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Reclassification of Myelodysplastic Neoplasms According to the 2022 World Health Organization Classification and the 2022 International Consensus Classification Using Open-Source Data: Focus on *SF3B1*- and *TP53*-Mutated Myelodysplastic Neoplasms

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Background: In 2022, the WHO and International Consensus Classification (ICC) published diagnostic criteria for myelodysplastic neoplasms (MDSs). We examined the influence of the revised diagnostic criteria on classifying MDSs in a large population.

Methods: We retrieved an open-source pre-existing dataset from cBioPortal and included 2,454 patients with MDS in this study. Patients were reclassified based on the new diagnostic 2022 WHO and ICC criteria. Survival analysis was performed using Cox regression to validate the new criteria and to assess risk factors.

Results: Based on the 2022 WHO criteria, 1.4% of patients were reclassified as having AML. The 2022 WHO criteria provide a superior prognostic/diagnostic model to the 2017 WHO criteria (Akaike information criterion, 14,152 vs. 14,516; concordance index, 0.705 vs. 0.681). For classifying MDS with low blast counts and *SF3B1* mutation, a variant allele frequency cut-off of 5% (2022 WHO criteria) and the absence of *RUNX1* co-mutation (2022 ICC criteria) are diagnostically relevant. For classifying MDSs with mutated *TP53*, a blast count cut-off of 10% (2022 ICC criteria) and multi-hit *TP53* (2022 WHO criteria) are independent risk factors in cases with ≥10% blasts.

Conclusions: Our findings support the refinements of the new WHO criteria. We recommend the complementary use of the new WHO and ICC criteria in classifying *SF3B1*- and *TP53*-mutated MDSs for better survival prediction.

Key Words: Information sources, International Consensus Classification, Myelodysplastic syndromes, *SF3B1*, *TP53*, WHO Classification

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INTRODUCTION

The WHO Classification of the diagnostic criteria for hematologic malignancies was revised in 2022 [1]. Meanwhile, clinical advisory committees developed the International Consensus Classification (ICC) of myeloid neoplasms (MNs) and acute leukemias [2]. The coexistence of two new diagnostic classification systems has led to confusion among many clinicians [3]. Numerous re-

searchers have investigated the reclassification of diagnostic entities according to the new criteria by recruiting and examining patient cohorts [4-8]. However, these studies often had a limited sample size.

The cBioPortal for Cancer Genomics is an open-source resource developed at the Memorial Sloan Kettering Cancer Center (New York, NY, USA) and hosted on GitHub (https://www.cbioportal.org/). It contains large-scale cancer genomics data and clinical profiles of various cancer types. The 2022 WHO and 2022 ICC diagnostic criteria for myelodysplastic neoplasms (MDSs, referred to as myelodysplastic syndromes in the previous WHO classification and current ICC) are similar in some aspects but differ in others. Using cBioPortal open-source data, we reclassified patients diagnosed with MDSs using the 2017 WHO criteria based on the 2022 WHO criteria and examined the differences in diagnoses. In addition, we compared the 2022 WHO and 2022 ICC diagnostic criteria in classifying two genetics-based MDS subtypes, *SF3B1*- and *TP53*-mutated MDS, which are newly introduced MDS subtypes with different definitions between the 2022 WHO and ICC criteria.

MATERIALS AND METHODS

Study population

We retrieved a dataset from a study by Bernard, *et al*. [9], which includes 2,957 representative MDS samples, because this dataset includes information on copy number variations of the *TP53* locus, which is essential for the diagnosis of MDS with biallelic *TP53* inactivation (MDS-bi*TP53*) according to the 2022 WHO criteria, from cBioPortal. Exclusion criteria included myelodysplastic/myeloproliferative neoplasms, unspecified diagnosis, and discrepancy between the diagnosis and copy number variation. The dataset does not describe dysplastic lineage. Thirty-nine patients with MDS, unclassifiable (MDS-U), who harbored an MDS-defining abnormality were omitted because, without information on dysplasia, these patients may have been classified as MDS-U based on defining cytogenetic abnormality. MDS-U, based on defining cytogenetic abnormality, is reclassified as clonal cytopenia of undetermined significance (CCUS) in the 2022 WHO criteria. Finally, 2,454 patients with MDS were included in the study. The flow of patient selection is summarized in Supplemental Data Fig. S1.

The study was exempt from approval by the Institutional Review Board of Chung-Ang University College of Medicine (Seoul,

Table 1. Comparison of the 2022 WHO and 2022 ICC diagnostic criteria in classifying MDS subtypes with *SF3B1* or *TP53* mutations

MDS subtype	Commonalities	Differences	
		2022 WHO	ICC
MDS-*SF3B1*$^{WHO/ICC}$	≥1 dysplastic lineage and cytopenia each Blasts: <5% BM, <2% PB Cytogenetics: absence of del(5q), -7/del(7q), or CK Mutations: absence of biallelic *TP53*	Erythroid lineage dysplasia is required Mutations: ≥5% VAF of *SF3B1*	Cytogenetics: absence of abn3q26.2 Mutations: ≥10% VAF of *SF3B1*, absence of *RUNX1*
MDS-LB-RS with wild-type *SF3B1*^{WHO}		Satisfied for MDS-*SF3B1*^{WHO} except for *SF3B1*$_{mut}$ ≥15% RS	Not defined and included in MDS, NOS
MDS-bi*TP53*^{WHO}/MDS with mutated *TP53*^{ICC}		≥1 dysplastic lineages and cytopenias Blasts: <20% BM and PB Genetics: ≥2 *TP53* mutations, or one mutation with evidence of *TP53* copy number loss or cnLOH	Not stated for dysplastic lineage/cytopenia Blasts: 0%–9% BM and PB Genetics: >10% VAF of *TP53*$_{mut}$ (prerequisite), 2 distinct *TP53*$_{mut}$ or 1 *TP53*$_{mut}$ with (1) del(17p) on cytogenetics (2) VAF>50% (3) cnLOH at *TP53* locus or (N/A for *TP53* locus LOH status) CK often with del(17p)
MDS/AML with mutated *TP53*^{ICC}		Not defined Cases with 10–19% blasts and biallelic *TP53* inactivation are classified as MDS-bi*TP53*	Blasts: 10%–19% BM and PB Any somatic *TP53* mutation (VAF>10%)

Abbreviations: ICC, International Consensus Classification; BM, bone marrow; PB, peripheral blood; CK, complex karyotype; del, deletion; VAF, variant allele frequency; abn, abnormality; LB, low blasts; RS, ring sideroblasts; NOS, not otherwise specified; cn, copy-neutral; LOH, loss of heterozygosity; mut, mutation; N/A, not available.

Korea) because it relied solely on open-source data. Patients were diagnosed according to the 2017 WHO [10] and 2022 WHO [11] classifications. The ICC criteria [2] were applied in diagnosing *SF3B1*- and *TP53*-mutated MDSs. Table 1 summarizes the commonalities and differences between the two criteria.

Statistical analyses

Continuous variables are expressed as medians and interquartile ranges, and categorical variables as numbers and percentages. Validation of the 2017 and 2022 WHO classifications and assessment of risk factors were conducted using Cox proportional-hazards models; hazard ratios (HRs) were calculated with 95% confidence intervals (CIs), and the Akaike information criterion (AIC) and concordance index (C-index) with standard errors (SEs) were derived. The Kaplan–Meier method and log-rank test were used to estimate overall survival and to evaluate differences among groups. All statistical analyses were performed using R software, version 4.2.3. Statistical significance was set at $P < 0.05$.

RESULTS

Reclassification of MDSs according to the 2022 WHO classification

The demographics of the 2,454 patients with MDSs are presented in Table 2. The median values for haemoglobin concentration, platelet count, and absolute neutrophil count were 9.6 g/dL, 127×10^9/L, and 1.8×10^9/L, respectively. The reclassification of the patients based on the 2022 WHO classification is summarized in Table 3. In total, 35 patients previously classified as having MDSs were reclassified as having AML because they harbored AML-defining genetic abnormalities irrespective of blast count, as follows: *DEK*::*NUP214* (N = 1), *KMT2A* rearrangement (N = 3), *MECOM* rearrangement (N = 5), and *NPM1* mutation (N = 26). As the information on erythroid lineage dysplasia was unavailable, cases in which *SF3B1* was mutated and ring sideroblast counts were < 5% or not assessed were considered "presumed MDS with low blasts and *SF3B1* mutation" ("MDS-*SF3B1*^{2022}").

Validation of the 2017 and 2022 WHO classifications in patients with MDSs

The results of survival analyses according to the 2017 and 2022 WHO classifications are presented in Supplemental Data Fig. S2A and S2B. Cox proportional-hazards models adjusted for sex, age, ontogeny, subtypes, and treatment revealed that the 2022

Table 2. Demographics of the study population

Characteristics	N (%)
Age (yrs)*	72 (63, 78)
Female sex	975 (39.7)
Ontogeny	
Primary	2185 (89.0)
Secondary/therapy-related	207 (8.4)
NA	62 (2.5)
WHO 2017 classification	
MDS-del(5q)	139 (5.7)
MDS-SLD	191 (7.8)
MDS-MLD	639 (26.0)
MDS-SLD/MLD†	91 (3.7)
MDS-RS-SLD	246 (10.0)
MDS-RS-MLD	212 (8.6)
MDS-RS-SLD/MLD†	3 (0.1)
MDS-EB-1	458 (18.7)
MDS-EB-2	429 (17.5)
MDS-U	46 (1.9)
IPSS-R	
Very low	383 (15.6)
Low	917 (37.4)
Intermediate	482 (19.6)
High	312 (12.7)
Very high	253 (10.3)
NA	107 (4.4)
IPSS-M	
Very low	302 (12.3)
Low	746 (30.4)
Moderately low	258 (10.5)
Moderately high	244 (9.9)
High	325 (13.2)
Very high	430 (17.5)
NA	149 (6.1)
Disease-modifying treatment	
None	1662 (67.7)
Lenalidomide alone	140 (5.7)
HMAs‡	377 (15.4)
Intensive chemotherapy§	28 (1.1)
Transplantation‖	247 (10.1)

*Ages are presented as median with interquartile range; data for one patient was missing.
†"MDS-SLD/MLD" and "MDS-RS-SLD/MLD" indicate that the number of dysplastic lineages was not specified, based on the pre-existing diagnosis assigned by Bernard, *et al*. [9].
‡HMAs (plus lenalidomide).
§Intensive chemotherapy (plus HMAs).
‖Hematopoietic stem cell transplantation (plus lenalidomide, HMA, or intensive chemotherapy).
Abbreviations: NA, not assessed; -del(5q), with isolated del(5q); -SLD, with single lineage dysplasia; -MLD, with multilineage dysplasia; -RS, with ring sideroblasts; -EB, with excess blasts; MDS-U, MDS, unclassifiable; IPSS-R, Revised International Prognostic Scoring System; IPSS-M, Molecular International Prognostic Scoring System; HMAs, hypomethylating agents.

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Table 3. Reclassification of patients with MDS using the 2022 WHO diagnostic criteria

MDS subtype	2022 WHO classification									
	MDS-5q	MDS-bi*TP53*	MDS-*SF3B1*	Presumed MDS-*SF3B1*	MDS-LB	MDS-LB-RS	MDS-IB1	MDS-IB2	AML	N (%)
2017 WHO classification										
MDS-del(5q)	134	5	0	0	0	0	0	0	0	139 (5.7)
MDS-SLD	0	4	0	22	165	0	0	0	0	191 (7.8)
MDS-MLD	0	32	0	39	561	0	0	0	7	639 (26.0)
MDS-SLD/MLD*	0	3	0	4	83	0	0	0	1	91 (3.7)
MDS-RS-SLD	0	1	214	0	3	28	0	0	0	246 (10.0)
MDS-RS-MLD	0	14	135	0	14	48	0	0	1	212 (8.6)
MDS-RS-SLD/MLD*	0	1	1	0	0	1	0	0	0	3 (0.1)
MDS-EB-1	0	59	0	0	0	0	392	0	7	458 (18.7)
MDS-EB-2	0	79	0	0	0	0	0	331	19	429 (17.5)
MDS-U	0	1	2	7	36	0	0	0	0	46 (1.9)
N (%)	134 (5.5)	199 (8.2)	352 (14.6)	72 (3.0)	862 (35.7)	77 (3.2)	392 (16.2)	331 (13.7)	35	2,454

*"MDS-SLD/MLD" and "MDS-RS-SLD/MLD" indicate that the number of dysplastic lineages was not specified, based on the pre-existing diagnosis assigned by Bernard, *et al*. [9]
Abbreviations: -del(5q), with isolated del(5q); -SLD, with single lineage dysplasia; -MLD, with multilineage dysplasia; -RS, with ring sideroblasts; -EB, with excess blasts; MDS-U, MDS, unclassifiable; -5q, with low blasts and isolated 5q deletion, -bi*TP53*, with biallelic *TP53* inactivation; -*SF3B1*, with low blasts and *SF3B1* mutation;-LB, with low blasts; -IB, with increased blasts.

WHO criteria stratified patients with MDSs more effectively than the 2017 WHO criteria: AIC, 14,516; C-index, 0.681 (SE, 0.009) for 2017 WHO vs. AIC, 14,152; C-index, 0.705 (SE 0.009) for 2022 WHO (Supplemental Data Fig. S2C and S2D). Patients whose diagnosis was changed from MDS to AML according to the new criteria had a median overall survival of 1.4 yrs, which was the shortest overall survival (excluding patients with MDS-bi*TP53* or MDS-IB2). This finding suggests that the definition of AML in the 2022 WHO criteria is well established.

Subgroup analyses focusing on *SF3B1*-mutated MDS

To evaluate factors affecting survival in *SF3B1*-mutated MDS, a Cox proportional-hazards model adjusted for sex, age, ontogeny, treatment, type of *SF3B1* variants, variant allele frequency (VAF) of *SF3B1* variants, and *RUNX1* co-mutation was used. The distribution of *SF3B1* variants in patients with MDS-*SF3B1*^{WHO} is plotted in Supplemental Data Fig. S3. Most variants were missense variants, and the SF3B1 K700E variant was the most frequently observed. Compared with K700E alone, the other variants, including non-K700E variants and K700E plus non-K700E variants, did not affect survival (Fig. 1A; HR, 0.85; 95% CI, 0.59–1.21). To evaluate the ICC criteria, we performed subgroup analyses of MDS-*SF3B1*^{WHO}. *SF3B1* variants with a VAF < 5% are excluded in the diagnosis of MDS-*SF3B1* by the WHO. Compared with VAF ≥ 10%, 5% ≤ VAF < 10% did not affect survival (Fig. 1B; HR, 0.97; 95% CI, 0.30–3.12). In contrast, *RUNX1* co-mutation (including multiple mutations) was associated with a worse prognosis than wild-type *RUNX1* (Fig. 1C; HR, 3.63; 95% CI, 1.83–7.19).

Subgroup analyses focusing on *TP53*-mutated MDS

We classified *TP53*-mutated MDS samples according to the 2022 WHO and ICC criteria. The relationship between the two criteria is shown in Fig. 2. When the ICC criteria were applied, 199 patients with MDS-bi*TP53*^{WHO} were classified as MDS with mutated *TP53*^{ICC} (N = 103), MDS/AML with mutated *TP53*^{ICC} (N = 76), and others (N = 20). The last group of 20 patients, referred to as "others," harbored *TP53* mutations with a VAF ≤ 10%, and the majority (17/20, 85%) had < 10% blasts. Thus, 103 patients with MDS and mutated *TP53*^{ICC} and 76 patients with MDS/AML and mutated *TP53*^{ICC} harbored multi-hit *TP53* mutations with a VAF > 10%. Among 331 patients with MDS-IB2^{WHO}, 10 patients (3.0%) were classified as having MDS/AML with mutated *TP53*^{ICC} because they harbored single *TP53* mutations with VAF > 10%.

A Cox proportional-hazards model adjusted for sex, age, ontogeny, diagnosis, and treatment was used to evaluate the prognostic impact in patients with MDS with mutated *TP53*^{ICC} and

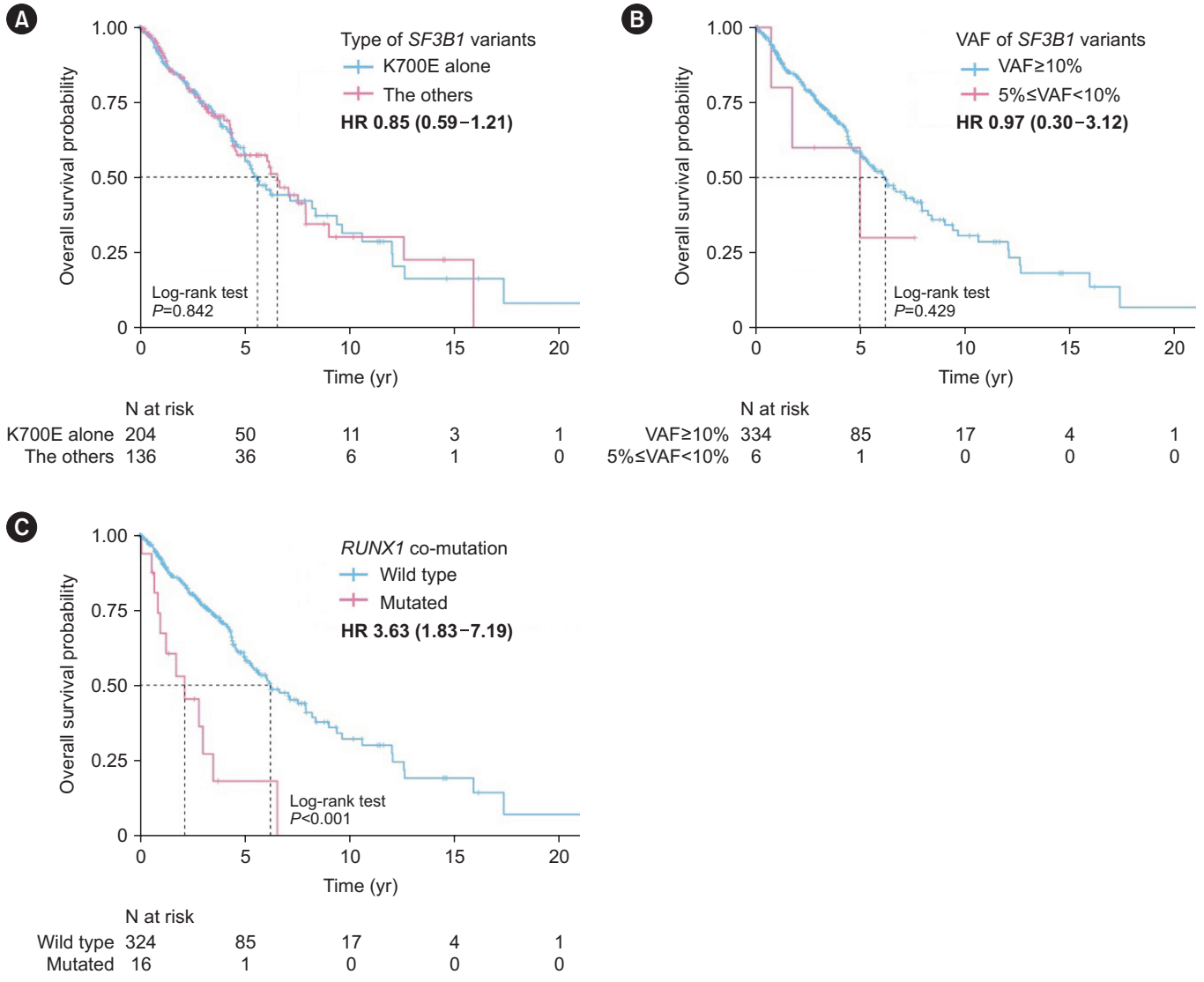

Fig. 1. Subgroup analyses in MDS-*SF3B1*^{WHO}. Kaplan–Meier curves of overall survival were plotted according to (A) type of *SF3B1* variants (K700E alone vs. others), (B) VAF of *SF3B1* variants (5%≤VAF<10% vs. VAF≥10%), and (C) *RUNX1* co-mutation (wild-type vs. mutated). HRs and 95% CIs were calculated using Cox proportional-hazards models adjusted for sex, age, ontogeny, treatment, type of *SF3B1* variants, VAF of *SF3B1* variants, and *RUNX1* co-mutation. The HR is shown with the 95% CI in parentheses.
Abbreviations: VAF, variant allele frequency; HR, hazard ratio; CI, confidence interval.

patients with MDS/AML with mutated *TP53*^{ICC}. Notably, patients with MDS/AML and mutated *TP53*^{ICC} (≥10% blasts) had a poorer prognosis than patients with MDS and mutated *TP53*^{ICC} (<10% blasts) (Fig. 3A, HR, 1.47; 95% CI, 1.04–2.08). Subgroup analysis of patients with MDS-bi*TP53*^{WHO} was performed using a Cox proportional-hazards model adjusted for sex, age, ontogeny, treatment, type of biallelic *TP53* inactivation, and VAF of *TP53* mutation. MDS-bi*TP53*^{WHO} can be diagnosed in cases harboring two or more mutations in *TP53* or one mutation with *TP53* locus loss or copy-neutral loss of heterozygosity (cnLOH). Patients with these two mutation types did not show a difference in survival: one *TP53* mutation with *TP53* locus loss or cnLOH vs. two or more mutations in *TP53*; HR, 1.30; 95% CI, 0.91–1.86 (Fig. 3B). Among patients with MDS-bi*TP53*^{WHO}, those with a VAF≤10% did not qualify for MNs with mutated *TP53*^{ICC}. Patients with a VAF>10% did not differ in survival compared with patients with VAF≤10% (Fig. 3C; HR, 1.55; 95% CI, 0.84–2.88). Patients with ≥10% blasts were categorized into three subgroups based on the combined 2022 WHO and ICC diagnoses: MDS-IB2^{WHO}|MDS/AML^{ICC} (N=321), MDS-IB2^{WHO}|MDS/AML with mutated

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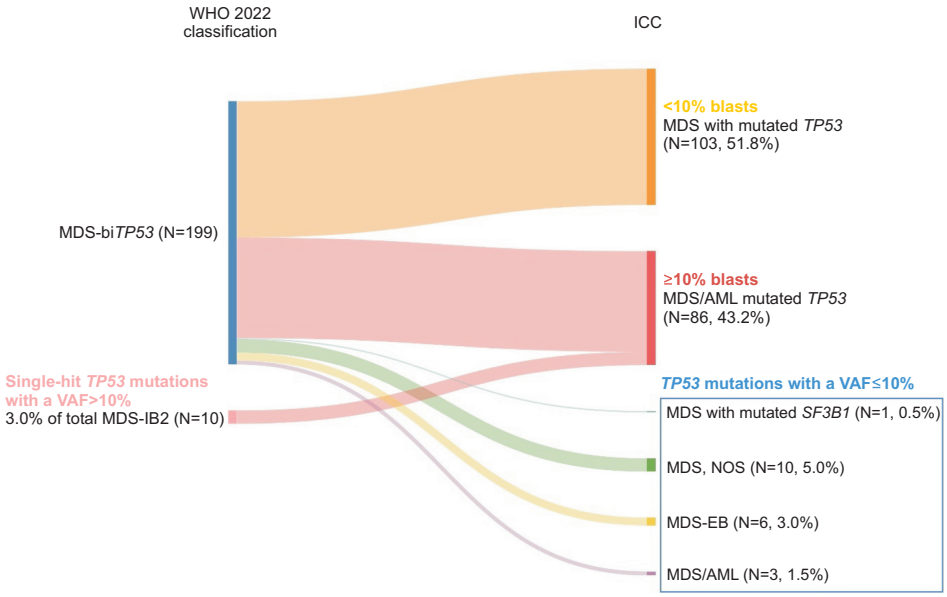

Fig. 2. Relationship between the 2022 WHO and ICC classifications focused on MDSs with mutated *TP53*.
Abbreviations: ICC, International Consensus Classification; VAF, variant allele frequency; -bi*TP53*, with biallelic *TP53* inactivation; -IB, with increased blasts; NOS, not otherwise specified; -EB, with excess blasts.

TP53^{ICC} (N=10), and MDS-bi*TP53*^{WHO}|MDS/AML with mutated *TP53*^{ICC} (N=76). MDS-IB2^{WHO}|MDS/AML with mutated *TP53*^{ICC} refers to cases with a single *TP53* mutation, which were relatively rare (2.5%) among patients with MDS with ≥10% blasts. Patients diagnosed as having MDS-bi*TP53*^{WHO}|MDS/AML with mutated *TP53*^{ICC} (*TP53* multi-hit) had a poorer prognosis than patients with MDS-IB2^{WHO}|MDS/AML^{ICC} (*TP53* wild-type, HR, 3.92; 95% CI, 2.85–5.39, Fig. 3D). Because of the small number of cases, a comparison with MDS-IB2^{WHO}|MDS/AML mutated *TP53*^{ICC} was not conducted.

DISCUSSION

Using a large open-source dataset, we reclassified MDS patients diagnosed based on the 2017 WHO criteria using the 2022 WHO criteria, and we focused on MDSs with mutated *SF3B1* and mutated *TP53* to compare the 2022 WHO and ICC criteria. MDS^{2017} changed to AML^{2022} or CCUS^{2022} in a subset of patients with MDS. MDS-U^{2017} is removed and allocated to specific MDS subtypes in the 2022 WHO classification. Zhang, *et al*. [4] compared the 2017 and 2022 WHO criteria in a cohort of 856 patients with MDSs and reclassified 30 patients (3.5%) previously diagnosed as having MDSs to having AML because they harbored *NPM1* mutations. In addition, among 21 patients with MDS-U^{2017}, nine patients (42.9%) were reclassified as having CCUS [4]. We validated the prognostic performance of the 2022 WHO criteria, which are superior to the previous criteria, using Cox proportional-hazards models adjusted for clinical variables.

The VAF cut-off for *SF3B1* mutation for the diagnosis of MDS-*SF3B1* is higher in the 2022 ICC criteria (10%) than in the 2022 WHO criteria (5%), and *RUNX1* co-mutation should be absent according to the ICC criteria (Table 1). Our study demonstrated that the VAF cut-off of 5% (2022 WHO criteria) and the absence of *RUNX1* co-mutation (2022 ICC criteria) are clinically relevant. However, the *SF3B1* variant type does not influence prognosis.

The 2022 WHO classification specifies MDS-bi*TP53* when the blast count is <20%, and AML with mutated *TP53* is not specified as a disease entity (Table 1). In contrast, the ICC defines a category termed "MNs with mutated *TP53*," which includes MDS (<10% blasts), MDS/AML (10%–19% blasts), and AML (≥20% blasts). In the ICC criteria, the *TP53* mutation status should be biallelic in MDS with mutated *TP53*, but it can be monoallelic or biallelic in MDS/AML with mutated *TP53* and AML with mutated *TP53* (Table 1). While the WHO does not specify a threshold for the VAF, the ICC mandates that the VAF for *TP53* mutations should be >10% (Table 1). In our study, when classifying *TP53*-mutated MDSs, using a blast cut-off of 10% (2022 ICC criteria) to distinguish MDS and MDS/AML was prognostically valuable. In MDS cases with blast counts ≥10%, *TP53* multi-hit (2022 WHO criteria) was an independent risk factor as compared with wild-type *TP53*. However, the *TP53* variant type within *TP53* multi-hit and a *TP53* VAF cut-off of 10% within MNs with mutated *TP53*^{ICC} were not prognostic indicators.

Our study had some limitations. First, the lack of information on bone marrow cellularity, fibrosis, and dysplastic lineage posed a challenge in the assessment of MDS, hypoplastic^{2022},

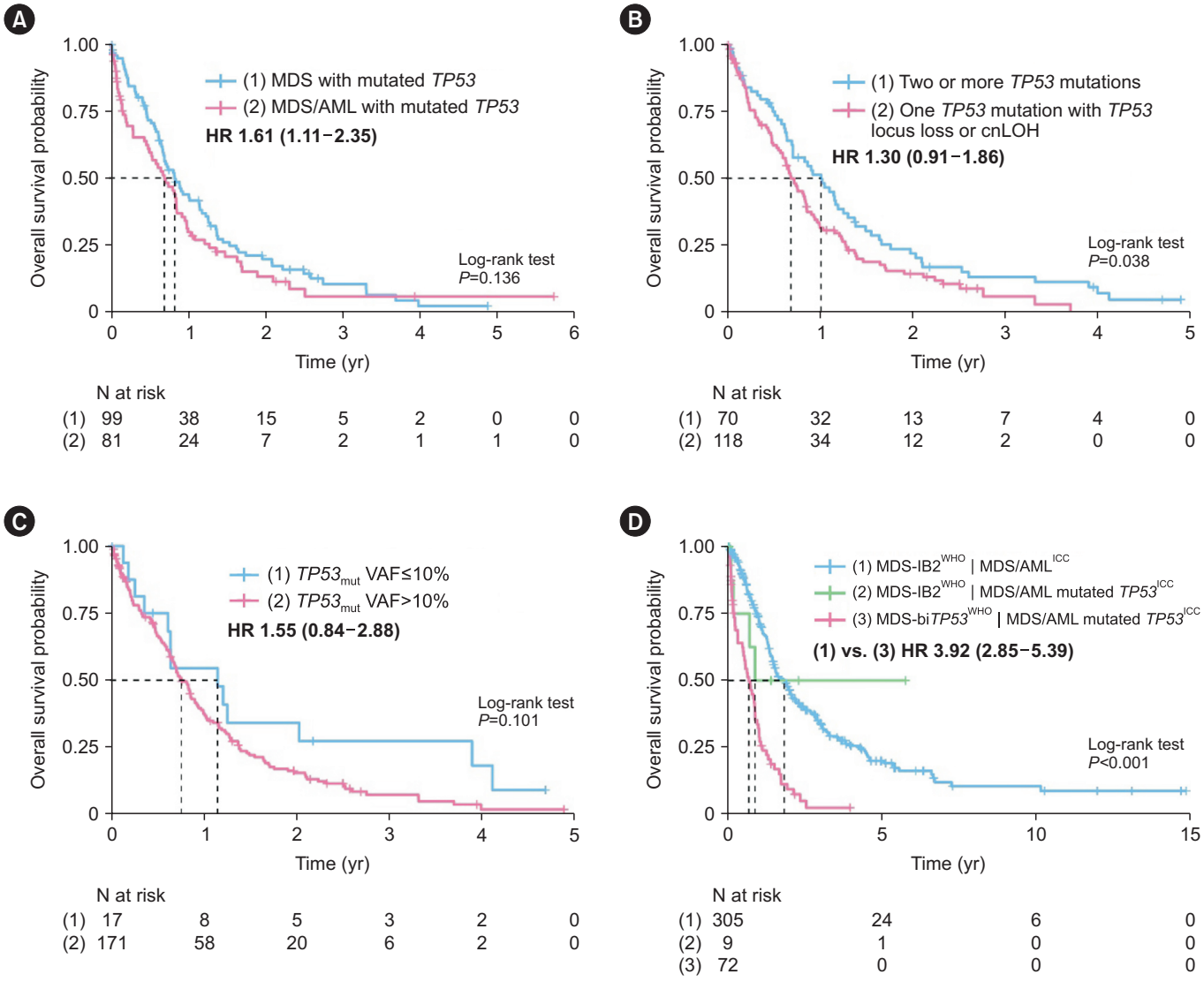

Fig. 3. Subgroup analyses of MDSs with mutated *TP53*. (A) Kaplan–Meier curves of overall survival were plotted for MDS with mutated *TP53*^{ICC} and MDS/AML with mutated *TP53*^{ICC}. The HR and 95% CI were calculated using a multivariate Cox regression model adjusted for sex, age, ontogeny, diagnosis, and treatment. Within MDS-bi*TP53*^{WHO}, Kaplan–Meier curves of overall survival were plotted according to (B) the type of biallelic *TP53* inactivation and (C) VAF of *TP53* mutations (whether the ICC diagnoses are MNs with mutated *TP53* or not). The HR and 95% CI were calculated using a multivariate Cox regression model adjusted for sex, age, ontogeny, treatment, type of biallelic *TP53* inactivation, and VAF of *TP53* mutations. (D) Within MDS cases with ≥10% blasts, Kaplan–Meier curves of overall survival were plotted in MDS-IB2^{WHO}|MDS/AML^{ICC}, MDS-IB2^{WHO}|MDS/AML with mutated *TP53*^{ICC}, and MDS-bi*TP53*^{WHO}|MDS/AML with mutated *TP53*^{ICC}. The HR and 95% CI were calculated using a multivariate Cox regression model adjusted for sex, age, ontogeny, treatment, and diagnosis. The HR is shown with the 95% CI in parentheses.

Abbreviations: ICC, International Consensus Classification; cnLOH, copy-neutral loss of heterozygosity; $TP53_{mut}$, *TP53* mutations; VAF, variant allele frequency; MNs, myeloid neoplasms;. -IB2, with increased blasts-2, -bi*TP53*, with biallelic *TP53* inactivation; HR, hazard ratio; CI, confidence interval.

MDS with increased blasts and fibrosis[2022], and MDS-*SF3B1*[2022], as well as the reclassification of MDS-U[2017]. This potentially introduced a selection bias and impacts the generalizability of our findings. Second, because this study relied on a pre-existing dataset, inherent biases were present. For example, the study population was biased toward European ethnicity, limiting the generalization of our results to other ethnicities. In the future, we aim to expand our analyses as more open-source data become available for other ethnicities. Finally, the observational and retrospective nature of this study limited the ability to establish causal relationships between variables.

In conclusion, our findings support the refinements of the

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2022 WHO classification of MDS. We comprehensively discussed the newly introduced *SF3B1*- and *TP53*-mutated MDSs according to the 2022 WHO and ICC. We advise clinicians to use both the 2022 WHO classification and ICC to appropriately diagnose patients with *SF3B1*- and *TP53*-mutated MDSs. Our study used well-validated open-source data and involved a significant number of patients, thereby ensuring both reliability and representativeness.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.3343/alm.2024.0079

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None.

AUTHOR CONTRIBUTIONS

Yun J and Kim HR designed the study; Yun J performed the research, analyzed the data, and wrote the original draft; Kim HR reviewed and revised the manuscript. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

CONFLICTS OF INTEREST

None declared.

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