Essential Thrombocythemia: Disease State Overview

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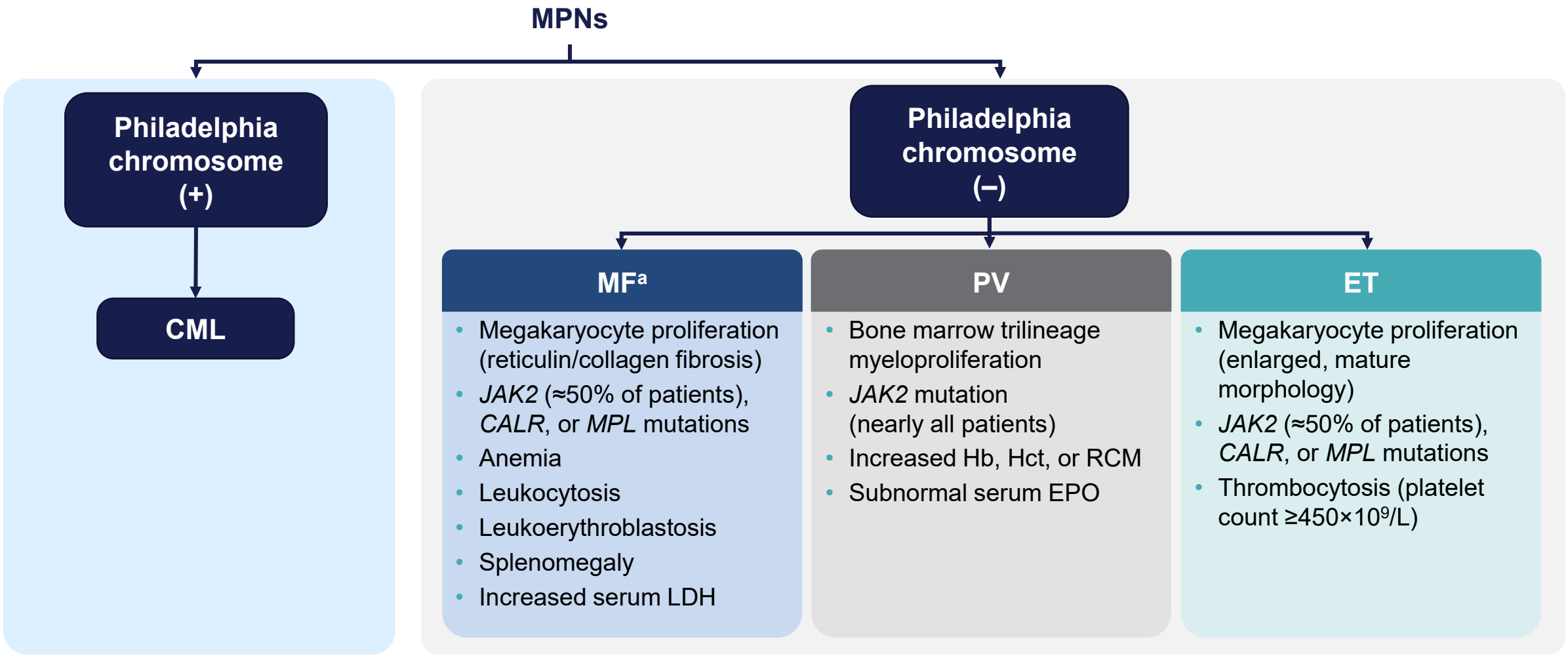
MPN Epidemiology and Overview

MF, PV, and ET Are Philadelphia-Negative MPNs



[a] MF includes primary MF, post-PV MF, and post-ET MF.

CALR, calreticulin; CML, chronic myeloid leukemia; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; Hct, hematocrit; JAK2, Janus kinase 2; LDH, lactate dehydrogenase; MF, myelofibrosis; MPL, MPL proto-oncogene thrombopoietin receptor; MPNs, myeloproliferative neoplasms; PV, polycythemia vera; RCM, red cell mass.

Arber DA, et al. *Blood*. 2016;127:2391-2405.

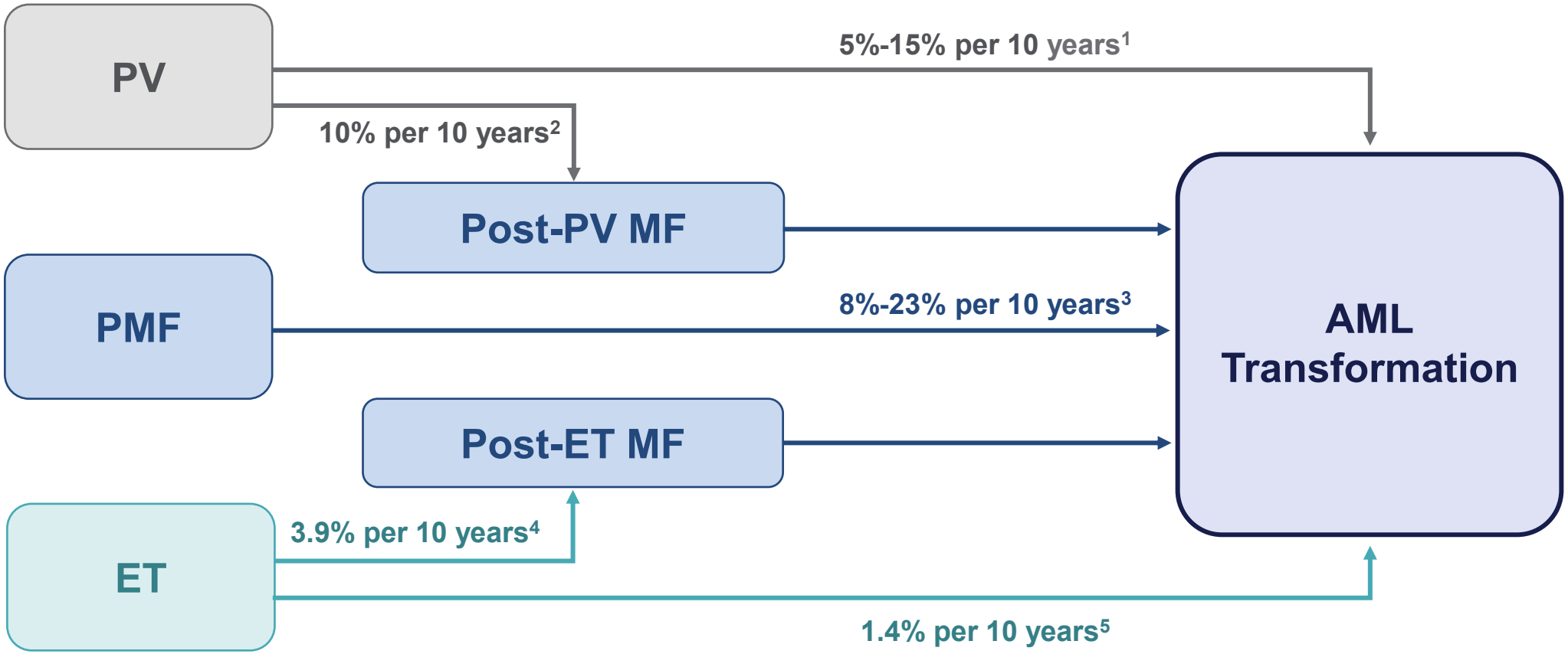
MPNs Are Rare and Usually Develop Later in Life

	MF	PV	ET
Prevalence	4-6 cases per 100,000[1,2]	44-57 cases per 100,000[1,3]	38-57 cases per 100,000[1]
Incidence	≈2-3 cases per 100,000[1,2]	≈1-3 cases per 100,000[4]	2.0-2.4 cases per 100,000[1,5]
Median age at diagnosis	>65 years and slightly more common in men than in women; ≈60% of affected patients are men[6]	60 years; similar frequency in men and women[7,8]	60 years[5]
Bone marrow abnormalities	Excess fibrous tissue and increase in megakaryocytes[9]	Trilineage myeloproliferation and pleomorphic megakaryocytes[10]	Increased megakaryocytes[9]
Blood cell abnormalities	Reduced RBCs;[9] variable/increased WBCs[9]	High Hct;[9] increased RCM[9]	Elevated platelets;[9] no or few WBCs or RBCs[9]
% with *JAK2* mutation[a]	≈50% of patients[10]	>99%[11,a]	≈50% of patients[10]
% with CALR mutation[b]	≈35% of patients[12]	Not observed[12]	≈25% of patients[12]
Median survival	4.4-7.4 years[13,14]	14-15 years after diagnosis[8,14]	15-20 years[14,15]

[a] *JAK2* alterations include *JAK2* V617F mutations and *JAK2* exon 12 mutations.
CALR, calreticulin; RBCs, red blood cells; WBCs, white blood cells. [b] Based on a MPN cohort of 896 patients.[12]

1. Mehta J, et al. *Leuk Lymphoma*. 2014;55:595-600. 2. Data on file, Incyte Corporation. 3. Stein B, et al. *J Clin Oncol*. 2015;33:3953-3960. 4. Johansson P. *Semin Thromb Hemost*. 2006;32:171-173. 5. Girodon F, et al. *Haematologica*. 2009;94:865-869. 6. Gangat N, et al. *J Clin Oncol*. 2010;29:392-397. 7. National Cancer Institute. Accessed Sep 2024. http://seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd538d/. 8. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 9. Campbell PJ, Green AR. *N Engl J Med*. 2006;355:2452-2466. 10. Arber DA, et al. *Blood*. 2016;127:2391-2405. 11. Pardanani A, et al. *Leukemia*. 2007;21:1960-1963. 12. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390 [supplementary appendix]. 13. Cervantes F, et al. *J Clin Oncol*. 2012;30:2981-2987. 14. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 15. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770.

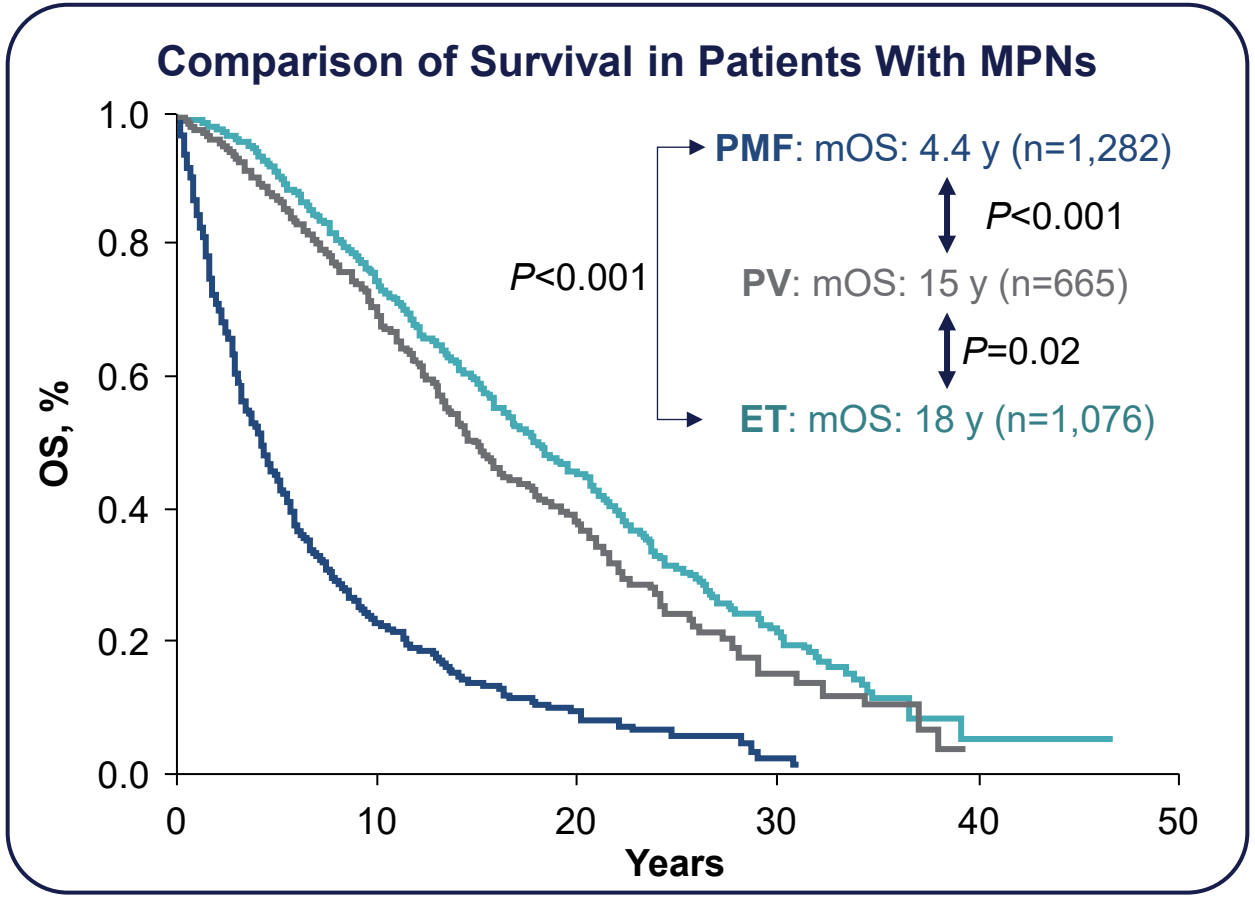
MPN Disease Progression and Transformation



AML, acute myeloid leukemia; PMF, primary myelofibrosis.

1. Finazzi G, et al. *Blood*. 2005;105:2664-2670. 2. Tefferi A. *Am J Hematol*. 2008;83:491-497. 3. Mesa RA, et al. *Blood*. 2005;105:973-977. 4. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 5. Wolanskyj AP, et al. *Mayo Clin Proc*. 2006;81:159-166.

MPN Survival Outcomes



MPN	Median Survival (All Patients)
PMF	4.4 years
PV	15 years
ET	18 years

MPN	Median Survival (High-Risk Patients)
PMF	1.5 years
PV	9.6 years
ET	10.2 years

mOS, median overall survival; OS, overall survival.

Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610.

BACK

Essential Thrombocythemia

- Mechanism of disease
- Disease Characteristics
- Clinical Work-Up, Diagnosis, and Stratification

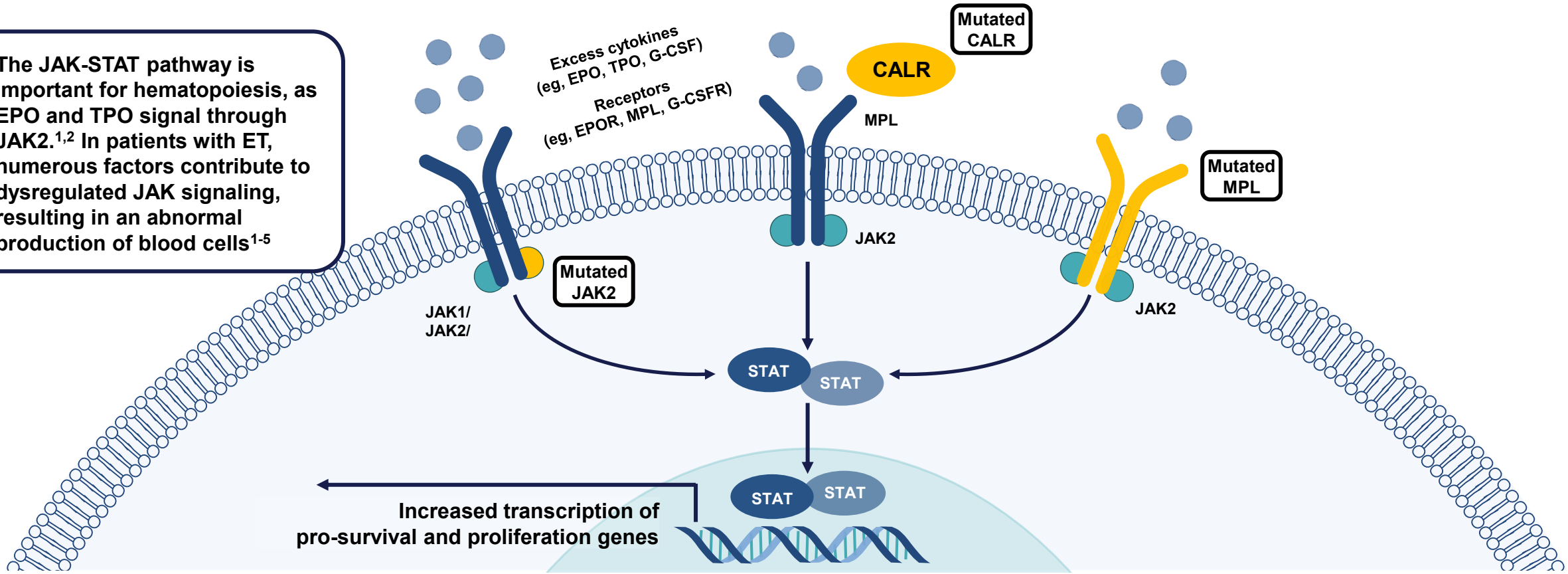
BACK

Mechanism of Disease

Essential Thrombocythemia

Overactive JAK Signaling Is Present in Most Patients With ET, Leading to Abnormal Blood Cell Production

The JAK-STAT pathway is important for hematopoiesis, as EPO and TPO signal through JAK2.[1,2] In patients with ET, numerous factors contribute to dysregulated JAK signaling, resulting in an abnormal production of blood cells[1-5]



CALR, calreticulin; EPO, erythropoietin; EPOR, erythropoietin receptor; G-CSF, granulocyte colony-stimulating factor; G-CSFR, granulocyte colony-stimulating factor receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, thrombopoietin receptor; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK2, tyrosine protein kinase 2.

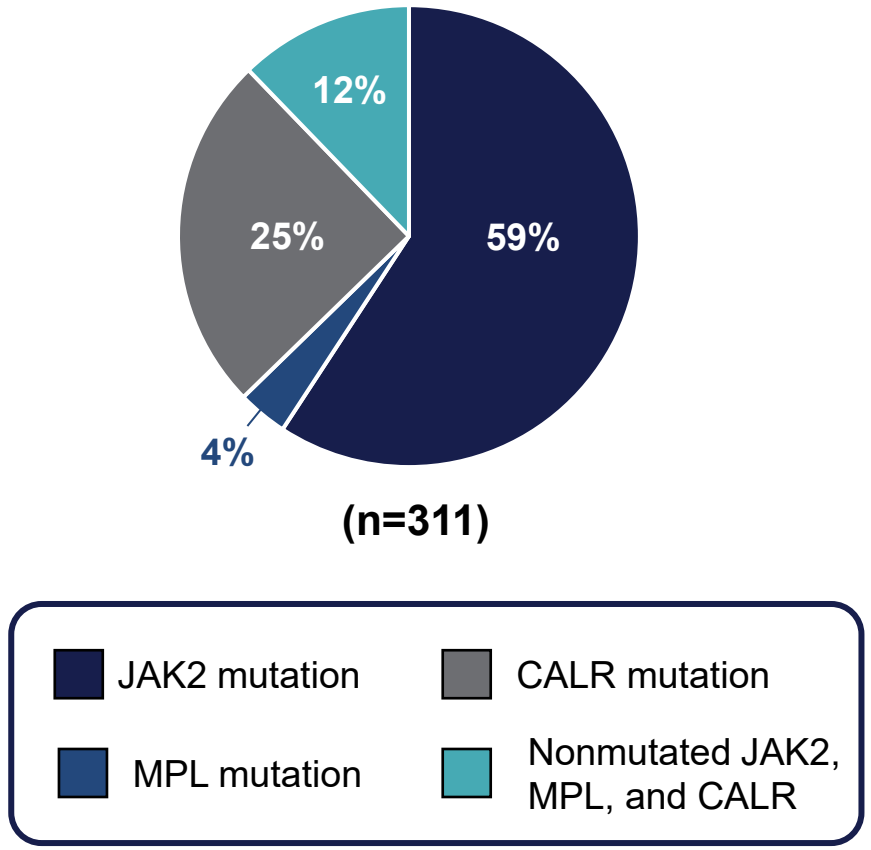
1. Quintás-Cardama A, et al. *Nat Rev Drug Discov.* 2011;10:127-140. 2. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390. 3. Vainchenker W, et al. *Blood.* 2011;118:1723-1735. 4. Vainchenker W, Kralovics R. *Blood.* 2017;129:667-679. 5. Jang MA, Choi CW. *Korean J Intern Med*. 2020;35:1-11.

Prevalence of Driver Mutations in Essential Thrombocythemia

Driver Mutations in ET

- **JAK2V617F**
  - Causes constitutive activation of the JAK-STAT pathway, leading to cytokine-independent megakaryocyte proliferation[1]
- **CALR mutations**
  - Mutant calreticulin binds and activates MPL, leading to JAK2 activation[2]
- **MPL mutations**
  - Thrombopoietin receptor mutations result in hypersensitivity to TPO and downstream JAK-STAT activation[3]
- **Triple negative**
  - Lack JAK2, CALR, or MPL mutations; disease mechanisms remain unclear in this subgroup[2]

Mutation Frequencies in ET[4]



1. James C, et al. *Nature*. 2005;434:1144–1148. 2. Klampfl T, et al. *N Engl J Med*. 2013;369:2391–2405. 3. Pikman Y, et al. PLoS Med. 2006;3:e270. 4. Klampfl T, et al. *N Engl J Med*. 2013;369:2391–2405[supplementary appendix].

BACK

Disease Characteristics

Essential Thrombocythemia

ET Hematologic Features and Epidemiology[1]

- ET is characterized by thrombocytosis and abnormal megakaryocyte proliferation[2]
- Patients with ET have increased risks of arterial and venous thrombosis, as well as major bleeding events[3,4]
- Within 10 years of diagnosis, a minority of patients will exhibit fibrotic or leukemic progression:[5-7]
  - ≈6-13% of patients will progress to post-ET MF
  - ≈1-4% of patients will progress to AML

Image Showing Megakaryocyte Dysplasia in a Patient Diagnosed With ET[5]

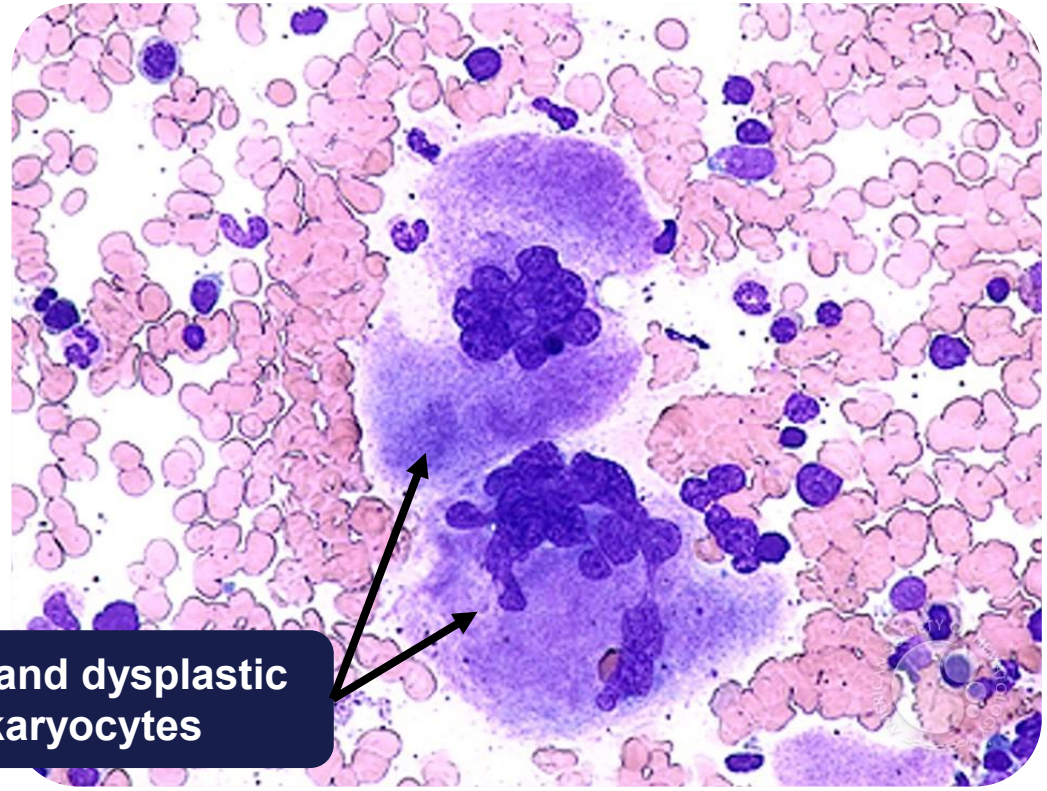


Image used with permission of the American Society of Hematology (ASH), from ASH image bank (https://imagebank.hematology.org [imagebank.hematology.org]) permission conveyed through Copyright Clearance Center, Inc.

AML, acute myeloid leukemia; ET, essential thrombocythemia; MF, myelofibrosis.

1. Godfrey AL, et al. *Blood*. 2023;141:1943-1953. 2. Arber DA, et al. *Blood.* 2022;140:1200-1228. 3. Kaifie A, et al. *J Hematol Oncol*. 2016;9:18. 4. Stuckey R, et al. *Int J Hematol*. 2023;118:589-595. 5. Gangat N, et al. *Blood Cancer J*. 2024;14:11. 6. Loscocco GG, et al. *Blood Cancer J*. 2024;14:10. 7. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 8. American Society of Hematology Image Bank. Accessed Jun 2025. https://imagebank.hematology.org/image/2736/essential-thrombocythemia--2.

Presenting Clinical Features in 2 Large Studies of Patients With ET

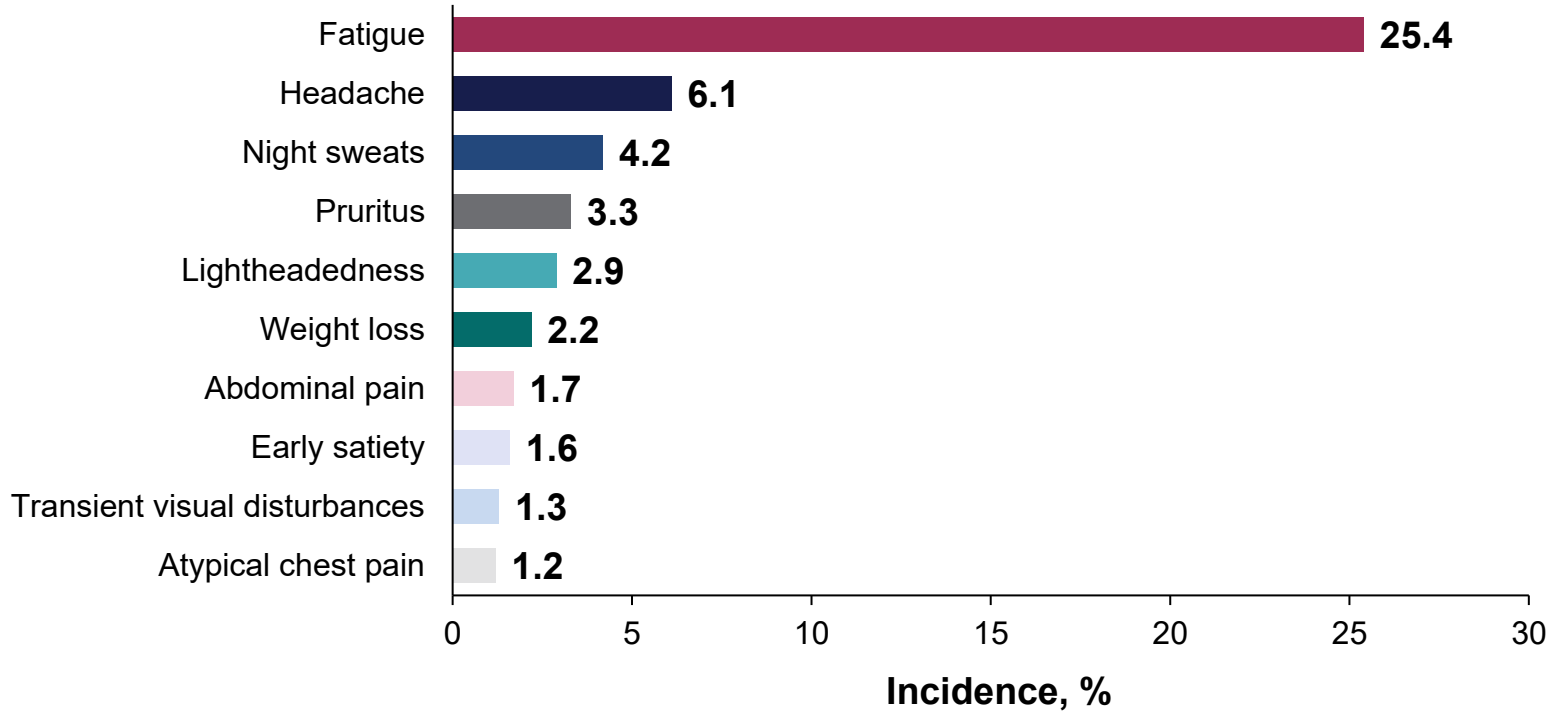
Clinical characteristics at time of presentation		
Presenting characteristic	**Mayo Clinic cohort (N=1,000)[1,a]**	**Florence-CRIMM cohort (N=1,000)[2,b]**
Median Hb, g/dL	13.9	14.0
Leukocyte count, $\times 10^9$/L	8.5	8.5
Platelet count, $\times 10^9$/L	777	715
Leukocytosis,[c] %	20	16
Extreme thrombocytosis,[d] %	26	16
Cardiovascular risk factors, %	54	52
Palpable splenomegaly, %	12	13
Abnormal karyotype, %	6	10
Microvascular symptoms, %	29	29
Major arterial thrombosis at or before diagnosis, %	14	13
Major venous thrombosis at or before diagnosis, %	10	6
Major hemorrhage at or before diagnosis, %	8	4

[a] 1,000 consecutive patients with ET (2022 ICC diagnostic criteria) evaluated at Mayo Clinic, Rochester, MN, United States between 1967-2023 who had bone marrow biopsy and driver mutation information available. [b] 1,000 consecutive patients with ET (2022 ICC and 5th edition WHO classification of myeloid neoplasms) routinely followed at the CRIMM in Florence, Italy, between 1980-2023 who had bone marrow biopsy and driver mutation information available. [c] Leukocyte count >11×10^9/L. [d] Platelet count ≥1,000×10^9/L.
CRIMM, Center Research and Innovation of Myeloproliferative Neoplasms; ICC, International Consensus Classification; WHO, World Health Organization.
1. Gangat N, et al. *Blood Cancer J*. 2024;14:11. 2. Loscocco GG, et al. *Blood Cancer J*. 2024;14:10.

Although ET is Often Indolent, Some Patients With ET May Exhibit a Substantial Symptom Burden

- 32% of patients reported at least 1 ET symptom at time of enrollment
- Several patients were unable to work owing to ET at time of enrollment

Most Common Symptoms at Enrollment for Patients With High-Risk ET or Low-Risk ET on Cytoreductive Therapy (n=1,195)[a]



[a] Of 1,207 total patients enrolled in the United States between 2016-2018, 1,195 were assessed for ET-related symptoms at enrollment. Patients were required to have a clinical diagnosis of ET. Eligible patients had either high-risk ET (≥60 years of age and/or history of thrombotic events) or exhibited low-risk ET and receipt of ET-directed cytoreductive therapy (149 patients with low-risk ET were included in the study; of those, 77% were receiving hydroxyurea, 10% interferon, 9% anagrelide, and 3% ruxolitinib).
Yacoub A, et al. *Clin Lymphoma Myeloma Leuk*. 2021;21:461-469.

BACK

Clinical Work-Up, Diagnosis, and Stratification

Essential Thrombocythemia

ET: 2016 WHO Diagnostic Criteria

2016 WHO Criteria: ☑ Must meet all 4 major OR the first 3 major and the minor

Major

- ☐ Platelet count ≥450×10^9/L
- ☐ Bone marrow 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
- ☐ Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
- ☐ Presence of *JAK2*, *CALR*, or *MPL* mutation

Minor

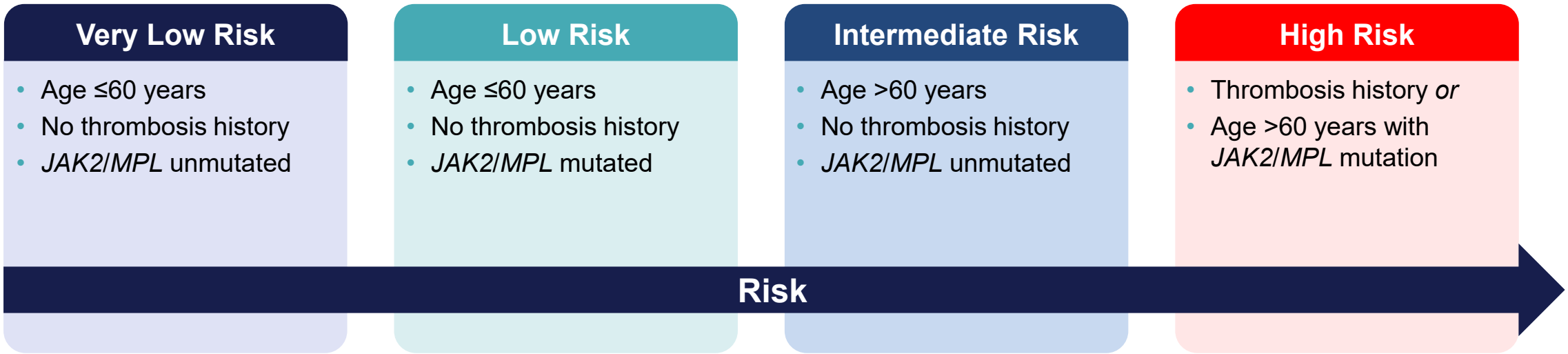
- ☐ Presence of a clonal marker or absence of evidence for reactive thrombocytosis

BCR-ABL, breakpoint cluster region–Abelson murine leukemia viral oncogene homologue; CALR, calreticulin; CML, chronic myeloid leukemia; JAK2, Janus kinase 2; MPL, MPL proto-oncogene thrombopoietin receptor; PMF, primary myelofibrosis; PV, polycythemia vera; WHO, World Health Organization.

Arber DA, et al. *Blood*. 2016;127:2391-2405.

Risk Stratification

Risk Stratification for ET Is Currently Divided Into 4 Major Categories



Because current therapy is aimed at lowering the risk of thrombosis, the most commonly used risk classification system is shaped according to thrombotic risk

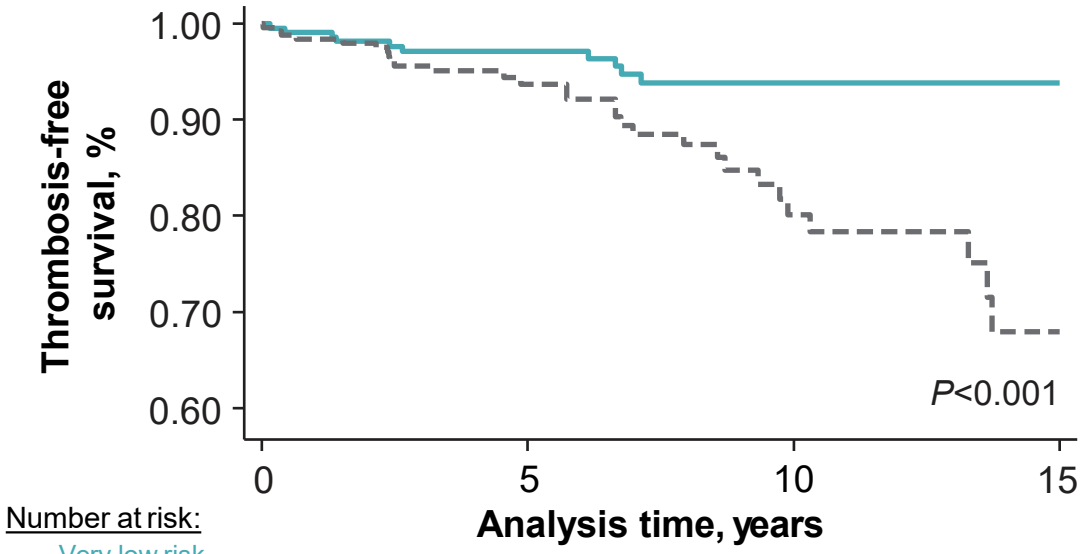
Tefferi A, Barbui T. *Am J Hematol*. 2017;92:94-108.

Thrombosis History, Age, and *JAK2* Mutation Status May Be Used to Predict Risk of Vascular Events

Revised IPSET-Thrombosis Classification Estimates Risk of Thrombosis in ET Using 4 Risk Categories

Very low risk
- Age ≤60 years
- *JAK2* unmutated
- No thrombosis history

Low risk
- Age ≤60 years
- *JAK2* mutation
- No thrombosis history

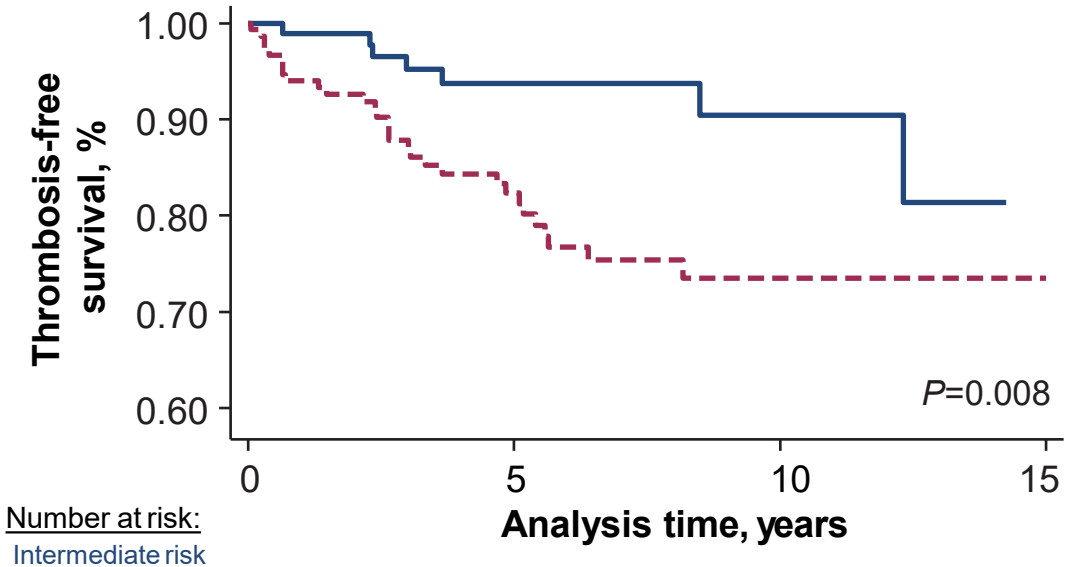


Number at risk:

Very low risk	234	150	75	34
Low risk	264	134	49	15

Intermediate risk
- Age >60 years
- *JAK2* unmutated
- No thrombosis history

High risk
- Age >60 years with *JAK2* mutation; or,
- Thrombosis history



Number at risk:

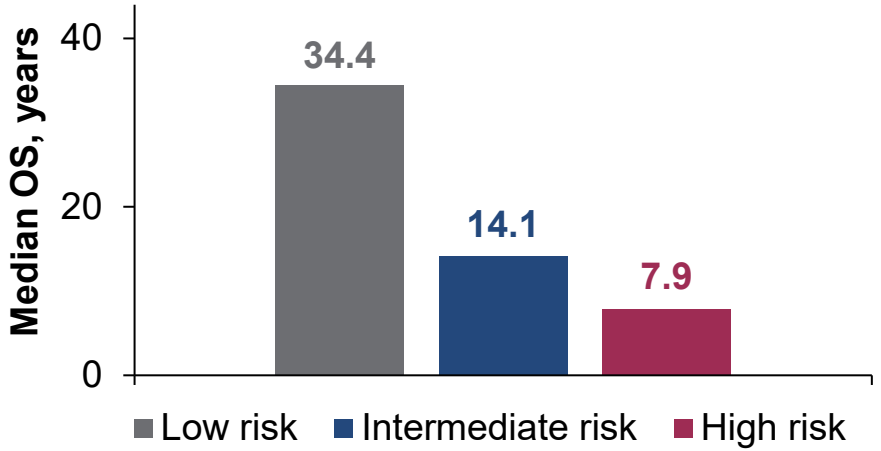
Intermediate risk	99	57	16	2
High risk	159	80	31	12

IPSET, International Prognostic Score of thrombosis in Essential Thrombocythemia.

Barbui T, et al. *Blood Cancer J.* 2015;5:e369.

Prognostic Models for OS in ET

MIPSS-ET[1]



Variable	Points
Male sex	1
Leukocyte count ≥11×10^9/L	1
Adverse mutations (*SRSF2*, *SF3B1*, *U2AF1*, *TP53*)	2
Age >60 years	4

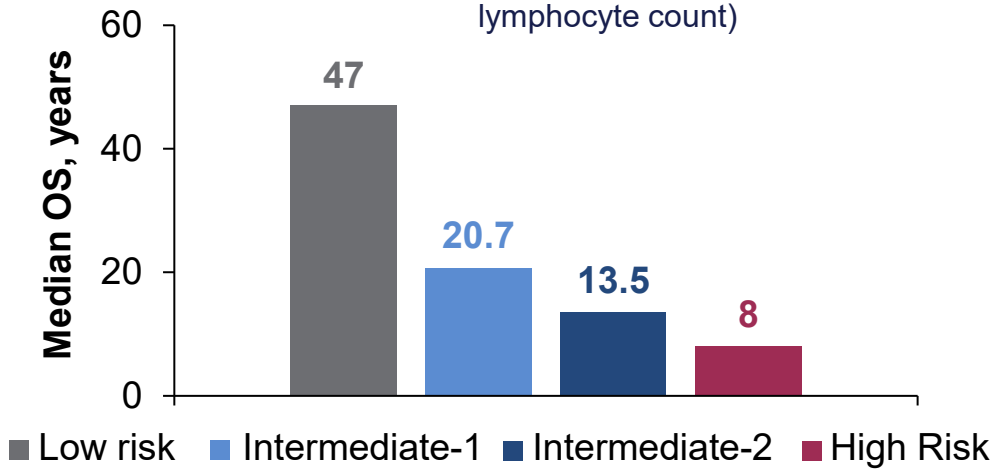
Low risk
0-1 points

Intermediate risk
2-5 points

High risk
≥6 points

"Triple A" Risk Model[2]

(Age, Absolute neutrophil count, Absolute lymphocyte count)



Variable	Points
Absolute lymphocyte count <1.7×10^9/L	1
Absolute neutrophil count ≥8×10^9/L	1
Age 50-70 years	2
Age >70 years	4

Additional prognostic relevance: Abnormal karyotype; mutations in *SRSF2*, *SF3B1*, *U2AF1*, *TP53*

Low risk
0-1 points

Intermediate risk
Int-1: 2-3 points
Int-2: 4 points

High risk
5-6 points

MIPSS, Mutation-Enhanced International Prognostic Scoring System.

1. Tefferi A, et al. *Br J Haematol*. 2020;189:291-302. 2. Tefferi A, et al. *Am J Hematol*. 2023;98:1829-1837.

Summary

- Essential thrombocythemia is defined by sustained thrombocytosis with abnormal megakaryocytic proliferation[1]
- Most cases are associated with JAK2, CALR, or MPL mutations, while a smaller subset remains triple-negative[2]
- Patients are frequently asymptomatic at diagnosis, although some present with vasomotor disturbances, constitutional complaints, or splenomegaly[3]
- The disease carries a risk of progression to MF or AML[4,5]
- Risk stratification is directed toward assessing thrombotic risk and guiding therapeutic decision-making[6]

1. Arber DA, et al. *Blood*. 2016;127:2391-2405. 2. Klampfl T, et al. *N Engl J Med*. 2013;369:2379–2390. 3. Godfrey AL, et al. Blood. 2023;141:1943–1953. 4. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 5. Wolanskyj AP, et al. *Mayo Clin Proc*. 2006;81:159-166. 6. Tefferi A, Barbui T. *Am J Hematol*. 2017;92(1):94-108.

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