Higher-risk MDS and AML: How new guidelines are changing diagnosis, classification and management

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Presenting symptoms and the diagnostic process for MDS and AML

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Presenting symptoms of MDS and AML

MDS[1]

- Easy bruising
- Pallor
- Pale conjunctiva
- Mucosal bleeding
- Hypotension
- Tachycardia
- Emphysema
- Heart failure

- Epistaxis[1,2]
- Petechiae[1,2]
- Fatigue[1,2]
- Headache[1,2]
- Angina pectoris[1,2]
- Frequent infections[1,2]
- Exercise intolerance[1,2]
- Major bleeding[1,2]

AML[2]

- Gingival haemorrhage
- Fever
- Adenopathy
- Dyspnoea
- Confusion
- Palpitations
- Coma visual disturbances
- Hypoxia
- Organomegaly
- Respiratory failure
- Seizures
- Menorrhagia
- Claudication

AML, acute myeloid leukaemia; GI, gastrointestinal; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Barzi A, Sekeres MA. *Cleve Clin J Med*. 2010;77:37–44; 2. Smith M, et al. *Crit Rev Oncol Hemat*. 2004;50:197–222.

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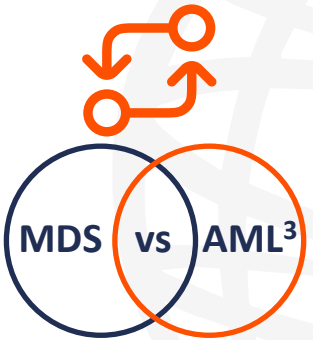
Modes of presentation

Incidental cytopenia[1]

- ICUS[2]
- CCUS[2]

Prior cytotoxic therapy[3]



AML, acute myeloid leukaemia; CCUS, clonal cytopenia of undetermined significance; ICC, International Consensus Classification; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Samiev D, et al. *Korean J Fam Med*. 2014;35:111–8; 2. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 3. Khoury JD, et al. *Leukemia*. 2022;36:1703–19.

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Diagnosing MDS or AML

Laboratory parameters (MDS only)[1]

- Ferritin
- Transferrin
- Transferrin saturation
- Reticulocyte counts
- Vitamin B12
- Folate concentrations
- Haptoglobin
- Creatinine levels

Blood counts (MDS only)[1]

Blood counts

- Evaluate cytopenia

Cytomorphology

- Dysplastic features

Bone marrow aspiration[1,2]

Cytomorphology

- Dysplastic features
- Blast counts

Cytogenetics

Molecular studies

Bone marrow biopsy[1,2]

Cellularity and fibrosis

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712.

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Categorization of MDS by WHO and ICC

<table>
<tr><th>Blast burden</th><th>Genetic</th><th colspan="4">WHO 2022[1]</th><th>ICC 2022[2]</th></tr>
<tr><td rowspan="3">BM blasts <5%
PB blasts <2%</td><td>del(5q)</td><td colspan="3">MDS-5q</td><td rowspan="5">AML with defining genetic abnormalities*</td><td>MDS-del(5q)</td></tr>
<tr><td>SF3B1</td><td colspan="3">MDS-SF3B1</td><td>MDS-SF3B1</td></tr>
<tr><td>Other</td><td colspan="2">MDS-LB</td><td rowspan="3">MDS-biTP53</td><td>MDS, NOS
Without dysplasia
or with SL/ML dysplasia</td></tr>
<tr><td>BM blasts 5–9%
PB blasts 2–4%</td><td>MDS-IB1</td><td rowspan="2">MDS-f</td><td>MDS-EB†</td></tr>
<tr><td>BM blasts 10–19%
PB blasts 5–19%
Auer rods</td><td>MDS-IB2</td><td>MDS/AML‡
Unless AML-defining cytogenetic or molecular abnormality*</td></tr>
</table>

*AML except *BCR::ABL* and *CEBPA* mut (≥20% blasts required). †PB blasts 2–9%. ‡PB blasts 5–19% and no requirement for auer rods.
AML, acute myeloid leukaemia; BM, bone marrow; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, MDS with excess blasts; MDS-f, MDS with fibrosis; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-NOS, MDS not otherwise specified; ML, multilineage; PB, peripheral blood; SL, single lineage; WHO, World Health Organization.
1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

WHO 2022 classification of AML[1]

Myeloid neoplasm post-cytotoxic therapy[1]

- Acute promyelocytic leukaemia with *PML::RARA* fusion
- AML with *RUNX1::RUNX1T1* fusion
- AML with *CBFB::MYH11* fusion
- AML with *DEK::NUP214* fusion
- AML with *RBM15::MRTFA* fusion
- AML with *BCR::ABL1* fusion
- AML with *KMT2A* rearrangement
- AML with *MECOM* rearrangement
- AML with *NUP98* rearrangement
- AML with *NPM1* mutation
- AML with *CEBPA* mutation

AML with defining genetic abnormalities[1]

AML, myelodysplasia-related[1]

Defining cytogenetic abnormalities

- Complex karyotype (≥3 abnormalities)
- 5q del or loss of 5q due to unbalanced translocation
- Monosomy 7, 7q del or loss of 7q due to unbalanced translocation
- 11q del
- 12p del or loss of 12p due to unbalanced translocation
- Monosomy 13 or 13q del
- 17p del or loss of 17p due to unbalanced translocation
- Isochromosome 17q
- Idic(X)(q13)

Defining somatic mutations

ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

AML with other defined genetic alterations[2]

- AML with *RUNX1T3(CBFA2T3)::GLIS2* fusion
- AML with *KAT6A::CREBBP* fusion
- AML with *FUS::ERG* fusion
- AML with *MNX1::ETV6* fusion
- AML with *NPM1::MLF* fusion

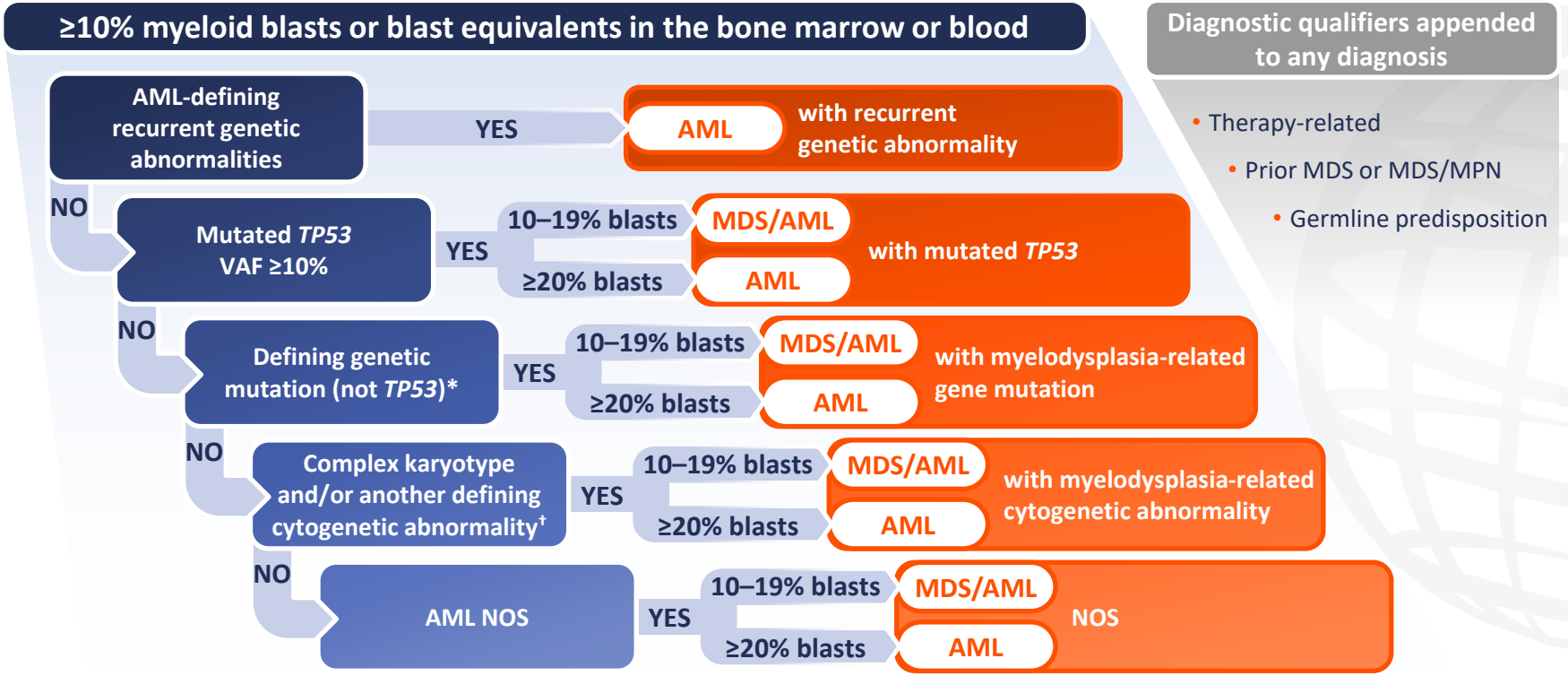
AML defined by differentiation[1]

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute basophilic leukaemia
- Acute myelomonocytic leukaemia
- Acute monocytic leukaemia
- Acute erythroid leukaemia*
- Acute megakaryoblastic leukaemia

*Previously pure erythroid leukaemia. AML, acute myeloid leukaemia; WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Li W. In: Li W (ed). *Leukemia*. Brisbane, Australia: Exon Publications, 2022;1–21.

Hierarchical classification of AML: ICC



**ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1* and/or *ZRSR2*. †del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/(add(12p), i(17q), -17/add(17p)/del(17p), del(20q) or idic(X)(q13). AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MPN, myeloproliferative neoplasms; NOS, not otherwise specified; VAF, variant allele frequency; WHO, World Health Organization.

Döhner H, et al. *Blood*. 2022;140:1345–77.

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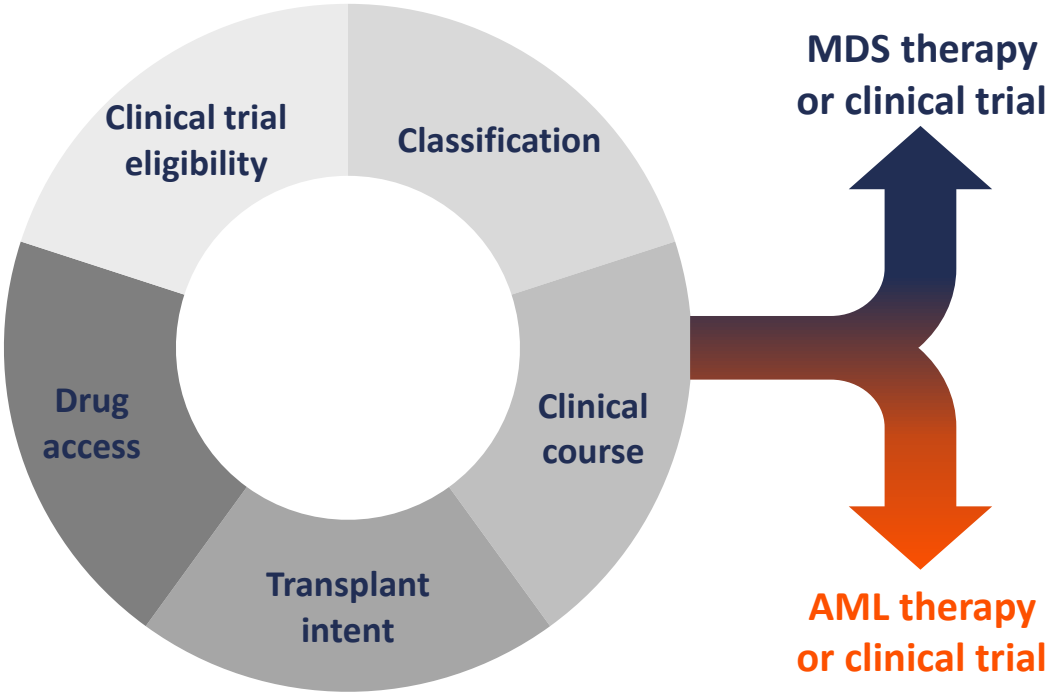
MDS vs AML: Treatment considerations[1–3]



AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712; 3. Döhner H, et al. *Blood*. 2022;140:1345–77.

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Pathophysiology of MDS and AML and how it relates to disease classification

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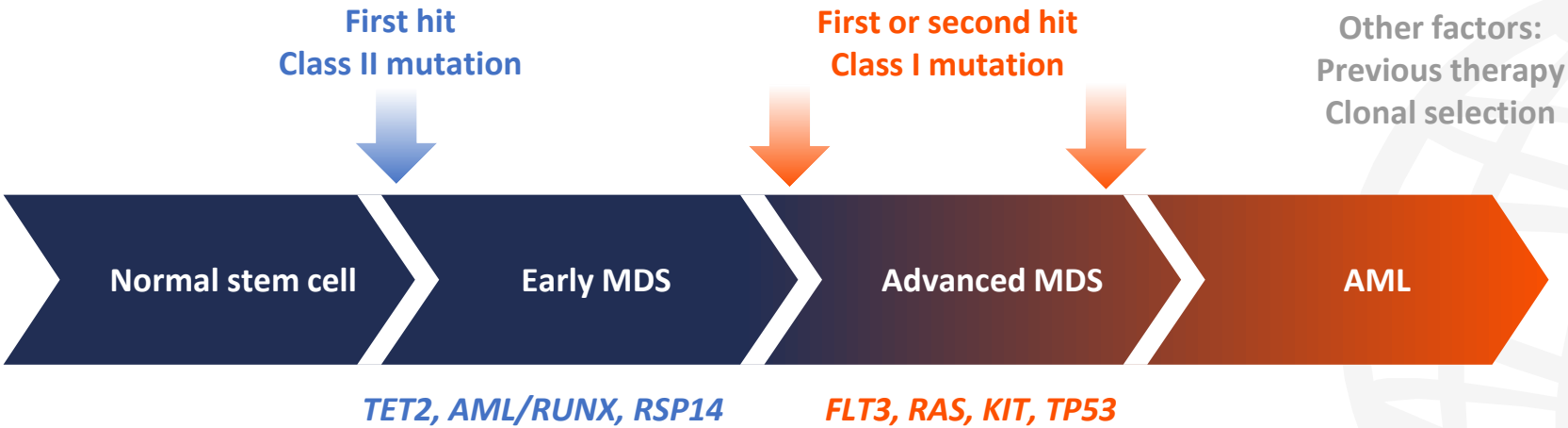
Model of progression from MDS to AML[1]



MDS[2]

- Cytopenia
- Inefficient haematopoiesis
- Dysplasia in one or more myeloid cell lineages
- Increased risk of development of AML

AML[3]

- Clonal expansion of myeloid blasts in the bone marrow, peripheral blood or other tissues

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022).

1. Porwit A, Saft L. *J Hematop.* 2011;4:69–79; 2. Visconte V, et al. *Blood Res*. 2014;49:216–27; 3. He GL, et al. *Cancer Cell Int*. 2014;14:111.

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WHO and ICC classification comparison

WHO[1]

MDS = myelodysplastic neoplasms

MDS with defining genetic abnormalities

- MDS with low blasts and isolated 5q deletion
- MDS with low blasts and *SF3B1* mutation
- MDS with biallelic *TP53* inactivation

MDS, morphologically defined

- MDS with low blasts (MDS-LB)
- MDS, hypoplastic (MDS-h)
- MDS with increased blasts (MDS-IB)
  - MDS-IB1
  - MDS-IB2
  - MDS with fibrosis (MDS-f)

ICC[2]

MDS = myelodysplastic syndromes

- MDS with del(5q)
- MDS with mutated *SF3B1*
- MDS with mutated *TP53*
- MDS, not otherwise specified (MDS, NOS)
  - MDS, NOS without dysplasia
  - MDS, NOS with single lineage dysplasia
  - MDS, NOS with multilineage dysplasia
- MDS with excess blasts (MDS-EB)
- MDS/AML
  - MDS/AML with mutated *TP53*
  - MDS/AML with myelodysplasia-related gene mutations
  - MDS/AML with myelodysplasia-related cytogenetic abnormalities
  - MDS/AML, not otherwise specified

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

Validation of MDS guideline updates (1/3)

Retrospective, single-centred cohort study of patients with MDS

Validation of WHO 2022 guidelines

Jan 2018 → Dec 2021

N=118

WHO 2022 classification	% lower-risk patients	Median OS
Genetically defined		
• MDS-*SF3B1*	91 (IPSS-R/IPSS-M)	7.0 years
• MDS-bi*TP53*	14 (IPSS-R/IPSS-M)	0.8 years
Morphologically defined		
• MDS-LB	71 (IPSS-R/IPSS-M)	NR
• MDS-IB1	21 (IPSS-R); 16 (IPSS-M)	NR
• MDS-IB2	0 (IPSS-R); 7 (IPSS-M)	1.5 years

- Differing mutational features were prominently associated with both morphologically and genetically defined subgroups
- OS differed between the defined subgroups

IPSS-M, international prognostic scoring system – molecular; IPSS-R, IPSS – revised; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; NR, not reached; OS, overall survival; WHO, World Health Organization.

Khanna V, et al. *Blood*. 2022;140(Suppl. 1):6955–7.

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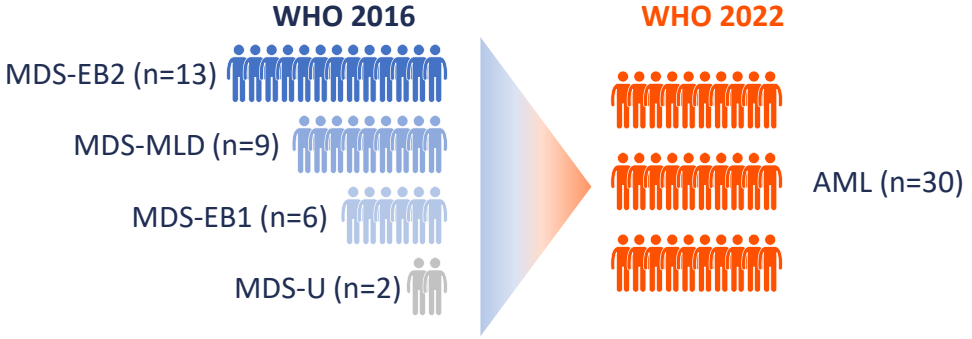
Validation of MDS guideline updates (2/3)

Patients with newly diagnosed MDS based on WHO 2016 criteria → **Reclassified according to WHO 2022 guidelines**

N=852

Aug 2016 → Sep 2021

30 subjects with *NPM1* mutation were reclassified as AML



WHO 2022 classification	Median OS
MDS-5q	24 months
MDS-*SF3B1*	58 months
MDS-bi*TP53*	10 months
MDS-LB	Unreached
MDS-h	Unreached
MDS-IB1	24 months
MDS-IB2	26 months
MDS-f	15 months

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-EB, myelodysplastic syndromes with excess blasts; MDS-f, MDS with fibrosis; MDS-h, MDS, hypoplastic; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; MDS-U, myelodysplastic syndromes, unclassifiable; OS, overall survival; WHO, World Health Organization. Zhang Y, et al. *Blood*. 2022;140(Suppl. 1):1343–5.

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Validation of MDS guideline updates (3/3)

Retrospective, single-centred cohort study of patients with MDS

N=2,231

Reclassified by WHO 2022 and ICC 2022 proposed criteria

WHO 2022

- MDS-IB1 and MDS-IB2 had similar mOS (p=0.726)

WHO 2022 and ICC 2022

- MDS with mutated *SF3B1* had best mOS across all subtypes
- Categories for MDS-m*TP53* had worst survival of all subtypes

ICC 2022

- MDS-MLD had significantly worse mOS compared with MDS-SLD (49.6 months vs 79.4 months; p<0.001)

ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-IB, MDS with increased blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-m*TP53*, MDS with mutated *TP53*; MDS-SLD, MDS with single lineage dysplasia; mOS, median overall survival; WHO, World Health Organization.

Ball S, et al. *Blood*. 2022;140(Suppl. 1):1118–20.

Impact of WHO and ICC 2022 on AML diagnosis

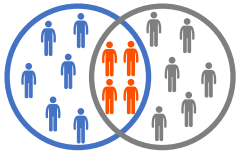
1,451 non-therapy-related cases with MDS or AML according to 2017 revised 4th edition WHO guidelines

WHO 2022 guidelines

- 746 patients diagnosed with AML
- **<1%** of cases were **upgraded from MDS to AML** compared with the revised 4th edition WHO guidelines

ICC 2022 guidelines

- 742 patients diagnosed with AML
- 137 patients diagnosed with MDS/AML
- **10%** of cases were **upgraded from MDS to AML** compared to the revised 4th edition WHO guidelines, **mainly due to the introduction of the MDS/AML class**



4/16 patients with **MDS-EB2 according to the revised 4th edition WHO** guidelines were **upgraded to AML using both the WHO 2022 and ICC 2022 guidelines**

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, myelodysplastic syndrome with excess blasts; WHO, World Health Organization.

Huber S, et al. *Blood*. 2022;140(Suppl. 1):555–6.

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Updated prognostic risk stratification and its impact on patient management

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Comparison between IPSS-R and IPSS-M

IPSS-R

Risk based on haematologic and cytogenetic features

- 5 cytogenetic risk categories
- Haemoglobin level
- Marrow blast percentage
- Platelet count

Factors from IPSS-R conserved in IPSS-M

IPSS-M

Risk based on haematologic parameters, cytogenetic abnormalities and somatic mutations

Additional factors in IPSS-M

- 16 main effect genes
- 15 residual genes
- Mutations associated with worse outcome:
  - *TP53*$^{\text{multihit}}$
  - *FLT3*
  - *MLL*$^{\text{PTD}}$

IPSS, International Prognostic Scoring System; M, Molecular; R, Revised.

Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

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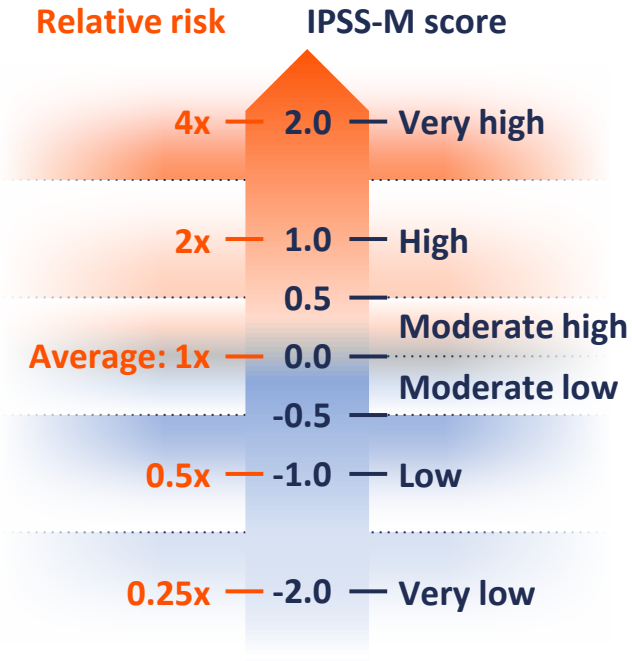
IPSS-M risk categories

The IPSS-M score corresponds to the relative risk compared with an ‘average’ patient



A patient’s IPSS-M score can be calculated using the IPSS-M web calculator*

*www.mds-risk-model.com
IPSS-M, Molecular International Prognostic Scoring System.
Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

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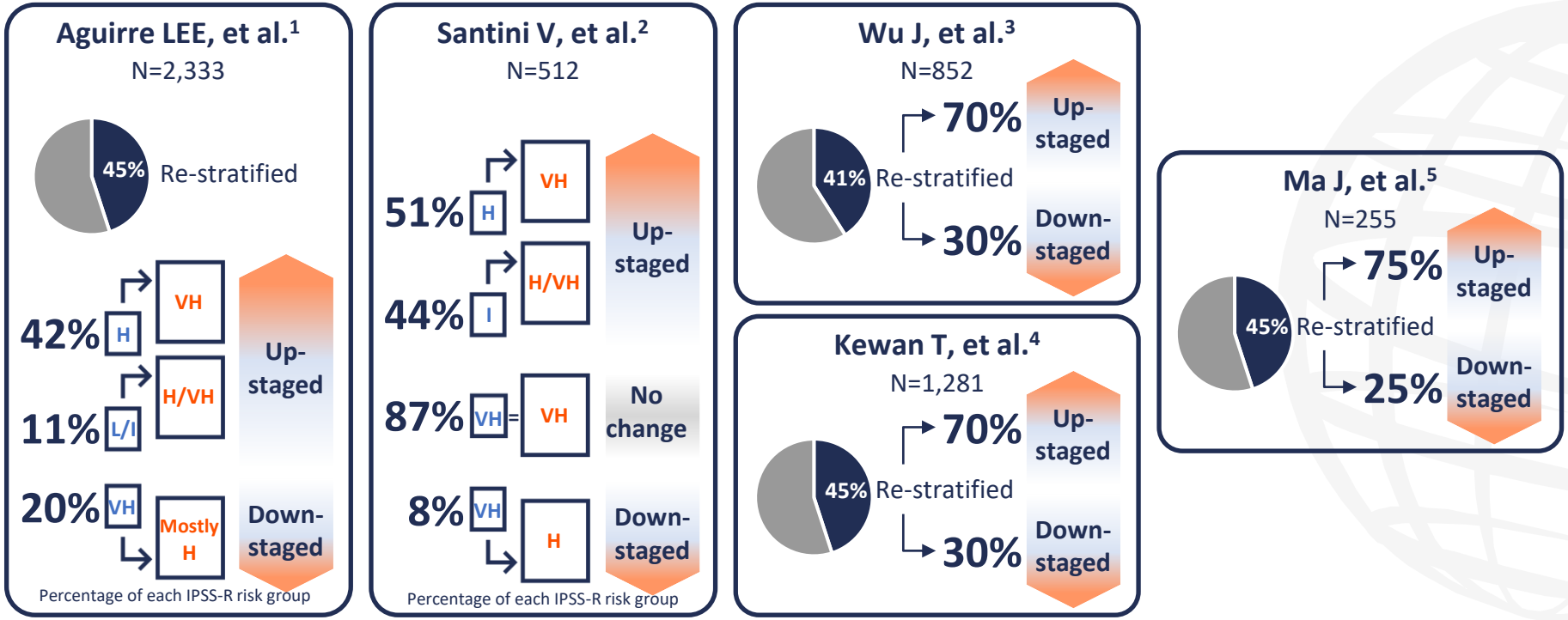
Validation of the IPSS-M: Data from ASH 2022



ASH, American Society of Hematology; H, high risk; I, intermediate risk; IPSS, International Prognostic Scoring System; L, low risk; M, Molecular; R, Revised. sig, significant; VH, very high risk. 1. Aguirre LEE, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 465; 2. Santini V, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 559; 3. Wu J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 1780; 4. Kewan T, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3087; 5. Ma J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 4400.

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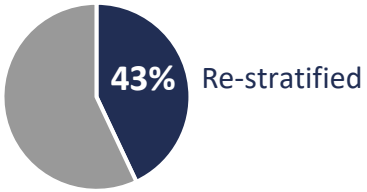
Real-world use of IPSS-R vs IPSS-M: Data from ASH 2022

Jáuregui SN, et al.

Patients with MDS from a single centre

N=126



17.4% of re-stratifications of patients had a potential impact on therapeutic choices

- Of these, 11.9% of patients were up-staged, 5.6% were down-staged

9.5% would have actually been treated differently if IPSS-M was initially applied

- Some of the higher-risk patients were not candidates for intensive care due to age and comorbidities

ASH, American Society of Hematology; IPSS, International Prognostic Scoring System; M, Molecular; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); R, Revised; WHO, World Health Organization.

Jáuregui SN, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3096.

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ELN 2022: Genetic risk classification changes

- ***FLT3*-ITD allelic ratio is no longer considered in the risk classification**
  - AML with *FLT3*-ITD (without adverse-risk genetic lesions) is categorized in the intermediate-risk group, irrespective of allelic ratio or concurrent presence of an *NPM1* mutation
- **AML with myelodysplasia-related gene mutations are now in the adverse-risk group**
  - Mutations include pathologic variants in at least one of the following:
    - *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **In-frame mutations in the leucine zipper region of *CEBPA* are now classified in the favourable-risk group**
  - Classification is irrespective of biallelic or monoallelic mutations
- **The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML are now classified as adverse risk**
- **Additional disease-defining, recurring cytogenetic abnormalities are now in the adverse-risk group**
  - Include mutations in t(3q26.2;v) involving the *MECOM* gene, or t(8;16)(p11.2;p13.3) associated with *KAT6A::CREBBP* gene fusion
- **Hyperdiploid karyotypes with multiple trisomies are no longer on the list of complex karyotypes or in the adverse risk group**

AML, acute myeloid leukaemia; ELN, European LeukemiaNet; ITD, internal tandem duplication.

Döhner H, et al. *Blood*. 2022;140:1345–77.

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