

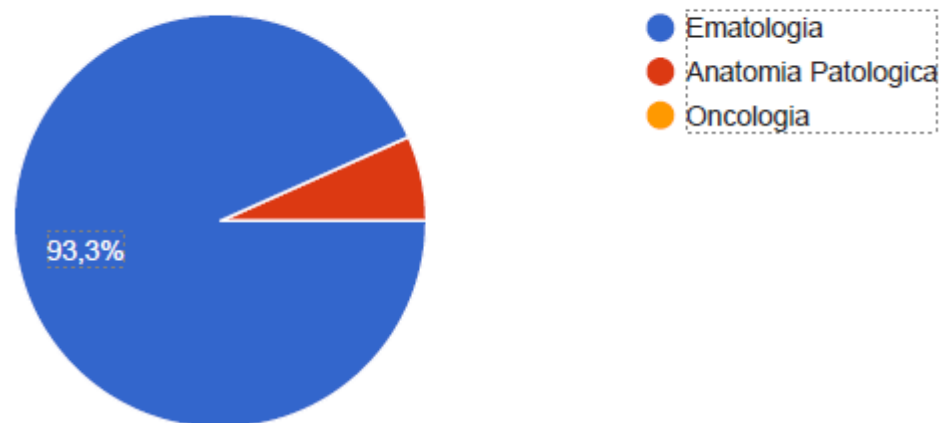
MIELOFIBROSI: DIAGNOSI E PROGNOSI ATTUALE CON FOCUS SUL PAZIENTE ANEMICO

**Survey sull'inquadramento diagnostico e prognostico nella mielofibrosi:
focus su anemia e implicazioni nella gestione clinica e nella scelta del
trattamento**

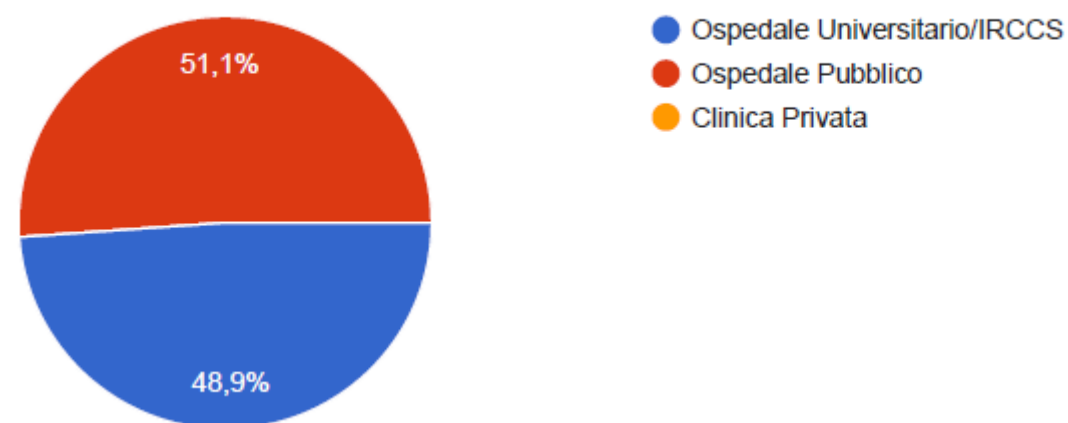
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Fondazione IRCCS San Gerardo dei Tintori, Monza

BACKGROUND

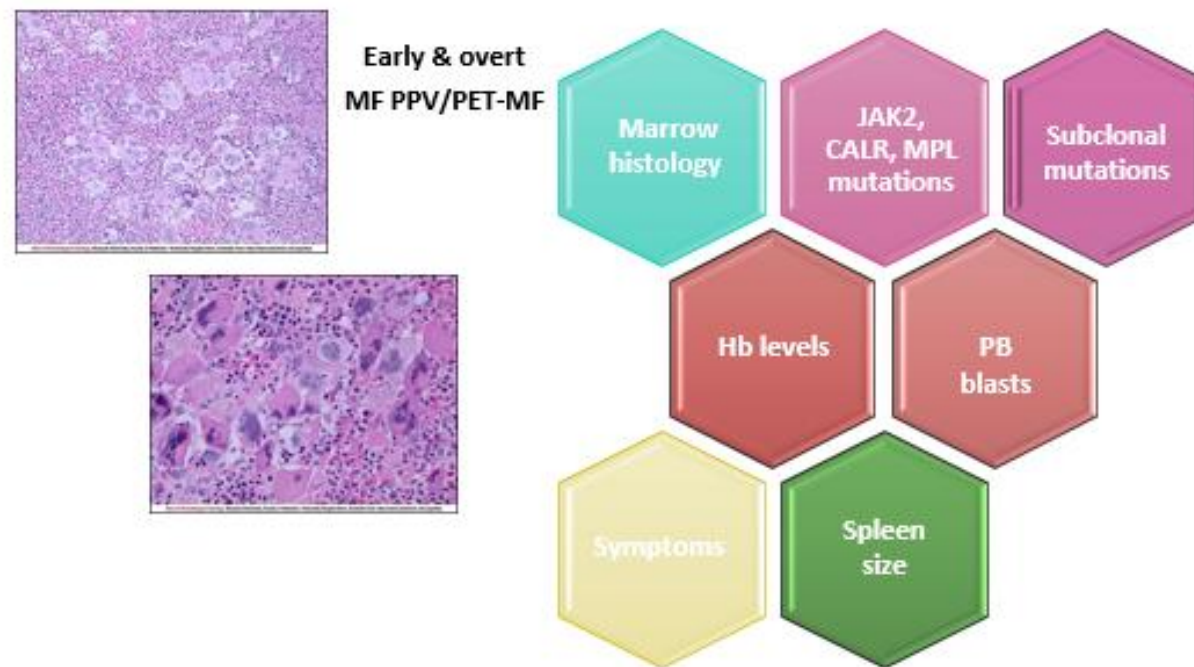
Qual è la tua specializzazione principale?



In che struttura lavori?



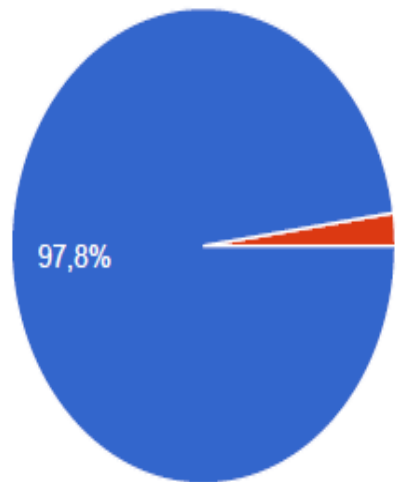
Il 55.6% dei colleghi ha più di 10 anni di esperienza nelle MPN, il 24.4% almeno 5 anni



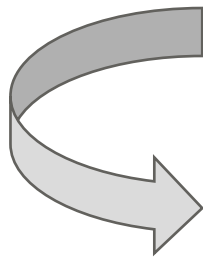
Criteri diagnostici e prognostici

CLASSIFICAZIONE WHO/ICC

Quali criteri diagnostici utilizzati OGGI per la diagnosi della mielofibrosi?



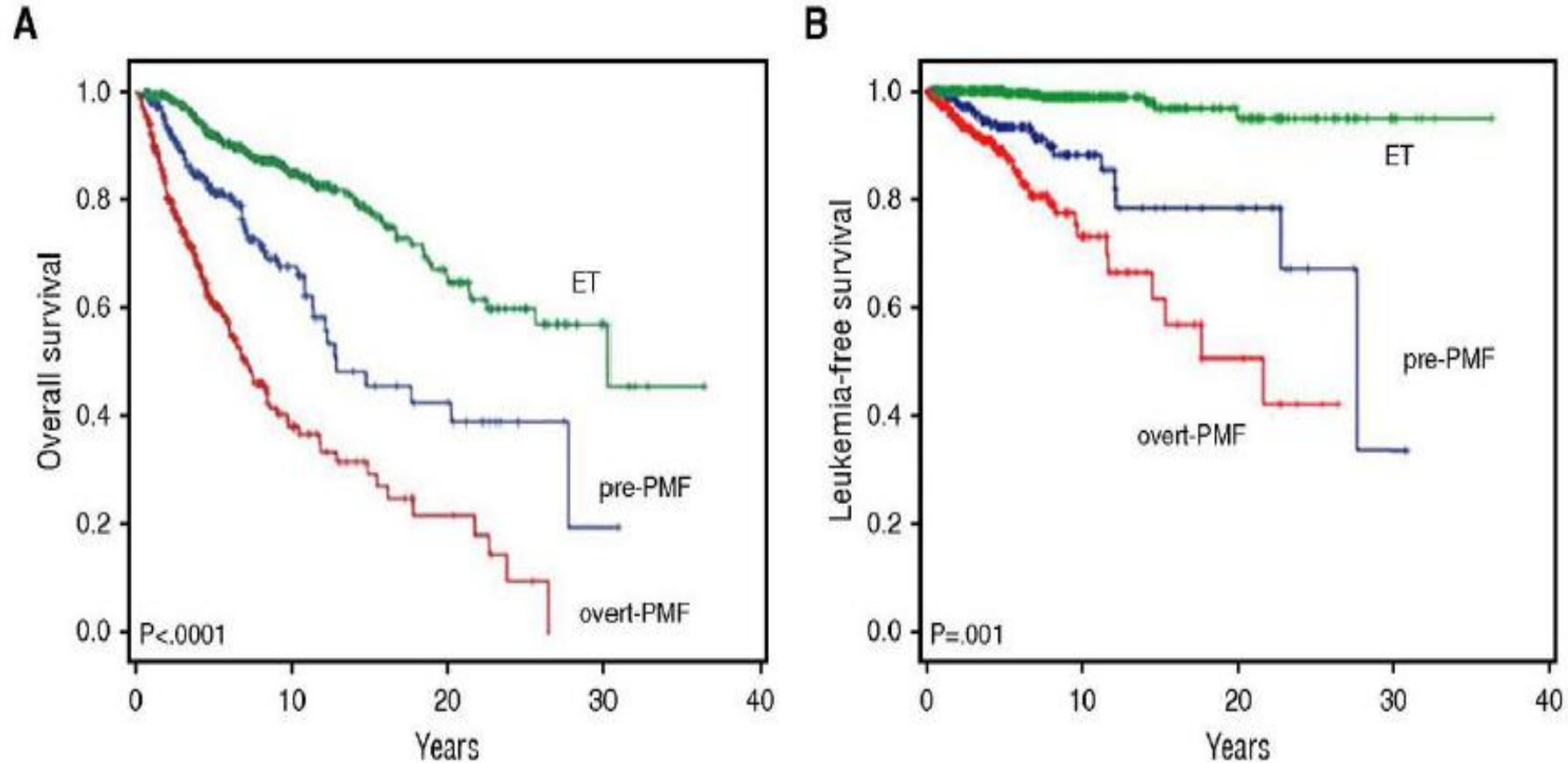
- WHO 2022 / ICC 2022
- WHO 2016



Il 100% dei rispondenti ritiene indispensabile distinguere una forma early da overt

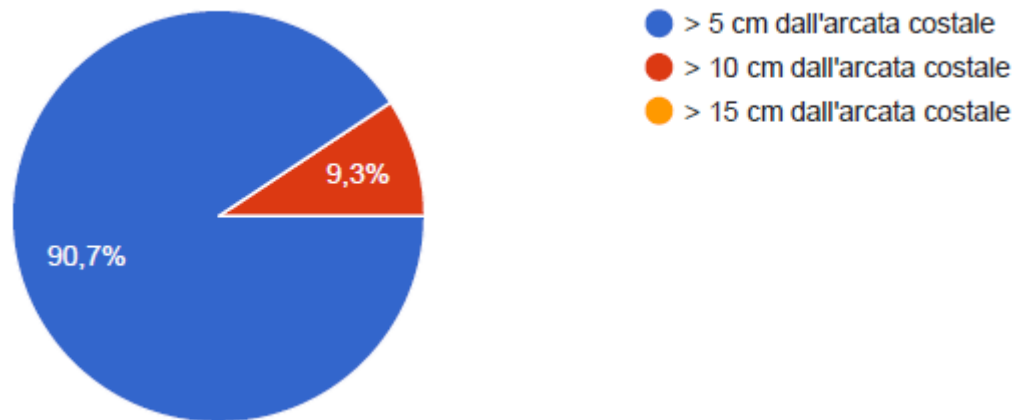
PMF, early/prefibrotic stage	PMF, overt fibrotic stage
Major criteria • BM biopsy showing megakaryocytic proliferation and atypia, BM fibrosis Grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis • <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis • Diagnostic criteria for <i>BCR-ABL1</i>-positive CML, PV, ET, MDS, or other myeloid neoplasms are not met	Major criteria • BM biopsy showing megakaryocytic proliferation and atypia⁶, accompanied by reticulin and/or collagen fibrosis grades 2/3 • <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation or presence of another clonal marker or absence of reactive MF • Diagnostic criteria for ET, PV, <i>BCR-ABL1</i>-positive CML, MDS, or other myeloid neoplasms are not met
Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • LDH level above the reference range	Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • LDH level above the reference range • Leukoerythroblastosis
Diagnosis The diagnosis of pre-PMF requires all 3 major criteria and ≥ 1 minor criterion	Diagnosis The diagnosis of overt PMF requires all 3 major criteria and ≥ 1 minor criterion confirmed in 2 consecutive determinations.

Prognostic Impact of Prefibrotic versus Overt PMF Diagnosis



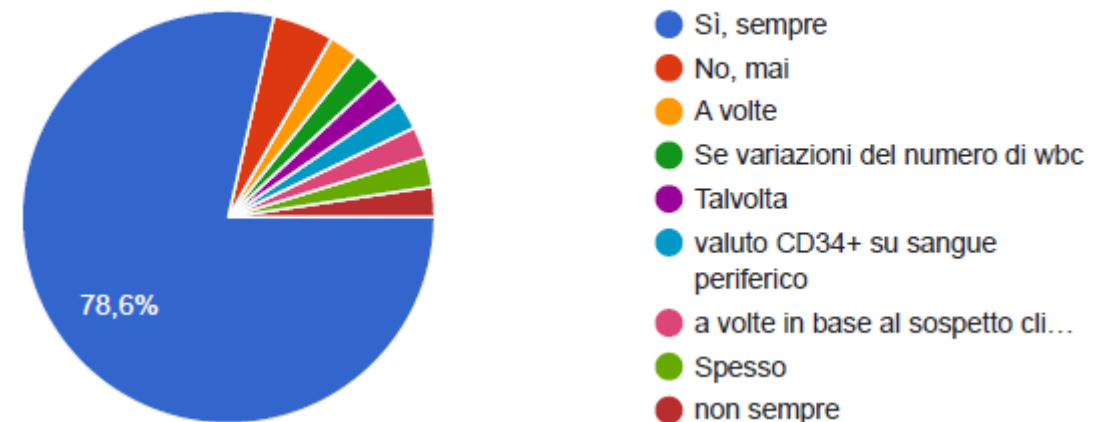
CLASSIFICAZIONE WHO/ICC 2022: CRITERI MINORI PER LA DIAGNOSI

Alla diagnosi, come definisci una splenomegalia significativa alla palpazione?



100% **eco addome**
come esame di
scelta

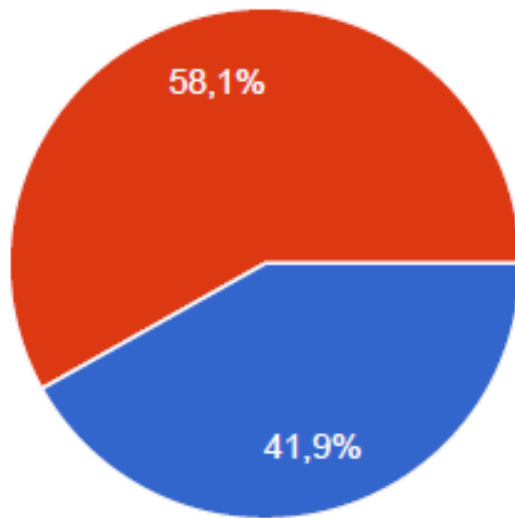
Eseguì sempre lo striscio al microscopio ottico?



CLASSIFICAZIONE WHO/ICC: CRITERI MAGGIORI PER LA DIAGNOSI

MUTAZIONI DRIVER ALLA DIAGNOSI

Esegui sempre la ricerca delle mutazioni driver?



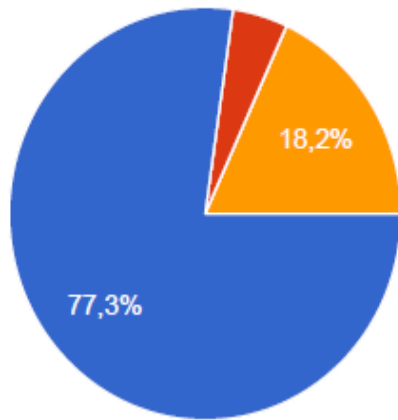
- Sì, tutte e 3
- Sì, partendo da JAK2 e, solo in caso di negatività, procedendo con CALR e MPL
- No, non sempre

Pro e contro

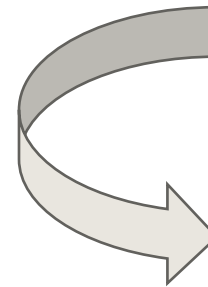
- ☐ Problematiche organizzative: tempi di refertazione
- ☐ Costi
- ☐ Identificazione dei co-mutati e quindi della vera «principale» mutazione driver

MUTAZIONI DRIVER ALLA DIAGNOSI

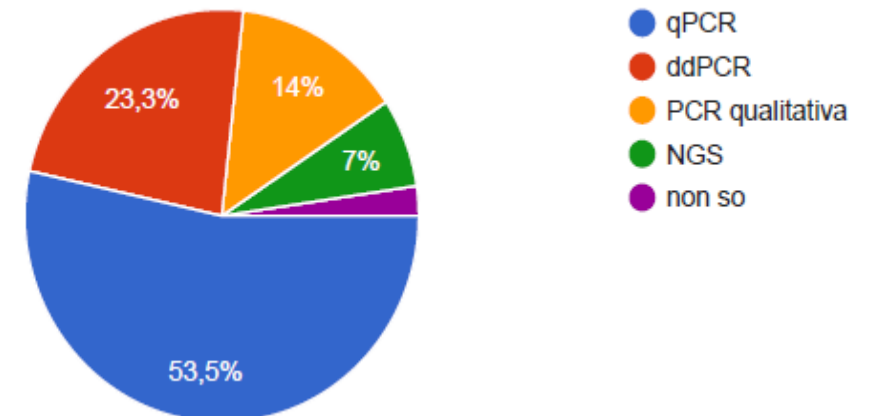
Che tipo di metodica usi per ricercare la mutazione
JAK2 V617F?



- Quantitativa (risultato espresso in termini di VAF)
- Semiquantitativa (risultato espresso come > o < rispetto ad una certa soglia, es. 50%)
- Qualitativa (risultato espresso come presente/assente)



Quale metodica quantitativa?



PMF: mutazioni driver e criteri per la diagnosi

*Adapted from Arber, *et al.*, *Blood* 2022

Table 3: Diagnostic criteria for primary myelofibrosis according to the 2022 International Consensus Classification of hematological neoplasms [1].

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for <i>BCR::ABL1</i>-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • Lactate dehydrogenase level above the reference range	Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, <i>BCR-ABL1</i>-positive CML, myelodysplastic syndrome, or other myeloid neoplasms are not met Minor criteria: • Anemia not attributed to a comorbid condition • Leukocytosis $\geq 11 \times 10^9/L$ • Palpable splenomegaly • Lactate dehydrogenase level above the reference range • Leukoerythroblastosis
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in two consecutive determinations	

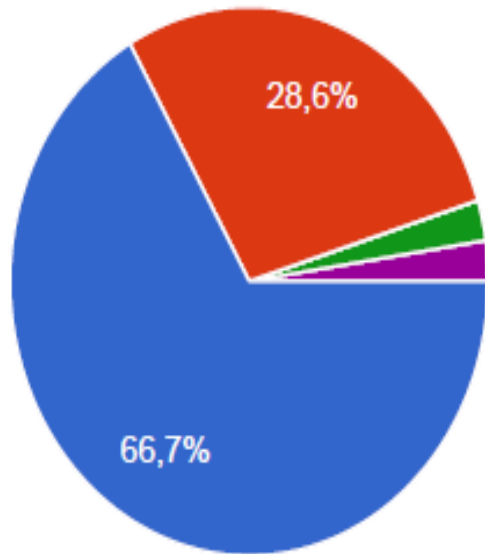
PMF: Primary Myelofibrosis; CML: Chronic Myeloid Leukemia; PV: Polycythemia Vera; ET: Essential Thrombocytopenia.

† It is recommended that highly sensitive assays are used for *JAK2* V617F (sensitivity level < 1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations

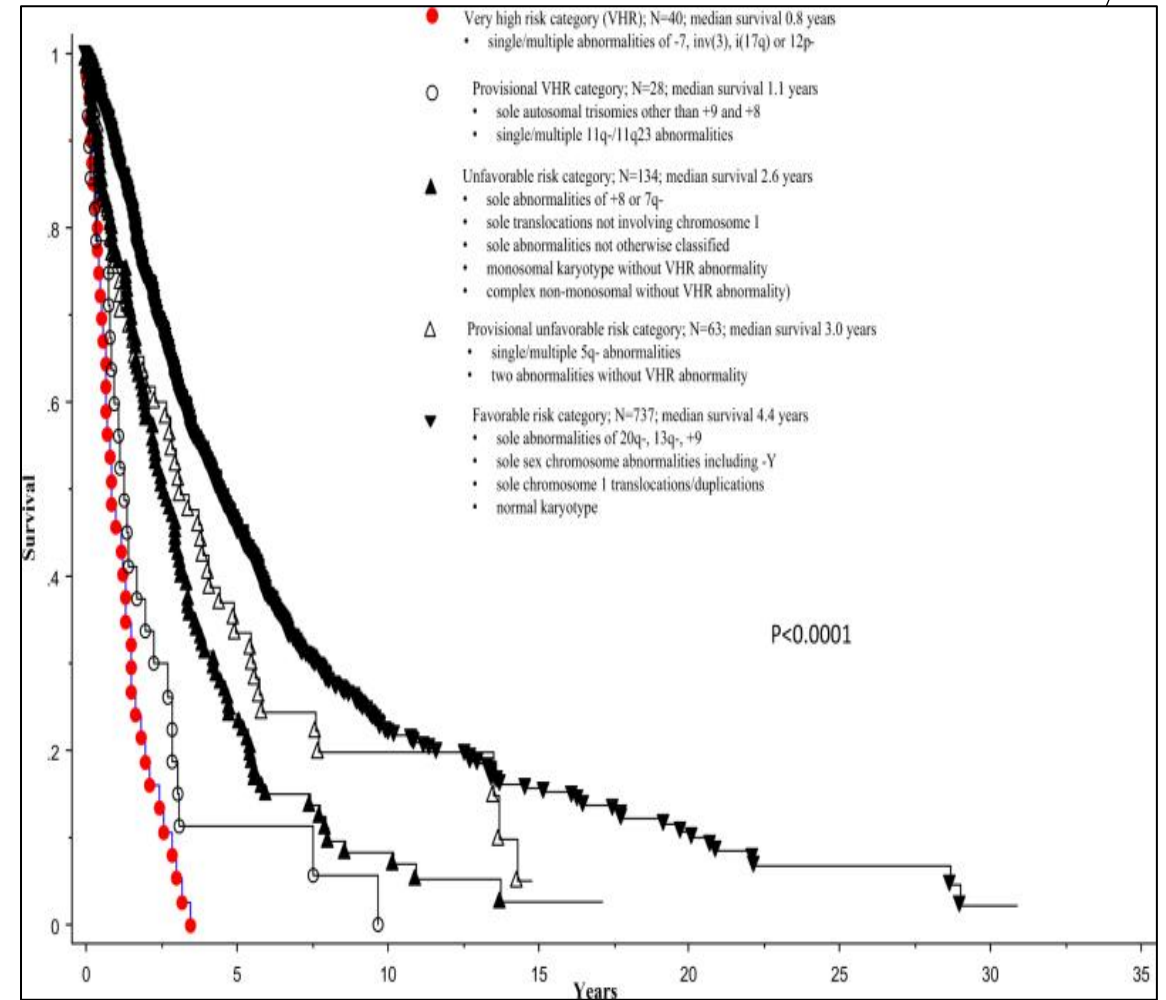
CLASSIFICAZIONE WHO/ICC: CRITERI MAGGIORI PER LA DIAGNOSI

CARIOTIPO ALLA DIAGNOSI

Esegui sempre l'analisi del cariotipo?



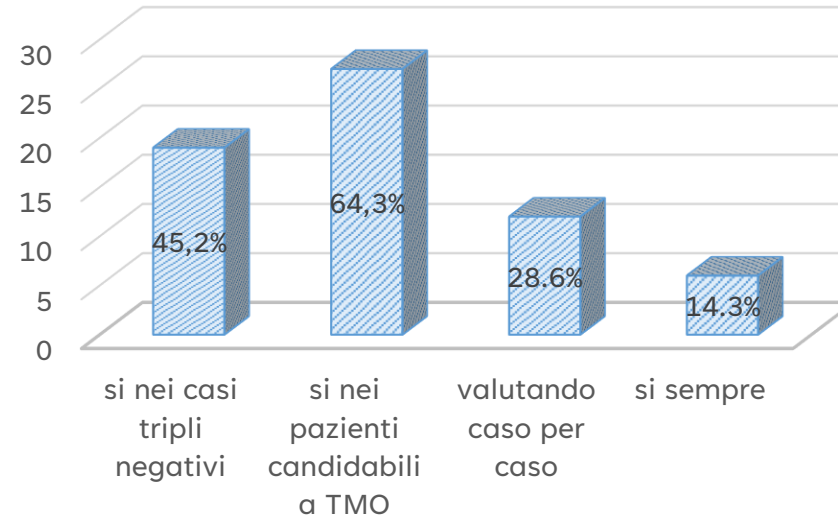
- Si, sempre
- Solo nei pazienti potenzialmente candidabili a trapianto
- No, mai
- nei pazienti candidati ad allogenico ed in generale nei pazienti <60 aa
- Nei pazienti fit candidabili a terapia



Revised cytogenetic risk stratification for primary myelofibrosis (Tefferi 2018)

NGS ALLA DIAGNOSI

Esegui sempre NGS alla diagnosi o a chi?



‡ Assessed by **cytogenetics or sensitive next-generation techniques**; detection of mutations associated with myeloid neoplasms (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2 and TET2 mutations) supports the clonal nature of the disease.

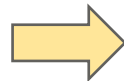


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The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in two consecutive determinations	

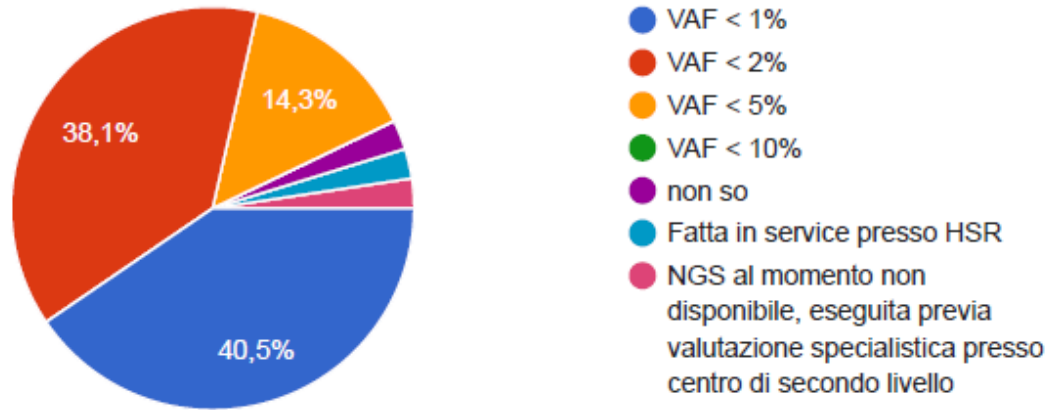
PMF: Primary Myelofibrosis; CML: Chronic Myeloid Leukemia; PV: Polycythemia Vera; ET: Essential Thrombocytopenia.

*Adapted from Arber, *et al.*, *Blood* 2022

CLASSIFICAZIONE WHO/ICC: CRITERI MAGGIORI PER LA DIAGNOSI

NGS ALLA DIAGNOSI

Sensibilità ha la metodica di NGS che usi?



	Pre-PMF
Major criteria	Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
	JAK2, CALR, or MPL mutation ⁽¹⁾ or presence of another clonal marker ⁽²⁾ or absence of reactive bone marrow reticulin fibrosis ⁽³⁾
	Diagnostic criteria for BCR::ABL1 positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met
Minor criteria	Anemia not attributed to a comorbid condition
	Leukocytosis $\geq 11 \times 10^9/L$
	Palpable splenomegaly
	Lactate dehydrogenase level above the reference range

- The diagnosis of pre-PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations

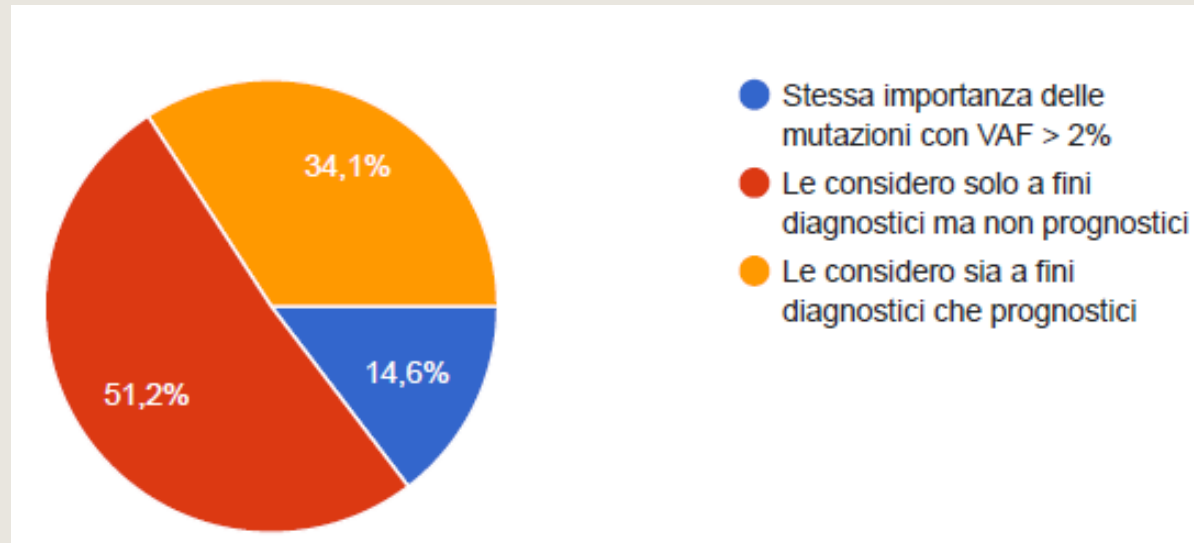
(1) It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level <1%) and CALR and MPL (sensitivity level 1–3%) — in negative cases, consider searching for non-canonical JAK2 and MPL mutations

(2) Assessed by cytogenetics or sensitive NGS techniques; detection of mutations associated with myeloid neoplasms (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations) supports the clonal nature of the disease

(3) Minimal reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies

NGS ALLA DIAGNOSI

Che peso dai alle mutazioni riscontrate in NGS VAF < 2%?

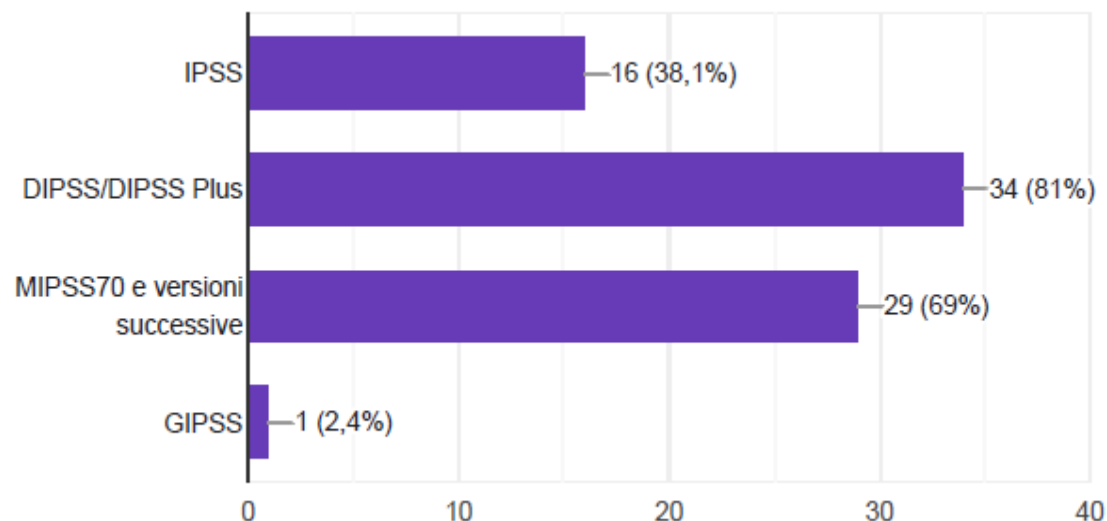


- ❑ Non tutte le mutazioni riscontrate hanno lo stesso valore e significato alla diagnosi (ex DNMT3A vs ASXL1 o TP53) per il rischio prognostico associato
- ❑ Mutazioni HRM a bassa VAF se isolate e condizionante unico aspetto biologico sfavorevole del paziente non si traducono nell'immediato in una decisione terapeutica attiva, ma si opta per monitoraggio nel tempo per intercettare variazioni
- ❑ NGS ripetuto nel tempo (annualmente?) per identificare evoluzione clonale e eventuale comparsa di mutazioni HMR che impattino sulla stratificazione del rischio del pz

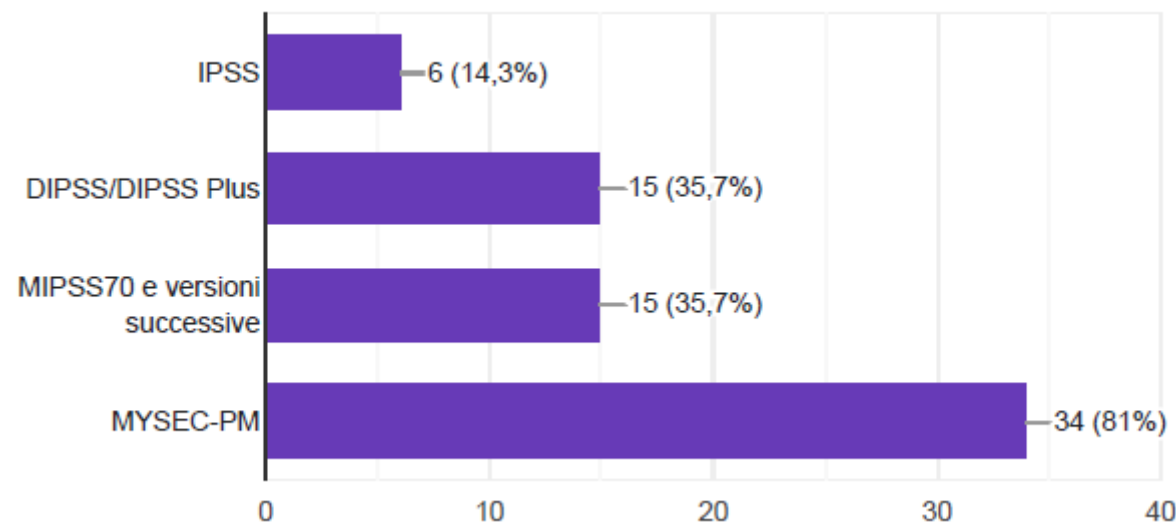
STRATIFICAZIONE PROGNOSTICA

Quale score utilizzi maggiormente per stratificare la MF primaria e secondaria nella pratica clinica?

MIELOFIBROSI PRIMARIA



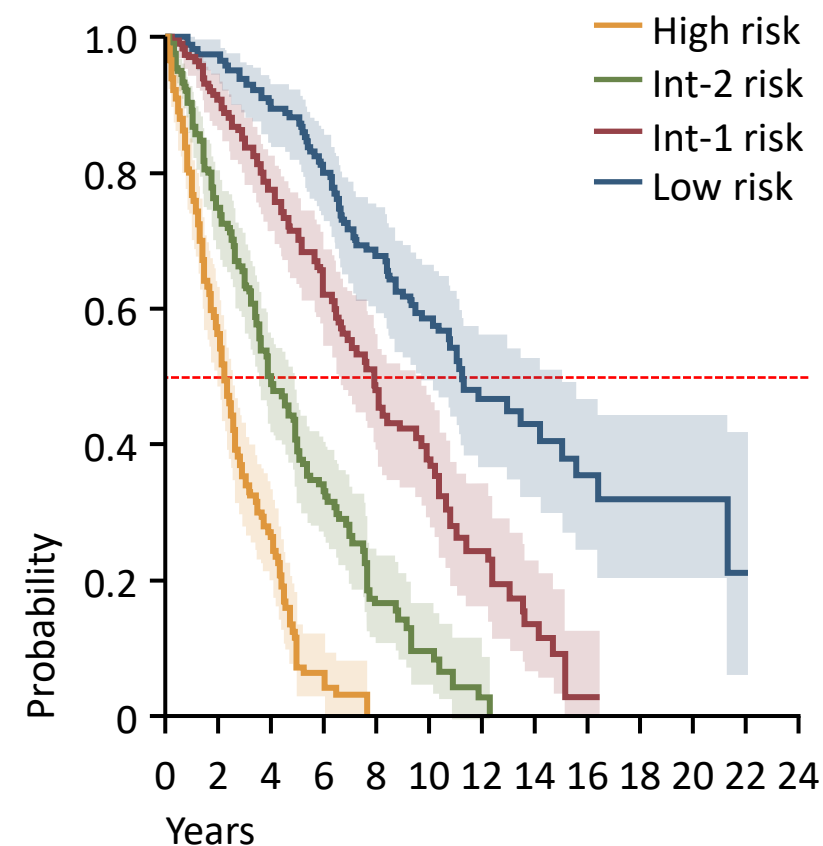
MIELOFIBROSI SECONDARIA



MODELLI PROGNOSTICI CLASSICI IN PMF

Variable	IPSS ¹	DIPSS ²	DIPSS-plus ³
Age >65 years	✓	✓	✓
Constitutional symptoms	✓	✓	✓
Hemoglobin <10 g/dL	✓	✓	✓
Leukocyte count >25×10 ⁹ /L	✓	✓	✓
Circulating blasts ≥1%	✓	✓	✓
Platelet count <100×10 ⁹ /L			✓
RBC transfusion need			✓
Unfavorable karyotype +8,-7/7q-, i(17q), inv(3), -5/5q-, 12p-, 11q23 rearr.			✓
Scoring system	1 point each	1 point each but Hb=2	1 point each
Risk categories			
Low risk	0	0	0
Intermediate-1 risk	1	1–2	1
Intermediate-2 risk	2	3–4	2–3
High risk	≥3	5–6	4–6

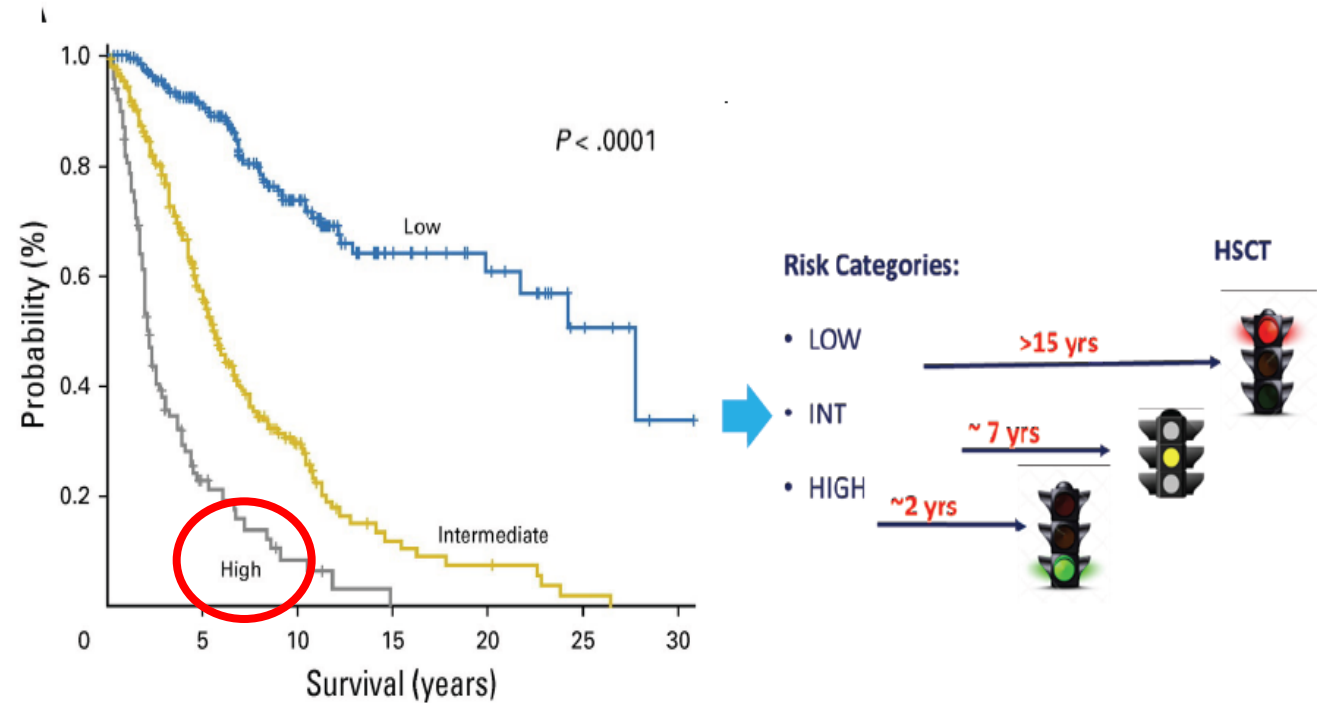
Actuarial survival curves of the 4 risk groups of patients according to IPSS^{1*}



MIPSS70: mutation enhanced prognostic score system for transplant-age patients PMF

Variables	Weighted value
Hb <100g/L	1
WBC >25x10 ⁹ /L	
PLT <100x10 ⁹ /L	2
PB blasts ≥2%	
Constitutional Symptoms	1
Grade ≥2 BM fibrosis	
Absence CALR Type1	1
HMR category*	
≥2 HMR mutations	2

Risk category	Score	OS (y)	HR
Low	0-1	27.7	1
Intermediate	2-4	7.1	5.5(3.8-8.0)
High	>5	2.3	16.0(10.2-25.1)



*HMR category= any mutation in: ASXL1, EZH2, SRSF2, IDH1/2, U2AF1 Q157

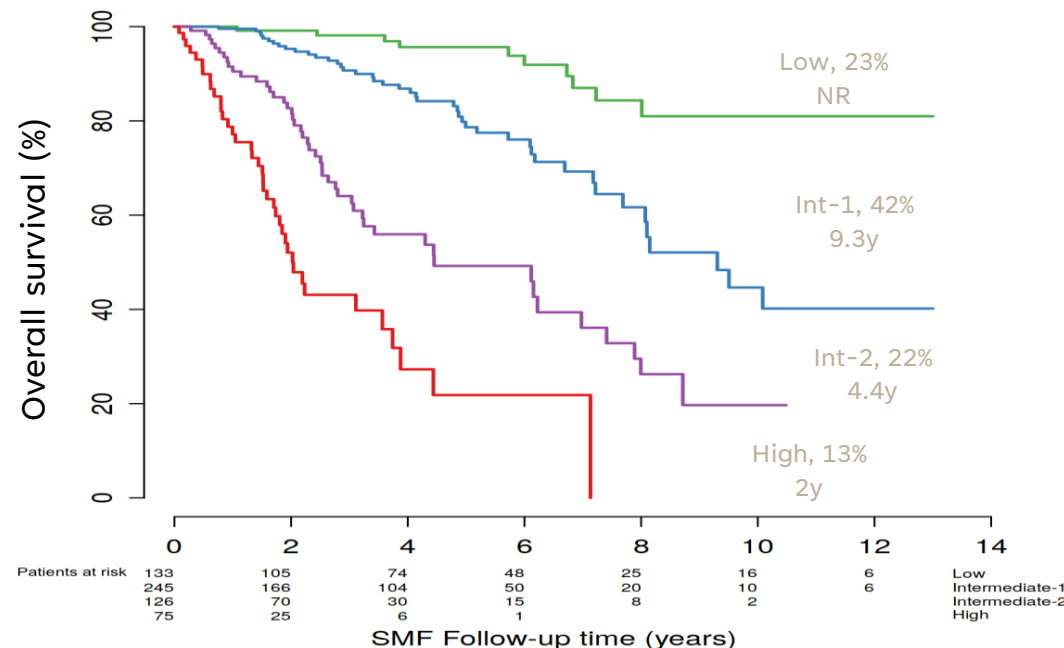
Learning cohort: Italian cohort

Version 2.0

The higher categories included 30% of patients originally classified as low or intermediate IPSS risk; conversely, 6 patients (3.5%) included in intermediate-2 IPSS group were downgraded to the lowest risk categories of MIPSS70

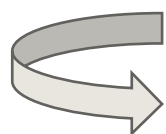
The integrated MYSEC-PM for post PV and post ET MF

LR: < 11
Int-1: 11-14
Int-2: 14-16
HIGH: ≥ 16



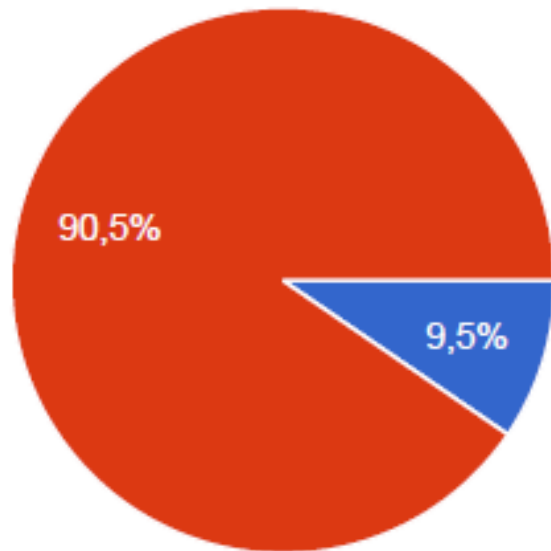
Covariates	Points
Age, years	0.15
Hb <11 g/dL	2
PLT <150 x10 ⁹ /L	1
Circulating blasts ≥3%	2
Constitutional symptoms	1
CALR-unmutated genotype	2

- MYSEC-PM was validated in Spain
- DIPSS-plus outperformed MYSEC-PM in a Japan, with higher C-index



- ❑ U2AF1, TP53 or SRSF2 (UTS) and ASXL1 variants without UTS confer worse overall survival in SMF, as well as complex/monosomal karyotype
- ❑ Models integrating molecular (**MYSEC-mPM**) and karyotype/molecular data (**MYSEC-kmPM**) outperform the MYSEC-PM prediction of survival in SMF

COME TI COMPORTI IN CASO DI DISCREPANZA TRA SCORE CLINICI (ES. IPSS/DIPSS) E SCORE CON DATI CLINICI-GENETICI INTEGRATI (ES. MIPSS 70)?



- Ritengo più attendibili i risultati degli score clinici
- Ritengo più attendibili i risultati degli score contenuti dati integrati (clinici, citogenetici e di biologia molecolare)

Considerazioni:

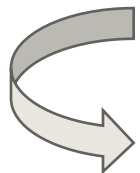
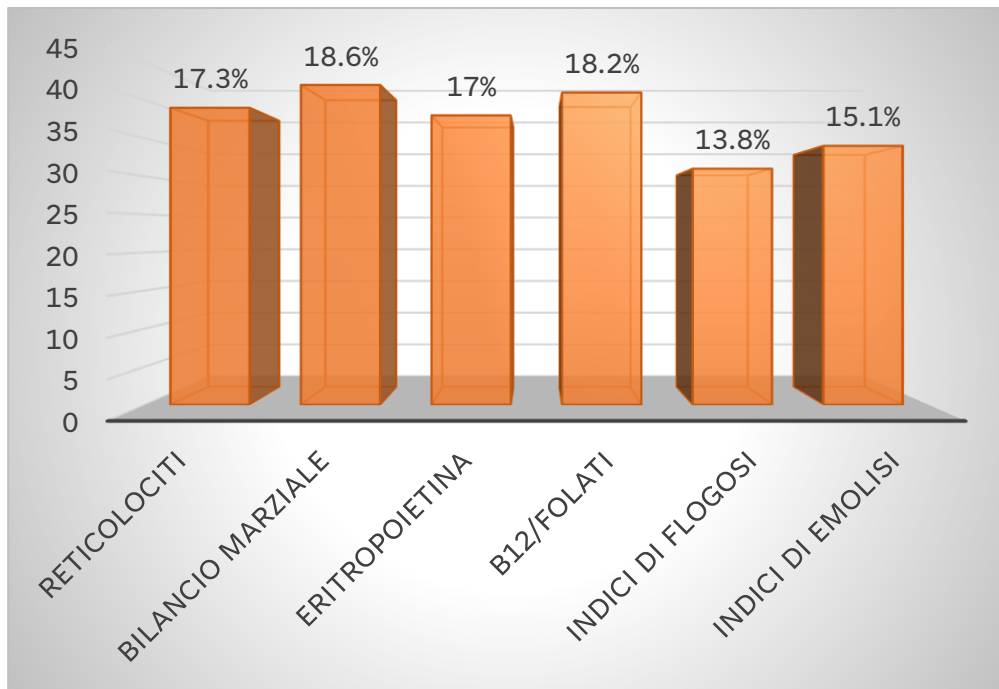
- ❑ Paziente e medico spesso hanno diversa percezione della malattia
- ❑ score integrato >> early intervention



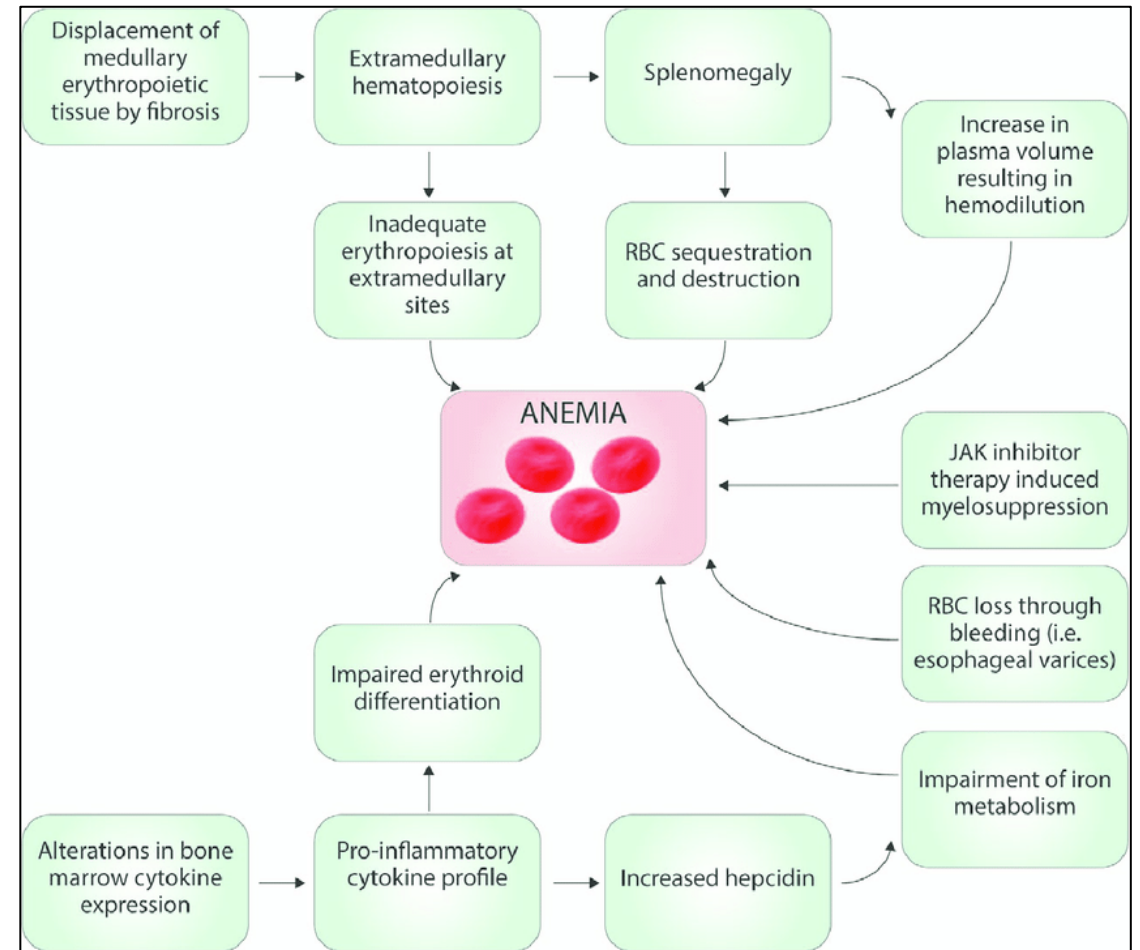
**ANEMIA:
INQUADRAMENTO
DIAGNOSI E PROGNOSI**

ANEMIA: QUALI ESAMI PER INQUADRAMENTO

In un paziente con mielofibrosi, quali esami richiedi per l'inquadramento dell'anemia?

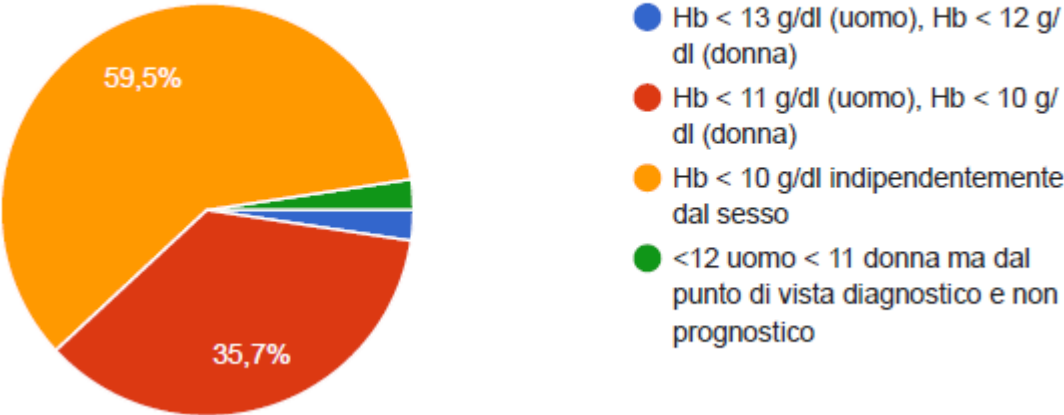


ANEMIA nella mielofibrosi ha cause multifattoriali



ANEMIA: DEFINIZIONE E INQUADRAMENTO

Qual è il valore soglia che ritieni clinicamente rilevante nel definire l'anemia in un paziente con mielofibrosi?



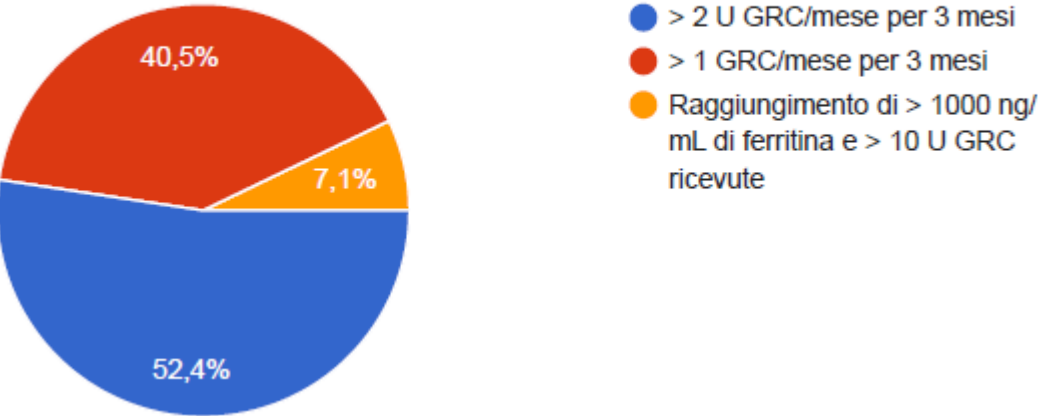
Proposals for revised International Working Group– European LeukemiaNet criteria for anemia response in myelofibrosis (Tefferi, Blood 2024)

Table 3. Proposals for revised IWG-ELN response criteria for anemia in MF

	2013 IWG-ELN criteria	2024 proposed IWG-ELN criteria
Definitions		
Hgb cutoffs for clinical trial inclusion or response adjudication	<10 g/dL	Men <11 g/dL*,† Women <10 g/dL*
TDA	≥6 units in the 12 wk before enrollment‡ (only transfusions for Hb <8.5 g/dL are counted)	≥3 units in the 12 wk before enrollment‡,§ (high transfusion burden defined as ≥6 units in the 12 wk before enrollment)
Baseline Hgb for TDA	Not clearly defined	Average of pretransfusion Hb levels in the 12 wk before enrollment/first dose§
Non-TDA	Not meeting criteria for TDA	Not meeting criteria for TDA
Baseline Hb for non-TDA	Hb level at time of screening	Average of the lowest 3 Hb levels in the 12 wk before enrollment/first dose, including one obtained in the 28 d before enrollment/first dose§,
Anemia response criteria		
Major response for TDA	No transfusions during any rolling 12-wk period + a documented Hb level of ≥8.5 g/dL	No transfusions × 12 wk¶ and rolling 12-wk average Hb increase of ≥1.5 g/dL from pretreatment baseline
Major response for non-TDA	Rolling 12-wk average Hb increase of ≥2.0 g/dL from pretreatment baseline#	Rolling 12-wk average Hb increase of ≥1.5 g/dL from pretreatment baseline (also requires no transfusions)
Minor response for TDA	Not included	A ≥50% reduction in transfusions** (and not meeting criteria for major response)
Minor response for non-TDA	Not included	Rolling 12-wk average Hb increase of ≥1.0 g/dL from pretreatment baseline** (also requires no transfusions and not meeting criteria for major response)
Loss of response	Loss of anemia response persisting for ≥1 mo	No longer meeting criteria for even minor response††
Duration of anemia response	Not defined	Interval between first time point of response to first time point of loss of response
Progressive anemia	Not defined	TDA: ≥50% increase in transfusion requirement** Non-TDA: Hb decrease of >1.5 g/dL from baseline or meeting criteria for TDA**
Stable anemia	Not defined	Not meeting criteria for response or progression

DEFINIZIONE SEVERITA' ANEMIA

Come definisci un paziente con anemia trasfusione dipendente?



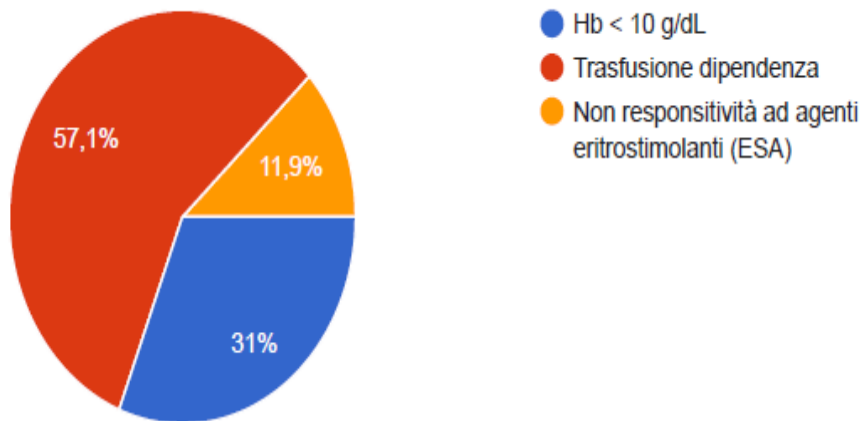
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Baseline Hgb for TDA	Not clearly defined	Average of pretransfusion Hb levels in the 12 wk before enrollment/first dose§
Non-TDA	Not meeting criteria for TDA	Not meeting criteria for TDA
Baseline Hb for non-TDA	Hb level at time of screening	Average of the lowest 3 Hb levels in the 12 wk before enrollment/first dose, including one obtained in the 28 d before enrollment/first dose§,
Anemia response criteria		
Major response for TDA	No transfusions during any rolling 12-wk period + a documented Hb level of ≥8.5 g/dL	No transfusions × 12 wk¶ and rolling 12-wk average Hb increase of ≥1.5 g/dL from pretreatment baseline
Major response for non-TDA	Rolling 12-wk average Hb increase of ≥2.0 g/dL from pretreatment baseline#	Rolling 12-wk average Hb increase of ≥1.5 g/dL from pretreatment baseline (also requires no transfusions)
Minor response for TDA	Not included	A ≥50% reduction in transfusions** (and not meeting criteria for major response)
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Loss of response	Loss of anemia response persisting for ≥1 mo	No longer meeting criteria for even minor response††
Duration of anemia response	Not defined	Interval between first time point of response to first time point of loss of response
Progressive anemia	Not defined	TDA: ≥50% increase in transfusion requirement** Non-TDA: Hb decrease of >1.5 g/dL from baseline or meeting criteria for TDA**
Stable anemia	Not defined	Not meeting criteria for response or progression

DEFINIZIONE SEVERITA' ANEMIA

Quale criterio usi maggiormente per identificare l'anemia ad alto rischio nel paziente con mielofibrosi?

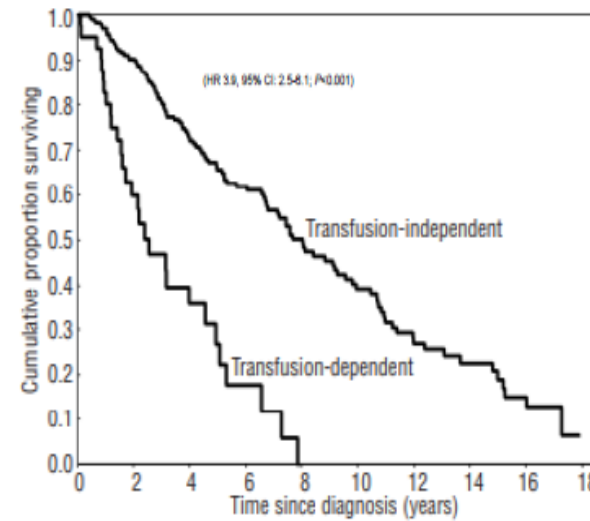


Transfusion dependency is associated with reduced OS in MF

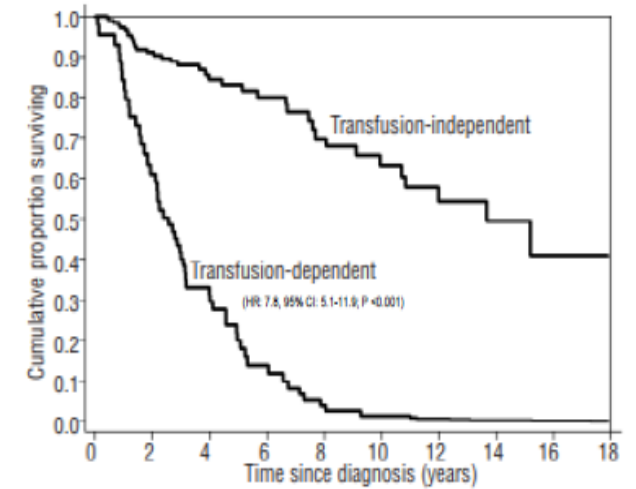
An analysis of 288 patients with primary MF demonstrated:

- TD of patients *at diagnosis* significantly affects survival (median survival 2.6 years), compared to patients who did not receive transfusions at diagnosis (median survival 8 years)
- TD of patients occurring *at any time* was also associated with worse survival, compared with patients who remained transfusion independent during follow-up

OS according to RBC-TD at time of diagnosis in 288 patients with primary MF

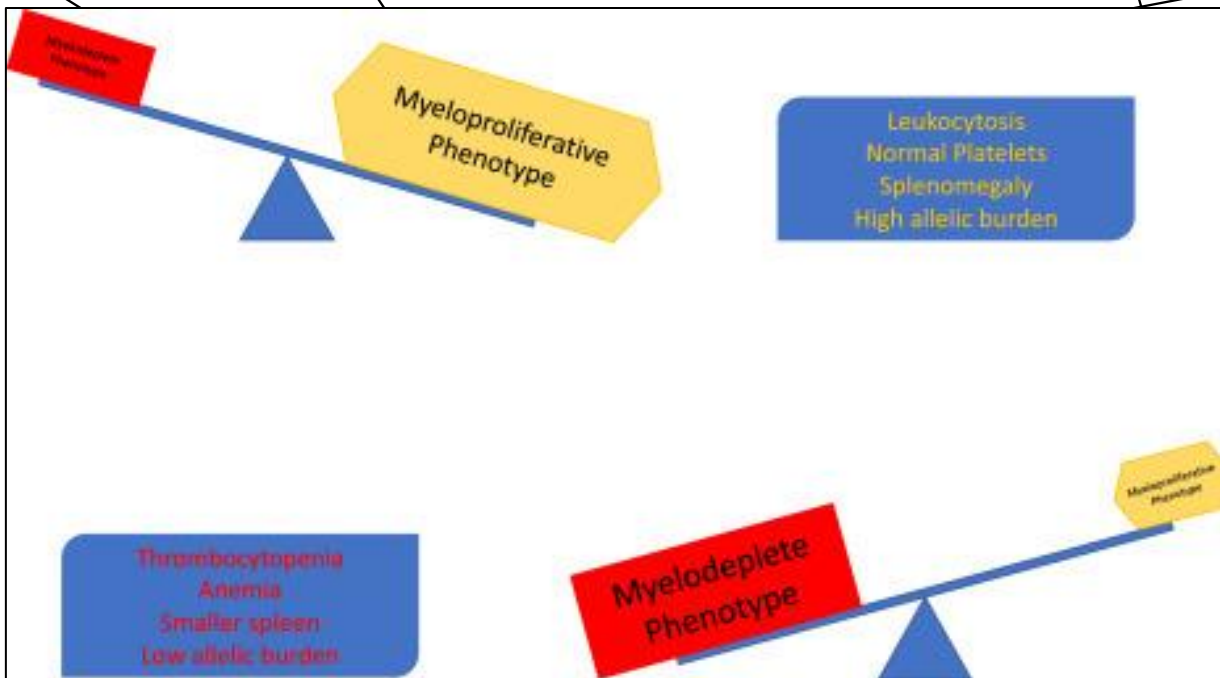
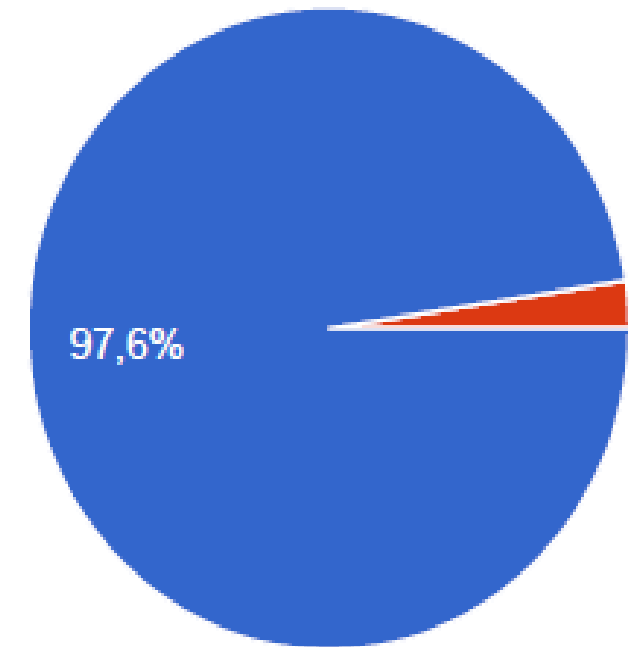


OS according to RBC-TD assessed as a time-dependent variable in 220 regularly followed patients with primary MF



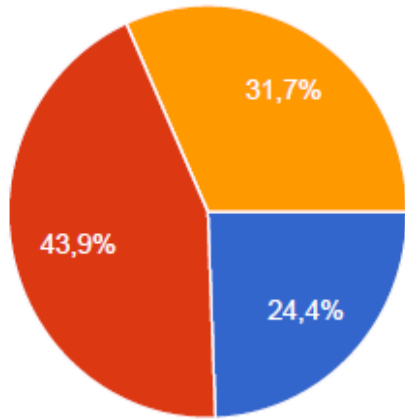
ANEMIA E FIBROSI

Secondo la tua esperienza clinica, ritieni che il grado di fibrosi midollare (grado 1, 2 o 3) abbia un impatto sull'incidenza o gravità dell'anemia nei pazienti con mielofibrosi?



ANEMIA E IMPATTO MUTAZIONI DRIVER

Ritieni che il tipo di mutazione driver abbia un impatto sull'anemia nei pazienti con mielofibrosi?

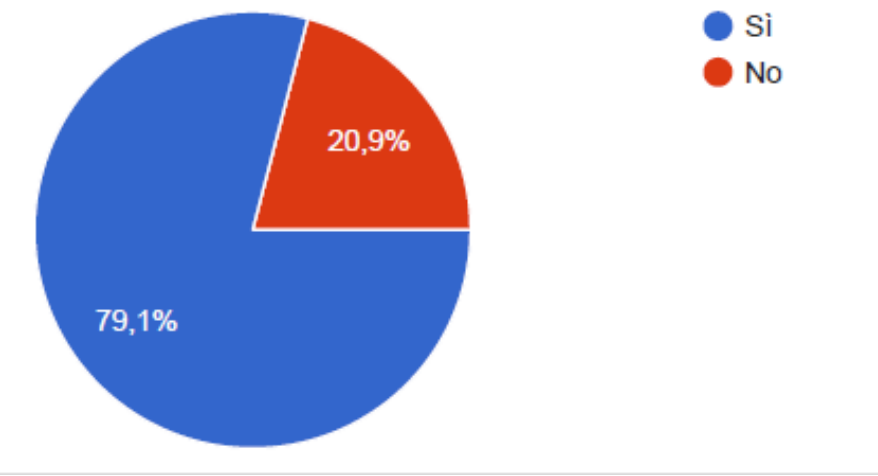


- Sì, alcune mutazioni si associano a minor incidenza/gravità di anemia
- Sì, alcune mutazioni si associano a maggior incidenza/gravità di anemia
- No, non ho mai notato alcuna correlazione

- ❑ **CALR:** pazienti con mutazione CALR tipo 1 si associa a prognosi migliore, ma spesso livelli Hb inferiori rispetto ai pazienti con mutazione JAK2.
- ❑ **JAK2V617F:** Un basso burden allelico (> 25%) di questa mutazione può indicare un fenotipo di malattia più aggressivo, associato a un maggiore rischio di anemia/citopenie
- ❑ Mutazione del gene **MPL** è spesso associata a un fenotipo anemico più marcato rispetto ad altre mutazioni driver nella mielofibrosi

ANEMIA E IMPATTO MUTAZIONI SUBCLONALI

Secondo la tua esperienza, ritieni che vi siano alcune mutazioni subclonali (non driver) in grado di influenzare l'incidenza e la severità dell'anemia nel paziente con mielofibrosi?

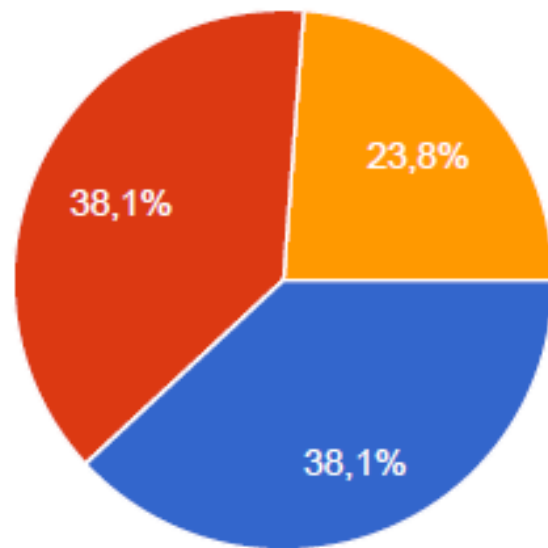


Mutazione	Impatto sull'Anemia	Rischio Prognostico
U2AF1	Molto Alto (spesso trasfusione-dipendente)	Elevato
SRSF2	Alto (anemia moderata-grave)	Elevato (HMR)
SF3B1	Specifico (inefficienza produzione globuli rossi)	Variabile
ASXL1	Significativo (associato a fibrosi progressiva)	Elevato (HMR)

U2AF1 associates with cytopenias and clusters with JAK2

Variables	All patients (n=250)	U2AF1 mutated (n=40)	U2AF1 wild-type (n=210)	P value
Constitutional symptoms; n (%)	86 (34.4)	18 (45)	68 (32.4)	0.12
Circulating blasts $\geq 1\%$; n (%)	143 (57.2)	14 (35)	115 (54.8)	0.07
Hemoglobin < 10 g/dl; n (%)	118 (47.2)	34 (85)	84 (40)	<0.0001
Transfusion requiring; n (%)	79 (31.6)	28 (70)	51 (24.3)	<0.0001
Leukocytes $> 25 \times 10^9/l$; n (%)	40 (16)	8 (20)	32 (15.2)	0.45
Leukocytes $< 4 \times 10^9/l$; n (%)	34 (13.6)	5 (12.5)	29 (13.8)	0.82
Platelets $< 100 \times 10^9/l$; n (%)	53 (21.2)	22 (55)	35 (16.7)	<0.0001
JAK2V617F-positive; n (%) 'N' evaluable=249	145 (58.2)	32 (80)	113(54.1)	0.002

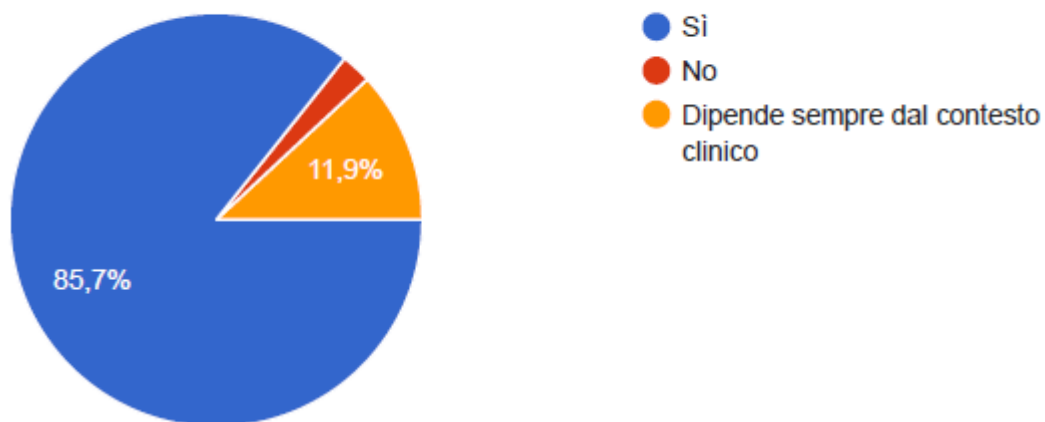
NELLA TUA ESPERIENZA, CHE PESO DAI ALL'ANEMIA IN UN PAZIENTE CON MIELOFIBROSI PRIMARIA RISPETTO AD UN PAZIENTE CON MIELOFIBROSI SECONDARIA?



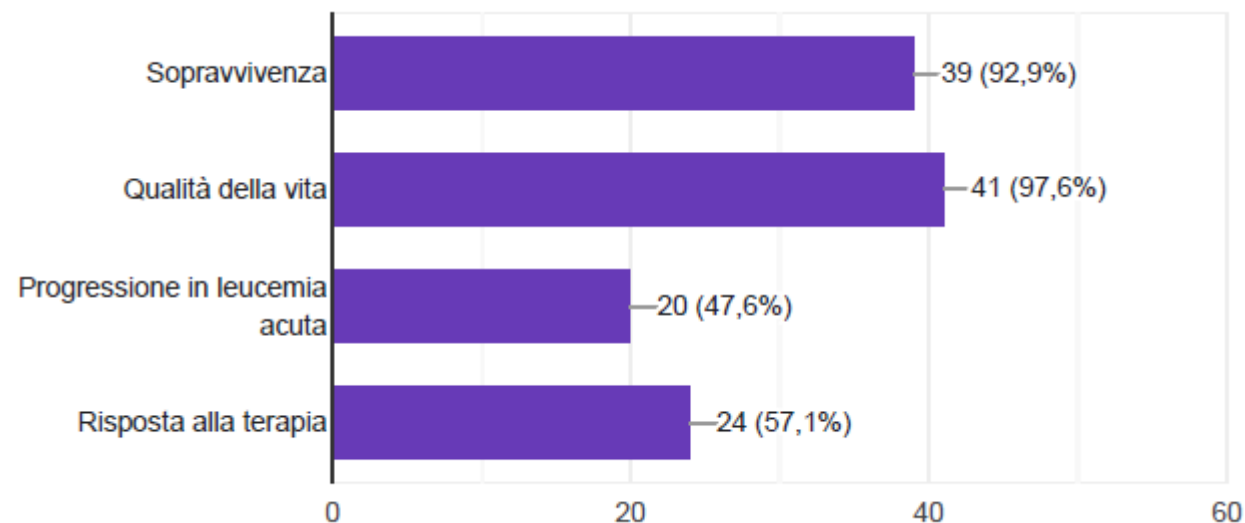
- Penso che l'anemia abbia lo stesso peso nelle forme primarie e secondaria
- Ritengo che l'anemia abbia un peso maggiore nelle forme primarie di mielofibrosi
- Ritengo che l'anemia abbia un peso maggiore nelle forme secondarie di mielofibrosi

RUOLO PROGNOSTICO ANEMIA ALLA DIAGNOSI

Ritieni che il riscontro di anemia alla diagnosi di mielofibrosi rappresenti un fattore di rischio indipendente?



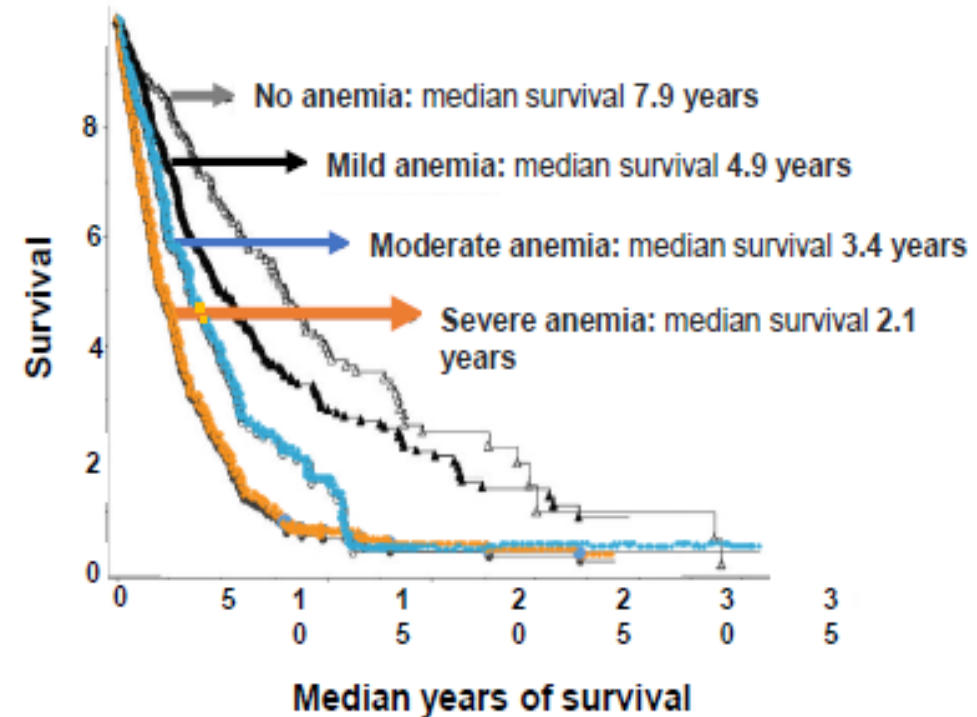
Su quali dei seguenti outcomes ritieni che l'anemia abbia un impatto?(Più risposte possibili)



Severity of anemia directly correlates with reduced survival in MF

Severity of anemia in MF is associated with median survival

Severity of anemia	Median survival, years
No anemia	7.9
Mild	4.9
Moderate	3.4
Severe	2.1

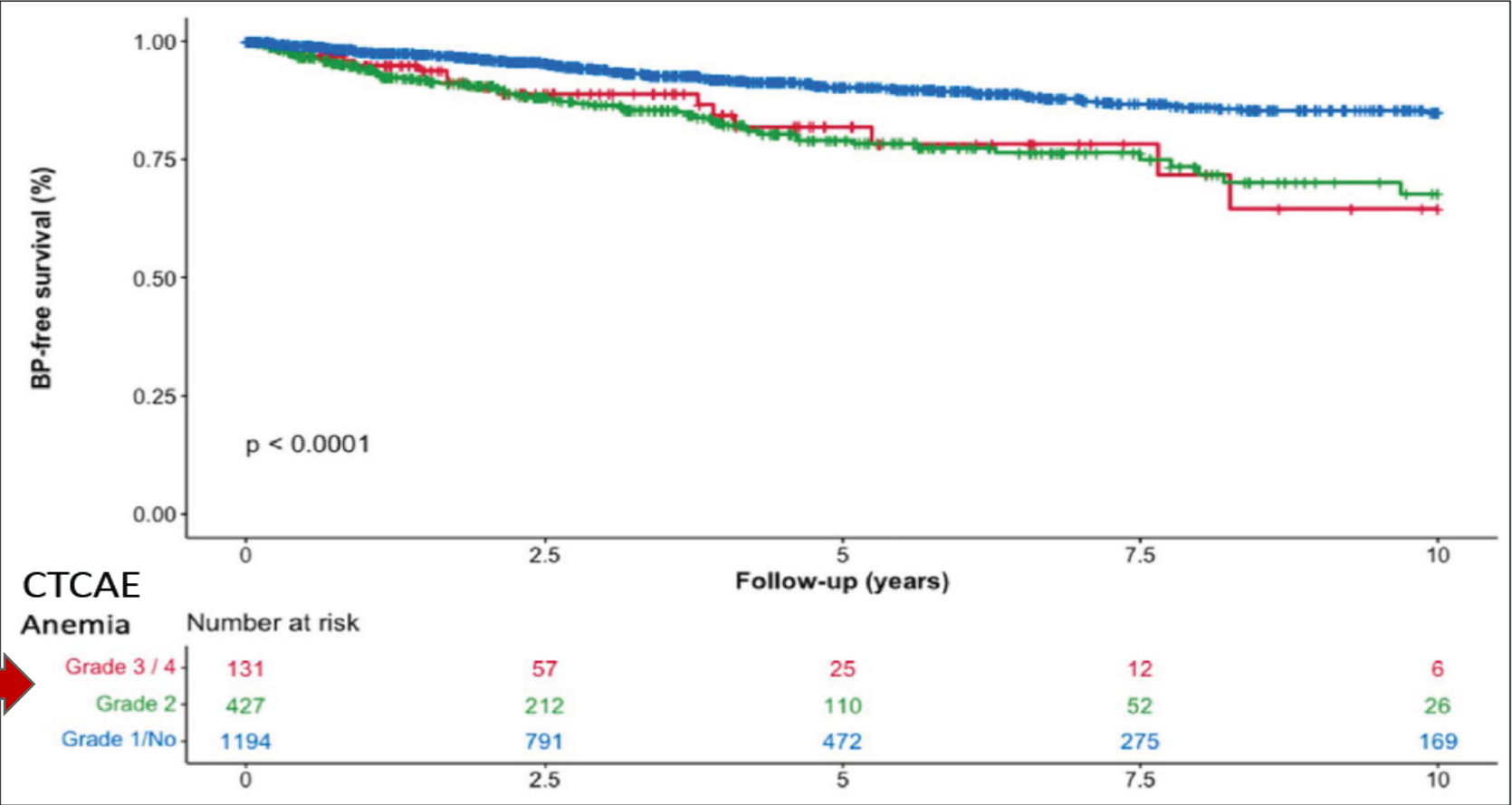


A study of 1109 patients with primary MF at the Mayo Clinic found that all grades of anemia adversely impact survival, with a nearly 4-fold shorter median survival for patients with severe anemia compared to patients with no anemia

Il grado di anemia alla diagnosi impatta sulla sopravvivenza libera da evoluzione leucemica

N= 136 pre-PMF, 638 overt-PMF and 978 SMF

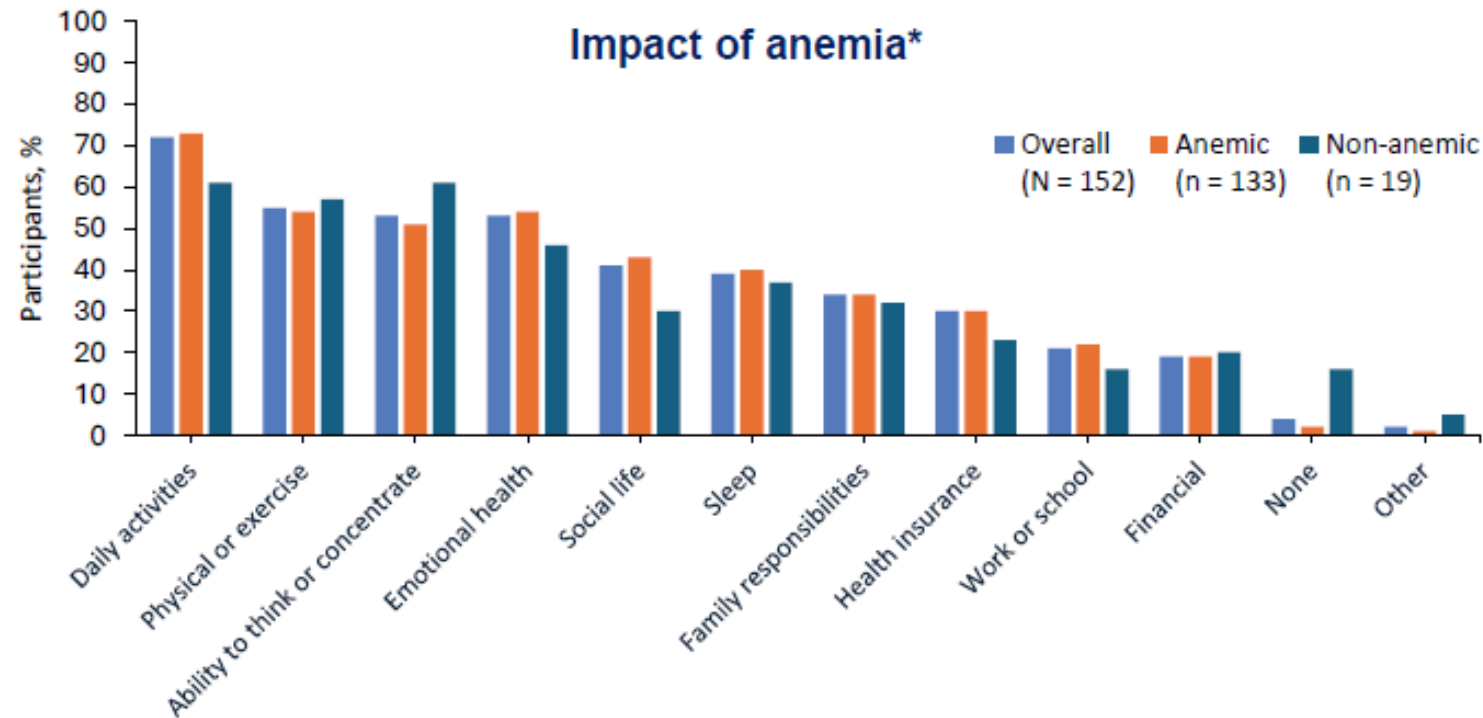
1752 pts



Legend: grade 3/4 anemia= Hb <8 g/dL; grade 2= Hb 8–10 g/dL; grade 1 (Hb >10 g/dL) anemia grouped together with normal Hb values.

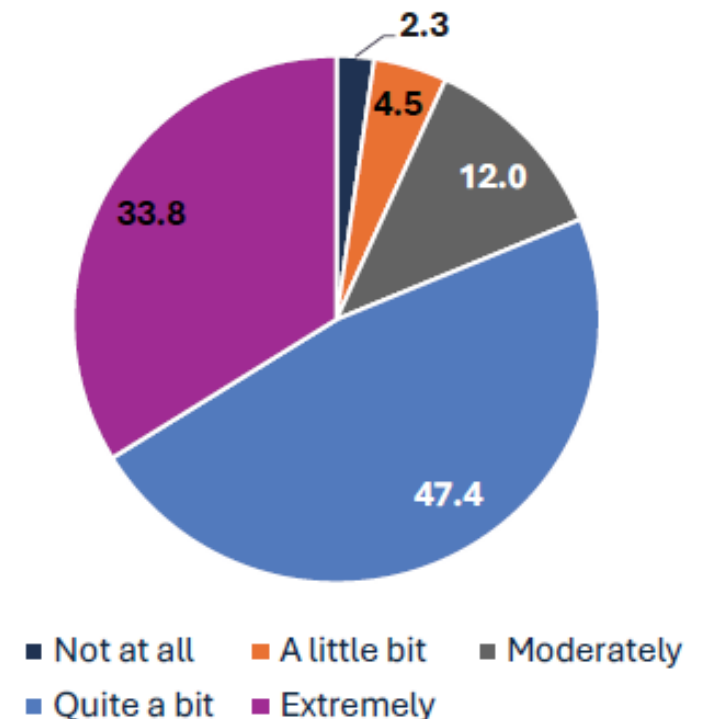
Impact of anemia: QoL

- Patients with MF and anemia view improving anemia as an important treatment outcome
- Anemia and RBC transfusion requirements can negatively impact the QoL of patients with MF.
- A multinational, cross-sectional, online survey study assessed the impact of anemia and RBC transfusion dependence on QoL in 155 patients with symptomatic MF and JAK inhibitor experience.



*Question was posed as experienced impacts for those with anemia and anticipated impacts for those who were non-anemic.

Importance of improving anemia among anemic patients (n = 133)



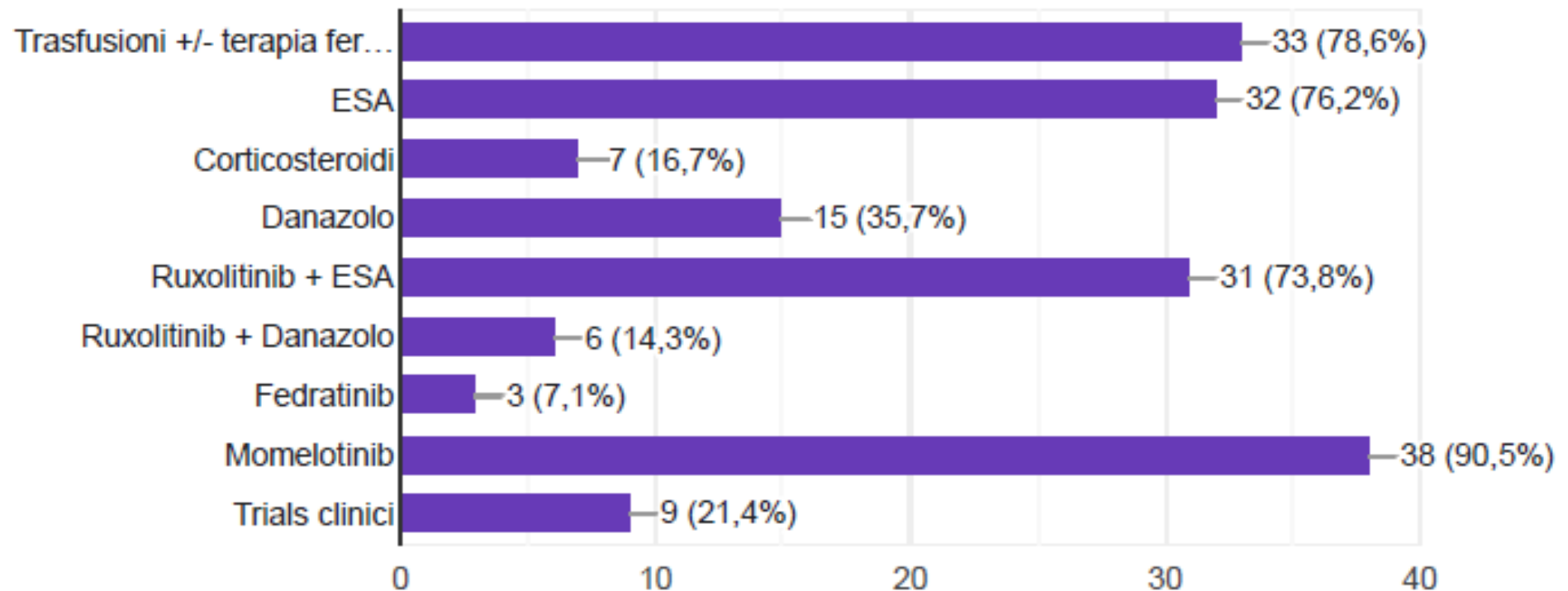
(42 RISPOSTE)



ANEMIA: CRITERI DI SCELTA TERAPIA E IMPATTO SUL TRATTAMENTO

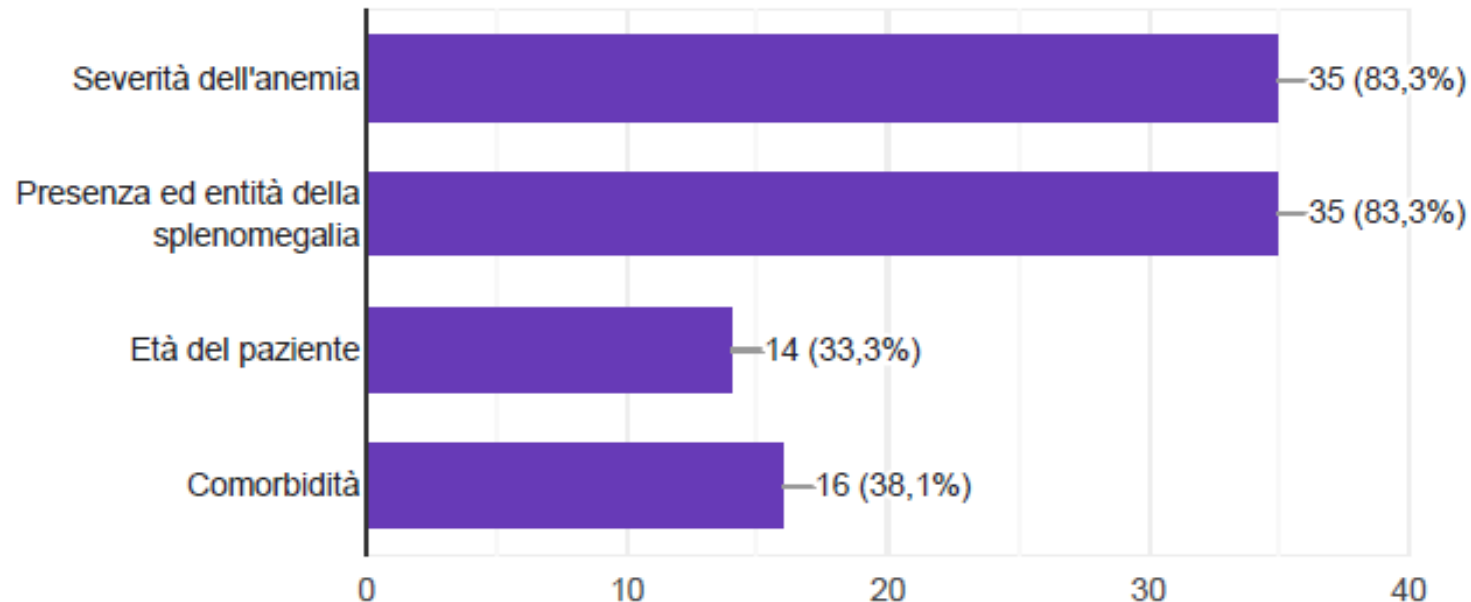
TERAPIE PER ANEMIA: MANAGEMENT

Nella tua pratica clinica, quali approcci utilizzi maggiormente per la gestione dell'anemia nella mielofibrosi?



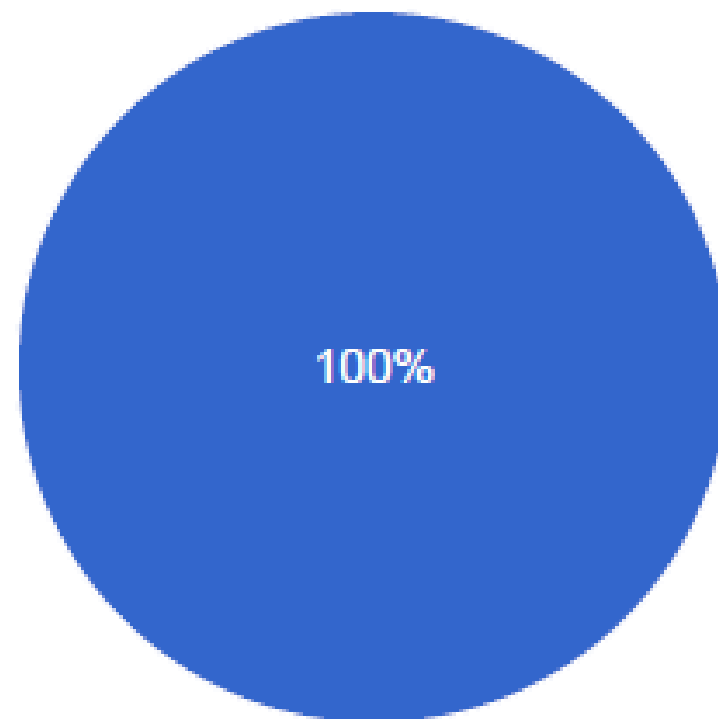
TERAPIE PER ANEMIA: FATTORI DI SCELTA

In un paziente con mielofibrosi e anemia, quali sono i fattori che influenzano maggiormente la tua scelta terapeutica?



IMPATTO TRASFUSIONE INDIPENDENZA

Pensi che il raggiungimento
della trasfusione indipendenza
abbia un impatto sull'outcome?



Biosimilar erythropoiesis-stimulating agents are an effective and safe option for the management of myelofibrosis-related anemia

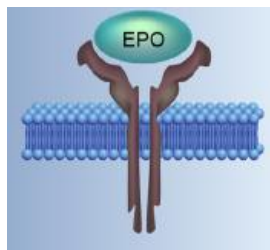
(Inzoli E & Elli EM et al, EJH 2023)

96 pz

Età mediana: 75 anni

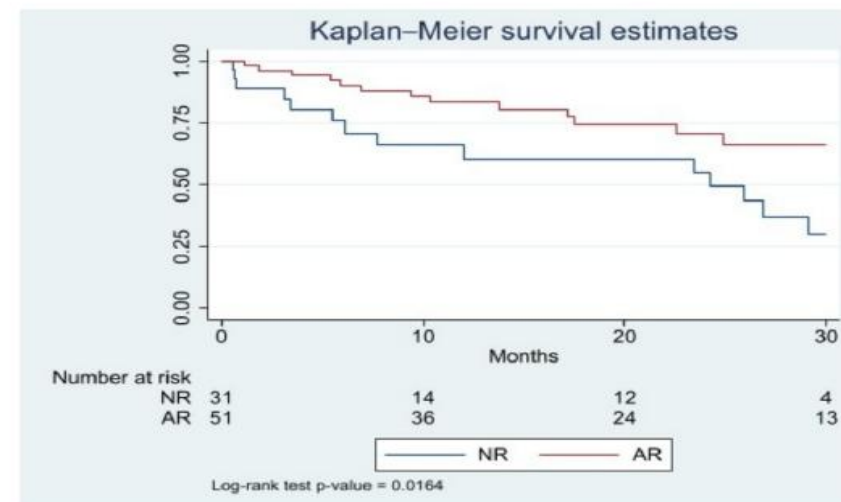
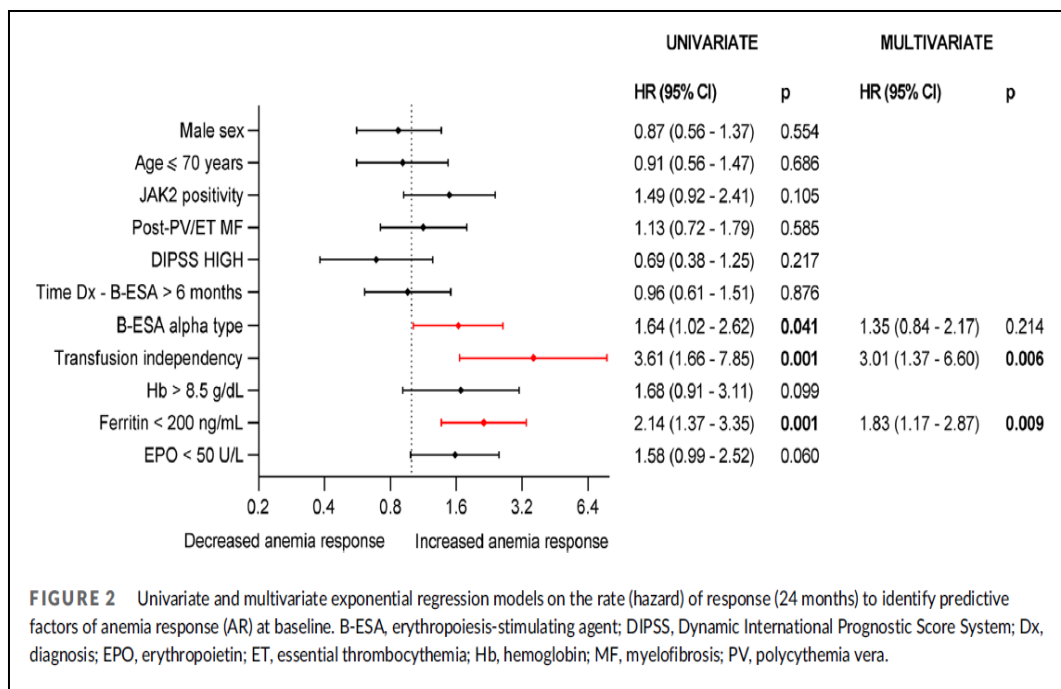
PMF 55%

59% Rux-treated



La risposta correla con outcome

- ❖ RR: 77 pz (80%), CR 67%
- ❖ Pazienti che ottengono una risposta eritroide hanno migliore sopravvivenza



SIMPLIFY-1 / SIMPLIFY-2: EFFICACY

SIMPLIFY-1¹

1st-Line Population
JAKi-naïve

Goal:	Non-Inferiority			
Endpoints at W24:	MMB	RUX		
SVR35 (primary)	26.5%	29.0%	Noninferiority proportion difference 0.09 (95% CI, 0.02-0.16)	$p=0.011$
TSS reduction $\geq 50\%$	28.4%	42.2%	Noninferiority proportion difference 0.00 (95% CI, -0.08-0.08)	$p=0.98$
TI at week 24	66.5%	49.3%	NR ^a	Nominal $p<0.001$
TD at week 24	30.2%	40.1%	NR ^a	Nominal $p=0.019$
Median rate of RBC transfusion through W24	0 units/mo	0.4 units/mo	NR ^a	Nominal $p<0.001$
Patients who achieved ≥ 2 predefined endpoints	38.6%	34.6%	NR ^a	NR ^a
Patients who achieved all 3 predefined endpoints ^b	10.2%	7.8%	NR ^a	NR ^a

^aBecause noninferiority of MMB to RUX on response rate in TSS at week 24 was not met, formal sequential testing was stopped and only nominal significance was reported for the remaining α -controlled secondary end points

^bSSR24, TSS response, or transfusion independence

SIMPLIFY-2²

2nd-Line Population
Prior RUX complicated by hematologic toxicity

Patients were currently or previously treated with RUX for at least 28 days and either: required RBC transfusion on RUX, or required a dose adjustment of RUX to less than 20 mg BID and also had anemia, grade 3 thrombocytopenia, or bleeding at grade 3 or worse when receiving RUX treatment

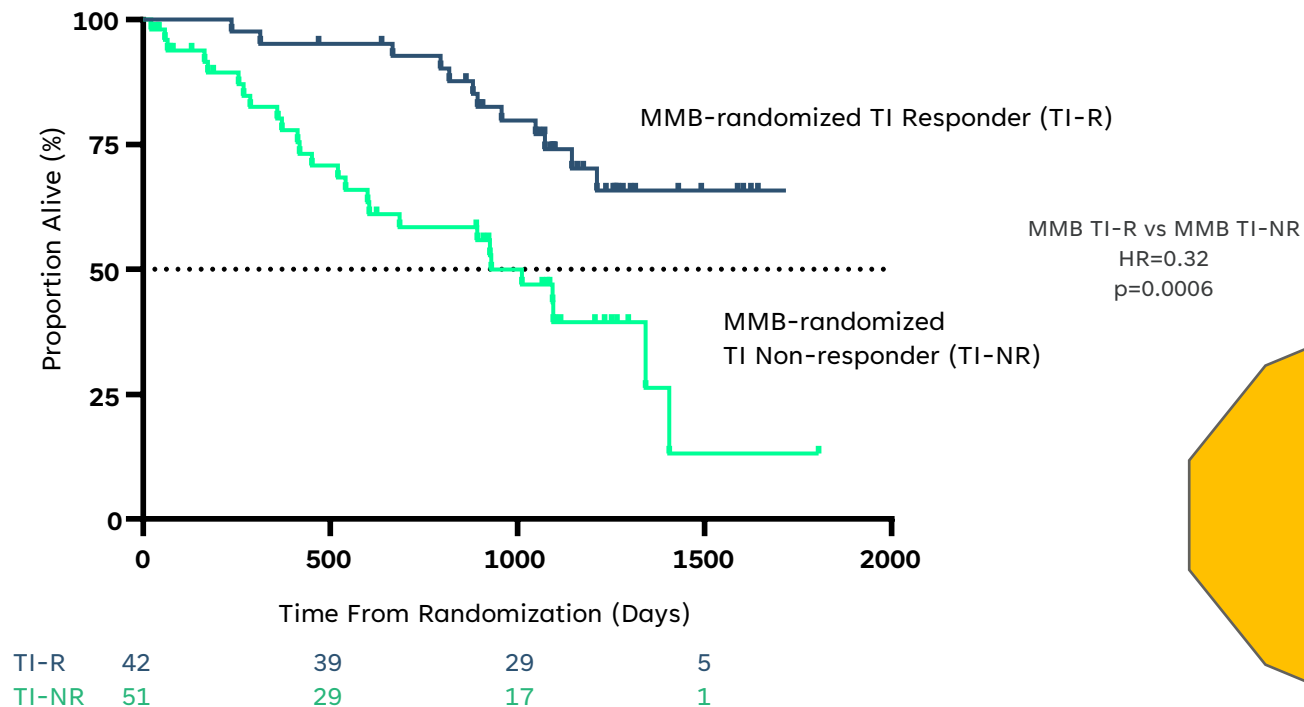
Goal:	Superiority			
Endpoints at W24:	MMB	BAT/RUX		
SVR35 (primary)	6.7%	5.8%	Proportion difference 0.01 (95% CI -0.09-0.10)	$p=0.90$
TSS reduction $\geq 50\%$	26.2%	5.9%	NR ^a	Nominal $p=0.0006$
TI at week 24	43.3%	21.2%	NR ^a	Nominal $p=0.0012$
TD at week 24	50%	64%	NR ^a	Nominal $p=0.10$
Median rate of RBC transfusion until W24	0.5 units/mo	1.2 units/mo	NR ^a	Nominal $p=0.39$
Zero transfusions through W24	40%	27%	NR ^a	NR ^a
Composite clinical improvement	38%	15%	NR ^a	NR ^a

1. Mesa R et al. J Clin Oncol 2017; 2. Harrison C et al. Lancet Haematol 2018

SIMPLIFY-1: TRANSFUSION INDEPENDENCE RESPONSE ASSOCIATED WITH IMPROVED OVERALL SURVIVAL IN ANEMIC* MMB-RANDOMIZED PATIENTS

SIMPLIFY-1 Week 24 TI response rates in patients with baseline anemia:

MMB = 45%
RUX = 26%



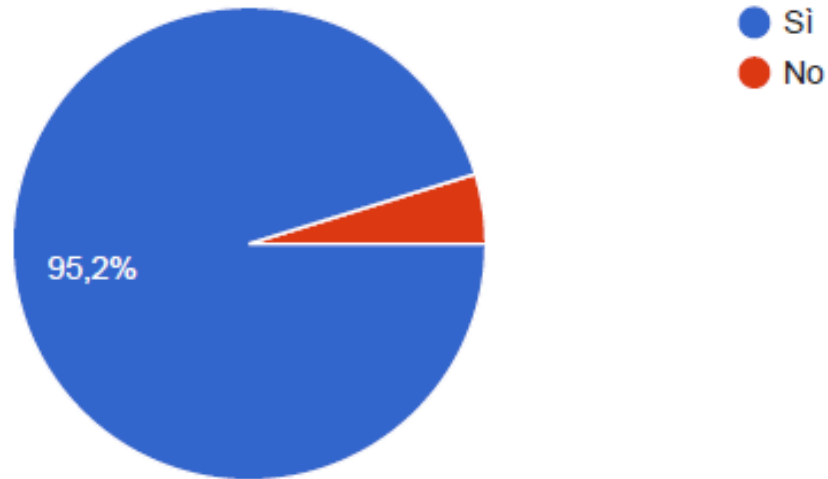
Achieving or Maintaining TI (anemia response) as a new predictor of Improved OS

Consistent with results in the total MMB population, achieving or maintaining TI predicted better survival in MMB-treated patients with anemia* at baseline

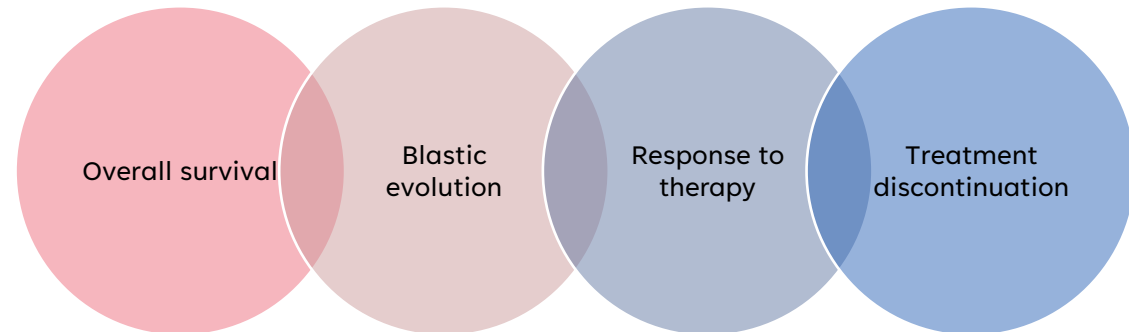
*Anemic at baseline defined as RBC transfusion ≤ 12 weeks before baseline, or baseline Hgb < 10 g/dL. Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL. As patients randomized to the control arm crossed over to open label MMB after W24, a valid comparison of OS with patients randomized to RUX was not possible; therefore, only the MMB arm was analyzed.

ANEMIA IN CORSO JAK INIBITORE

In base alla tua esperienza, ritieni che l'anemia abbia un impatto negativo sull'outcome del paziente con mielofibrosi in **trattamento con JAK inibitore**?



ANEMIA E RUXOLITINIB



Palandri F, et al. Cancer. 2023;1–10. Maffioli M, Mora B, Ball S, et al. Blood Adv. 2022;6(6):1855-1864
Maffioli M et al, AJH 2025

The 2024 Three-Strata Baseline Anemia Definition of the Revised IWG-ELN Criteria Dissects Survival in Ruxolitinib-Treated Myelofibrosis Patients

The revised IWG-ELN criteria proposed 3 strata for anemia definition, and we applied them to the RUXOREL-MF cohort.

Inclusion pts: Hb < 10 g/l, irrespective of gender

N = 205

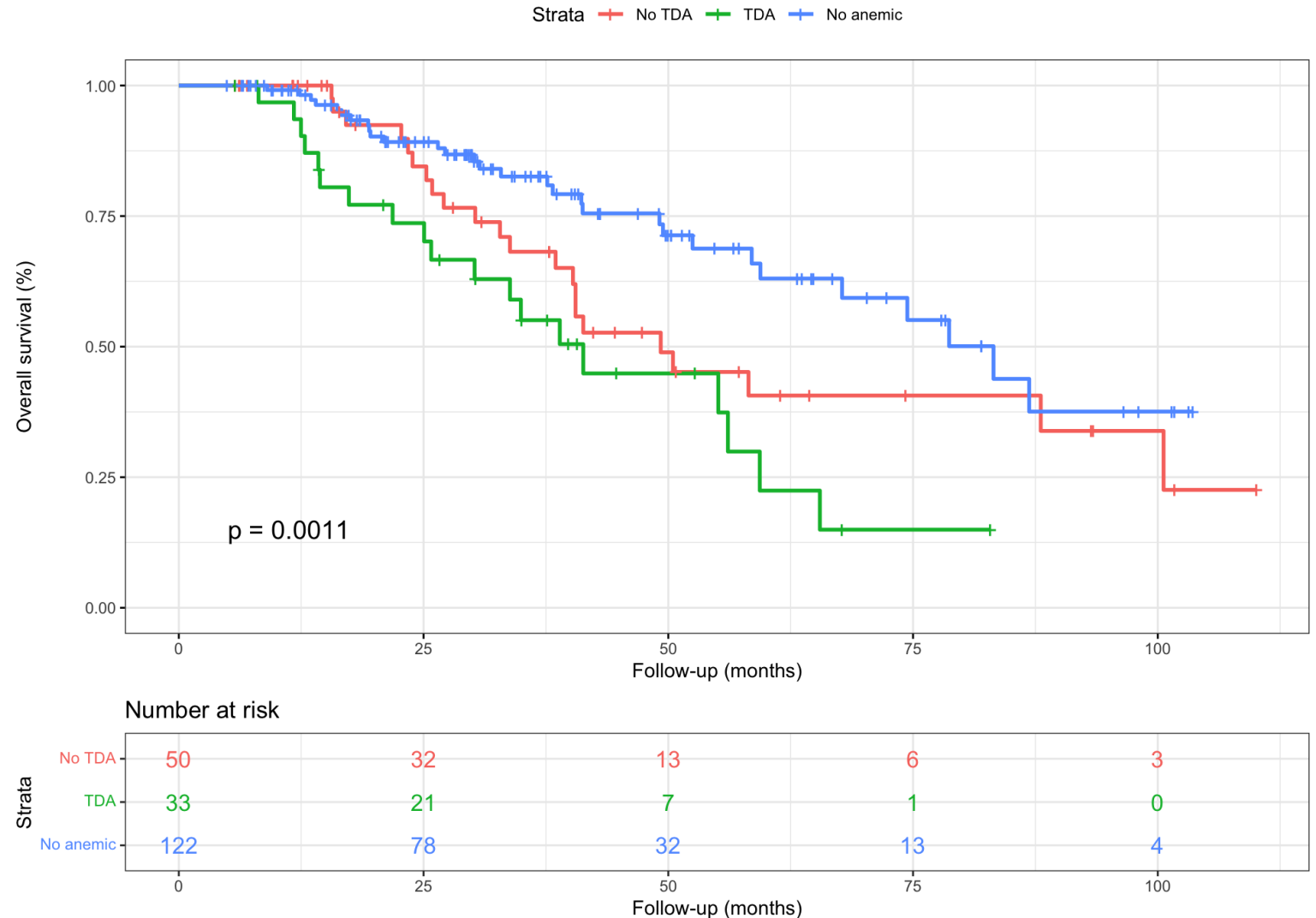
TDA



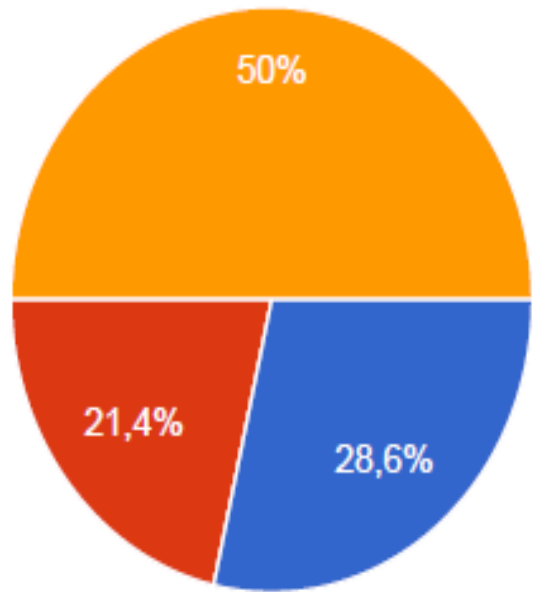
for ≥ 3 units GRC/12 weeks.

Non-TDA

anemic subjects who do not qualify for TDA

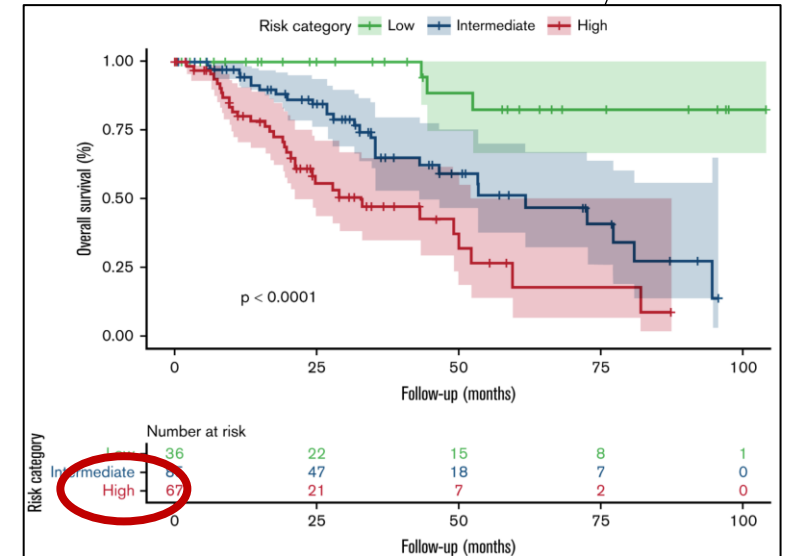


**NELLA TUA PRATICA CLINICA UTILIZZI
LO SCORE RR6 PER IDENTIFICARE UN
PAZIENTE A PEGGIOR PROGNOSI IN
CORSO DI JAK INIBITORE?**



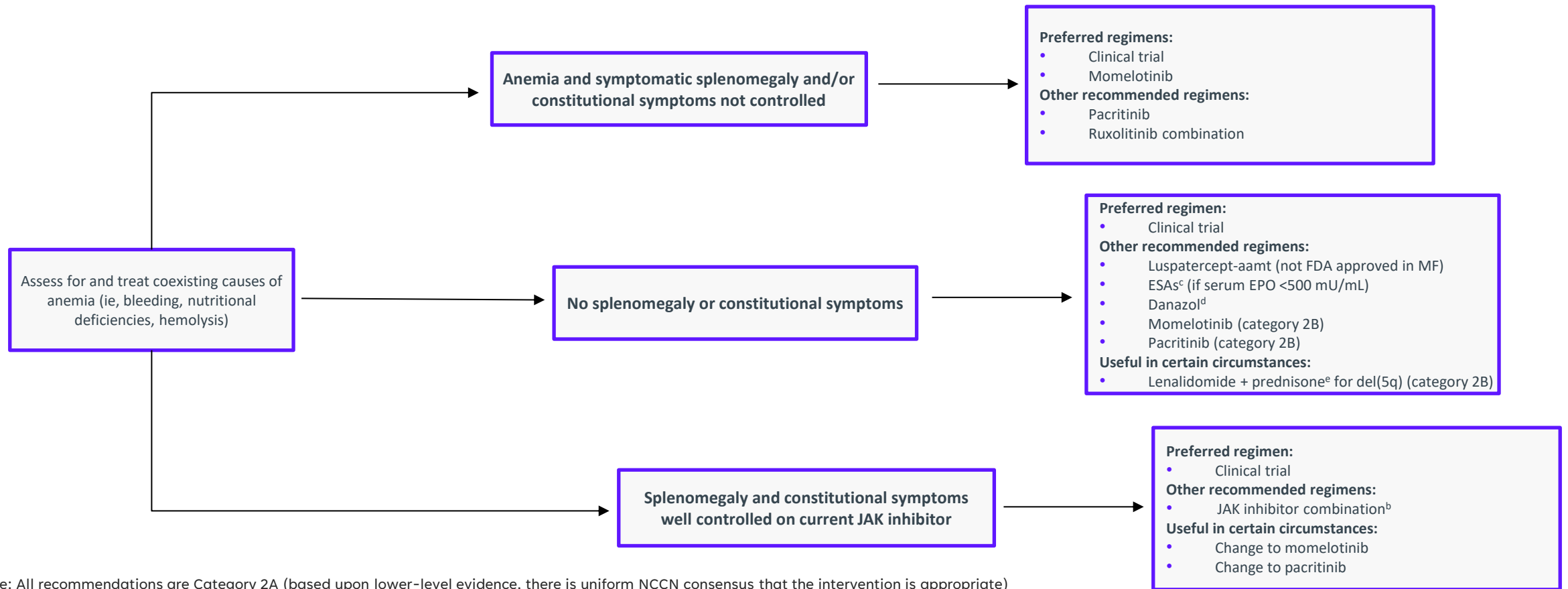
- Sì, sempre
- No, mai
- A volte, in base al contesto clinico

	Ruxolitinib start	+3 mo	+6 mo
	✓	✓	✓
	✓	✓	✓
 mg	✓	✓	✓



- Maffioli M et al *Blood Advances* 2022; 6 (6): 1855–1864

NCCN GUIDELINES: MANAGEMENT OF MF-ASSOCIATED ANEMIA



Note: All recommendations are Category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) unless otherwise indicated. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; JAK, Janus kinase; LFT, liver function test; MF, myelofibrosis; MPN, myeloproliferative neoplasm; NCCN, National Comprehensive Cancer Network.

a Supportive Care for Patients With MPN (MPN-G).

b JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.

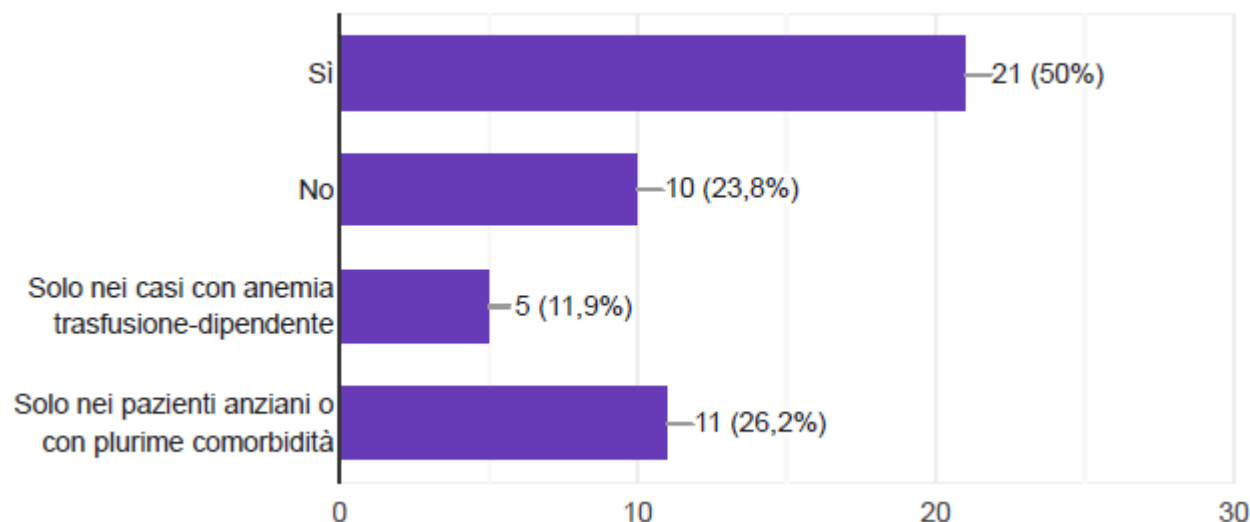
c ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.

d Prostate cancer screening and monitoring of LFTs as well as the use of concomitant medications such as statins are recommended due to concerns about increased risk of rhabdomyolysis.

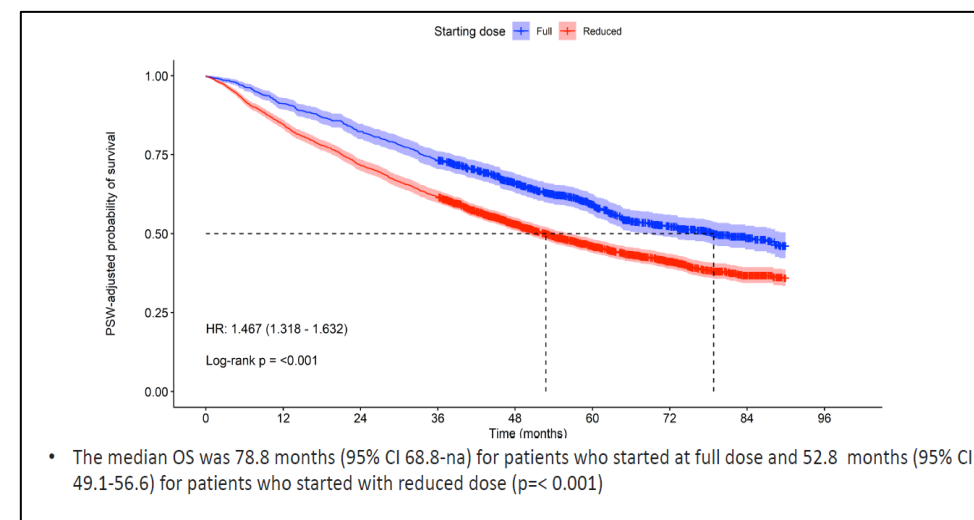
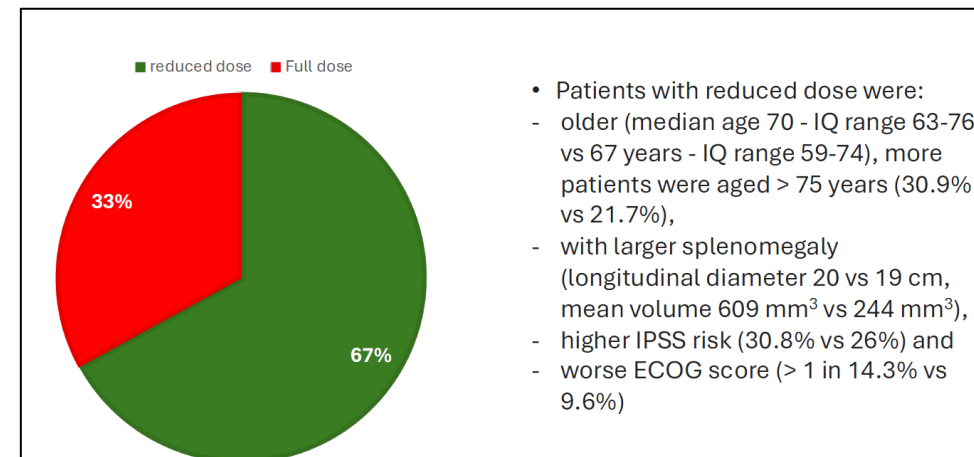
e Start as a combination followed by tapering of prednisone over 3 months.

ANEMIA E SCELTA JAK INIBITORE

Nella tua esperienza clinica, hai modificato una terapia o ritardato l'avvio di una terapia a causa della presenza di anemia?



Rux dose reduction at start:

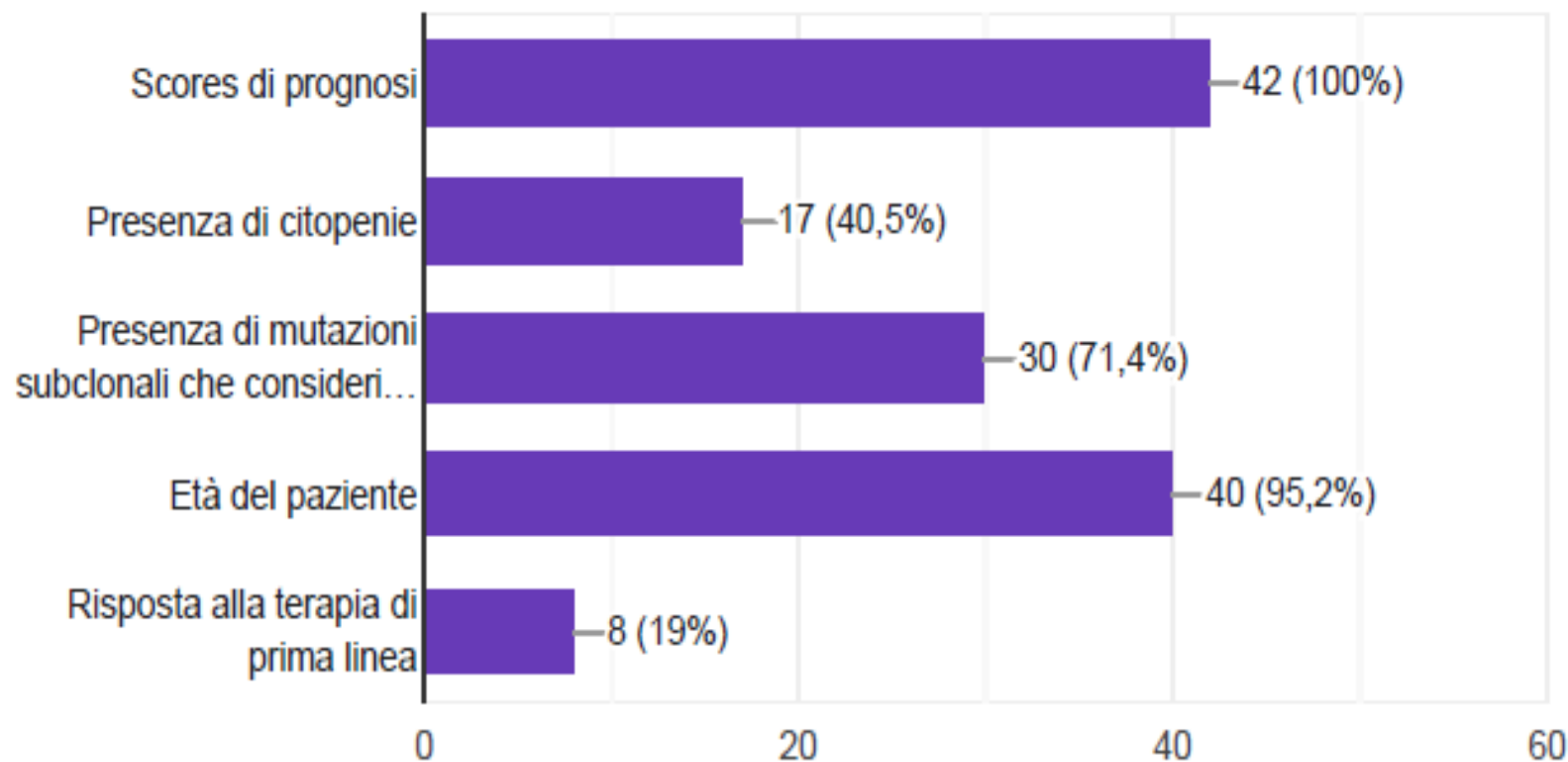


(42 RISPOSTE)



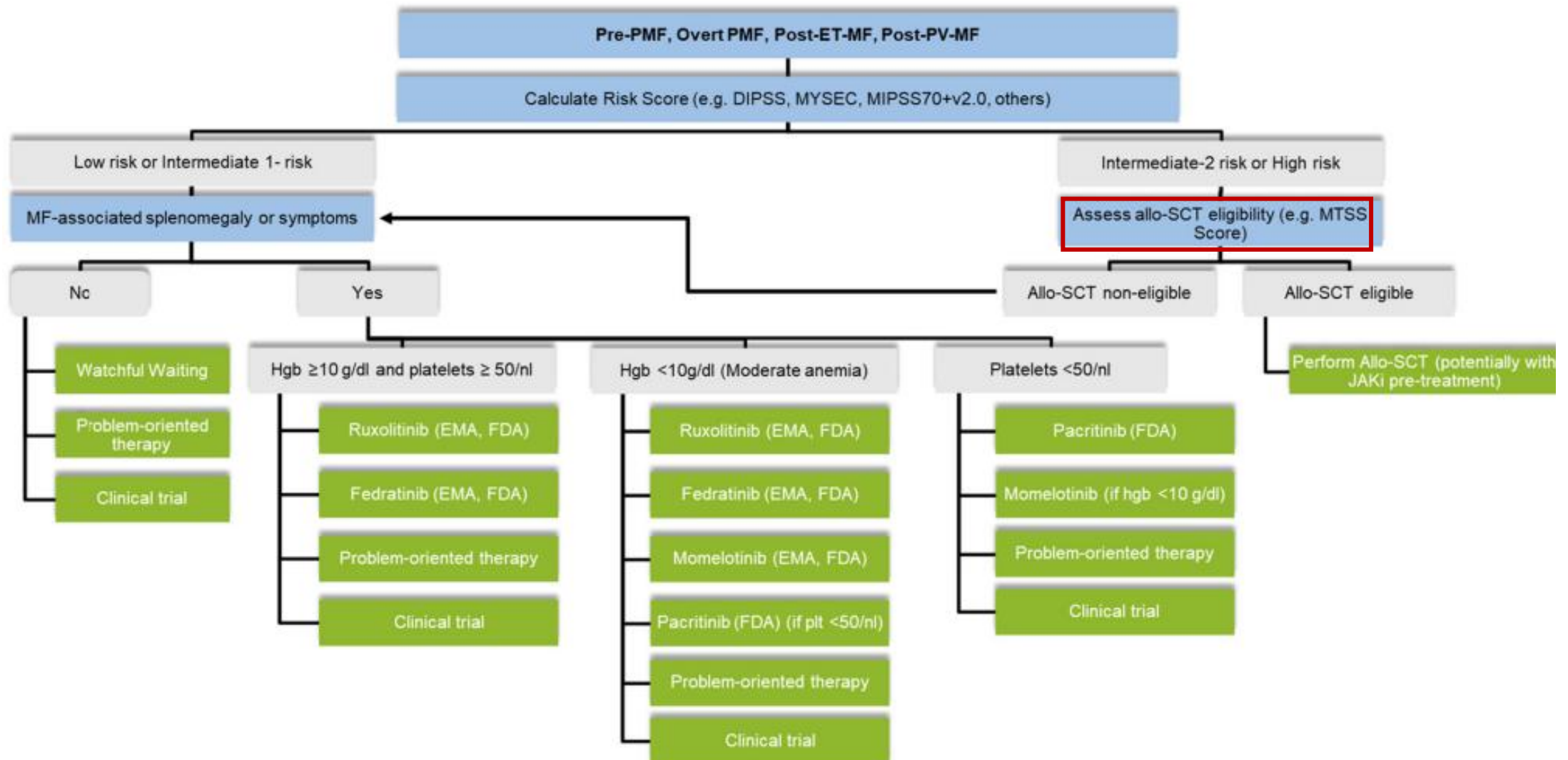
TRAPIANTO

MIELOFIBROSI E TRAPIANTO

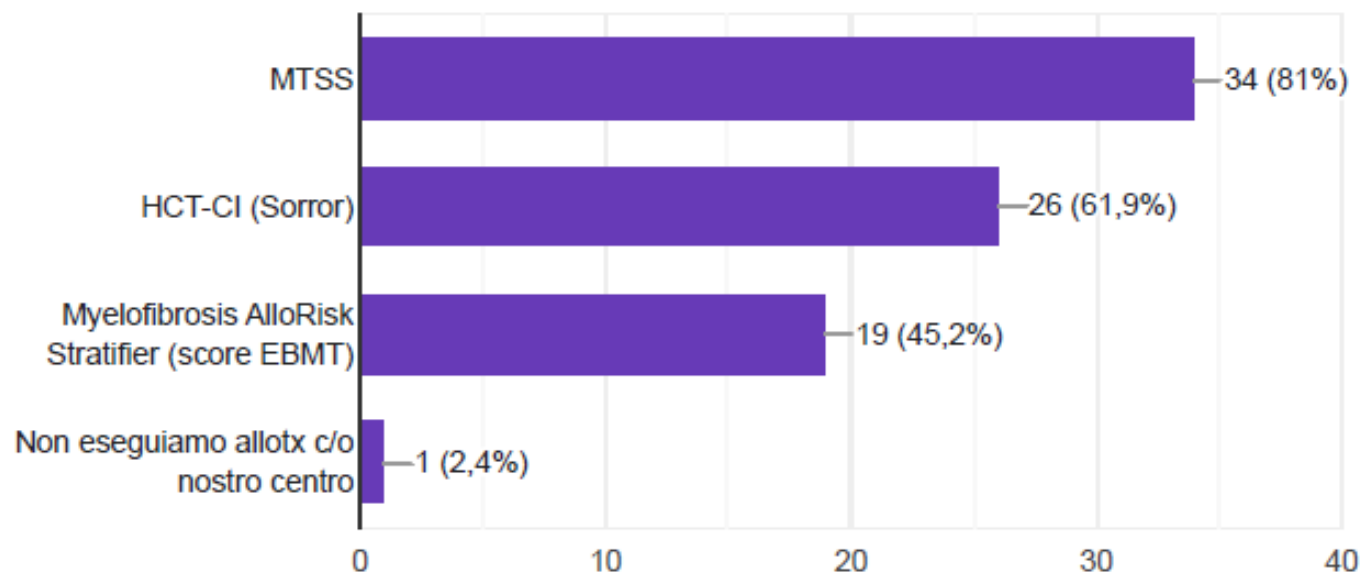


Nella tua pratica clinica, quali criteri utilizzi per decidere se avviare il work up trapiantologico nel paziente con mielofibrosi?

Treatment strategy in MF – transplant eligible or not



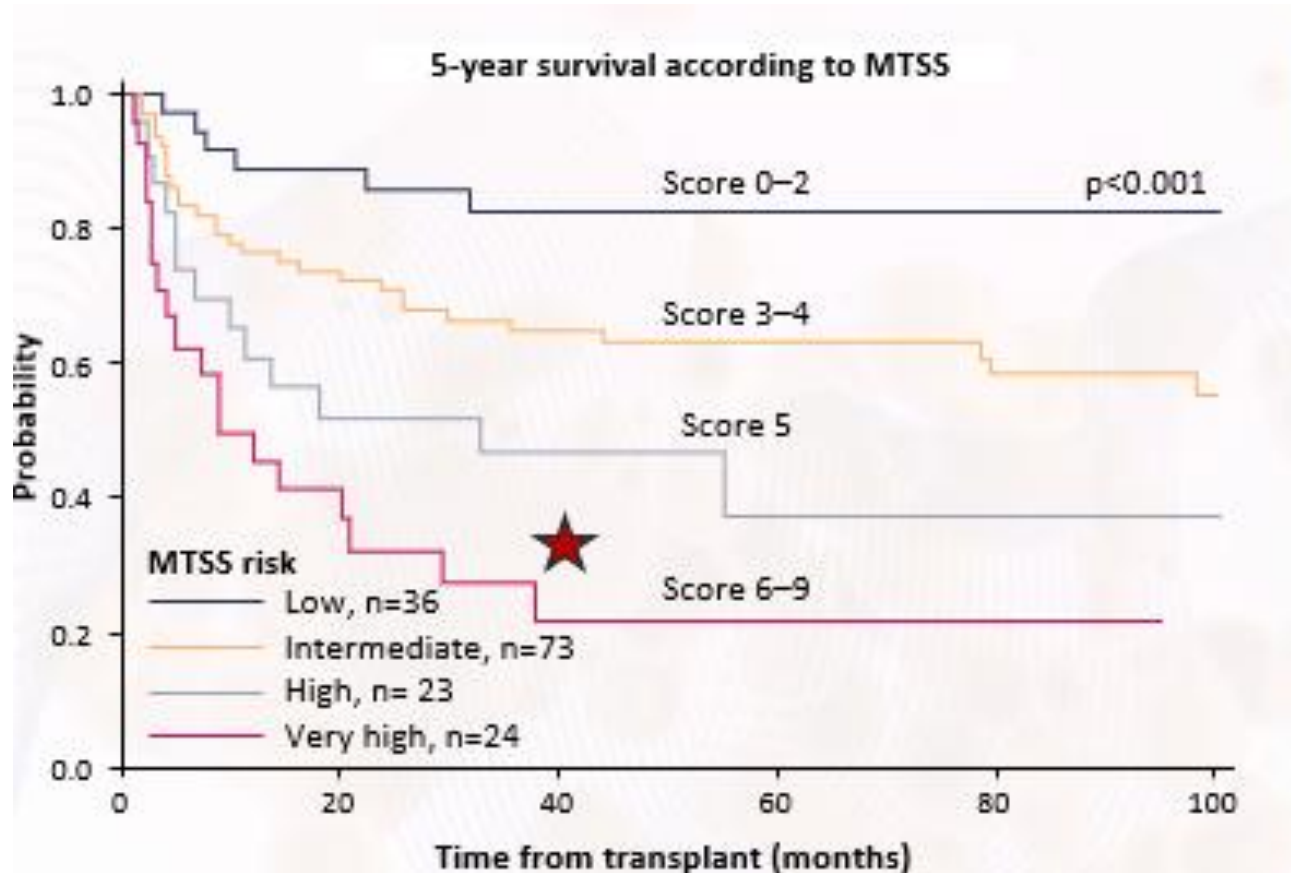
QUALE SCORE PER RISCHIO OUTCOME POST TRAPIANTO IN MF



Quali scores utilizzati per valutare la trapiantabilità del paziente con mielofibrosi a cui hai posto indicazione trapiantologica?

MTSS DETERMINES PROGNOSIS AFTER ALLOGENEIC HSCT

CLINICAL-MOLECULAR MYELOFIBROSIS TRANSPLANT SCORING SYSTEM VALIDATED IN 156 PATIENTS



Variable	HR*	Score
Platelet count <150×10 ⁹ /L	1.67	1
Leukocyte count >25×10 ⁹ /L	1.57	1
KPS <90%	1.50	1
Age ≥57 years	1.65	1
Non-CALR/MPL driver mutation genotype	2.40	2
ASXL1 mutation	1.42	1
HLA-mismatched unrelated donor	2.08	2

*Multivariate analysis.

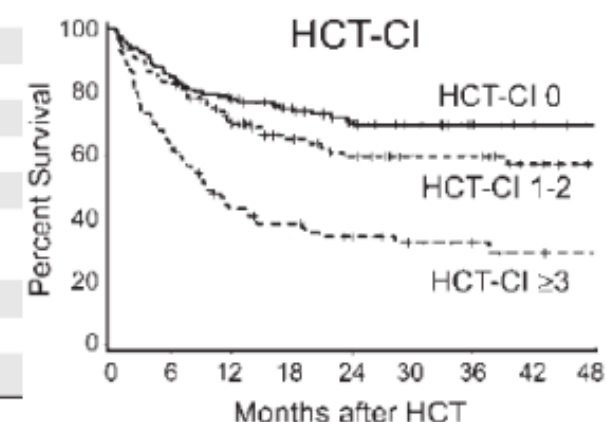
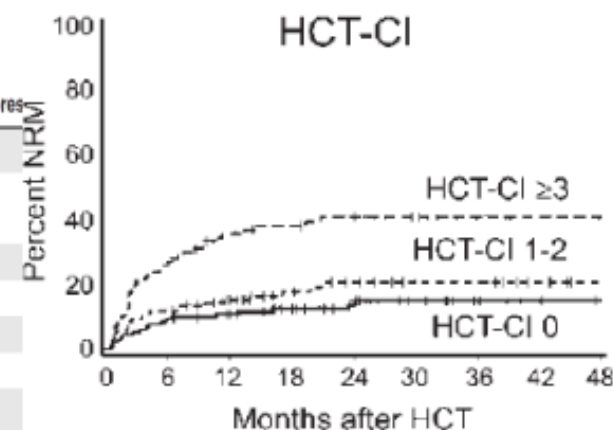
HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation ; KPS, Karnofsky performance status; MTSS, myelofibrosis transplant scoring system.

Gagelmann N, et al. *Blood* 2019; **133**:2233–2242.

Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool for risk assessment before allogeneic HCT

Mohamed Sorrow, Michael Maris, Rainer Storb, Frederic Baron, Brenda Sandmaier, David Maloney, Barry Storer

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity†	Patients with a body mass index > 35 kg/m ²	1
Infection†	Requiring continuation of antimicrobial treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary‡	DLco and/or FEV ₁ 66%-80% or dyspnea on slight activity	2
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary‡	DLco and/or FEV ₁ ≤ 65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3



A Machine Learning Model To Predict Survival After Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis

Context of Research

Allogeneic transplantation remains the only curative treatment for patients with MF. However, its significant morbidity and mortality require a careful risk-benefit analysis to identify suitable candidates.

Aim of This Study

Using data from 5,183 MF patients who underwent allogeneic transplantation at EBMT centers, we examined different machine learning models to predict overall survival after transplant.

Findings



Images are in part from Servier Medical Art, which is licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>)

Conclusions: A machine learning model, available as an interactive web application, was created to predict survival after transplant in myelofibrosis. This tool is a step toward personalized medicine, enabling the identification of 25% of patients with poor transplantation outcomes.

Hernández-Boluda et al. DOI: 10.1182/**blood**.2024027287

blood
Visual
Abstract

An abstract graphic on a light gray background. Two thin, dark gray lines intersect diagonally. One line runs from the top-left towards the bottom-right, and the other runs from the top-right towards the bottom-left. They cross each other in the upper-left quadrant of the image. To the right of the intersection, the word "GRAZIE!" is written in a bold, black, sans-serif font.

GRAZIE!