Nouveau score pronostique dans les SMD

IPSS-M

Jean-Baptiste GAILLARD

Génétique des Hémopathies

CHU Montpellier

ADHET – 04/04/2023

Evolution des scores pronostiques dans les SMD

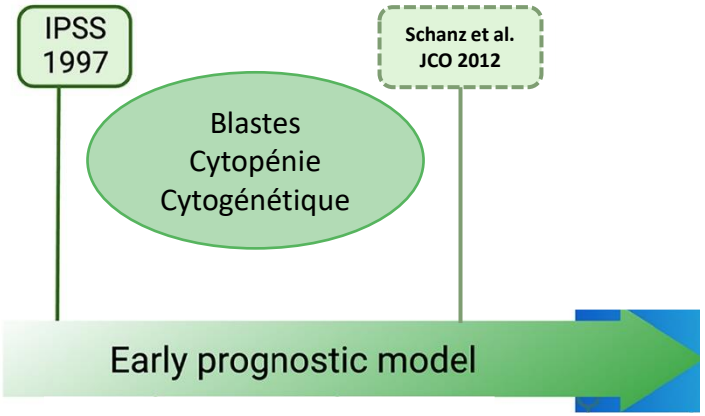


Table 3. Design of Cytogenetic Scoring System (n = 2,754)*

Prognostic Subgroup	Abnormality: No. of Patients	%	Single	Double	Complex	Overall Survival: Median (months)†	95% CI	HR	95% CI	AML Transformation: Median (months)†	95% CI	HR	95% CI
Very good	81	2.9	del(11q) −Y	—	—	60.8	50.3 to NR	0.5†	0.3 to 0.7	NR	121.2 to NR	0.5	0.2 to 1.2
Good (reference)	1,809	65.7	Normal del(5q) del(12p) del(20q)	Including del(5q)	—	48.6	44.6 to 54.3	1.0	0.9 to 1.1	NR	189.0 to NR	1.0	0.9 to 1.2
Intermediate	529	19.2	del(7q) +8 i(17q) +19 Any other Independent clones	Any other	—	26.0	22.1 to 31.0	1.6†	1.4 to 1.8	78.0	42.6 to NR	2.2†	1.8 to 2.7
Poor	148	5.4	inv(3)/t(3q)/ del(3q) −7	Including −7/del(7q)	3	15.8	12.0 to 18.0	2.6†	2.1 to 3.2	21.0	13.4 to 42.2	3.4†	2.5 to 4.6
Very poor	187	6.8	—	—	> 3	5.9	4.9 to 6.9	4.2†	3.4 to 5.2	8.2	6.4 to 15.4	4.9†	3.6 to 6.7

Abbreviations: AML, acute myeloid leukemia; HR, hazard ratio; NR, not reached.
*Patients with complete data.
†$P < .01$.

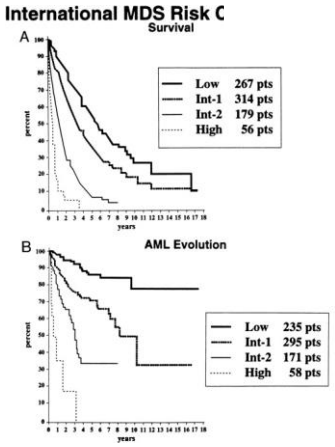


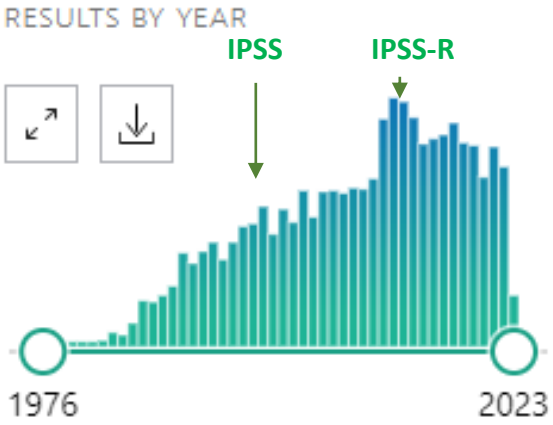
Table 3. IPSS for MDS: Survival and AML Evolution

Prognostic Variable	Score Value: 0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

PubMed®

Myelodysplastic + Cytogenetic



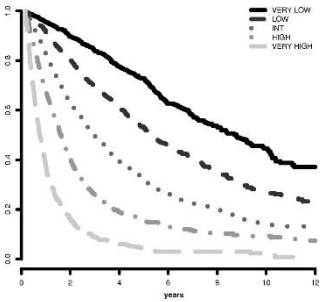


Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50- < 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

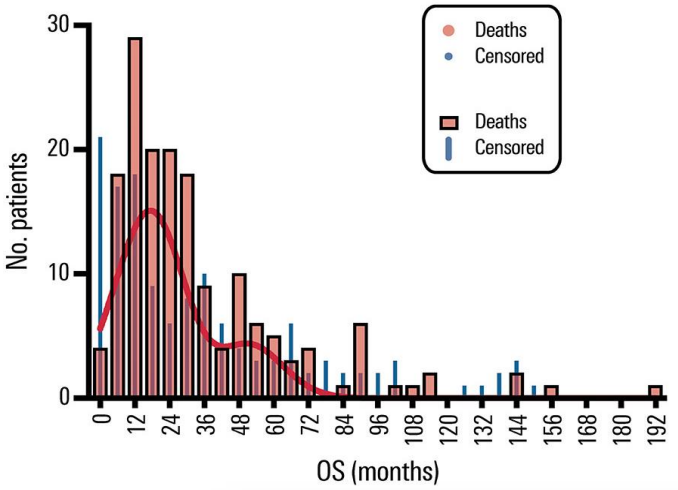
Xie Z et *al*. 2022

American Journal of Hematology AJH

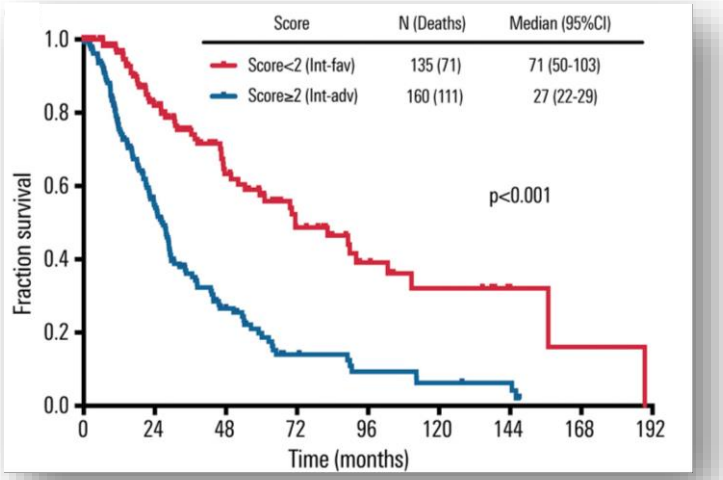
IPSS-R : Intermédiaire homogène?

N= 298 pts Intermédiaire

Validation modèle cohorte 700 pts

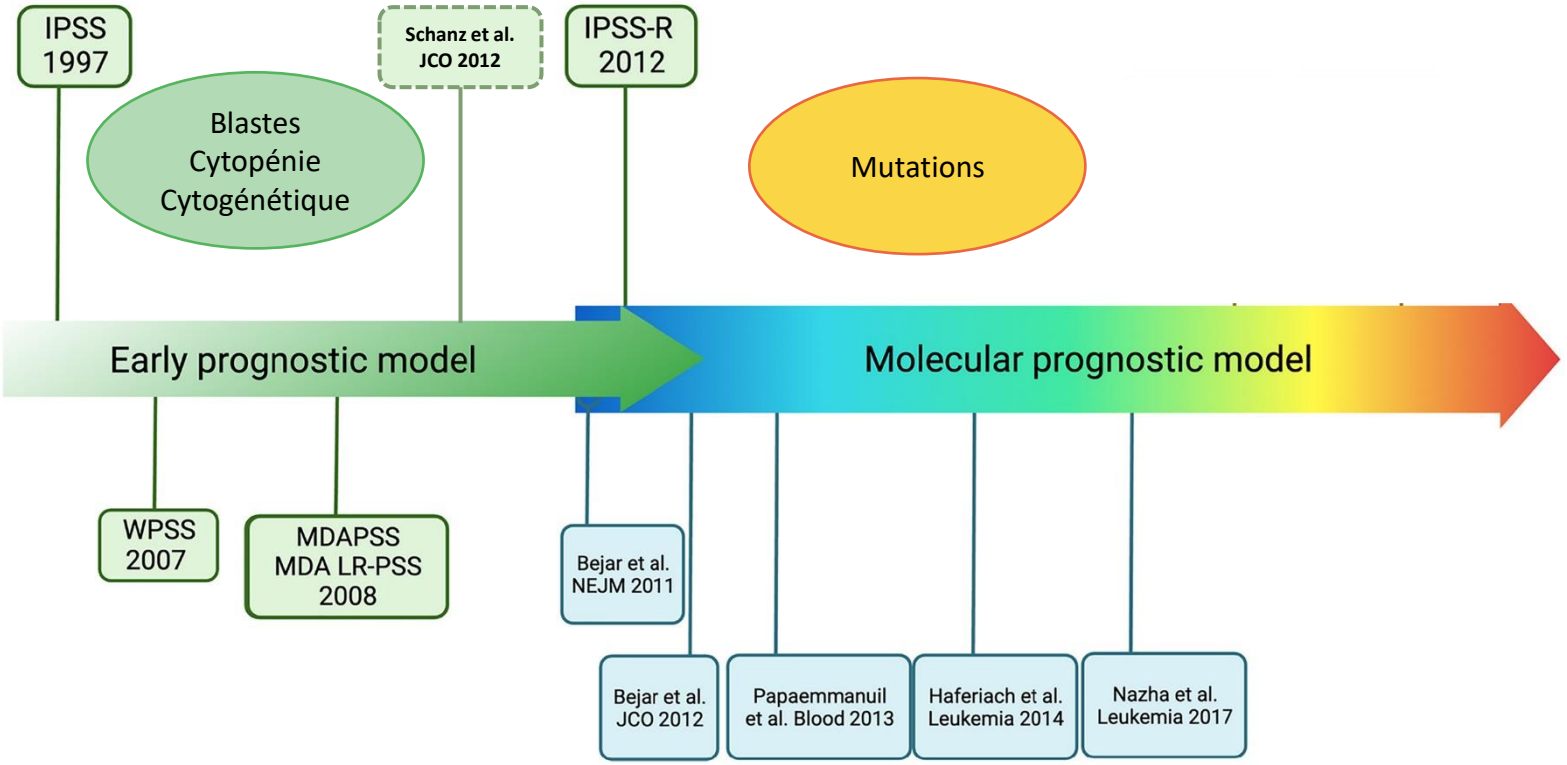


Variable	Coefficient	HR (95% CI)	p	Score
Age ≥ 66 years[a]				
No				0
Yes	0.87	2.43 (1.74-3.38)	<.001	2
Peripheral blood blasts ≥2%[a]				
No				0
Yes	0.52	1.69 (1.14-2.50)	.009	1
Red blood cell transfusion				
No				0
Yes	0.51	1.66 (1.18-2.32)	.003	1

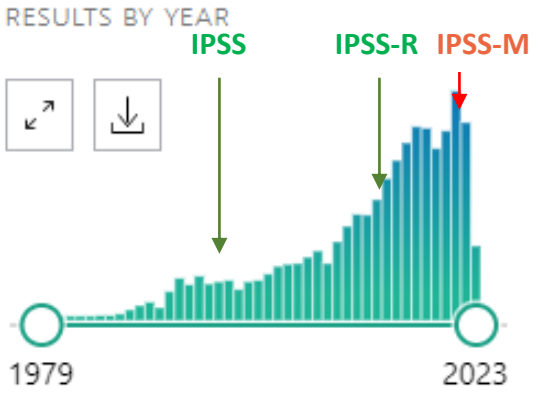


Benton CB et *al*. 2018

Evolution des scores pronostiques dans les SMD



Myelodysplastic + Molecular



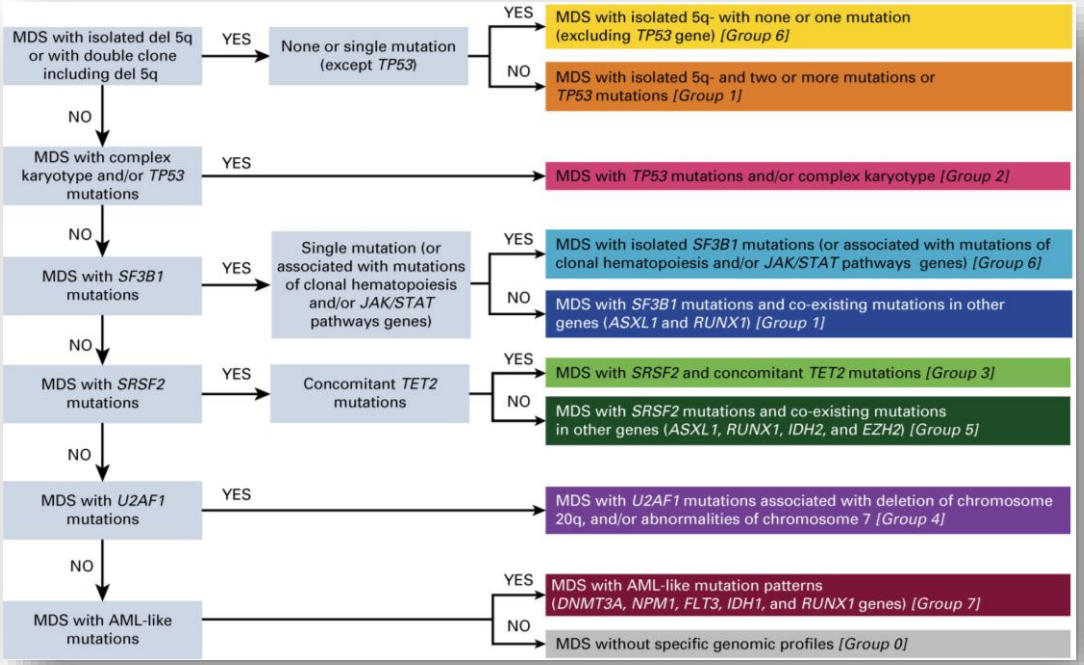
Xie Z et *al*. 2022

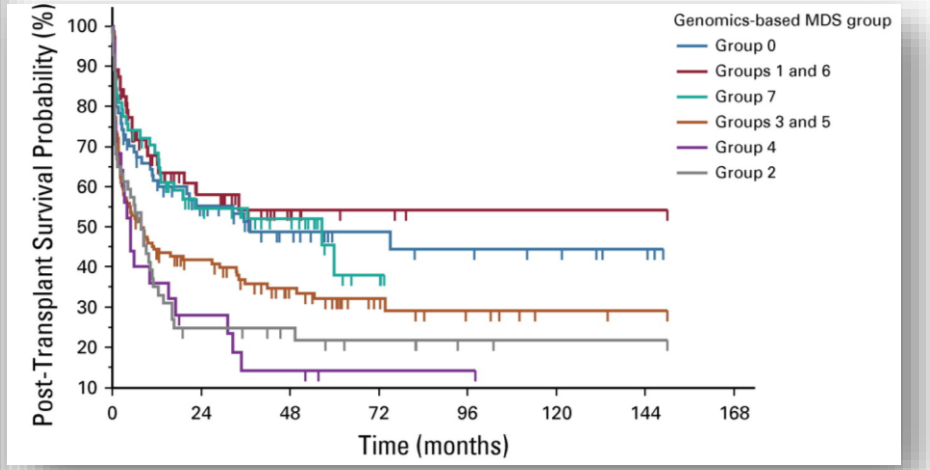
Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes

Journal of Clinical Oncology
Volume 39, Issue 11 1223

Matteo Bersanelli, PhD[1,2]; Erica Travaglino, BSc[3]; Manja Meggendorfer, PhD[4]; Tommaso Matteuzzi, PhD[1,2]; Claudia Sala, PhD[1,2];

N= 2043
De novo





Random-effects Cox multistate model incorporating 63 clinical and genomic variables are developed to estimate personalized probability of surviva

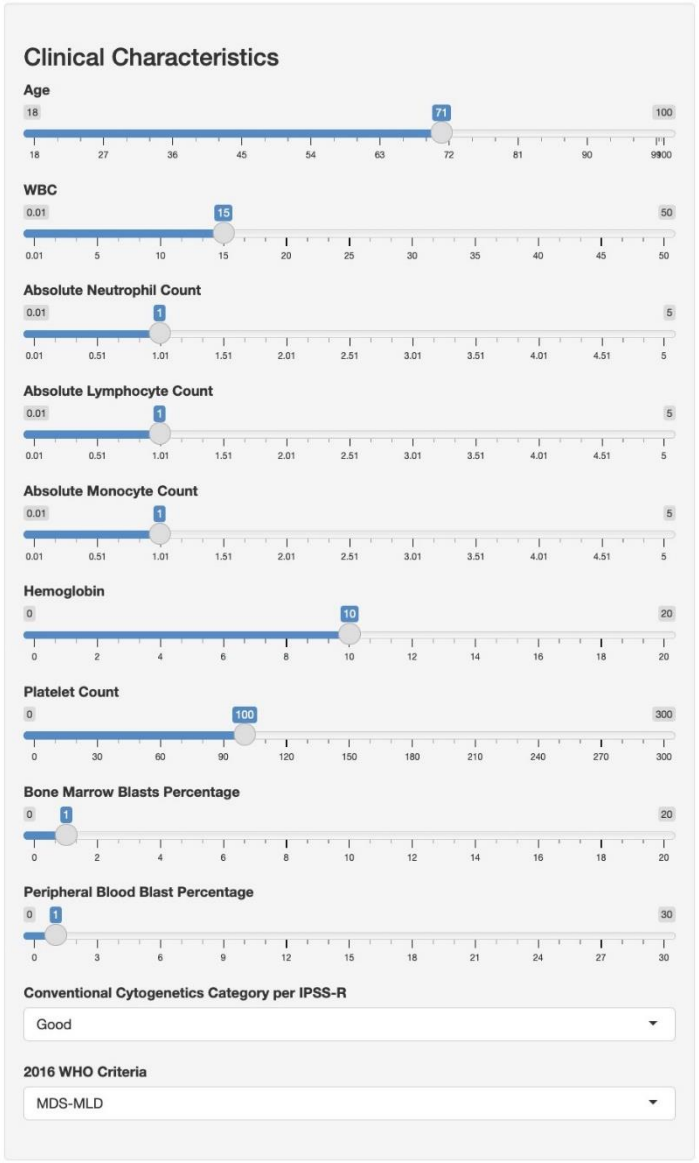
Because the underlying survival model is complex, specific information technology support is needed to combine all the information at individual patient level and to translate it into a personalized outcome prediction. With the aim to help clinicians

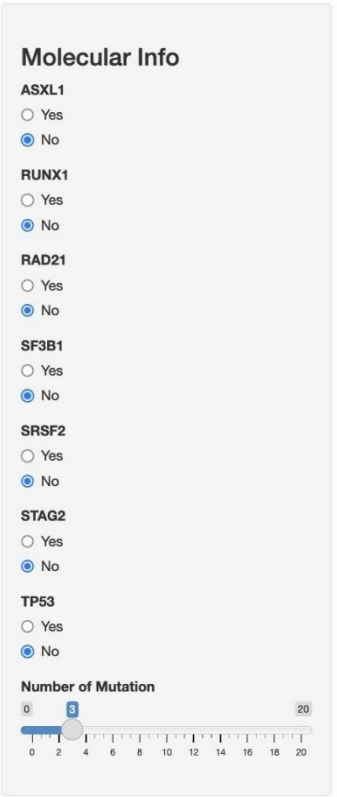
Bersanelli S et *al*. 2021

Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes

Journal of Clinical Oncology
Volume 39, Issue 11 1223

Aziz Nazha, MD[1,2]; Rami Komrokji, MD[3]; Manja Meggendorfer, PhD[4]; Xuefei Jia, MS[5]; Nathan Radakovich, MS[6]; Jacob Shreve, MD[1];





N= 1936

De novo et secondaire

Machine learning

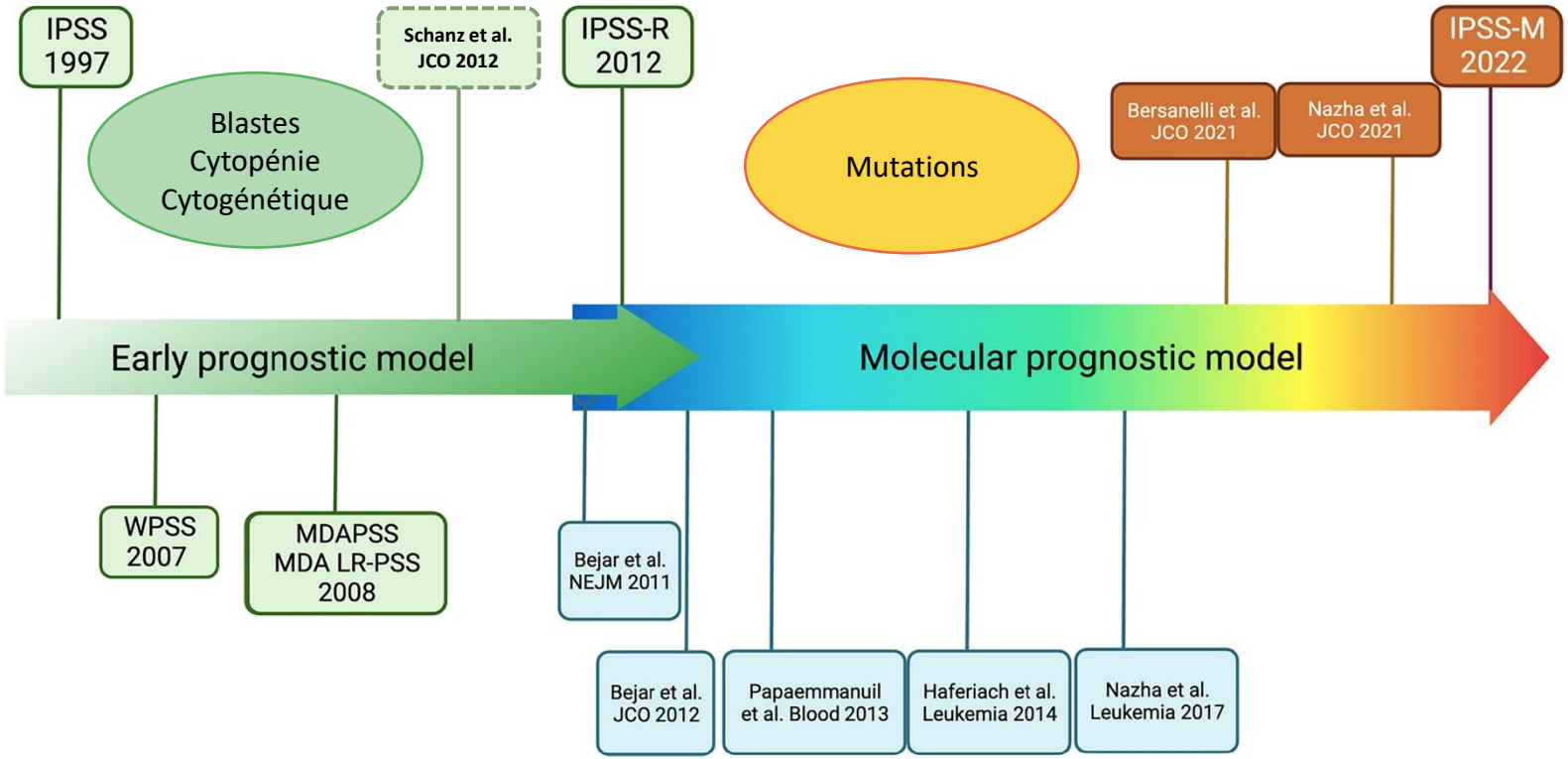
Peu de mutations

Poids de l'âge : risque de traitement moins intensif chez les sujets jeunes

Basée sur la classification 2016

Nazha A et *al*. 2021

Evolution des scores pronostiques dans les SMD



Xie Z et *al*. 2022

ORIGINAL ARTICLE

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

Elsa Bernard, Ph.D.,[1] Heinz Tuechler, Peter L. Greenberg, M.D.,[2] Robert P. Hasserjian, M.D.,[3] Juan E. Arango Ossa, M.S.,[1]

NEJM Evidence

N= 2957

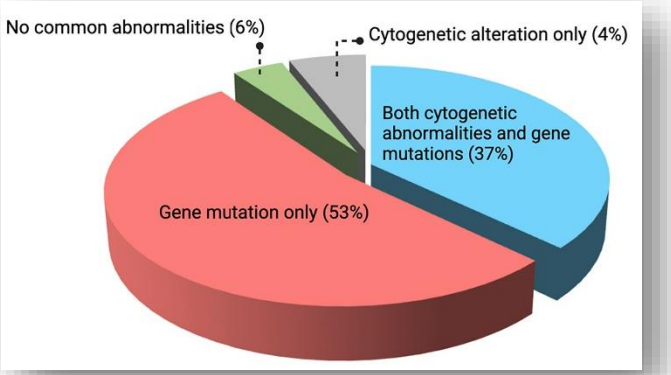
De novo et secondaire

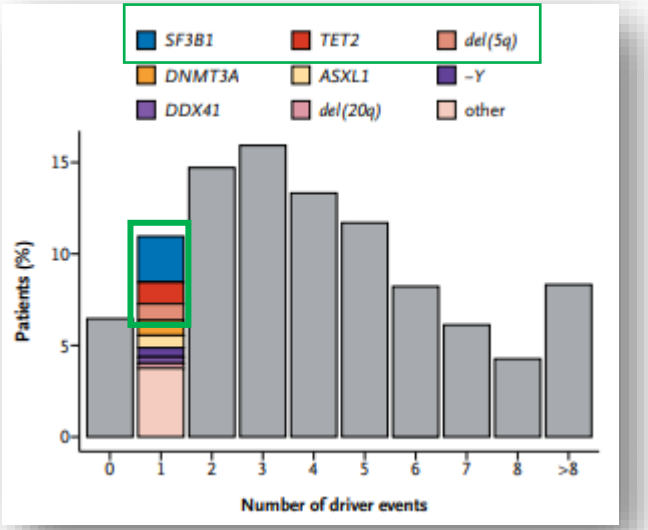
Dont 894 traités

Caractérisation Génétique

Caryotype

Panel de 152 gènes





Médiane d'anomalies : 4

Bernard E et *al*. 2022

ORIGINAL ARTICLE

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NEJM Evidence

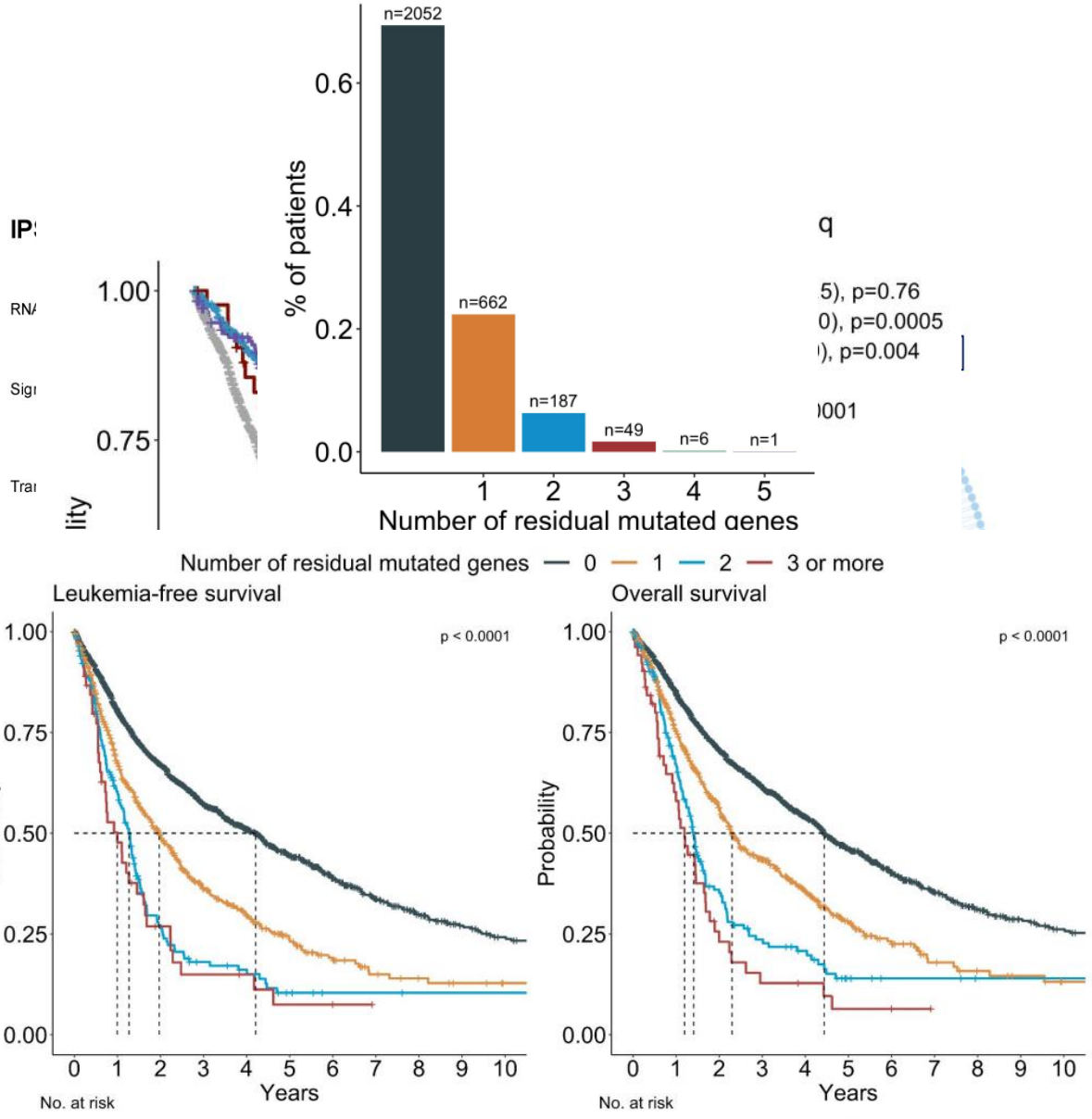
>1% : 48 gènes

Impact sur OS, LFS, AML-t

Cox

16 gènes pronostiques

15 gènes
1 variable



Bernard E et *al*. 2022

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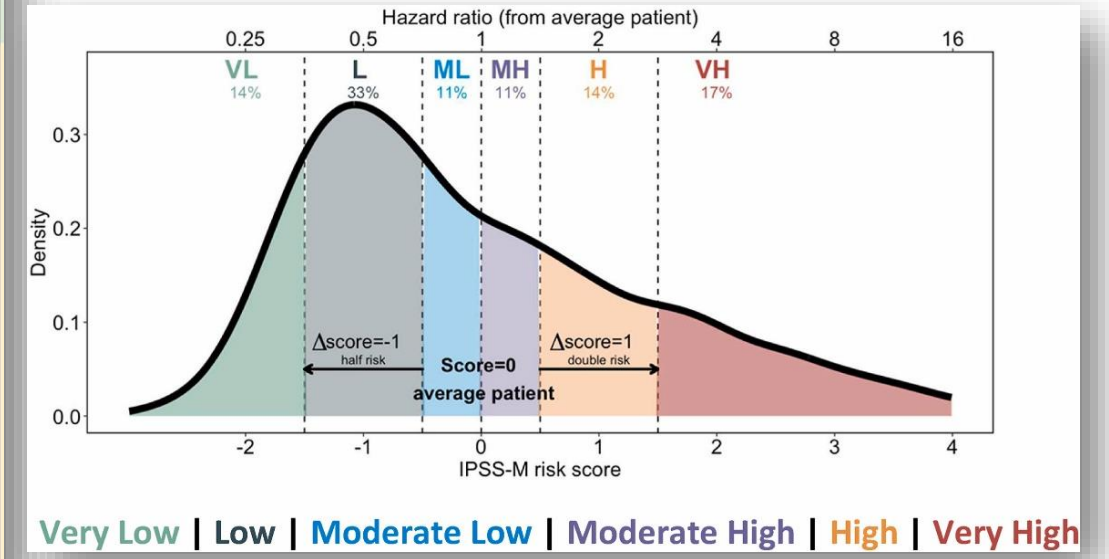
NEJM Evidence

Category	Variable	Multivariable model: hazard ratio[#] (95% CI)	Weight w
confounder	⅟₁₀ **Age**, in years	1.23 (1.05 - 1.43)	N/A
	Sex:Male	1.22 (1.06 - 1.41)	N/A
	Type:Secondary/Therapy-related	1.36 (1.10 - 1.68)	N/A
clinical	% **Bone Marrow Blasts**, in %	1.42 (1.30 - 1.55)	0.352
	⅟₁₀₀ min(**Platelets**,250), in x10^9/L	0.80 (0.72 - 0.89)	-0.222
	Hemoglobin, in g/dL	0.84 (0.81 - 0.88)	-0.171
cytogenetics	**IPSS-R category vector**[&]	1.33 (1.21 - 1.47)	0.287
gene main effects 17 variables, 16 genes	*TP53*^{multi}	3.27 (2.38 - 4.48)	1.18
	MLL^{PTD}	2.22 (1.49 - 3.32)	0.798
	FLT3$^{ITD+TKD}$	2.22 (1.11 - 4.45)	0.798
	SF3B1^{Sq}	1.66 (1.03 - 2.66)	0.504
	NPM1	1.54 (0.78 - 3.02)	0.430
	RUNX1	1.53 (1.23 - 1.89)	0.423
	NRAS	1.52 (1.05 - 2.20)	0.417
	ETV6	1.48 (0.98 - 2.23)	0.391
	IDH2	1.46 (1.05 - 2.02)	0.379
	CBL	1.34 (0.99 - 1.82)	0.295
	EZH2	1.31 (0.98 - 1.75)	0.270
	U2AF1	1.28 (1.01 - 1.61)	0.247
	SRSF2	1.27 (1.03 - 1.56)	0.239
	DNMT3A	1.25 (1.02 - 1.53)	0.221
	ASXL1	1.24 (1.02 - 1.51)	0.213
	KRAS	1.22 (0.84 - 1.77)	0.202
	SF3B1$^{\#}$	0.92 (0.74 - 1.16)	-0.0794
gene residuals[$] 1 variable, 15 genes	min(**Nres**,2) Possible values are 0,1 or 2	1.26 (1.12 - 1.42)	0.231

0.5 1 2 3 5

IPSS-R cytogenetic categories : numerical vector with values ranging from 0 (Very Good) to 4 (Very Poor).



Bernard E et *al*. 2022

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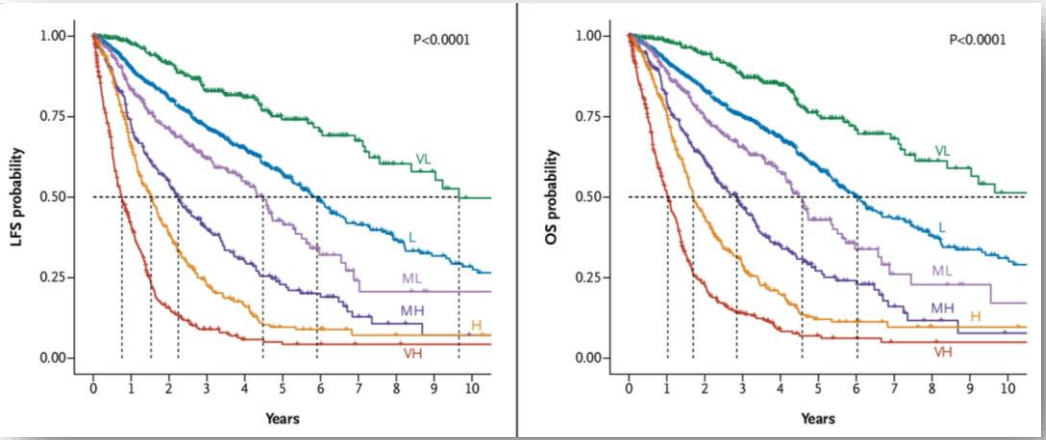
NEJM Evidence

De Novo

Secondaire/t-MDS



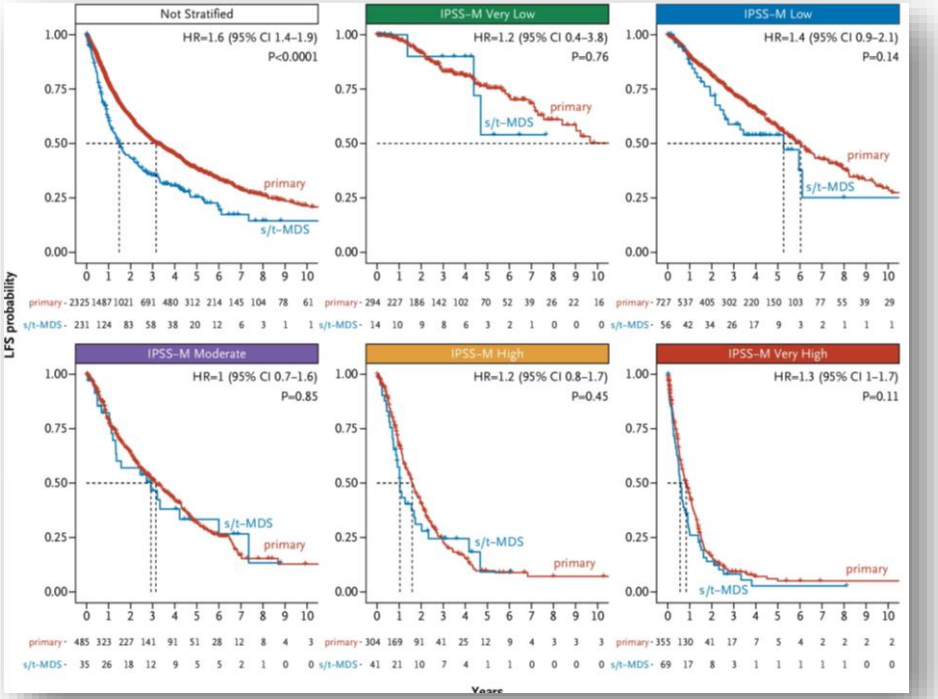


Table 2. Summary of Clinical Outcomes for 2701 Patients by IPSS-M Risk Category.*

Characteristic	IPSS-M Risk Category					
	Very Low	Low	Moderate Low	Moderate High	High	Very High
Patients — No. (%)	381 (14)	889 (33)	302 (11)	281 (11)	379 (14)	469 (17)
Risk score	≤−1.5	>−1.5 to −0.5	>−0.5 to 0	>0 to 0.5	>0.5 to 1.5	>1.5
Hazard ratio (95% CI)†	0.51 (0.39–0.67)	1.0 (Reference)	1.5 (1.2–1.8)	2.5 (2.1–3.1)	3.7 (3.1–4.4)	7.1 (6.0–8.3)
Median LFS (25–75% range) — yr‡	9.7 (5.0–17.4)	5.9 (2.6–12.0)	4.5 (1.6–6.9)	2.3 (0.91–4.7)	1.5 (0.80–2.8)	0.76 (0.33–1.5)
Median OS (25–75% range) — yr	10.6 (5.1–17.4)	6.0 (3.0–12.8)	4.6 (2.0–7.4)	2.8 (1.2–5.5)	1.7 (1.0–3.4)	1.0 (0.5–1.8)
AML-t — %						
By 1 yr	0.0	1.7	4.9	9.5	14.3	28.2
By 2 yr	1.2	3.4	8.8	14.0	21.2	38.6
By 4 yr	2.8	5.1	11.4	18.9	29.2	42.8
Death without AML — %						
By 1 yr	2.2	8.5	12.0	18.0	19.3	30.6
By 2 yr	7.0	16.2	19.8	31.1	39.8	45.6
By 4 yr	15.9	29.5	33.6	51.1	54.2	51.3

Bernard E et *al*. 2022

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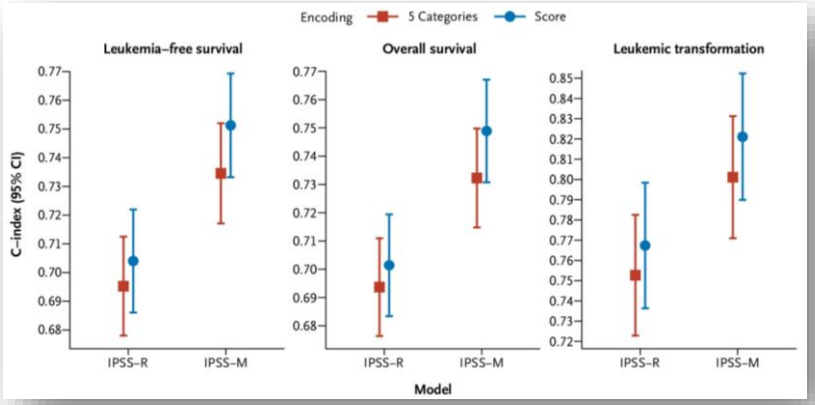
NEJM Evidence

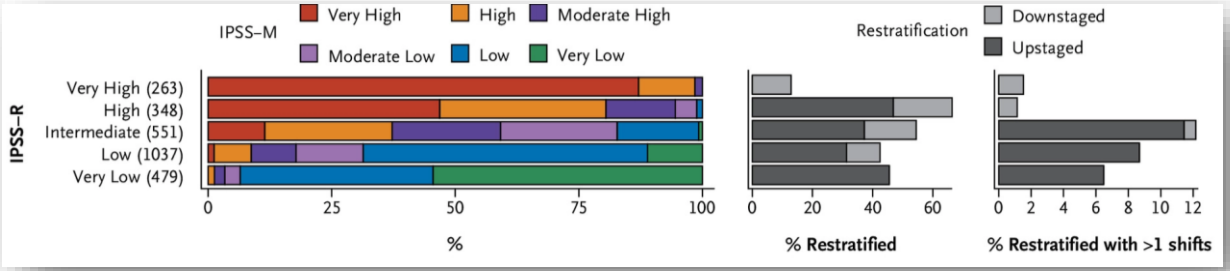


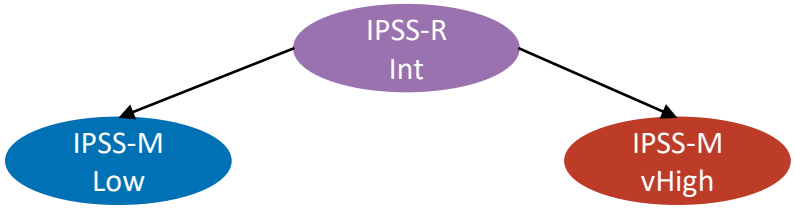
Capacité de discrimination de l'IPSS-M supérieure à celle de l'IPSS-R

Re-stratification de 46% des patients en comparaison avec IPSS-R

74% ↗
26% ↘

7% des patients





LFS : 6,1 ans

LFS : 0,87 ans

Bernard E et *al*. 2022

Outil en ligne pour le calcul de l'IPSS-M

https://mds-risk-model.com/

CLINICAL DATA

*Bone Marrow Blasts
Percentage: 5 [0-30%]

*Hemoglobin
g/dL | Change: 10 [4-20 g/dL]

*Platelet Count
1e9/L: 100 [0-2000 1e9/L]

OPTIONAL IPSS-R DATA

Absolute Neutrophil Count
1e9/L: [0-15 1e9/L]

Age
Years: [18-120 years]

CYTOGENETICS

*Presence of

del(5q)	No	Yes
-7/del(7q)	No	Yes
-17/del(17p)	No	Yes
Complex Karyoptype	No	Yes

*Cytogenetics Category

Very Good	-Y, del(11q).
Good	Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones.
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities.
Very Poor	Complex: > 3 abnormalities

MOLECULAR DATA

*Number of TP53 mutations

Mutation Count	0	1	2+

*Loss of heterozygosity at TP53 locus (if known)

TP53 LOH	No	Yes	N/A

*MLL (KMT2A) and FLT3 Mutations

MLL PTD	No	Yes	Not Assessed
FLT3 ITD or TKD	No	Yes	Not Assessed

*Genes (individual weights)

ASXL1	Non-mutated	Mutated	Not Assessed
CBL	Non-mutated	Mutated	Not Assessed
DNMT3A	Non-mutated	Mutated	Not Assessed
ETV6	Non-mutated	Mutated	Not Assessed
EZH2	Non-mutated	Mutated	Not Assessed
IDH2	Non-mutated	Mutated	Not Assessed

STRATIFICATION RESULTS

IPSS-M Score: **-0.83** LOW

IPSS-R Score: Not calculated

IPSS-R Score (Age-adjusted): Not calculated

ENDPOINTS

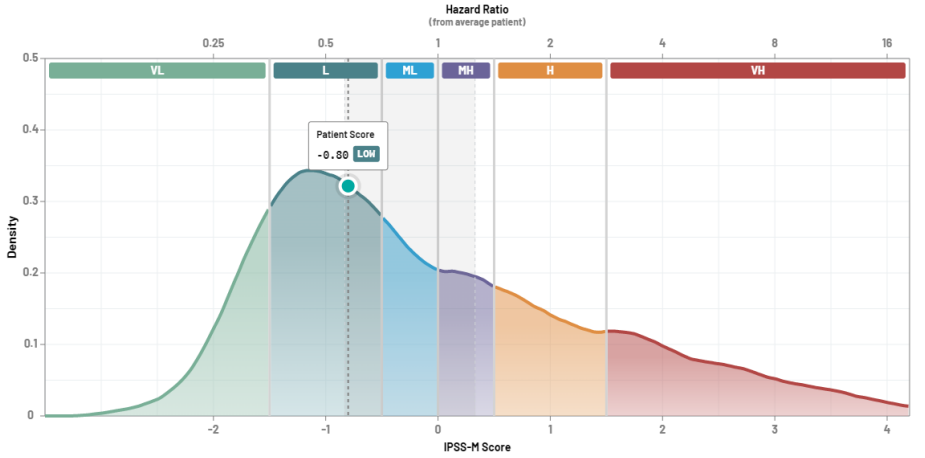
Leukemia-Free Survival (IPSS-M): **5.9 years** median
2.6-12 years, 25%-75% range

Overall Survival (IPSS-M): **6 years** median
3-12.8 years, 25%-75% range

AML Transformation (IPSS-M): **1.7%** by 1 year
5.1% by 4 years

Risk Stratification | Clinical Outcomes

Graph | Table



*Hazard ratio for risk of AML-t or death from the average patient.

Bernard E, Tuechler H, Greenberg PL, et al. The Molecular International Prognosis Scoring System (IPSS-M) for risk stratification in myelodysplastic syndromes. New Eng J Med Evidence, 1(7). doi:10.1056/evidoa2200008
Study supported by the MDS Foundation.

NGS et nouvelles données moléculaires

Sample #	with *KMT2A*^{PTD} worst case scenario	without *KMT2A*^{PTD} best case scenario
1	2.88 (VH)	1.72 (VH)
2	2.58 (VH)	1.44 (H)
3	0.98 (H)	- 0.17 (ML)
4	0.75 (H)	- 0.40 (ML)
5	0.55 (H)	- 0.61 (L)
6	- 0.20 (ML)	- 1.35 (L)

Imprécision de la stratification en absence du statut KMT2A-PTD

TP53$^{multi-hit}$:

- Mutation TP53
- Délétion TP53 -> FISH indiquée en cas de mutation TP53
- CN-LOH : VAF>55% en absence de délétion peut être le reflet d'une perte d'hétérozygotie

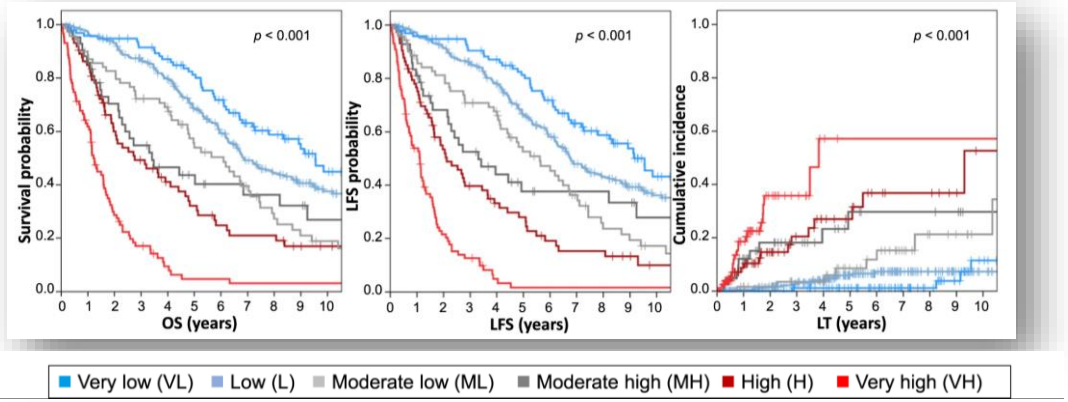
Baer et al. 2023

Validation IPSS-M : cohortes indépendantes

	Baer et al. 2023	Santa et al. 2023	Kewan et al. 2023	Cohorte IPSS-M
Caractéristiques				
Inclusion N=	626	2876	1281	2957
Non-traités	100%	33%	38%	70%
Traités	0%	67%	62%	30%
Catégories IPSS-M				
Very Low	15%	9,6%	14%	14%
Low	41%	27,7%	30%	33%
Moderate Low	11%	10,6%	13%	11%
Moderate High	7%	11,1%	12%	11%
High	12%	19,3%	16%	14%
Very High	14%	21,7%	15%	17%
Restratification IPSS-R				
↗	25%	23,6%	32%	34%
↘	19%	22,4%	14%	12%
>= 2 catégories	6%	4%	-	7%

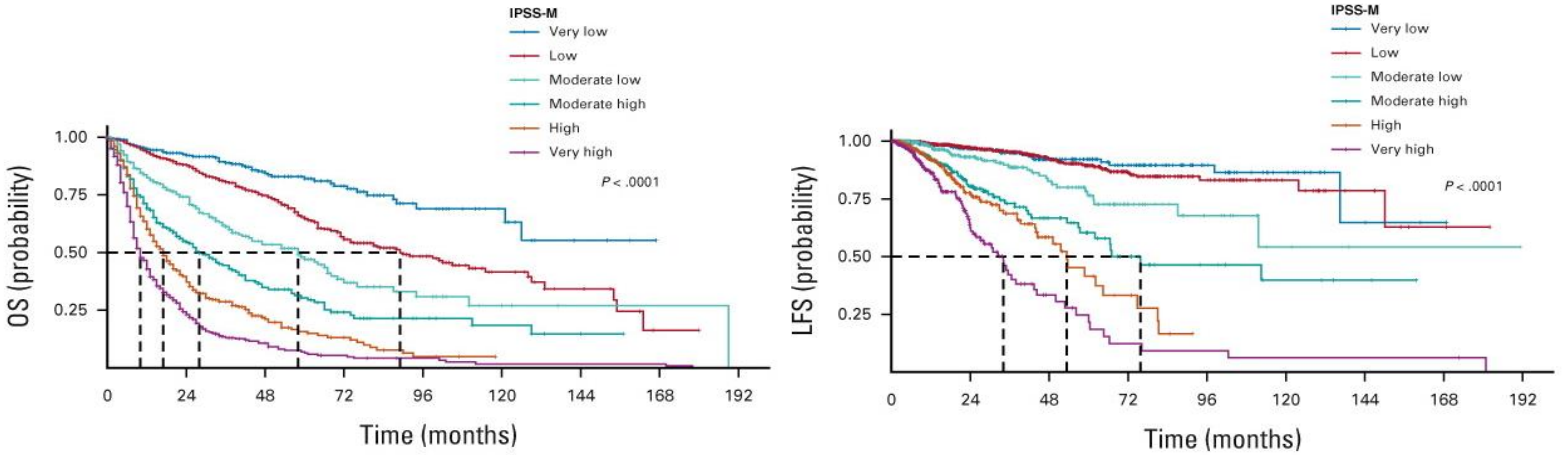
Leukemia Journal of Clinical Oncology blood

IPSS-M : impact sur OS, LFS et LT



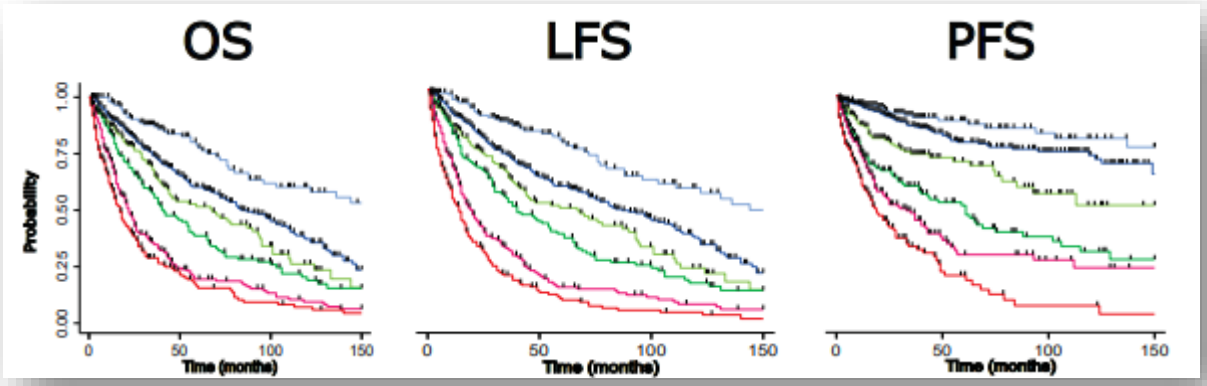
Baer et al. 2023

Leukemia



Santa et al. 2023

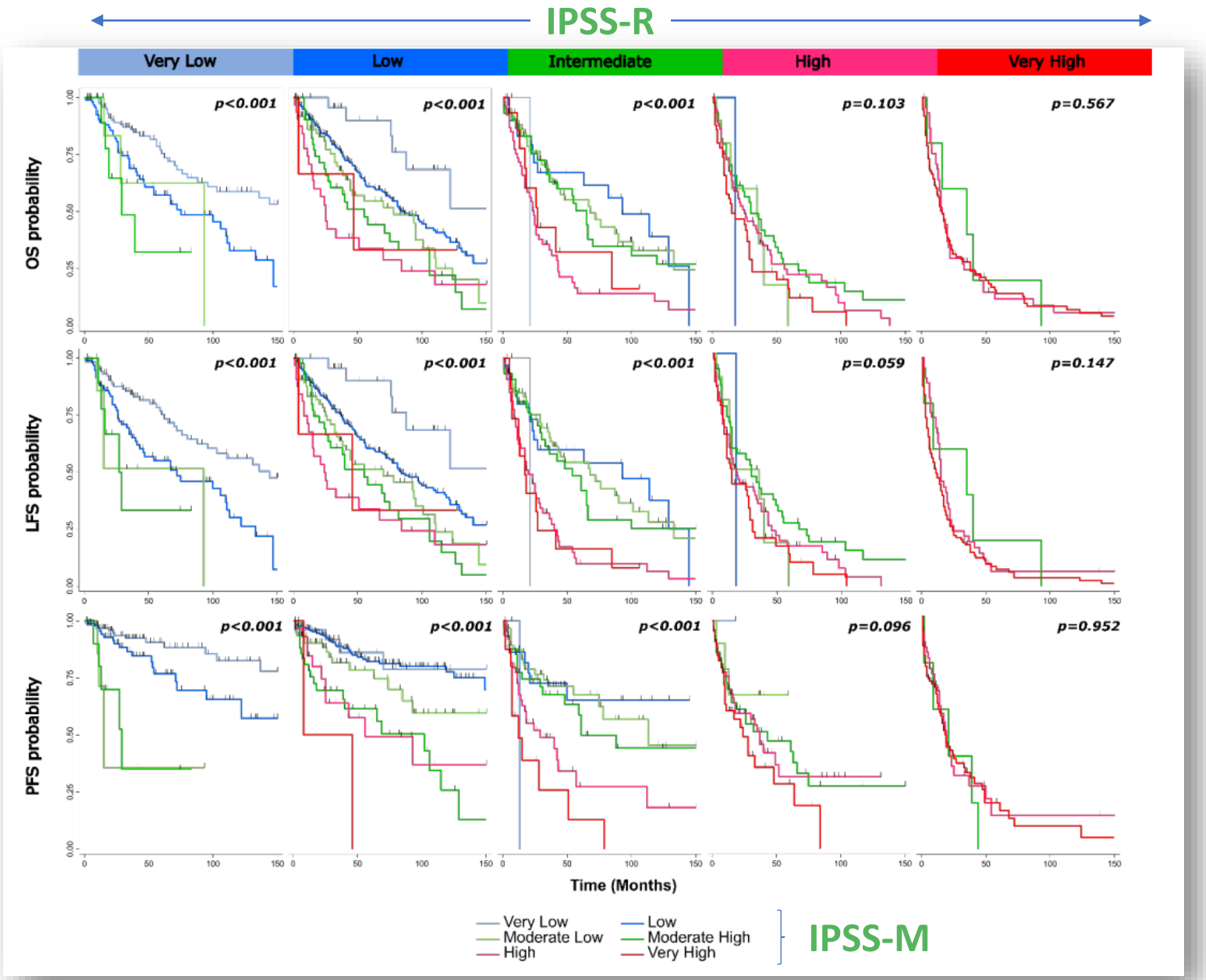
Journal of Clinical Oncology®



Kewan et al. 2023

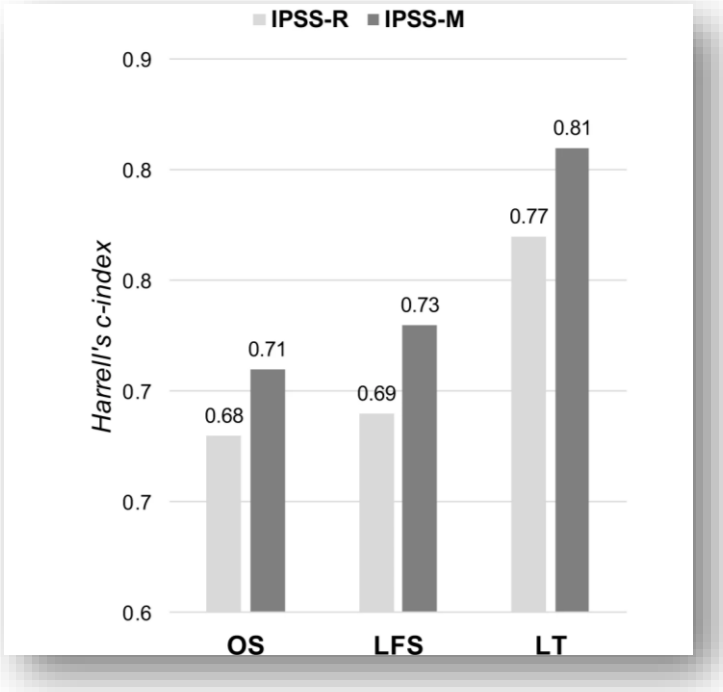
blood®

Impact IPSS-M important sur la restratification des « bas risques »



Kewan et *al*. 2023

IPSS-M : confirmation du pouvoir discriminant supérieur à celui de l'IPSS-R



Baer et al. 2023

Leukemia

Mutations et pronostic :

- Impact des mutations sur le changement de catégories
- En absence de mutations, la stratification de l'IPSS-M est supérieure à celle de l'IPSS-R

Santa et al. 2023

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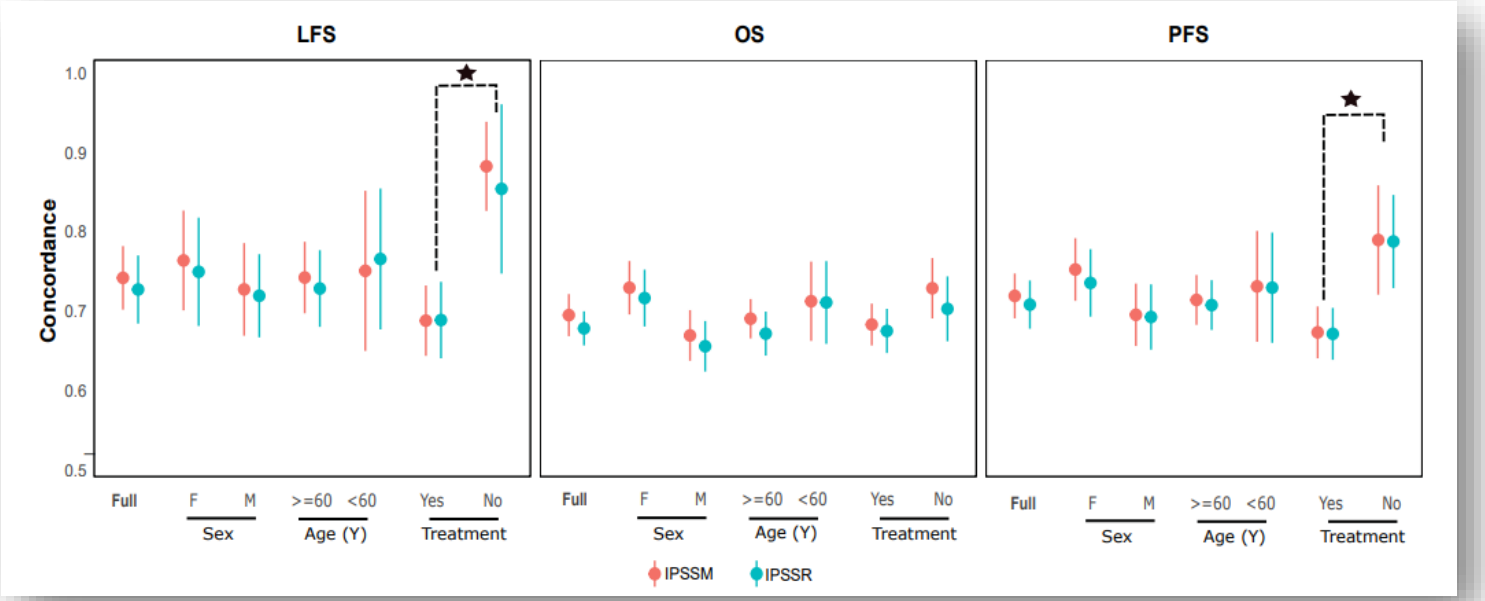
Oui… mais… essentiellement chez les non-traités



Pas de différence significative entre IPPS-R et IPSS-M

- surreprésentation des patients non traités dans la cohorte IWG-PM

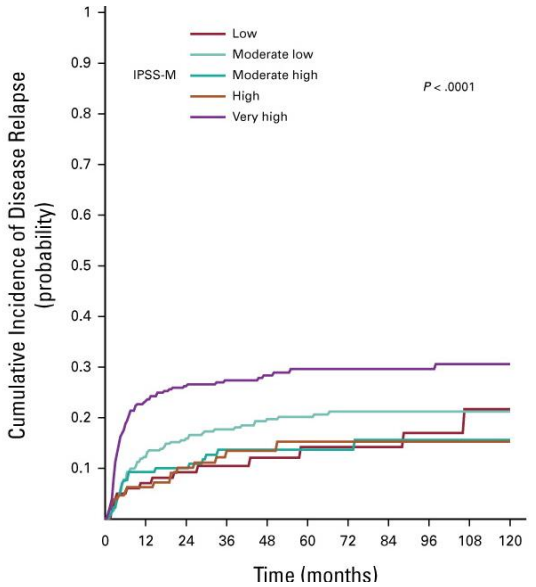
Impact du modèle important chez les patients non traités

Kewan et *al*. 2023

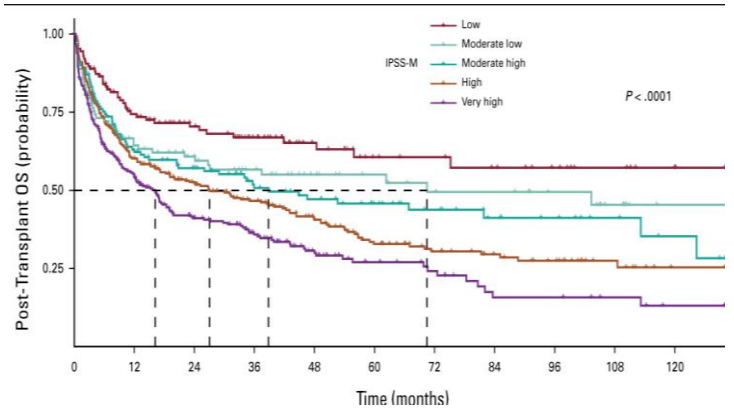
IPSS-M et allogreffe

N= 964
34% cohorte

Valeur prédictive IPSS-M? ➔ risque de rechute



Valeur pronostique IPSS-M? ➔ OS à partir de l'allogreffe



Performance de l'IPSS-M>IPSS-R dans un contexte d'allogreffe

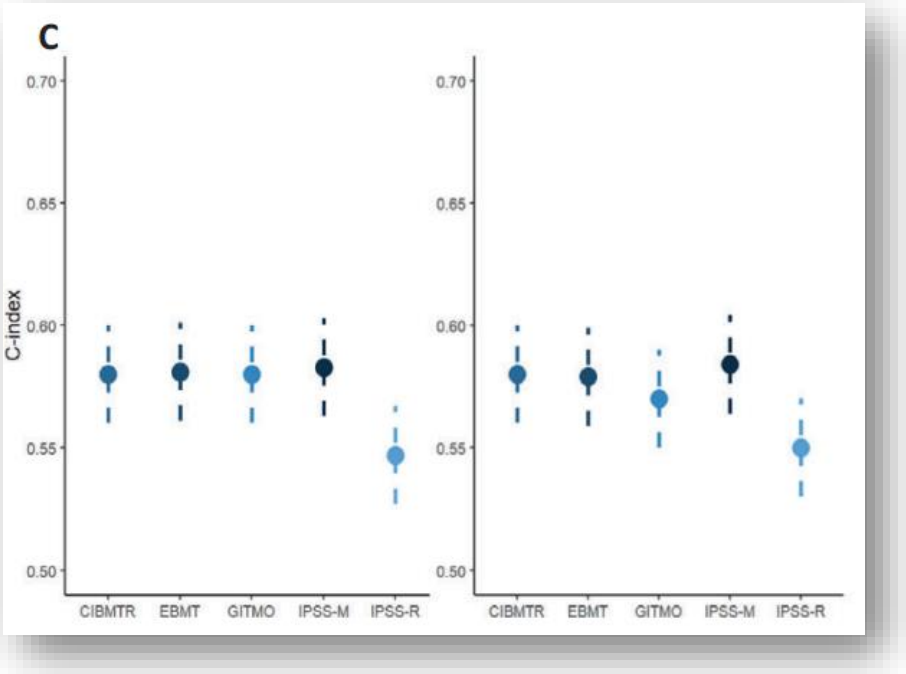
Santa et al. 2023

Outcome prediction in myelodysplastic neoplasm undergoing hematopoietic cell transplant in the molecular era of IPSS-M

Carmelo Gurnari[1,2,6], Nico Gagelmann[3,6], Anita Badbaran[3], Hussein Awada[1], Danai Dima[1], Simona Pagliuca[4,5],

Leukemia

N= 416
36% natifs traitement
Traités : 85% HMA



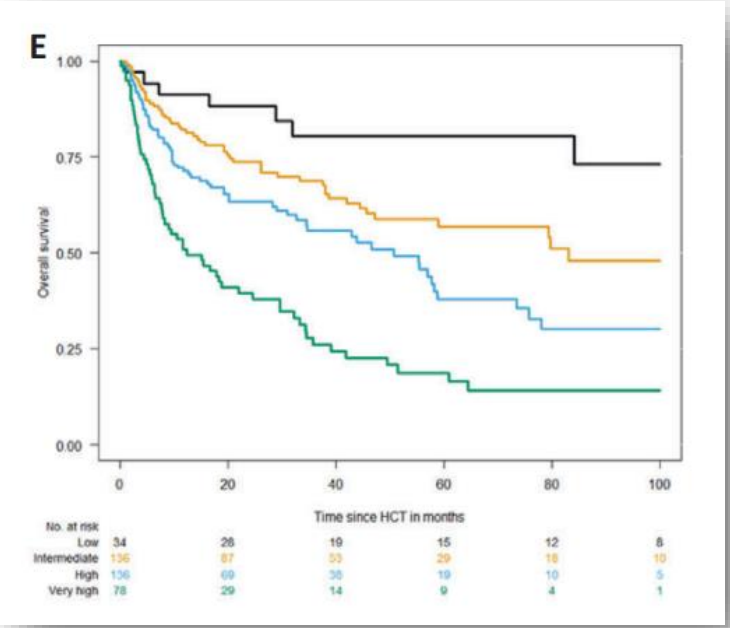
OS RFS

D

Combined clinical-molecular MDS transplant model

Factor	Hazard ratio	95% confidence interval	P	Score
Age				
≤50	Reference			
>50	1.342	1.06-1.65	0.01	1
Performance status				
90-100	Reference			
<90	1.55	1.15-2.10	0.004	1
Monosomal karyotype				
Absent	Reference			
Present	2.34	1.61-3.40	<0.001	2
TP53				
Absent	Reference			
Present	2.41	1.66-3.51	<0.001	2

C-index: 0.638
Low = 0
Intermediate = 1
High = 2
Very high >2



Supériorité du modèle par rapport à IPSS-R

Mais pas de gain par rapport à d'autres scores

Gurnari et al. 2023

IPSS-M et agents hypométhylants (HMA)

N= 268 (Haut-Risque)
9% cohorte

Médiane de 6 cycles

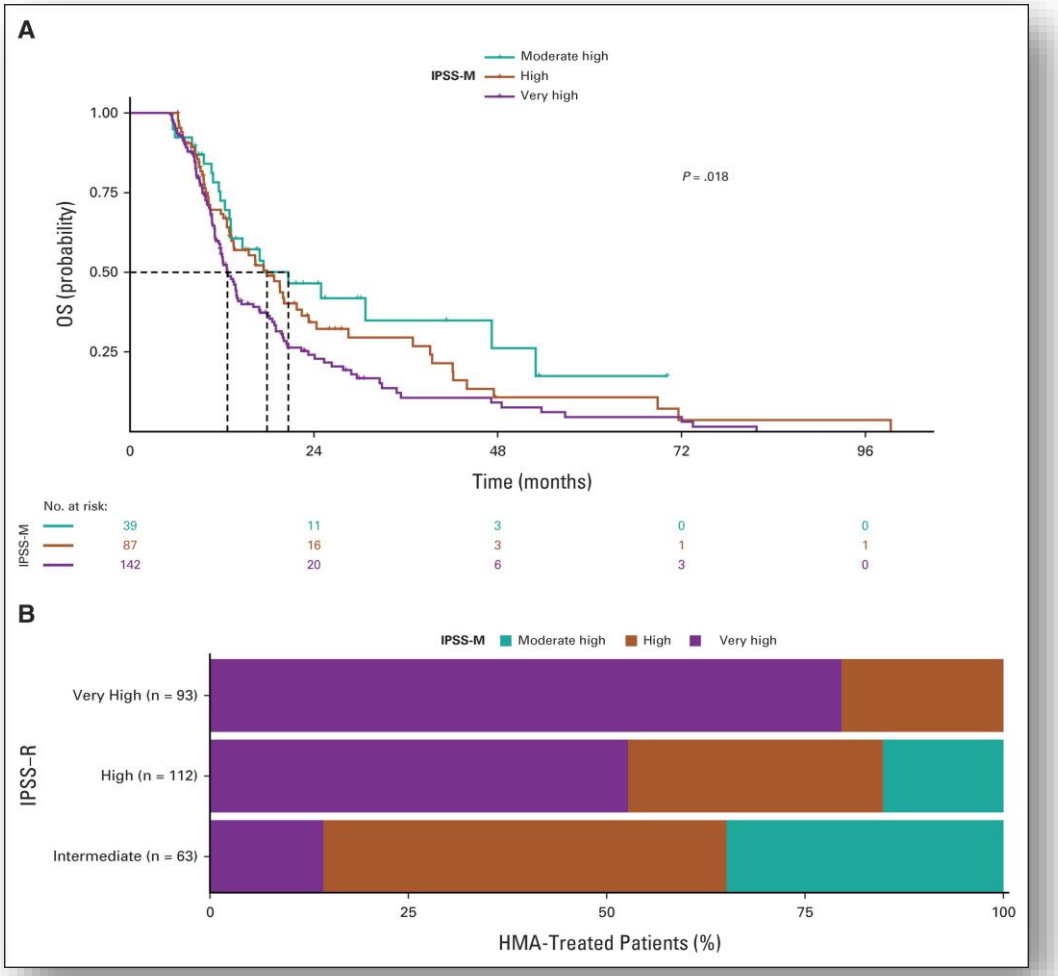
↓

Rémission complète
Rémission partielle
Maladie stable
(Critères IWG 2006)

↓

Taux global : 42%

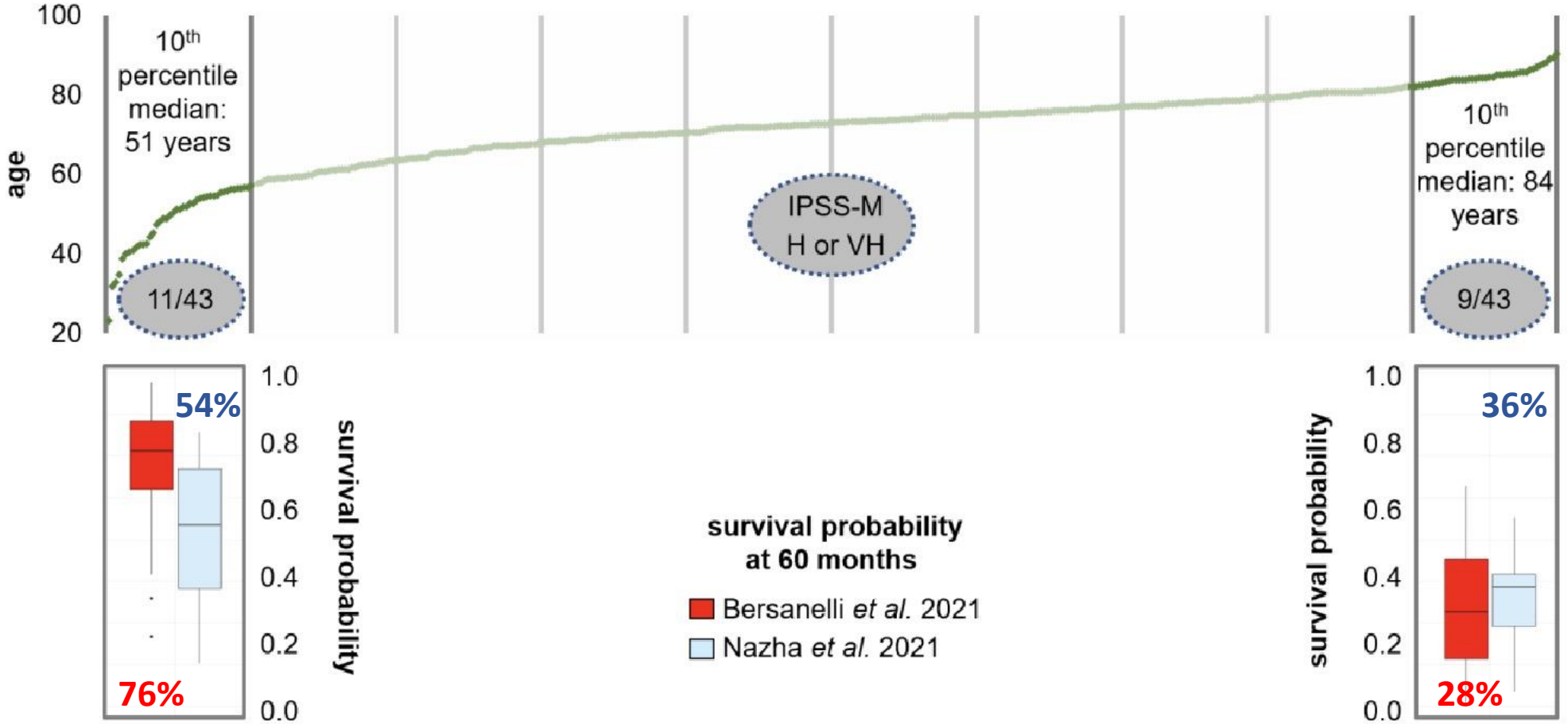
Pas de différence selon l'IPSS-M sur le taux de réponse



Différence significative sur survie globale

Santa et al. 2023

Impact de l’âge sur IPSS-M

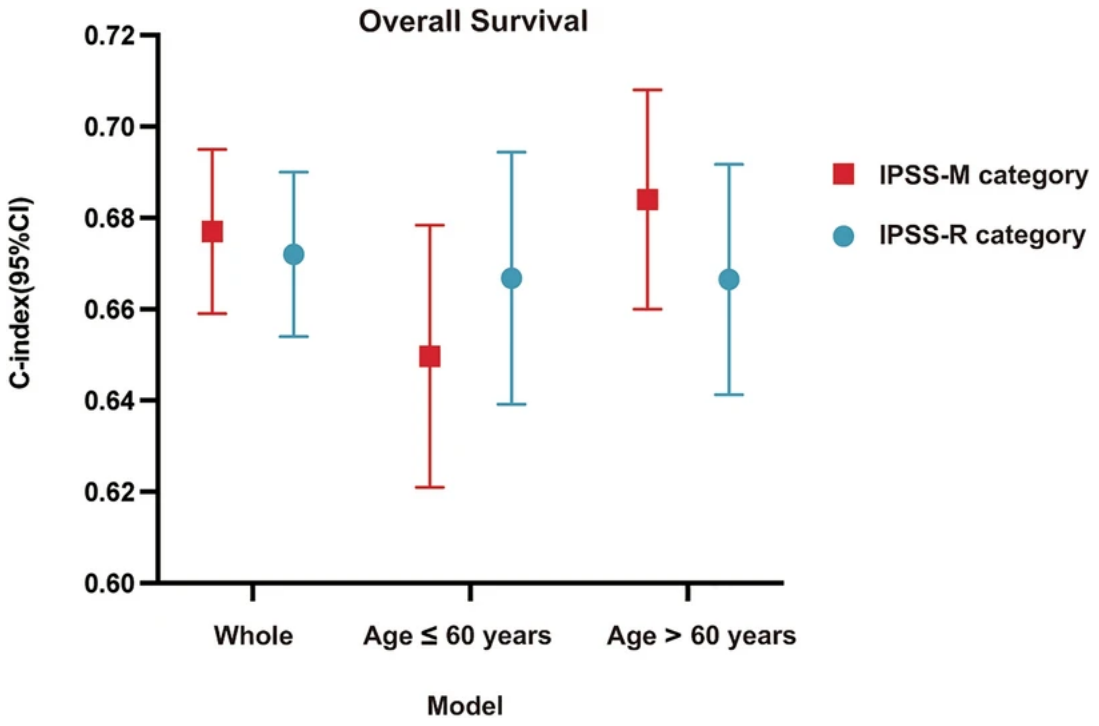


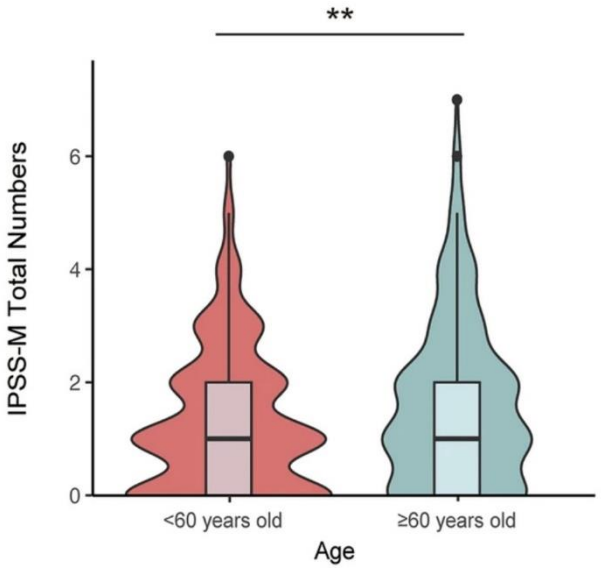
Baer et al. 2023

IPSS-M has greater survival predictive accuracy compared with IPSS-R in persons ≥ 60 years with myelodysplastic syndromes

Junying Wu[1†], Yudi Zhang[1†], Tiejun Qin[2], Zefeng Xu[1,2], Shiqiang Qu[1,2], Lijuan Pan[2], Bing Li[1,2], Yujiao Jia[3],

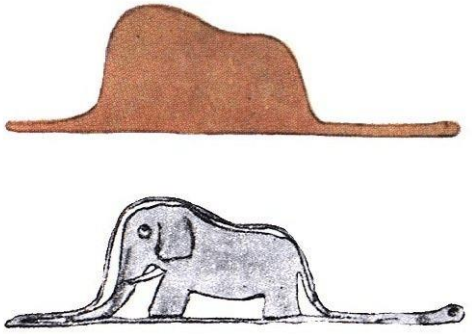
N= 852 *de novo*





Wu et al. 2022

IPSS-M en 2023



- L'IPSS-M affine la stratification des patients
- Importance de nouvelles données moléculaires dont certaines sont difficiles à mettre en évidence en NGS
- Impact important sur les patients non traités et les « bas-risques »
- Pas de gain significatif en allogreffe
- Questions en suspens :
  - HMA?
  - Cytopénie clonale?