Mutation-Enhanced International Prognostic Scoring System (MIPSS) for Primary Myelofibrosis: An AGIMM & IWG-MRT Project

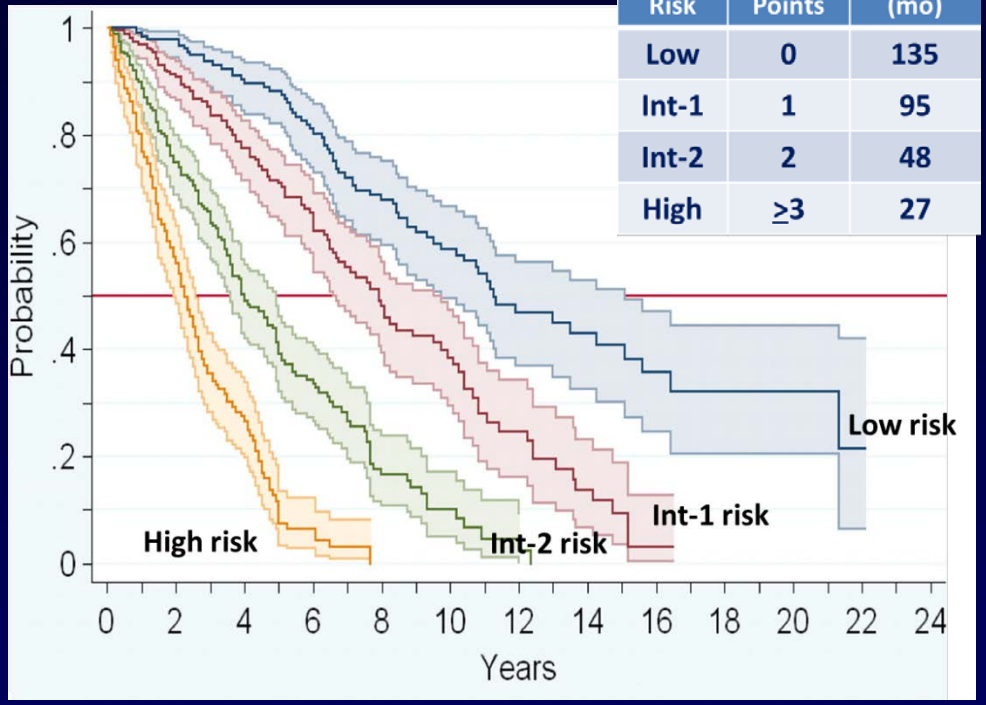
Abstract #405

Vannucchi AM

Background - I

- In primary myelofibrosis (PMF), survival from time of diagnosis is predicted by the International Prognostic Scoring System (IPSS).
- Variables included are age, leukocytosis, blasts, anemia, constitutional symptoms.

Risk	Points	Survival (mo)
Low	0	135
Int-1	1	95
Int-2	2	48
High	≥3	27



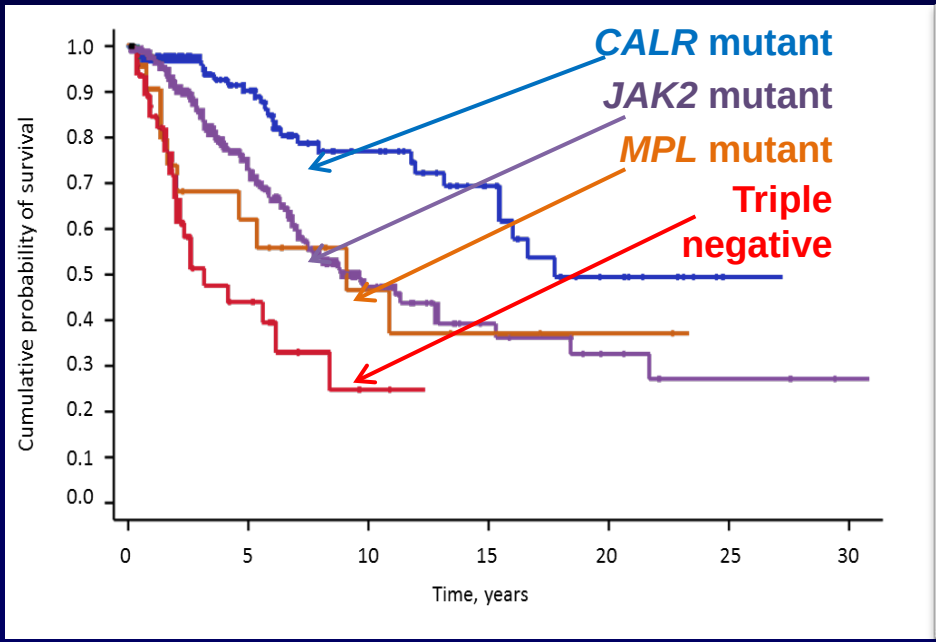
- The dynamic IPSS (DIPSS) or DIPSS-plus provide survival estimates from time of patient referral.

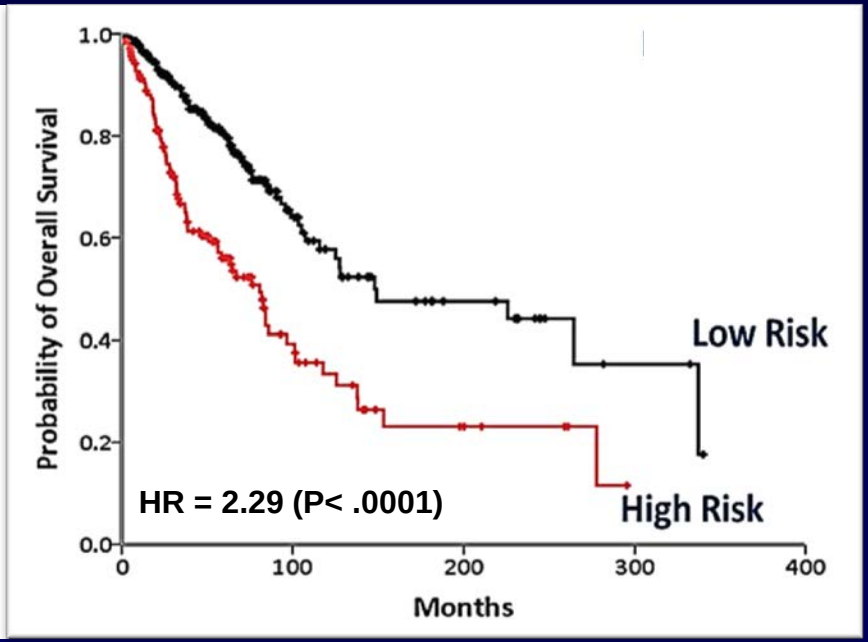
Cervantes F, et al. *Blood.* 2009;113:2895-2901. Passamonti F, et al. *Blood.* 2010;115:1703-1708. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25-33.

Vannucchi AM, et al. *Blood.* 2014;124: Abstract 405.

Background - II

- **The mutational status of *JAK2*, *MPL* and *CALR* and the presence and number of other prognostically-relevant mutations (*ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*) provide IPSS/DIPSS-plus independent prognostic information.**





HR: 2.3 for *JAK2*V617F (P<.001)
2.6 for *MPL* (*P = .009*)
6.2 for TN (*P<.001*)

High risk: Any mutation in *ASXL1, EZH2, SRSF2, IDH1/2*

Rumi E, et al. *Blood.* 2014;124:1062-1069. Vannucchi AM, et al. *Leukemia.* 2013;27:1861-1869.

Vannucchi AM, et al. *Blood.* 2014;124: Abstract 405.

Aim and Design

- The objective of the current study was to devise a new score by including clinical and mutation-relevant prognostic information.
- The prognostic model (MIPSS) was developed through a stepwise selection process, based on a *z-test* of the regression coefficients, and its relative quality was measured by means of the Akaike information criterion.
- We used a "*learning cohort*" (European; n = 588 PMF patients at diagnosis) and a "*validation cohort*" (Mayo Clinic, Rochester; n = 398 PMF patients at the time of referral)
- Mutations were analyzed by deep target resequencing (Ion PGM platform), RTQ-PCR, bidiretional Sanger sequencing, as appropriate

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Patients' Characteristics

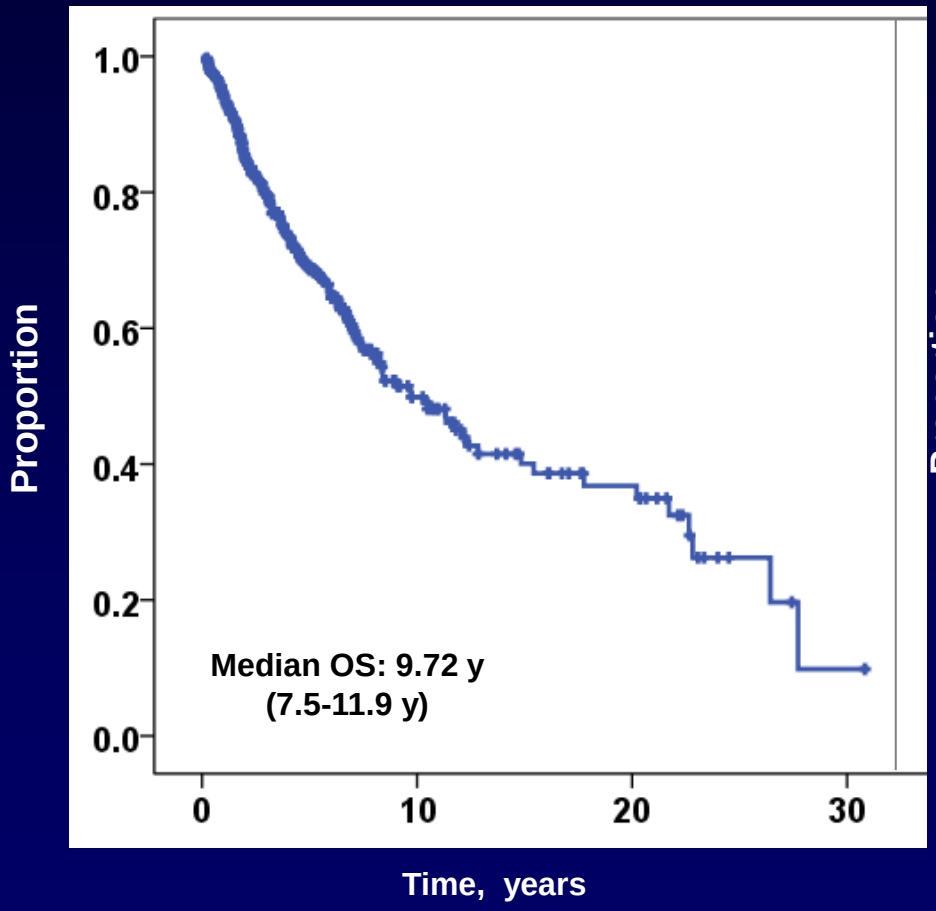
Variables		European cohort (n = 588)
Age in years; median (range)		61.9 (14-90)
Males (%)		361 (61.4%)
Hemoglobin, g/L; median (range)		117 (40-155)
Leukocytes, x 10^9/L; median (range)		8.9 (1.4-109)
Platelets, x 10^9/L; median (range)		309 (19-3279)
Circulating blasts ≥1%; n (%)		102 (17.3%)
Constitutional symptoms; n (%)		168 (28.6%)
Palpable splenomegaly; n (%)		440 (74.8%)
>10 cm from LMC; n (%)		104 (17.7%)
Unfavorable karyotype 8(n = 252)*		24 (9.5%)
IPSS Risk categories N (%)	Low	126 (25.5%)
	Intermediate-1	147 (29.8%)
	Intermediate-2	116 (23.5%)
	High	104 (21.1%)
Progression to leukemia; n (%)		67 (11.4%)
Death; n (%)		196 (33.3%)

*Unfavorable karyotype: +8,-7/7q-,i(17q),inv(3), -5/5q-,12p-, 11q23 rearr

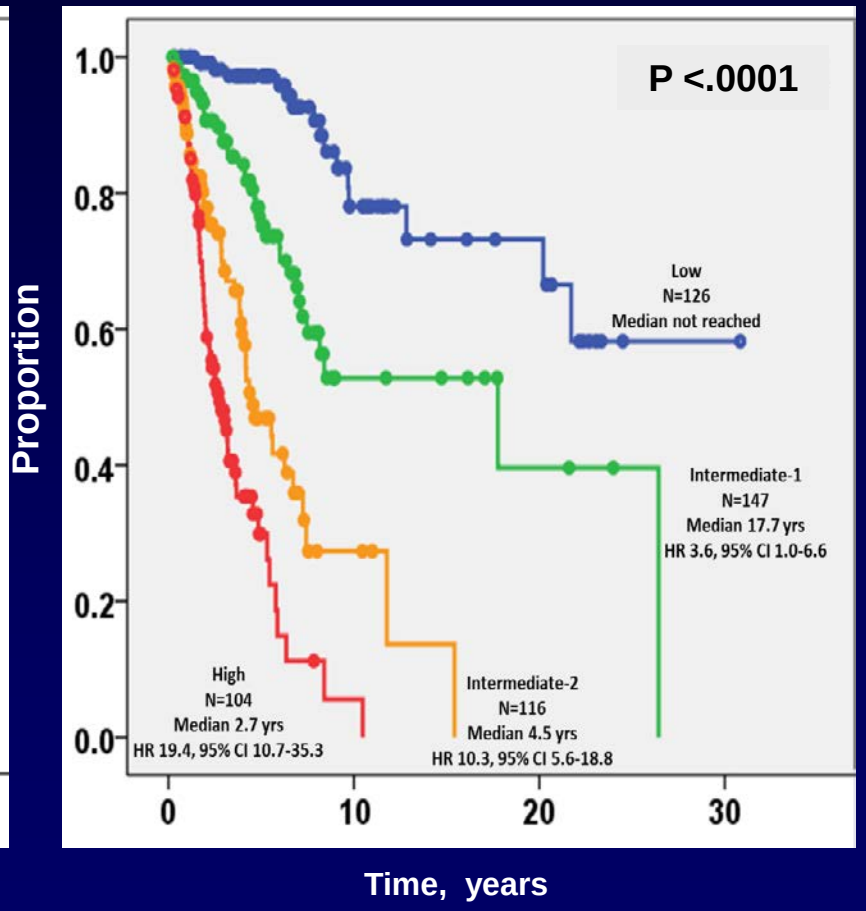
Vannucchi AM, et al. *Blood.* 2014;124: Abstract 405.

Learning Cohort: Survival by IPSS Score

Overall Survival



IPSS Stratification



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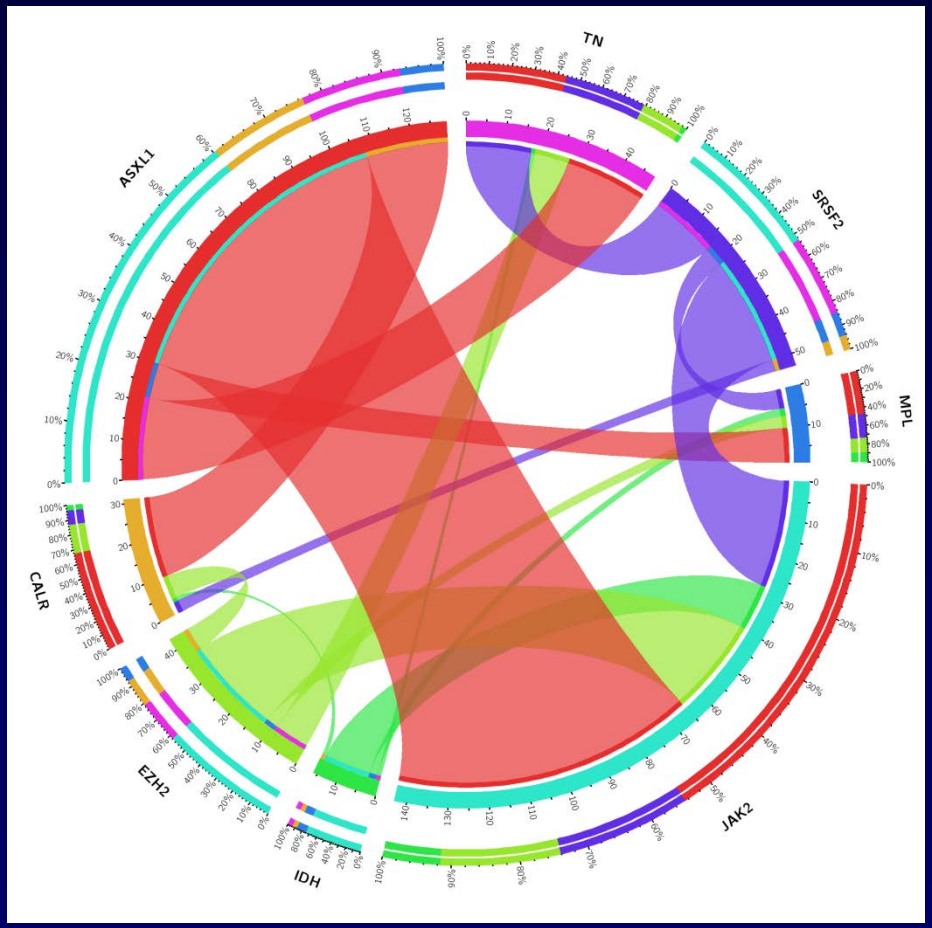
Mutation Profile in the Learning Cohort

Mutation	% Mutated
JAK2 V617F	63.1
CALR	19.7
MPL W515	6.0
ASXL1	21.8
SRSF2	9.01
EZH2	7.14
IDH1/2	2.55



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Variables Associated With Reduced OS
(Univariate Analysis)

Variables	HR (95% CI)	P	
Age >60yrs	5.19 (3.71-7.23)	<0.0001	IPSS
WBC >25x10^9/L	4.4 (2.89-6.71)	<0.0001	
Hb <100g/L	3.20 (2.37-4.33)	<0.0001	
PB Blasts ≥1%	2.4 (1.7-3.4)	<0.0001	
Constitutional Symptoms	2.33 (1.7-3.1)	<0.0001	
PLT <200x10^9/L	3.79 (2.79-5.15)	<0.0001	DIPSS-plus
Unfavorable Karyotype	2.9 (1.7-5.0)	<0.0001	
Splenomegaly >10 cm from LCM	2.0 (1.4-2.8)	<0.0001	
Grade 2-3 BM fibrosis	9.6 (3.0-30.3)	<0.0001	
Triple negativity	3.39 (2.40-4.79)	<0.0001	
***CALR* mutation**	0.34 (0.22-0.52)	<0.0001	
***ASXL1* mutation**	1.95 (1.45-2.63)	<0.0001	HMR
***SRSF2* mutation**	3.15 (2.14-4.63)	<0.0001	
***EZH2* mutation**	1.8 (1.13-3.0)	0.014	
***IDH1/2* mutation**	2.9 (1.3-6.2)	0.006	

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MIPSS: Molecular International Prognostic Score System

MULTIVARIATE ANALYSIS		
Variables	**HR (95% CI)**	**P**
Age >60yrs	3.8 (2.60-5.51)	<0.0001
Hb <100g/L	1.4 (1.01-1.99)	0.04
Constitutional symptoms	1.5 .(1.13-2.16)	0.007
PLT <200x10^9/L	2.5 (1.77-3.42)	<0.0001
Triple Negativity	3.9 (2.20-6.80)	<0.0001
***JAK2/MPL* mutation**	1.8 (1.11-2.90)	0.016
***ASXL1* mutation**	1.4 (1.06-1.99)	0.02
***SRSF2* mutation**	1.7 (1.08-2.58)	0.02

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MIPSS: Molecular International Prognostic Score System

MULTIVARIATE ANALYSIS			Weighted value
Variables	**HR (95% CI)**	**P**	
Age >60yrs	3.8 (2.60-5.51)	<0.0001	**1.5**
Hb <100g/L	1.4 (1.01-1.99)	0.04	**0.5**
Constitutional symptoms	1.5 .(1.13-2.16)	0.007	**0.5**
PLT <200x10^9/L	2.5 (1.77-3.42)	<0.0001	**1.0**
Triple Negativity	3.9 (2.20-6.80)	<0.0001	**1.5**
***JAK2/MPL* mutation**	1.8 (1.11-2.90)	0.016	**0.5**
***ASXL1* mutation**	1.4 (1.06-1.99)	0.02	**0.5**
***SRSF2* mutation**	1.7 (1.08-2.58)	0.02	**0.5**

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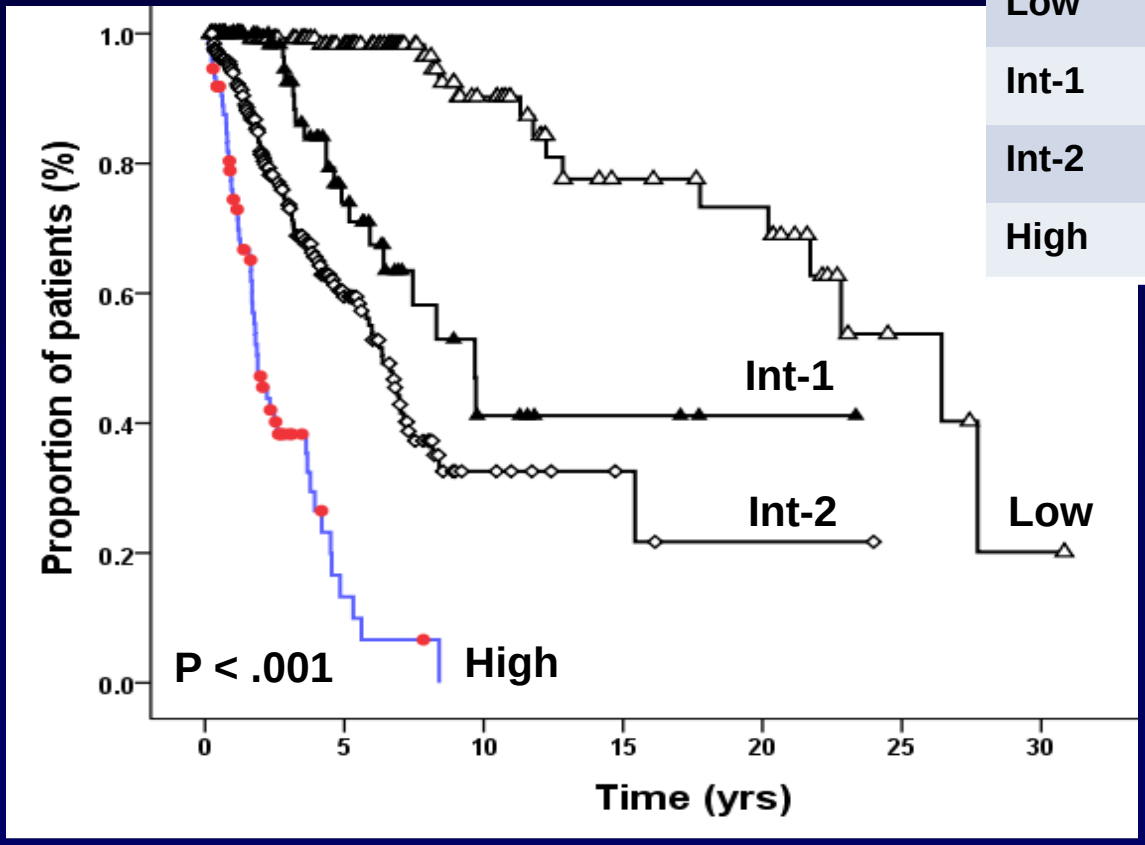
Development of the MIPSS Score in the Learning Cohort

Risk category	Score	% of pts	OS (y)	HR
Low	0-0.5	27	26.4	1
Int-1	1-1.5	14	9.7	4.7
Int-2	2-3.5	46	6.4	9.9
High	≥4	13	1.9	36.5



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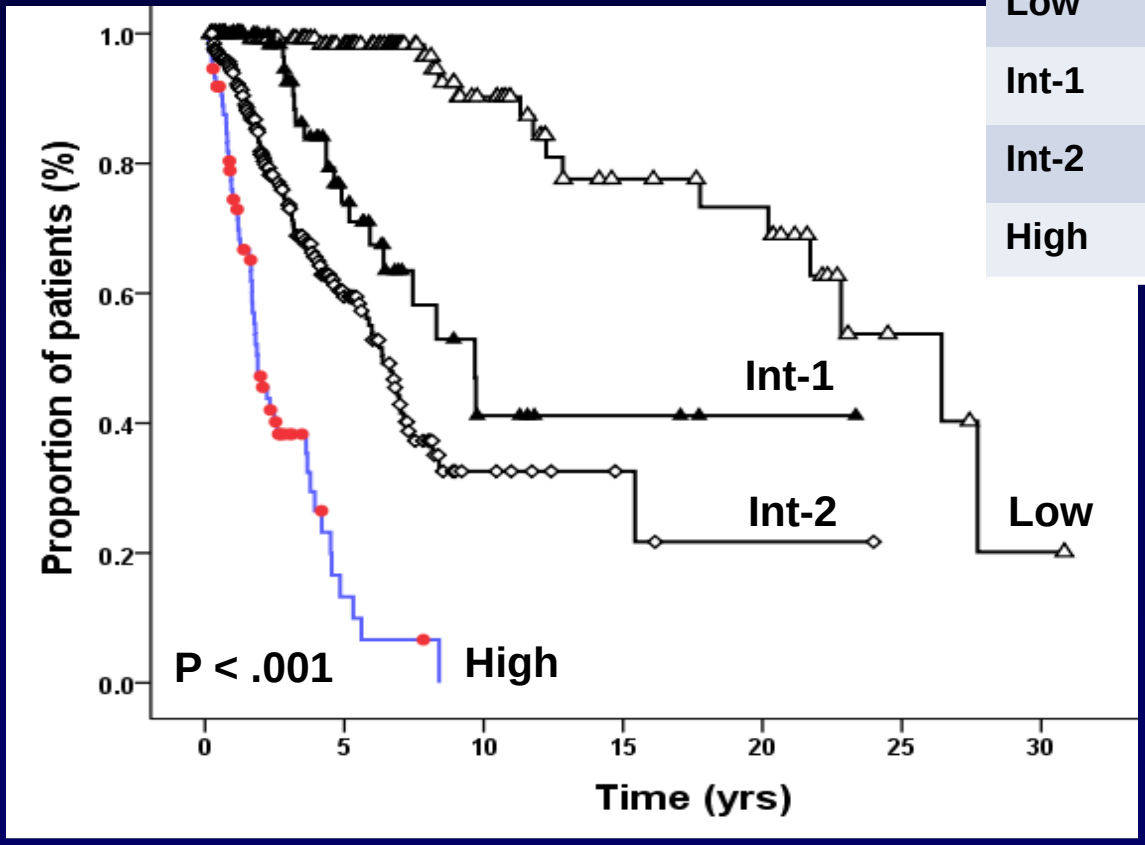

Akaike information criterion indicated that MIPSS performed better than IPSS in predicting survival (1611.6 *vs* 1649.0).

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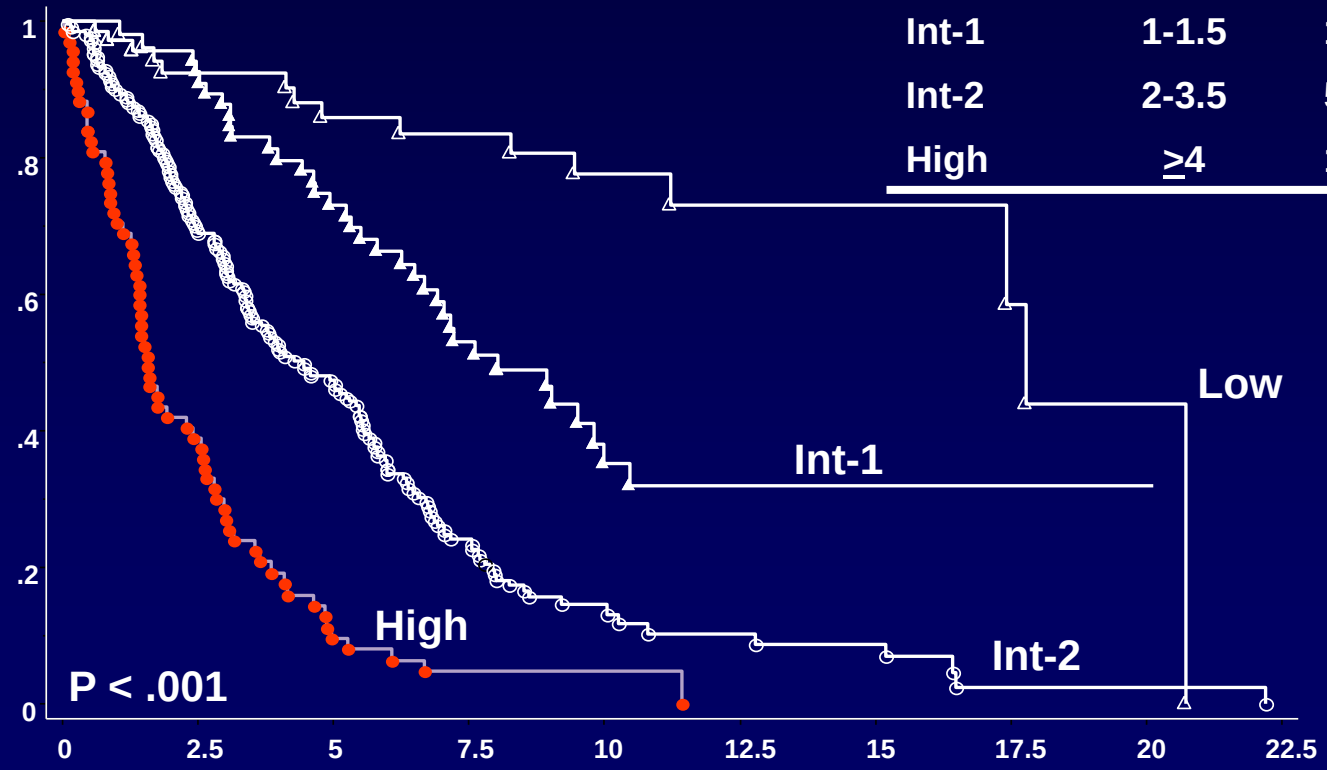
Performance of the MIPSS Score in the "Mayo" Validation Cohort

Risk category	Score	% of pts	OS (y)	HR
Low	0-0.5	13	17.6	1
Int-1	1-1.5	17	7.8	2.6
Int-2	2-3.5	53	4.3	6.3
High	≥4	17	1.6	15.9



***N* = 398 DIPSS-plus patients**

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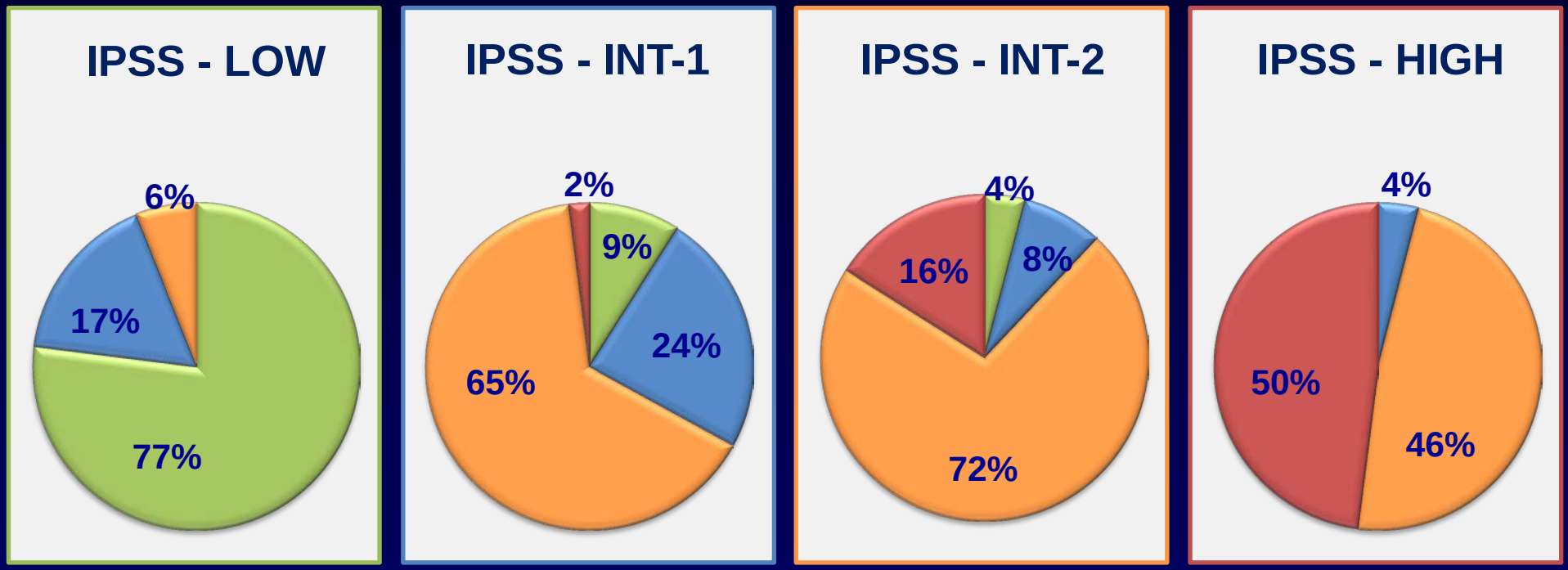
Comparison of IPSS and MIPSS



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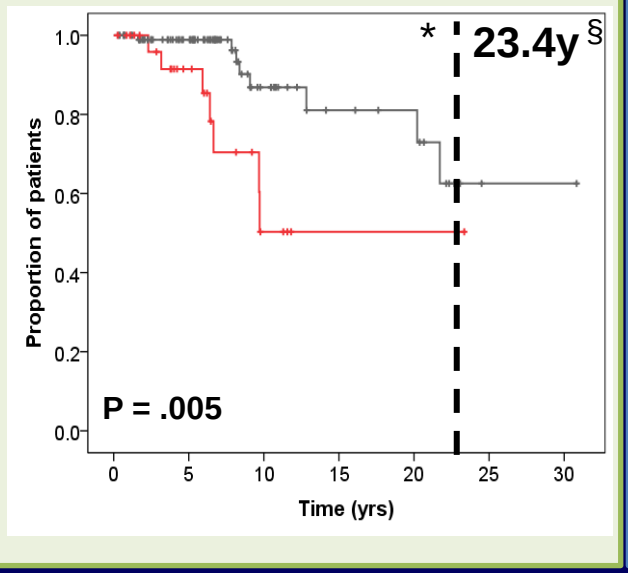
MIPSS Permits to Refine Prognostic Stratification Within the IPSS Categories

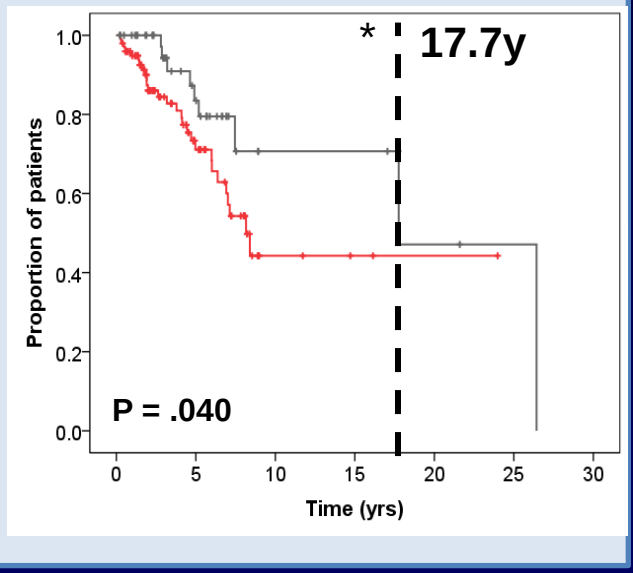
IPSS - LOW



Low 24.9y §

>Low 15.3y §

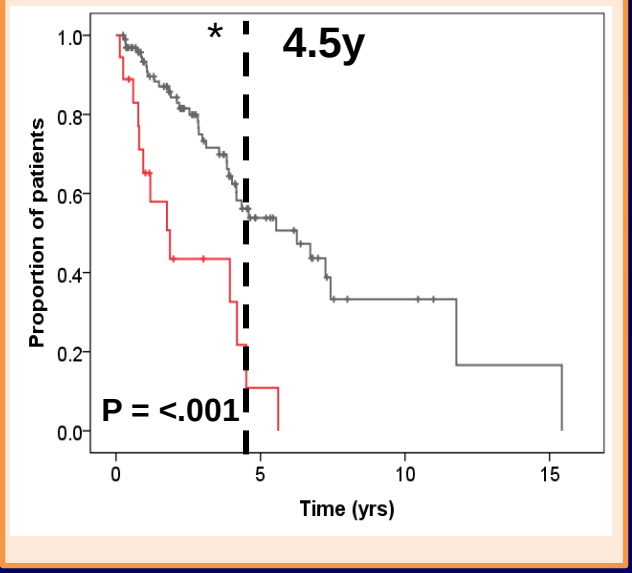
IPSS - INT-1



≤ Int-1 17.7y

>Int-1 8.1y

IPSS - INT-2



≤ Int-2 6.2y

>Int-2 1.9y

§Estimated

*IPSS median survival – – – – –

MIPSS

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Conclusions

- **MIPSS, a novel clinico-molecular score for patients with PMF, incorporates 4 clinical variables (age, HB, platelet count, constitutional symptoms) and 4 molecular variables (Triple negativity, *JAK2/MPL* mutation, *ASXL1* and *SRSF2* mutations)**
- **MIPSS proved better performing than IPSS for predicting survival in PMF patients by Akaike information criterion**
- **MIPSS allows to identify subgroups of patients with less favorable prognosis within the conventional IPSS categories**

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MIPSS: When and for Whom?

A) in the setting of HSCT:

- **For potential candidates falling in the Int-1 and Int-2 IPSS risk category**

B) in the setting of clinical trials:

- **For “personalized” medicine approach**

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