FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

Le sindromi mielodisplastiche ipocellulari

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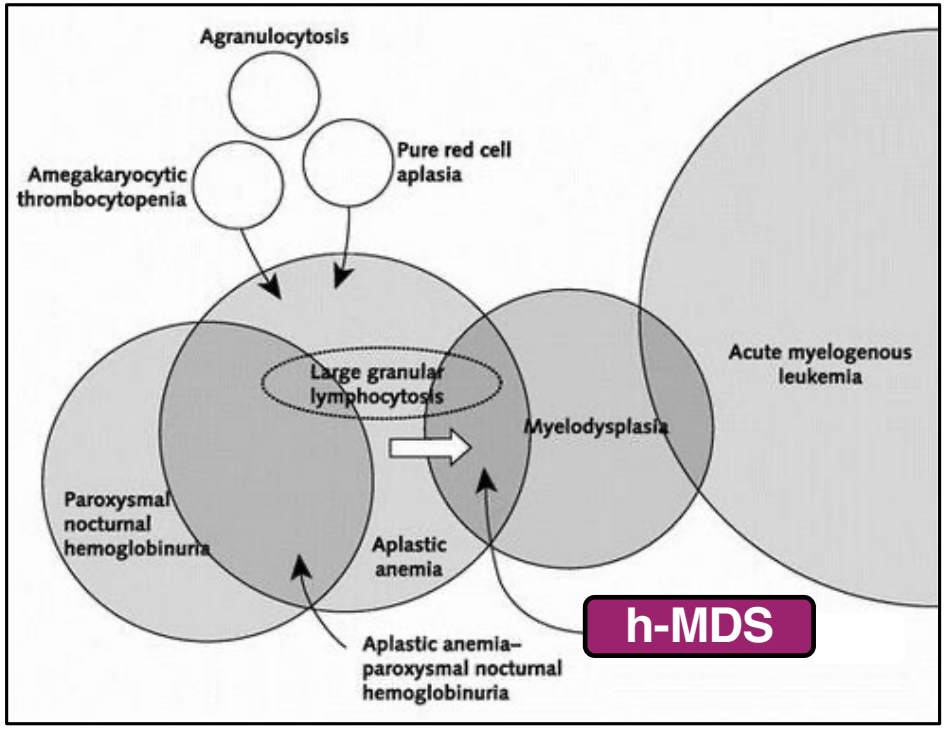
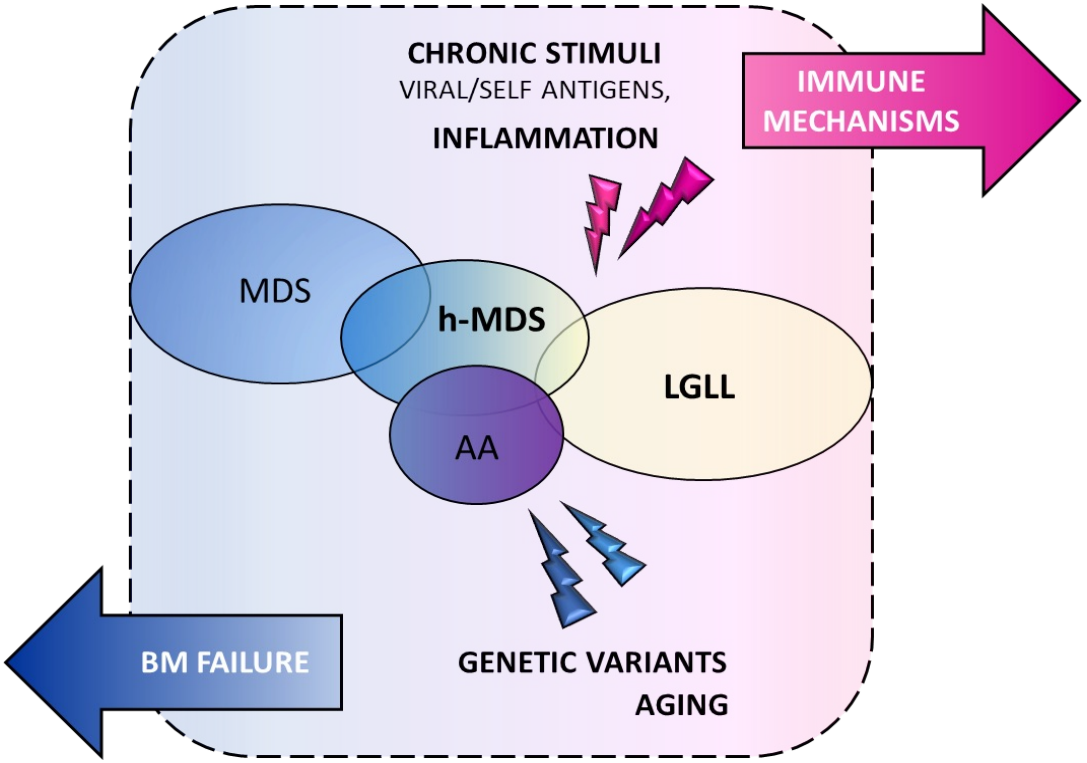
h-MDS: AN OVERLAP AREA BETWEEN MDS, AA AND LGLL



Young NS. Ann Intern Med. 2002.



2016 WHO CLASSIFICATION OF MYELOID NEOPLASM AND ACUTE LEUKEMIA

MDS with fibrosis

Hypocellular MDS

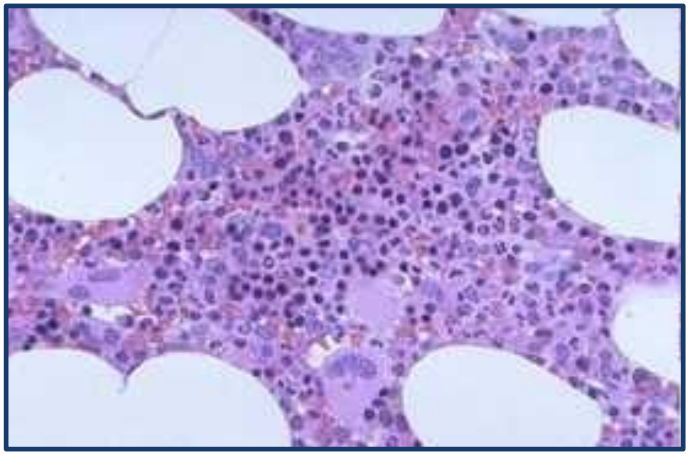
10-15% of MDS

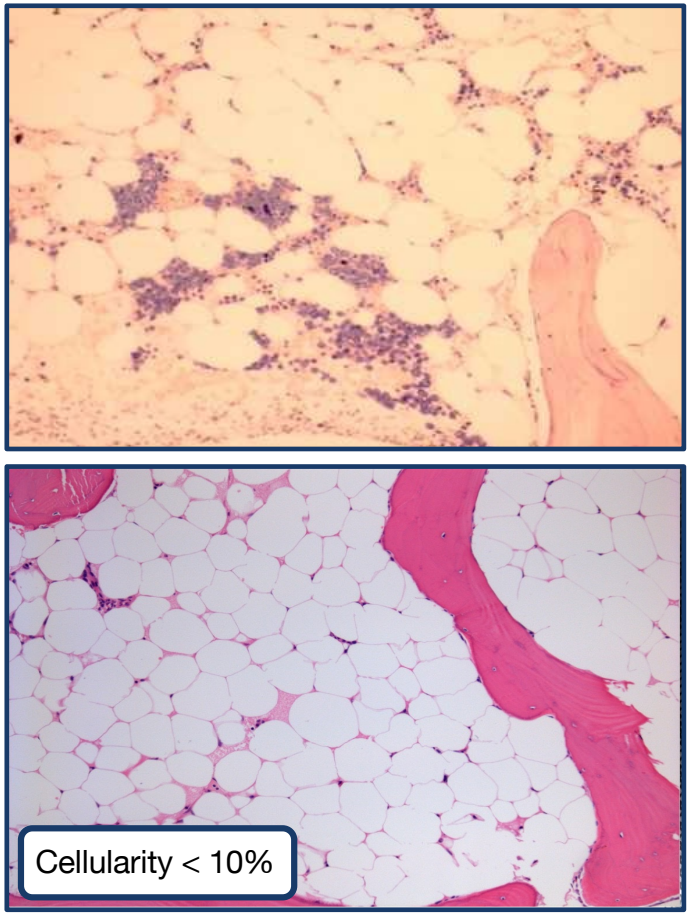
Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

h-MDS are STILL not recognized as a distinct subgroup of MDS,
but are rather defined by an age-adjusted reduction of bone marrow (BM) cellularity
or, according to AA definition, by a BM cellularity ≤ 30%

BONE MARROW HYSTOLOGY

NORMAL CELLULARITY





Hypocellularity (<25%)
(rather than aplastic)

BONE MARROW CELLULARITY IS AGE DEPENDENT

Table 1
Characterization of patients

Age (years)	Number of cases	Male/female	Bone marrow cellularity (%)[a]
0–9	9	6/3	60.0 ± 20.0[b]
10–19	13	4/9	56.5 ± 4.4
20–29	12	7/5	54.6 ± 4.6
30–39	11	4/7	54.6 ± 4.6
40–49	10	6/4	54.6 ± 18.2
50–59	9	9/0	52.4 ± 9.5
60–69	12	6/6	58.3 ± 8.3
70–79	13	9/4	56.5 ± 8.7
80–100	11	3/8	41.2 ± 5.9
Total	100	54/46	

[a] Bone marrow cellularity was measured by the image analyzing system and determined by the percentage of cellular marrow, represented by the formula: (area of hematopoietic cells)/(total area of bone marrow examined) × 100 (%).
[b] Values presented as mean ± S.E.M.

Ogawa et al. Mechanisms of Ageing and Develop 2000

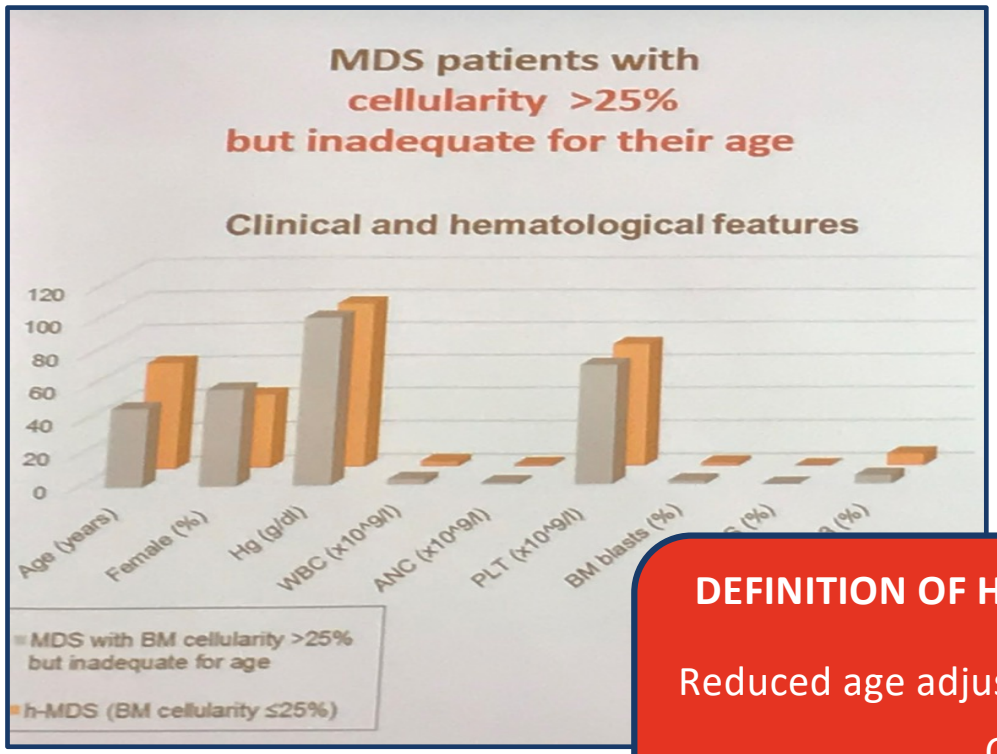
European consensus on grading bone marrow fibrosis and assessment of cellularity

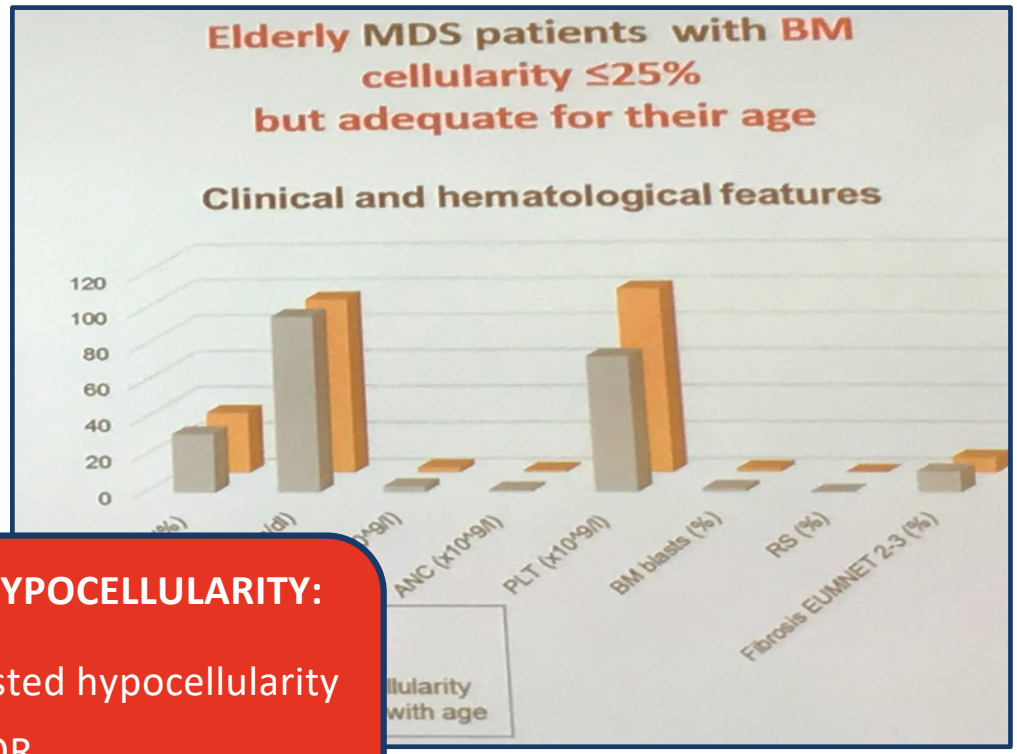
Table 2. Normal ranges of bone marrow cellularity for selected age groups, as adapted from the literature.[27-29,3,31]

Age (years)	*% Hematopoietic area**
20-30	60-70
40-60	40-50
≥70	30-40

Thiele et al. Haematologica 2005

HOW TO DEFINE BONE MARROW CELLULARITY?





DEFINITION OF HYPOCELLULARITY:

Reduced age adjusted hypocellularity

OR

Bone Marrow cellularity ≤25%

Bono E, et al. Leukemia. 2019

h-MDS: AN OVERLAP AREA BETWEEN n-MDS AND AA

DIFFERENTIAL DIAGNOSIS

	n-MDS	h-MDS	AA
MARROW CELLULARITY	Normal/Increased	**Decreased**	Decreased
MACROCYTOSIS	+	**+**	- (except for PNH clones)
DYSGRANULOPOIESIS	+	**+**	-
DYSMEGAKARYOPOIESIS	+	**+**	-
BLASTS	Often increased	**+/-**	Absent
RING SIDEROBLAST	+	**+/-**	-
FIBROSIS	Occasional	**Occasional**	-
KARYOTYPIC ABNORMALITIES	++	**+**	-/+
PROGRESSION	>25%	**>25%**	≈10%
RESPONSE TO IST	-	**+**	++
PNH DEFECT	Absent	**Rare**	≈30%
LGL	+	**++**	-
EXTRAHEMATOLOGICAL AUTOIMMUNITY	-	**++**	+/-
SOMATIC MUTATIONS	MDS related variant	**↓SF3B1 ↓SRSF2, ZRSR2, U2AF1 ↓Co-mutatios**	↑BCOR/BCORL ↓TET2
CLONE SIZE	++	**+**	-
LEUKEMIC EVOLUTION	+	**+/-**	-

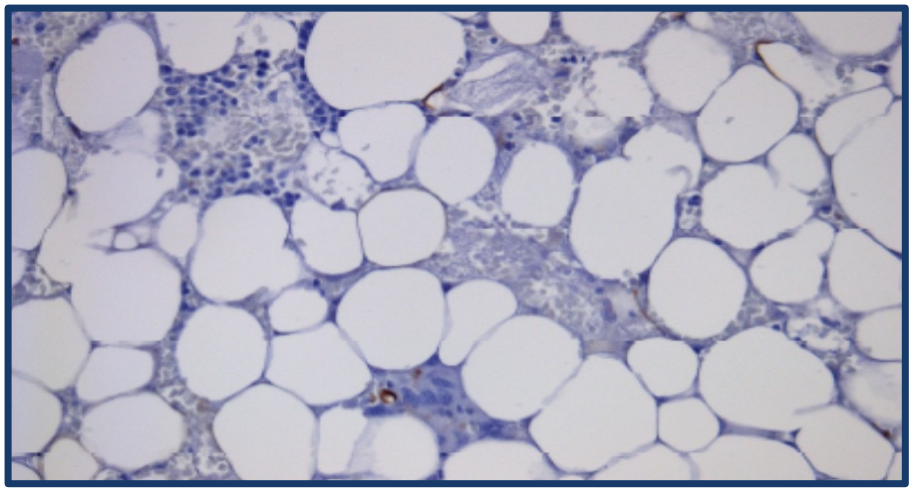
⇨ BM HYSTOLOGY

⇨ GENETICS

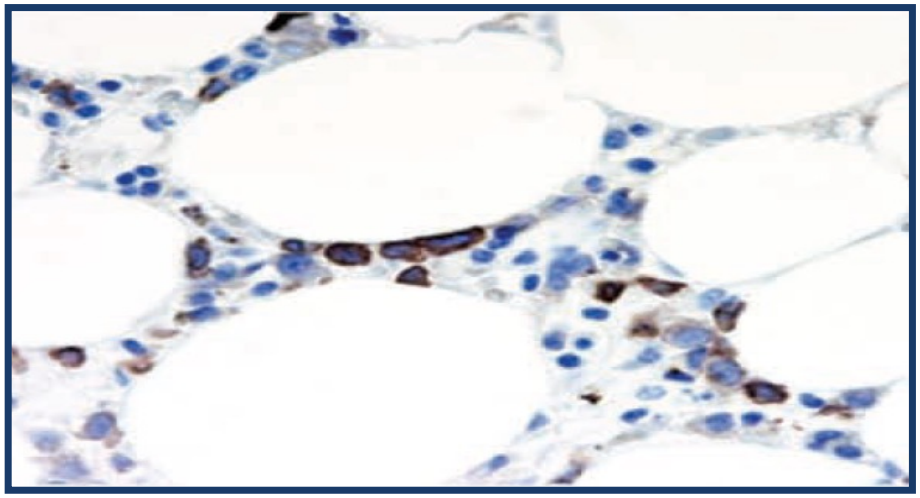
Adapted from J. Durrani, J.P. Maciejewski. Blood. 2019

DIFFERENTIAL DIAGNOSIS: BM HYSTOLOGY

APLASTIC ANEMIA



h-MDS



CD34+ CELLS

..but they are not always present

DIFFERENTIAL DIAGNOSIS: ROLE OF GENETICS

Table 2: Comparison of genetic alterations between patients with h-MDS and NH-MDS

Variables	Number examined	Total cohort (%)	h-MDS (%)	NH-MDS (%)	*P* value
		Mutated	Mutated	Mutated	
FLT3/ITD	366	1.1%	1.0%	1.1%	>0.999
NRAS	369	2.2%	1.0%	2.6%	0.688
KRAS	367	1.1%	0%	1.5%	0.578
JAK2	368	0.8%	1.0%	0.7%	>0.999
RUNX1	367	11.4%	4.0%	14.2%	0.005*
MLL/PTD	352	0.6%	0%	0.8%	>0.999
IDH1	368	0.5%	1.0%	0.4%	0.470
IDH2	366	2.2%	0%	3.0%	0.113
ASXL1	366	17.8%	7.1%	21.7%	0.001*
TET2	282	12.4%	11.4%	12.7%	>0.999
DNMT3A	369	10.0%	3.0%	12.6%	0.006*
TP53	369	8.7%	3.0%	10.8%	0.020*
SETBP1	369	2.4%	1.0%	3.0%	0.454
EZH2	369	3.8%	0%	5.2%	0.014*
SF3B1	369	11.4%	12.0%	11.2%	0.854
U2AF1	369	7.9%	5.0%	8.9%	0.278
SRSF2	369	10.8%	6.0%	12.6%	0.089

*Statistically significant if $P<0.05$.

Chi-Yuan Yao, et al. Oncotarget. 2016

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 39

Research Paper

Distinct mutation profile and prognostic relevance in patients with hypoplastic myelodysplastic syndromes (h-MDS)

Chi-Yuan Yao[1,*], Hsin-An Hou[1,*], Tzung-Yi Lin[1], Chien-Chin Lin[1,2], Wen-Chien Chou[1,2], Mei-Hsuan Tseng[1], Ying-Chieh Chiang[1], Ming-Chih Liu[3], Chia-Wen Liu[3], Yuan-Yeh Kuo[4], Shang-Ju Wu[1], Xiu-Wen Liao[5], Chien-Ting Lin[1,5], Bor-Shen Ko[1], Chien-Yuan Chen[1], Szu-Chun Hsu[2], Chi-Cheng Li[5], Shang-Yi Huang[1], Ming Yao[1], Jih-Luh Tang[1,5], Woei Tsay[1], Chieh-Yu Liu[6], Hwei-Fang Tien[1]

.....Our findings provide evidence that h-MDS indeed represent a distinct clinico-biological subgroup of MDS and can predict better leukemia-free survival and OS.

⇨ LOW INCIDENCE IN h-MDS

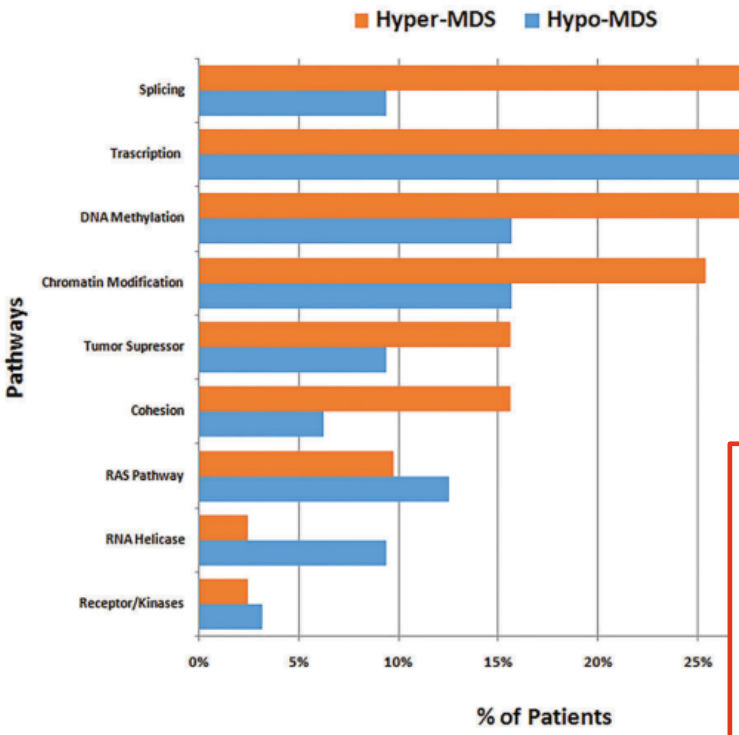
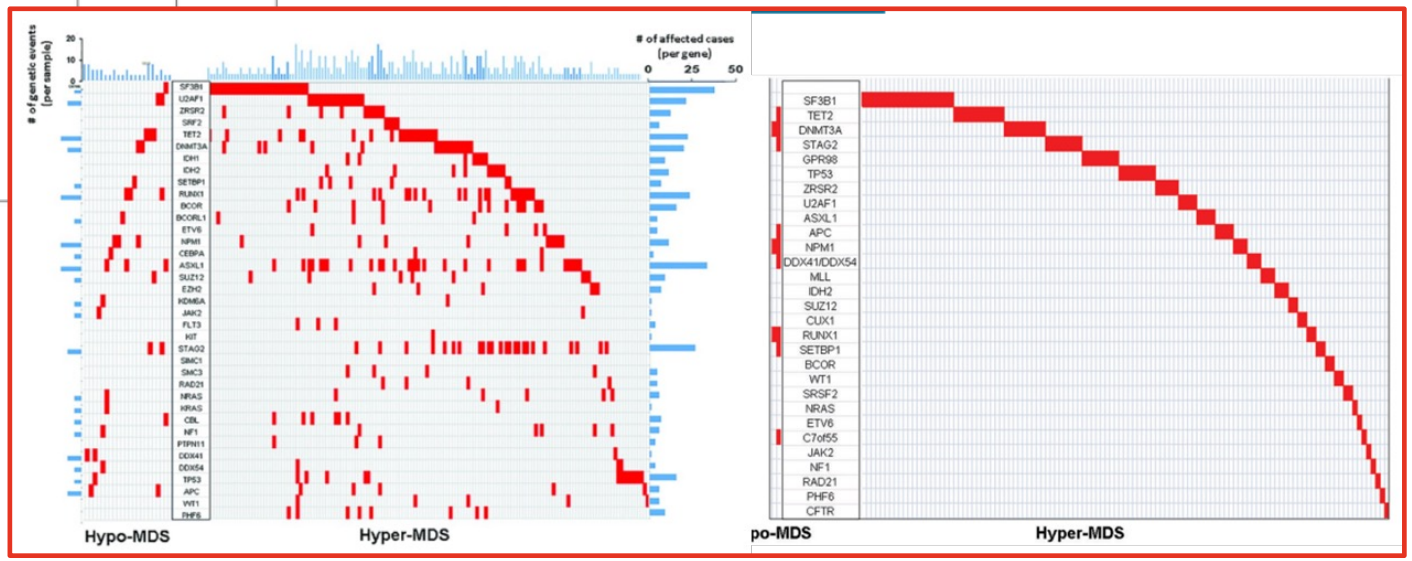


Figure 1. Frequency of gene mutations involved in common functional pathways. Genes included in common functional pathways: Splicing: *SF3B1, SRSF2, ZRSR2, U2AF1/2*. DNA methylation: *TET2, DNMT3A, IDH1/2*. Transcription: *SETBP1, RUNX1, BCOR/BCORL1, ETV6, NPM1, CEBPA, GATA2*. Chromatin Modification: *ASXL1, SUZ12, EZH2, MLL, KDM6A*. Receptor/Kinases: *JAK2, FLT3, KIT*. Cohesion: *STAG2, SMC3, SIMC1, RAD21*. RAS Pathway: *KRAS/NRAS, CBL, NF1, PTPN11*. RNA Helicase: *DDX41, DDX54, DHX29*. Tumor Suppressor: *TP53, APC, WT1, PFH6*.

Patients:
237 MDS
32 h-MDS



Nazha A, et Al. Haematologica. 2015

Leukemia (2019) 33:2495–2505
https://doi.org/10.1038/s41375-019-0457-1

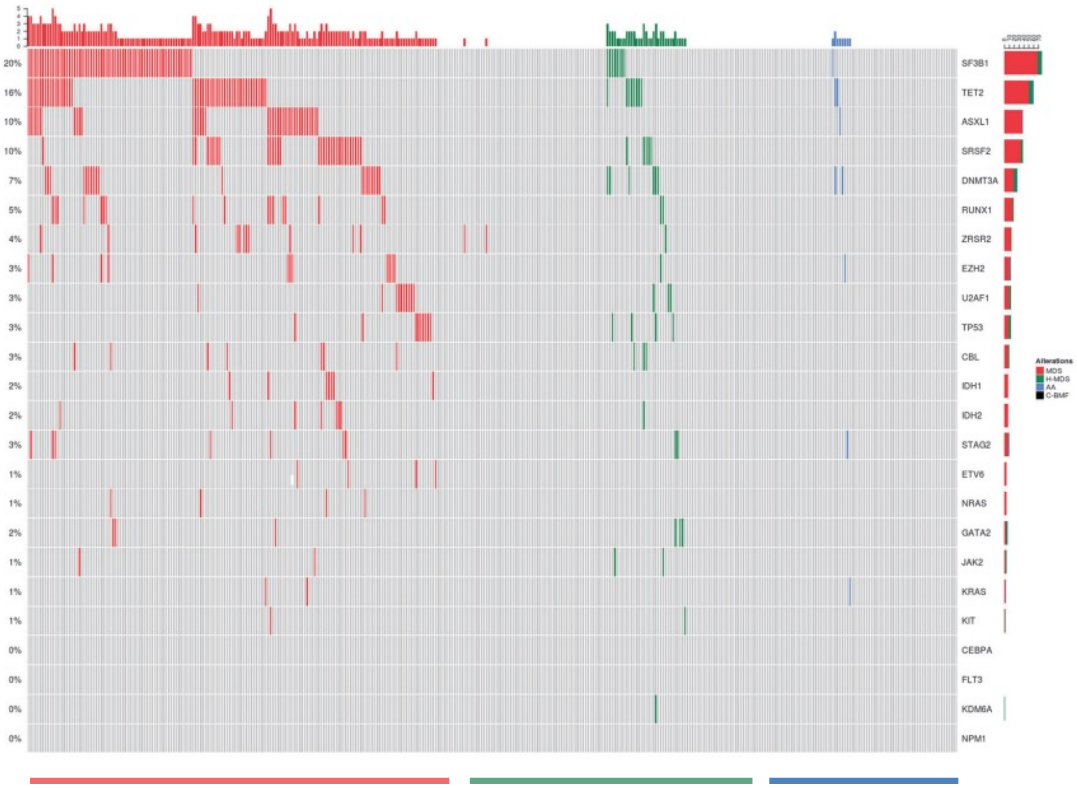
ARTICLE

Myelodysplastic syndrome

Clinical, histopathological and molecular characterization of hypoplastic myelodysplastic syndrome

Elisa Bono[1] · Donal McLornan[2,3] · Erica Travaglino[1] · Shreyans Gandhi[2] · Anna Gallì[1] · Alesia Abigael Khan[3] · Austin G. Kulasekararaj[2] · Emanuela Boveri[4] · Kavita Raj[2] · Chiara Elena[1] · Robin M. Ireland[2] · Antonio Bianchessi[1,5] · Jie Jiang[2] · Gabriele Todisco[1,5] · Virginia Valeria Ferretti[5] · Mario Cazzola[1,5] · Judith. C. W. Marsh[2] · Luca Malcovati[1,5] · Ghulam J. Mufti[2]

nMDS: n 727
hMDS: n 278
AA: n 136



Bono E, et Al. Leukemia. 2019

Leukemia (2019) 33:2495–2505
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ARTICLE

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Austin G. Kulasekararaj[2] · Emanuela Boveri[4] · Kavita Raj[2] · Chiara
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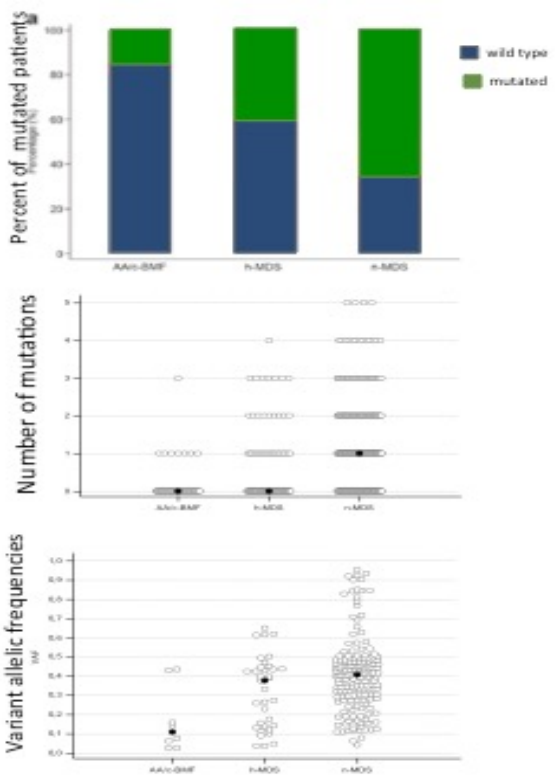
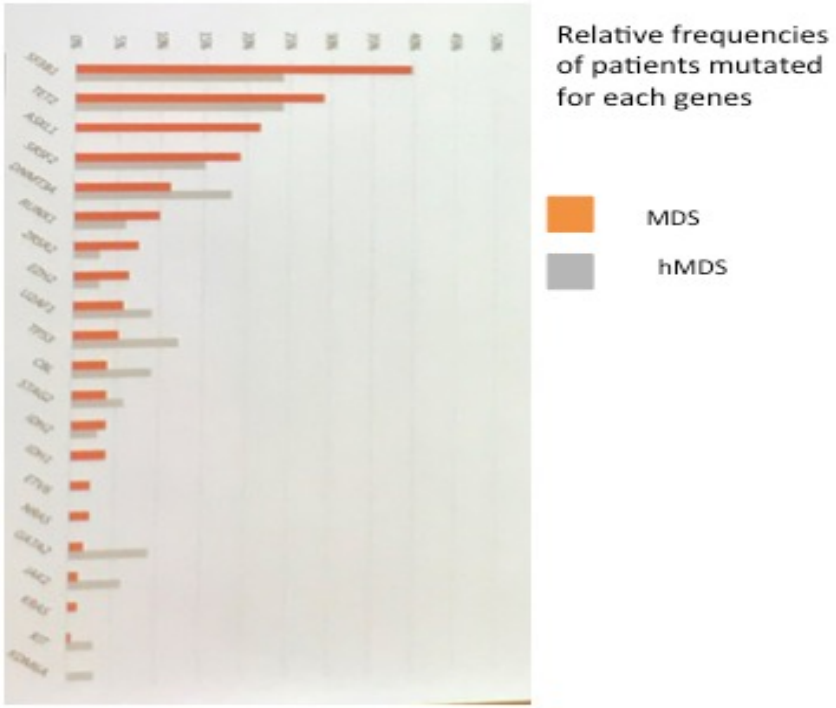
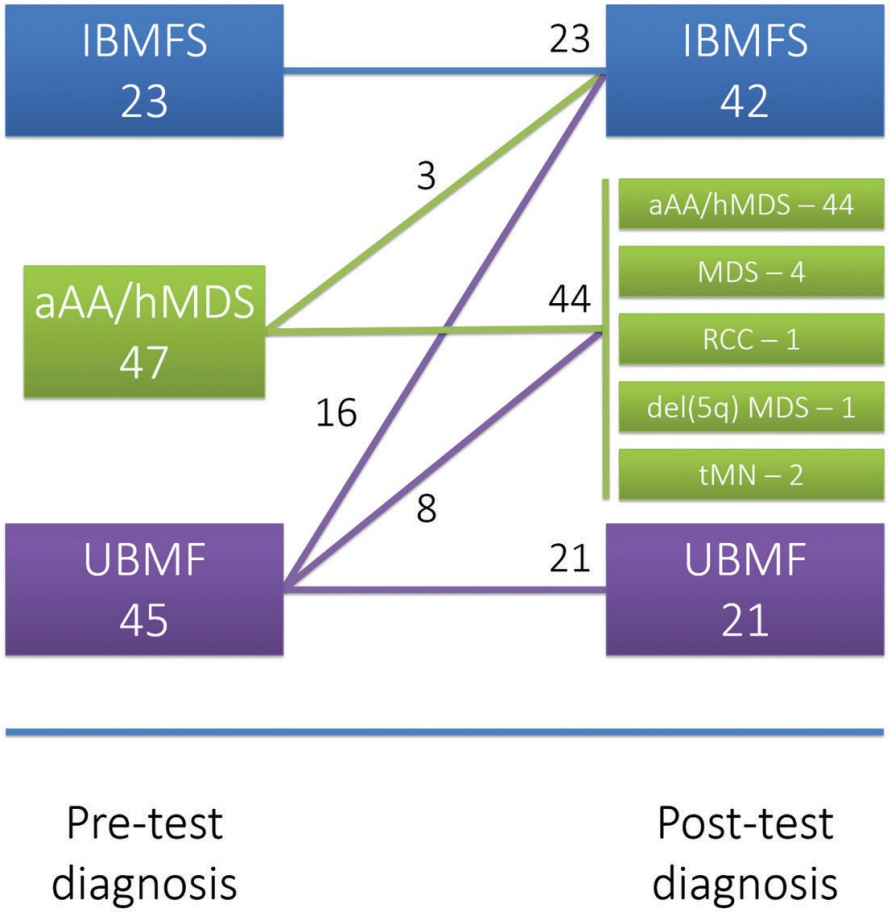




Bono E, et Al. Leukemia. 2019

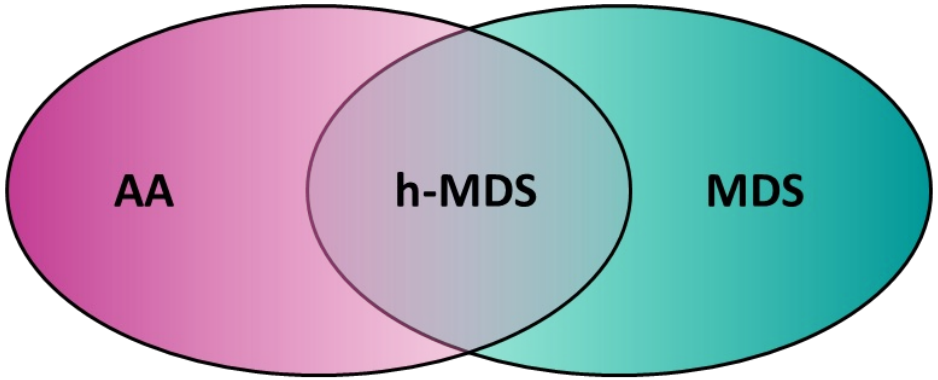
Utility of clinical comprehensive genomic characterization for diagnostic categorization in patients presenting with hypocellular bone marrow failure syndromes

Piers Blombery,[1,2,3] Lucy C. Fox,[3,4,5*] Georgina L. Ryland,[3*] Ella R. Thompson,[2,3] Jennifer Lickiss,[3] Michelle McBean,[3] Satwica Yerneni,[3] David Hughes,[6] Anthea Greenway,[6] Francoise Mechinaud,[6] Erica M. Wood,[5] Graham J. Lieschke,[1,7] Jeff Szer,[1] Pasquale Barbaro,[8] John Roy,[8] Joel Wight,[9] Elly Lynch,[10,11,12] Melissa Martyn,[10,11,12] Clara Gaff[2,10,12] and David Ritchie[1]



Haematologica 2021

h-MDS: A GREY ZONE AREA?



AA - LIKE

↑ cytotoxic and proinflammatory cells
↓ regulatory cells
↑ immune activation
↑ Response to IST, better prognosis

MDS - LIKE

↓ immunosurveillance
↑ regulatory tumor permissive cells
↑ survival of dysplastic cells
↑ burden of genetic lesions
↑ Leukemic evolution, worse prognosis

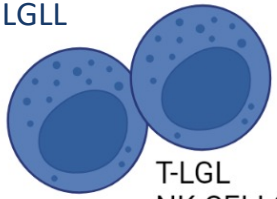
Adapted from Fattizzo B. Cancers. 2021

h-MDS: BIOLOGICAL FEATURES

ALTERATIONS OF BOTH INNATE AND ADAPTIVE IMMUNITY, CO-OCCURRENCE WITH LGLL

Types	Normocellular/Hypercellular MDS	hMDS
T-cytotoxic cells (CTLs)	Increased and oligoclonal. In high-risk patients, IFN-γ-producing CTLs decrease favoring leukemia evolution.	Increased and clonal; produce interferon-gamma (IFN-γ) and decrease after response to IST.
T-CD4+ cells Th and Tregs	Increased T regs collaborate in the suppression of immune surveillance and leukemic evolution.	Increased and polyclonal Th cells producing IFN-γ. Tregs are reduced and correlate with dyserythropoiesis.
LGL clones	Increased polyclonal and oligoclonal (both T-LGL and NK-LGL) more than in AA.	

Fattizzo B. Cancers. 2021



T-LGL
NK CELLS

Large granular lymphocytic leukemia coexists with myeloid clones and myelodysplastic syndrome

Jibran Durrani[1] · Hassan Awada[1] · Ashwin Kishtagari[1,2] · Valeria Visconte[1] · Cassandra Kerr[1] · Vera Adema[1] · Yasunobu Nagata[1] · Teodora Kuzmanovic[1] · Sanghee Hong[1] · Bhumika Patel[1,2] · Aziz Nazha[1,2] · Alan Lichtin[2] · Sudipto Mukherjee[2] · Yogen Saunthararajah[1,2] · Hetty Carraway[2] · Mikkael Sekeres[2] · Jaroslaw P. Maciejewski[1,2]

Durrani J, Leukemia, 2019

13/240 (5%)

Characterization of myelodysplastic syndromes (MDS) with T-cell large granular lymphocyte proliferations (LGL)

Rami S. Komrokji[1] · Najla al Ali[1] · David Sallman[1] · Eric Padron[1] · Jeffrey Lancet[1] · Lubomir Sokol[1] · Christa Varnadoe[2] · P. K. Burnette[3] · Alan List[4]

Komrokji R, Leukemia, 2020

322/1177 (27%)

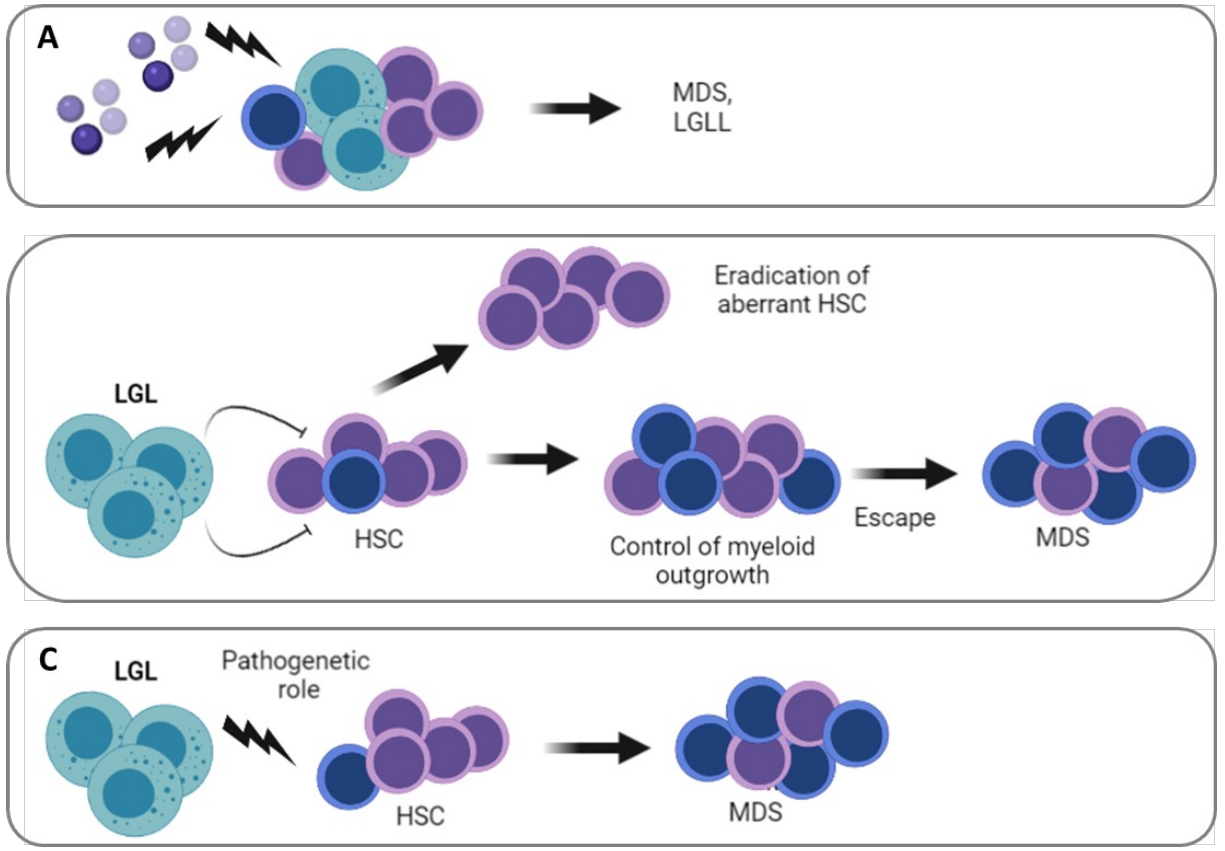
COEXISTENCE OF H-MDS AND LGLL: MORE THAN A COINCIDENCE?

PATHOGENETIC HYPOTHESES

COMMON MECHANISMS
(mutations, inflammation, antigenic pressure, aging)

LGLL AS A CONSEQUENCE
(reactive response towards an aberrant HSC clone)

LGLL AS A CAUSE
(Pathogenetic role, promotes a BM damage)



FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

H-MDS: RESULTS OF THE FISiM h-MDS MULTICENTER STUDY

Leukemia

Online ahead of print. May 21, 2022

www.nature.com/leu

LETTER OPEN

Check for updates

MYELODYSPLASTIC SYNDROME

Hypocellular myelodysplastic syndromes (h-MDS): from clinical description to immunological characterization in the Italian multi-center experience

Giulia Calabretto[1,2,14], Enrico Attardi[3,4,14], Antonella Teramo[1,2], Valentina Trimarco[1], Samuela Carraro[1], Sandra Mossuto[4], Gregorio Barilà[5], Cristina Vicenzetto[1,2], Vanessa Rebecca Gasparini[1,2], Monica Crugnola[4,6], Pasquale Niscola[4,7], Antonella Poloni[4,8], Valentina Giai[4,9], Valentina Gaidano[4,10], Carlo Finelli[4,11], Roberta Bertorelle[12], Cinzia Candiotto[12], Marco Pizzi[13], Gianni Binotto[1,3], Monica Facco[1,2], Fabrizio Vianello[1], Livio Trentin[1], Gianpietro Semenzato[1,2], Renato Zambello[1,2,4,14]✉ and Valeria Santini[3,4,14]✉

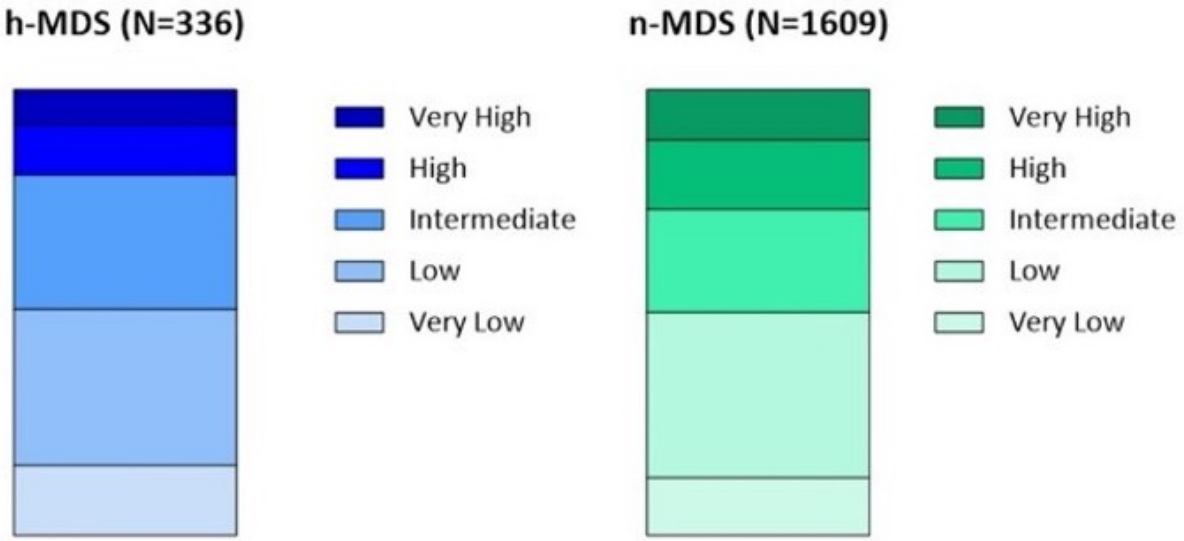
- COMPARISON (clinical features, treatment, OS) of h-MDS vs n-MDS
- PHENOTYPIC AND MOLECULAR CHARACTERIZATION OF h-MDS AT THE DIAGNOSIS (Cytotoxic T lymphocytes, NK cells)

RESULTS

CLINICAL FEATURES
(N = 1945 PATIENTS)

MDS (N)	h-MDS (336)	n-MDS (1609)
BM Cellularity	≤ 30%	> 30%
Age (median)	75 years	74 years
Sex (M/F)	1.14	1.67

p < 0.01



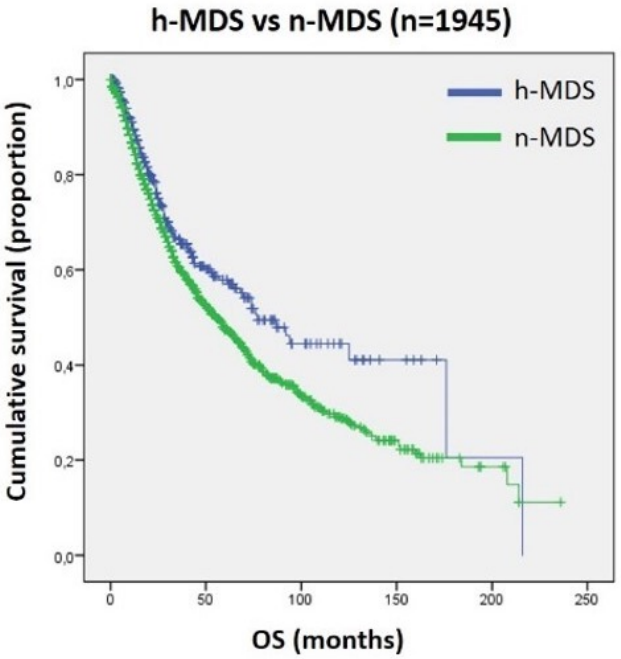
LR = IPSS-R < 3.5
HR = IPSS-R ≥ 3.5

271/336 (81%) LR
65/336 (19%) HR

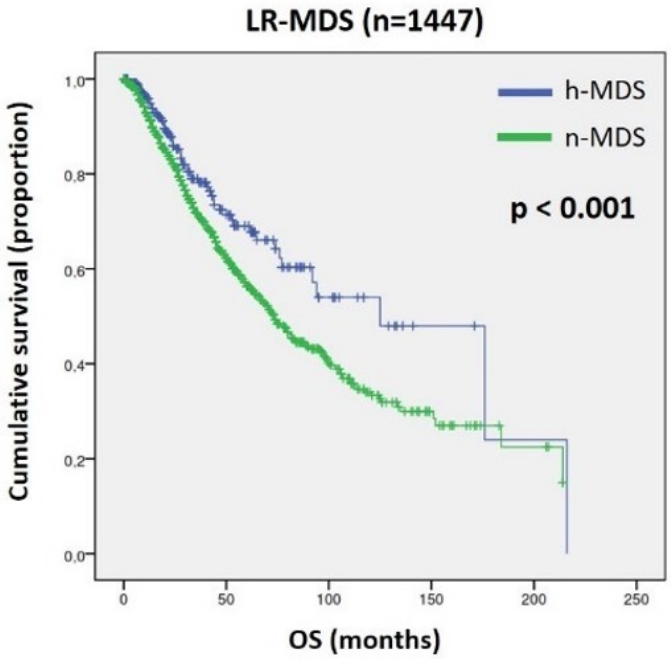
1176/1609 (73%) LR
433/1609 (27%) HR

Calabretto G, Attardi E et al Leukemia 2022

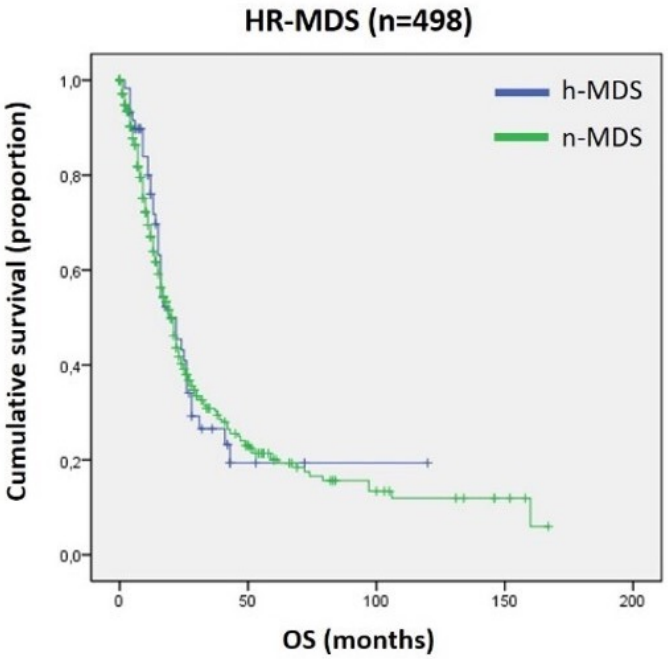
RESULTS



77 months for h-MDS
vs 56 months for n-MDS
(p > 0.05)



125 months for LR h-MDS
vs 74 months for LR n-MDS
(p < 0.001)

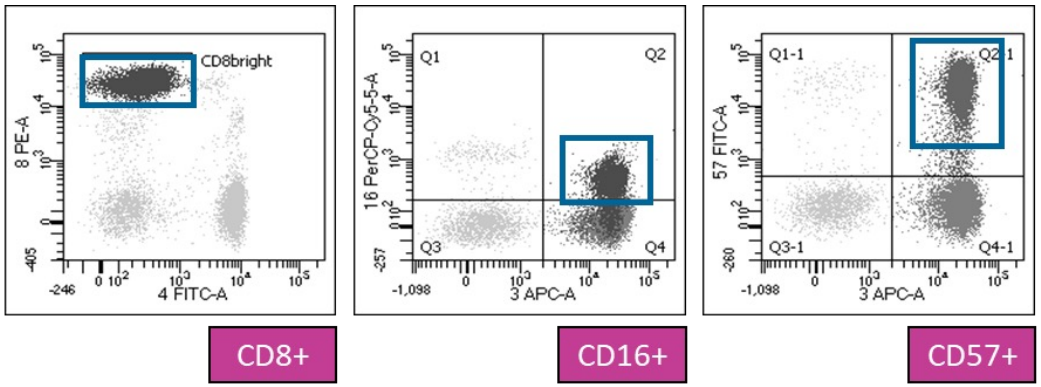


19 months for HR h-MDS
vs 20 months for HR n-MDS
(p > 0.05)

Calabretto G, Attardi E et al Leukemia 2022

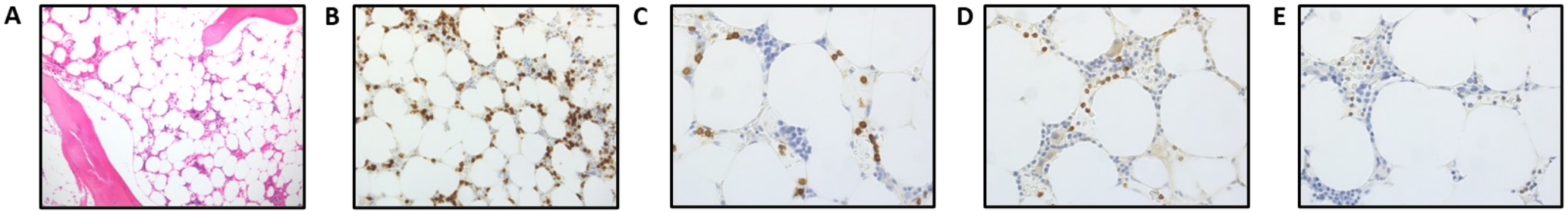
RESULTS

IMMUNOPHENPTYPICAL ANALYSIS (PB and BM)
CD3+ T CELL CHARACTERIZATION



CLONAL EXPANSION of CD3+/CD8+/CD16±/CD56-/CD57+ cytotoxic T-cell subset in **6/12 (50%)** cases
No recurrent TCR-Vβ immunodominant expansions

BM INFILTRATION OF CYTOTOXIC T CELL



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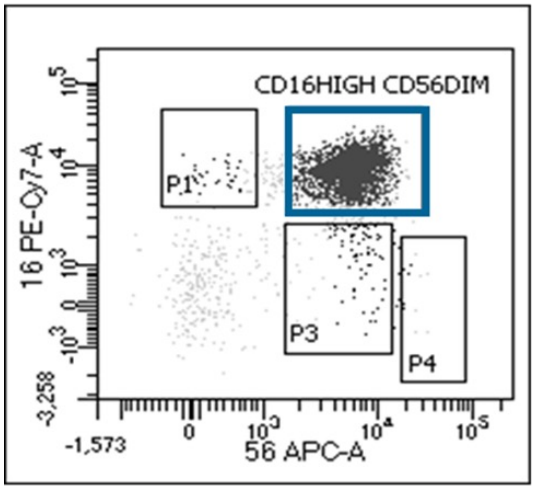
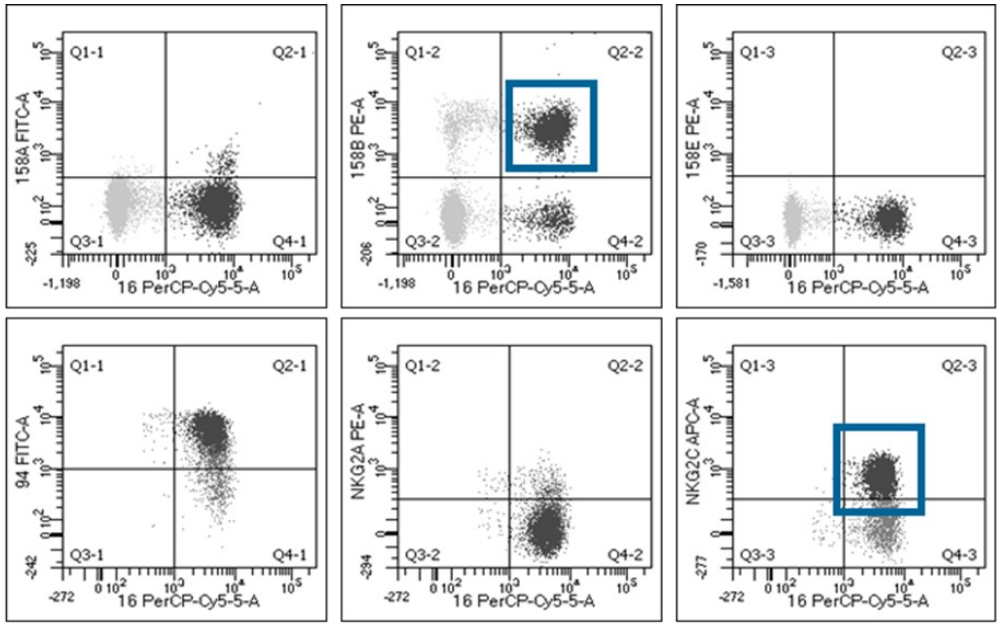
RESULTS

IMMUNOPHENPTYPICAL ANALYSIS (PB and BM)
CD3- NK CELL CHARACTERIZATION



CD16^{HIGH}CD56^{DIM}



CD158b+

NKG2C

NK cell expansions in cells in **4/12 (33%)** cases
CD16^{HIGH}CD56^{DIM}, CD57+, CD62L-,
restricted pattern of NK cell receptor (CD158b+, NKG2C)

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RESULTS

EVALUATION OF CLONALITY

T CELL CLONES ASSOCIATED WITH HR H-MDS 5/6 (83%)

TCR-γ GENE REARRANGEMENT

NK CELL CLONES ASSOCIATED WITH LR H-MDS 3/4 (75%)

KIR EXPRESSION (Flow cytometry)

	Clonal expansion			
IPSS-R	HR		LR	
Pt.	T	NK	T	NK
h-MDS 1				
h-MDS 2				
h-MDS 3				
h-MDS 4				
h-MDS 5				
h-MDS 6				
h-MDS 7				
h-MDS 8				
h-MDS 9				
h-MDS 10				
h-MDS 11				
h-MDS 12				

T CELL CLONE

NK CELL CLONE

NO CLONAL EXPANSIONS

T AND NK CELL CLONE MUTUALLY EXCLUSIVE IN h-MDS

Detection of monoclonal T populations in patients with KIR-restricted chronic lymphoproliferative disorder of NK cells

Cristina Gattazzo,[1,2] Antonella Teramo,[2] Francesca Passeri,[1,2] Elena De March,[1] Samuela Carraro,[1] Valentina Trimarco,[1,2] Federica Frezzato,[1,2] Tamara Berno,[1] Gregorio Barilà,[1] Veronica Martini,[1,2] Francesco Piazza,[1,2] Livio Trentin,[1,2] Monica Facco,[1,2] Gianpietro Semenzato,[1,2] and Renato Zambello[1,2]

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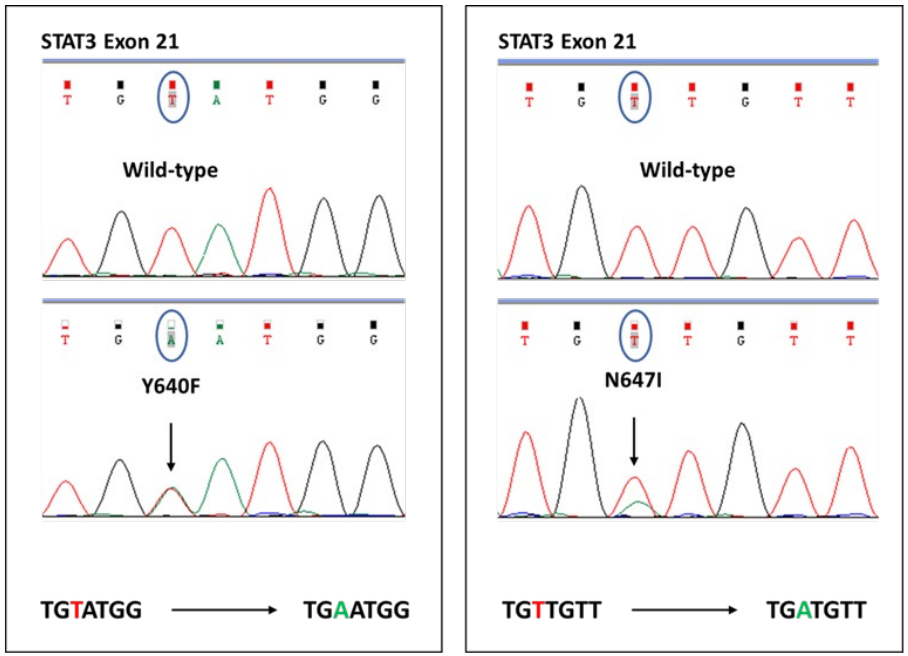
RESULTS

EVALUATION OF STAT3 and STAT5b MUTATIONS

Pt.	IPSS-R	STAT3	STAT5b
h-MDS 1	HR	WT	WT
h-MDS 2	HR	WT	WT
h-MDS 3	HR	N447I	WT
h-MDS 4	HR	Y640F	WT
h-MDS 5	HR	WT	WT
h-MDS 6	HR	WT	WT
h-MDS 7	HR	WT	WT
h-MDS 8	LR	WT	WT
h-MDS 9	LR	WT	WT
h-MDS 10	LR	WT	WT
h-MDS 11	LR	WT	WT
h-MDS 12	LR	WT	WT



2/12 (17%) h-MDS patients harbore **STAT3 somatic mutations** in CD3+/CD57+ T-Lymphocytes

DIAGNOSIS OF LGLL

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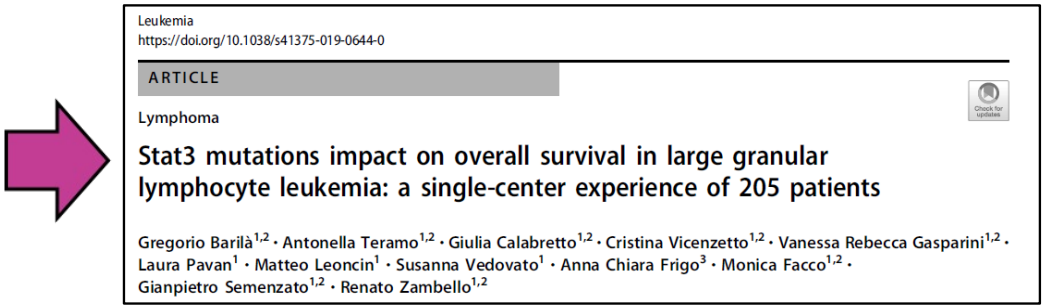
RESULTS

EVALUATION OF STAT3 and STAT5b MUTATIONS

Pt.	IPSS-R	STAT3	STAT5b
h-MDS 1	HR	WT	WT
h-MDS 2	HR	WT	WT
h-MDS 3	HR	N447I	WT
h-MDS 4	HR	Y640F	WT
h-MDS 5	HR	WT	WT
h-MDS 6	HR	WT	WT
h-MDS 7	HR	WT	WT
h-MDS 8	LR	WT	WT
h-MDS 9	LR	WT	WT
h-MDS 10	LR	WT	WT
h-MDS 11	LR	WT	WT
h-MDS 12	LR	WT	WT



Leukemia
https://doi.org/10.1038/s41375-019-0644-0

ARTICLE

Lymphoma

Stat3 mutations impact on overall survival in large granular lymphocyte leukemia: a single-center experience of 205 patients

Gregorio Barilà[1,2] · Antonella Teramo[1,2] · Giulia Calabretto[1,2] · Cristina Vicenzetto[1,2] · Vanessa Rebecca Gasparini[1,2] · Laura Pavan[1] · Matteo Leoncin[1] · Susanna Vedovato[1] · Anna Chiara Frigo[3] · Monica Facco[1,2] · Gianpietro Semenzato[1,2] · Renato Zambello[1,2]

NEGATIVE PROGNOSTIC ROLE?

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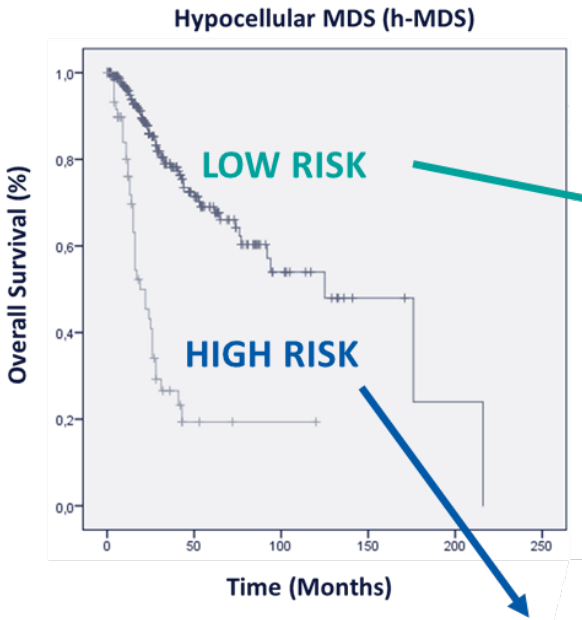
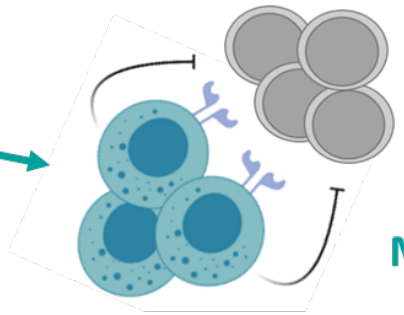
SUMMARY

- **Clonal LGL expansion in almost all h-MDS patients**
- **LR h-MDS showed enrichment of NK cell subsets with restricted patterns of NK receptors**
- **T cytotoxic clones, with molecular findings typical of leukemic LGL (STAT3 mutations), were prevalent in HR h-MDS patients**
- **T and NK cell clone are mutually exclusive in h-MDS patients**

DISCUSSION

IPSS-R	Clonal expansion			
	HR		LR	
Pt.	T	NK	T	NK
h-MDS 1				
h-MDS 2				
h-MDS 3				
h-MDS 4				
h-MDS 5				
h-MDS 6				
h-MDS 7				
h-MDS 8				
h-MDS 9				
h-MDS 10				
h-MDS 11				
h-MDS 12				

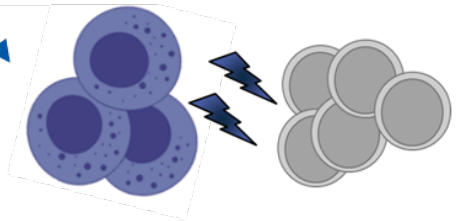




CLONAL NK CELL EXPANSIONS

CONTROL OF MYELOID OUTGROWTH?

IMMUNOSUPPRESSIVE THERAPY?



T CELL CLONES

PATHOGENETIC ROLE?

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

RESULTS

MDS (N)	h-MDS (336)		n-MDS (1609)	
BM Cellularity	≤ 30%		> 30%	
Age (median)	75		74	
Sex (M/F)	1.14		1.67	
IPSS-R (N, %)	**LR (271, 80.7)**	**HR (65, 19.3)**	**LR (1176, 73.1)**	**HR (433, 26.9)**
Therapy (%)				
Observation/BSC	33.8	12.1	31.6	16.1
ESA	42.6	29.3	41.2	24.8
Lenalidomide	3.8	0	0.7	0.5
Differentiation therapy (ATRA)	4.6	5.2	6.4	7.9
IST	**0.4**	**0**	**1.2**	**0.5**
Azacitidine	5.1	36.2	2.8	25.1
Low-dose Chemotherapy	0	0	4.7	5.0
AML-Like Chemotherapy	0.4	1.7	0.3	6.2
HSCT	0	1.7	0.1	1.0
Experimental trials	1.7	5.2	3.9	6.2
Others	7.6	8.6	7.1	6.7

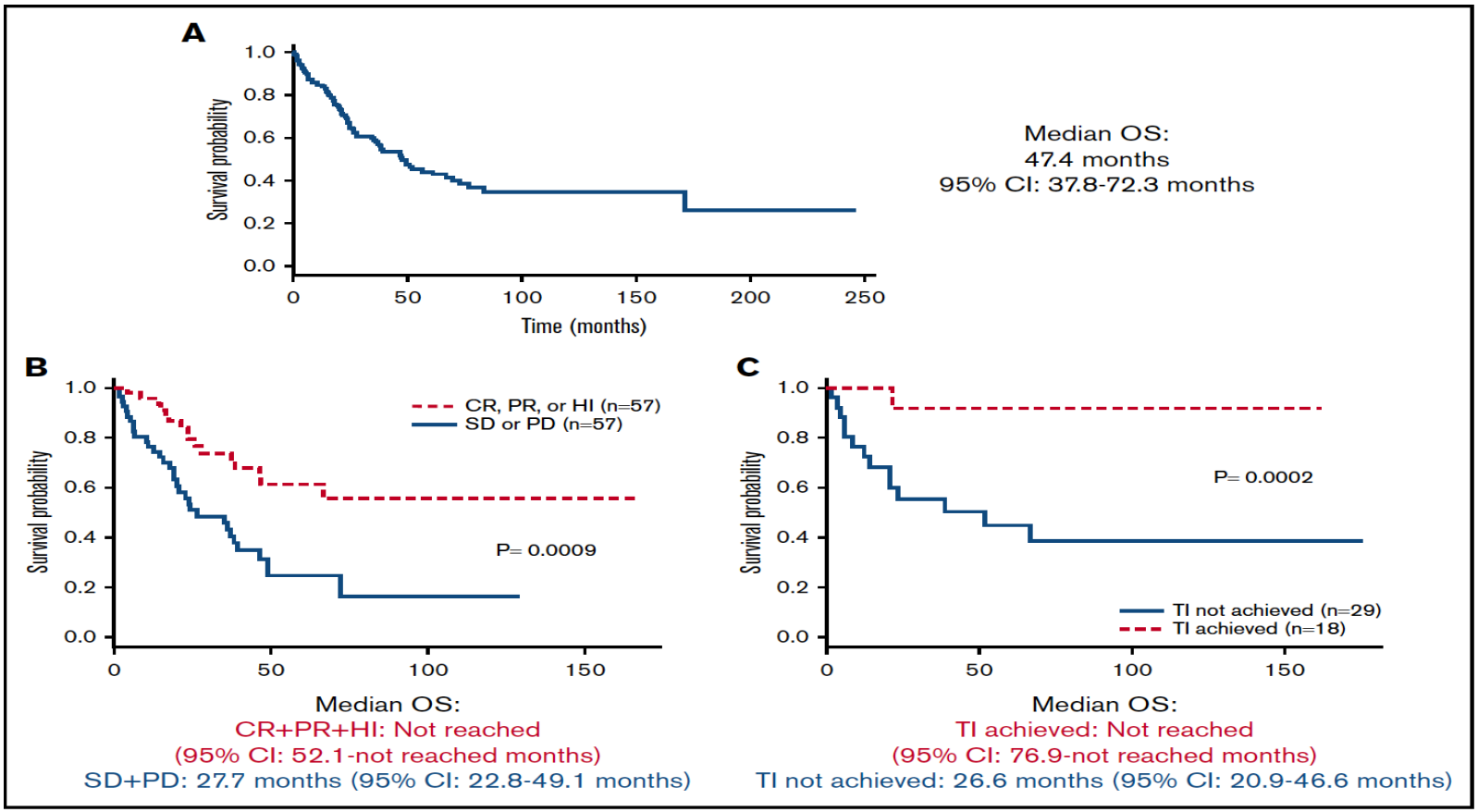
IN our cohort,
IST was rarely applied,
irrespective of BM cellularity

IST CLINICAL TRIALS OF ATG BASED REGIMEN

Author (pub year)	Country	N	Age (median)	Treatment	RA (%)	HR (%)
Molldrem (2002)	US	61	60	hATG	61	34
Saunthararajah (2002)	US	72	59	hATG and/or CyA	46	29
Yazji (2003)	US	31	59	hATG and CyA	58	23
Steensma (2003)						0
Stadler (2004)						40 27
Broliden (2006)	Sweden	20	64	rATG and CyA	85	30
Lim (2007)	UK, Germany Italy	96	56	hATG	84	42
Sloand (2008)	US	116	60	hATG and CyA hATG	67	48 24
Passweg (2011)	Swiss, Germany	45	62	hATG and CyA vs BSC	47 41	31 9
Kadia (2012)	USA	24	62	rATG and CyA	ND (low/int1)	25

ORR ranging from 25% to 80%

OS IN PATIENTS WITH MDS TREATED WITH IST



Stahl et al Blood Advances 2018

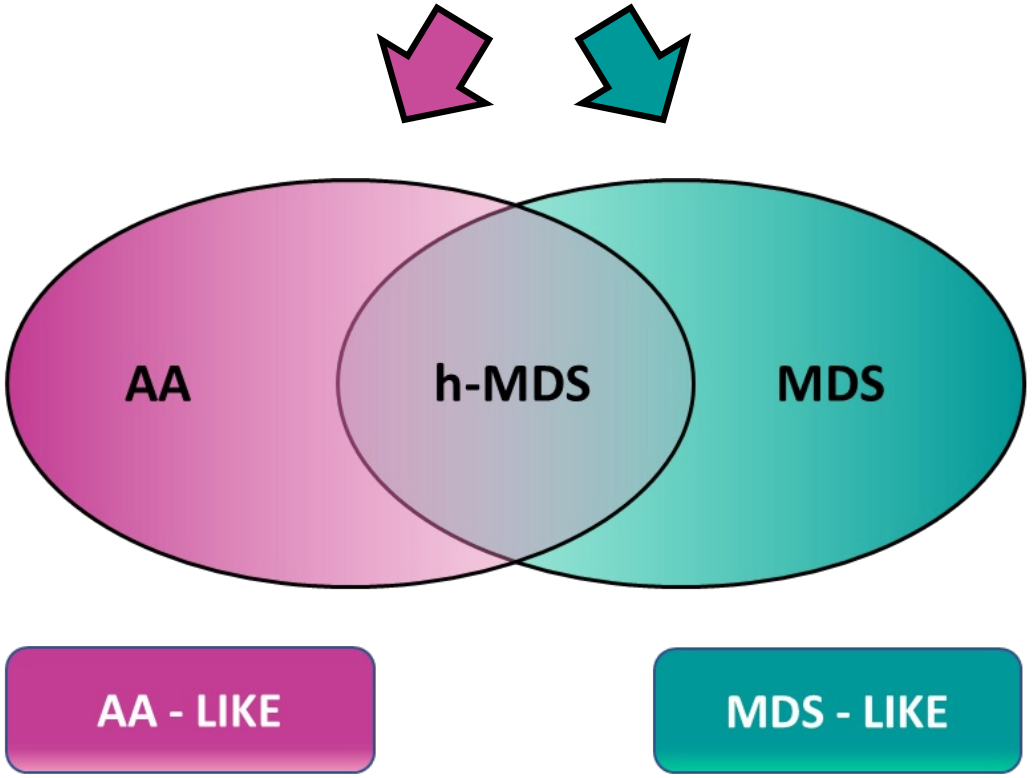
CONCLUSIONS

- Hypocellular LR MDS is characterized by a better prognosis, irrespective of WHO classification;

- Despite IST is recommended for h-MDS, is still administered to exiguous proportion of LR h-MDS cases (at least in Italy) and the choice of therapy is not influenced by BM cellularity;

- KIR/NKG2 restricted NK cell expansions are detected in LR h-MDS, whereas cytotoxic clonal T cell populations in HR h-MDS. Prospective studies are needed to better define the prognostic roles of T and NK subsets in h-MDS.

CHOICE OF THERAPY



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