Essential Thrombocythemia: Disease State Overview

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BACK

MPN Epidemiology and Overview

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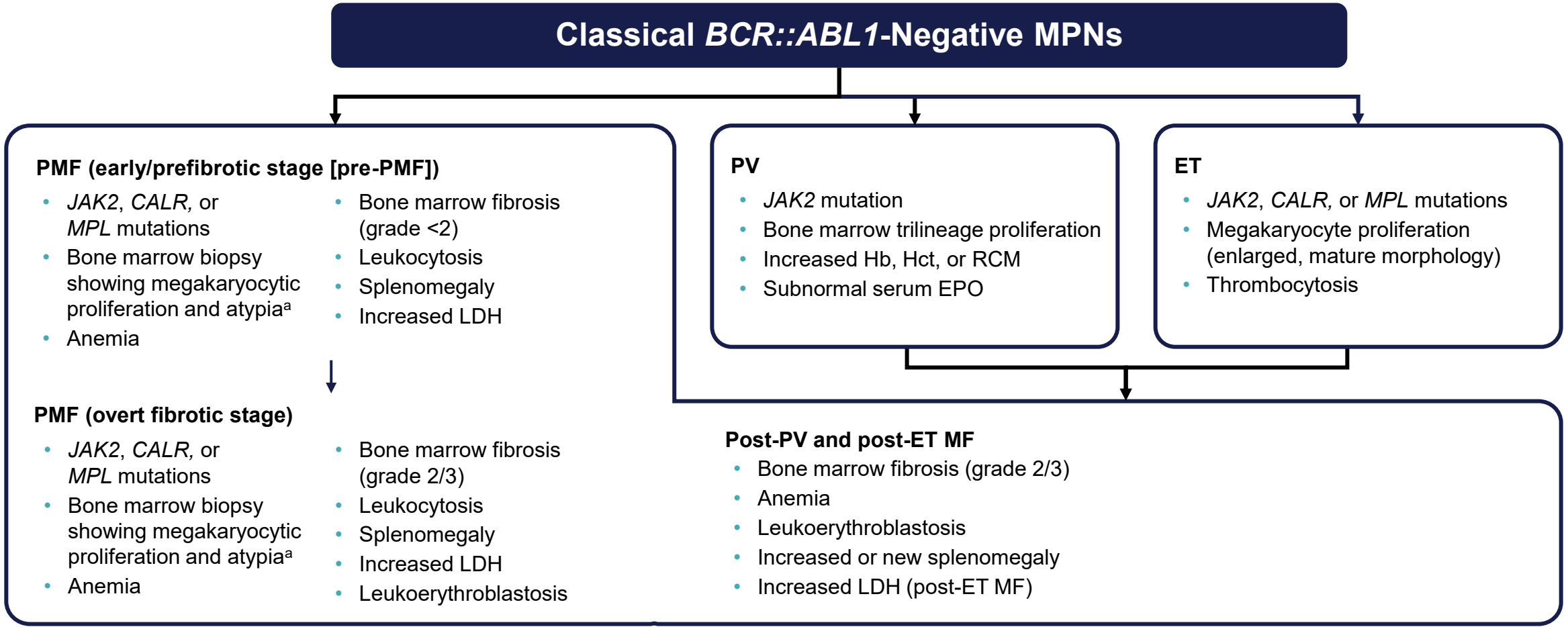
MF, PV, and ET Are *BCR::ABL1*-Negative MPNs



[a] Morphology of megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other MPN subtype.
ABL1, Abelson murine leukemia viral oncogene homolog 1; BCR, breakpoint cluster region; CALR, calreticulin; EPO, erythropoietin; ET, essential thrombocytopenia; Hb, hemoglobin; Hct, hematocrit; JAK, Janus kinase; LDH, lactate dehydrogenase; MF, myelofibrosis; MPL, myeloproliferative leukemia proto-oncogene, thrombopoietin receptor; MPN, myeloproliferative neoplasm; PMF, primary MF; PV, polycythemia vera; RCM, red blood cell mass.
Arber DA, et al. *Blood.* 2022;140:1200-1228.

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MPNs Are Rare and Usually Develop Later in Life

	MF	PV	ET
Prevalence	4-6 cases per 100,000[1]	44-57 cases per 100,000[1]	38-57 cases per 100,000[1]
Incidence	2-3 cases per 100,000 patient-years[1]	1.57 cases per 100,000 patient-years[2]	1.55 cases per 100,000 patient-years[2]
Median age at diagnosis	65 years; slightly more common in men than in women, with men making up ≈60% of patients[3]	61-62 years; similar frequency in men and women[4-6]	58 years[4]
Bone marrow abnormalities	Excess fibrous tissue, megakaryocytes proliferation and atypia[7]	Bone marrow trilineage proliferation and pleomorphic megakaryocytes[7]	Increased megakaryocytes[7]
Blood cell abnormalities	Reduced RBCs, increased WBCs[7]	Elevated Hb, evelated Hct, increased RCM[7]	Elevated platelets[7]
% with *JAK2* mutation	*JAK2*V617F mutation: ≈60% of patients[8]	*JAK2*V617F mutation: ≈96% of patients[9] *JAK2* exon 12 mutation: ≈3% of patients[9]	*JAK2*V617F mutation: ≈55% of patients[9]
% with *CALR* mutation[a]	≈35% of patients[10]	Not observed[10]	≈25% of patients[10]
Median survival	3.6-7.4 years[2,4,11,12]	11.9-14.1 years[2,4,5,11,12]	12.0-20.6 years[2,4,11-13]

[a] Based on an MPN cohort of 896 patients.[10]

RBC, red blood cell; WBC, white blood cell.

1. Mehta J, et al. *Leuk Lymphoma*. 2014;55:595-600. 2. Verstovsek S, et al. *Leuk Lymphoma.* 2022;63:694-702. 3. Gangat N, et al. *J Clin Oncol*. 2010;29:392-397. 4. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 5. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 6. Tefferi A, et al. *Am J Hematol.* 2023; 98(9):1465-1487. 7. Arber DA, et al. *Blood.* 2022;140:1200-1228. 8. Rafati M, et al. *Blood Adv.* 2023;7(24):7506-7515. 9. Tefferi A. *Am J Hematol*. 2021;96:145-162. 10. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390. 11. Tefferi A, et al. *Blood*. 2014;124:2507-2513. 12. Smith CJ, et al. *Am J Hematol*. 2021;96:E464-E468. 13. Gangat N, et al. *Blood Cancer J*. 2024;14:11.

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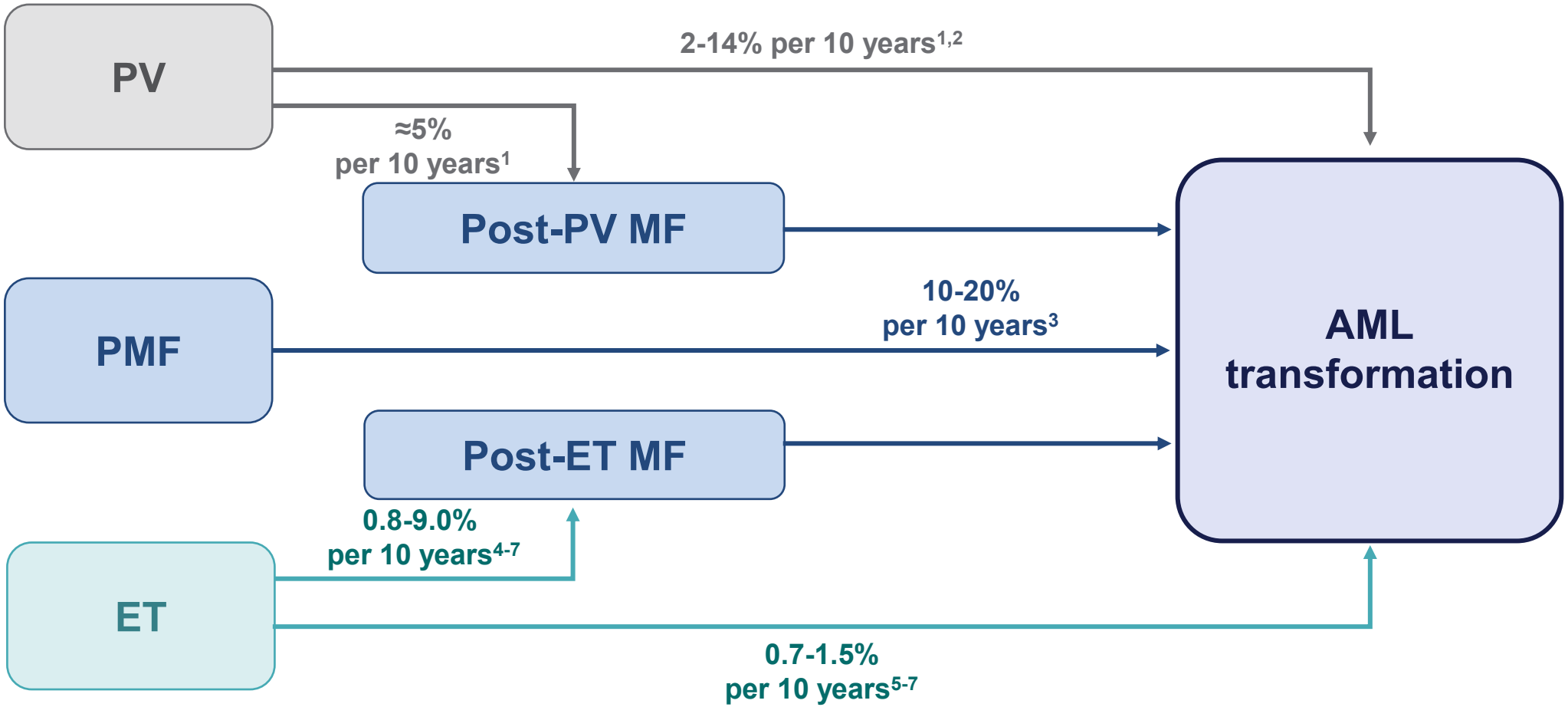
MPN Disease Progression and Transformation



AML, acute myeloid leukemia.

1. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 2. Tefferi A, et al. *Leukemia.* 2013;27(9):1874-1881. 3. Yogarajah M, Tefferi A. *Mayo Clin Proc*. 2017;92(7):1118-1128. 4. Arber DA, et al. *Blood.* 2022;140:1200-1228. 5. Tefferi A, et al. *Am J Hematol.* 2024;99:697-718. 6. Gangat N, et al. *Blood Cancer J*. 2024;14:11. 7. Barbui T, et al. *J Clin Oncol*. 2011;29(23):3179-3184.

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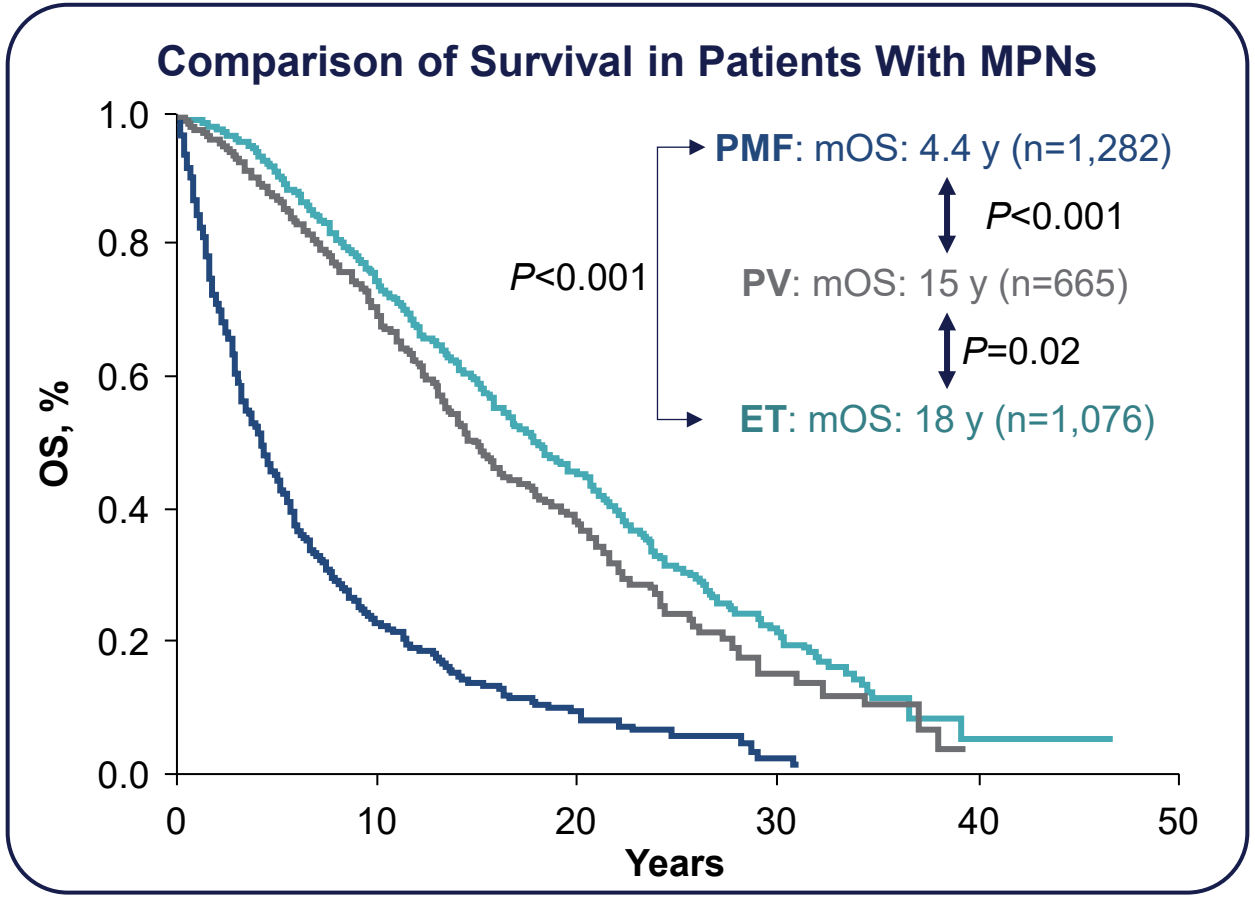
MPN Survival Outcomes



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 OS; OS, overall survival.

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

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BACK

Essential Thrombocythemia

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

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BACK

Mechanism of Disease

Essential Thrombocythemia

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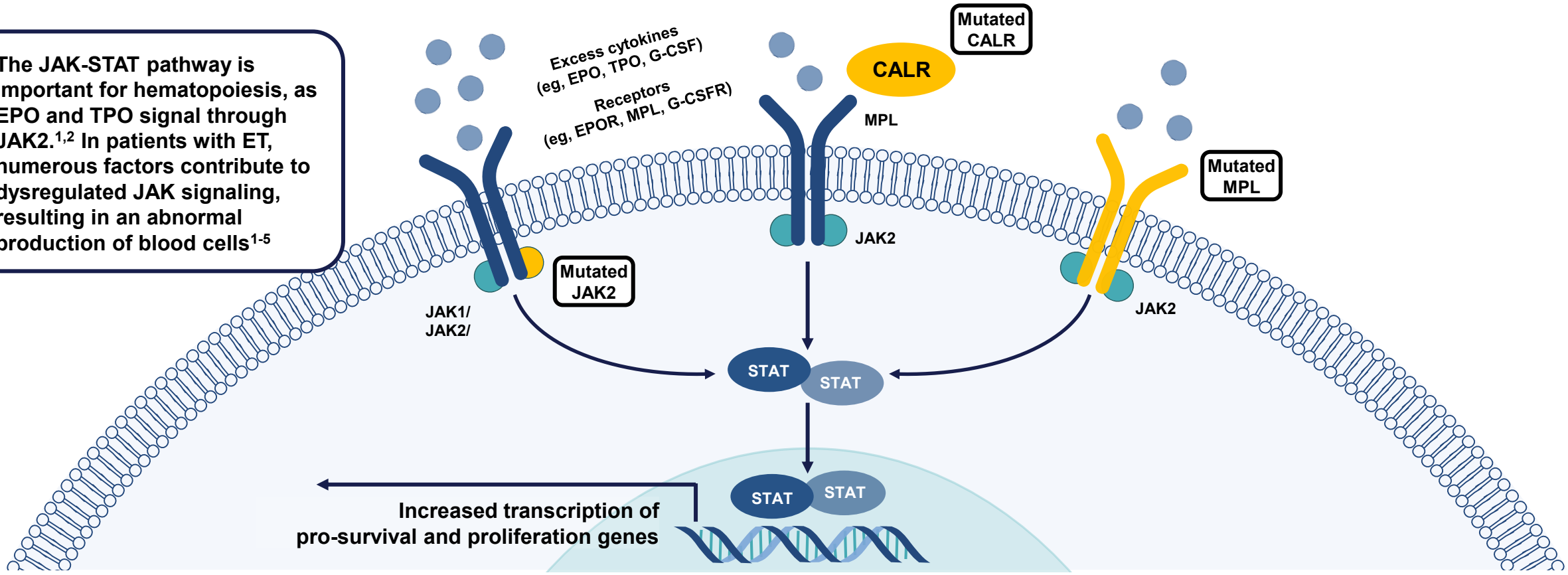
Overactive JAK Signaling Is Present in Most Patients With ET, Leading to Abnormal Blood Cell Production

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.

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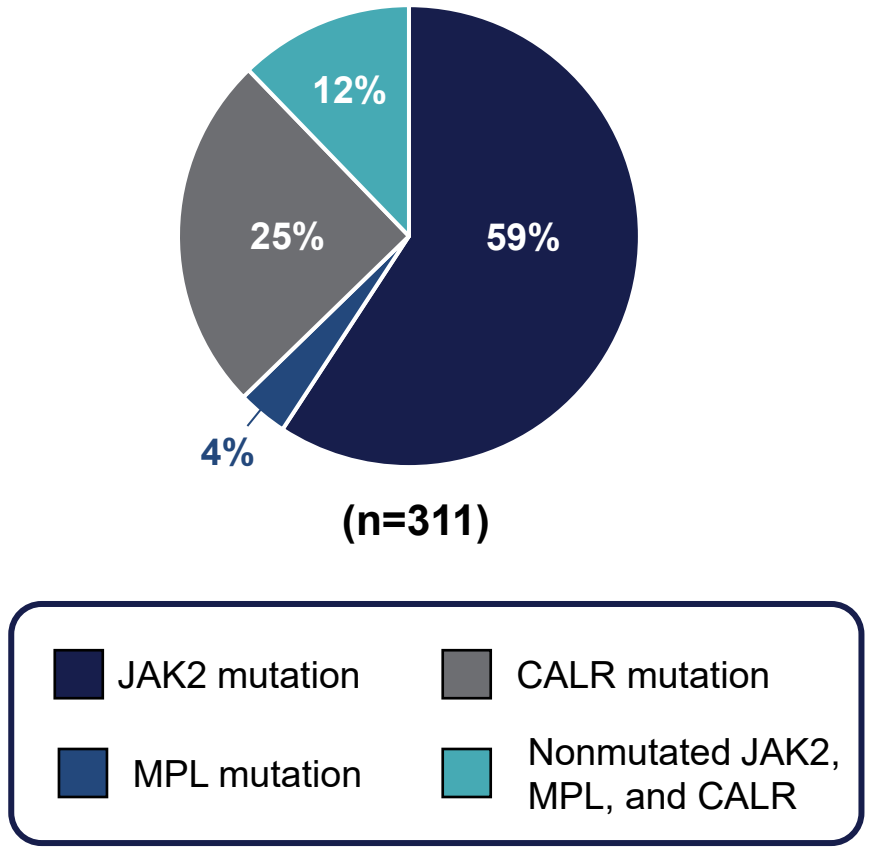
Prevalence of Driver Mutations in Essential Thrombocythemia

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].

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Disease Characteristics

Essential Thrombocythemia

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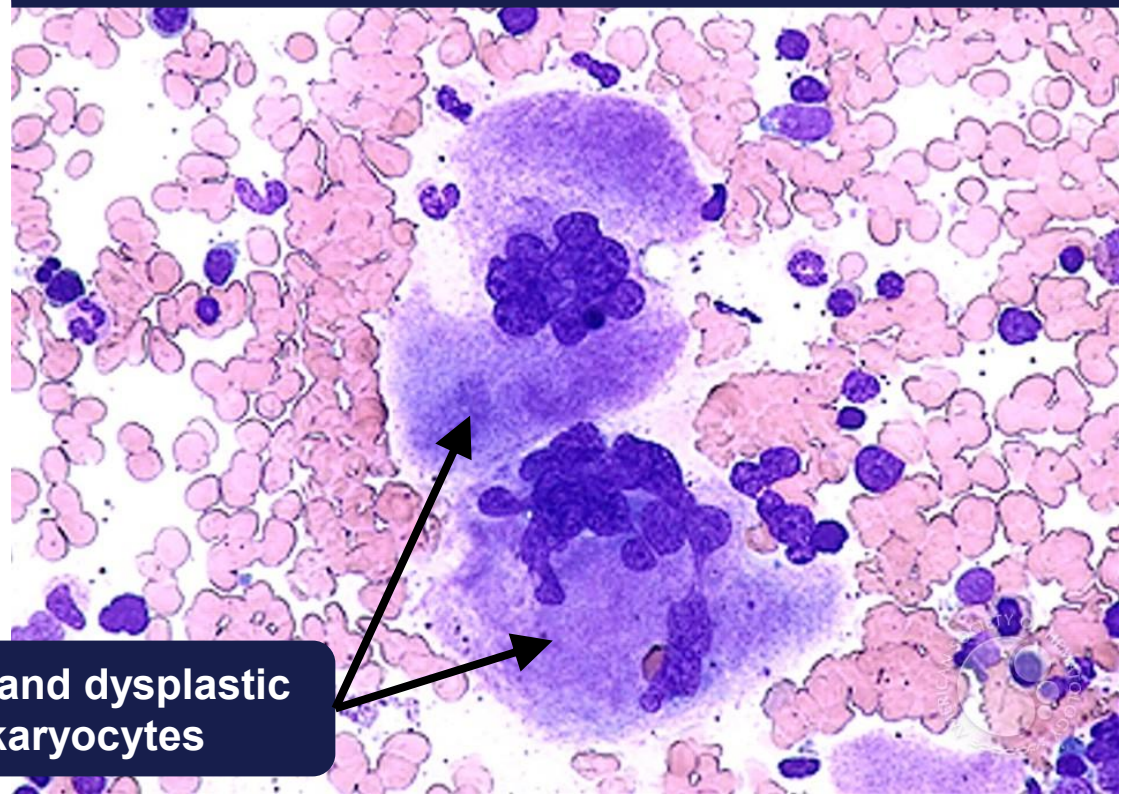
ET May Be Identified in Patients With Thrombotic or Hemorrhagic Events or as an Asymptomatic Chance Finding[1]

- ET is characterized by thrombocytosis and abnormal megakaryocyte proliferation[2]
- Patients with ET have increased risks of arterial and venous thrombosis,[3] as well as major bleeding events[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

Megakaryocyte Dysplasia in a Patient With ET[8]



AML, acute myeloid leukemia.

Image reprinted from the ASH Image Bank, Essential Thrombocythemia - 2, https://imagebank.hematology.org/image/2736/essential-thrombocythemia--2 [imagebank.hematology.org], with permission from the American Society of Hematology.

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 Nov 2025. https://imagebank.hematology.org/image/2736/essential-thrombocythemia--2

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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.

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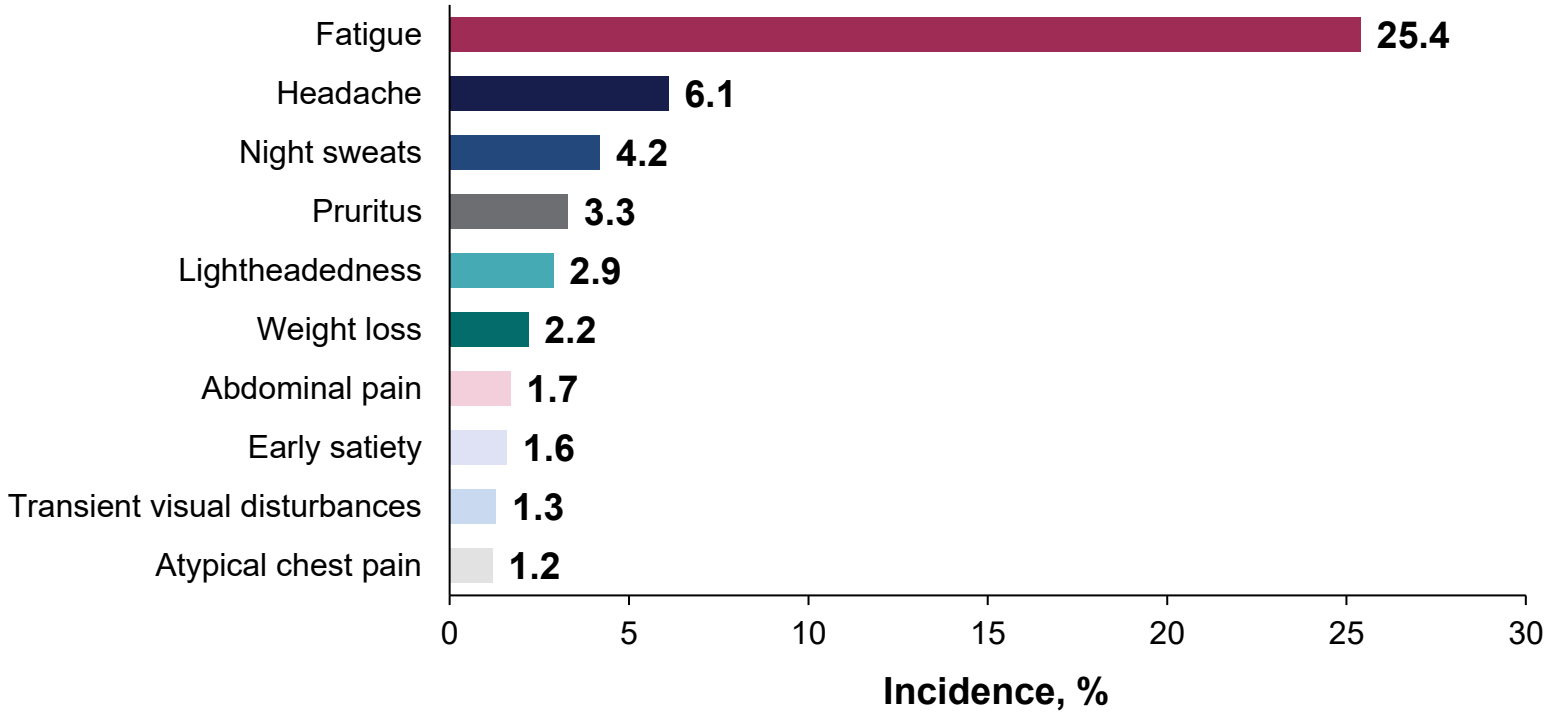
Although ET is Often Indolent, Some Patients With ET May Exhibit a Substantial Symptom Burden

- 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.

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BACK

Clinical Work-Up, Diagnosis, and Stratification

Essential Thrombocythemia

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Diagnostic Criteria for ET

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias

- ☑ Diagnosis is based on a composite assessment of clinical, morphologic, genomic, and laboratory features
- ☑ Must meet all 4 major criteria OR the first 3 major criteria plus the minor criterion

Major

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

Minor

- ☐ Presence of a clonal marker[d] or absence of evidence of reactive thrombocytosis[e]

[a] Three or more megakaryocytes lying adjacent without other bone marrow cells in between; in most of these rare clusters, ≤6 megakaryocytes may be observed; increase in huge clusters (>6 cells) accompanied by granulocytic proliferation is a morphologic hallmark of pre-PMF. [b] Very rarely a minor increase in reticulin fibers may occur at initial diagnosis (grade 1). [c] It is recommended to use highly sensitive assays for *JAK2*V617F (sensitivity level <1%), *CALR*, and *MPL* (sensitivity level 1-3%); in negative cases, consider a search for noncanonical *JAK2* and *MPL* mutations. [d] Assessed by cytogenetics or sensitive NGS techniques. [e] Reactive causes of thrombocytosis include a variety of underlying conditions such as iron deficiency, chronic infection, chronic inflammatory disease, medication, neoplasia, or history of splenectomy.

CML, chronic myeloid leukemia; NGS, next-generation sequencing.

Arber DA, et al. *Blood.* 2022;140:1200-1228.

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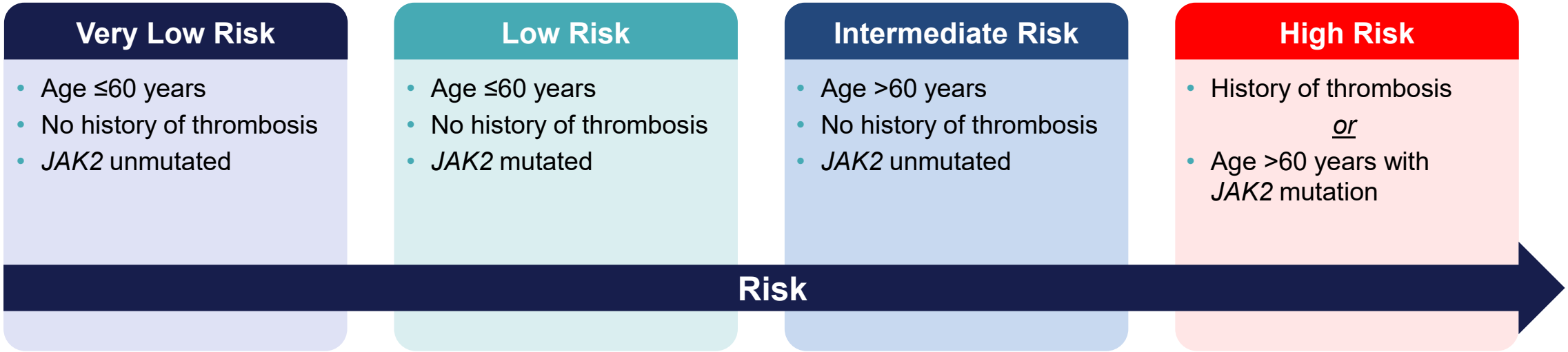
Risk Stratification

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, et al. *Am J Hematol.* 2024;99:697-718.

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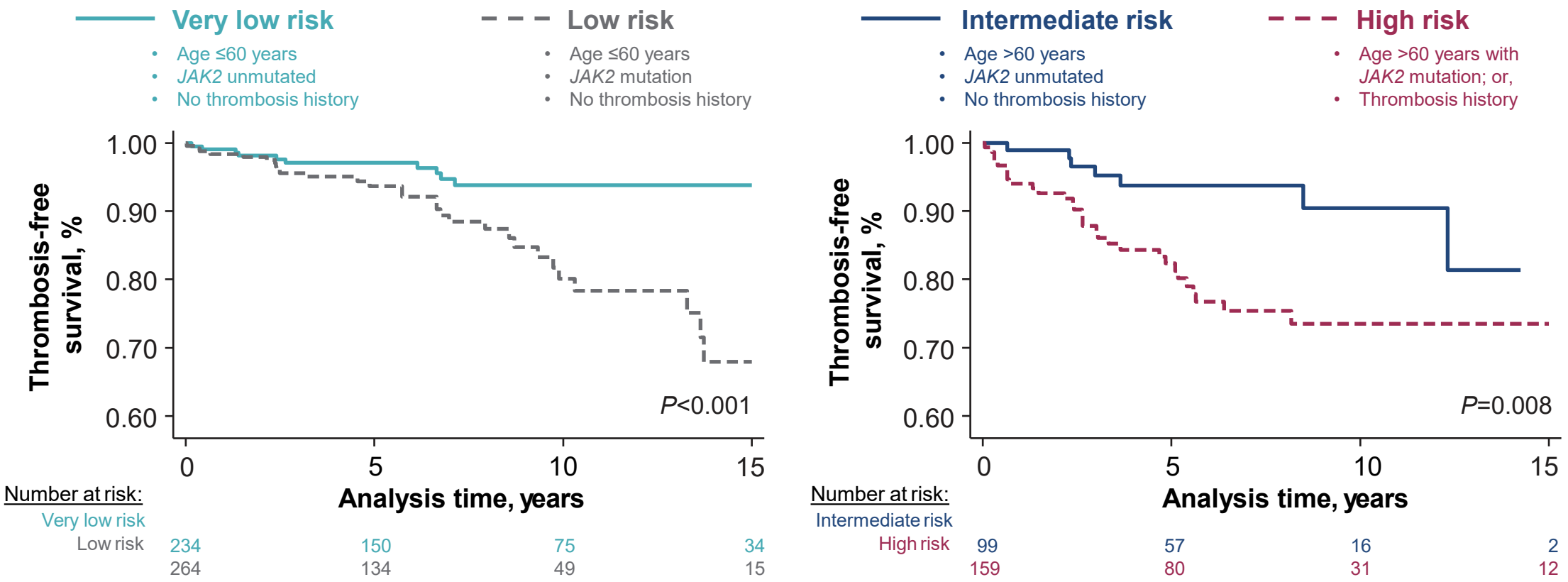
Thrombosis History, Age, and *JAK2* Mutation Status May Be Used to Predict Risk of Vascular Events

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



Figures reprinted from Barbui T, et al. *Blood Cancer J.* 2015;5:e369, Copyright © 2015 under a Creative Commons Attribution 4.0 International license https://creativecommons.org/licenses/by/4.0

IPSET, International Prognostic Score of thrombosis in Essential Thrombocythemia.

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

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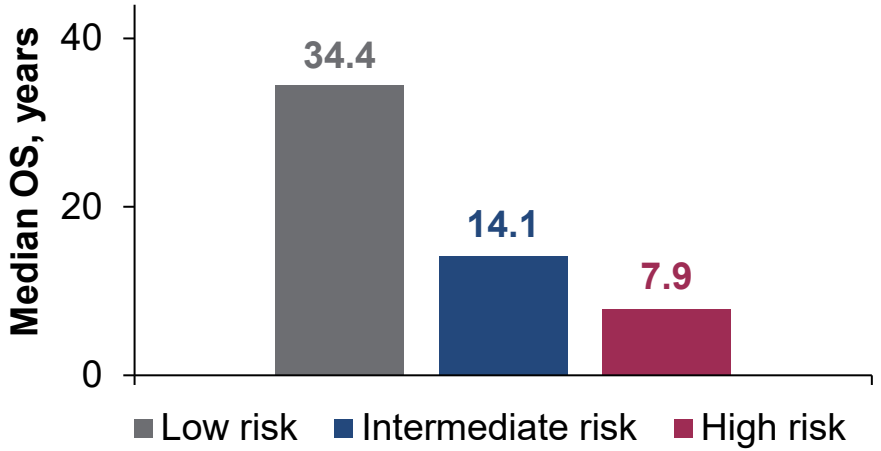
Prognostic Models for OS in ET

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

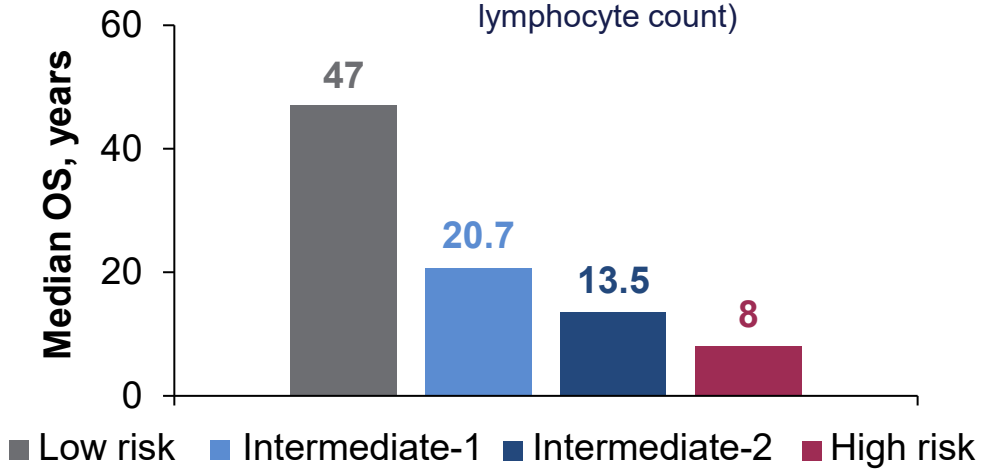
Low risk
0-1 points

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; OS, overall survival; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2; TP53, tumor protein p53; U2AF1, U2 small nuclear RNA auxiliary factor 1

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

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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.* 2022;140:1200-1228. 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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