Stem cell transplantation for myelofibrosis YES!!

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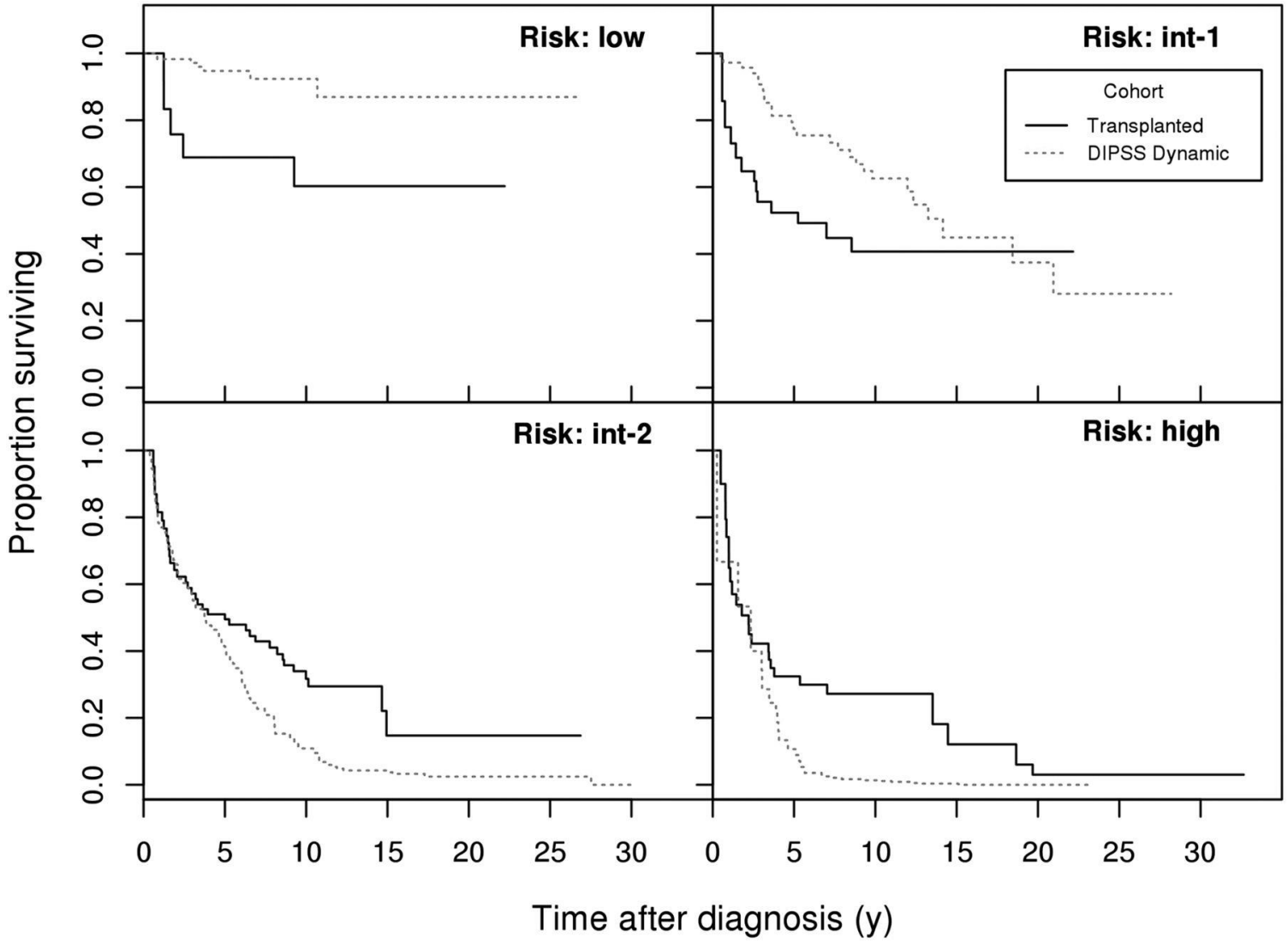
Introduction

- Allogeneic SCT remain the only potentially curative therapy in MF
- SCT is limited by significant morbidity and treatment related mortality
  - Graft failure
  - Mixed chimerism
  - Poor graft function
  - Slow blood count recovery
  - Disease recurrence
  - Non relapse mortality

- MF is a heterogeneous disease: variable rates of progression and survival
- Early SCT is associated with better outcome but does it justify the risk?
- No randomized studies comparing SCT and no SCT and most of the retrospective data is from the pre Ruxolitinib era

Who, When and How to transplant patients with myelofibrosis?

Survival for SCT vs non-SCT by DIPSS subgroup



Blood 2015;125:3347-3350

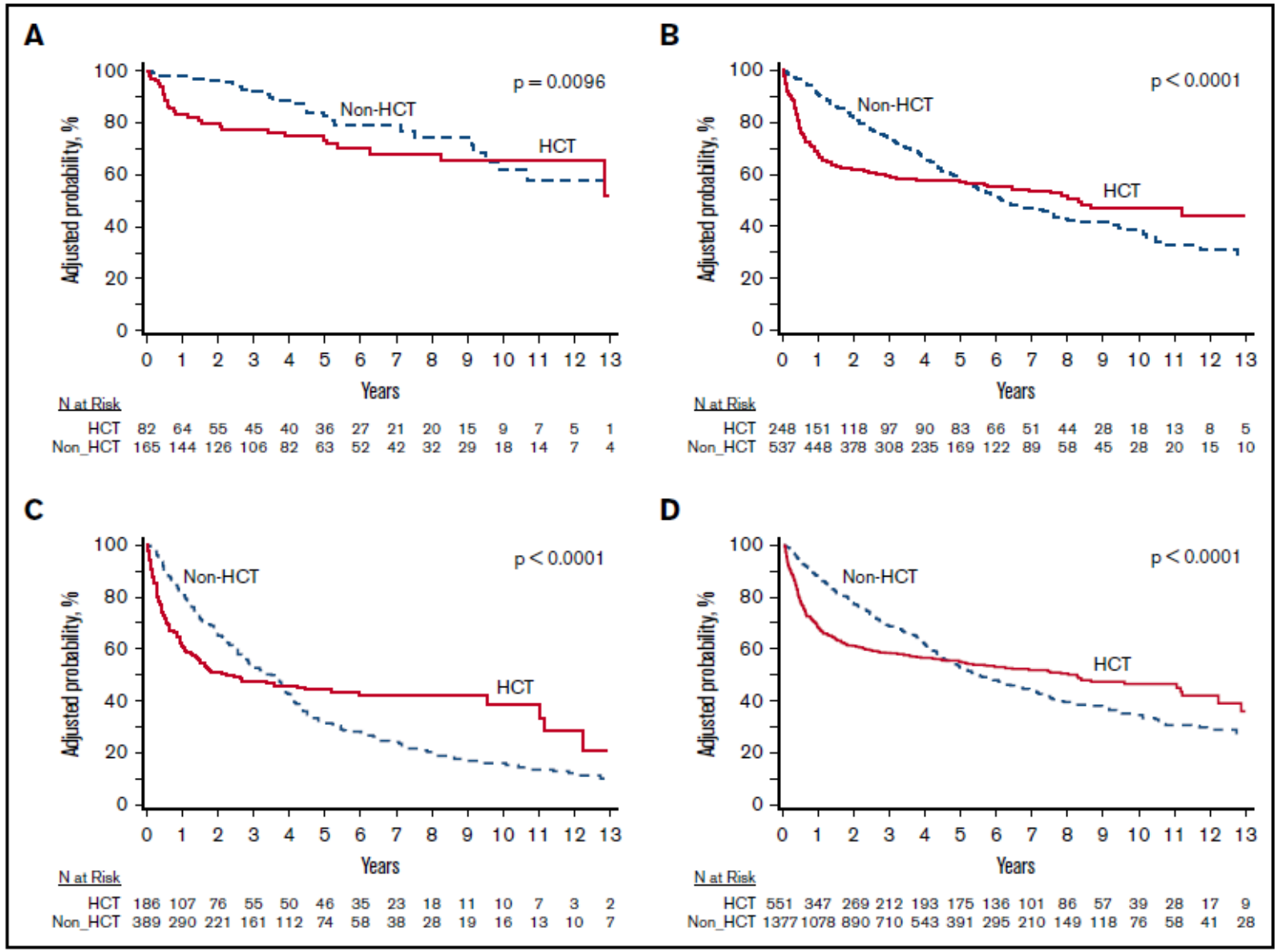
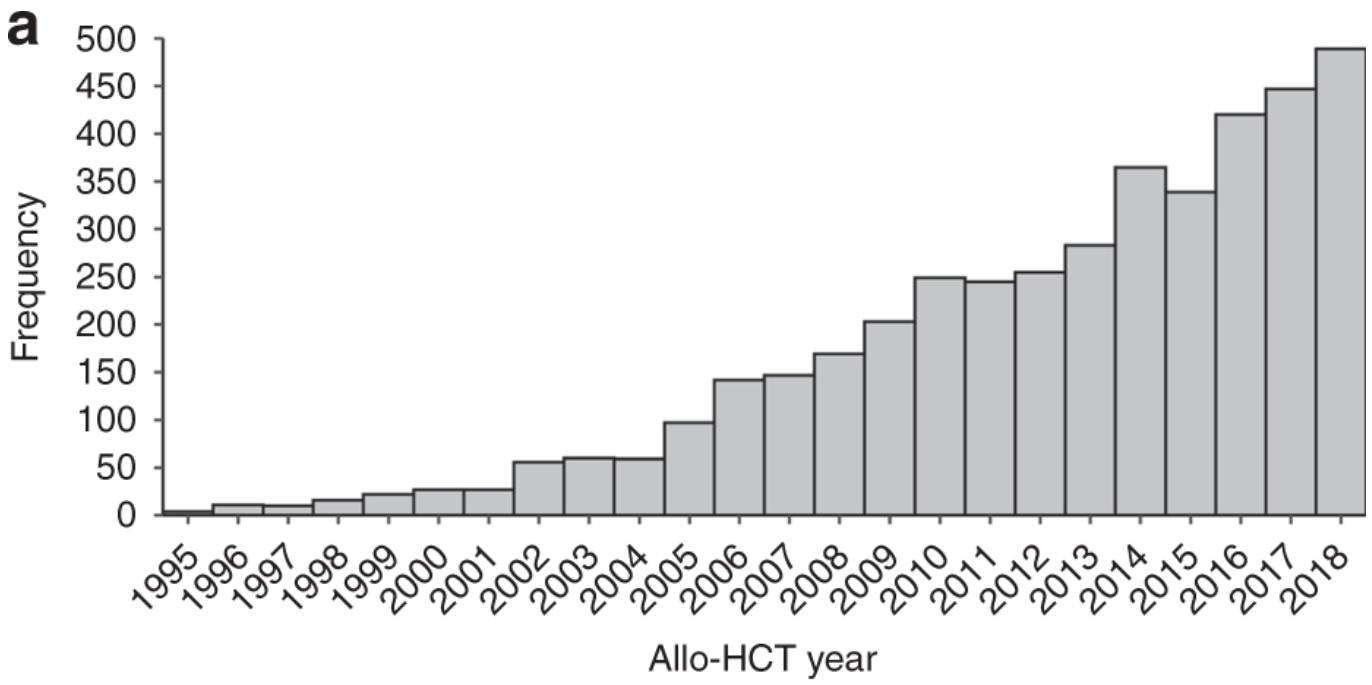


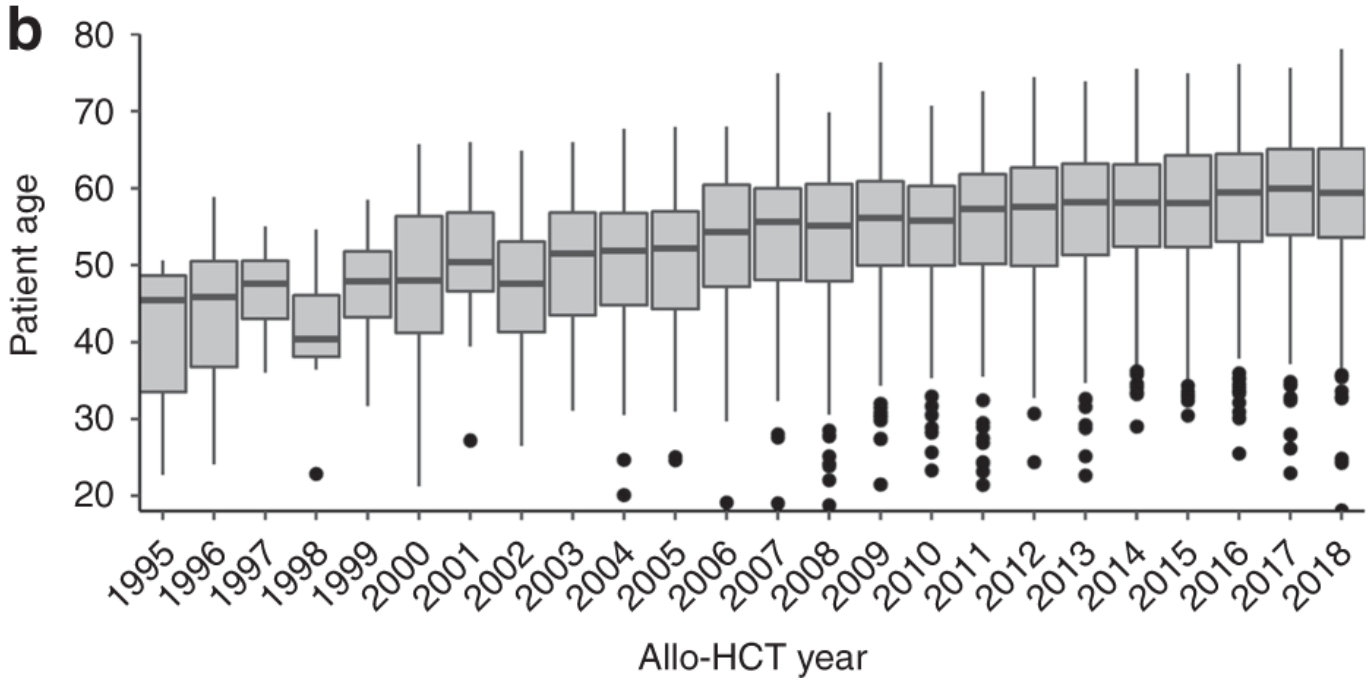
Figure 1. Survival probabilities for the DIPSS risk groups in MF receiving HCT vs non-HCT therapy. (A) DIPSS low risk. (B) DIPSS Int-1. (C) DIPSS Int-2 or higher. (D) Overall (all DIPSS groups). The survival curves presented here, stratified by DIPSS risk score, are a representation of the interventions (ie, HCT vs non-HCT therapy) over a median follow-up of ~6 years. The curves cross much later in the clinical course than 12 months; however, the slope of the curves changes much earlier (12 months) and then plateaus, indicating the OS benefit associated with HCT begins much earlier than when the curves actually cross. A long-term survival advantage with HCT was observed for patients with Int-1 or higher risk MF, but at the cost of early mortality. The magnitude of OS benefit increased as DIPSS risk score increased.

Large CIBMTR study comparing 551 pts SCT and 1377 pts with no SCT

More contemporary study including Ruxolitinib treated patients

Blood Adv 2020





EBMT data

Transplant activity has increased

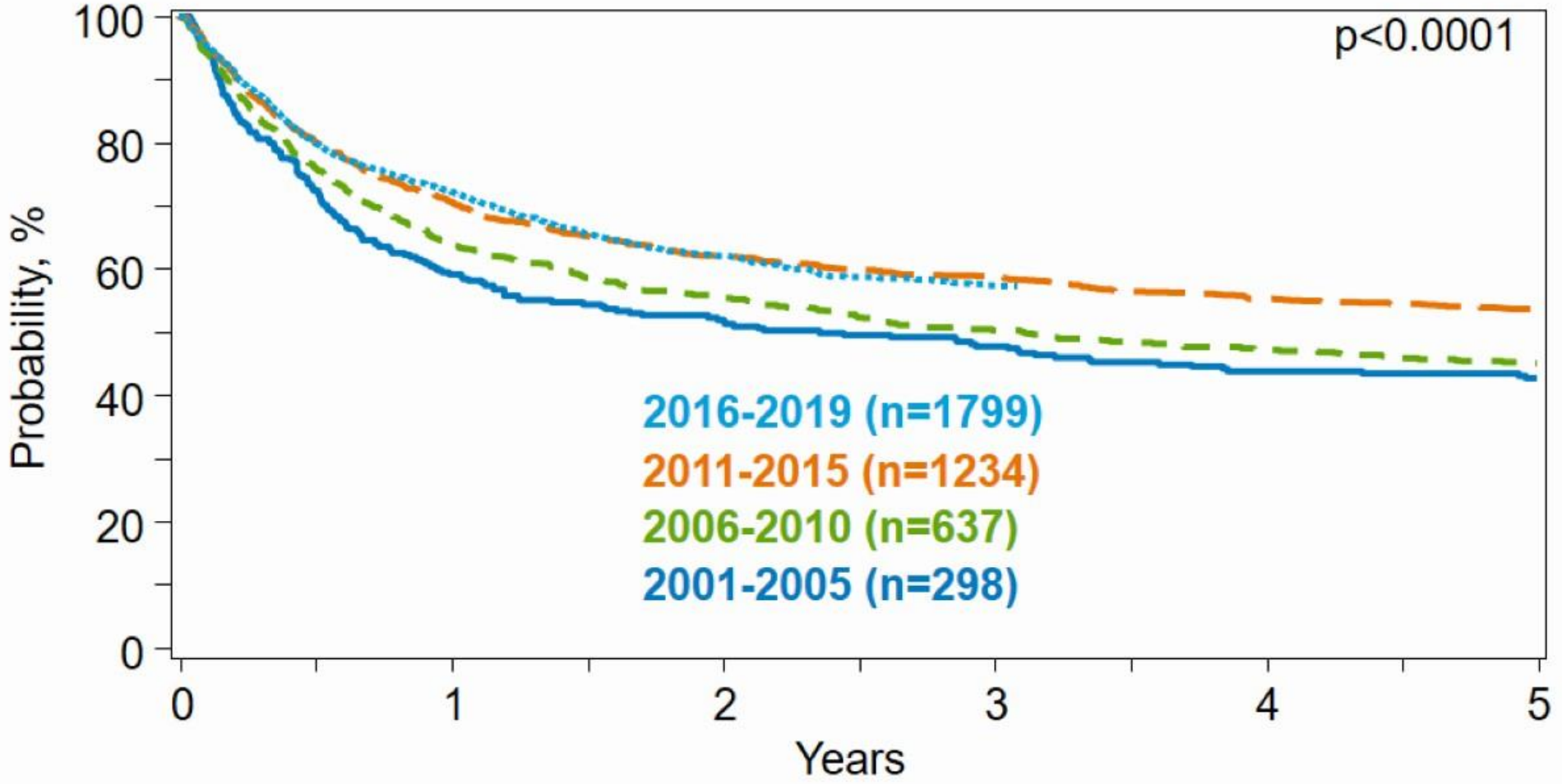
Patient age has increased

Duration of response alloSCT has also improved with better supportive care, conditioning regimens and GVHD prevention

NRM has not increased and OS has improved

BMT 2021

Trends in Survival after Allogeneic HCTs for Myeloproliferative Neoplasms (MPN), in the US, 2001-2019



OS	60%
NRM	30%
Relapse	20%

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Table 1. **Identifying high-risk patients with survival less than 5 years in myelofibrosis**

Risk stratification model	Risk group	Median OS, y	Pros	Cons
DIPSS[14]	Intermediate-2	4.0	Easy applicability based on clinical/laboratory variables	Does not include any information on genetic variables that may have significant impact on the natural history of the disease
	High	1.5		
DIPSS +[15]	Intermediate-2	2.9	Includes cytopenias and cytogenetic data	No mutational data
	High	1.3		
MIPSS70*[16]	High	3.1	Includes impact of MPN driver genes and HMR† genes	No cytogenetic data
MIPSS70 + 2.0*[17]	High	4.1	Cytogenetic data Driver/HMR‡ genes	
	Very high	1.8		
MPN personalized risk§[18]	TP53/–17p/–5/–5q	2.4	Combination of clinical/genetic/ cytogenetic data	Study heavily weighted toward PV/ET patients Copy number variation not included in most clinical NGS reports

*http://www.mipss70score.it/.
†HMR (*ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*).
‡Includes *ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*; adds *U2AF1* Q157.
§https://www.sanger.ac.uk/science/tools/progmod/progmod/.
NGS, next-generation sequencing.

TRANSPLANTATION

Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation

Nico Gagelmann,[1] Markus Ditschkowski,[2] Rashit Bogdanov,[2] Swann Bredin,[3] Marie Robin,[3] Bruno Cassinat,[4] Rabia Shahswar,[5] Felicitas Thol,[5] Michael Heuser,[5] Gerard Socié,[3] Dietrich Beelen,[2] Ioanna Triviai,[1] Anita Badbaran,[1] and Nicolaus Kröger[1]

KEY POINTS

- **The MTSS includes clinical-molecular and transplant-specific factors predicting posttransplant outcome.**
- **The MTSS is applicable to primary and post-ET/PV myelofibrosis reflecting posttransplant outcome better than disease-specific systems.**

Age > 57 years
KPS < 90
PLT < 150
WBC > 25
HLA mismatched unrelated donor
ASXL1 mutation
Non CALR/ MPL driver mutation

Low	(0-2)
Intermediate	(3-4)
High	(5)
Very high	(>5)

~~Hemoglobin~~
~~Transfu[illegible]icy,~~
~~Constitu[illegible]toms~~
~~Periph[illegible] blasts~~
Karyotype

Blood 2019

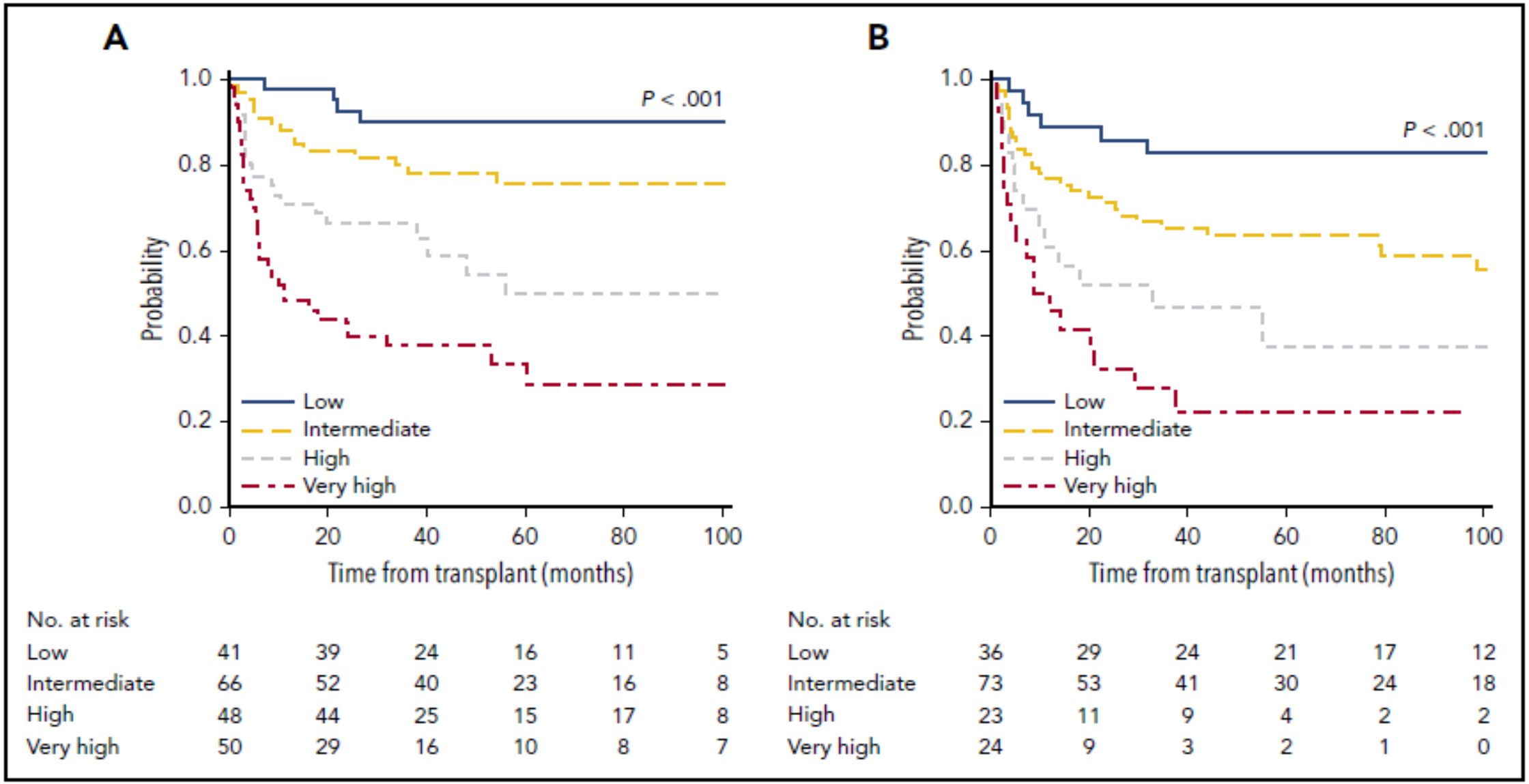


Figure 1. 5-year overall survival according to MTSS. OS for training (A) and validation cohort (B) according to the MTSS risk stratification. The 5-year survival rates according to each cohort and corresponding risk group were 90% (low), 77% (intermediate), 50% (high), and 34% (very high) for the training cohort (n = 205) and 83% (low), 64% (intermediate), 37% (high), and 22% (very high) for the validation cohort (n = 156; $P < .001$, respectively).

Pre-transplant therapy

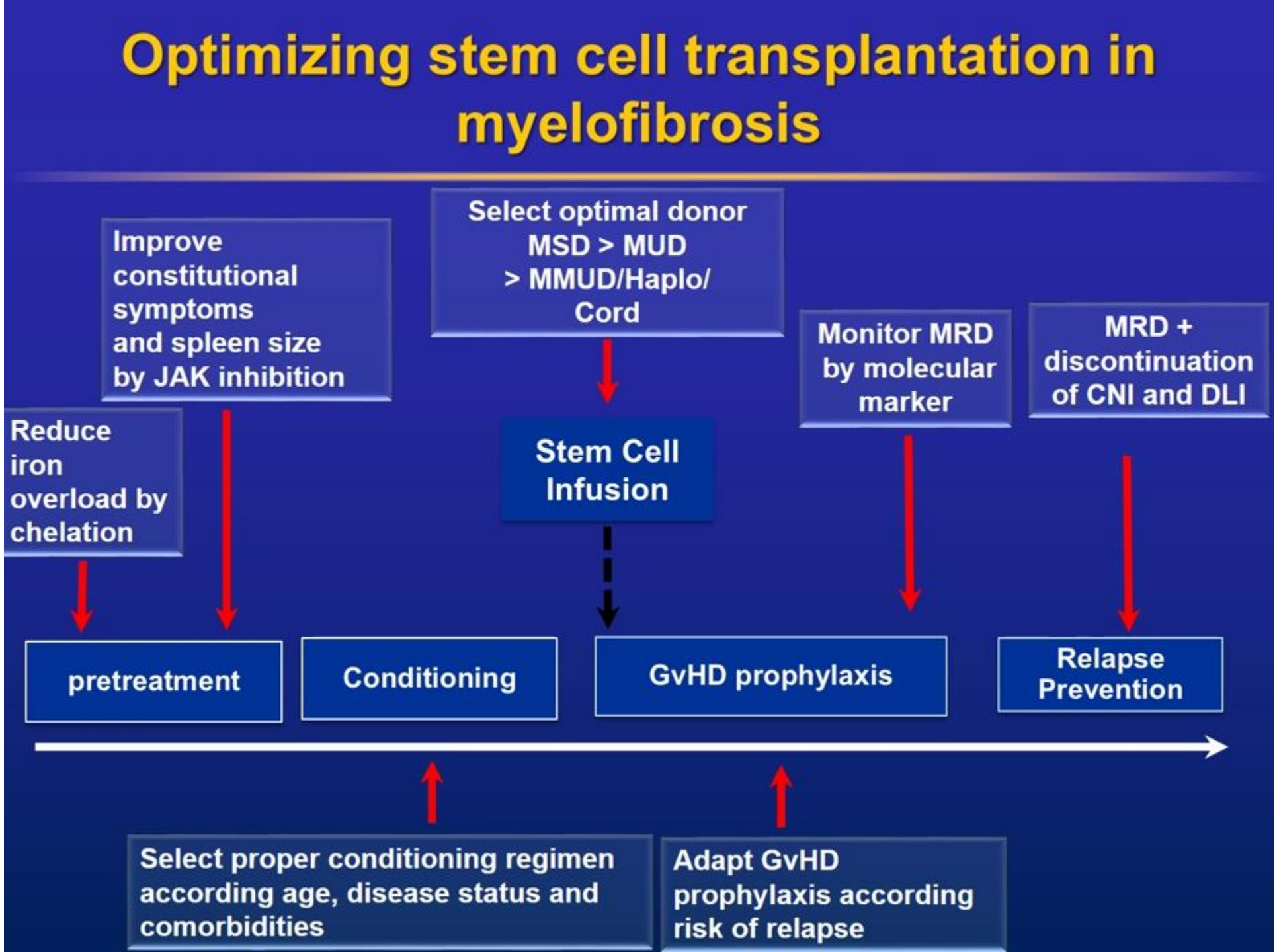
- Ruxolitinib
- Splenectomy
- Chelating therapy

Peri-transplant therapy

donor and conditioning

Post-transplant monitoring and therapy

Optimizing stem cell transplantation in myelofibrosis

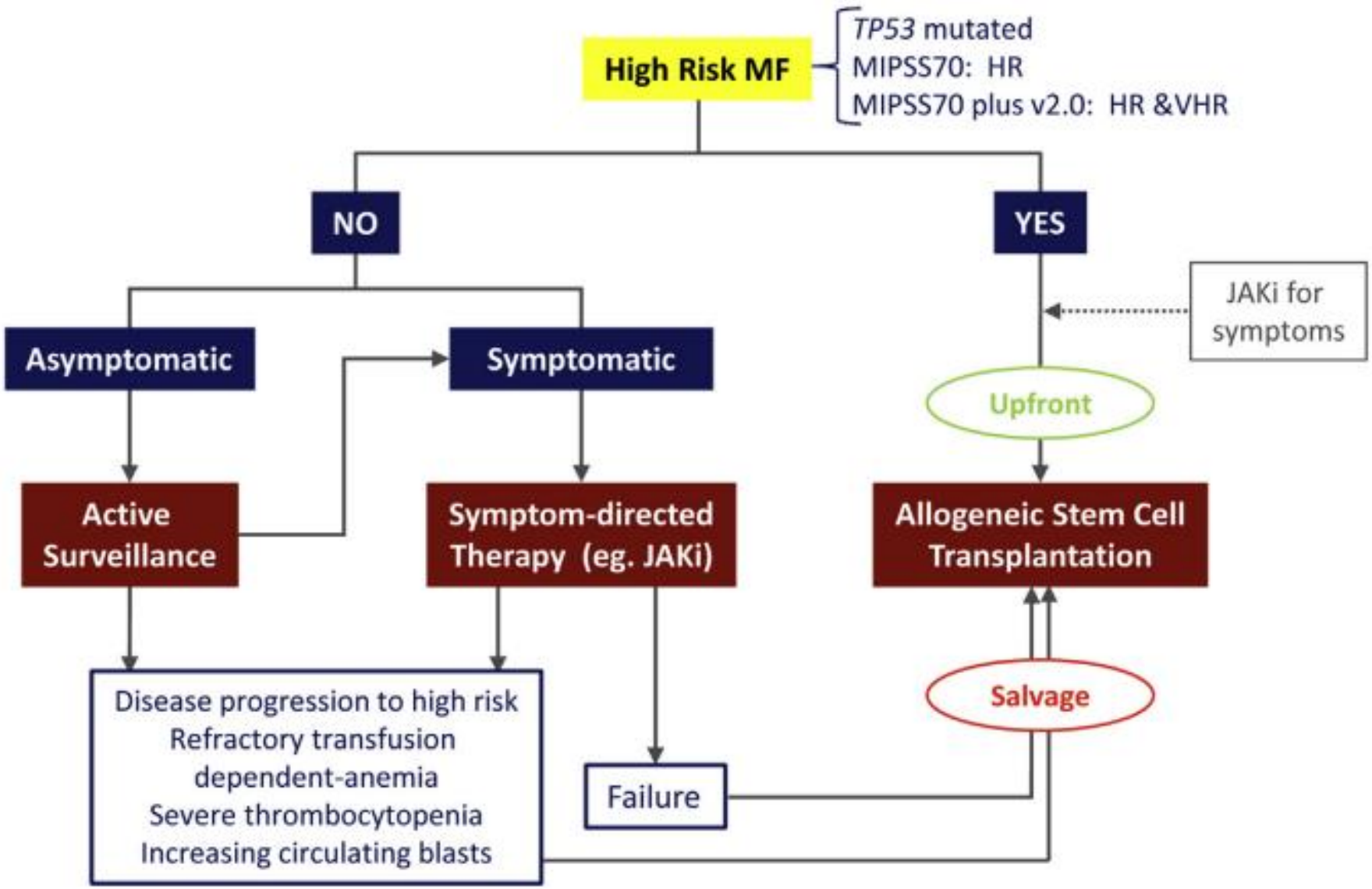


Allogeneic stem cell transplant-meta-analysis of 8379 patients: 5 year outcomes

Extensive/severe cGVHD (%)	Non relapse mortality (%)	Overall survival (%)
26	30	55

Bewersdorf, Trans Cell Ther 2021

Who should be transplanted, and when?



Davidson, Hem Onc Clin NA 2021