POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

La policitemia vera: come si diagnostica?

Dott. Giuseppe Carli

UOS Centro per le Malattie Emorragiche e Trombotiche (CMET)

UOC Ematologia

Ospedale San Bortolo, Vicenza

REGIONE DEL VENETO
ULSS8 BERICA

Conflitti d'interesse

Partecipazione ad Advisory Board

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Relatore a congressi

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PV an easy diagnosis….but not be shallow!

F 45y

<u>2018:</u>

Thrombocytosis (650x10e9), Ht 47%, WBC 9x10e9, no splenomegaly, no symptoms

Mild hypertension

JAK2+, no BOM

Diagnosis: «*malattia mieloproliferativa cronica JAK2 ad impronta piastrinosica, verosimile Trombocitemia Essenziale*»

ASA and follow-up

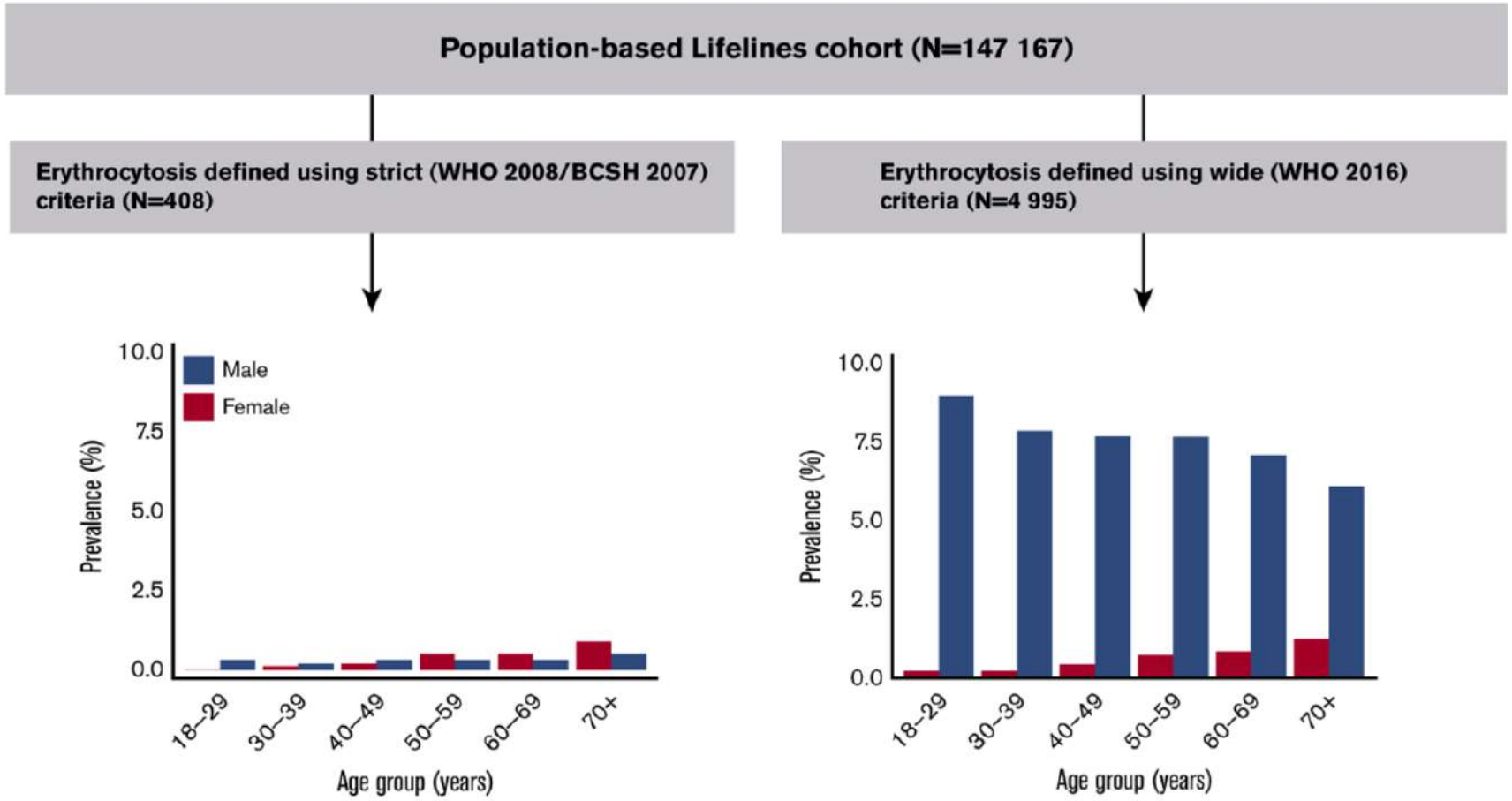
<u>2022</u>:

ER for a TIA episode

Ht 52%, Plts 815x10e9, WBC 9.5x10e9

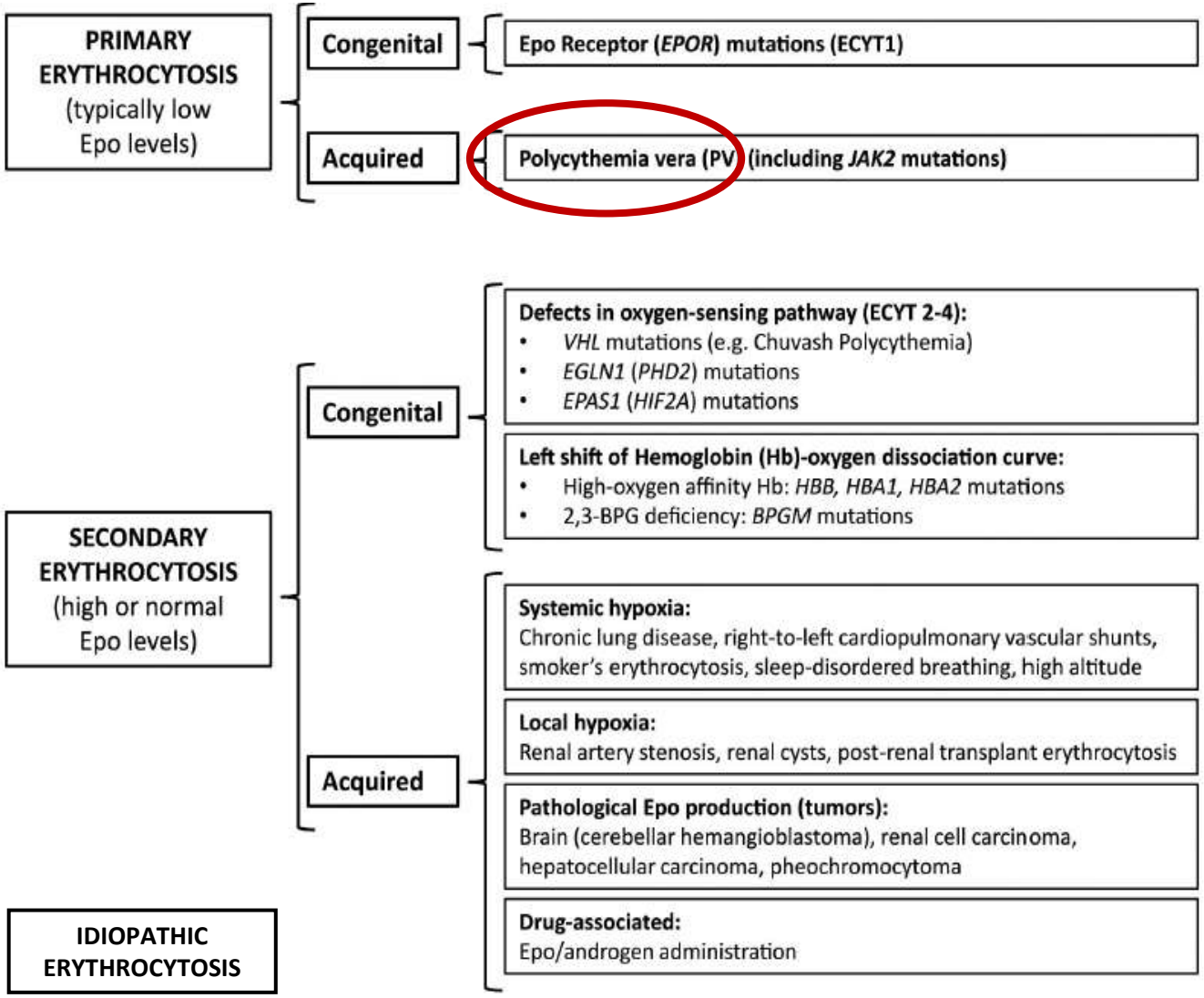
<u>EPO: 2 U/L</u> **BOM: MPN-PV**

Erythrocytosis in general population



Wouters et al, Blood Adv 2020

Classification of erythrocytosis



Camps, Haematologica 2016

Polycythemia Vera vs Non clonal Erythrocytosis

	PV	Erythrocytosis
Hyperviscosity symptoms	Frequent	Non frequent
Systemic symptomps	Frequent	Absent
Splenomegaly	Frequent	Absent
Thrombotic risk/events	High	Variable
EPO	Low	High or normal
Platelets	High	Normal
WBC	High	Normal
LDH	High	Normal
JAK2 mutation	**99%**	**0%**

PV diagnostic criteria

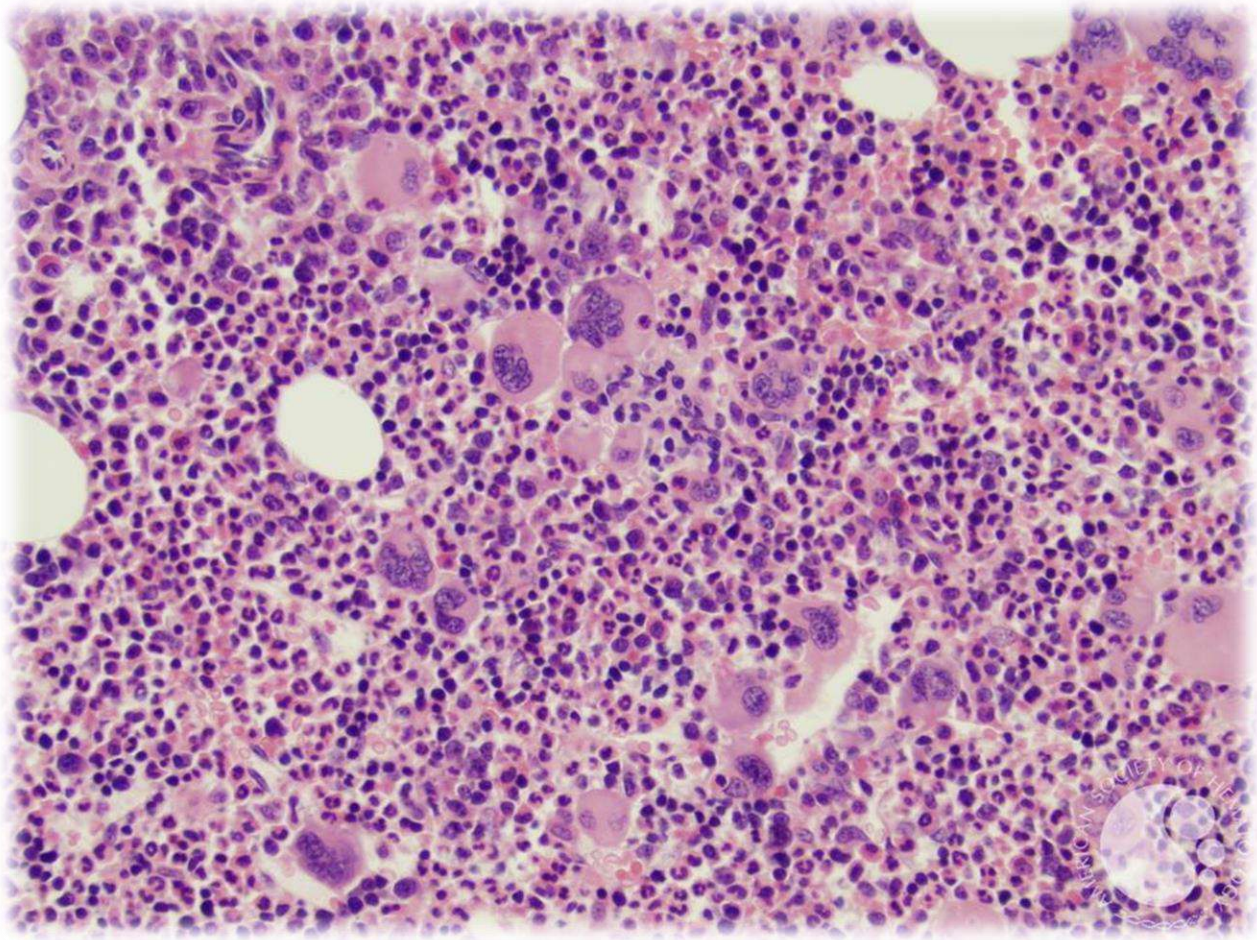
	2008	***2016***
Major criteria	• Hb > 18.5 g/dL for men or >16.5 g/dL for women or other evidence of increased red blood cell volume[d] • Presence of *JAK2V617F* or *JAK2* exon 12 mutation	Major criteria 1 Hemoglobin >16.5 g/dl (men) >16 g/dl (women) or hematocrit >49% (men) >48% (women) or increased red cell mass (RCM) 2 BM with age-adjusted hypercellularity and trilineage myeloproliferation with pleomorphic, mature megakaryocytes (differences in size) 3 Presence of *JAK2* mutation
Minor criteria	• Bone marrow biopsy showing hypercellularity for age with trilineage proliferation • Serum Epo below reference range for normal • Endogenous erythroid colony formation in vitro	Minor criteria 1 Subnormal serum erythropoietin level

[a] Diagnosis of PV requires meeting both major criteria and 1 minor criterion or first major criterion and 2 minor criteria.

PV diagnosis requires meeting either all three major criteria or the first two major criteria and one minor criterion.

Barbui et al, Blood Review 2016

Bone marrow biopsy



ASH Image Bank

- hypercellular marrow for age with **PANMYELOSIS** (proliferation of the erythroid, granulocytic, and megakaryocytic lineages)
- Megakaryocytes are increased and include frequent hyperlobated forms

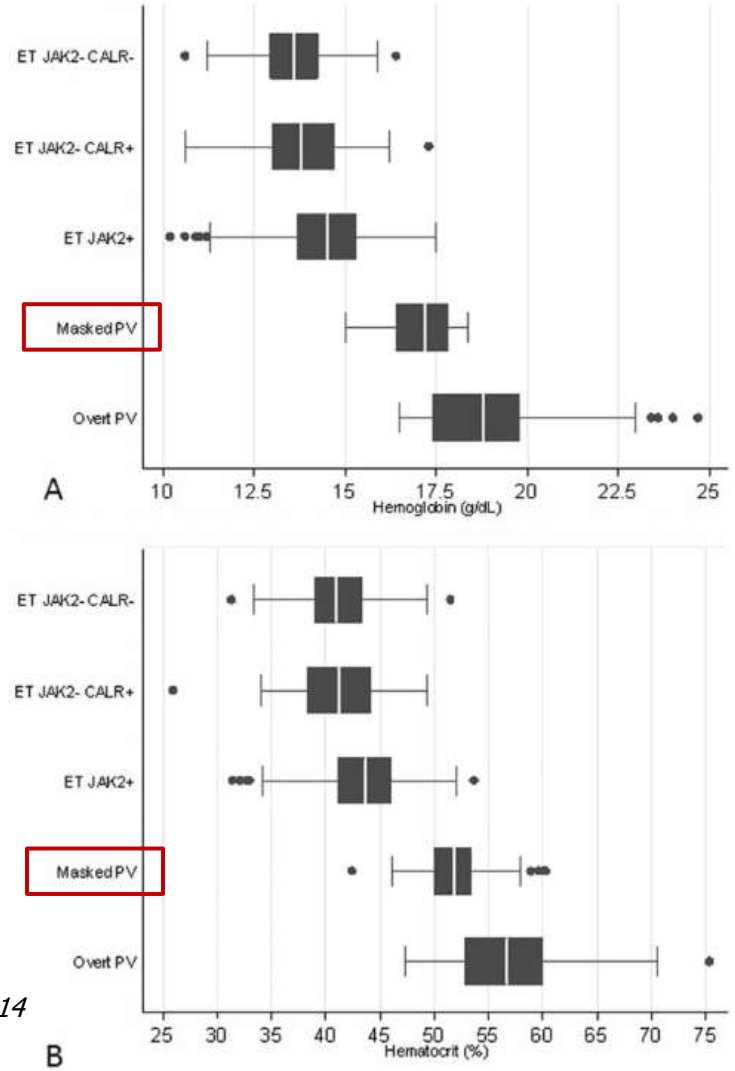
PITFALLS

- ***TE JAK2+***
- ***preMF***

→ Pathologist's expertise

→ Pathologist – Hematologist collaboration

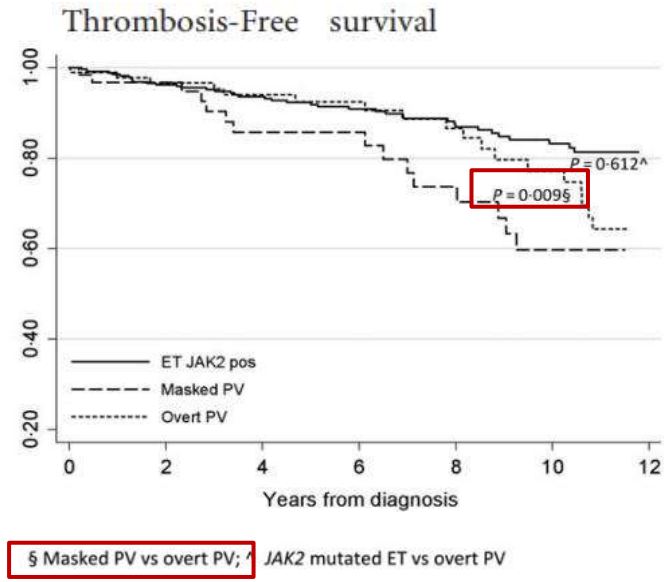
Revealing early stage PV: masked PV



Barbui et al, Am J Hematol 2014

mPV *vs* overt PV

- more frequently thrombocytosis
- Lower Hb/Ht level
- Features on BM biopsy superimposable

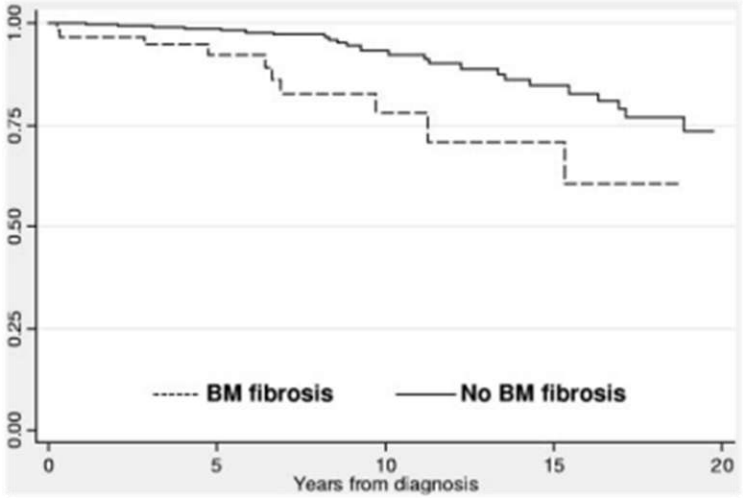


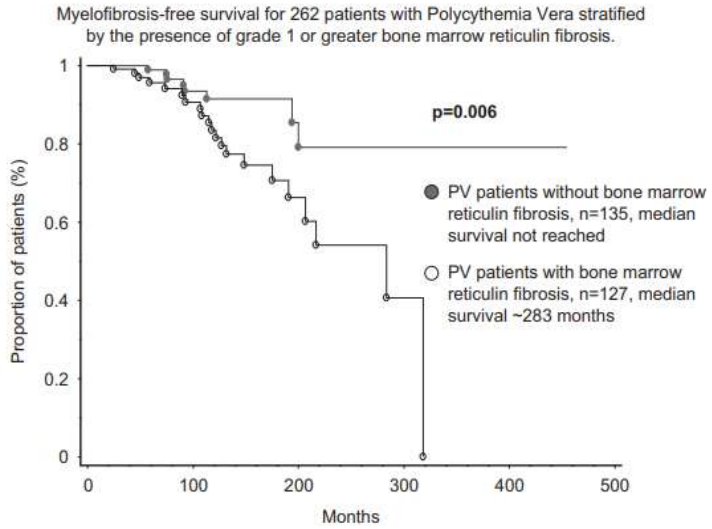
§ Masked PV vs overt PV; ^ *JAK2* mutated ET vs overt PV

Lussana et al, BJH 2014

Role of fibrosis

- Incidence ~ 14% (MF ≥1)
- No impact on overall survival
- No impact on Leukemia-free survival
- **<u>Higher risk of MF transformation</u>**





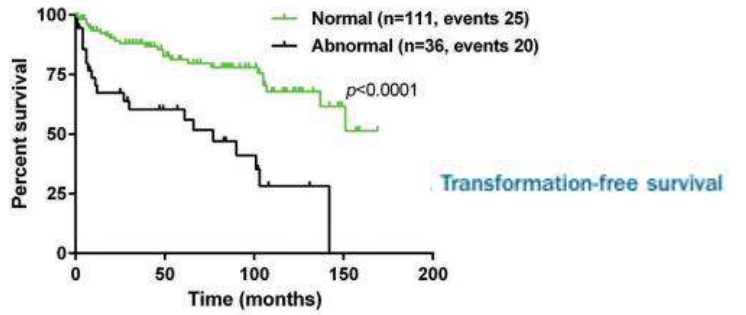
Barbui et al, Blood 2014

Barraco et al, Blood Cancer Journal 2017

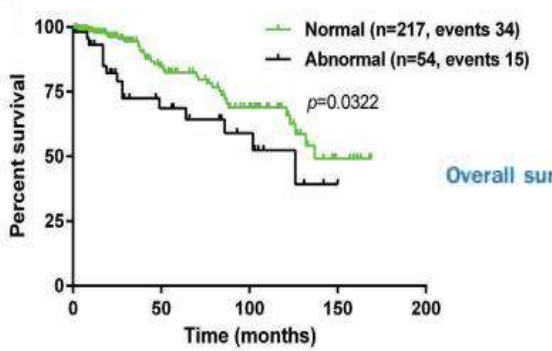
Karyotype

Cytogenetic abnormalities detected at the diagnosis (first bone marrow evaluation).

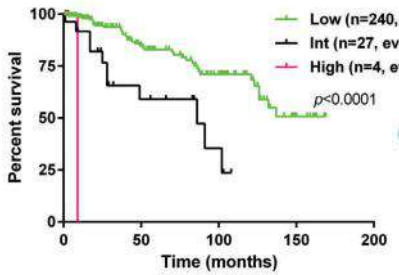
	Polycythemic phase (n=271)	Post-PV MF (n=112)	AP/BP phase (n=39)	Total (n=422)
Normal karyotype	217 (80%)	62 (55%)	4 (10%)	283 (67%)
Abnormal karyotype	54 (20%)	50 (45%)	35 (90%)	139(33%)
Single abnormalities	41 (76%)	29 (58%)	5 (14%)	75 (54%)
- del20q	18	12	1	31
- +9	10	0	0	10
- +8	6	1	1	8
- other single	7	16	3	26
Double abnormalities	9 (17%)	9 (18%)	6 (17%)	24 (17%)
- +1q	4	7	4	15
- other two	5	2	2	9
Complex	4 (7%)	12 (24%)	24 (69%)	40 (29%)
- del5q/-5	0	4	14	18
- del7q/-7	1	2	15	18
- del17p/-17/i(17q)	1	4	9	14



Transformation-free survival



Overall survival of patients



Overall survival of patients with low-intermediate-, and high-risk cytogenetics.

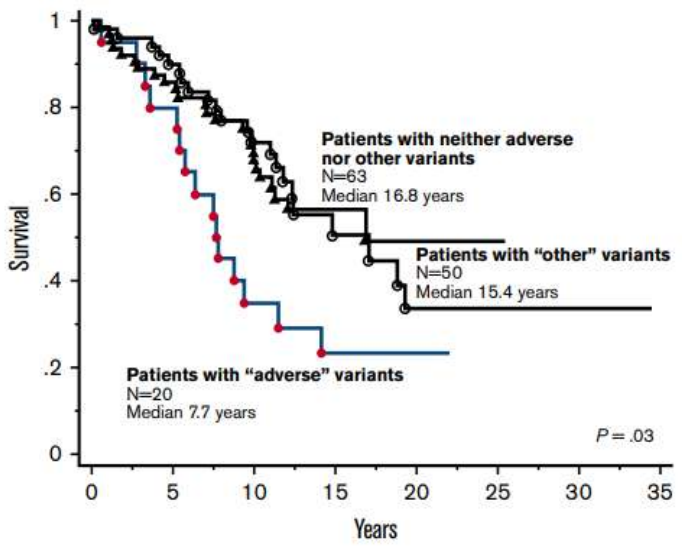
- **Up to 20% of patients with PV have karyotipic abnormalities at the initial diagnosis**
- **Abnormal karyotype is an independent risk factor for OS**

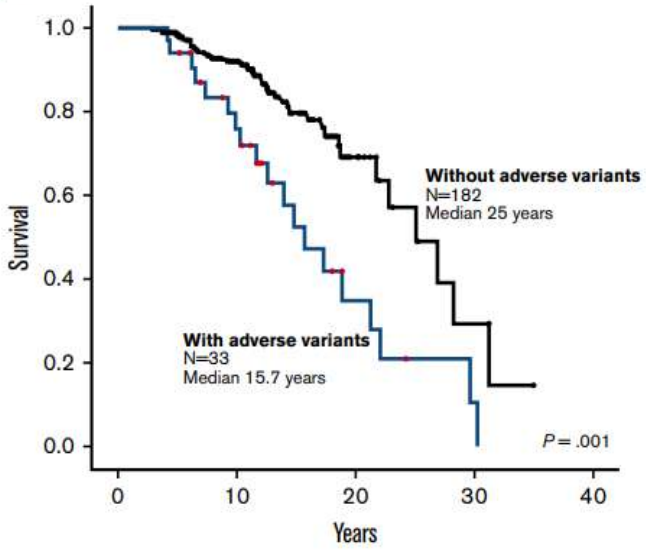
Tang et al, Haematologica 2017

Tefferi et al, Leukemia 2013

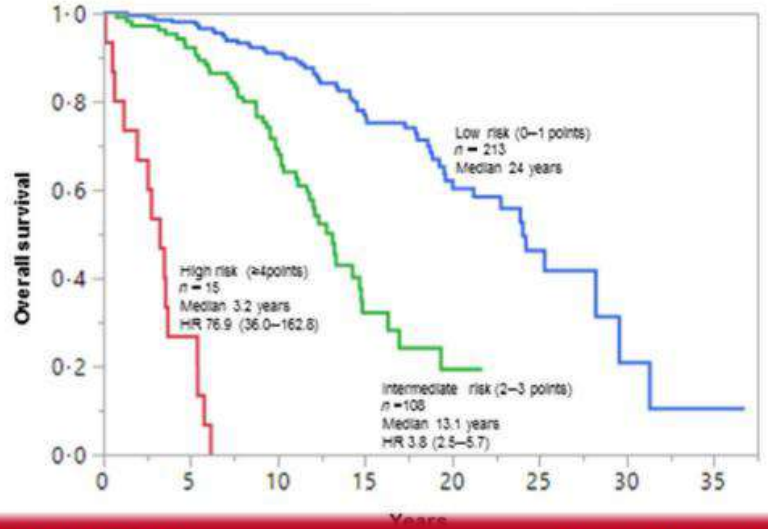
NGS

	Total #	% Total
JAK2	130	98%
TET2	29	22%
ASXL1	16	12%
SH2B3	12	9%
CEBPA	8	6%
ZRSR2	6	5%
SF3B1	4	3%
CSF3R	4	3%
KIT	4	3%
SRSF2	4	3%
IDH2	3	2%
DNMT3A	3	2%
SUZ12	2	2%
SETBP1	2	2%
RUNX1	2	2%
CBL	1	1%
TP53	1	1%
FLT3	1	1%
CALR	0	0%
MPL	0	0%
EZH2	0	0%
NRAS	0	0%
NPM1	0	0%
IDH1	0	0%
U2AF1	0	0%
PTPN1	0	0%
IKZF1	0	0%





MIPSS-PV



MIPSS-PV was based on four risk factors

- adverse mutations (SRSF2) (3 points)
- age >67 years (2 points)
- leukocyte count ≥15.000/mmc (1 point)
- thrombosis history (1 point)

Tefferi et al, Blood Adv 2016

Tefferi et al, BJH 2020

Cardiovascular risk factors

ECLAP

Cardiovascular risk factors	%
Hypertension	39.5
High blood cholesterol	3.5
Diabetes mellitus	7.1
Current smokers	12.8
Congestive heart failure	7.9
Angina pectoris	7.3
Myocardial revascularization procedures	2.4

CYTO-PV

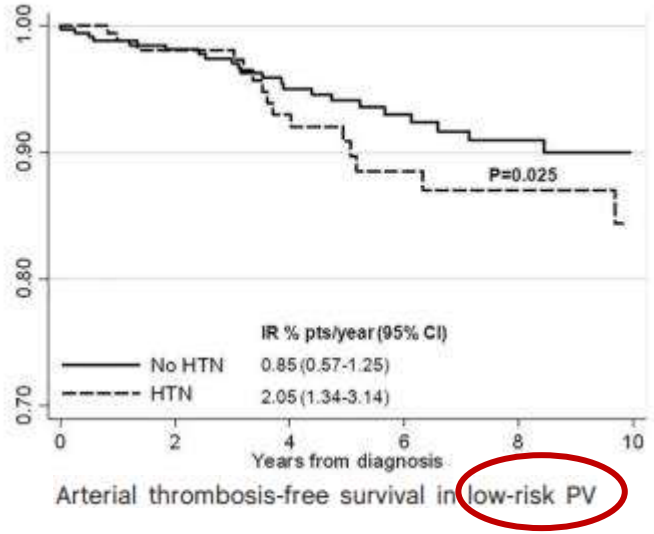
Treatments for cardiovascular risk factors — no. (%)	
Hypocholesterolemic medication	47 (12.9)
Antidiabetic medication	17 (4.7)
Antihypertensive medication	176 (48.2)

LOW-PV

Cardiovascular risk factors		
Hypertension	11 (22%)	13 (26%)
Hypercholesterolaemia	3 (6%)	4 (8%)
Diabetes	0 (0%)	1 (2%)
Intermittent claudication	0 (0%)	0 (0%)
History of coronary arterial disease	0 (0)	0 (0)
History of smoking	16/47 (34%)	14/46 (30%)
Currently smoking	8/47 (17%)	6/49 (12%)

Marchioli et al, JCO 2005
Marchioli et al, NEJM 2013
Barbui et al, Lancet 2021

Among risk factors arterial hypertension had the most relevant prognostic role for the incidence of arterial thrombosis

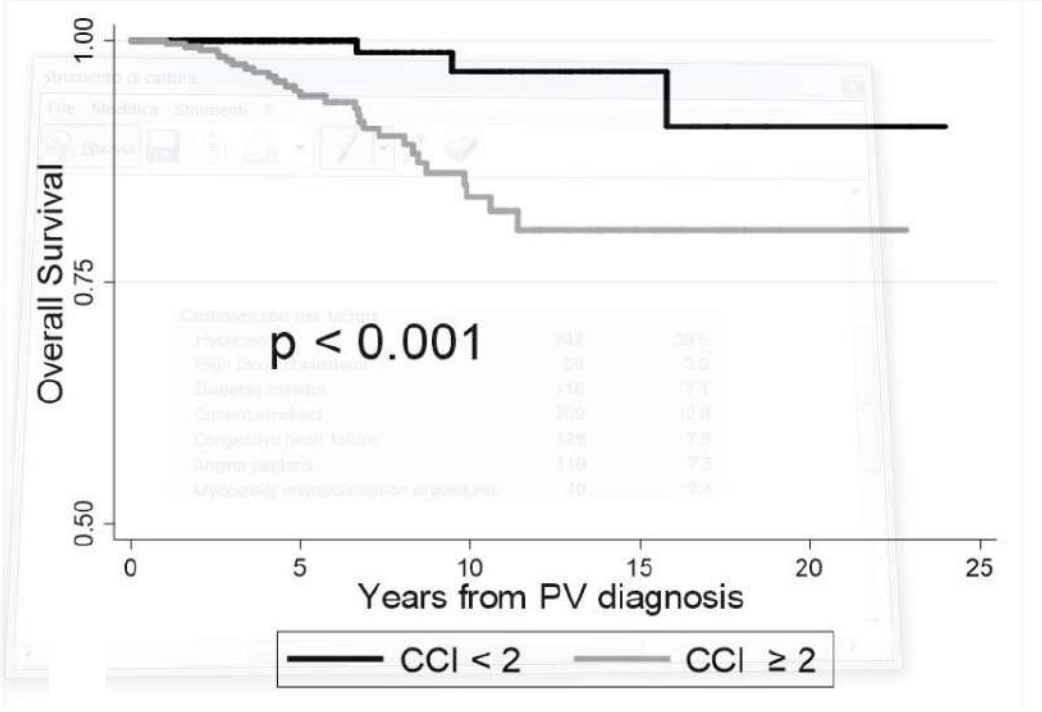


Arterial thrombosis-free survival in low-risk PV

Tang et al, Haematologica 2017

Role of comorbidities in PV

Overall Survival according to Charlson Comorbidity Index (CCI)

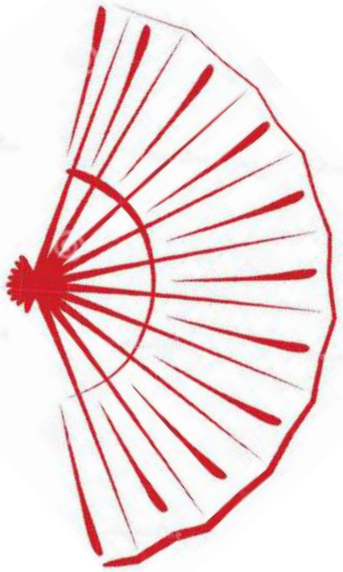


Benevolo et al, Hematological Oncology 2021

Thrombotic risk

MILESTONES

- Age > 60 years
- History of thrombosys



RISK OF ARTERIAL EVENTS

- History of arterial thrombosys
- Hypertension*
- Diabetes*
- Dyslipidemia*
- Leukocytosis*

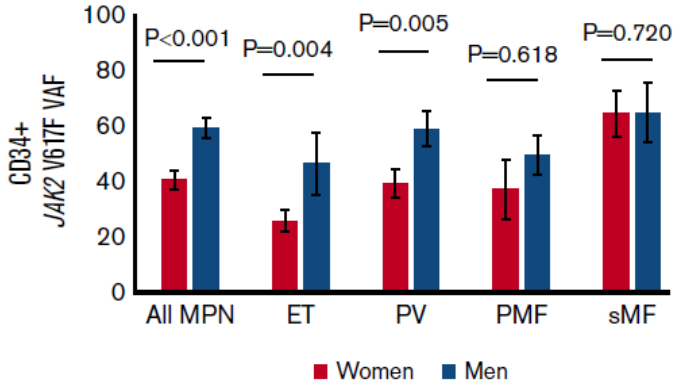
RISK OF VENOUS EVENTS

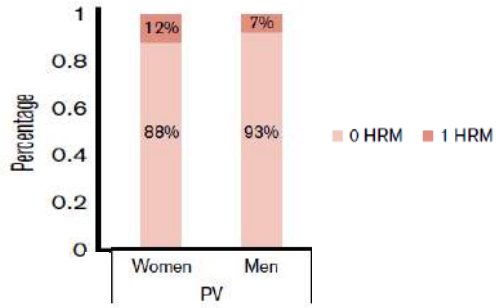
- Age ≥ 65 years
- History of venous thrombosys
- Neutrophil/lymphocyte ratio ≥5*
- JAK2 VAF >50% *

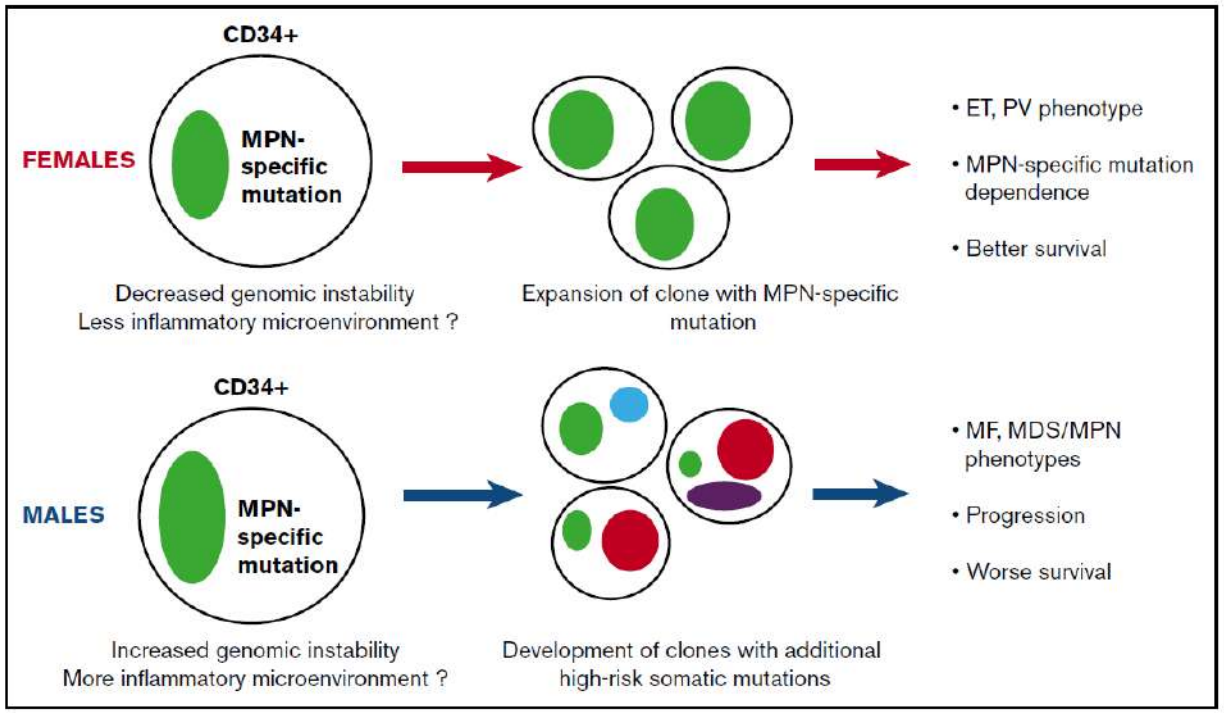
** Not yet included in risk scores*

Barbui et al, Blood 2014
Cerquozzi et al, Blood Cancer J 2017
Guglielmelli et al, Blood Cancer J 2021
Carobbio et al, Blood Cancer J 2022

Gender and PV

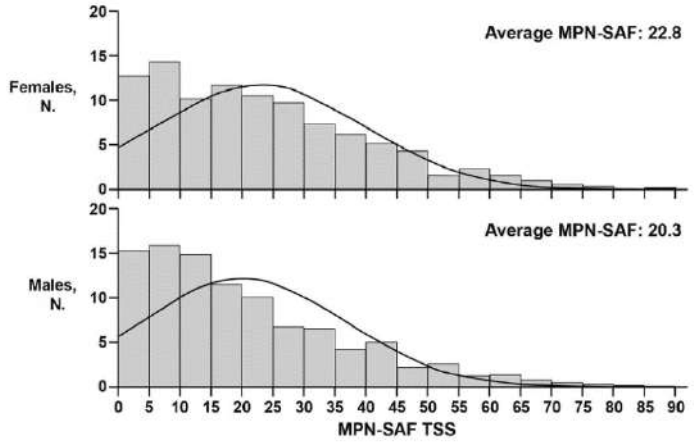


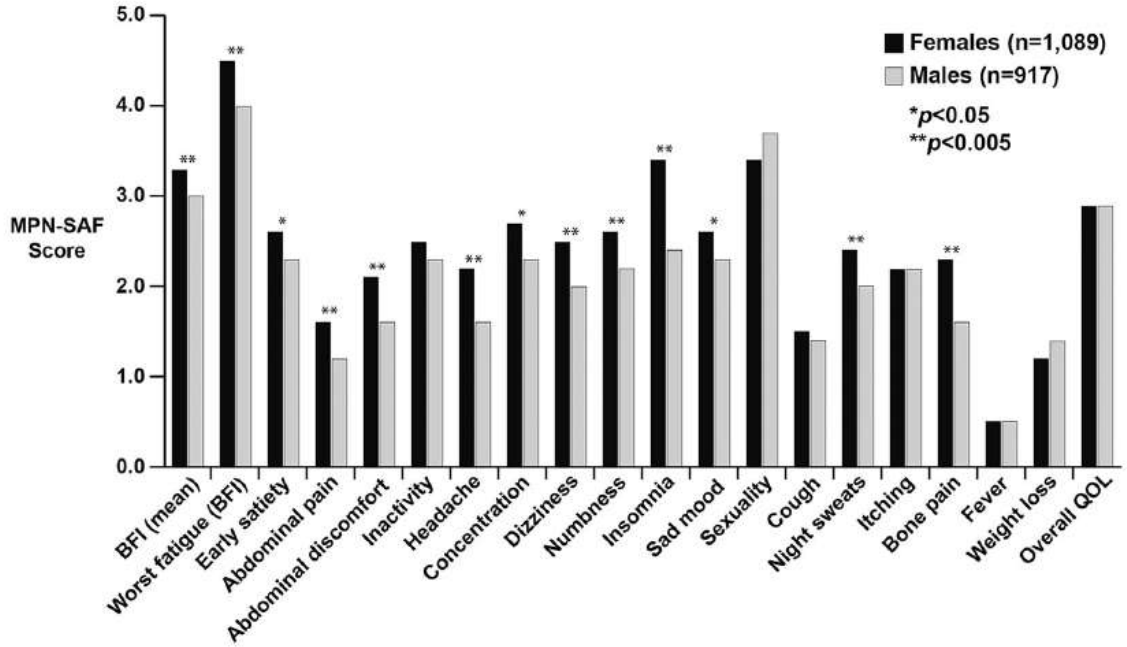




Karantanos et al, Blood Adv 2021

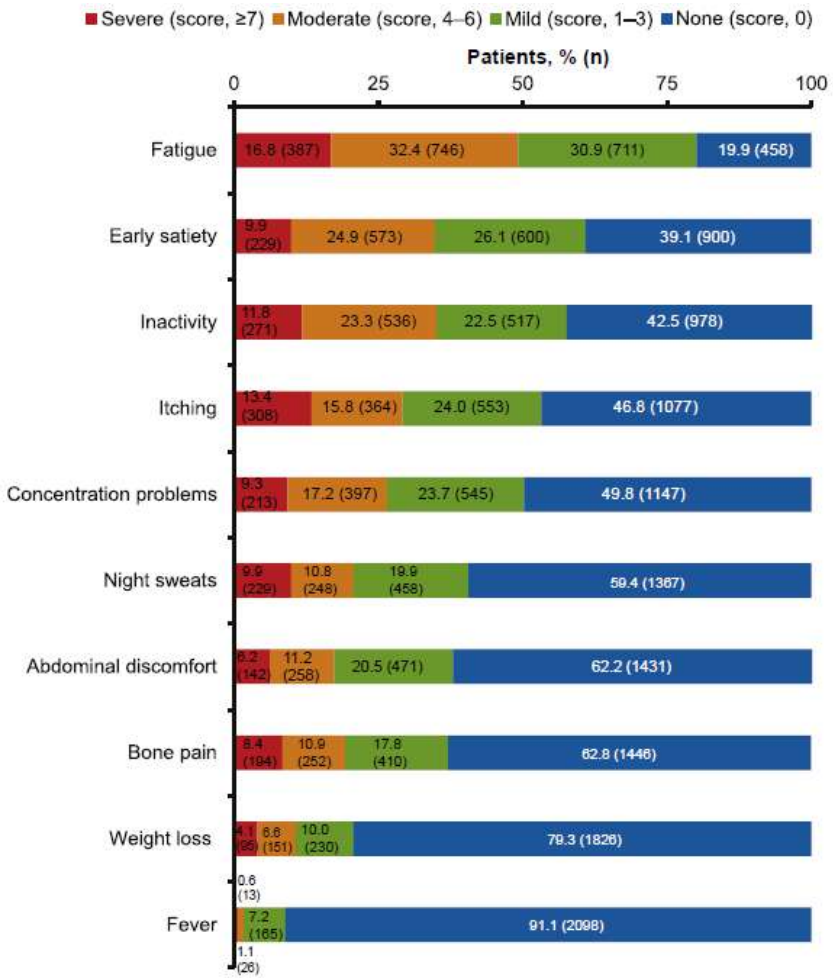
Gender and PV

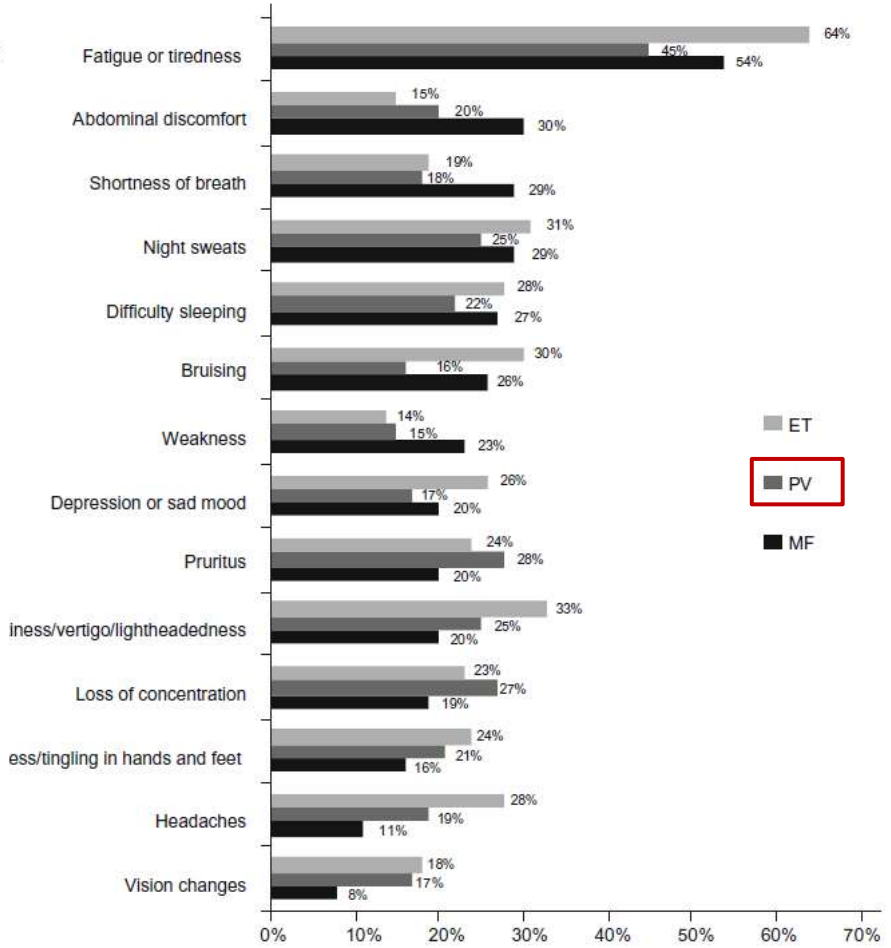




Geyer et al, Haematologica 2017

Symptomatic burden in PV

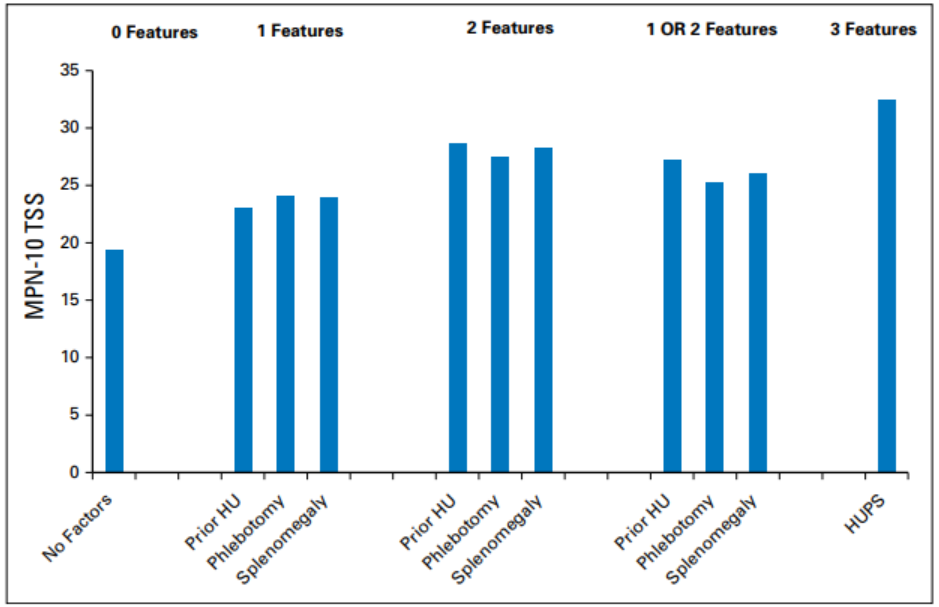


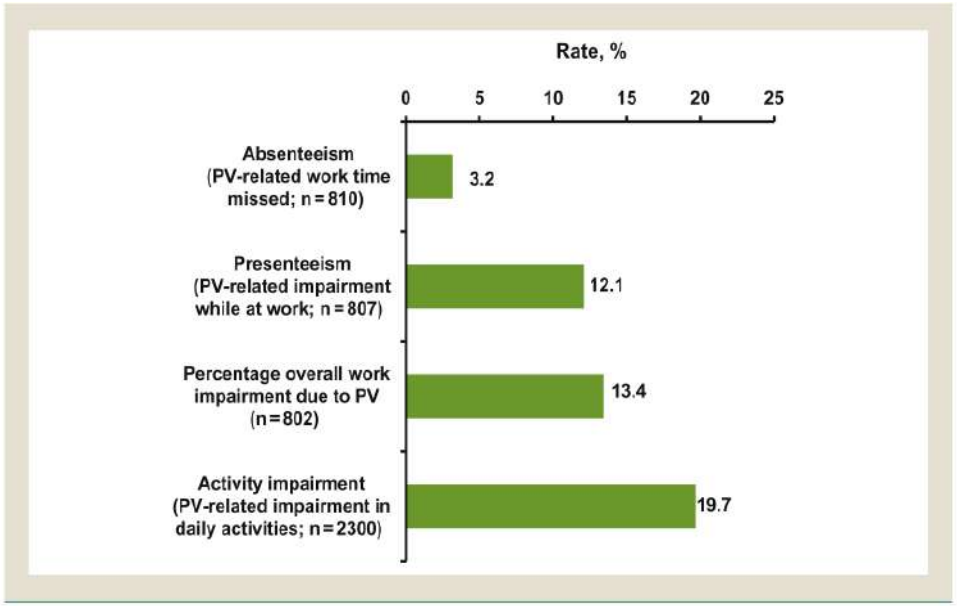


Mesa et al, Clinical Lymphoma, Myeloma & Leukemia 2018

Harrison et al, Ann Hematol 2017

Symptomatic burden in PV





Geyer et al, JCO 2016

Mesa et al, Clinical Lymphoma, Myeloma & Leukemia 2018

Patient vs Physician perspective

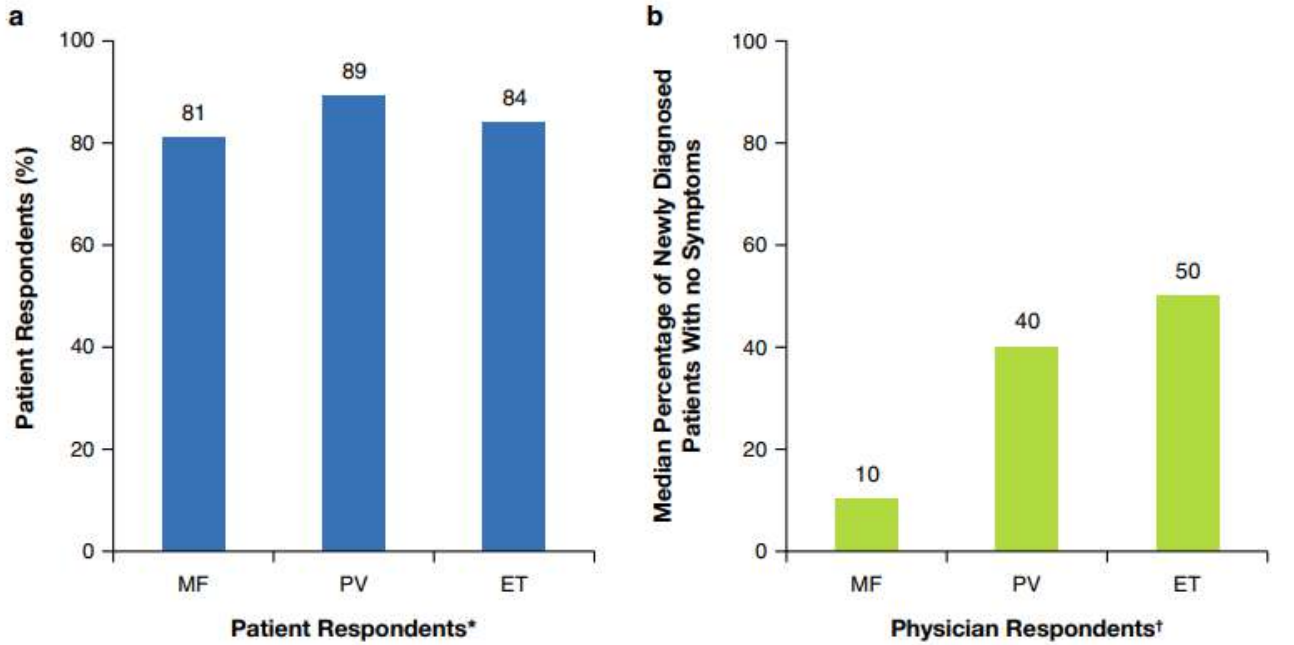
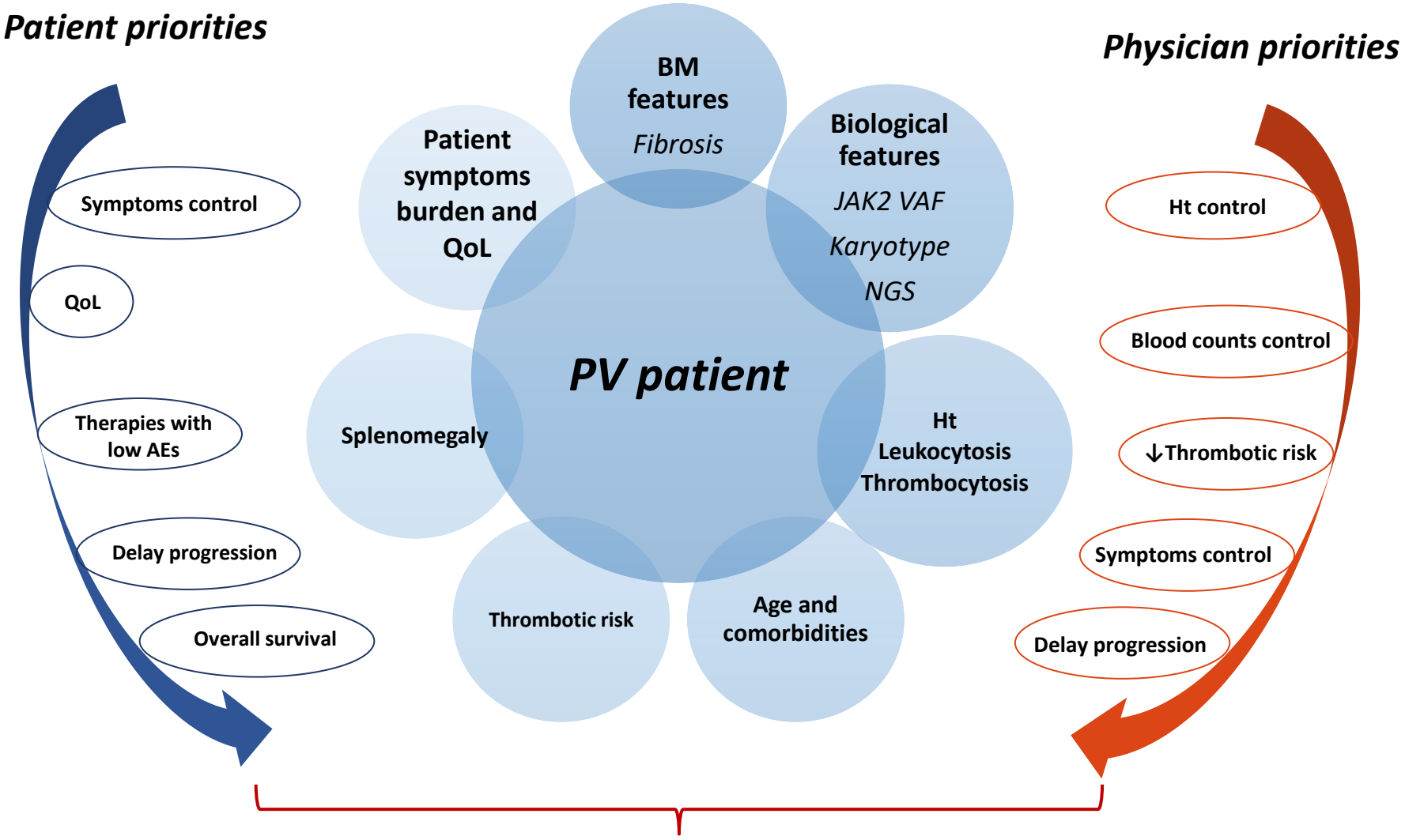


Fig. 3 Myeloproliferative neoplasm-related symptoms at diagnosis among **a** patient and **b** physician respondents. *The question to patient respondents was "Which of these symptoms were you experiencing at the time of diagnosis?" The analysis included the percentages of patient respondents who did not answer "none." †The question to physician respondents was "Out of 100%, what proportion of all newly diagnosed patients do you estimate have no symptoms?" The analysis included the median value provided by physician respondents for the proportion of newly diagnosed patients with symptoms. ET essential thrombocythaemia, MF myelofibrosis, PV polycythaemia

Petruk, Adv Ther 2020


Patient priorities
Physician priorities
BM features
Fibrosis
Patient symptoms burden and QoL
Biological features
JAK2 VAF
Karyotype
NGS
PV patient
Splenomegaly
Ht
Leukocytosis
Thrombocytosis
Thrombotic risk
Age and comorbidities
Symptoms control
QoL
Therapies with low AEs
Delay progression
Overall survival
Ht control
Blood counts control
↓Thrombotic risk
Symptoms control
Delay progression
Impact on diagnosis, prognosis and treatment plan definition

Conclusions

- PV is a complex disease with many aspects that can deeply influence patients life, QoL and prognosis
- Even low-risk patients can present a highly symptomatic disease
- A modern diagnostic approach must take all these aspects into consideration
- With the advent of new drugs capable of profoundly modifying the control of the disease and symptoms, a multifactorial assessment is essential at diagnosis and during the treatment phase of the patient

A. Palladio, Villa «la Rotonda», Vicenza

Grazie