
MDS-5q (6)
MDS-SLD (58)
MDS-RS-SLD (10)
MDS-RS-MLD (27)
MDS-MLD (266)
MDS-EB1 (144)
MDS-EB2 (97)
MDS-U (31)
MDS-5q (5)
MDS-SF3B1 (41)
MDS-biTP53 (34)
MDS-LB (245)
hMDS (73)
MDS-IB1 (108)
MDS-IB2 (75)
MDS-F (11)
AML (24)
CCUS (6)
CMML (17)
MDS-5q (5)
MDS-SF3B1 (39)
MDS-NOS-SLD (77)
MDS-NOS-MLD (251)
MDS-EB (129)
MDS-TP53 (28)
MDS/AML-TP53 (11)
MDS/AML-gene (32)
MDS/AML-cyto (9)
MDS/AML-NOS (29)
AML (5)
CCUS (7)
CMML (17)


A. MDS-5q
Overall survival
Years
Low, N = 3
High, N = 1
Moderate low, N =1
p = 0.099
B. MDS-SF3B1
Very low, N = 1
Low, N = 20
Moderate low, N = 11
High, N = 3
Moderate high, N = 5
p < 0.001
C. hMDS
Very low, N = 10
Moderate high, N = 11
Very high, N = 3
High, N = 13
Moderate low, N = 12
Low, N = 21
p = 0.332
D. MDS-LB
Very low, N = 15
Low, N = 83
Moderate low, N = 46
Moderate high, N = 40
High, N = 68
Very high, N = 17
p < 0.001
E. MDS-IB1
Very low, N = 1
Low, N = 17
Moderate low, N = 21
High, N = 37
Moderate high, N = 14
Very high, N = 16
p < 0.001
F. MDS-IB2
Very low, N = 1
Low, N = 1
Moderate high, N = 10
High, N = 14
Moderate low, N = 4
Very high, N = 39
p = 0.059
G. MDS-F
p = 0.416
High, N = 2
Very high N = 6
Moderate high, N = 3
H. MDS-biTP53
p = 0.221
High, N = 3
Very high, N = 31

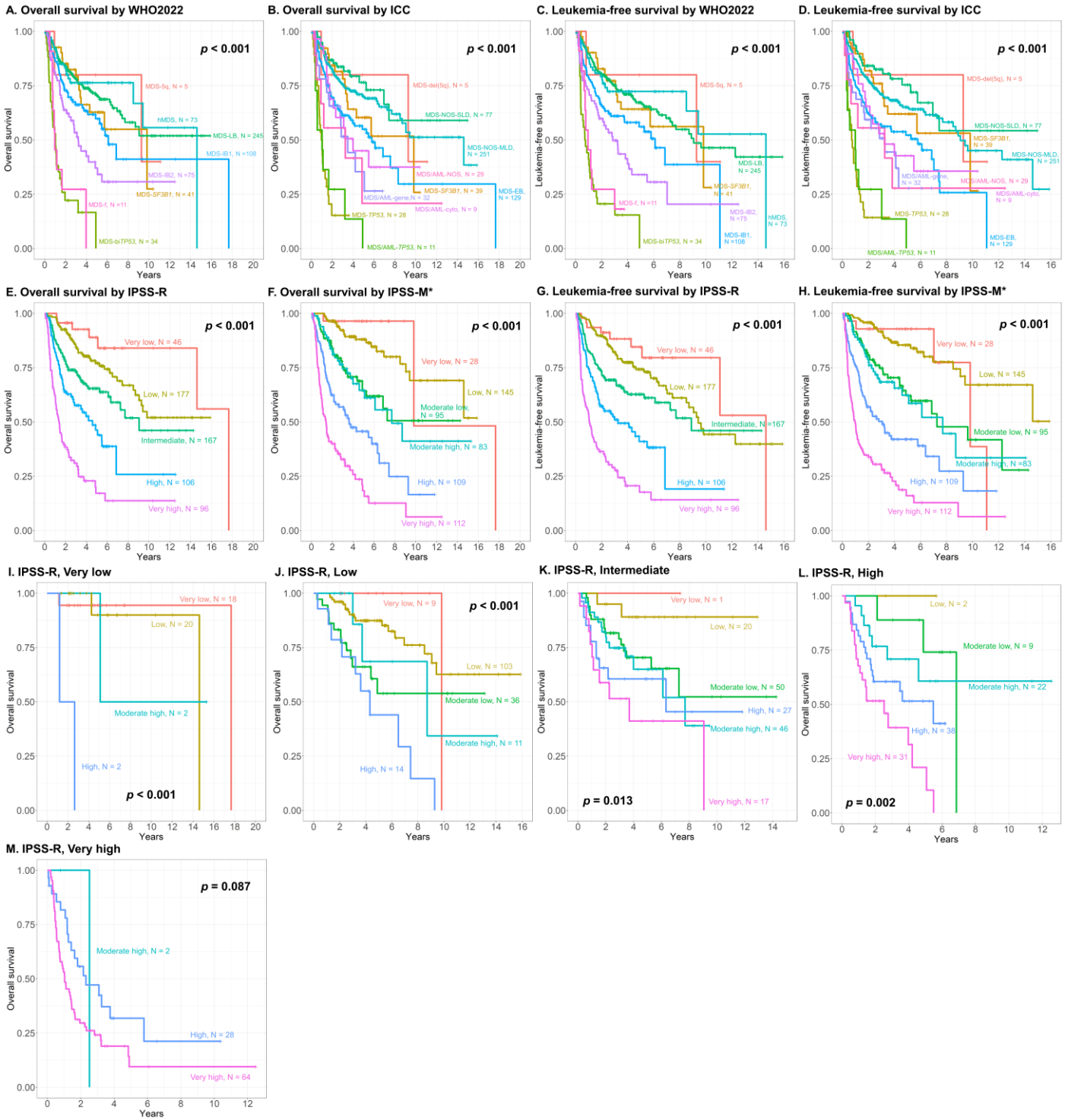
Supplementary Table S1. Multivariate survival analysis for overall survival in various MDS subgroups.

Subgroup	MDS-IB and MDS-F (WHO2022)		MDS-LB and hMDS (WHO2022)		MDS-NOS-SLD and MDS-NOS-MLD (ICC)		MDS/AML-gene, cyto, NOS (none *TP53* mutated) (ICC)		MDS-TP53 and MDS/AML-*TP53* (ICC)	
	HR (95% CI)	*P*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex (Female)	0.64 (0.39-1.06)	0.077	0.61 (0.96-0.95)	0.027	0.63 (0.40-0.99)	0.039	0.92 (0.40-2.11)	0.843	0.89 (0.41-1.93)	0.767
IPSS-M (per 1)	1.77 (1.45-2.16)	< 0.001	2.09 (1.74-2.50)	< 0.001	1.59 (1.71-2.46)	< 0.001	1.72 (1.16-2.54)	0.006	1.28 (0.66-2.48)	0.447
HSCT†	0.36 (0.23-0.56)	< 0.001	0.62 (0.39-0.97)	0.037	0.56 (0.37-0.95)	0.030	0.21 (0.09-0.45)	< 0.001	0.42 (0.19-0.93)	0.029
Subtype		0.677		0.415		0.582		0.371		0.693
IB1	1.0		LB 1.0		SLD 1.0		gene 1.0		MDS 1.0	
IB2	1.12 (0.69-1.85)	0.635	hypoplastic 1.24 (0.74-2.08)		MLD 1.17 (0.67-2.04)		cyto 2.08 (0.77-5.65)	0.149	MDS/AML 0.81 (0.29-2.29)	
F	1.44 (0.64-3.23)	0.373					NOS 1.38 (0.56-3.37)	0.484		

†This variable was treated as time-dependent variable.

MDS myelodysplastic neoplasm, WHO World Health Organization classification, ICC International Consensus Classification, MDS-SLD MDS with single-lineage dysplasia, MDS-MLD MDS with multilineage dysplasia, MDS-LB MDS with low blasts, hMDS MDS, hypoplastic, MDS-IB1 MDS with increased blasts-1, MDS-IB2 MDS with increased blasts-2, MDS-F MDS with increased blasts and fibrosis, NOS not otherwise specified, MDS-TP53 MDS with mutated *TP53*, MDS/AML-gene MDS/AML with myelodysplasia-related gene mutations, MDS/AML-cyto MDS/AML with myelodysplasia-related cytogenetic abnormalities. IPSS-M Molecular International Prognostic Scoring System, HSCT hematopoietic stem cell transplantation, HR hazard ratio, CI confidence interval

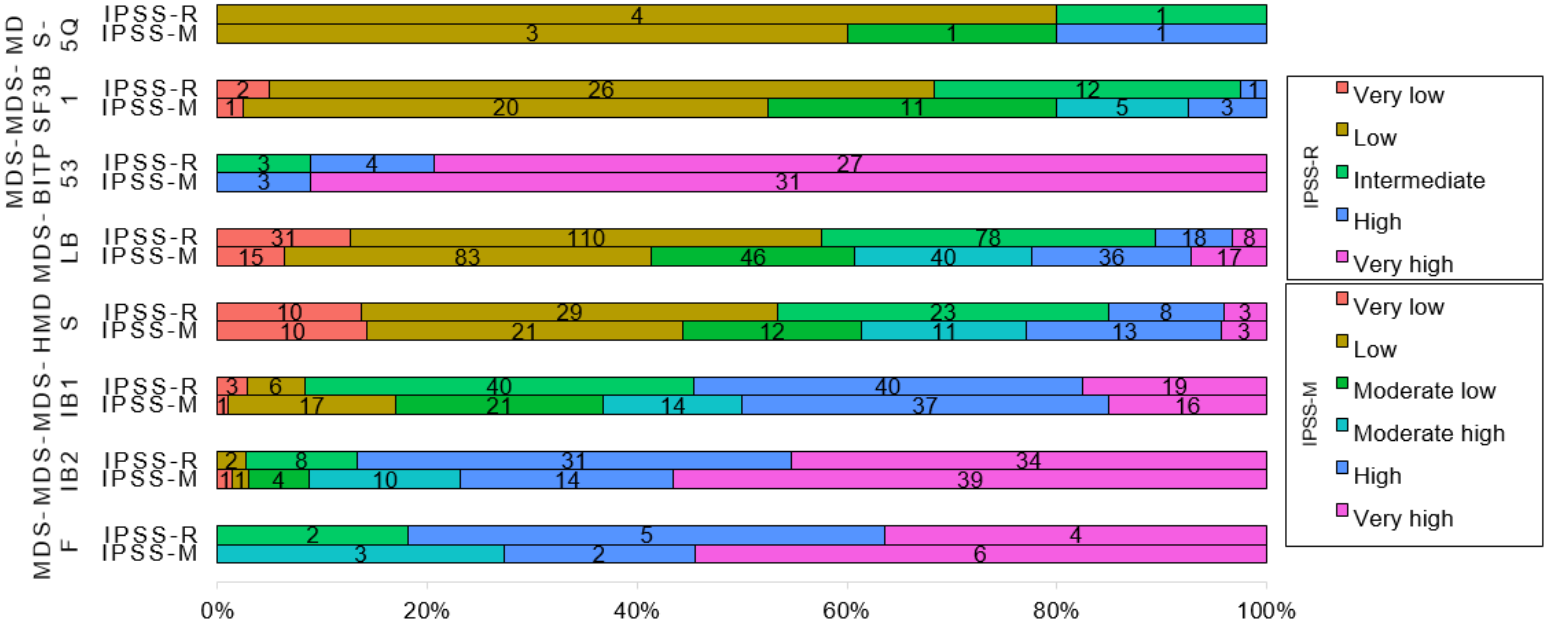
Supplementary Figure S1. Survival outcomes of myelodysplastic neoplasms according to WHO2022, ICC, IPSS-R, and IPSS-M classifications. (A–B) Overall survival stratified by WHO2022 and ICC. (C–D) Leukemia-free survival stratified by WHO2022 and ICC. (E–F) Overall survival stratified by IPSS-R and IPSS-M. (G–H) Leukemia-free survival stratified by IPSS-R and IPSS-M. (I–M) Overall survival by IPSS-M within each IPSS-R risk group.



*20 patients were excluded due to limited genetic information

ICC: The International Consensus classification, IPSS-M: Molecular International Prognostic Scoring System, IPSS-R: revised International Prognostic Scoring System, WHO2022: 2022 World Health Organization classification.

Supplementary Figure S2. The distribution of IPSS-R/IPSS-M risk categories across WHO2022 classifications



IPSS-M Molecular International Prognostic Scoring System, IPSS-R Revised International Prognostic Scoring System, MDS myelodysplastic neoplasm, MDS-5q MDS with low blasts and 5q deletion, MDS-SF3B1 MDS with low blasts and SF3B1 mutation, MDS-biTP53 MDS with biallelic TP53 inactivation, MDS-LB MDS with low blasts, hMDS MDS, hypoplastic, MDS-IB1 MDS with increased blasts-1, MDS-IB2 MDS with increased blasts-2, MDS-F MDS with increased blasts and fibrosis.