FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

Fattori predittivi e sistemi prognostici nelle MDS

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Background

- Stratification of MDS patients is essential for decision making at diagnosis and at each time of follow-up.
- This information is used to guide therapeutic recommendations for patients, which range from watchful waiting to palliation of symptomatic cytopenias to disease altering treatments, such as chemotherapy and potentially curative allogeneic haematopoietic cell transplantation.

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

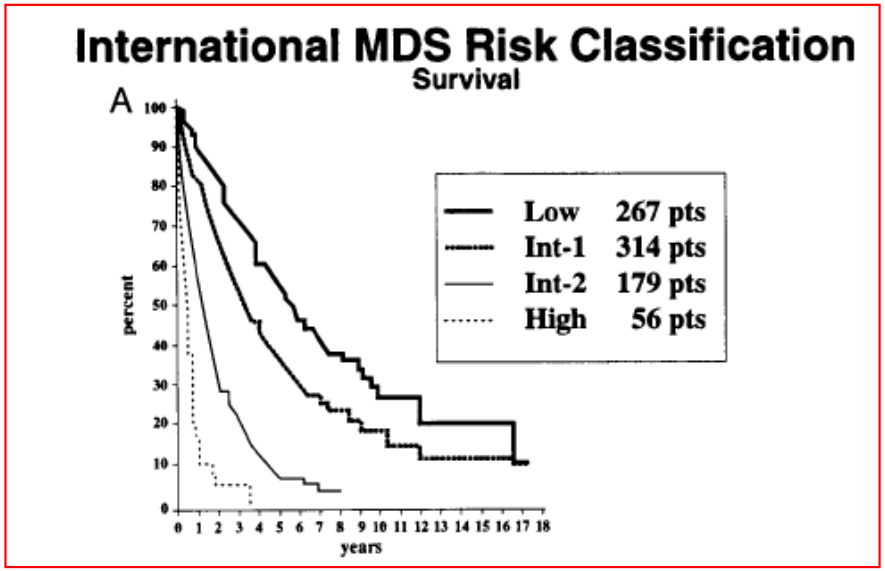
1997

International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

By Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti, and John Bennett

blood

Score	0	0.5	1	1.5	2
BM Blasts	<5%	5-10%		11-20%	21-30%
PB Cytopenia	0-1	2-3			
Karyotype	good	intermediate	poor		



Limits

- ✓ It was not a dynamic model that can provide serial prognostication
- ✓ Only 3 cytogenetic sub-groups
- ✓ Did not consider depth of cytopenias
- ✓ Potentially had a bias related to survival times being calculated from time to presentation to a tertiary care centre.
- ✓ Concentrate on the disease only, without considering patient characteristics

Additional attempts at refining MDS prognostic scoring systems

Table 1
Prognostic classification systems for MDS and CMML.[a]

System	Blasts	Cyto	Hgb	Plts	ANC	Age	RBC txn	PS
IPSS	+	+	+	+	+	+		
WPSS	+[b]	+	+				+[c]	
MDA-LR	+	+	+	+		+		
MDAS	+	+	+	+	+[d]	+	+	+
FPSS	+(PB)	+					+	+
CPSS[e]	+	+	+		+[d]		+[c]	
IPSS-R[f]	+	+	+	+	+	+		+

[a] Table adapted from Refs. [1–7].
[b] WHO MDS subtype.
[c] RBC transfusion dependency can be substituted by haemoglobin (Hgb) level.
[d] Leucocytosis.
[e] CMML: FAB and WHO MDS subtypes.
[f] Plus other variables: LDH, ferritin, b2-microglobulin, fibrosis.

Jonas B & Greenberg P , Best Prac & Res Clin Hem 2015

JOURNAL OF CLINICAL ONCOLOGY

2005

Prognostic Factors and Life Expectancy in Myelodysplastic Syndromes Classified According to WHO Criteria: A Basis for Clinical Decision Making

Luca Malcovati, Matteo Giovanni Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Marina Boni, Erica Travaglino, Francesco Passamonti, Luca Arcaini, Margherita Maffioli, Paolo Bernasconi, Mario Lazzarino, and Mario Cazzola

Score	0	1	2	3
WHO Category	RA, RARS 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Transfusion Requirement	no	regular		
Karyotype	good	intermediate	poor	

- ✓ RBC transfusion-dependence with development of secondary iron overload had a worse prognosis in multivariate analysis.
- ✓ The main advantage of the WPSS was the ability to be used for serial prognostication.
- ✓ It had similar limitations as the IPSS and did not account for degree of cytopenias,
- ✓ Relied on detailed morphologic analysis (e.g., dysplasia) to determine WHO subtype that has not been universally discernable.

Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS)

Table 2. WHO classification-based Prognostic Scoring System (WPSS)[7] as refined by the findings on prognostic significance of the degree of anemia obtained in this work.

Variable	Variable scores			
	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated deletion (5q)	RCMD	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	-
Severe anemia (Hb <9 g/dL in males or <8 g/dL in females)	Absent	Present	-	-

WPSS risk	Sum of individual variable scores
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

*Hb: hemoglobin concentration. *Good: normal, -Y, del(5q), del(20q); Poor: complex, chromosome 7 anomalies; Intermediate: other chromosomal abnormalities.*[6]

The latter parameter was replaced by haemoglobin (Hgb) level, changing the transfusion-dependency variable to Hgb <9 g/dL for males and <8 g/dL for females

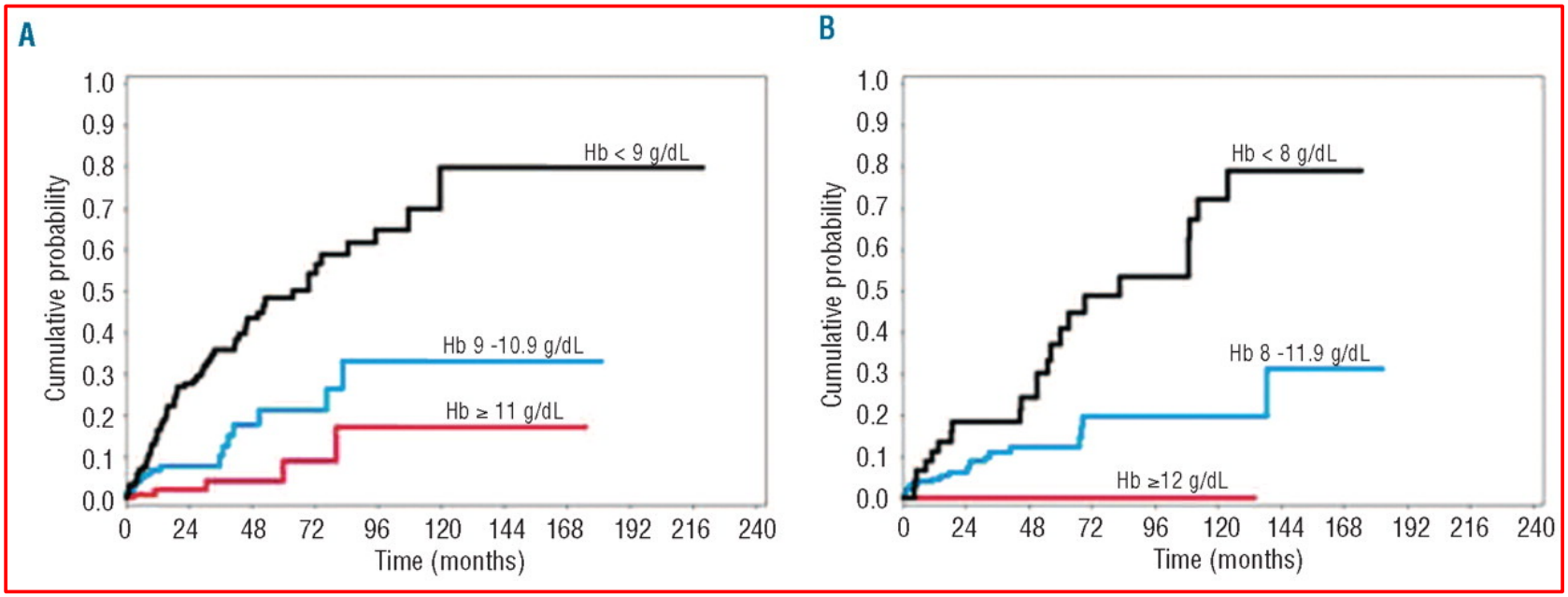
Limits

Only transfusion-dependent anemia considered by WPSS.

WBC and PLTS counts not evaluated

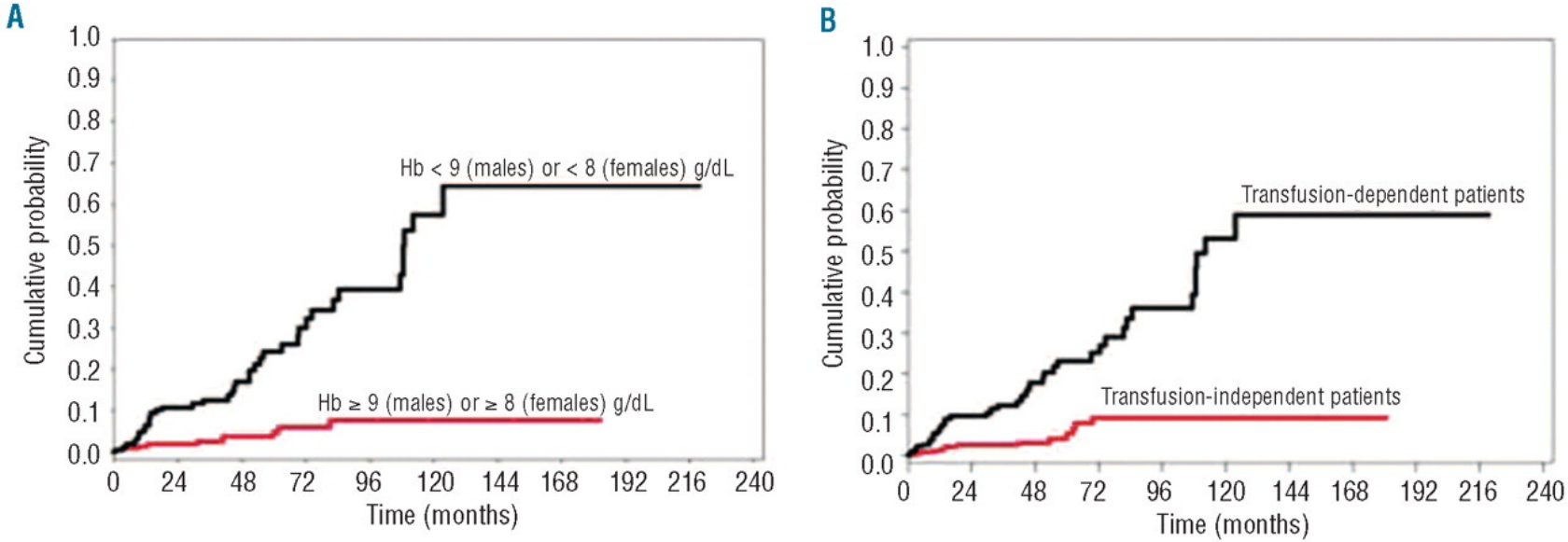
Malcovati L et al, Haematol 2011

Prognostic relevance of the degree of anemia in patients with MDS.



Chronic anaemia is associated with an increased risk of NLD

Relationship between severe anemia and cardiac disease.



Malcovati L et al. Haematol 2011

Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes

2012

blood

- ✓ Data from 7012 patients from multiple institutional databases in the combined IWG-PM database were evaluated.
- ✓ Median age: 71 years, 77% were >60 years
- ✓ Male: female ratio 1.5:1
- ✓ Median follow-up time 3.9 years.
- ✓ The 7012 patients obtained for evaluation were classified by FAB (n=7000, 99.8%) and additionally by WHO (n=5504, 78.5%) and/or WPSS (n=2325, 33.2%)

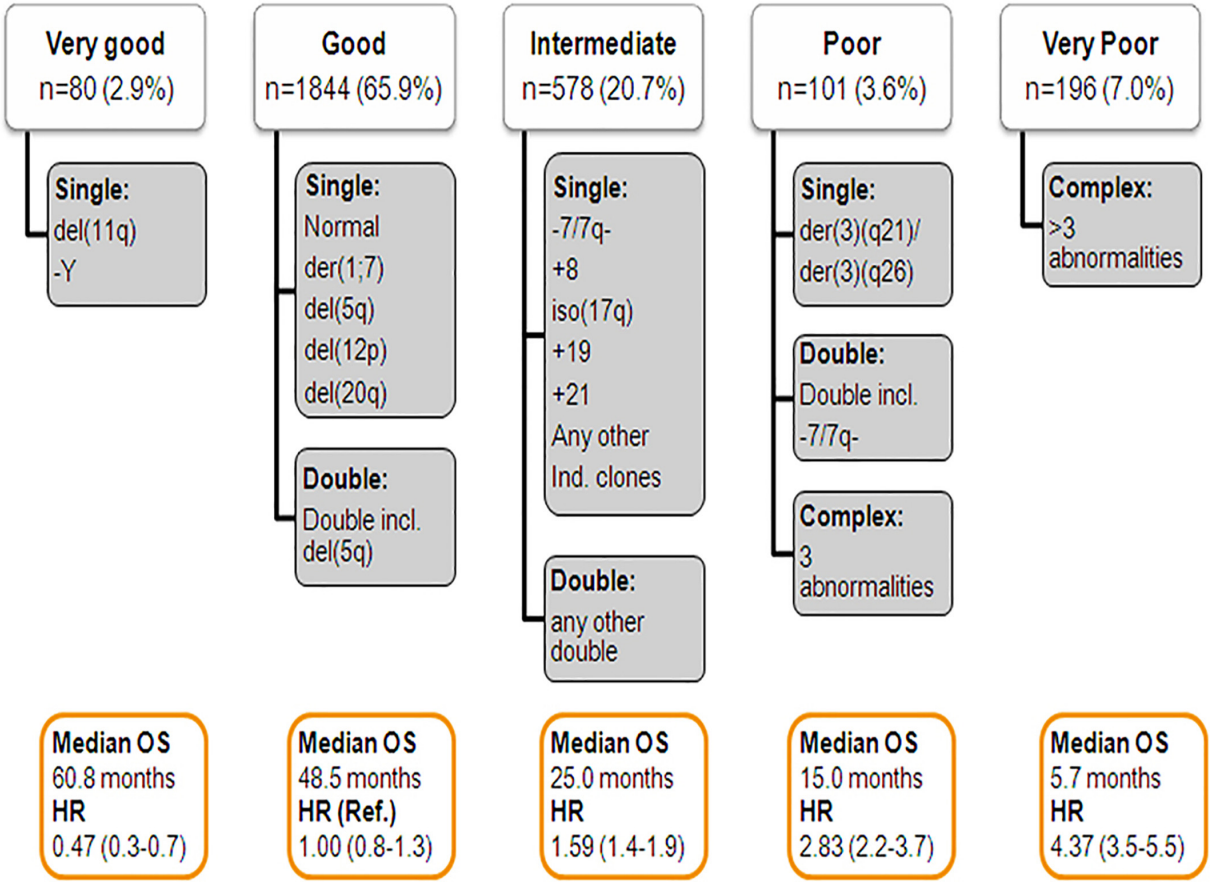
Table 8. Refinements of the IPSS-R beyond the IPSS

1. New marrow blast categories
≤ 2%, > 2%-< 5%, 5%-10%, > 10%-30%
2. Refined cytogenetic abnormalities and risk groups
16 (vs 6) specific abnormalities, 5 (vs 3) subgroups
3. Evaluation of depth of cytopenias
Clinically and statistically relevant cutpoints used
4. Inclusion of differentiating features*
Age, Performance Status, serum ferritin, LDH; β_2-microglobulin†
5. Prognostic model with 5 (vs 4) risk categories
Improved predictive power

*For survival.
†Provisional.

Greenberg P et al, Blood 2012

A new cytogenetic classification scheme for MDS was proposed to replace the original risk groups proposed in the IPSS



Greenberg et al. Blood 2012, Garcia-Manero et al Am J Hem 2020

Scoring for the IPSS-R

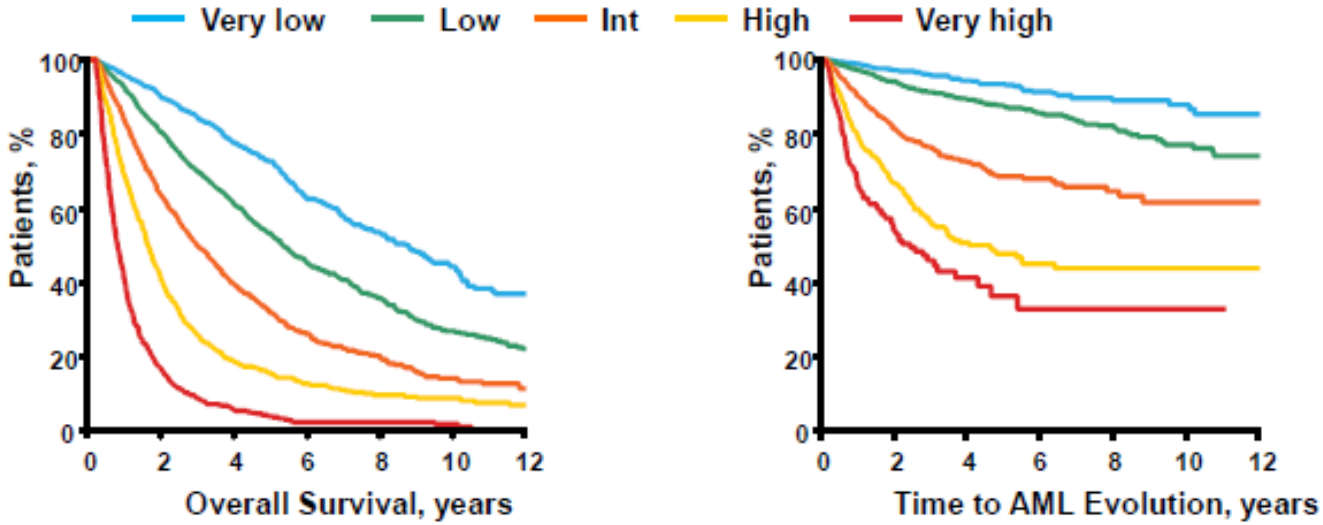
Parameter	Categories and Associated Scores				
Cytogenetic risk group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Marrow blast proportion	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Possible range of summed scores: 0-10

Greenberg et al. *Blood*. 2012:120:2454-65.

Risk Groups for the IPSS-R

Risk group	Points	% of Patients	Median survival, years	Time until 25% of patients develop AML, years
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



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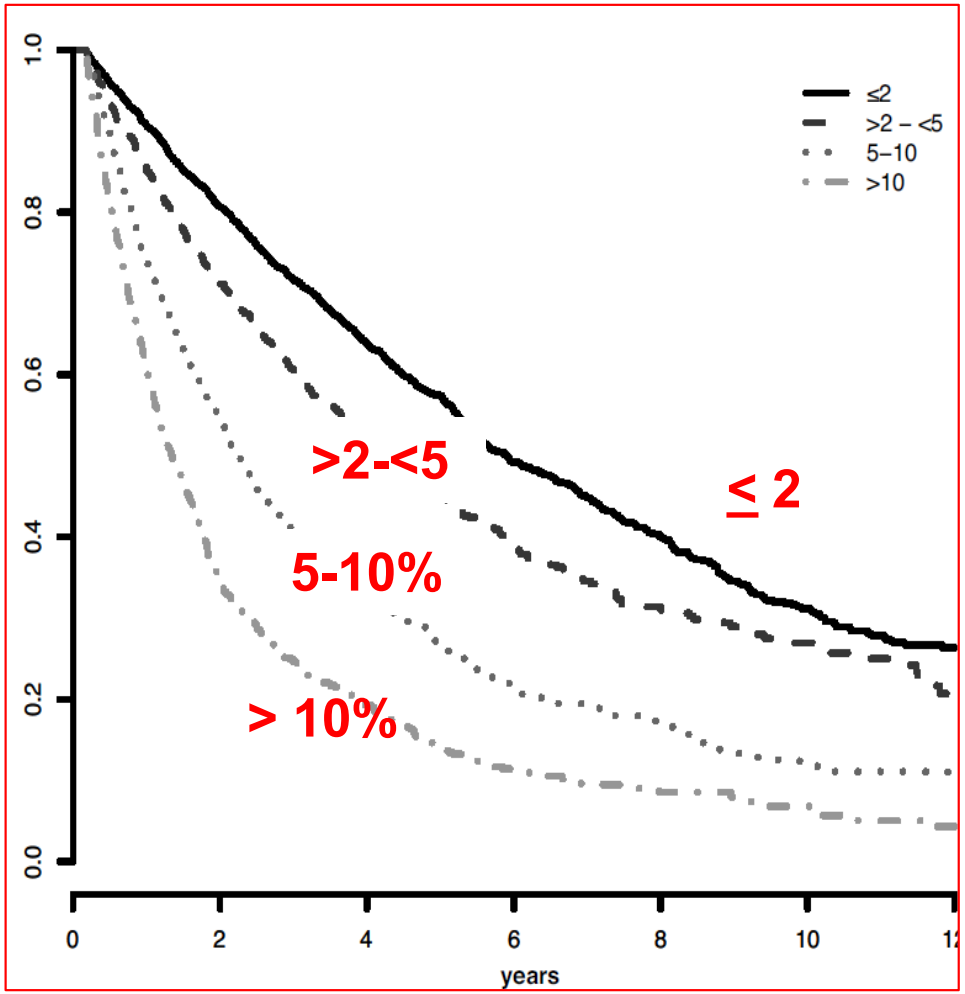
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet count (x 10^9/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Abs. neutrophil count (x 10^9/L)	≥ 0.8	< 0.8			
	0	0.5			

Possible range of summed scores: 0-10

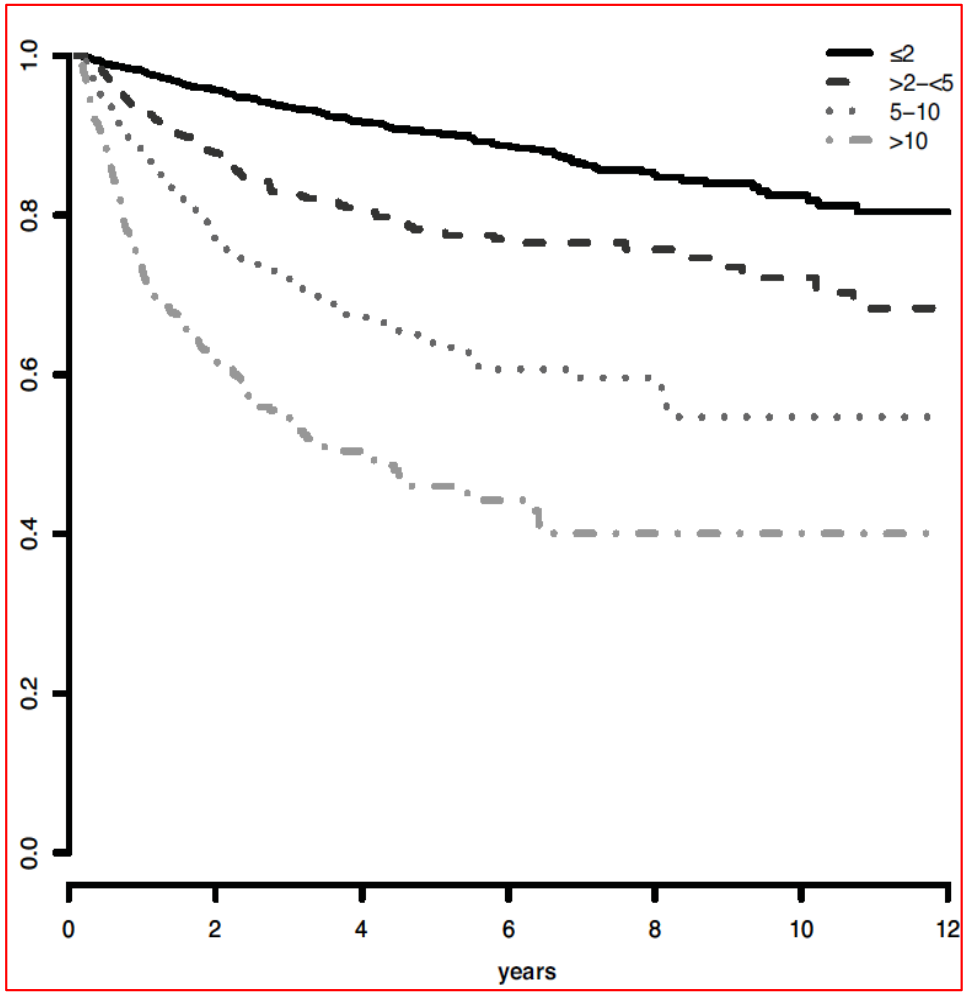
Greenberg et al. *Blood*. 2012:120:2454-65.

BM -blast subgroups

Overall Survival



Leukemia-Free Survival



Greenberg et al. Blood 2012

Revised IPSS
Score Points due to additional prognosticators

Variables	Variables	Prognostic power (gain in Dxy)	Raw score Points
Performance status/ ECOG score	O vs 1 vs 2-4	0.02	-0.8 / 0.2 / 1.0
Serum ferritin	≤ vs >350 ng/ml	0.01	-0.4 /0.5
Serum LDH	Normal vs High	0.01	-0.2 / 0.5
Serum beta-2 microglobulin	≤ vs >2 g/ml	0.03	-0.1 / 0.5
Marrow fibrosis	No vs Yes	0	NANS

- ✓ Ferritin may be a reflection of both clinical (transfusion burden) and biological (degree of ineffective erythropoiesis and inflammation) features of MDS
- ✓ These factors could shift a patient to a higher or lower category based on dichotomized values although their effect was less significant compared to the five main prognostic features.

Greenberg et al. Blood 2012

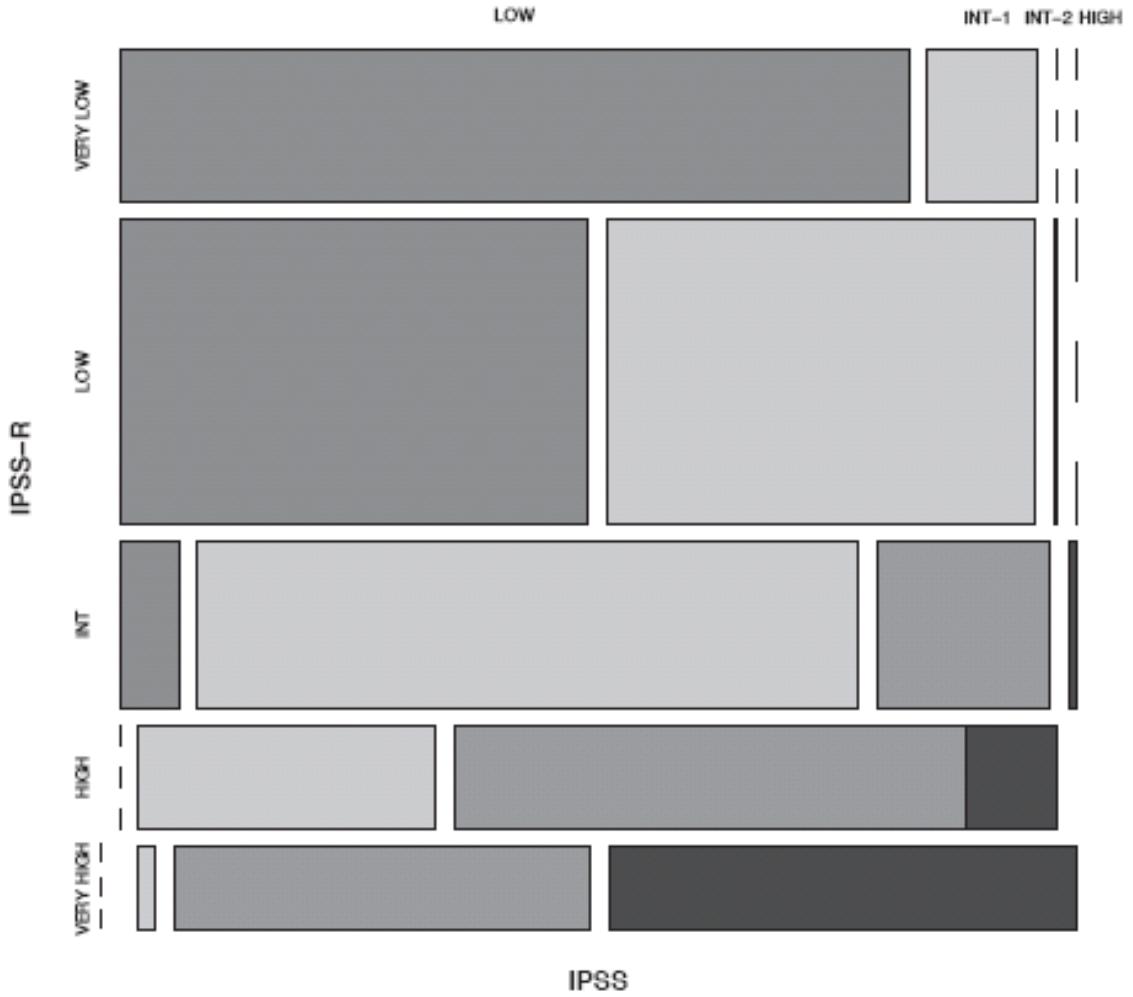


Table 9. Distribution (%) of IWG-PM patients who would previously have been categorized by IPSS now categorized by IPSS-R

IPSS	Very low	Low	Intermediate	High	Very High
Low (37)	44	52	4	0	0
Intermediate-1 (40)	6	45	38	10	1
Intermediate-2 (16)	0	1	24	45	30
High (7)	0	0	3	19	78
Total	19	38	20	13	10

% indicated within rows. Kendall tau = 0.73.

The IPSS-R has permitted improved refinement of risk categories for the IPSS Int-1 and Int-2 patients because a substantial portion of the patients who would have been categorized as IPSS Int-1 are now in the IPSS-R Low category.

A substantial portion of the patients who would have been categorized as IPSS Int-2 are now in the IPSS-R High category.

The IPSS-R had several strengths and some limitations

- It improved on the original IPSS for primary untreated MDS with consideration of depth of cytopenias and improved classification of BM blasts and cytogenetics.
- The model has been validated by several groups and was extended to and validated in treated patients and at times other than at diagnosis

Revised International Prognostic Scoring System (IPSS) Predicts Survival and Leukemic Evolution of Myelodysplastic Syndromes Significantly Better Than IPSS and WHO Prognostic Scoring System: Validation by the Gruppo Romano Mielodisplasie Italian Regional Database

Voso MT et al , JCO 2013

Validation of WHO classification-based Prognostic Scoring System (WPSS) for myelodysplastic syndromes and comparison with the revised International Prognostic Scoring System (IPSS-R). A study of the International Working Group for Prognosis in Myelodysplasia (IWG-PM)

Della Porta MG et al, Leukemia 2015

blood

2016

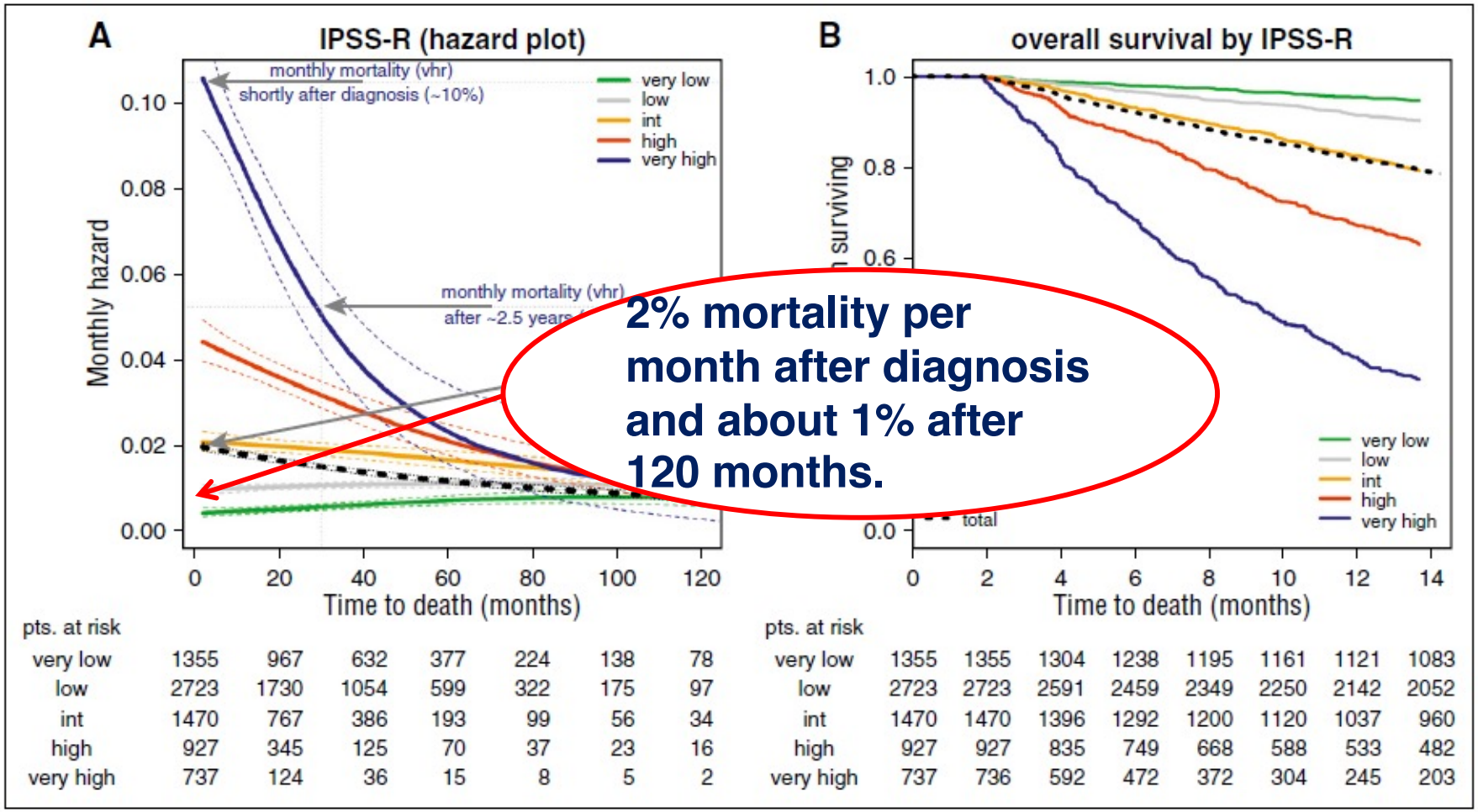
Time-dependent changes in mortality and transformation risk in MDS

Michael Pfeilstöcker,[1] Heinz Tuechler,[2] Guillermo Sanz,[3] Julie Schanz,[4] Guillermo Garcia-Manero,[5] Francesc Solé,[6] John M. Bennett,[7] David Bowen,[8] Pierre Fenaux,[9] Francois Dreyfus,[10] Hagop Kantarjian,[5] Andrea Kuendgen,[11] Luca Malcovati,[12] Mario Cazzola,[12] Jaroslav Cermak,[13] Christa Fonatsch,[14] Michelle M. Le Beau,[15] Marilyn L. Slovak,[16] Alessandro Levis,[17] Michael Luebbert,[18] Jaroslaw Maciejewski,[19] Sigrid Machherndl-Spandl,[20] Silvia M. M. Magalhaes,[21] Yasushi Miyazaki,[22] Mikkael A. Sekeres,[19] Wolfgang R. Sperr,[23] Reinhard Stauder,[24] Sudhir Tauro,[25] Peter Valent,[26] Teresa Vallespi,[27] Arjan A. van de Loosdrecht,[28] Ulrich Germing,[11] Detlef Haase,[4] and Peter L. Greenberg[29]

Multicenter retrospective study among 7212 primary untreated MDS patients from the IWG for Prognosis in MDS database with the aim to:

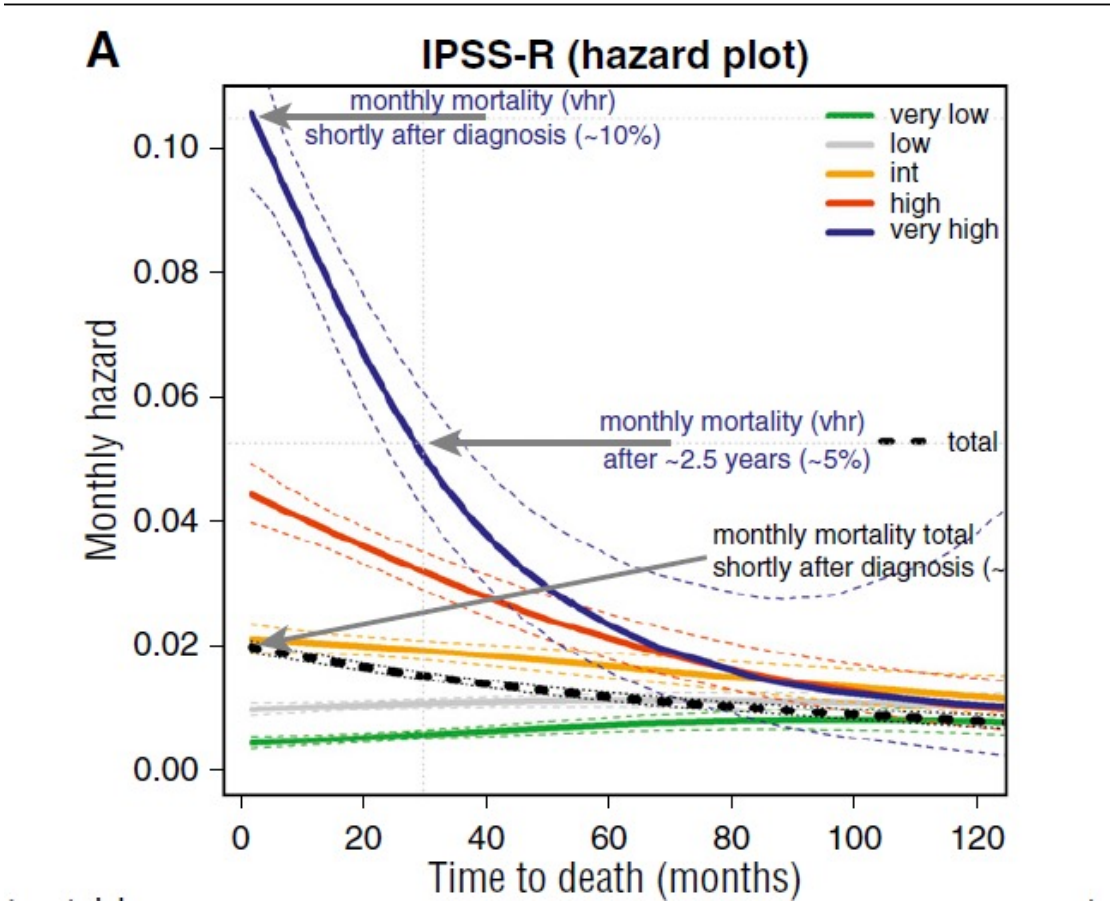
- ✓ To assess the relative stability of the newly developed scoring systems over time
- ✓ To compare the observed time-related changes in prognostic power among these systems
- ✓ To relate these changes to the time dependence of hazards.

Survival of IPSS-R–classified patient subgroups using smoothed hazard plots (A) and corresponding Kaplan-Meier curves (B).



- ✓ The smoothed hazard for very high risk indicates 10% monthly mortality risk in the beginning in agreement with the Kaplan-Meier curve.
- ✓ After approximately 30 months (A, middle arrow), 5% monthly mortality for the very-HR group is shown, which is not clearly visible in the Kaplan-Meier curve.

Pfeiilstocker M et al, Blood 2016

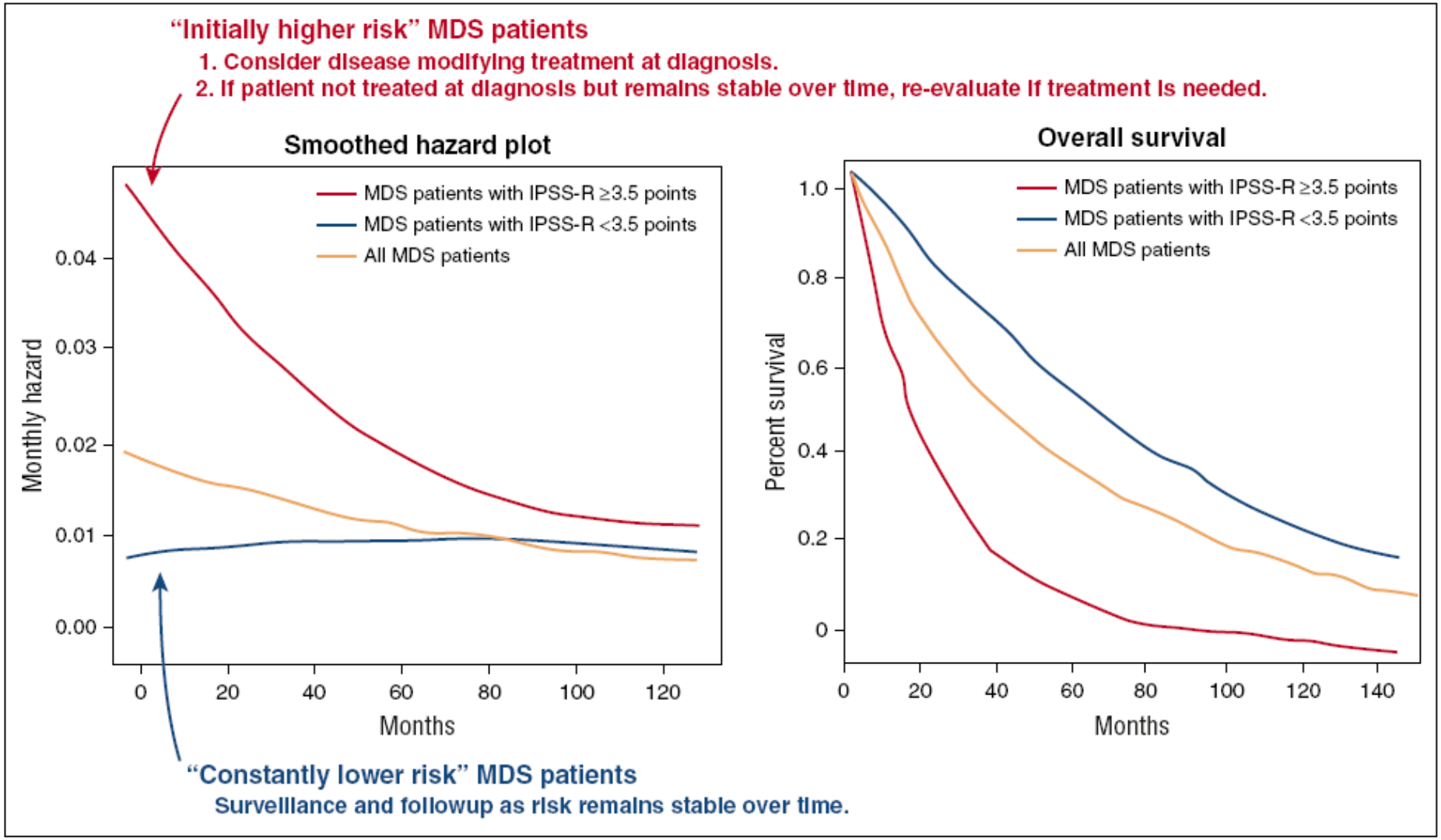


The mortality risks of the remaining patients for all risk groups are similar after about 60 months.

The graph illustrates that similarity of risks derives mainly from a decline in the higher-risk groups (IPSS-R very high and high), whereas the mortality risk in the lower-risk groups (IPSS-R low and very low) remains essentially unchanged.

Pfeiilstocker M et al, Blood 2016

The multicenter retrospective study of 7212 untreated MDS patients clearly shows that there is a decrease in risk of mortality and leukemic transformation over time from diagnosis in higher-risk but not in lower-risk patients.



Pfeiilstocker M et al, Blood 2016

Natural history of lower risk MDS is very heterogeneous

MDACC evaluated outcomes in a large series of patients with low or intermediate-1 disease by IPSS:

- ✓ prognosis varied significantly in patients with lower risk MDS
- ✓ a lower-risk MDS specific prognostic score was developed

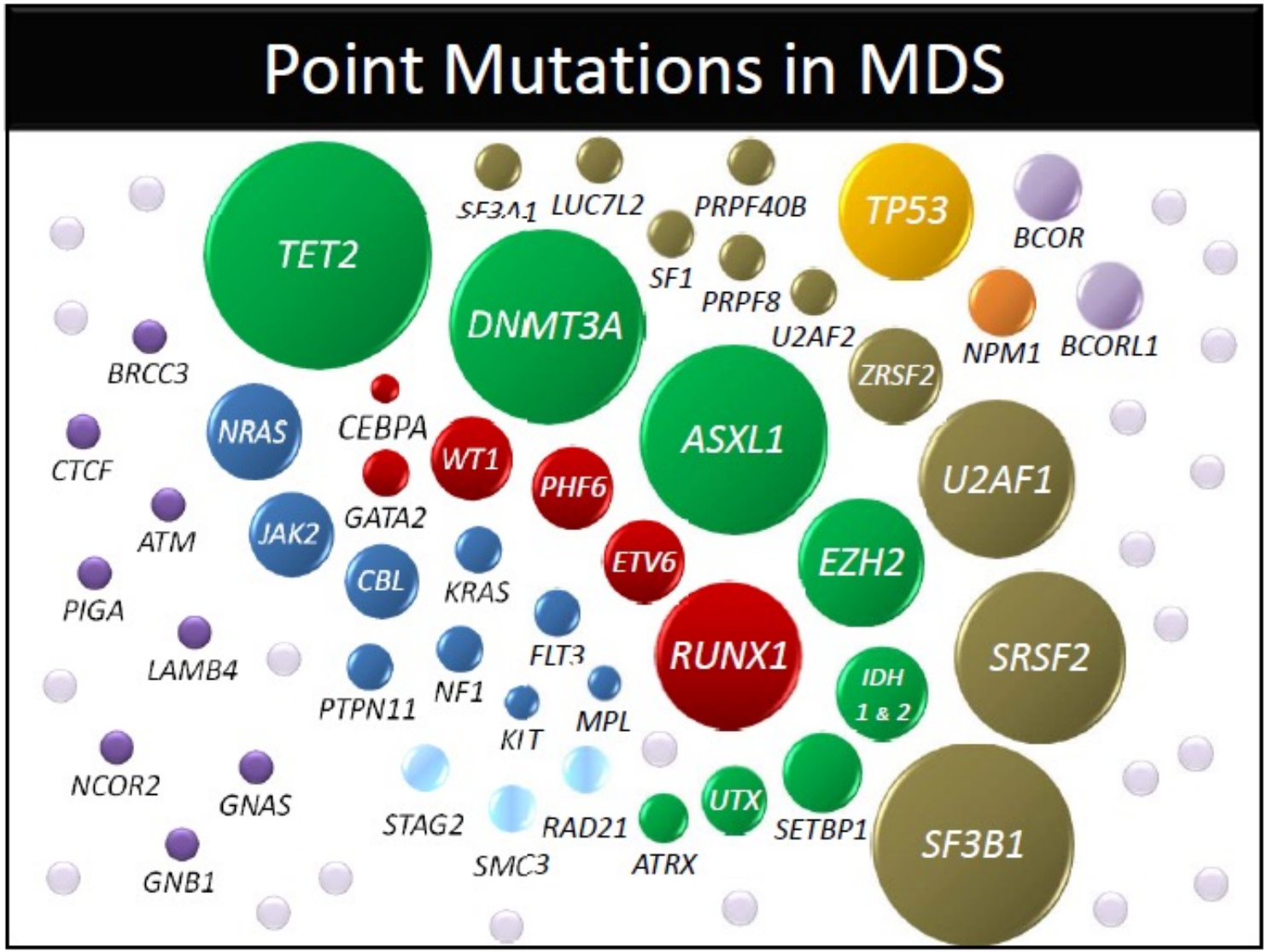
This model has been validated on several occasions, and it is being used to identify patients with poor prognosis, lower risk disease that could be candidates for early intervention.

TABLE 2 MDACC MDS lower risk prognostic model[41]

Characteristics		Points
Unfavorable cytogenetics		1
Age ≥ 60 y		2
Hemoglobin <10 (g/dL)		1
Platelets < 50 x 10^9/L 50-200 x 10^9/L		2 1
Bone marrow blasts ≥4%		1
Score	**Median survival**	**4-y OS (%)**
0	NR	78
1	83	82
2	51	51
3	36	40
4	22	27
5	14	9
6	16	7
7	9	N/A

Note: Characteristics were selected from multivariate analysis model in patients with lower risk MDS. Each characteristic is associated with a number of points. Score is calculated by adding all points. Each score allows calculation of median survival (in mo) and probability of survival at 4 y. Adapted from Garcia-Manero G, et al.[41]

Garcia Manero et al, Leukemia 2008

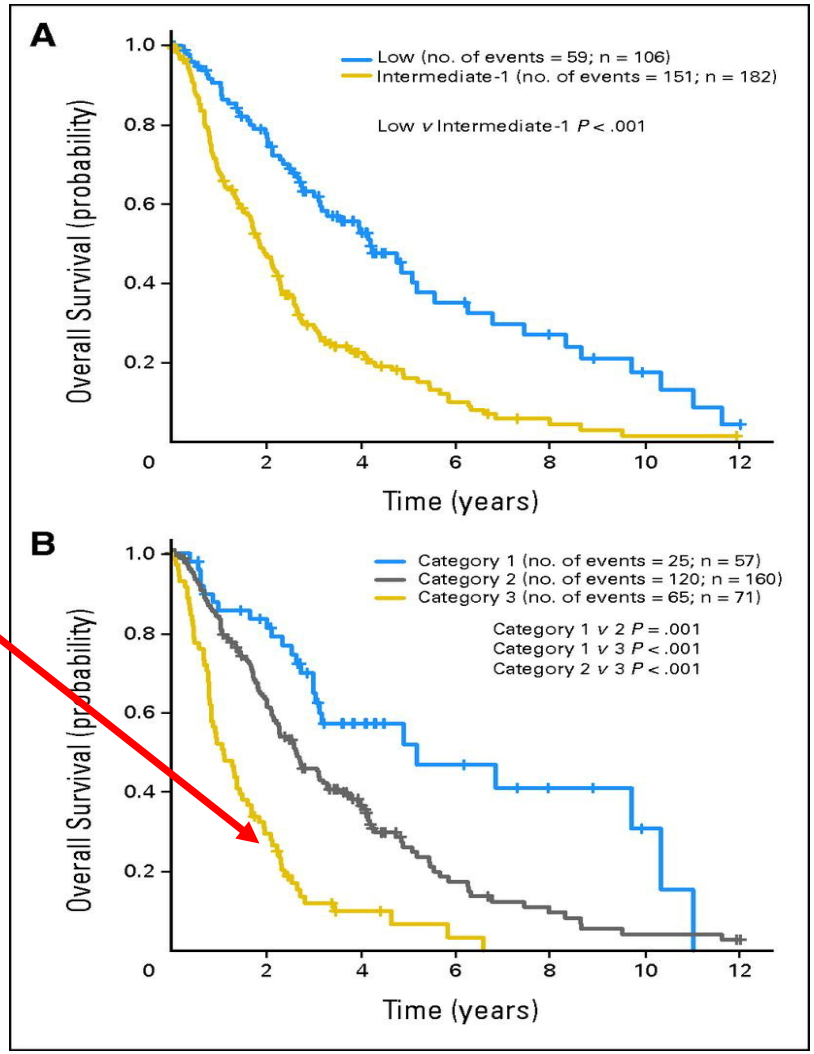


Several studies have confirmed the added value of mutational data in risk stratification when compared to the current prognostic models.

Validation of a Prognostic Model and the Impact of Mutations in Patients With Lower-Risk Myelodysplastic Syndromes

The outcome for patients assigned to category 3 is similar to the published median survival of patients with intermediate-2 IPSS risk MDS

Bone marrow blasts	1
Risk group assignment (total points)	
Category 1	0-2
Category 2	3-4
Category 3	5-7



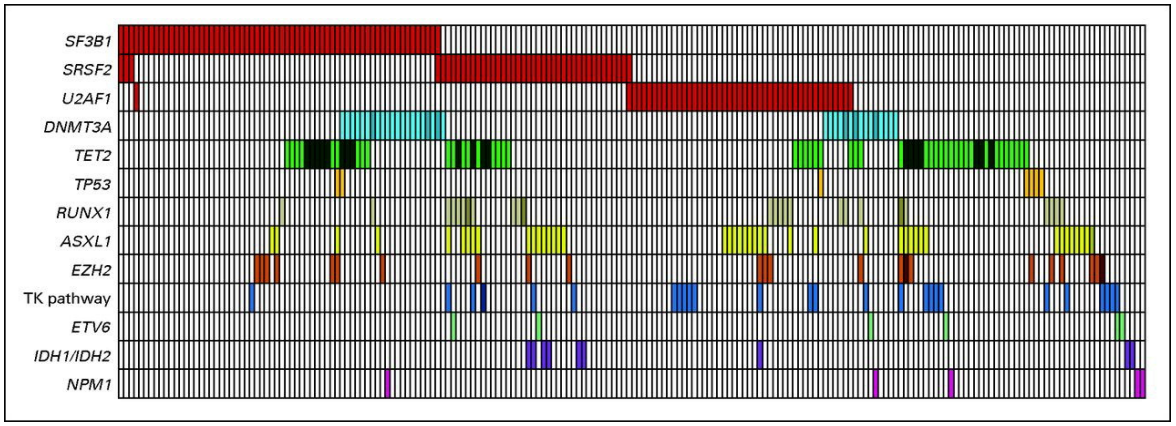
Bejar R et al, JCO 2012

Validation of a Prognostic Model and the Impact of Mutations in Patients With Lower-Risk Myelodysplastic Syndromes

Table 1. Lower-Risk Prognostic Scoring System (LR-PSS)

Clinical Variables	Points
Unfavorable cytogenetics (not normal or del(5q) alone)	1
Age ≥ 60 years	2
Hemoglobin < 10 g/dL	1
Platelet count (×10⁹/L)	
< 50	2
50-200	1
Bone marrow blasts ≥ 4%	1
Risk group assignment (total points)	
Category 1	0-2
Category 2	3-4
Category 3	5-7

Distribution of mutations in 204 of 288 samples from patients with lower-risk myelodysplastic syndromes with one or more mutations



The most commonly mutated genes in lower-risk MDS were TET2 (23% of samples), SF3B1 (22%), U2AF1 (16%), ASXL1 (15%), SRSF2 (15%), and DNMT3A (13%).

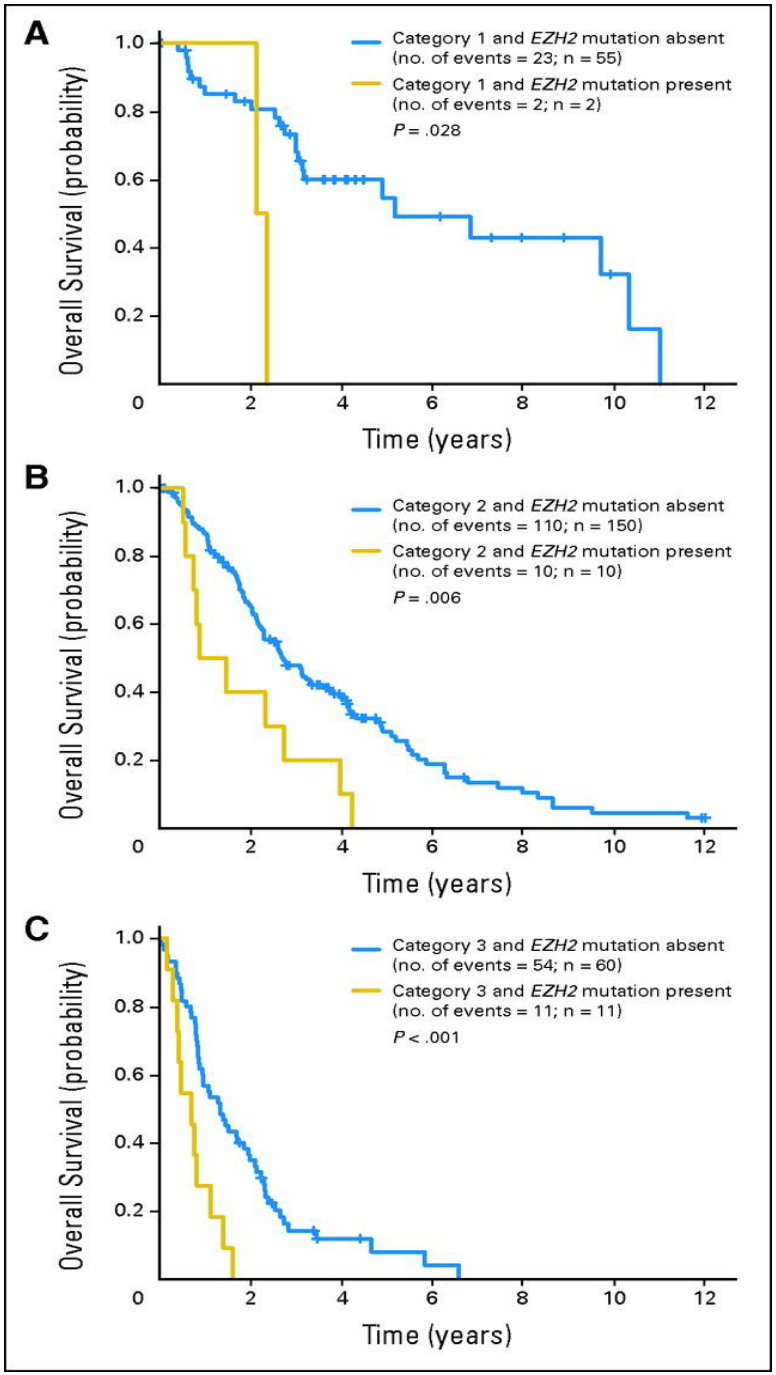
✓ Patients with poorer prognosis and lower-risk disease accumulate a higher number of mutational events than their better-risk counterparts

Bejar R et al, JCO 2012

Mutations are significantly associated with specific parameters that are used to calculate the LR-PSS.

Age> 60	Presence of one or more mutations (48% < 60 years *v* 77% ≥ 60 years; *P* ≤ .001)
Hb <10 g/dl	Mutations of ASXL1, RUNX1, and EZH2 (P ≤ .008 for each comparison).
BM blasts>4%	Mutations in SRSF2, ASXL1, RUNX1, NRAS, and CBL (P < .005 for each comparison)
PLT <50x10 ^{9}/l	Mutations in U2AF1, ASXL1, RUNX1, and NRAS (P < .01 for each comparison).
PLT 50-200X10$^{9/L}$	SF3B1 mutation was associated with a normal or increased platelet count

Bejar R et al, JCO 2012

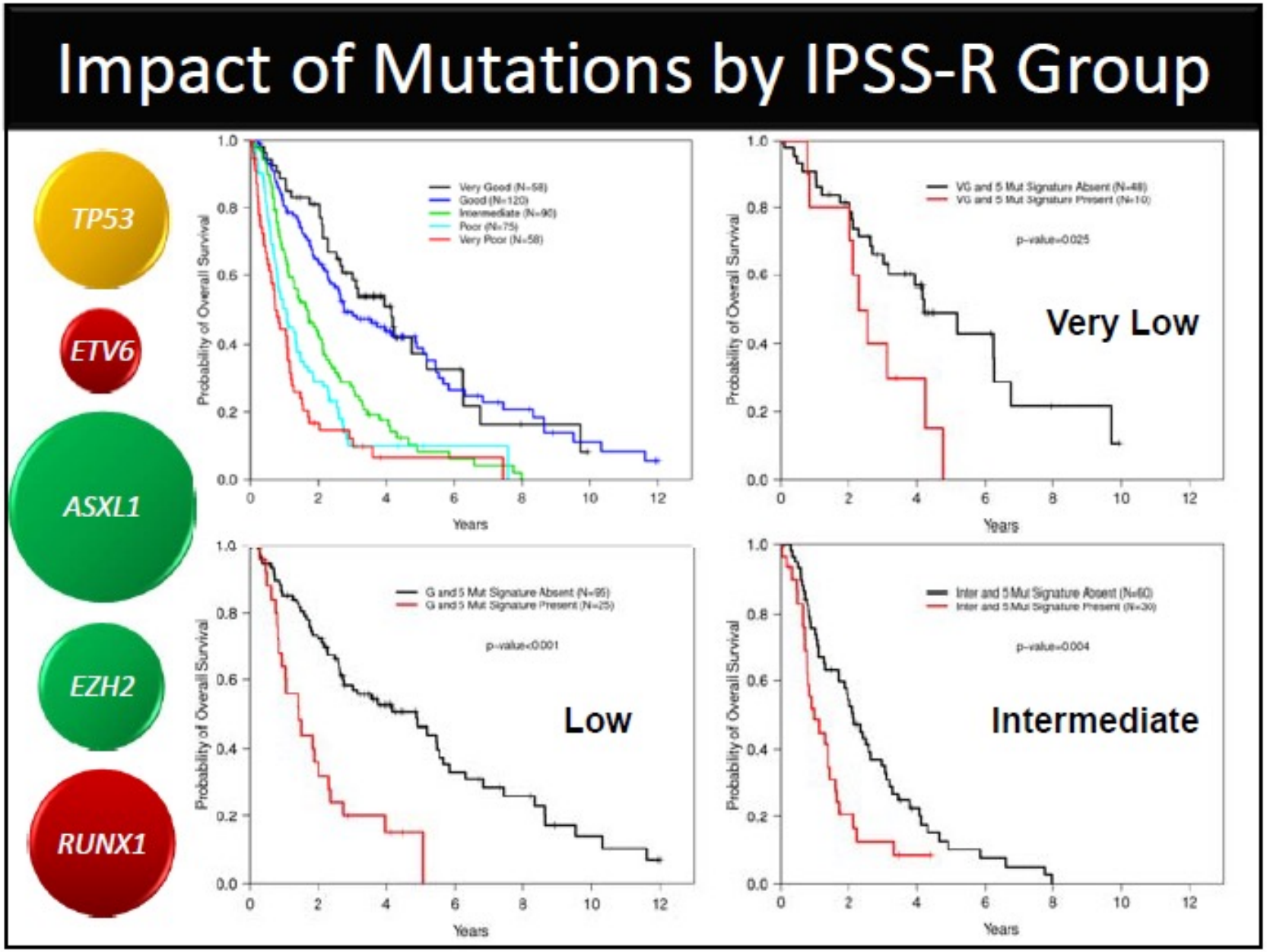


Mutations of EZH2, RUNX1, TP53, and ASXL1 were associated with shorter overall survival independent of the LR-PSS.

Only EZH2 mutations retained prognostic significance in a multivariable model that included LR-PSS and other mutations (hazard ratio, 2.90; 95% CI, 1.85 to 4.52)

Bejar R et al, JCO 2012

Impact of Mutations by IPSS-R Group



Bejar R et al, NEJM 2011

Impact of Mutations by IPSS-R Group

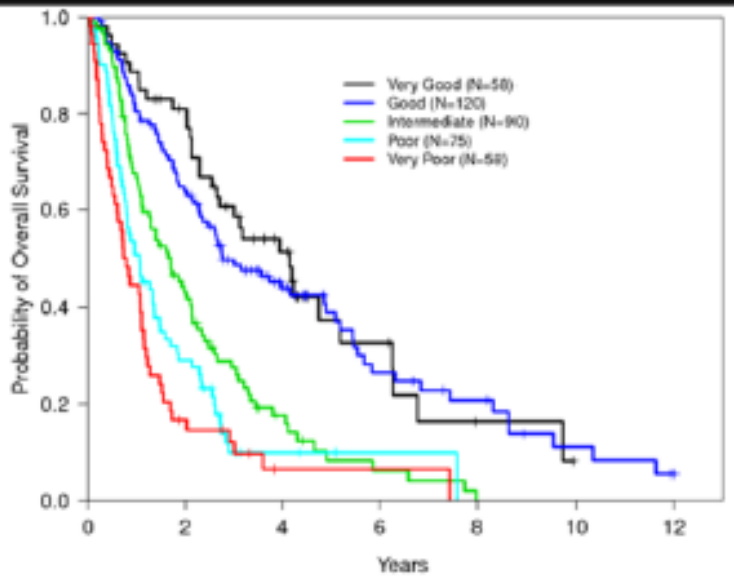
TP53

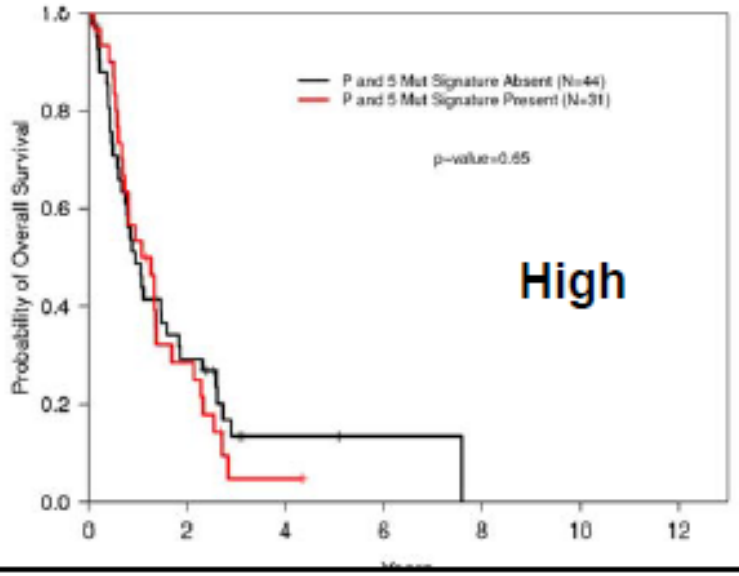
ETV6

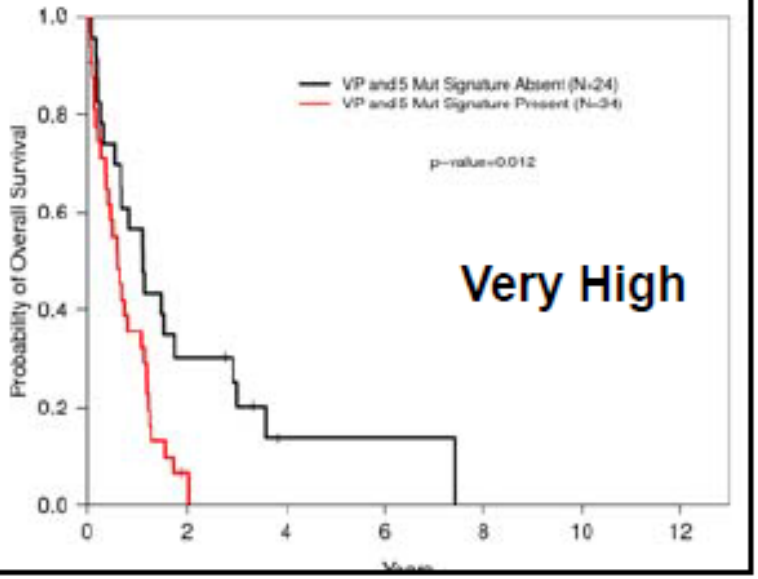
ASXL1

EZH2

RUNX1







Bejar R et al, NEJM 2011

Comparison of clinical outcomes and prognostic utility of risk stratification tools in patients with therapy-related vs de novo myelodysplastic syndromes: a report on behalf of the MDS Clinical Research Consortium

Table 3. Results from Cox proportional hazards models of OS comparing t-MDS to d-MDS adjusting for risk model (covariate model = MDS type+risk category)

Risk model	*OS hazard ratio of t-MDS vs d-MDS (95% CI for HR)*	*P-value for HR = 1*	*P-value for interaction of MDS type and risk model*
IPSS	1.57 (1.37, 1.81)	< 0.0001	0.48
IPSS-R	1.69 (1.47, 1.94)	< 0.0001	0.72
MPSS	1.53 (1.33, 1.76)	< 0.0001	0.67
WPSS	1.52 (1.32, 1.76)	< 0.0001	0.35

Abbreviations: d-MDS, de novo MDS; CI, confidence interval; HR, hazard ratio; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; MDS, myelodysplastic syndromes; t-MDS, therapy-related MDS; WPSS, WHO Prognostic Scoring System. Last column gives *P*-value comparing additive model (MDS type+risk category) to interactive model (MDS type × risk category).

Patients with t-MDS had a significantly higher hazard of death relative to d-MDS in every risk model, and had inferior survival compared to patients with d-MDS within all risk group categories.

Table 1. Demographics and baseline characteristics of the study cohort as stratified by the type of MDS (t-MDS vs d-MDS)

	Therapy-related MDS (n = 370)	*De novo MDS (n = 1576)*	*P-value*
Age > 60 years	281 (76%)	1283 (81%)	0.02
Gender: female	166 (45%)	515 (33%)	< 0.005
WHO subtype			
RA/RARS/RCMD	180 (48%)	778 (49%)	< 0.005
RAEB-1/RAEB-2	157 (43%)	572 (36%)	
other	33 (9%)	226 (15%)	
Karyotype			
Poor risk	177 (49%)	272 (18%)	< 0.005
Complex (>3 abnormalities)	101 (28%)	162 (11%)	
Del 5/−5	106 (30%)	214 (14%)	
Del 7/−7	106 (30%)	142 (9%)	
Circulating myeloblasts	61 (17%)	199 (13%)	0.05
IPSS			
Low	52 (14%)	449 (30%)	< 0.005
Int-1	134 (37%)	659 (43%)	
Int-2	132 (37%)	322 (21%)	
High	42 (12%)	112 (7%)	
IPSS-R			
Very low	30 (9%)	215 (14%)	< 0.005
Low	87 (25%)	509 (34%)	
Intermediate	71 (20%)	337 (22%)	
High	71 (20%)	236 (16%)	
Very high	94 (26%)	217 (14%)	
MPSS			
Low	41 (11%)	329 (21%)	< 0.005
Int-1	103 (29%)	611 (40%)	
Int-2	89 (25%)	318 (21%)	
High	127 (35%)	278 (18%)	
TPSS			
Low	92 (25%)	NA	
Intermediate	200 (55%)		
High	75 (20%)		
WPSS			
Very low	9 (3%)	112 (8%)	< 0.005
Low	40 (12%)	307 (22%)	
Intermediate	57 (17%)	303 (22%)	
High	140 (42%)	460 (33%)	
Very high	84 (25%)	193 (14%)	

Zeidan AM, Leukemia 2017

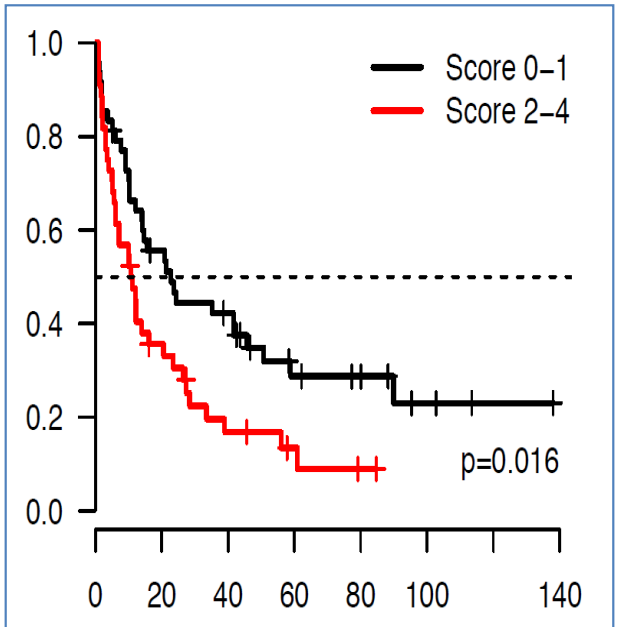
Prognostic scores in t-MDS

Table I OS according to prognostic scores identified in epidemiological studies on t-MN patients

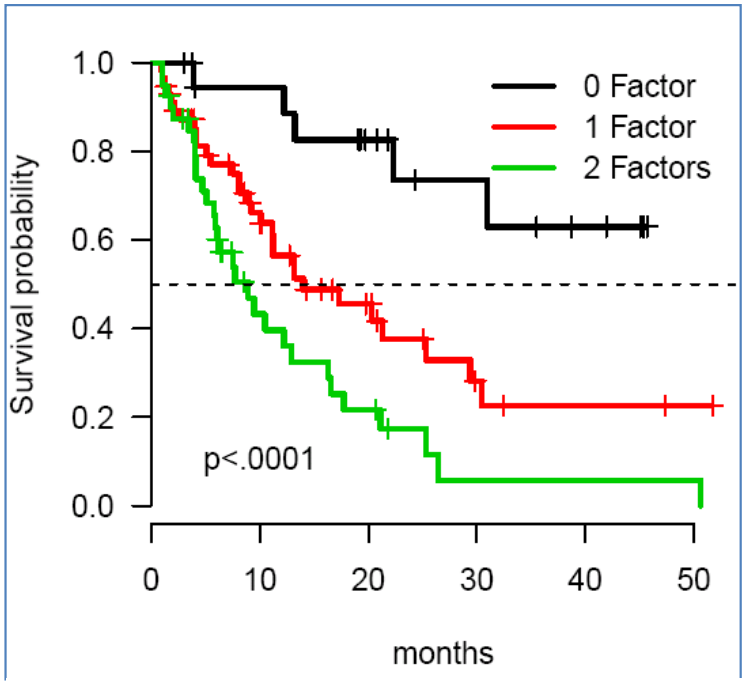
Study	No of patients	Prognostic factors	Score	Median OS according to score
Quintás-Cardama et al[39]	279	Age>65 years, ECOG PS>1, monosomy 7 or complex karyotype	0–2	34.0
		RARS or RAEB-1/2, Hb<11 g/dL, PLT<50×10⁹/L, transfusion dependency	3–4	12.0
			5–7	5.0
Ornstein et al[27]	58	Unfavorable cytogenetics	0–1	30.4
		Antecedent hematologic or autoimmune disease vs solid tumor	2–4	11.2
		Age>60 years		
		PLT<30×10⁹/L		
Fianchi et al[31,48]	277	Age>60 years	0	Not reached
		Unfavorable karyotype	1	14.0
			2	8.9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PLT, platelet; PS, performance status; RAEB-1/2, refractory anemia with excess blasts types 1 and 2; RARS, refractory anemia with ringed sideroblast; t-MNs, therapy-related myeloid neoplasms.

Fianchi L et al, Onco Targets Ther. 2018.



Ornstein et al, Am J Hematol 2014



Fianchi et al, Am J Hematol 2015

Therapy-related myelodysplastic syndromes deserve specific diagnostic sub-classification and risk-stratification -an approach to classification of patients with t-MDS

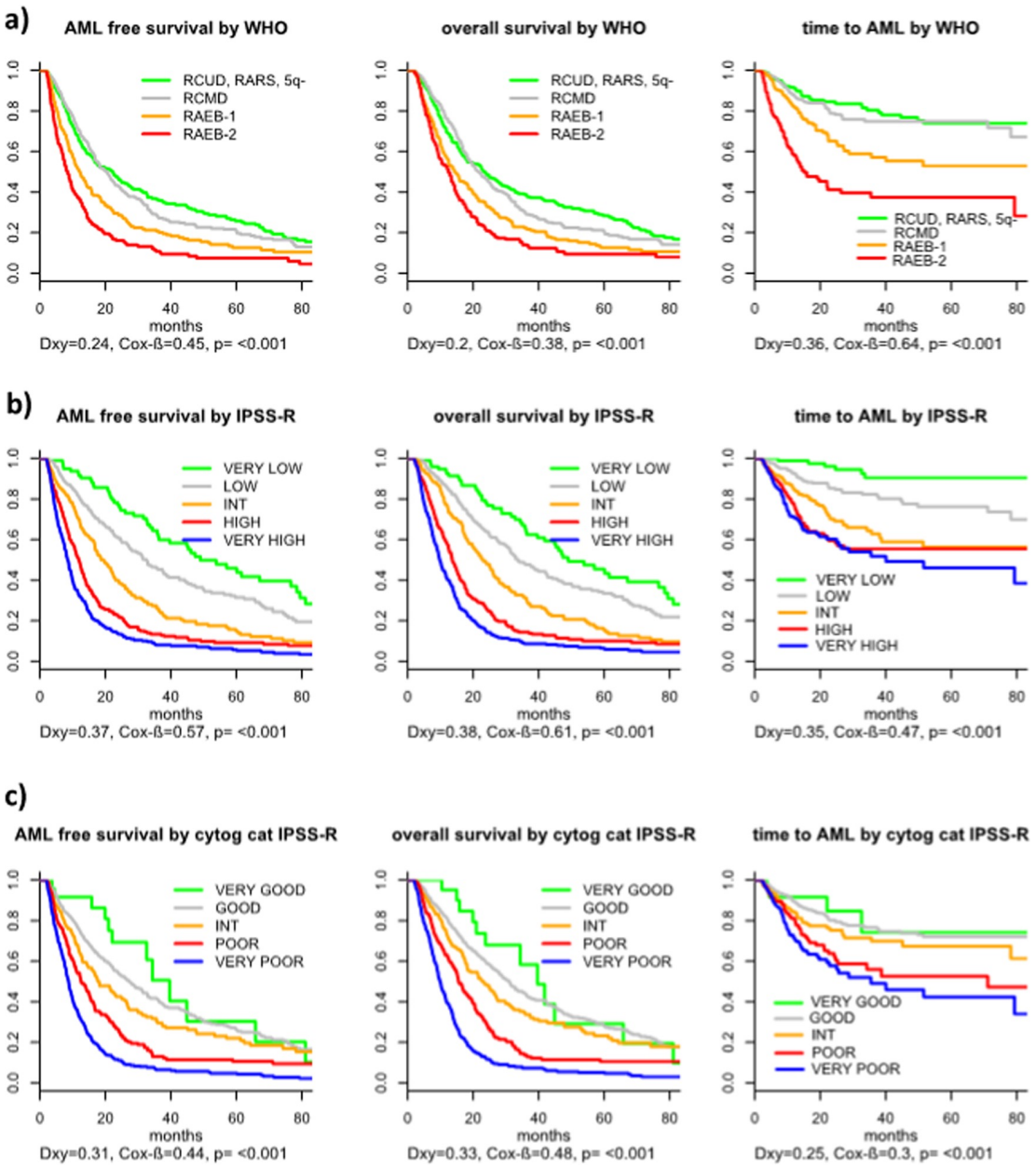
Analyzing data of 2087 t-MDS patients from different international MDS groups to evaluate classification and prognostication tools

Applying the WHO classification for p-MDS successfully predicts time to transformation and survival (both $p < 0.001$).

t-MDS are similarly heterogeneous as p-MDS and therefore deserve the same careful differentiation regarding risk.

These results were compared with 4593 primary MDS (p-MDS) patients represented in the International Working Group for Prognosis in MDS database (IWG-PM)

Kuendgen et al. Leukemia. 2021

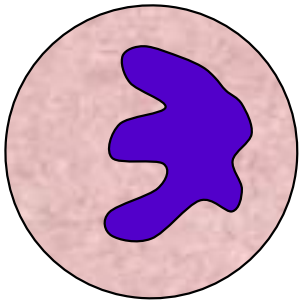


Outcome of patients with t-MDS according to different tools for classification and prognosis.

Although a less favorable clinical outcome occurred in each t-MDS subset compared with p-MDS subgroups, FAB and WHO-classification, IPSS-R, and WPSS-R separated t-MDS patients into differing risk groups effectively, indicating that all established risk factors for p-MDS maintained relevance in t-MDS, with cytogenetic features having enhanced predictive power.

Kuendgen et al. Leukemia. 2021

ADDITIONAL PROGNOSTIC FACTORS



- **DISEASE-RELATED:**
  - **LDH**
  - **β-2 Microglobulin**
  - **Ferritin**
  - **Bone Marrow Fibrosis**

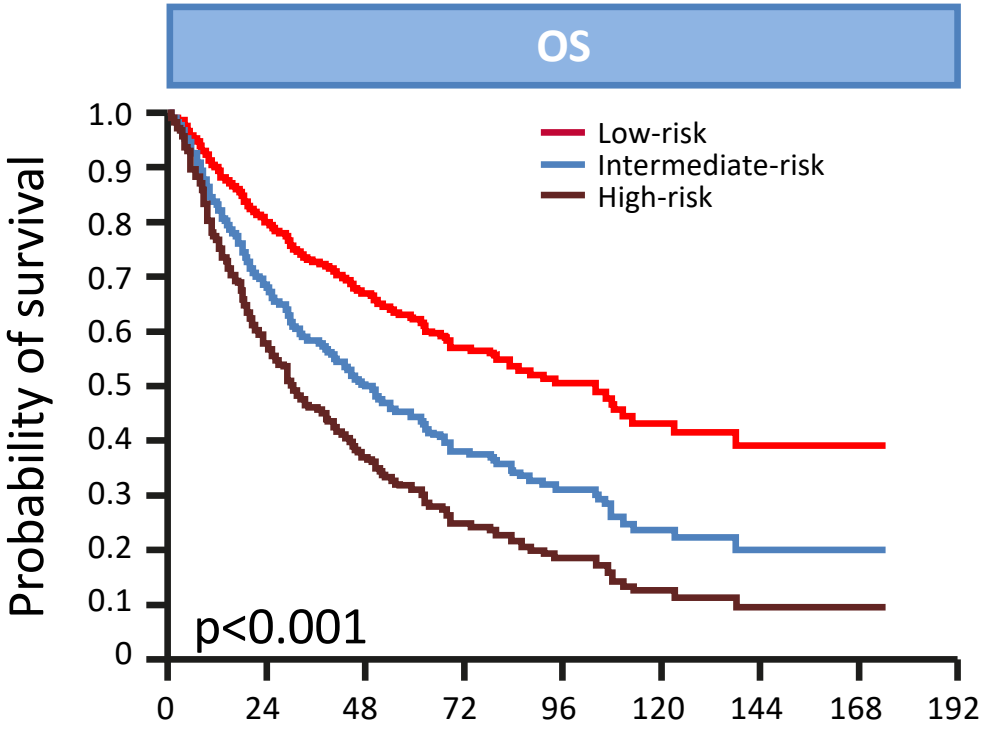
- **PATIENT RELATED:**
  - **Age**
  - **Performance status**
  - **Comorbidities**

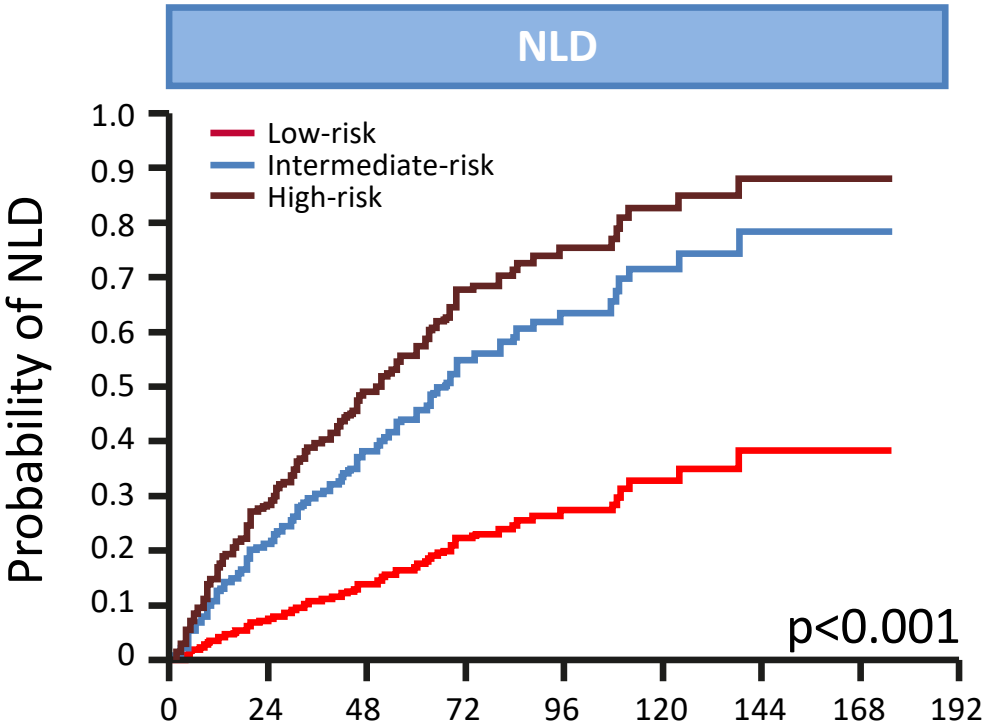
MDS-Comorbidity Index

Comorbidity	HR obtained through a multivariable Cox's survival analysis with NLD as an outcome	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	3.57 (P<0.001)	2
Moderate-to-severe hepatic disease	2.55 (P=0.01)	1
Severe pulmonary disease	2.44 (P=0.005)	1
Renal disease	1.97 (P=0.04)	1
Solid tumor	2.61 (P<0.001)	1

MDS-CI risk	Sum of individual variable scores	Proportion of patients in the learning cohort belonging to the risk group (%)
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	>2	50/840 (6%)

NLD: non-leukemic death.





Della Porta, et al. Haematologica 2011

Association of Comorbidities With Overall Survival in Myelodysplastic Syndrome: Development of a Prognostic Model

Retrospective cohort study of 600 consecutive patients with MDS who presented to MDACC from January 2002 to December 2004

The Adult Comorbidity Evaluation-27 (ACE-27) scale was used to assess comorbidities.

According to the ACE-27 categories, median survival was 31.8, 16.8, 15.2, and 9.7 months for those with none, mild, moderate, and severe comorbidities, respectively (*P* .001).

Table 3. Final Multivariate Survival Model and Risk Score

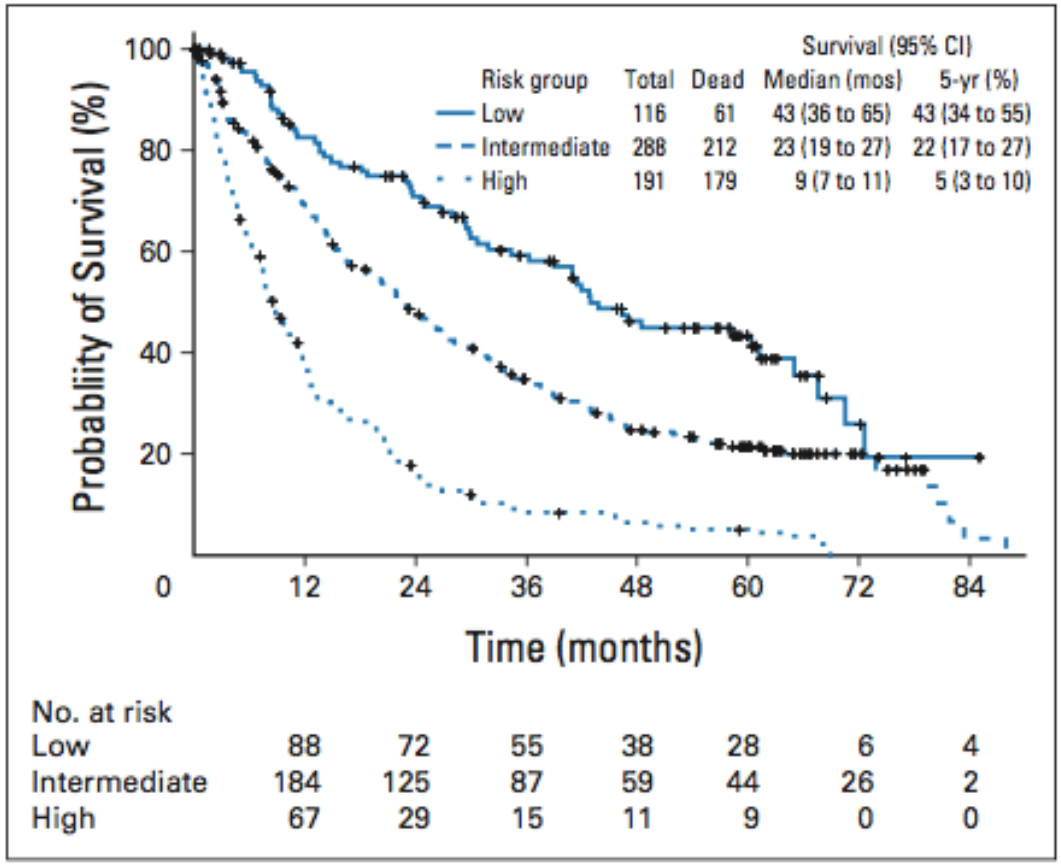
Prognostic Factor	Coefficient	Score*
Age, years		
> 65	0.582	2
Comorbidity (ACE-27)		
Mild or moderate	0.301	1
Severe	0.782	3
IPSS		
Intermediate 2	0.512	2
High	0.769	3

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; IPSS, International Prognostic Scoring System.
*Score points were obtained by dividing estimated coefficients by 0.3.

The final prognostic model for OS was developed as:

- low (score 0 to 1)
- intermediate (score 2 to 4)
- high (score 5 to 8).

Naqvi K et al. JCO. 2011

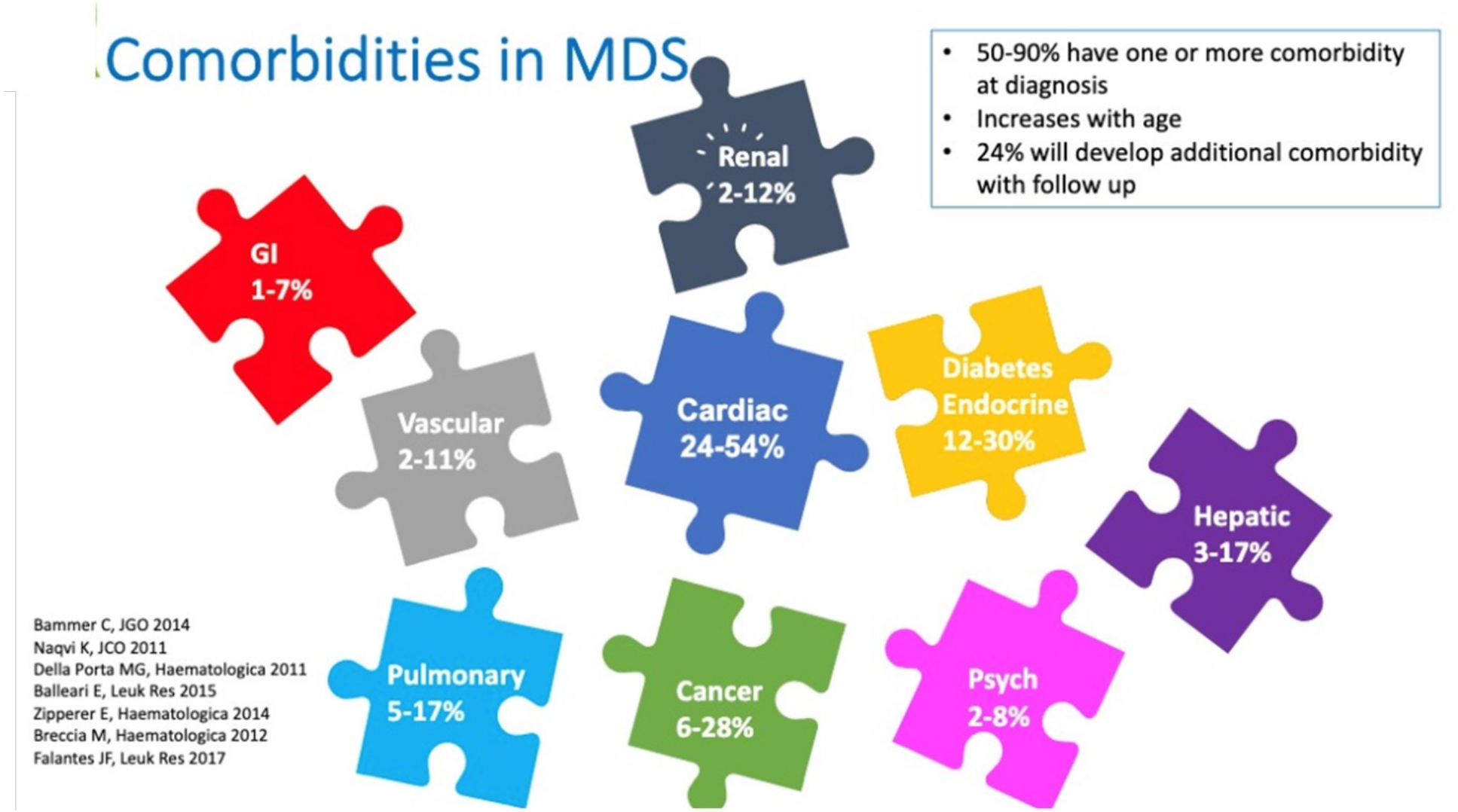


The model predicted survival on the entire patient group

Concomitant comorbidity has a significant impact on the survival of patients with MDS and comorbidity assessment needs to be part of new prognostic models.

Naqvi K et al. JCO. 2011

The presence of comorbidities had a significant independent impact on survival, and a prognostic score could be developed that included age, IPSS and ACE-27 score.



Garcia-Manero et al Am J Hem 2020

Fattori predittivi…
Risposta a trattamento?

Erythropoietin in MDS

MDS

		Score
Serum EPO (U/L)	< 500 U/L	0
	≥ 500 U/L	1
Transfusion requirement	< 2 pRBC per month	0
	≥ 2 pRBC per month	1

Probability of erythroid response

Score: 0	74%	High
Score: 1	23%	Intermediate
Score: 2	7%	Low

This predictive scoring system could be used in decisions regarding use of EPO (and G-CSF) for treating anaemia in MDS patients

EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; pRBC, packed red blood cells.

Hellström-Lindberg E, et al. Br J Haematol. 1997

ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems

By multivariate analysis

		Score
Serum EPO (U/L)	< 100 U/L	1
Transfusion independence	< 1 U RBC every 8 weeks	1
IPSS risk	Low	1

Response rate

Score 0 — 22%

Score 1 — 43%

Score 2 — 65%

Score 3 — 81%

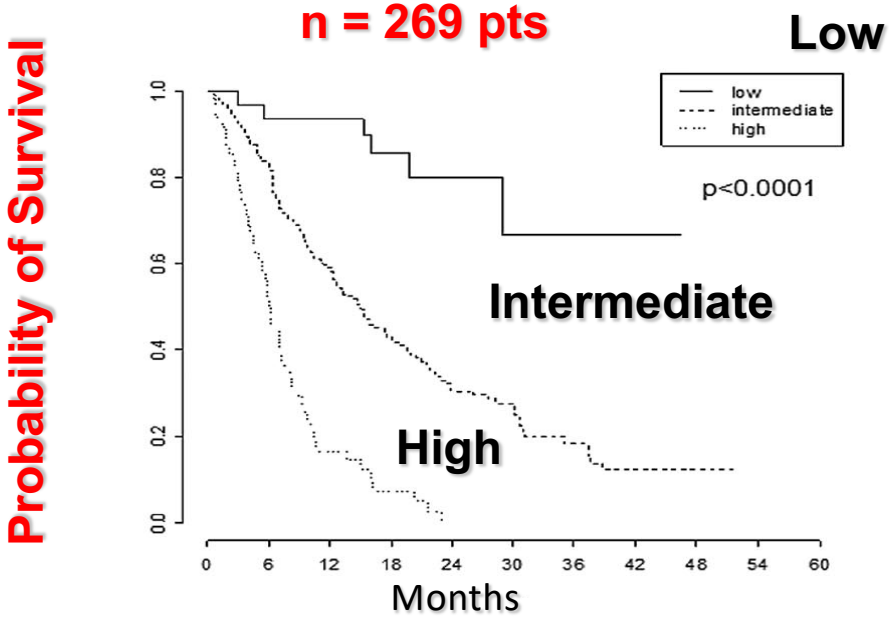
Buckstein et al, Am J Hem 2017

Clinical Prognostic Factors

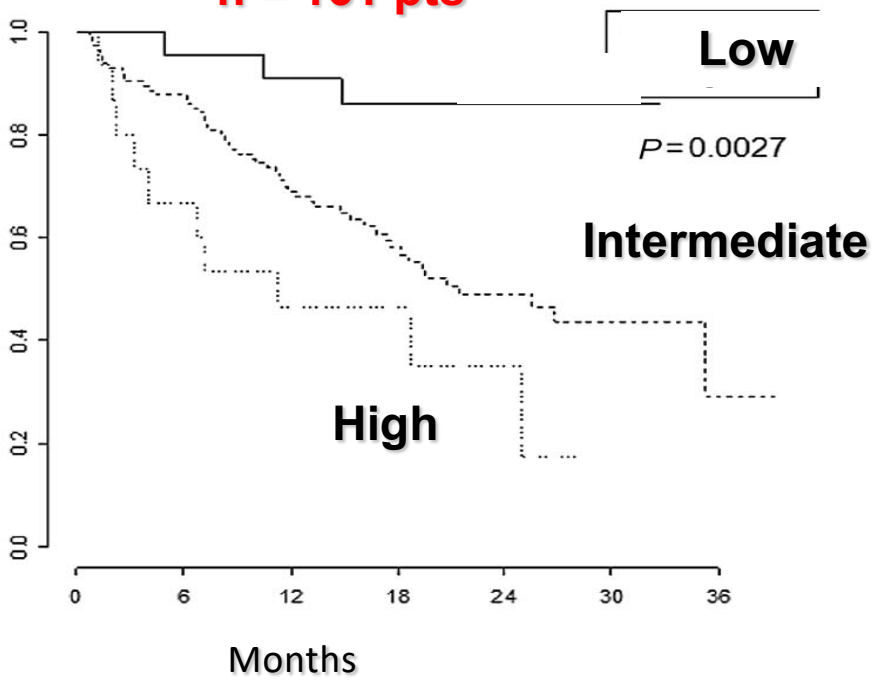
Factor	Points
ECOG PS > 2	1
Presence of PB-blasts	1
RBC TD > 4 RBC units/8 weeks	1
Intermediate-risk Cytogenetics	1
High-risk cytogenetics	2

Score	Points	Median OS (months)
Low	0	N.R.
Intermediate	1-3	15
High	4-5	6.1

ATU Cohort (development)
n = 269 pts



AZA-001(validation)
n = 161 pts



Itzykson et al, Blood 2011

Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R

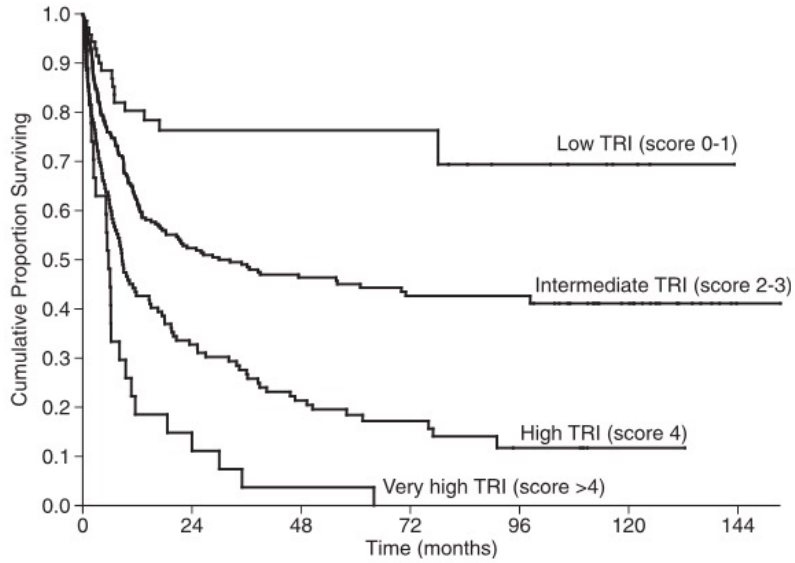
519 patients with MDS or oligoblastic AML (<30% marrow blasts) who received an allogeneic HSCT and were reported to the GITMO registry between 2000 and 2011.

A *MDS transplantation risk index (TRI) calculation*

Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

TRI is calculated as the sum of individual score values

B *Posttransplantation outcome according to TRI*



Key Points

- Disease relapse is a common cause of failure of allogeneic hematopoietic stem cell transplantation in patients with advanced MDS.
- High IPSS-R prognostic risk category and monosomal karyotype are independent predictors of relapse after allogeneic transplantation in MDS.

Della Porta MG et al, Blood 2014

Conclusions (I)

- ✓ Given its more accurate risk stratification, the **IPSS-R** categorization is preferred although the other systems also have good value.

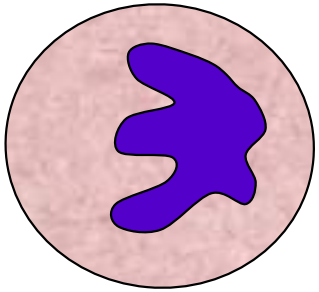
- ✓ IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as:
  - Age
  - Performance status
  - Serum ferritin levels
  - Serum LDH levels.

Conclusions (II)

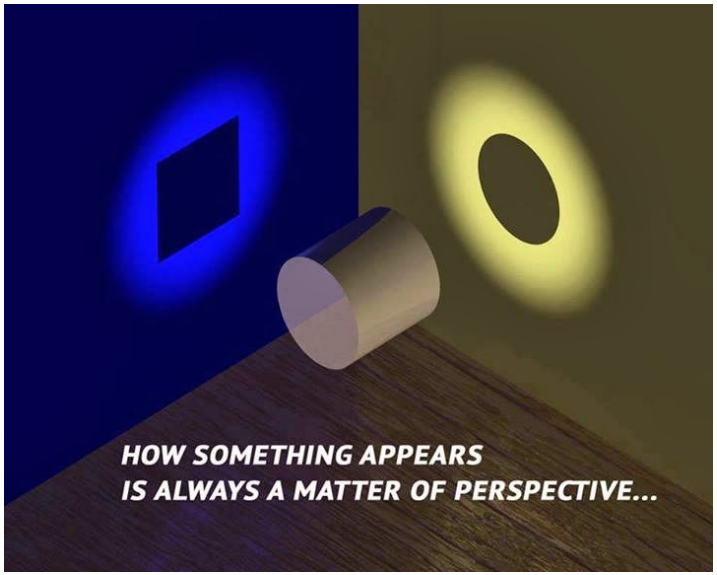
- ✓ The integration of comorbidity scores and time-dependent scores, which consider the evolutive nature of MDS, may further address the decision- making process for a correct treatment approach.

- ✓ The early recognition of patients at high risk of progression to aggressive disease may also optimize treatment timing, before worsening of comorbidities.

- ✓ IPSS-R is now the standard tool to assess risk, but a new molecular IPSS system is expected.



Grazie dell'attenzione!!!



GROM·L
GRUPPO ROMANO - LAZIALE MDS