Data-driven, harmonised classification system for myelodysplastic syndromes: a consensus paper from the International Consortium for Myelodysplastic Syndromes

Rami S Komrokji, Luca Lanino*, Somedeb Ball*, Jan P Bewersdorf*, Monia Marchetti, Giulia Maggioni, Erica Travaglino, Najla H Al Ali, Pierre Fenaux, Uwe Platzbecker, Valeria Santini, Maria Diez-Campelo, Avani Singh, Akriti G Jain, Luis E Aguirre, Sarah M Tinsley-Vance, Zaker I Schwabkey, Onyee Chan, Zhouer Xie, Andrew M Brunner, Andrew T Kuykendall, John M Bennett, Rena Buckstein, Rafael Bejar, Hetty E Carraway, Amy E DeZern, Elizabeth A Griffiths, Stephanie Halene, Robert P Hasserjian, Jeffrey Lancet, Alan F List, Sanam Loghavi, Olatoyosi Odenike, Eric Padron, Mrinal M Patnaik, Gail J Roboz, Maximilian Stahl, Mikkael A Sekeres, David P Steensma, Michael R Savona, Justin Taylor, Mina L Xu, Kendra Sweet, David A Sallman, Stephen D Nimer, Christopher S Hourigan, Andrew H Wei, Elisabetta Sauta, Saverio D'Amico, Gianluca Asti, Gastone Castellani, Mattia Delleani, Alessia Campagna, Uma M Borate, Guillermo Sanz, Fabio Efficace, Steven D Gore, Tae Kon Kim, Navel Daver, Guillermo Garcia-Manero, Maria Rozman, Alberto Orfao, Sa A Wang, M Kathryn Foucar, Ulrich Germing, Torsten Haferlach, Phillip Scheinberg, Yasushi Miyazaki, Marcelo Iastrebner, Austin Kulasekararaj, Thomas Cluzeau, Shahram Kordasti, Arjan A van de Loosdrecht, Lionel Ades, Amer M Zeidan†, Matteo G Della Porta†, on behalf of the International Consortium on Myelodysplastic Syndromes*

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*Contributed equally as joint first authors

†Contributed equally as joint senior authors

Department of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA (Prof R S Komrokji MBBS, N H Al Ali MSc, S M Tinsley-Vance PhD, Z I Schwabkey MD, O Chan MD, Z Xie MD, A T Kuykendall MD, J Lancet MD, E Padron MD, K Sweet MD, D A Sallman MD); **Center for Accelerating Leukemia/Lymphoma Research at Comprehensive Cancer Center, IRCCS Humanitas Research Hospital, Milan, Italy** (L Lanino MD, G Maggioni MD, E Sauta PhD, S D'Amico MSc, G Asti MSc, M Delleani MSc, A Campagna MD, Prof M G Della Porta MD); **Department of Biomedical Sciences, Humanitas University, Milan, Italy** (L Lanino, G Maggioni, Prof M G Della Porta); **Division of Hematology and Oncology, Vanderbilt Ingram Cancer Center and Vanderbilt University School of Medicine, Nashville, TN, USA** (S Ball MD, Prof M R Savona MD, T K Kim MD); **Leukemia Service,**

The WHO and International Consensus Classification 2022 classifications of myelodysplastic syndromes enhance diagnostic precision and refine decision-making processes in these diseases. However, some discrepancies still exist and potentially cause inconsistency in their adoption in a clinical setting. We adopted a data-driven approach to provide a harmonisation between these two classification systems. We investigated the importance of genomic features and their effect on the cluster assignment process to define harmonised entity labels. A panel of expert haematologists, haematopathologists, and data scientists who are members of the International Consortium for Myelodysplastic Syndromes was formed and a modified Delphi consensus process was adopted to harmonise morphologically defined categories without a distinct genomic profile. The panel held regular online meetings and participated in a two-round survey using an online voting tool. We identified nine clusters with distinct genomic features. The cluster of highest hierarchical importance was characterised by biallelic *TP53* inactivation. Cluster assignment was irrespective of blast count. Individuals with monoallelic *TP53* inactivation were assigned to other clusters. Hierarchically, the second most important group included myelodysplastic syndromes with del(5q). Isolated del(5q) and less than 5% of blast cells in the bone marrow were the most relevant label-defining features. The third most important cluster included myelodysplastic syndromes with mutated *SF3B1*. The absence of isolated del(5q), del(7q)/-7, abn3q26.2, complex karyotype, *RUNX1* mutations, or biallelic *TP53* were the basis for a harmonised label of this category. Morphologically defined myelodysplastic syndrome entities showed large genomic heterogeneity that was not efficiently captured by single-lineage versus multilineage dysplasia, marrow blasts, hypocellularity, or fibrosis. We investigated the biological continuum between myelodysplastic syndromes with more than 10% bone marrow blasts and acute myeloid leukaemia, and found only a partial overlap in genetic features. After the survey, myelodysplastic syndromes with low blasts (ie, less than 5%) and myelodysplastic syndromes with increased blasts (ie, 5% or more) were recognised as disease entities. Our data-driven approach can efficiently harmonise current classifications of myelodysplastic syndromes and provide a reference for patient management in a real-world setting.

Introduction

Myelodysplastic syndromes are myeloid neoplasms characterised by bone marrow dysplasia leading to ineffective haematopoiesis and increased risk of evolution to acute myeloid leukaemia (AML).[1] Over the years, the WHO classification of myeloid neoplasms has been used as a reference for diagnosis, treatment decisions, clinical trial eligibility, and drug approvals in people with myelodysplastic syndromes.[2,3]

Recent advancements in genome characterisation have transformed the study of myeloid neoplasms.[4] A high proportion of people with myelodysplastic syndromes exhibit recurrent chromosomal alterations or somatic mutations that drive the clinical phenotype and disease evolution on an individual basis.[5] Accordingly, there is a shift from traditional classification schemes, primarily based on morphological and clinical features, to next-generation systems that integrate genomic features, providing a more accurate representation of the disease biology and better capturing clinical-pathological entities.[6–8] In 2022, two distinct classification systems for myeloid neoplasms were released by the WHO and the International Consensus Classification (ICC) committees, each incorporating an increased amount of molecular information to identify specific entities as well as refining morphologically defined categories.[9,10]

Both WHO and ICC classifications introduced new genetically defined myelodysplastic syndrome categories based on *SF3B1* and *TP53* mutations, with subtle differences in criteria for individual subgroups.[9–11] From the morphological standpoint, ICC 2022 included categories for myelodysplastic syndromes with single-lineage and multilineage dysplasia. In contrast, WHO 2022 maintained the morphological entity of myelodysplastic

syndromes with ring sideroblasts and introduced two additional morphological subgroups—hypoplastic myelodysplastic syndromes and myelodysplastic syndromes with fibrosis—that are not included in the ICC proposal.[9–11] A blast percentage cutoff in the bone marrow of 5% is used to differentiate myelodysplastic syndromes with low blasts from those with increased blasts 1 (MDS-IB1) in WHO 2022, whereas individuals with 10–19% blasts are now classified as having myelodysplastic syndromes with increased blasts 2 (MDS-IB2) per WHO and as myelodysplastic syndromes–AML per ICC 2022.[9–11]

Although many definitions proposed by the ICC and WHO 2022 are concordant, several key differences as outlined above exist and could affect patient diagnostic assessment, the design and outcome of clinical trials, patient care and outcomes, drug development, and regulatory approval.[11,12] There is an urgent need to establish a uniform consensus for myelodysplastic syndrome diagnosis and stratification in clinical practice by addressing the divergences in the current competing classifications.[11]

This project, conducted by the International Consortium for Myelodysplastic Syndromes (icMDS), aims to provide a harmonised classification approach for myelodysplastic syndromes as a basis for stratification of patients in a real-world clinical setting. We hypothesise that the creation of a large, comprehensive patient dataset, together with the use of advanced methods of statistical inference, can provide a solid basis for the harmonisation of myelodysplastic syndrome classifications.

Methods

Study design, data sources, and procedures

This retrospective consensus analysis was conducted by icMDS; the study protocol was approved by the institutional review boards at the participating institutions. Due to its retrospective nature, informed consent for the study was waived by the institutional ethics boards.

The study population consisted of an international cohort of 7017 individuals with myelodysplastic syndromes defined according to WHO 2016 classification criteria.[2] The date range of diagnosis was from Nov 3, 1994, to Nov 22, 2021. The cohort was formed with 4780 individuals from the European repository of the GenoMed4All consortium, diagnosed between March 16, 1995, and Feb 17, 2021, and 2237 from the Moffitt Cancer Center (Tampa, FL, USA), diagnosed between Nov 3, 1994, and Nov 22, 2021 (appendix p 11). All individuals with a diagnosis of primary myelodysplastic syndrome by 2016 WHO criteria were potentially eligible (those with therapy-related disease were excluded). Only individuals with comprehensive information available on demographics, clinical and haematological features, cytogenetics and mutational profile (collected at diagnosis), treatments received, and outcomes were selected for the analysis. To validate the clinical value (defined in terms of prognostic relevance and treatment response) of the 2022 WHO and ICC classification systems, the study population with myelodysplastic syndromes was split into the two original cohorts (GenoMed4All consortium and Moffitt Cancer Center cohorts).

Additionally, a population of 1002 individuals with AML was considered to specifically address the biological continuum between myelodysplastic syndromes with 10% or more blasts and acute leukaemia. People with AML were retrospectively collected in centres that participate in the Genomed4All consortium. Eligible

	All participants with MDS (n=7017)
Age at diagnosis, years	70 (62–77)
Sex	
Male	4315 (61·5%)
Female	2702 (38·5%)
Haemoglobin concentration, g/dL	9·7 (2·1–19·6)
Absolute neutrophil count, ×10³/μL	1·7 (0–104)
Platelet count, ×10³/μL	117 (2–1491)
WHO 2016 classification	
MDS single-lineage dysplasia	666 (9·5%)
MDS single-lineage dysplasia with ring sideroblasts	539 (7·7%)
MDS multilineage dysplasia	1868 (26·6%)
MDS multilineage dysplasia with ring sideroblasts	635 (9·0%)
MDS del(5q)	373 (5·3%)
MDS excess blasts 1	1321 (18·8%)
MDS excess blasts 2	1509 (21·5%)
MDS unclassified	106 (1·5%)
IPSS-R risk categories	
Very low	980 (14·0%)
Low	2424 (34·5%)
Intermediate	1449 (20·6%)
High	1086 (15·5%)
Very high	1078 (15·4%)
IPSS-M risk categories	
Very low	588 (8·4%)
Low	2092 (29·8%)
Moderate low	928 (13·2%)
Moderate high	891 (12·7%)
High	1258 (17·9%)
Very high	1260 (18·0%)
Treatment modalities	
Erythropoiesis-stimulating agents	1977 (28·2%)
Lenalidomide	736 (10·5%)
Hypomethylating agents	2330 (33·2%)
Allogeneic haematopoietic stem-cell transplantation	1504 (21·4%)

Data are median (IQR) or n (%). MDS=myelodysplastic syndromes. IPSS-R=Revised International Prognostic Scoring System. IPSS-M=Molecular International Prognostic Scoring System. The characteristics for the GenoMed4All cohort (n=4780) and Moffitt Cancer Center cohort (n=2237) are in the appendix (p 11).

Table 1: **Characteristics of MDS study population**

Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA (J P Bewersdorf MD); **Azienda Ospedaliera Nazionale SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy** (M Marchetti MD); **IRCCS Polilcinico San Matteo, Pavia, Italy** (E Travaglino BSc); **Saint Louis Hospital, Paris Cité University, Paris, France** (Prof P Fenaux MD, Prof L Ades MD); **University Hospital Leipzig, Leipzig, Germany** (Prof U Platzbecker MD); **University of Florence, Florence, Italy** (V Santini MD); **Haematology Department, University Hospital Salamanca, Salamanca, Spain** (M Diez-Campelo MD, Prof A Orfao MD); **Cleveland Clinic, Cleveland, OH, USA** (A Singh MD, A G Jain MD, Prof H E Carraway MD); **Dana Farber Cancer Institute, Boston, MA, USA** (L E Aguirre MD, A M Brunner MD, M Stahl MD); **University of Rochester Medical Center, Rochester, NY, USA** (Prof J M Bennett MD); **Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (R Buckstein MD); **University of California San Diego, San Diego, CA, USA** (R Bejar MD); **The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA** (Prof A E DeZern MD); **Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA** (E A Griffiths MD); **Hematology Section, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA** (Prof S Halene MD, A M Zeidan MD); **Massachusetts General Hospital, Boston, MA, USA** (Prof R P Hasserjian MD); **Precision BioSciences, Durham, NC, USA** (A F List MD); **Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (S Loghavi MD, S A Wang MD); **Leukemia Program, University of Chicago Medicine and University of Chicago Comprehensive Cancer Center, Chicago, IL, USA** (Prof O Odenike MD); **Division of Hematology, Department of Internal Medicine, Mayo Clinic,**

Rochester, MN, USA (M M Patnaik MBBS); **New York-Presbyterian/Weill Cornell Medicine, New York, NY, USA** (Prof G J Roboz MD); **Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA** (Prof M A Sekeres MD, J Taylor MD, Prof S D Nimer MD); **Ajax Therapeutics, Cambridge, MA, USA** (D P Steensma MD); **Department of Pathology and Laboratory Medicine, Yale School of Medicine, New Haven, CT, USA** (Prof M L Xu MD); **Virginia Tech FBRI Cancer Research Center, Washington, DC, USA** (Prof C S Hourigan DM); **Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia** (Prof A H Wei MBBS); **Train, Milan, Italy** (S D'Amico); **Department of Medical and Surgical Sciences—DIMEC, University of Bologna, Bologna, Italy** (Prof G Castellani PhD); **Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA** (U M Borate MD); **Instituto de Salud Carlos III, Valencia, Spain** (Prof G Sanz MD); **Data Center and Health Outcomes Research Unit, Italian Group for Adult Haematologic Diseases (GIMEMA), Rome, Italy** (F Efficace PhD); **Division of Cancer Prevention, National Cancer Institute, Rockville, MD, USA** (S D Gore MD); **Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (N Daver MD, Prof G Garcia-Manero MD); **Hospital Clínic Barcelona, Barcelona, Spain** (M Rozman MD); **University of New Mexico, Albuquerque, NM, USA** (Prof M K Foucar MD); **Department of Haematology, Oncology, and Clinical Immunology, Heinrich Heine University, Düsseldorf, Germany** (Prof U Germing MD); **MLL Munich Leukemia Laboratory, Munich, Germany** (Prof T Haferlach MD); **Beneficência Portuguesa de São Paulo Hospital, São Paulo, Brazil** (P Scheinberg MD); **Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan** (Prof Y Miyazaki MD); **Sanatorio Sagrado Corazón, Buenos Aires, Argentina** (M Iastrebner MD);

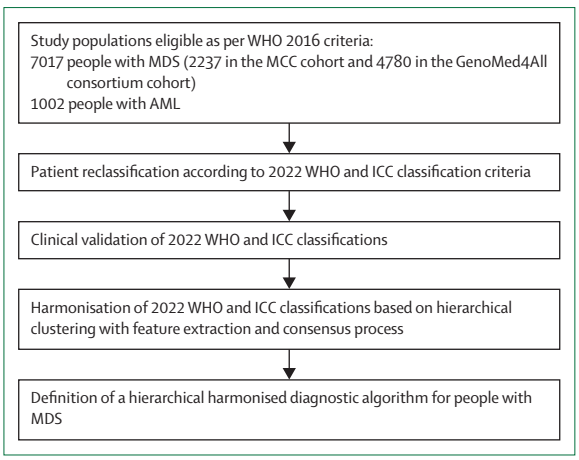


Figure 1: **Study flow**
AML=acute myeloid leukaemia. ICC=International Consensus Classification. MDS=myelodysplastic syndromes.

participants had a diagnosis of AML according to the WHO 2016 classification. Individuals with comprehensive clinical, cytogenetic, and molecular information were selected for the study. Enrolment dates spanned from July 12, 1994, to Nov 16, 2020.

All participants underwent cytogenetic analysis and molecular profiling by targeted DNA sequencing on blood or bone marrow samples at diagnosis (appendix pp 2–3).

Statistical and clustering analysis

According to the inclusion criteria of the study, 8019 (94·0%) of the 8531 individuals from GenoMed4all and Moffitt Cancer Center cohorts were eligible. Numerical variables were summarised by median and range; categorical variables were described with count and relative frequency of subjects in each category. Probability of overall survival and leukaemia-free survival were estimated with the Kaplan–Meier method and compared by log-rank test. Survival analyses were carried out using survival R package version 3.3.1. $p<0·05$ was considered to indicate a significant difference. 95% CIs were computed using the R summary function applied to the fitted survival analysis. Participants were censored at time of haematopoietic stem-cell transplantation, when applicable (analyses without censoring participants at time of transplantation were also performed and provided similar results).

Clustering analyses were performed using MOSAIC, a statistical and artificial-intelligence-based framework for multimodal analysis, classification, and personalised prognostic assessment in rare cancers.[13] In brief, hierarchical Dirichlet processes were used to infer the structure of conditional dependencies among mutations, ie, how the presence of a given mutation influences the probability of the others (causality), and to define clusters capturing broad dependencies among all gene mutations and cytogenetic abnormalities.[7,14] Shapley Additive exPlanations (SHAP) analysis was applied to investigate and report features of importance and their effects on the cluster assignment.[15]

Consensus process

We aimed to generate consensus-based recommendations to define disease entities and diagnostic qualifiers among morphologically defined myelodysplastic syndromes without distinct genomic profiles. We assembled an international panel of haematologists, haematopathologists, and data scientists with expertise in the field of myelodysplastic syndromes, consisting of 71 experts from 11 countries across five continents. The icMDS core group (RSK, SB, LL, JPB, MM, AMZ, and MGDP) conducted multiple virtual meetings in 2023 and proposed recommendations based on the analysis of the study population. Recommendations were distributed among the panellists using an online survey and were assessed for comments and consensus using a modified Delphi process.[16,17] During the first round of voting, panellists voted on a five-level Likert scale (from strongly disagree to strongly agree) with an option for free-text comments. Based on the results of the first round, recommendations that received at least 75% consensus (agree or strongly agree) were accepted, whereas statements with less than 75% consensus were revised. Revision of the consensus statements was informed by fuzzy analysis.[17] We classified a disease entity as a fuzzy average greater than 6 for both prognostic and therapeutic effect and a strict convergence (distance from average <2) reported by at least 75% of respondents in at least one dimension. A diagnostic qualifier was defined as a fuzzy average of greater than 6 for at least prognostic or therapeutic effect and wide convergence (distance from average <3) reported by at least 75% of respondents in at least one dimension. In the second round of voting, panellists voted to either agree or disagree with comments. Only recommendations that achieved at least 75% consensus after two rounds of voting were included in the final proposal.[17]

Results

The study population included 7017 participants with myelodysplastic syndromes diagnosed according to WHO 2016 criteria.[2] Clinical features are reported in table 1. The study participants comprised 4315 (61·5%) men and 2702 (38·5%) women. The median age at diagnosis was 70 years (IQR 62–77). Follow-up was updated on Dec 31, 2022. Median follow-up was 56·1 months (IQR 26·2–78·4). Participants were reclassified per WHO 2022 and ICC 2022 criteria (figure 1).[9,10]

Considering genomic features captured by the Molecular International Prognostic Scoring System (IPSS-M),[18,19] we identified 11 312 genomic lesions at diagnosis (median 1 [range 0–10]) in all participants with myelodysplastic syndromes. 6362 (90·7%) participants had one or more genomic alterations (mutations or

chromosomal abnormalities). 5434 (77·4%) participants had one or more somatic mutations in 31 IPSS-M captured genes (appendix p 4), and 3001 (42·8%) showed abnormal karyotype. The failure rate for conventional cytogenetic analysis was 322 (4·6%). Probabilities of overall survival and leukaemia-free survival in participants with myelodysplastic syndromes classified by 2016 WHO, Revised International Prognostic Scoring System (IPSS-R), and IPSS-M categories are reported in the appendix (pp 5–6).

Participants with myelodysplastic syndromes and AML were reclassified according to 2022 WHO and ICC criteria (table 2, figure 2A–D).[9,10] We analysed the concordance between the two systems in terms of assigning participants to specific clinical entities. Overall, we observed discordance in 3202 (45·6%) participants, including 382 (19·1%) of 2003 in genetically defined subgroups. Discordant classification was observed in 233 (35%) of 657 participants with myelodysplastic syndromes with *TP53* mutations, 149 (14·7%) of 1017 participants with myelodysplastic syndromes with *SF3B1* mutations, no participants with myelodysplastic syndromes with del(5q), and 2820 (56·2%) of 5014 participants in morphologically defined subgroups, thus providing evidence of the need for a harmonisation process (figure 2E, appendix p 7).

Both 2022 WHO and ICC systems showed substantial prognostic power in the GenoMed4All consortium and the Moffitt Cancer Center subcohorts of patients with myelodysplastic syndromes. The results of this analysis are extensively reported in the appendix (pp 8–23). Unless stated, all the results were confirmed in both cohorts. Considering the genetically defined subgroups, by applying either 2022 WHO or ICC criteria, myelodysplastic syndromes with *SF3B1* mutations had the most favourable outcomes, whereas T*P53*-mutated myelodysplastic syndromes had the worst outcomes of all subgroups (appendix pp 9–10). Participants with myelodysplastic syndromes–AML with myelodysplasia-related gene mutations had worse overall survival than myelodysplastic syndromes–AML not otherwise specified (appendix p 20).

Considering morphologically defined categories, we observed that: *SF3B1* wild-type myelodysplastic syndromes with ring sideroblasts by WHO 2022 had similar leukaemia-free survival and overall survival to myelodysplastic syndromes with low blasts (appendix p 12); hypoplastic myelodysplastic syndromes were found to have similar median leukaemia-free survival and overall survival to other non-genetically defined low-blast subgroups by WHO 2022 (myelodysplastic syndromes with low blasts and with ring sideroblasts combined; appendix p 13); considering number of dysplastic linages by ICC 2022 criteria, myelodysplastic syndromes not otherwise specified with multilineage dysplasia had statistically significantly worse leukaemia-free survival and overall survival than myelodysplastic syndromes with single-lineage dysplasia (appendix p 14); and MDS-IB1 by WHO 2022 was associated with shorter leukaemia-free survival and overall survival than non-genetically defined myelodysplastic syndromes with low blasts (appendix p 15).

In the Moffitt Cancer Center subcohort, participants with MDS-IB2 by WHO 2022 had statistically significantly worse leukaemia-free survival than MDS-IB1, but there was no difference in overall survival (appendix p 15). Use of hypomethylating agents and allogeneic transplantation led to similar outcomes between MDS-IB1 and MDS-IB2 (appendix p 9). In the GenoMed4All cohort, MDS-IB2 also had shorter leukaemia-free survival and overall survival than MDS-IB1 (appendix p 16), and considering participants undergoing transplantation, MDS-IB2 had shorter overall survival than IB1 (appendix p 16). Among participants with myelodysplastic syndromes and increased blasts by WHO 2022, myelodysplastic syndromes with fibrosis had statistically significantly shorter leukaemia-free survival and overall survival than MDS-IB1 and MDS-IB2 (appendix p 17). Participants with myelodysplastic syndromes–AML with *TP53* mutation showed statistically significantly shorter survival than

	All participants with MDS (n=7017)
WHO 2022 classification	
MDS biallelic *TP53* inactivation	657 (9·4%)
MDS del(5q)	329 (4·7%)
MDS mutated *SF3B1*	1017 (14·5%)
MDS low blasts	2259 (32·2%)
MDS low blasts with ring sideroblasts	215 (3·1%)
MDS hypoplastic	94 (1·3%)
MDS increased blasts 1	1058 (15·1%)
MDS increased blasts 2	1166 (16·6%)
MDS with fibrosis	113 (1·6%)
AML	109 (1·6%)
ICC 2022 classification	
MDS mutated *TP53*	484 (6·9%)
MDS–AML mutated TP53	261 (3·7%)
MDS del(5q)	334 (4·8%)
MDS mutated *SF3B1*	871 (12·4%)
MDS single-lineage dysplasia	772 (11·0%)
MDS multilineage dysplasia	1913 (27·3%)
MDS without dysplasia	31 (0·4%)
MDS excess blasts	1112 (15·8%)
MDS–AML cytogenetic abnormalities	131 (1·9%)
MDS–AML gene mutations	737 (10·5%)
MDS–AML not otherwise specified	290 (4·1%)
AML	81 (1·2%)

Data are n (%). ICC=International Consensus Classification. MDS=myelodysplastic syndromes. AML=acute myeloid leukaemia.

Table 2: **Classification of the MDS study population according to 2022 WHO and ICC criteria**

King's College Hospital NHS Foundation Trust, NIHR/Wellcome King's Clinical Research Facility, London, UK (A Kulasekararaj MD); **Nice University Hospital, Nice, France** (Prof T Cluzeau MD); **Comprehensive Cancer Centre, School of Cancer and Pharmaceutical Sciences, King's College, London, UK** (S Kordasti MD); **Department of Hematology, Amsterdam University Medical Center, VU University Medical Center—Cancer Center, Amsterdam, Netherlands** (Prof A A van de Loosdrecht MD)

Correspondence to:
Matteo G Della Porta, Center for Accelerating Leukemia/Lymphoma Research at Comprehensive Cancer Center, IRCCS Humanitas Research Hospital, Milan 20089, Italy
matteo.della_porta@hunimed.eu

See **Online** for appendix

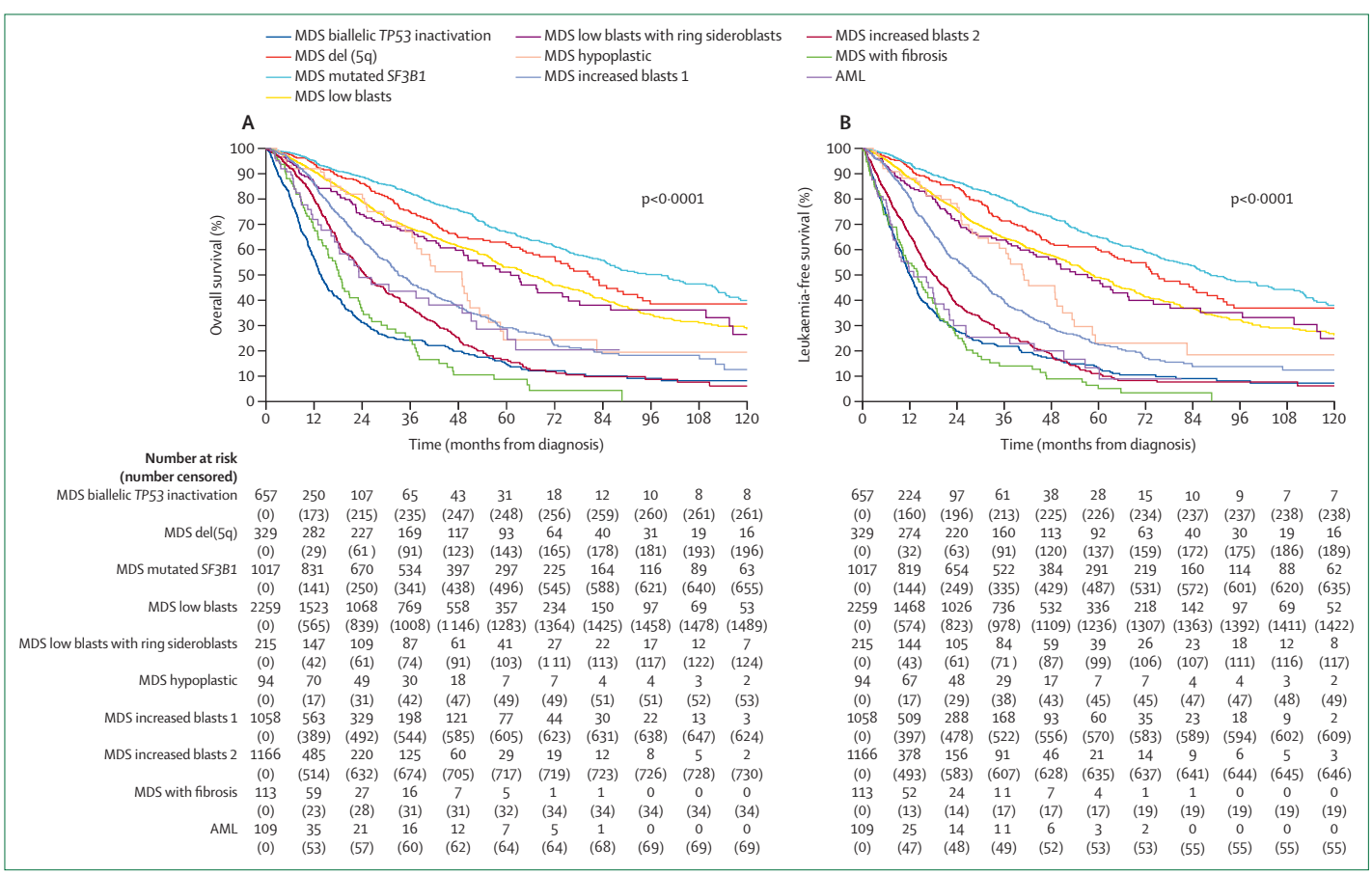
myelodysplastic syndromes with mutated *TP53* in both subcohorts, according to ICC 2022 (appendix p 18). The same was observed in individuals with biallelic *TP53* inactivation according to WHO 2022, where participants with 10% or more marrow blasts showed statistically significantly shorter survival (appendix p 19).

The presence of cytogentic abnormalities or gene mutations related to myelodysplastic syndromes in participants with myelodysplastic syndromes–AML correlated with statistically significantly shorter survival compared with myelodysplastic syndromes–AML not otherwise specified, according to ICC 2022 (appendix pp 20–21). Subcohort survival analysis according to WHO and ICC 2022 can be found in the appendix (pp 22–23).

Clustering analysis identified nine clusters with distinctive cytogenetic and molecular characteristics (panel, appendix p 24). The results of clustering and SHAP analysis were used as a reference for harmonising the definition of genetically defined subgroups by 2022 WHO and ICC classifications.

The cluster of highest hierarchical importance (cluster 2) was characterised by *TP53* mutations consistent with biallelic inactivation of the gene. According to SHAP analysis, *TP53* biallelic inactivation was defined as the presence of two or more *TP53* mutations, or one mutation with copy number loss or copy-neutral loss of heterozygosity. 718 (77·9%) of 922 participants assigned to this cluster had *TP53* variant allele frequency of at least 10%, and 646 (70·1%) had complex karyotype. Assignment to this cluster was irrespective of blast count. Participants with del(5q) or *SF3B1* mutations and concurrent biallelic *TP53* inactivation were classified in cluster 2 (ie, *TP53* mutations supersede del(5q) and *SF3B1* mutations); participants with monoallelic *TP53* inactivation were segregated into other clusters (cluster 1, namely myelodysplastic syndromes with mutated *SF3B1* and concurrent higher-risk mutations, and cluster 8, myelodysplastic syndromes with del[5q]). According to genomic features, the harmonised name of this entity was myelodysplastic syndromes with mutated *TP53*.

Hierarchically, the second cluster (cluster 8) included participants with deletion 5q. SHAP analysis highlighted isolated del(5q), or with one other chromosomal abnormality other than del(7q)/-7, and absence of biallelic *TP53* inactivation as the most relevant features of this cluster. 304 (88%) of 345 participants in this cluster had



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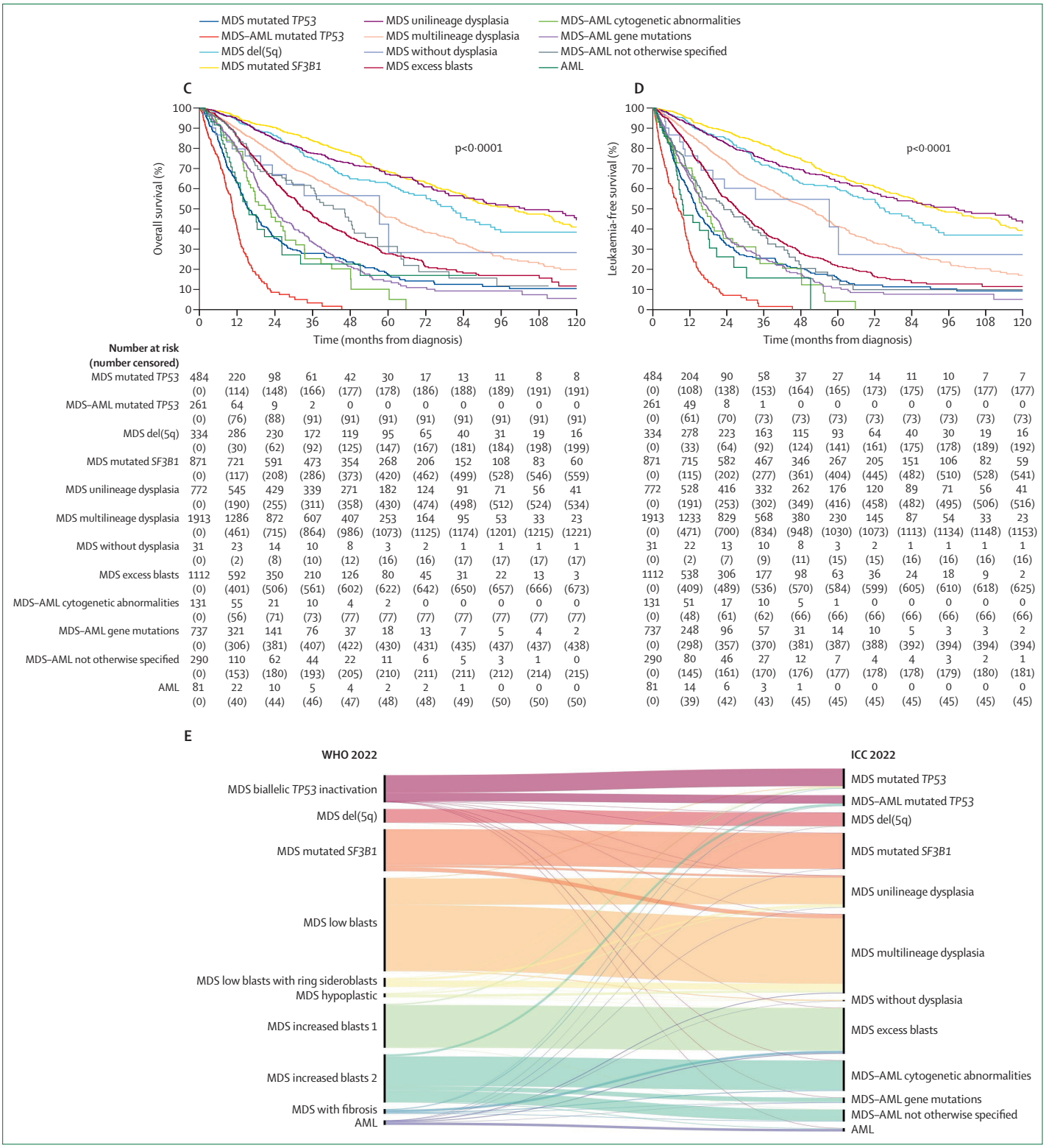

Figure 2: **Probability of overall survival and leukaemia-free survival of people with MDS**

Probability of overall survival stratified according to 2022 WHO criteria (A) and ICC criteria (B). Probability of leukaemia-free survival stratified according to 2022 WHO criteria (C) and ICC criteria (D). Alluvial diagram representing the concordance and discordance of patient classification between the two schemes (E). AML=acute myeloid leukaemia. ICC=International Consensus Classification. MDS=myelodysplastic syndromes.

Panel: **Harmonised definition of genetically defined myelodysplastic syndrome subgroups**

Myelodysplastic syndromes with mutated *TP53*

- Two or more *TP53* mutations, or one mutation with *TP53* locus copy number loss or copy-neutral loss of heterozygosity
- Bone marrow blasts less than 20%
- *TP53* mutation supersedes presence of del(5q) or *SF3B1* mutation
- Complex karyotype frequently detected
- *TP53* variant allele frequency of more than 10% frequently detected

Myelodysplastic syndromes with del(5q)

- Presence of del(5q)
- Bone marrow blasts less than 5%
- Absence of del(7q)/-7 or complex karyotype
- Absence of biallelic *TP53* inactivation
- Del(5q) supersedes *SF3B1* mutations

Myelodysplastic syndromes with mutated *SF3B1*

- Presence of *SF3B1* mutation
- Bone marrow blasts less than 5%
- Absence of isolated del(5q), del(7q)/-7, abn(3q26.2), or complex karyotype
- Absence of biallelic *TP53* inactivation
- Absence of *RUNX1* mutations
- *SF3B1* variant allele frequency of more than 10% in 96% of individuals, and more than 5% in 100% of individuals

blast count less than 5% (individuals showing excess blasts were mainly classified in cluster 1). On the basis of these findings, the harmonised name of this entity was myelodysplastic syndromes with del(5q).

The third distinct cluster (cluster 6) included participants with *SF3B1* mutations in the absence of concurrent del(7q)/-7, abn3q26.2, complex karyotype, or *RUNX1* mutation. 665 (94%) of 706 participants in this cluster had less than 5% blasts. Variant allele frequency for *SF3B1* mutations was 5% or more in all participants, and 10% or more in 96% of participants. Common co-mutated variants in this cluster included *TET2* (270 [38%] participants) and *DNMT3A* (178 [25%] participants). The harmonised name of this entity was myelodysplastic syndromes with mutated *SF3B1*.

The myelodysplastic syndrome cases not meeting the criteria for the above three genomic entities were preferentially assigned to the following additional clusters (appendix p 27): myelodysplastic syndromes with mutated *SF3B1* and concurrent higher-risk mutations (ie, *RUNX1* and *ASXL1*, cluster 1), myelodysplastic syndromes with mutated *SRSF2* and concurrent *TET2* mutations (with or without higher-risk mutations, mainly including *RUNX1* and *ASXL1*, cluster 3 and cluster 5), myelodysplastic syndromes with mutated *U2AF1* and concurrent del 20q, or del(7q)/-7 (cluster 4), and myelodysplastic syndromes with AML-like genomic signatures (cluster 7; appendix pp 24–27).

We then applied the genomic clustering analysis to myelodysplastic syndromes defined by morphological features in 2022 ICC and WHO classifications, and we observed that these morphologic entities failed to identify groups of participants with distinctive genomic profiles (appendix p 30).

Moreover, we specifically addressed the issue of quantifying the genomic overlap between high-risk myelodysplastic syndromes and AML: 1491 participants with myelodysplastic syndromes with bone marrow blasts of 10% or more and 1002 participants with AML were included in the analysis (n=2493; appendix pp 25–26). The participant characteristics for the AML population are in the appendix (p 24). Similarities were observed between the AML-like myelodysplastic syndrome clusters and selected AML genomic signatures (*CEBPA*, *NPM1*, and core binding factor AML) and between myelodysplastic syndromes and AML with myelodysplastic syndrome-related mutations or genomic features (appendix p 31). Overall, the overlap in genomic signatures between the two populations was 29%. According to these findings, a 10% marrow blast threshold might not be suitable to recognise different disease entities from a biological point of view. Because morphologically defined myelodysplastic syndromes entities were not associated with specific genomic profiles, we aimed to generate consensus-based recommendations to define disease entities and diagnostic qualifiers among this population.

We conducted fuzzy analyses on the results of the first round of the Delphi process (appendix p 28). Besides the genetically defined entities, there was a consensus to retain myelodysplastic syndromes with increased blasts as a separate entity as it has both prognostic and therapeutic implications. Similarly, there was a consensus to retain morphological myelodysplastic syndrome subtypes for individuals who do not fit into established genetically defined entities. However, the panel proposed to include the number of dysplastic lineages, hypoplastic bone marrow, degree of marrow fibrosis, and germline predisposition as diagnostic qualifiers rather than as distinct myelodysplastic syndrome entities. Additionally, the panel agreed to retain ring sideroblasts status (when testing for *SF3B1* mutation is not available or the participant is *SF3B1* wild type), and therapy-related myelodysplastic syndromes as diagnostic qualifiers using the definitions previously proposed by the ICC and WHO classifications. The retention of such features as diagnostic qualifiers allows the inclusion of features with a potential therapeutic or prognostic effect in the classification workup. Finally, there was no consensus among panellists regarding the preferred terminology of myelodysplastic syndromes (ie, myelodysplastic syndromes *vs* myelodysplastic neoplasms) or the use of myelodysplastic syndromes–AML as a synonymous term for MDS-IB2 (appendix p 28).

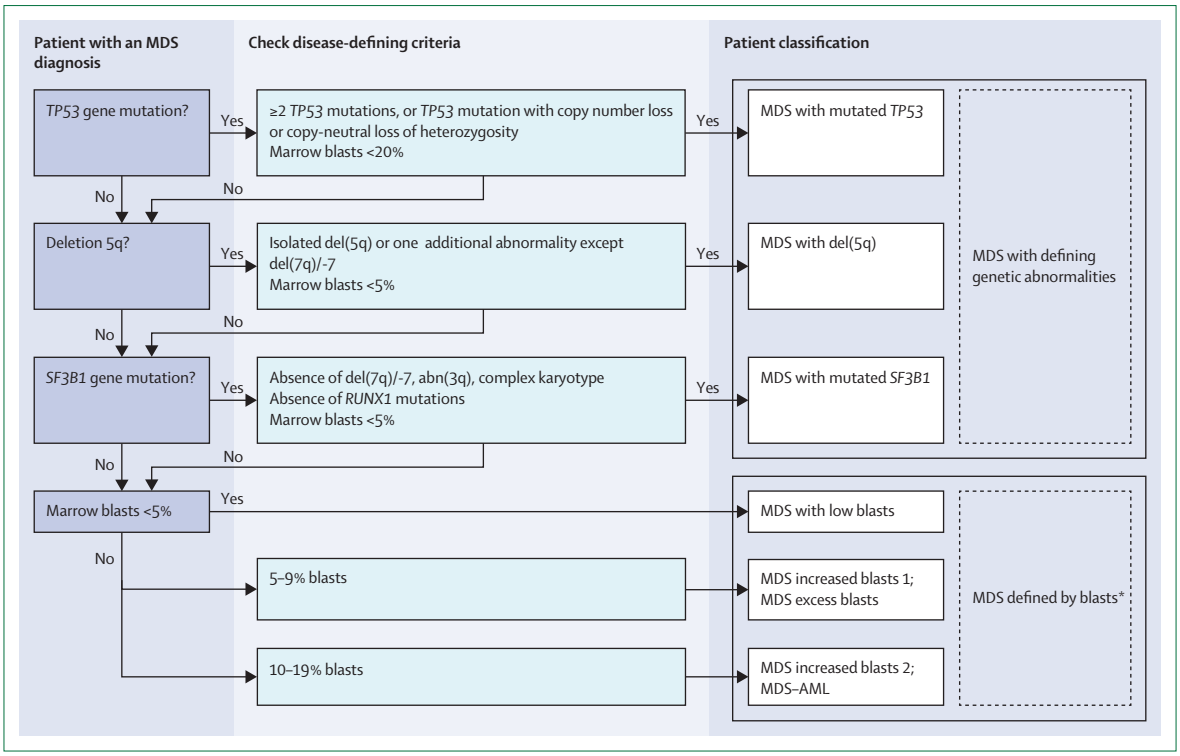

Figure 3: **WHO and International Consensus Classification harmonised classification algorithm for people with MDS**
AML=acute myeloid leukaemia. MDS=myelodysplastic syndromes. *Diagnostic qualifiers: unilineage or multilineage dysplasia; hypoplastic; fibrotic; ring sideroblasts; therapy-related; or germline predisposition.

In summary, we propose two harmonised morphological myelodysplastic syndrome entities for individuals not belonging to genetically defined subgroups, termed myelodysplastic syndromes with low blasts (including individuals with bone marrow blasts less than 5%) and myelodysplastic syndromes with increased blasts (including individuals with 5–19% bone marrow blasts, stratified into two groups by using the blast threshold of 10%).

The results of the clustering and consensus analyses were used as a basis to build a hierarchical harmonised diagnostic algorithm for people with myelodysplastic syndromes for clinical use (figure 3). The algorithm provides a clear representation of the order in which different genomic alterations (somatic mutations and cytogenetic abnormalities) should be evaluated to perform a correct patient classification. Regarding the reliability of the harmonised definition of myelodysplastic syndrome categories, we observed that patient reclassification according to this algorithm was concordant with 2022 WHO labels in 6820 (97·2%) cases and with 2022 ICC labels in 6883 (98·1%) cases. Survival analysis (overall survival and leukaemia-free survival) according to the harmonised classification is reported in the appendix (p 29).

Discussion

Thus far, the mechanism by which the classification of haematological neoplasms has been developed has relied on interactions within groups of experts in the field.[2,20] Ad hoc reviews of the literature have been performed and consensus decision making has been used to generate final recommendations. These procedures have historically been appropriate, but with the increasing complexity of additional data layers (such as genomics) in the disease classification, this conventional approach presents potential limitations. For instance, because agreement has not been reached on the involvement and role of clinicians and pathologists in the advisory committee, two different and not completely overlapping schemes have been released.[9–12,20] Moving forward, innovative approaches will be required to harness the potential of emerging data and new technologies to analyse them, which can be useful for better defining disease subtypes (especially in complex and heterogeneous diseases, such as myeloid neoplasms) as well as for identifying novel disease entities.[20,21]

In this paper, we have addressed the critical challenge of harmonising the two existing classification systems for myelodysplastic syndromes. We took advantage of the abundance of detailed clinical and genomic information that is being collected on individuals within the context of real-world clinical care. We applied innovative, scalable, and fully explainable models combining advanced statistical and machine-learning methods, available from MOSAIC, an open-source platform for personalised medicine in rare cancers.[13]

We provided evidence that a data-driven approach can establish a solid basis for the harmonisation process.[13,20]

As a result, we created a simple hierarchical algorithm to assign an individual to a specific disease category that can improve the quality of the implementation of myelodysplastic syndrome molecular classifications in clinical practice.

The most relevant innovation of the 2022 WHO and ICC classifications was the definition of new disease entities based on specific genomic features.[9,10] The integration of genomic profiling into the classification of myelodysplastic syndromes is anticipated to substantially affect clinical practice; it enables the categorisation of morphologically defined neoplasms into distinct genomic subgroups with different therapeutic responses and outcomes. Additionally, it offers the potential for identifying biomarkers for disease monitoring, thereby laying the groundwork for personalised treatments.[7,20,22] The genetically defined entities of the 2022 WHO and ICC classification systems are clearly unique, as supported by the results of the Dirichlet–SHAP analysis and distinct survival outcomes observed in our study.[8,23,24] Consistent with published literature, myelodysplastic syndromes with mutated *SF3B1* had the best outcomes of all subgroups, followed by myelodysplastic syndromes with del(5q).[23,24] On the other hand, the subgroup with mutated *TP53* consistent with biallelic gene inactivation had the worst outcomes of all, in line with published studies showing poor treatment response, high rates of leukaemic transformation, and dismal outcome.[25,26] Despite this result, the new genetically defined myelodysplastic syndrome categories by the 2022 WHO and ICC systems present subtle differences in criteria for individual subgroups, as evidenced by a discordant assignment in 19% of cases by the two systems (most regarding cases with *TP53* mutations). A harmonised label of genetically defined myelodysplastic syndrome categories can maximise the efficacy of the implementation of personalised medicine approaches in these individuals. Furthermore, establishing a hierarchical order of relevance for different mutations (*TP53* mutations supersede both del[5q] and *SF3B1* mutations, and del[5q] supersedes *SF3B1* mutations) can contribute to a clearer implementation of the classification in real-world scenarios.[27]

In our study, morphologically defined myelodysplastic syndromes exhibited large heterogeneity in terms of mutation profiles, which was not fully captured by the presence of single-lineage or multilineage dysplasia, bone marrow blast percentage, and marrow hypocellularity or fibrosis. On the other hand, our analysis (along with increasing evidence from other investigations) suggests that additional subgroups of individuals with distinct clinical features and outcome can be identified based on specific molecular signatures.[7,22] In many cases, dominant genomic features include splicing gene mutations other than *SF3B1* (*SRSF2* and *U2AF1*) that occur early in disease history, determine specific phenotypes, and drive disease evolution.[7,22] These groups display different haematological phenotypes and prognoses, and importantly, specific co-mutation patterns (especially involving the higher-risk mutations of *RUNX1* and *ASXL1* genes) that account for clinical heterogeneity within each category.[5] These findings provide a solid basis for considering new genetically defined entities in future classification schemes.[11,12,20]

Regarding the clinical relevance of morphological features in the population of people with myelodysplastic syndromes, our study confirms existing evidence regarding no favourable prognosis with increased ring sideroblasts in the absence of *SF3B1* mutations, as well as the prognostic value of the number of dysplastic lineages.[5,6,23,28] These features are maintained in the harmonised classification as diagnostic qualifiers, alongside hypoplastic myelodysplastic syndromes, which identifies individuals with a high response rate to immunosuppressive treatments but with a heterogeneous genomic background.[3,9,29,30]

When focusing on individuals with increased blasts, our study confirms the prognostic relevance of bone marrow blast percentage,[10,31] with minor discrepancies possibly associated with different drug availability and treatment strategies across Europe and the USA. Consequently, the threshold of 10% bone marrow blasts is maintained in the harmonised myelodysplastic syndrome classification to define two distinct entities.[9]

However, our findings based on the analysis of genomic features from large populations of people with myelodysplastic syndromes with more than 10% blasts and AML suggest that the current threshold of 10% marrow blasts might not be suitable to recognise different disease entities from a biological point of view.[6,7] Similarities were observed between the AML-like myelodysplastic syndrome cluster and selected AML genomic signatures (*CEBPA*, *NPM1*, and *CBF*) and between myelodysplastic syndromes with splicing mutations and AML with myelodysplastic syndrome-related genomic abnormalities. Overall, a clear overlap in genomic signatures between myelodysplastic syndromes with more than 10% of blasts and AML was observed in 29% of cases. The increasing implementation of mutational screening could improve the definition of higher-risk myelodysplastic syndromes versus AML and perhaps optimise the inclusion of individuals in clinical trials according to molecular signatures.[11,12]

The most notable limitations of our study are its retrospective design and the restricted availability of data on loss of heterozygosity mapping, which might have resulted in missed cases of myelodysplastic syndromes with biallelic *TP53* inactivation in our cohorts.[8–10] Insufficient information on marrow cellularity and fibrosis in a subset of cases is likely to have resulted in underestimation of discordances related to myelodysplastic syndromes with fibrosis and hypoplastic myelodysplastic syndromes. Additionally, differences in practice patterns across participating centres from Europe and the USA might have had a differential effect on outcomes. Finally, a further validation of the reliability of the proposed harmonised system is needed.

Search strategy and selection criteria

No systematic literature search was conducted for this study. Relevant research papers, guidelines, and previous myelodysplastic syndrome classifications were considered.[3,7–10,18]

In summary, our study findings should contribute to the growing body of evidence for the evaluation of myelodysplastic syndrome classifications and provide a roadmap to harmonise the two classifications into a unified and globally adopted system.

Contributors

MDP, RSK, and AMZ designed the study and supervised the execution. MDP, RSK, AMZ, LL, SB, JPB, MM, SD, ES, GA, and MD collected and analysed the data. GM and ET accessed and verified the data. All authors participated in both rounds of the survey for definition of harmonised entities. MDP, RSK, AMZ, LL, SB, and JPB wrote the initial manuscript draft. All authors reviewed the initial draft, provided feedback, and agreed on the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Requests for access to data from the study should be addressed to the corresponding authors. All proposals requesting data access will need to specify how the data will be used, and all proposals will need the approval of the icMDS, GenoMed4All, and Synthema scientific committees before data release.

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References

1 Cazzola M. Myelodysplastic syndromes. *N Engl J Med* 2020; **383:** 1358–74.
2 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; **127:** 2391–405.
3 Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood* 2013; **122:** 2943–64.
4 Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. *Blood* 2013; **122:** 4021–34.
5 Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 2013; **122:** 3616–27.
6 Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood* 2015; **126:** 233–41.
7 Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. *J Clin Oncol Off J Am Soc Clin Oncol* 2021; **39:** 1223–33.
8 Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med* 2020; **26:** 1549–56.
9 Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia* 2022; **36:** 1703–19.
10 Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood* 2022; **140:** 1200–28.
11 Zeidan AM, Bewersdorf JP, Buckstein R, et al. Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the International Workshop for Myelodysplastic Syndromes. *Leukemia* 2022; **36:** 2939–46.
12 Shallis RM, Daver N, Altman JK, et al. Standardising acute myeloid leukaemia classification systems: a perspective from a panel of international experts. *Lancet Haematol* 2023; **10:** e767–76.
13 D'Amico S, Dall'Olio L, Rollo C, et al. MOSAIC: an artificial intelligence-based framework for multimodal analysis, classification, and personalized prognostic assessment in rare cancers. *JCO Clin Cancer Inform* 2024; **8:** e2400008.
14 Teh YW, Jordan MI, Beal MJ, Blei DM. Hierarchical Dirichlet processes. *J Am Stat Assoc* 2006; **101:** 1566–81.
15 Welcome to the SHAP documentation. 2018. https://shap.readthedocs.io/en/latest/# (accessed Feb 9, 2024).
16 Zeidan AM, Platzbecker U, Bewersdorf JP, et al. Consensus proposal for revised International Working Group response criteria for higher risk myelodysplastic syndromes. *Blood* 2023; **141:** 2047–61.

17 Roldán López De Hierro AF, Sánchez M, Puente-Fernández D, Montoya-Juárez R, Roldán C. A fuzzy Delphi consensus methodology based on a fuzzy ranking. *Mathematics* 2021; **9:** 2323.

18 Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. *NEJM Evid* 2022; **1:** EVIDoa2200008.

19 Sauta E, Robin M, Bersanelli M, et al. Real-world validation of molecular international prognostic scoring system for myelodysplastic syndromes. *J Clin Oncol Off J Am Soc Clin Oncol* 2023; **41:** 2827–42.

20 Cazzola M, Sehn LH. Developing a classification of hematologic neoplasms in the era of precision medicine. *Blood* 2022; **140:** 1193–99.

21 Bernard E, Hasserjian RP, Greenberg PL, et al. Molecular taxonomy of myelodysplastic syndromes and its clinical implications. *Blood J* 2024; published online July 3. http://doi.org/10.1182/blood.2023023727.

22 Nazha A, Komrokji R, Meggendorfer M, et al. Personalized prediction model to risk stratify patients with myelodysplastic syndromes. *J Clin Oncol Off J Am Soc Clin Oncol* 2021; **39:** 3737–46.

23 Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood* 2020; **136:** 157–70.

24 Gurnari C, Piciocchi A, Soddu S, et al. Myelodysplastic syndromes with del(5q): a real-life study of determinants of long-term outcomes and response to lenalidomide. *Blood Cancer J* 2022; **12:** 132.

25 Haase D, Stevenson KE, Neuberg D, et al. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. *Leukemia* 2019; **33:** 1747–58.

26 Ball S, Loghavi S, Zeidan AM. TP53-altered higher-risk myelodysplastic syndromes/neoplasms and acute myeloid leukemia: a distinct genetic entity with unique unmet needs. *Leuk Lymphoma* 2023; **64:** 540–50.

27 Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022; **140:** 1345–77.

28 Malcovati L, Della Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol Off J Am Soc Clin Oncol* 2005; **23:** 7594–603.

29 Lim ZY, Killick S, Germing U, et al. Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin. *Leukemia* 2007; **21:** 1436–41.

30 Della Porta MG, Malcovati L, Boveri E, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. *J Clin Oncol Off J Am Soc Clin Oncol* 2009; **27:** 754–62.

31 Estey E, Hasserjian RP, Döhner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. *Blood* 2022; **139:** 323–32.