

Essential Thrombocythemia and Polycythemia Vera Diagnosis and Prognosis: A Resource for Global Healthcare Professionals



Essential thrombocythemia (ET) and polycythemia vera (PV) are myeloproliferative neoplasms associated with prevalent *JAK2* gain-of-function mutations.^{1,2} PV is associated with *JAK2* mutations in nearly 100% of cases, but in ET, *JAK2* mutations comprise approximately 60% of cases, with *CALR* (25%) and *MPL* (5%–7%) mutations also being prevalent drivers of the disease. Patients with ET and PV are at increased risk for thrombosis, hemorrhage, constitutional symptoms, and disease transformation to myelofibrosis and acute myeloid leukemia with a reduced life expectancy compared with age-matched controls.^{1–3}

Clinical Presentation

ET¹

- More than 50% of patients are diagnosed incidentally based on an abnormal platelet count on a CBC
- Approximately 30% of patients present with microcirculatory symptoms (eg, erythromelalgia, burning toes/fingers, blurred vision, migraine headaches)
- Additional disease-related symptoms include fatigue, which can be particularly troublesome
- Other signs at diagnosis include palpable splenomegaly (12%), arterial thrombosis (14%), venous thrombosis (8%), major hemorrhage (4.5%)

PV²

- Similar to ET, patients may be asymptomatic with an incidental finding on a CBC (primarily erythrocytes but also leukocytes and thrombocytes) or present with microcirculatory symptoms; fatigue is also common and can affect quality of life and ability to work
- Pruritus is common (48%)
- Other signs at diagnosis include palpable splenomegaly (36%), arterial thrombosis (15%–16%), venous thrombosis (8%–13%), major hemorrhage (4%)

WHO and ICC 2022 Criteria for Diagnosis of ET and PV^{4,5}

	ET	PV
Major criteria	- PLT $\geq 450 \times 10^9/L$ - BM biopsy with predominant proliferation of megakaryocytes - Not meeting criteria for other MPN subtype <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation	- Hb >16.5 g/dL in men, Hb >16.0 g/dL in women OR Hct $>49\%$ in men, Hct $>48\%$ in women OR increased red cell mass (ICC only) - BM biopsy showing trilineage proliferation (panmyelosis) <i>JAK2</i> mutation
Minor criteria	Presence of a clonal marker or absence of evidence for reactive thrombocytosis	Subnormal serum EPO level
Diagnosis	All 4 major criteria or the first 3 major criteria and 1 of the minor criteria	All 3 major criteria or the first 2 major criteria and the minor criterion

Diagnostic Pearls for ET¹

- Exclude secondary thrombocytosis ($\approx 85\%$ – 90% of cases of elevated platelets) because of inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosus, infections, splenectomy, incidental trauma or surgery, iron deficiency anemia, and solid tumors, such as lung cancer
- If the initial assessment does not suggest a secondary cause of thrombocytosis, patients should undergo peripheral blood testing for *JAK2*, *CALR*, and *MPL* gene variants (note that up to 10% of patients with ET lack these mutations)

Diagnostic Pearls for PV²

- JAK2 V617F and exon 12 mutations present in ≈99% of patients, and a low erythropoietin (EPO) level is very helpful
 - In the absence of a JAK2 mutation, a diagnosis of PV is extremely unlikely
- Bone marrow biopsy may not be required for PV diagnosis if hemoglobin >18.5 g/dL in men or >16.5 g/dL in women, hematocrit >55.5% in men or >49.5% in women; however, this can be useful to identify initial myelofibrosis in up to 20% of patients with prediction of more rapid progression to post-PV myelofibrosis and for detection of abnormal karyotype associated with worse survival
- Exclude secondary erythrocytosis, which can occur commonly because of testosterone supplementation, medications (eg, aromatase inhibitors, SGLT2 inhibitors), chronic cardiopulmonary disease, bilateral renal artery stenosis, or EPO-secreting cysts; serum EPO level can be helpful in this case as it should be suppressed in PV and normal/elevated in secondary etiologies

Prognostic Scoring for ET and PV

Various prognostic scoring systems incorporating clinical and molecular features are available for risk assessment of ET and PV.⁶ Prognosis has historically been based on thrombosis risk (refer to Tables); risk scoring systems increasingly incorporate mutational status (eg, the presence or absence and allele frequency of the JAK2 mutation).⁶ Wider mutation screening (eg, using a next-generation sequencing panel) is not often of utility but has been incorporated into some newer prognostic scores.

There is increasing interest in therapies that may affect the occurrence of fibrotic or perhaps leukemic transformation. In particular, the ability of interferon formulations to delay fibrotic transformation is an ongoing topic of debate. Both interferon formulations and the JAK2 inhibitor ruxolitinib have been shown to reduce JAK2 allele fractions and improve event-free survival. Impact on CALR mutations is also of evolving interest. To that end, prognosis and treatment are guided primarily by thrombotic risk and symptom management.^{1,2,6}

Risk of Thrombosis

Category	Very Low Risk	Low Risk	Intermediate Risk	High Risk
	Criteria			
ET (Revised IPSET-Thrombosis) ^{7,8}	■ ≤60 yr of age ■ No history of thrombosis ■ No JAK2 V617F mutation	■ ≤60 yr of age ■ No history of thrombosis ■ JAK2 V617F mutation present	■ >60 yr of age ■ No history of thrombosis ■ No JAK2 V617F mutation	■ >60 yr of age and JAK2 V617F mutation ■ History of thrombosis
PV ⁹		■ ≤60 yr of age ■ No history of thrombosis		■ >60 yr of age OR ■ History of thrombosis

Clinical and Molecular Features Associated With Thrombosis⁶

Disease	Clinical Factors	Biologic Factors	Molecular Factors	Thrombosis Rate (Patient-Yr)
ET	■ Age at diagnosis ■ Male gender ■ History of thrombosis ■ CV risk factors	■ WBC >15 G/L	■ JAK2 V617F driver mut	1.6%
PV	■ Age at diagnosis ■ History of thrombosis ■ CV risk factors	■ WBC >15 G/L ■ PNN/lymphocyte >5	■ JAK2 V617F VAF >50%	3.0%

References

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