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APOIO
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bp Educação
e Pesquisa

A nova classificação para SMD: o que muda, o que fica, e o que irá mudar?

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•De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e com a RDC 96/2008 da ANVISA, declaro que:

- Pesquisa Clínica – como investigador: Roche, Novartis, BioCryst, AstraZeneca
- Apresentações Científicas – Novartis, Roche, Alexion, Janssen, AstraZeneca
- Atividades de Consultoria – Roche, Alexion, Janssen, Pfizer, BioCryst, AstraZeneca
- Speaker - Novartis, Pfizer, Alexion, AstraZeneca

•Declaro não ter ações, opções, patentes ou royalties das empresas supracitadas.

Meus pré-requisitos para participar destas atividades são o intercâmbio científico, a autonomia do pensamento científico, a independência de opinião e a liberdade de expressão, aspectos estes respeitados pela Novartis.

Esta apresentação reflete a minha opinião pessoal e não a do meu empregador ou universidade; é para efeitos de discussão científica independente Por favor, consulte a informação de prescrição nas bulas aprovadas no Brasil.

MYELOYDYSPLASTIC NEOPLASMS (MDS)

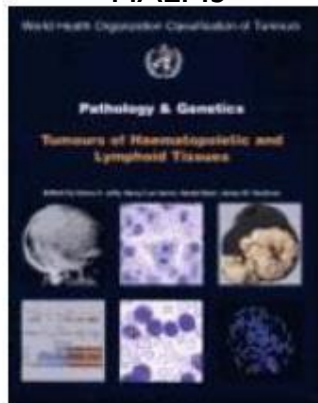
- Threshold for dysplasia set at 10% for all lineages
- Single lineage and multilineage dysplasia is optional- No. of dysplastic lineages is dynamic ,represents phenotypic manifestation of clonal evolution
- MDS, Unclassifiable has been removed due to incorporation of CCUS
- MDS with low blasts (MDS-LB) and MDS with increased blasts (MDS-IB) – cut offs retained.

CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

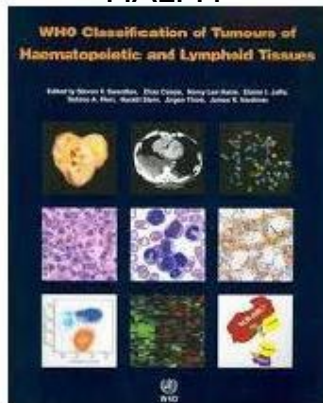
FAB 1976



WHO 2001 HAEM3



WHO 2008 HAEM4



WHO 2016 HAEM4R



WHO 2022 HAEM5



ICC 2022



FUTURE?



CLASSIFICATIONS OF HEMATOLOGICAL MALIGNANCIES

Special Report

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elise Campo,¹ Elaine S. Jaffe,² James R. Cook,³ Lenica Quintanilla-Martinez,⁴ Steven H. Swerdlow,⁵ Kenneth C. Anderson,⁶ Pierre Brousset,⁷ Lorenzo Corioni,⁸ Laurence de Leval,⁹ Stefan Dirnhofer,¹⁰ Ahmet Dogan,¹¹ Andrew L. Feldman,¹² Falco Fend¹³, Jonathan W. Friedberg,¹⁴ Philippe Gaulard,¹⁵ Paolo Ghia,¹⁶ Steven M. Horowitz,¹⁷ Rebecca L. King,¹⁸ Gilles Salles,¹⁹ Jesu San-Miguel,²⁰ John F. Seymour,²¹ Steven P. Treon,²² Julie M. Vose,²³ Emanuele Zuccato,²⁴ Francesco d'Amore,²⁵ Stephen Davies,²⁶ Wing-Yan Au,²⁷ Carlos Barronuevo,²⁸ Leif Bergsagel,²⁹ Wing C. Chan,³⁰ Jeffrey I. Cohen,³¹ Eric D. Hsi,³² Brad S. Kahl,³³ Won-Seog Kim,³⁴ Shaji Kumar,³⁵ Am S. Lacasse,³⁶ Camille Laurent,³⁷ John P. Lazarus,³⁸ Frank Morschhauser,³⁹ Eric D. Hsi,⁴⁰ Brad S. Kahl,⁴¹ Marina Narbaitz,⁴² Maria Victoria Mateos,⁴³ Stefano A. Pileri,⁴⁴ Elizabeth Macintyre,⁴⁵ An M. Melnick,⁴⁶ Michael P. Linch,⁴⁷ Shigeo Nalamura,⁴⁸ Marina Narbaitz,⁴⁹ Astrid Pavlovsky,⁵⁰ Stefano A. Pileri,⁵¹ Margareta A. Shepp,⁵² Barbara Pro,⁵³ Louis M. Staudt,⁵⁴ Vincent Tournayre,⁵⁵ Thomas Toussy,⁵⁶ Laurie Selim,⁵⁷ Margaret A. Sherr,⁵⁸ Sonali M. Sweth,⁵⁹ Louis M. Staudt,⁶⁰ Catherine Thieblemont,⁶¹ Steven T. Rosen,⁶² Birgitta Toussy,⁶³ and Andrew D. Zelenetz,⁶⁴

Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,¹ Antillo Orazi,² Robert P. Hasserjian,³ Michael J. Borowitz,⁴ Katherine R. Calvo,⁵ Hans-Michael Kvasnicka,⁶ Sa A. Wang,⁷ Adnan Bajaj,⁸ Tiziana Barbui,⁹ Susan Branford,¹⁰ Carlos E. Bueso-Ramos,¹¹ Jorge E. Cortes,¹² Paola Di Ci, Courtney D. D'Amico,¹³ Henri Domitrov,¹⁴ Eric J. Duncavage,¹⁵ Benjamin L. Ebert,¹⁶ Elinor H. Estey,¹⁷ Fabio Facchetti,¹⁸ Kathryn Foucar,¹⁹ Naama Ganig,²⁰ Gabriela S. Hobbs,²¹ Ronald Giannelli,²² Lucy A. Godley,²³ Benjamin L. Ebert,²⁴ Nicola Gökbuget,²⁵ Jason Gotlib,²⁶ Eva Hellstrom-Lindberg,²⁷ Naama Ganig,²⁸ Umberto Gianni,²⁹ Eric J. Duncavage,³⁰ Benjamin L. Ebert,³¹ Nicola Gökbuget,³² Jason Gotlib,³³ Michelle M. Le Beau,³⁴ Mignon L.-C. Loh,³⁵ Bob Löwenberg,³⁶ Ronald Hoffman,³⁷ Elias J. Jabbour,³⁸ Jean-Jacques Kiladjan,³⁹ Kimmo Niemeyer,⁴⁰ Olatoye M. Odunle,⁴¹ Umberto Gianni,⁴² Lucy A. Godley,⁴³ Benjamin L. Ebert,⁴⁴ Nicola Gökbuget,⁴⁵ Jason Gotlib,⁴⁶ Charles A. Schiffer,⁴⁷ Ching-Hon Pui,⁴⁸ Jerald P. Radich,⁴⁹ Sushil Ogawa,⁵⁰ Alessandro M. Vannucchi,⁵¹ Parvath M. Stone,⁵² Martin S. Tallman,⁵³ Annette Schmitt-Graeff,⁵⁴ Akiko Shimamura,⁵⁵ Anders Reiter,⁵⁶ Maria Rozman,⁵⁷ Martina Rudelius,⁵⁸ Charles G. Mullighan,⁵⁹ Andrew H. Wei,⁶⁰ Olga K. Weinberg,⁶¹ Hwei-Fang Tien,⁶² Agnieszka Wierzbowska,⁶³ Mario Cazzola,⁶⁴ Jarmut Doliner,⁶⁵ and Ayalew Tefferi,⁶⁶

Special Report

WHO 2022 HAEM5

ICC 2022

The classification of myeloid neoplasms and acute leukemias is a dynamic process that evolves with the discovery of new genetic and clinical data. The 2016 WHO classification of myeloid neoplasms and acute leukemias (ICC 2016) was a landmark document that provided a common framework for the classification of these disorders. The 2022 WHO classification (ICC 2022) represents a significant update to the 2016 classification, reflecting the latest advances in our understanding of the biology of these disorders. The 2022 classification is based on a consensus process that involved the collaboration of experts from around the world. The 2022 classification is a dynamic process that will continue to evolve as new data emerge.

The classification of myeloid neoplasms and acute leukemias was last updated in 2016 within a collaboration between the World Health Organization (WHO), the European Association for Hematopathology, and the International Society for Hematopathology. This collaboration was primarily based on input from a clinical advisory committee composed of pathologists, hematologists, and oncologists. The 2016 classification was a landmark document that provided a common framework for the classification of these disorders. The 2022 classification is a dynamic process that will continue to evolve as new data emerge.

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Validation of WHO 2022 and ICC 2022 MDS Classification Systems: Background

- 2 sets of guidelines published in 2022 replace WHO 2016 for classification of myeloid neoplasms
 - WHO 5th edition¹
 - ICC²
- Some parameters differ between WHO and ICC 2022 classification systems³
 - Inclusion of MDS with ring sideroblasts in WHO but not ICC
 - Nomenclature for categories of MDS with excess blasts
 - Details of genetically defined subgroups of *SF3B1* and *TP53* mutation
- Current International Consortium for MDS report examined outcomes for WHO and ICC MDS subtypes using large dataset of patients³

Definition of Cytopenia

- Cytopenia definitions are harmonized for CCUS, MDS, and MDS/MPN

Anaemia- **Hb <13g/dL** in males and **<12 g/dL** in females

Leukopenia -Absolute neutrophil count $<1.8 \times 10^9/L$

Thrombocytopenia -**Platelets $<150 \times 10^9/L$**

CLONAL HAEMATOPOIESIS

Both classifications now include clonal haematopoiesis

WHO HAEM 5

2. Myeloid proliferations and neoplasms

Myeloid precursor lesions

Clonal Haematopoiesis

Introduction

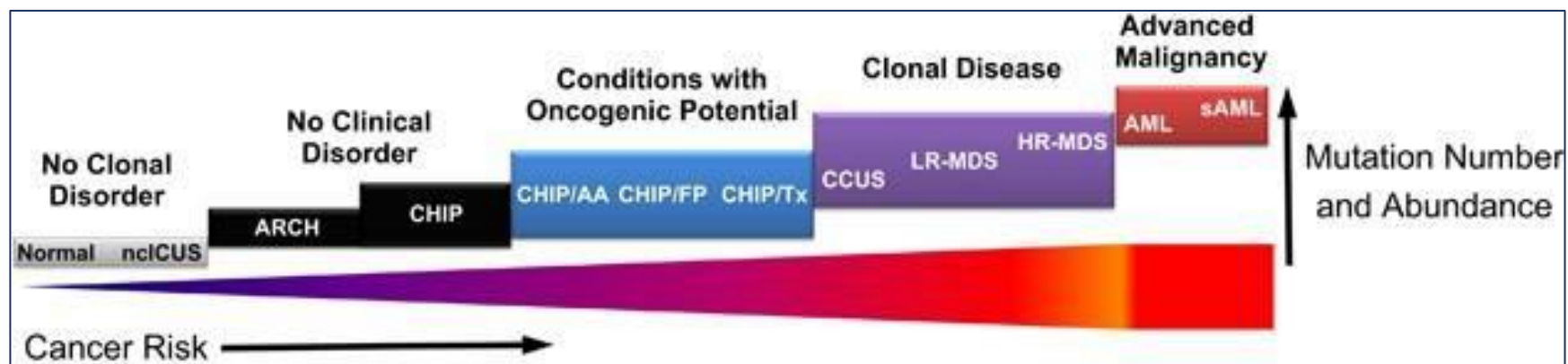
Clonal haematopoiesis

Clonal cytopenias of undetermined significance

ICC 2022

Premalignant clonal cytopenias and MDSs

Clonal cytopenia of undetermined significance (CCUS) and other pre-malignant clonal cytopenias





MYELOID PRECURSOR LESIONS (NEW)

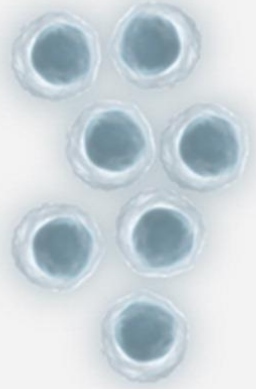
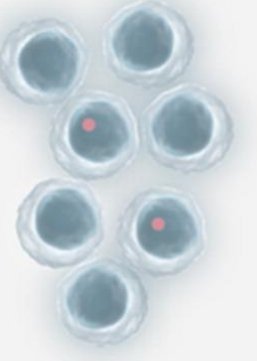
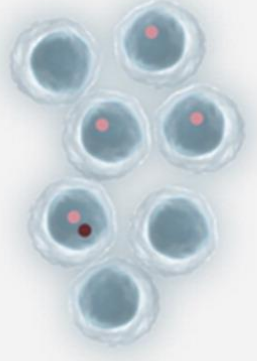
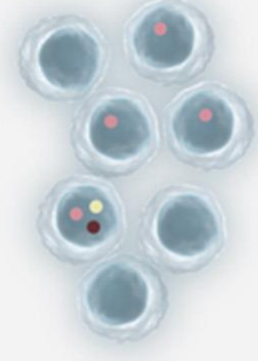
- **Clonal haematopoiesis**
- **CH** is included in the classification is to codify these myeloid precursor lesions
- **Def:** Clonal haematopoiesis (CH) refers broadly to the presence of a population of cells derived from a mutated multipotent stem/progenitor cell harbouring a selective growth advantage in the absence of unexplained cytopenias, haematological cancers, or other clonal disorders.
- More specific emerging associations, such as those characterizing the VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic UBA1 mutations) : Inflammation-→CH



MYELOID PRECURSOR LESIONS (NEW)

- *Clonal haematopoiesis of indeterminate potential (CHIP)* :
 - CH harbouring somatic mutations of myeloid malignancy-associated genes
 - variant allele fraction (VAF) of $\geq 2\%$ ($\geq 4\%$ for X-linked gene mutations in males)
 - No diagnosed haematologic disorder or unexplained cytopenia
- *Clonal cytopenia of undetermined significance (CCUS)* is defined as CHIP detected in the presence of one or more persistent cytopenias that are otherwise unexplained by haematologic or non-haematologic conditions and that do not meet diagnostic criteria for defined myeloid neoplasms.

MDS Precursor States

	Normal Hematopoiesis	CHIP	CCUS	Myeloid Neoplasm
Genotype				
Phenotype	Normal blood count; nonclonal cytopenia	Normal blood count; CHIP might be incidentally detected in a nonclonal cytopenia of other origin	Varying degree of uni- or multilineage cytopenia	Varying degree of uni- or multilineage cytopenia; abnormal morphologic features or immature cells as in WHO classification

CLONAL HAEMATOPOIESIS

Idiopathic Cytopenia of Undetermined Significance (ICUS)	Clonal Hematopoiesis of Indeterminate Potential (CHIP)	Clonal Cytopenia of Undetermined Significance (CCUS)	MDS/AML
<p>Cytopenia: Yes</p> <p>Dysplasia: No/≤10</p> <p>Mutations: No</p> <p>VAF: N/A</p>	<p>Cytopenia: No</p> <p>Dysplasia: No/≤10</p> <p>Mutations: Yes</p> <p>VAF: ≥2%</p>	<p>Cytopenia: Yes (≥4 months)</p> <p>Dysplasia: No/≤10</p> <p>Mutations: Yes</p> <p>VAF: ≥2%</p>	<p>Cytopenia: Yes</p> <p>Dysplasia: Yes/≥10%</p> <p>Mutations: Yes</p> <p>VAF: ?</p>

Hb <13 g/dl (M) and <12 g/dL (F), ANC <1,8x10⁹/L, PLT <150x 10⁹/L

TET2, DNMT3A, ASXL1, SRSF2, ZRSR2, SF3B1, U2AF1, IDH1/2, RUNX1, EZH2, JAK2, CBL, KRAS, CUX1, TP53

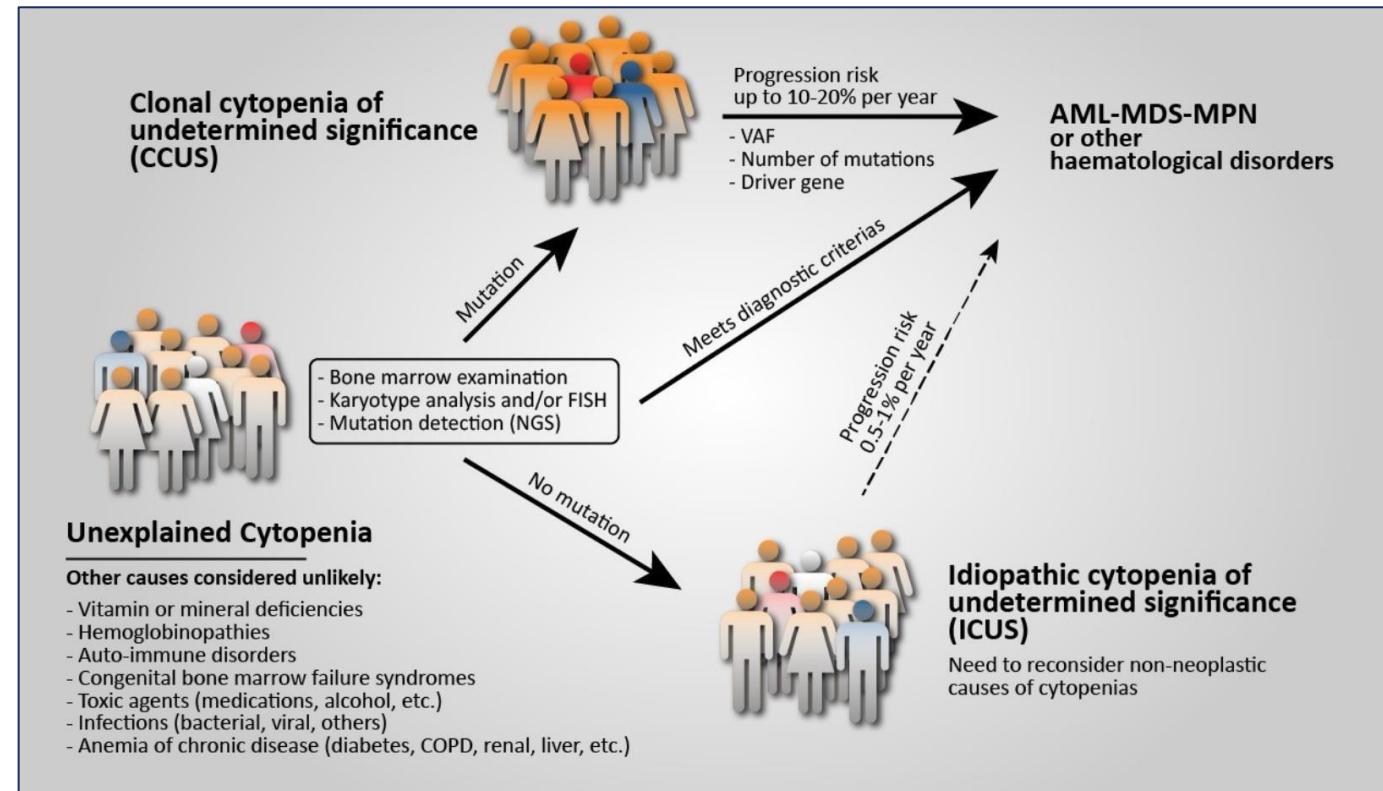




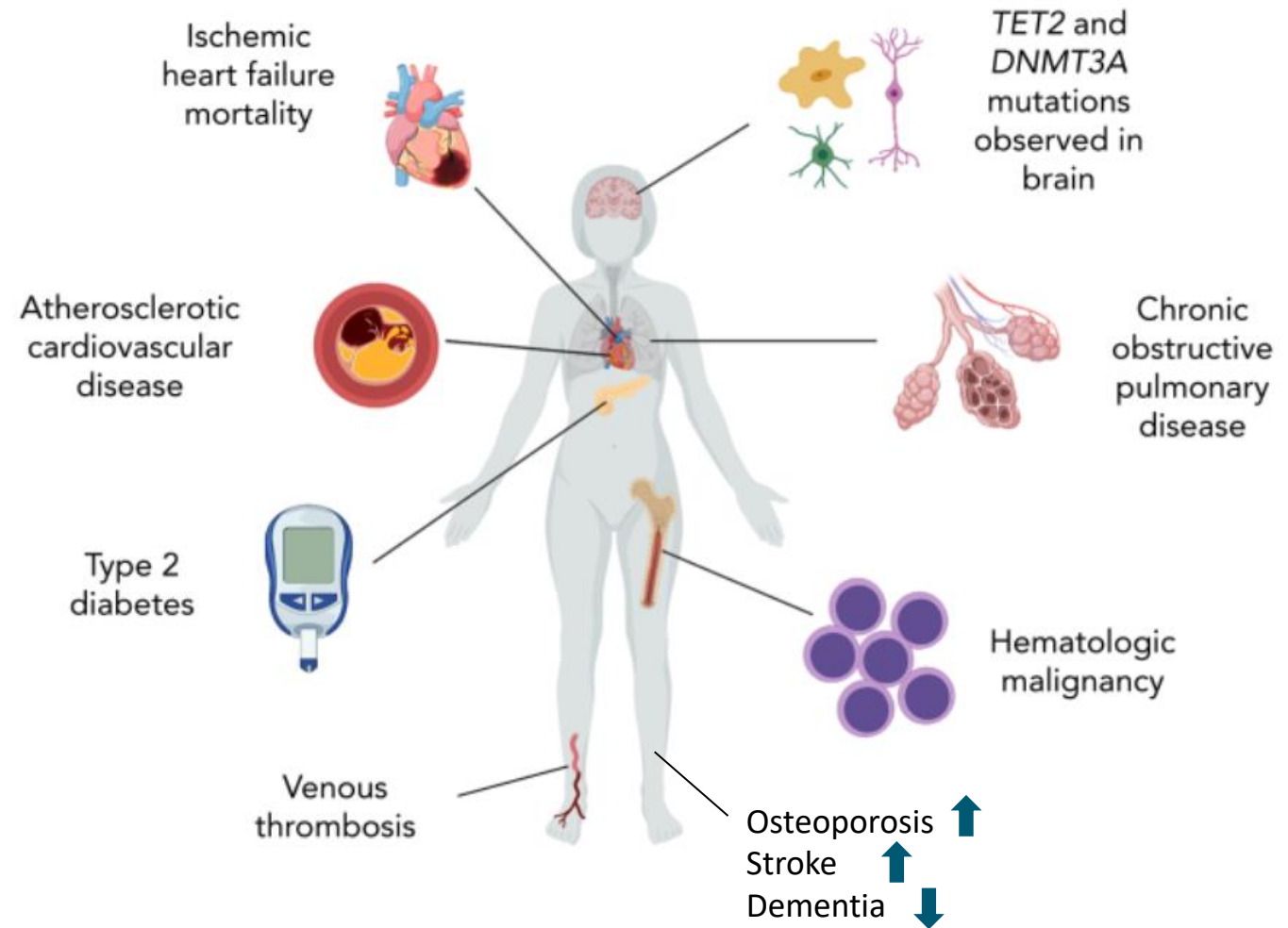
TABLE 2 Characteristics of ICUS/CHIP/CCUS.^{7,28,29,56}

Features	CHIP	ICUS	CCUS	MDS
Cytopenia	No	Yes	Yes	Yes
Dysplasia	No	No or minimal (nondiagnostic for MDS)	No or minimal (nondiagnostic for MDS)	Yes
Somatic mutations	Yes at a variant allele frequency $\geq 2\%$. Most commonly: <i>DNMT3A</i> , <i>TET2</i> , <i>ASXL1</i>	No. ICUS defined by absence of clonality	<ul style="list-style-type: none"> • Yes, as in CHIP 	Yes. Up to 85% of patients
Risk of progression	Very low (0.5%–1% per year) outside of therapy related setting.	Very low	Up to 80% at 5 years but determined by mutational patterns.	-

Abbreviations: CCUS, clonal cytopenia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic syndromes.

The Consequences of CHIP

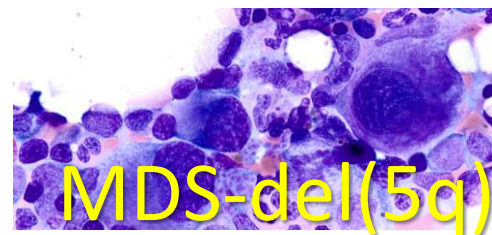
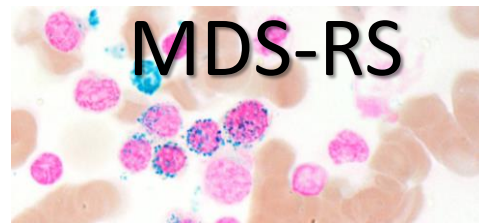
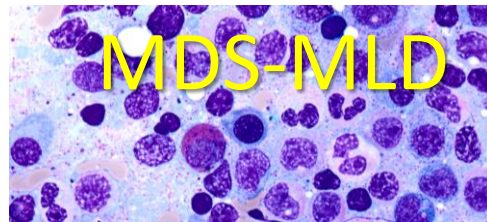
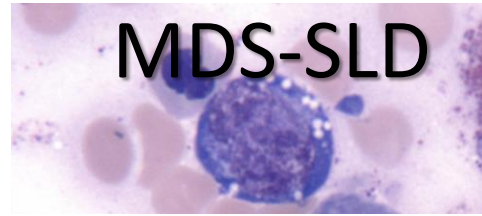
- Hematologic malignancies (HR: 11.1; 95% CI: 3.9-32.6)
- Increased all-cause mortality (HR: 1.4; 95% CI: 1.1-1.8)
- Cardiovascular disease (HR: 2.0; 95% CI: 1.2-3.4)
- Stroke (HR: 2.6; 95% CI: 1.4-4.8)



2017 WHO MDS Classification: Disease Subtypes

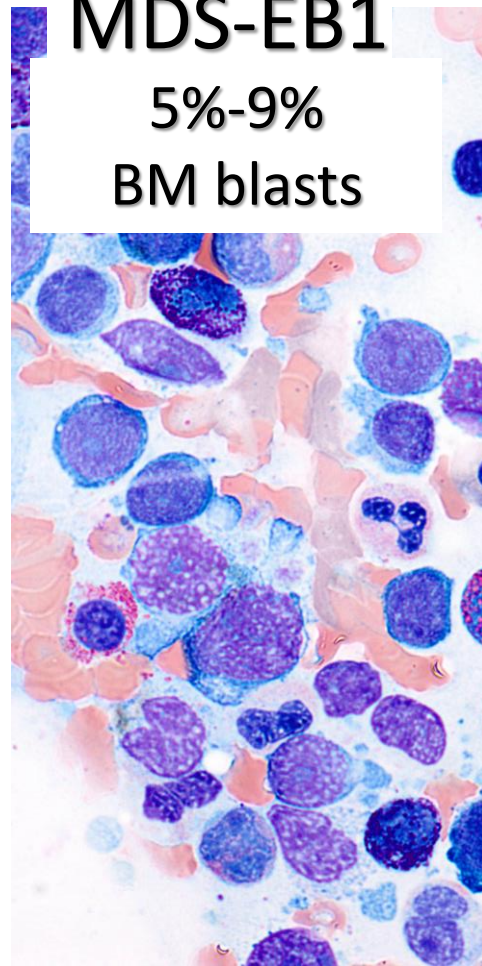
Single vs
multilineage
dysplasia,
ring sideroblasts,
isolated del(5q)

<5% BM blasts



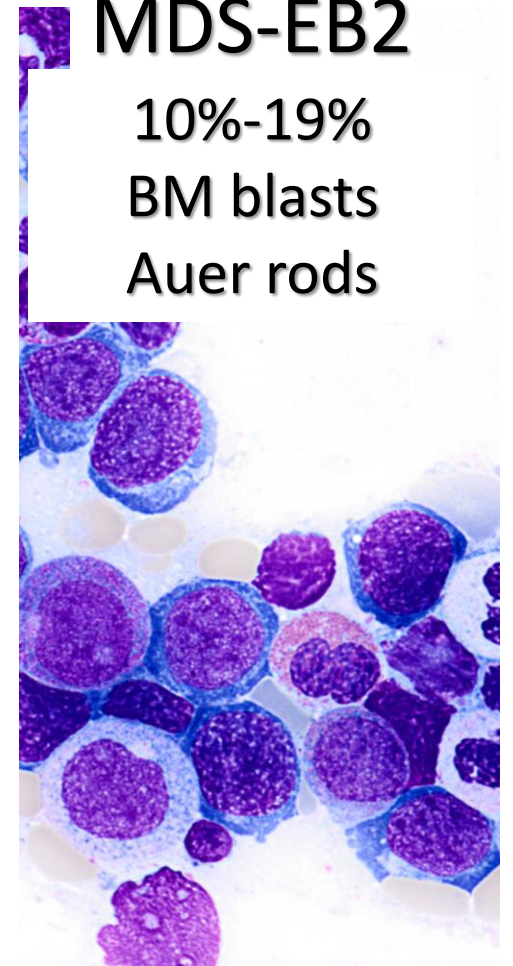
MDS-EB1

5%-9%
BM blasts



MDS-EB2

10%-19%
BM blasts
Auer rods



MDS with defining genetic abnormalities

- **MDS with low blasts and isolated 5q deletion** – (Blasts <5% BM and <2% PB)
 - With/without SF3B1 or a TP53 mutation(not multi-hit)
 - No monosomy 7 or 7q deletion
- **MDS with low blasts and SF3B1 mutation (MDS-SF3B1)**
 - Includes over 90% of MDS with $\geq 5\%$ ring sideroblasts
 - MDS with low blasts and ring sideroblasts retained - used for cases with wild-type SF3B1 and $\geq 15\%$ ring sideroblasts.
- **MDS with biallelic TP53 inactivation(MDS-biTP53)**- <20% blasts in BM & PB
 - Multihit mutational status with no residual wild type p53 protein
 - AML equivalent for therapeutic considerations

MDS, morphologically defined

- MDS with low blasts (MDS-LB) - <5% BM and <2% PB
- MDS, hypoplastic (MDS-h)-(≤25% bone marrow cellularity, age adjusted)
- MDS with increased blasts (MDS-IB)
 - MDS-IB1 : 5–9% BM or 2–4% PB
 - MDS-IB2 : 10-19% BM or 5–19%PB or Auer rods
 - MDS with fibrosis (MDS-f): 5–19% BM; 2–19% PB

BLAST COUNTS IN MDS AND AML

- HAEM 4R: a 20% blast cut-off has been used
 - Exceptions for (t(15;17), t(8;21) and inv(16)/t(16;16)
- Blast quantification can vary between : interobserver variability, blast/blast equivalents
- Blast cut-off is somewhat arbitrary, and the disease lie on a continuum
- May be influenced by sampling
- Newer therapies and clinical trials have shown to have efficacy in patients with 10-30% blasts



WHO HAEM 5 maintains a 20% cut-off between MDS and AML, BUT removes cut-off from most genetically defined AML

ICC 2022 favors having 10-19% blasts being diagnosed as MDS/AML, to reflecting the spectrum between AML and MDS

Consensus

- Eliminating blast cutoffs for most AML types with defining genetic alterations
- Retaining a 20% blast cutoff to delineate MDS from AML.
- MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations

Genetically Defined Subtypes in 2022: ICC and WHO

Lower-risk MDS subtypes: <5% BM and <2% PB blasts

- MDS with mutated *SF3B1*
- MDS with del(5q)

- MDS with low blasts and *SF3B1* mutation
- MDS with low blasts and del(5q)

Higher-risk MDS subtype: any blast percentage up to 20%

- MDS with mutated *TP53* (blasts 0%-9%)
- MDS/AML with mutated *TP53* (blasts 10%-19%)

- MDS with biallelic *TP53* inactivation

Diverted to AML: cases with AML-defining genetic abnormalities
(ICC: only if $\geq 10\%$ blasts)

- *PML::RARA*, *RUNX1::RUNX1T1*, *CBFB::MYH11*, *KMT2A* rearranged, *DEK::NUP214*, *MECOM* rearranged, *NUP98* rearranged, *NPM1* mutated, *CEBPA* mutated, *bZIP CEBPA**

*ICC only.

Morphologically Defined Subtypes in 2022: ICC and WHO

Lower-risk MDS subtypes: <5% BM and <2% PB blasts

- MDS-NOS with single-lineage dysplasia
- MDS-NOS with multilineage dysplasia
- MDS-NOS without dysplasia

- MDS with low blasts
- MDS with low blasts and ring sideroblasts
- Hypoplastic MDS

Higher-risk MDS subtypes: $\geq 5\%$ BM/ $\geq 2\%$ PB blasts or Auer rods

- MDS with excess blasts

- MDS with increased blasts: 1
- MDS with increased blasts: 2
- MDS with fibrosis

Diverted to new entity intermediate between MDS and AML: 10%-19% blasts

- MDS/AML

Effort to acknowledge continuum between MDS and AML, expand patient treatment options, and stimulate research to achieve more rational (likely genetic) distinction between MDS and AML than arbitrary blast cutoff

IPSS-Revised

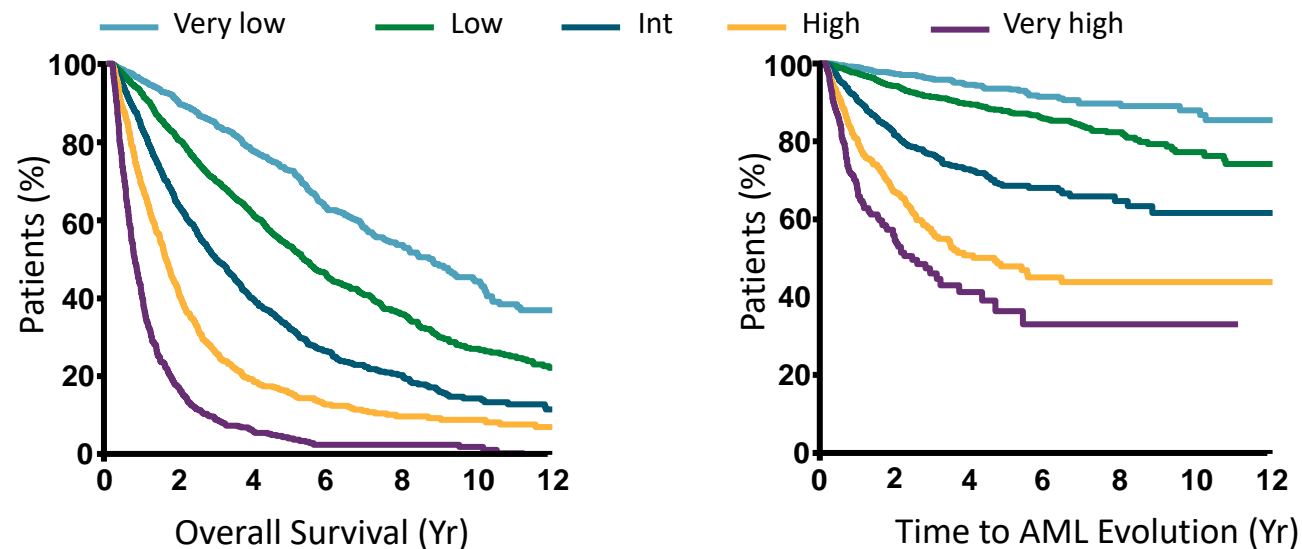
Prognostic variable	Score Value						
	0	0.5	1.0	1.5	2.0	3	4
Cytogenetics	Very good	--	Good	--	Intermediate	Poor	Very poor
BM blast, %	≤2	--	>2-<5	--	5-10	>10	--
Hemoglobin, g/dL	≥10	--	8-<10	<8	--	--	--
Platelets, x 10 ⁹ /L	≥100	50-<100	<50	--	--	--	--
ANC, x 10 ⁹ /L	≥0.8	< 0.8	--	--	--	--	--

Risk	Score
Very low	≤1.5
Low	>1.5-3.0
Intermediate	>3.0-4.5
High	>4.5-6.0
Very high	>6.0



Risk Groups for the IPSS-R

Risk Group	Points	Patients, %	Median Survival, Yr	Time Until 25% of Patients Develop AML, Yr
Very low	≤1.5	19	8.8	Not reached
Low	>1.5-3	38	5.3	10.8
Intermediate	>3-4.5	20	3.0	3.2
High	>4.5-6	13	1.6	1.4
Very high	>6	10	0.8	0.73

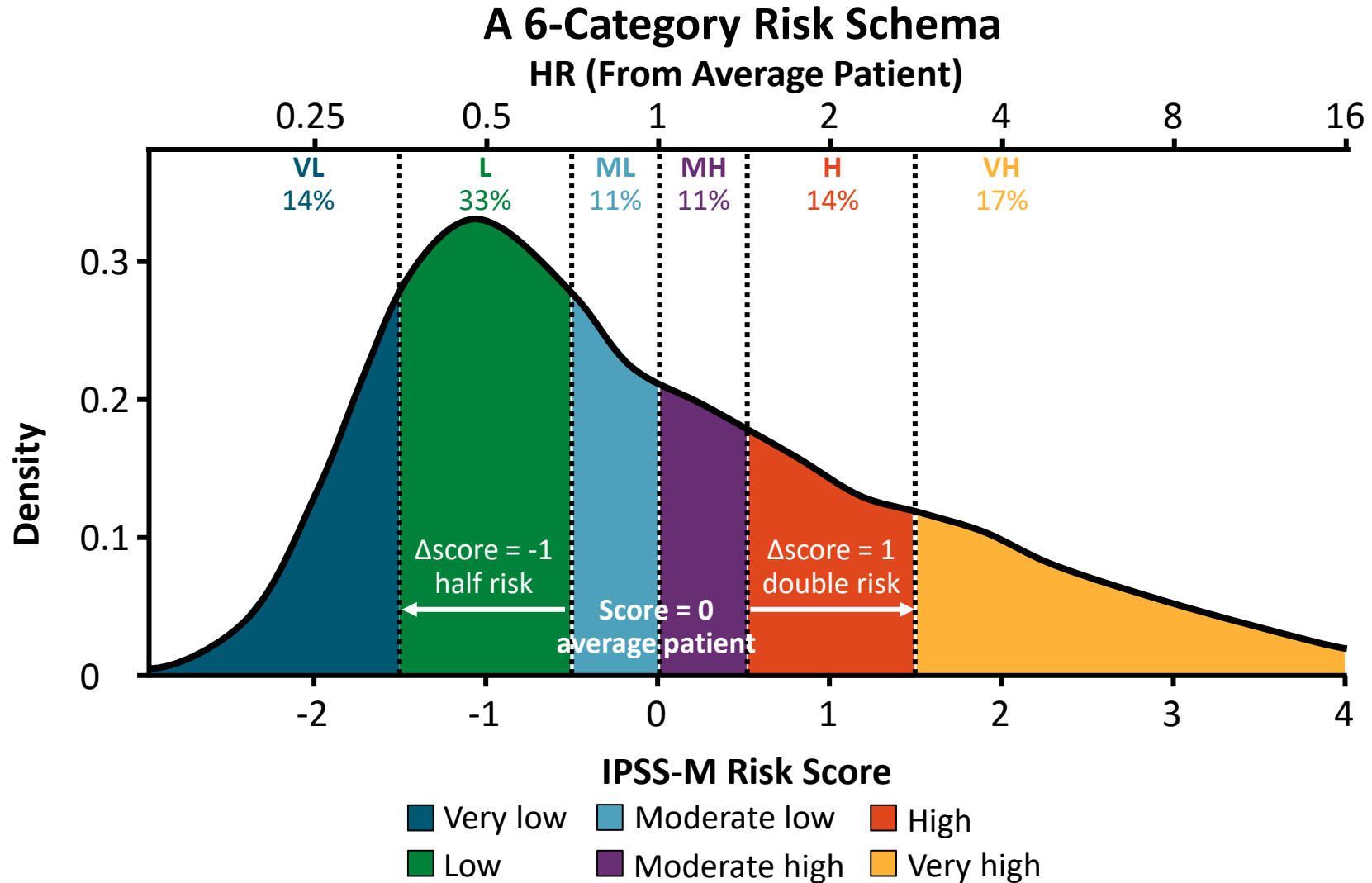


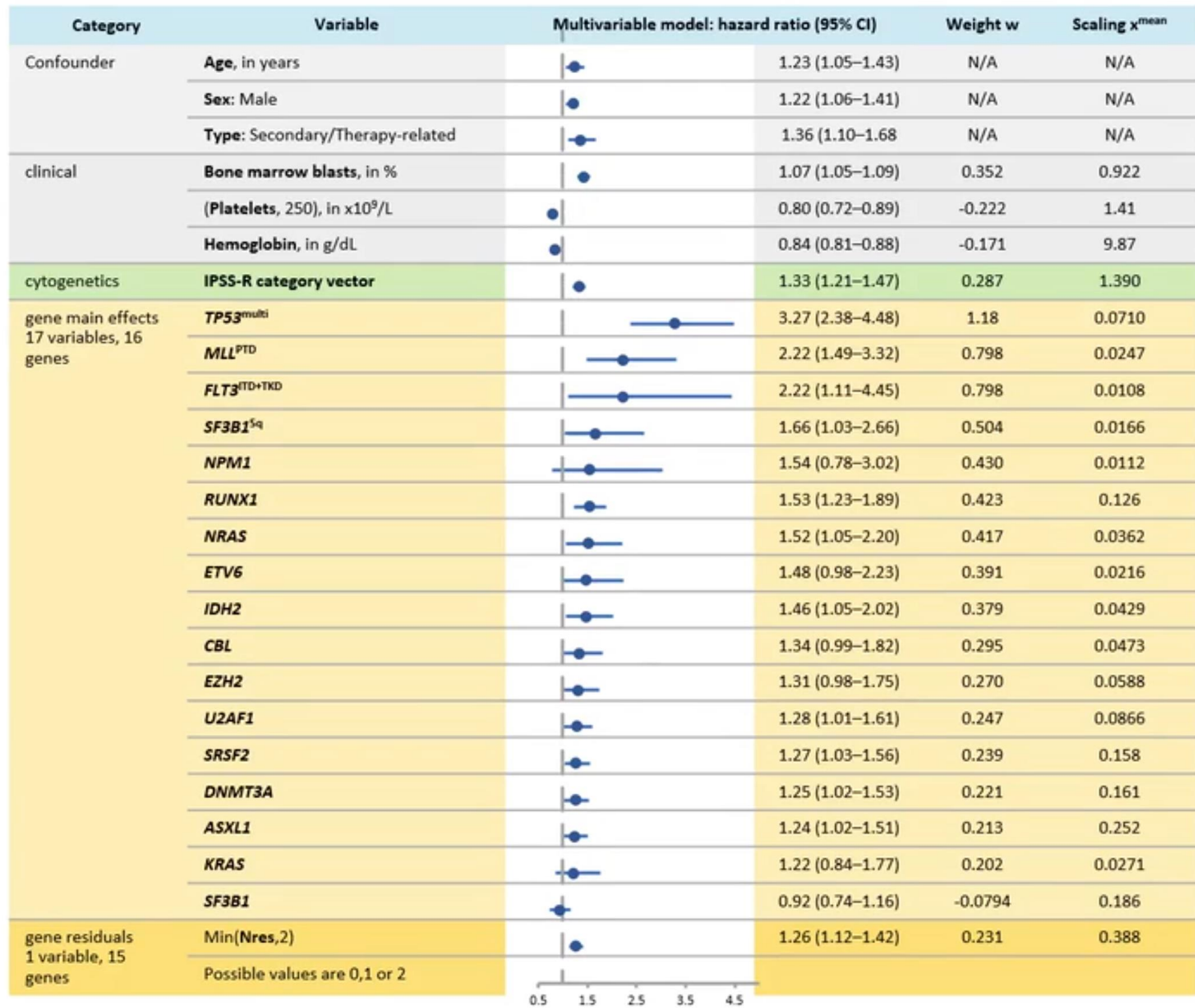
Development of IPSS-M:

Model Development Steps 1 and 2

Step	Development
Encoding for clinical and molecular variables	<ul style="list-style-type: none">▪ Continuous encoding of clinical variables; linear function for BM blasts, Hg▪ Platelet values capped at $250 \times 10^9/L$; ANC not included▪ Maintained 5 IPSS-R cytogenetic categories▪ Gene mutations incorporated as binary variables aside from <i>TP53</i> allelic state and <i>SF3B1</i> subsets accounting for comutations
Determination of independent IPSS-M prognostic variables	<ul style="list-style-type: none">▪ Model fit with a Cox multivariable regression adjusted for confounder variables (age, sex, primary vs therapy-related MDS)▪ Continuous clinical parameters▪ IPSS-R cytogenetic categories▪ 17 genetic variables from 16 main effect genes▪ 1 genetic variable from 15 residual genes (<i>BCOR</i>, <i>BCORL1</i>, <i>CEBPA</i>, <i>ETNK1</i>, <i>GATA2</i>, <i>GNB1</i>, <i>IDH1</i>, <i>NF1</i>, <i>PHF6</i>, <i>PPM1D</i>, <i>PRPF8</i>, <i>PTPN11</i>, <i>SETBP1</i>, <i>STAG2</i>, <i>WT1</i>)

IPSS-M Risk Categories





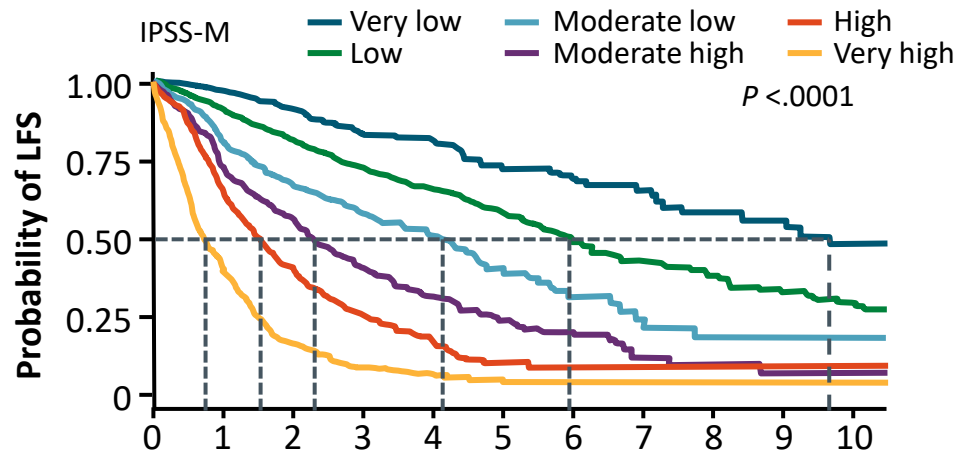
Molecular IPSS for MDS

- Discovery cohort: diagnostic MDS samples (N = 2957) with <20% blasts and WBC <13 x 10⁹/L were profiled for mutations in 152 driver genes
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders

Restratification of Patients From IPSS-R to IPSS-M Categories

- 46% (n = 1223) of patients were restratified
- 7% (n = 196) of patients were restratified by more than 1 strata

Leukemia-Free Survival



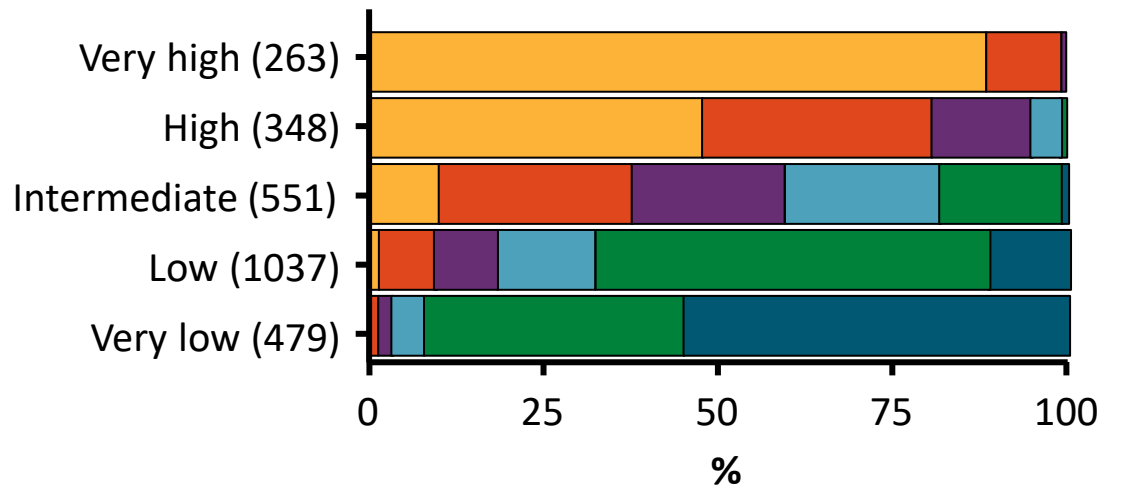
Patients at Risk, n

Very low	315	243	199	153	110	75	55	40	26	22	16
Low	788	584	442	331	240	162	107	80	56	40	30
Moderate low	274	188	135	92	62	34	16	7	6	3	3
Moderate high	258	166	114	65	41	25	18	8	4	2	1
High	353	194	101	48	29	13	10	4	3	3	3
Very high	440	152	50	21	8	6	5	3	3	2	2

IPSS-M

- Very low
- Moderate low
- High
- Low
- Moderate high
- Very high

IPSS-R



Conceptual classification of MDS: RSK classification

Chronic phase MDS

- MDS-*SF3B1*
- MDS-del5q
- MDS-LB

Accelerated phase MDS

- MDS-EB (5-19% myeloblasts) (cutoff to be refined)
- Bi-allelic *TP53* MDS
- MDS-f

AML-MDS related (AML-MR)

- $\geq 20\%$ myeloblasts (cutoff to be refined) with prior history of MDS or AML with MDS defining cytogenetic abnormalities or gene mutations.

Conclusões

- As classificações atuais na SMD são da OMS e ICC, de 2022
 - O foco passou nas mutações, diminuí a ênfase na morfologia e contagem de blastos
 - O IPPS-M vem ganhando tração
 - Pense em termos de risco, ou seja, alterações genéticas e moleculares de baixo e alto risco
 - Haverá uma tendência de junção em uma única classificação
 - Tanto a classificação da OMS e ICC foram válidas em coortes distintos
 - A diferenciação de SMD e LMA vem se tornando menos clara
-

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e Pesquisa