UNIKLINIK RWTH AACHEN

Centrum für Integrierte Onkologie – CIO Aachen

Diagnostic Criteria for ET, PV & MF, biological aspects

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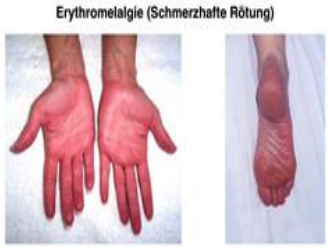
Conflicts of interest

1. **Employment**
   none
2. **Advisory role**
   Ariad/Incyte, Novartis, Pfizer, GSK
3. **Stock ownership**
   none
4. **Honoraria**
   Ariad/Incyte, BMS, Novartis, Pfizer, GSK, AOP Orphan
5. **Financing of research projects**
   none
6. **Consultancy**
   none
7. **Travel reimbursement**
   Alexion, Amgen, Hexal, Mundipharma, Novartis, Pfizer, Roche, AOP Orphan
8. **Others**
   none

Questions to be covered:

- What brings patients to their physician?
- What tests are run by the doctor?
- What are the diagnostic criteria for ET, PV and MF?
- Why is it important to distinguish between the different subtypes?

What brings the patient to the physician?



Source: http://o.quizlet.com/1-uSJoUw.oTB8DHQuXKEUw_m.png; https://www.nature-et-forme.com/page/dossier/de-quelle-fatigue-sagit-il ; https://virinchihospitals.com/stomach-pain-causes/ ; https://stress.app/blog/concentration-disorder-what-solutions/ ; https://www.sleepadvisor.org/night-sweats/ ; https://www.acsh.org/news/2017/01/09/when-itching-bigger-deal-10706 ; https://mobilephysiotherapyclinic.in/bone-pain/ ; https://thedoctorskitchen.com.au/blogs/news/5-percent-weight-loss

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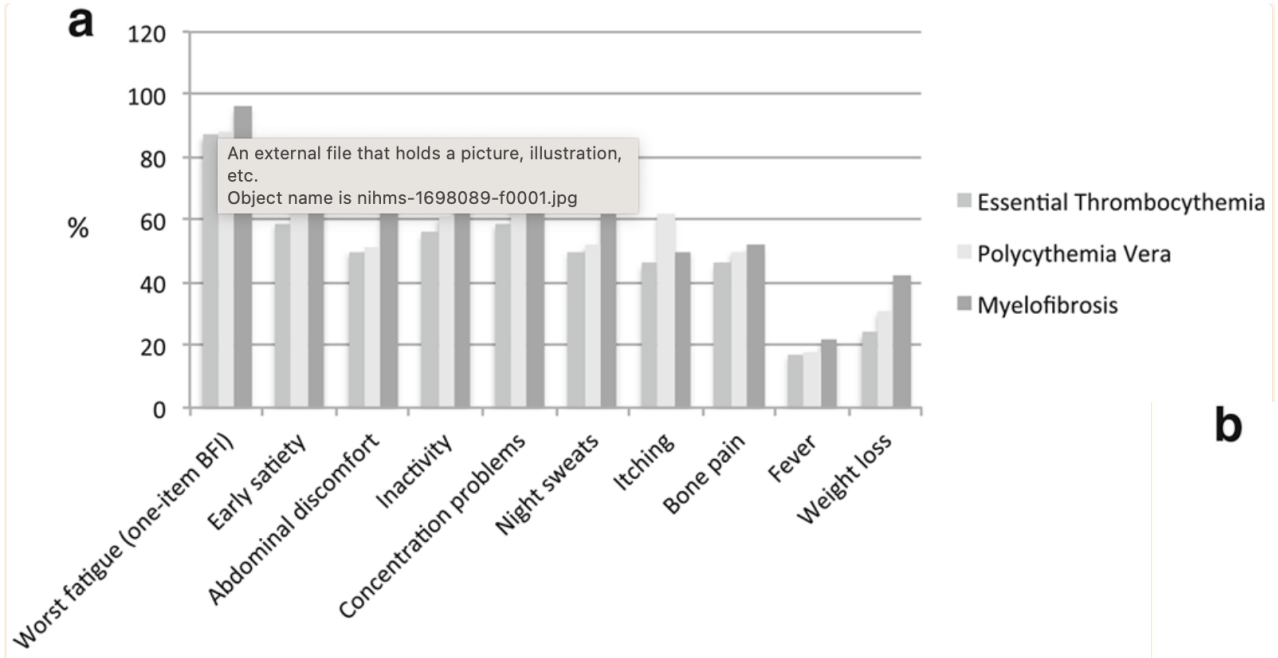
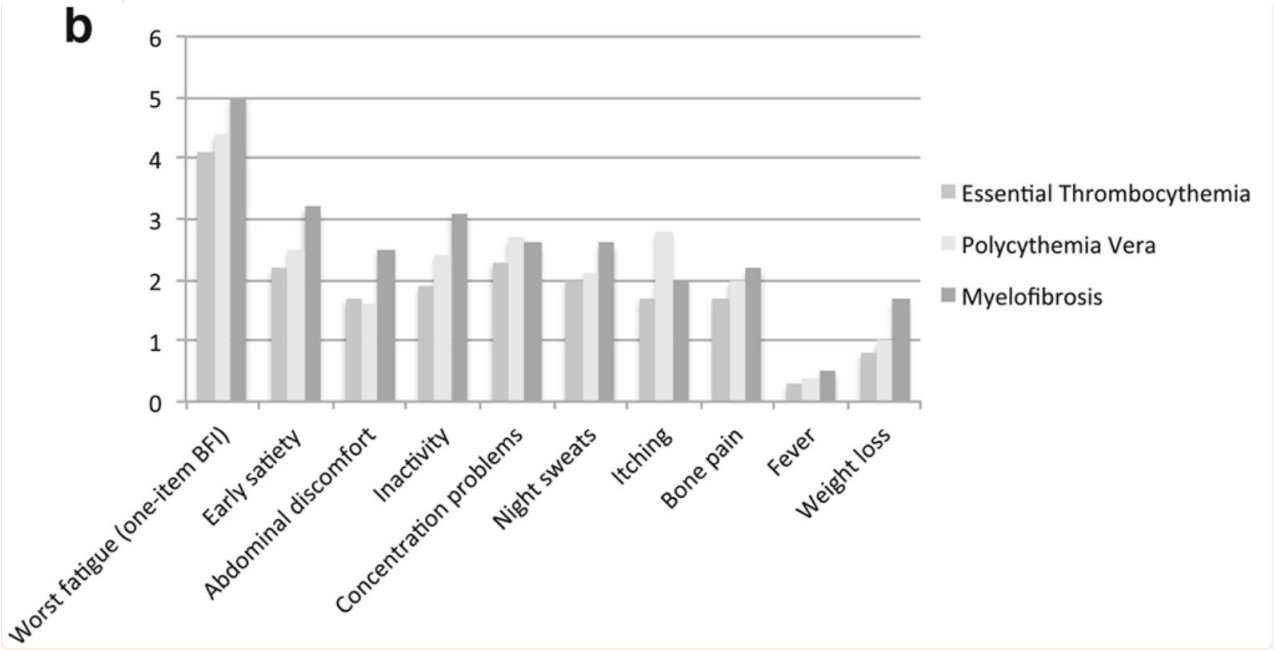
PV & ET & MF – frequencies of symptoms





Source: Geyer H. et al.; Curr Hematol Malig Rep. 2017 Oct; 12(5): 381–388.

PV & ET & MF – Why brings GPs to send a patient to the hematologist?

	Hb	Hct	Platelet count	WBC	Blasts	LDH	Spleen
PV	>16.5 g/dL in men >16.0 g/dL in women	>49% men >48% women	possibly raised	possibly raised	none	normal	possibly enlarged (70%)
ET	normal	normal	≥450 x 10^9/L	normal	none	normal	possibly mildly enlarged (50%)
pre-PMF	normal or decreased	normal	possibly raised	≥11 x 10^9/L	not increased	discretely raised	possibly enlarged
PMF	decreased	normal or decreased	both raised and decreased	≥11 x 10^9/L	possibly raised	raised	enlarged >19 cm (9)

Source: adapted from Njue I et al., . *healthbook TIMES Oncology Hematology*. 2020;6(4):24-34. doi:10.36000/hbT.OH.2020.06.024

PV & ET & MF – What complications might occur before diagnosis?

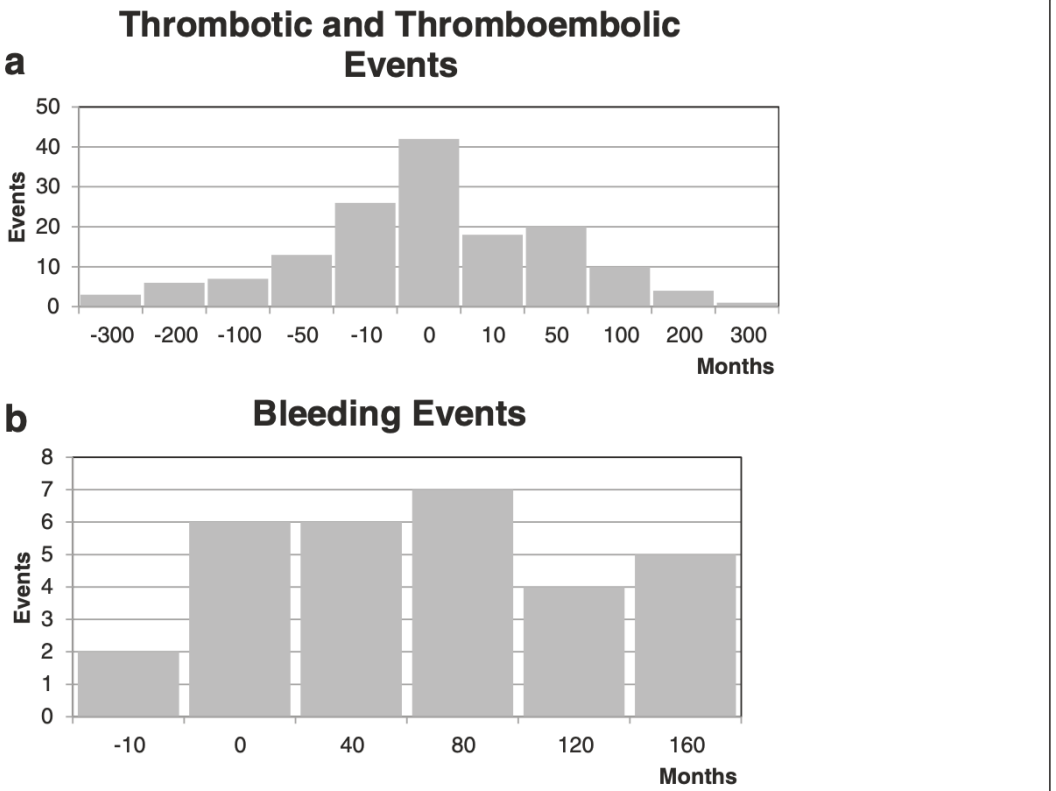


Fig. 2 Number of thrombotic/thromboembolic (**a**) and major bleeding events (**b**) in MPN over time in months. The *0* (zero) marks the date of diagnosis. In **a** (thrombotic and thromboembolic events), there are several events before and after diagnosis which presents almost like a normal distribution. While in **b** (bleedings events), there were only two cases of major bleedings described before date of diagnosis—all other major bleedings occurred after that date

Source: Kaifie et al., *Journal of Hematology & Oncology* **volume 9**, Article number: 18 (2016)

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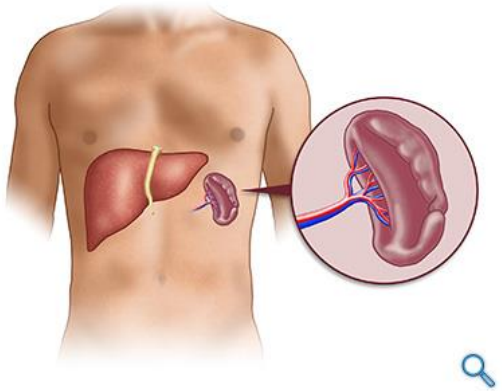
PV & ET & MF – Diagnostics

- Focused interview of the patient:
  - Symptoms including date of onset, intensity
  - Former blood counts
  - Former thrombembolic events
- Physical examination, with special focus on:
  - Cardiopulmonal auscultation results
  - Spleen and liver size
  - Signs of microcirculation problems
  - Skin inspection
- Abdominal ultrasound:
  - Special focus on spleen, liver and kidneys
- On special occasions:
  - Pot. ECG, Echocardiogram
  - Lung function tests



Source:adapted from DGHO Leitlinie zur PV, Onkopedia 2021, https://www.cml-wissen.de/grafik_01_Symptome-Milz-Leber_klein.jpg

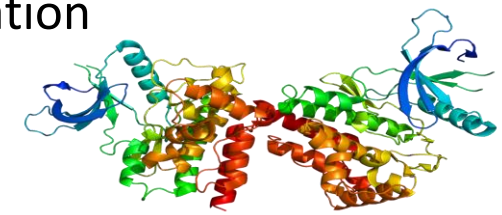
PV & ET – Lab diagnostics

- Full clood counts including differential blood count and blood smear
- Pot. arterial blood gas analysis
- Inflammation parameters (erythrocyte sedimentation rate or CRP)
- LDH, ferritin, AST, ALT, gGT, ALP, bilirubin, uric acid
- Coagulation parameters (INR, PTT)
- Erythropoetin levels
- Pot. ristocetin-cofactor

Source: DGHO Leitlinie zur PV, Onkopedia 2021

PV & ET & MF – Further diagnostics

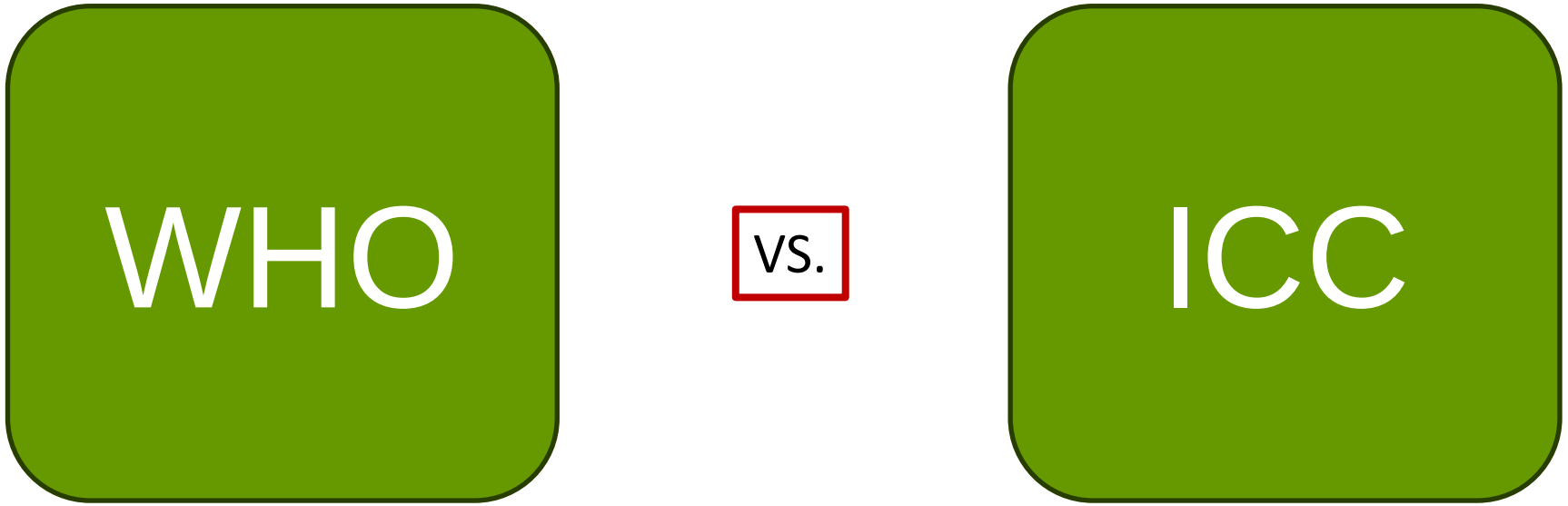
- Molecular genetic analysis
  - JAK2V617F-mutation
  - Exon-12-mutation of the JAK2 gene
  - BCR-ABL-fusion gene, in case of negative JAK2-mutation
  - CALR and MPL-mutations



- Bone marrow biopsy:
  - Mandatory in ET, MF and most cases of PV
  - In all cases meaningful regarding assessment of disease progression, initial fibrosis, blast counts
  - Aspiration and histology including iron- and fibre staining
  - In unclear cases directly include a reference pathologist

Source: adapted DGHO Leitlinie zur PV, Onkopedia 2021;
http://en.wikipedia.org/wiki/Janus_kinase_2

Diagnostic criteria of MPN in 2023



Diagnostic criteria of MPN according to WHO

The 2016 WHO Classification of MPN:

The 2008 WHO Classification of MPN	The 2016 WHO Classification of MPN
Chronic myeloid leukemia, *BCR-ABL1*–positive	Chronic myeloid leukemia, *BCR-ABL1*–positive
Chronic neutrophilic leukemia	Chronic neutrophilic leukemia
Polycythemia vera	Polycythemia vera
Primary myelofibrosis (PMF)	Primary myelofibrosis (PMF) Primary myelofibrosis, prefibrotic/early stage Primary myelofibrosis, overt fibrotic stage
Essential thrombocythemia	Essential thrombocythemia
Mastocytosis	Chronic eosinophilic leukemia, not otherwise specified (NOS)
Chronic eosinophilic leukemia, not otherwise specified (NOS)	Myeloproliferative neoplasm, unclassifiable
Myeloproliferative neoplasm, unclassifiable	

WHO-Classification of 2022 had only minimal changes in comparison to 2016

Source: Vardiman JW et al; Blood 2008; Arber DA et al; Blood 2016

Diagnostic criteria for ET (WHO & ICC)

2008 WHO diagnostic criteria

	Essential thrombocythemia[a]
1	Platelet count $\geqslant 450 \times 10^9 l^{-1}$
2	Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid Proliferation.
3	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm
4	Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive thrombocytosis

Table 5. WHO criteria for ET

WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

ET

Major criteria
- Platelet count ≥450 × 10^9/L
- BM biopsy showing proliferation of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters‡; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis
- Diagnostic criteria for *BCR*::*ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met
- *JAK2*, *CALR*, or *MPL* mutation

Minor criterion
- Clonal marker or absence of evidence of reactive thrombocytosis

Diagnosis
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criterion

Source: Vardiman JW et al; Blood 2008; Arber DA et al; Blood 2016 ; Arber DA,, et al. Blood. 2022;140(11):1200-1228. DOI: 1182/blood.2022015850

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Diagnostic criteria for PV (WHO & ICC)

2008 WHO diagnostic criteria

		Polycythemia vera[a]
Major criteria	1	Hgb $>18.5\,g\,dl^{-1}$ (men) $>16.5\,g\,dl^{-1}$ (women) or Hgb or Hct >99th percentile of reference range for age, sex or altitude of residence or Hgb $>17\,g\,dl^{-1}$ (men), or $>15\,g\,dl^{-1}$ (women) if associated with a sustained increase of $\geqslant 2\,g\,dl^{-1}$ from baseline that cannot be attributed to correction of iron deficiency or Elevated red cell mass >25% above mean normal predicted value
	2	Presence of *JAK2*V617F or similar mutation
Minor criteria	1	BM trilineage myeloproliferation
	2	Subnormal serum Epo level
	3	EEC growth

Table 4. WHO criteria for PV

WHO PV criteria
Major criteria
1. Hemoglobin >16.5 g/dL in men
Hemoglobin >16.0 g/dL in women
or,
Hematocrit >49% in men
Hematocrit >48% in women
or,
increased red cell mass (RCM)*
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion†

*More than 25% above mean normal predicted value.

†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

PV

Major criteria
- Elevated Hb concentration haematocrit or increased RBC mass†
- *JAK2*^{V617F} or *JAK2* exon 12 mutation
- BM biopsy showing age-adjusted hypercellularity with trilineage proliferation, including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia

Minor criterion
- Subnormal serum erythropoietin level

Diagnosis
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion

Source: Vardiman JW et al; Blood 2008; Arber DA et al; Blood 2016 ; Arber DA,, et al. Blood. 2022;140(11):1200-1228. DOI: 1182/blood.2022015850

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Diagnostic criteria for PMF (WHO & ICC)

2008 WHO diagnostic criteria

Primary myelofibrosis[a]

1 Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).

2 Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm

3 Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive marrow fibrosis

1 Leukoerythroblastosis
2 Increased serum LDH
3 Anemia
4 Palpable splenomegaly

2016 WHO -Kriterien

Table 6. WHO criteria for prePMF

WHO prePMF criteria
Major criteria
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting the WHO criteria for *BCR-ABL1*$^+$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of minor reactive BM reticulin fibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^9/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

Table 7. WHO criteria for overt PMF

WHO overt PMF criteria
Major criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^+$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive myelofibrosis‡
Minor criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^9/L
c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range
e. Leukoerythroblastosis
Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

PMF, early/prefibrotic 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
- *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis
- Diagnostic criteria for *BCR-ABL1*-positive CML, PV, ET, MDS, or other myeloid neoplasms are not met

Minor criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10^9/L
- Palpable splenomegaly
- LDH level above the reference range

Diagnosis
The diagnosis of pre-PMF requires all 3 major criteria and ≥1 minor criterion

PMF, overt fibrotic stage

Major criteria
- BM biopsy showing megakaryocytic proliferation and atypia[§], accompanied by reticulin and/or collagen fibrosis grades 2/3
- *JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of reactive MF
- Diagnostic criteria for ET, PV, *BCR-ABL1*-positive CML, MDS, or other myeloid neoplasms are not met

Minor criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10^9/L
- Palpable splenomegaly
- LDH level above the above the reference range
- Leukoerythroblastosis

Diagnosis
The diagnosis of overt PMF requires all 3 major criteria and ≥1 minor criterion confirmed in 2 consecutive determinations.

Source: Vardiman JW et al; Blood 2008; Arber DA et al; Blood 2016 ; Arber DA,, et al. Blood. 2022;140(11):1200-1228. DOI: 1182/blood.2022015850

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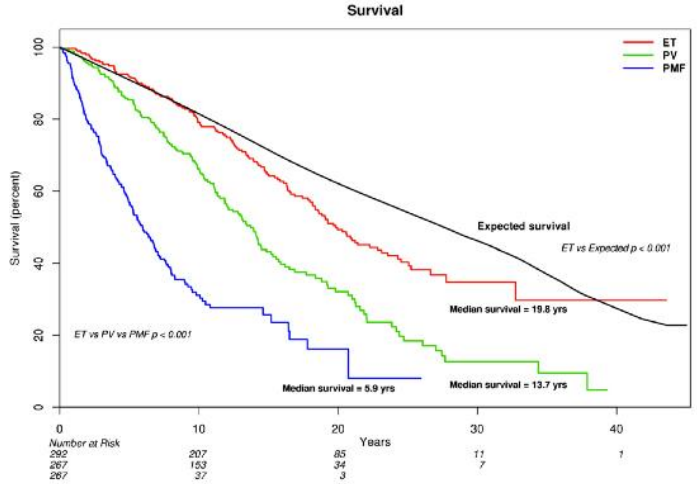
Why is it important to distinguish between all 4 subtypes?

- Prognosis of MPN subentities is different



- Therapies and labels for drugs are different

Treatment at registration (first-treatment analysis)	Anagrelide N=804		Other CRT N=2666		Anagrelide + other CRT N=141	
	Patients (events) n	Event rate	Patients (events) n	Event rate	Patients (events) n	Event rate
Myelofibrosis	28 (28)	1.04	29 (29)	0.30	7 (7)	1.91
Myelodysplasia	0	0	12 (12)	0.12	0	0
Acute leukemia	2 (2)	0.07	27 (27)	0.28	2 (2)	0.53
Other leukemia*	5 (5)	0.18	13 (13)	0.13	0	0
Treatment at time of event (overall-treatment analysis)	**Anagrelide N=1127**		**Other CRT N=2909**		**Anagrelide + other CRT N=451**	
Myelofibrosis	45 (45)	1.31	35 (35)	0.32	11 (11)	1.27
Myelodysplasia	1 (1)	0.03	14 (14)	0.13	2 (2)	0.23
Acute leukemia	6 (6)	0.17	36 (36)	0.33	4 (4)	0.46
Other leukemia*	5 (5)	0.14	13 (13)	0.12	1 (1)	0.11

*"Other leukemia" includes chronic myelogenous leukemia and unclassified leukemia. CRT: cytoreductive therapy.

Table 4.*Cumulative transformation event rates by first- and overall-treatment analysis populations.

Source: Birgegard G. et al.; Haematologica Vol. 103 No. 1 (2018): January, 2018 ; Tefferi et al. , Blood, 2014

Thank you for your attention!

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Starting december 2023 in Hannover