Received: 4 January 2024 | Accepted: 8 January 2024

DOI: 10.1002/ajh.27216

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management

Ayalew Tefferi[1] | Alessandro Maria Vannucchi[2] | Tiziano Barbui[3]

[1]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

[2]CRIMM, Center Research and Innovation of Myeloproliferative Neoplasms, University of Florence, AOU Careggi, Florence, Italy

[3]Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy

Correspondence
Ayalew Tefferi, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
Email: tefferi.ayalew@mayo.edu

Abstract

Overview: Essential thrombocythemia is a Janus kinase 2 (*JAK2*) mutation-prevalent myeloproliferative neoplasm characterized by clonal thrombocytosis; clinical course is often indolent but might be interrupted by thrombotic or hemorrhagic complications, microcirculatory symptoms (e.g., headaches, lightheadedness, and acral paresthesias), and, less frequently, by disease transformation into myelofibrosis (MF) or acute myeloid leukemia.

Diagnosis: In addition to thrombocytosis (platelets ≥450 × 10^9/L), formal diagnosis requires the exclusion of other myeloid neoplasms, including prefibrotic MF, polycythemia vera, chronic myeloid leukemia, and myelodysplastic syndromes with ring sideroblasts and thrombocytosis. Bone marrow morphology typically shows increased number of mature-appearing megakaryocytes distributed in loose clusters.

Genetics: Approximately 80% of patients express myeloproliferative neoplasm driver mutations (*JAK2*, *CALR*, *MPL*), in a mutually exclusive manner; in addition, about 50% harbor other mutations, the most frequent being *TET2* (9%–11%), *ASXL1* (7%–20%), *DNMT3A* (7%), and *SF3B1* (5%). Abnormal karyotype is seen in <10% of patients and includes +9/20q−/13q-.

Survival and Prognosis: Life expectancy is less than that of the control population. Median survival is approximately 18 years but exceeds >35 years in younger patients. The triple A survival risk model, based on Age, Absolute neutrophil count, and Absolute lymphocyte count, effectively delineates high-, intermediate-1-, intermediate-2-, and low-risk disease with corresponding median survivals of 8, 14, 21, and 47 years.

Risk Factors for Thrombosis: Four risk categories are considered: very low (age ≤60 years, no thrombosis history, *JAK2* wild-type), low (same as very low but *JAK2* mutation present), intermediate (same as low but age >60 years), and high (thrombosis history or age >60 years with *JAK2* mutation).

Mutations and Prognosis: *MPL* and *CALR-1* mutations have been associated with increased risk of MF transformation; spliceosome with inferior overall and MF-free survival; *TP53* with leukemic transformation, and *JAK2*V617F with thrombosis. Leukemic transformation rate at 10 years is <1% but might be higher in *JAK2*-mutated patients with extreme thrombocytosis and those with abnormal karyotype.

Treatment: The main goal of therapy is to prevent thrombosis. In this regard, once-daily low-dose aspirin is advised for all patients and twice daily for low-risk disease.

Cytoreductive therapy is advised for high-risk and optional for intermediate-risk disease. First-line cytoreductive drugs of choice are hydroxyurea and pegylated interferon-α and second-line busulfan.

Additional Content: The current review includes specific treatment strategies in the context of extreme thrombocytosis, pregnancy, splanchnic vein thrombosis, perioperative care, and post-essential thrombocythemia MF, as well as new investigational drugs.

1 | DISEASE CLASSIFICATION AND INCIDENCE

Essential thrombocythemia (ET) is one of four Janus kinase 2 (*JAK2*) mutation-prevalent myeloproliferative neoplasms (MPNs), which also include polycythemia vera (PV), primary myelofibrosis (PMF), and MPN, unclassifiable (MPN-U).[1–3] In addition, about 15% of patients with ET or PV develop a PMF-like phenotype, over time, referred to as post-ET or post-PV MF.[4] MPNs are included in the 2022 International Consensus Classification (ICC) category of myeloid neoplasms and acute leukemia (Table 1), which also includes acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[3,5] Of note, the ICC is separate from the World Health Organization (WHO) classification system,[6] which was also revised in 2022 (5th edition);[7] however, subclassification of MPN is similar between the two classification systems. In a population-based study of 6281 Swedish patients with MPN, registered between 2000 and 2014, the age-standardized incidence for all MPNs was 4.45/100 000 person-years, for PV 1.48, for ET 1.6, and for PMF 0.52;[8] incidence rates were higher in the older age groups and increased during the study period.

2 | PATHOGENESIS

The year 2005 was an important milestone in the science and practice of MPN and was associated with the seminal discovery of a *JAK2* (located on chromosome 9p24) gain-of-function mutation (*JAK2*V617F; a G to T somatic mutation at nucleotide 1849, in exon 14, resulting in the substitution of valine to phenylalanine at codon 617) in PV, ET, and PMF.[9–12] Additional MPN "driver mutations" have since been described and include *JAK2* exon 12 described in *JAK2*V617F-negative PV;[13] *CALR* (calreticulin; located on chromosome 19p13.2)[14,15] and *MPL* (myeloproliferative leukemia virus oncogene; located on chromosome 1p34).[16] Among these mutations, *JAK2* is the most frequent with frequencies of ca. 98% in PV (95% *JAK2*V617F and 3% *JAK2* exon 12), 50%–60% in ET, and 55%–65% in PMF.[17,18] *CALR* and *MPL* mutations are often absent in PV, save for rare exceptions,[19,20] while their frequencies in ET are estimated at 20%–25% and 3%–4%, respectively, and in PMF at 20%–25% and 6%–7%.[21] Approximately 10%–15% of patients with PMF or ET do not express any one of the three MPN driver mutations and are operationally referred to as being "triple-negative," although that might not be the case during higher sensitivity testing.[18,22] MPN driver mutations have also been reported in other myeloid malignancies, including MDS with ring sideroblasts associated with marked thrombocytosis (MDS-RS-T; 50% frequency).[23,24]

The pathogenetic role of MPN driver mutations is highlighted by their origin at the stem cell level and the demonstration of persistent JAK–STAT activation and induction of mutant *JAK2*/*CALR*/*MPL*-driven MPN phenotype in mice.[10,25] *JAK2* and *MPLW515K/L/A/R* and S505N mutations are believed to directly activate JAK2-STAT (signal transducer and activator of transcription 5) resulting in clonal myeloproliferation that is cytokine independent or hypersensitive.[16,26] Frameshift *CALR* mutations mostly include type 1 (52-bp deletion in exon 9) or type 2 (5-bp insertion in exon 9) and less frequently a myriad of type 1-like or type 2-like variants.[27] The precise mechanism of mutant *CALR*-induced myeloproliferation is less clear, but one possibility includes mutant CALR binding to the extracellular domain of MPL in the endoplasmic reticulum leading to dimerization and transfer to cell surface and activation of JAK–STAT.[28,29] Mutant *CALR*-harboring mouse models have suggested a primary effect on platelet production and development of the ET phenotype.[30] Although the central role of JAK–STAT activation in MPN has been highlighted,[28,31] the particular concept is confounded by the co-existence of an inflammatory state with aberrant cytokine expression and the fact that activated JAK–STAT is a non-specific phenomenon in cancer.[32] Furthermore, "targeted therapy" with JAK inhibitors has so far failed to induce selective suppression of the disease clone in MF.[33]

It is currently assumed that the phenotypic differences between MPN variants are in part contributed by differences in the conformations of specific cytokine receptors that lead to distinct signaling outcomes for EPOR and MPL and further modified by interactions with other co-occurring mutations, including those of epigenetic regulators and their order of acquisition.[25,28] Additional mechanisms of phenotype diversity associated with MPN-driving mutations include variations in signal intensity (often related to mutant allele burden) and specificity of downstream signals, including STAT5, STAT1, and STAT3.[34] Recently published mouse studies appear to recapitulate the phenotypic differences seen among patients with different driver mutations.[35,36] Regardless, the underlying mechanisms that enable single mutations to result in different MPN phenotypes remain not fully understood.[37–40] The pathogenetic role of mutations other than *JAK2*/*CALR*/*MPL* in MPN is much less understood but believed to involve cooperation with driver mutations leading to downstream disruption of epigenetic (e.g., *ASXL1*, *TET2*, *EZH2*, *IDH1*, *IDH2*, *DNMT3A*),

TABLE 1 International Consensus Classification of myeloid neoplasms (*see text for references*).

1. Acute myeloid leukemia (AML)
   a. AML diagnosis requiring ≥10% BM or PB blasts
      i. Acute promyelocytic leukemia
      ii. Core binding factor AML
      iii. AML with *KMT2A* rearrangement
      iv. AML with *DEK::NUP214*
      v. AML with *MECOM* rearrangements
      vi. AML with *NPM1* mutation
      vii. AML with in-frame *bZIP CEBPA* mutations
      viii. AML with other rare recurring translocations
      ix. MDS/AML with *TP53* mutations
      x. MDS/AML with myelodysplasia-related mutations
      xi. MDS/AML with myelodysplasia-related karyotype
      xii. MDS/AML not otherwise specified (NOS)
   b. AML diagnosis requiring ≥20% BM or PB blasts
      i. AML with t(9;22)-*BCR::ABL1*
      ii. AML with *TP53* mutations, other than PEL
      iii. AML with myelodysplasia-related gene mutations
      iv. AML with myelodysplasia-related karyotype
      v. AML not otherwise specified (NOS)
2. AML-related disorders
   a. Pure erythroid leukemia (PEL; *TP53* mutated)
   b. Myeloid sarcoma
   c. Blastic plasmacytoid dendritic cell neoplasm
   d. Acute leukemia of ambiguous lineage
   e. Acute undifferentiated leukemia
   f. Mixed phenotype acute leukemia
3. Myelodysplastic syndromes (MDS)
   a. MDS with mutated *TP53*
   b. MDS with excess blasts (5%–9% BM or 2%–9% PB)
   c. MDS without excess blasts (<5% BM and <2% PB)
      i. MDS with del(5q) (isolated or accompanied by only one other cytogenetic abnormality other than 7/del(7q); no multi-hit *TP53*)
      ii. MDS with *SF3B1* (VAF ≥10%/ no RUNX1 or multi-hit TP53; no del(5q), −7/del(7q), complex karyotype, or abnormal 3q26.2)
      iii. MDS, NOS-single lineage dysplasia
      iv. MDS, NOS-multilineage dysplasia
      v. MDS, NOS without dysplasia
4. MDS/AML
   a. MDS/AML (BM/PB blasts 10%–19%)
   b. MDS/AML with mutated *TP53*
5. Myeloproliferative neoplasms (MPN)
   a. Chronic myeloid leukemia
   b. Polycythemia vera
   c. Essential thrombocythemia
   d. Primary myelofibrosis (PMF)
      i. Early/prefibrotic PMF
      ii. Overt PMF
   e. MPN, unclassifiable (MPN-U)
   f. Chronic neutrophilic leukemia
   g. Chronic eosinophilic leukemia, NOS
6. MDS/MPN
   a. Chronic myelomonocytic leukemia (CMML) (≥0.5 × 10^9/L absolute and ≥10% PB monocytes)
      i. CMML-1 (<10% BM and <5% PB blasts)
      ii. CMML-2 (10%–19% BM or 5%–19% PB blasts)
   b. Atypical chronic myeloid leukemia
   c. MDS/MPN with mutated *SF3B1* and thrombocytosis
   d. MDS/MPN with RS and thrombocytosis, NOS
   e. MDS/MPN, NOS
      i. MDS/MPN with isolated isochromosome (17q)
7. Eosinophilic disorders
8. Mastocytosis
9. Hematologic neoplasms with germline predisposition
10. Pediatric myeloid malignancies
11. Pre-malignant clonal hematopoiesis

RNA splicing (e.g., *SRSF2*, *U2AF1*, *SF3B1*), or transcriptional (*TP53*, *IKZF1*, *NF-E2*, *CUX1*) regulation, which might facilitate disease progression and leukemic transformation.[41,42] The recent demonstration of *TET2*, *ASXL1*, and *DNMT3A* mutations in "normal" elderly individuals has added to the complexity regarding their precise pathogenetic contribution.[43,44]

3 | PREVALENCE AND PHENOTYPE OF MPN DRIVER MUTATIONS IN ET

In two recent publications, we have reported on 2000 patients with ET, recruited from the Mayo Clinic, USA ($N = 1000$),[45] and the University of Florence, Italy ($N = 1000$),[46] and retrospectively studied over four to five decades. In these Mayo and Florence patient cohorts, the *JAK2/CALR/MPL* mutational frequencies were 62%/27%/3% and 66%/19%/4% and the *JAK2/CALR-1/CALR-2/MPL* frequencies 62%/15%/11%/3% and 66%/12%/7%/4%, respectively. Median age was significantly higher in *JAK2* (71/62 years) and *MPL* (66/59 years) versus *CALR* (52/53 years) mutated or triple-negative (50/53 years), in the Mayo/Florence cohorts;[45,46] females were more represented in *JAK2*-mutated (69%/67%) and triple-negative (73%/76%) versus *CALR*-mutated (49%/6%) cases. *JAK2*-mutated cases, compared to those with other MPN driver mutations, displayed higher hemoglobin level and leukocyte counts while *CALR*-mutated and triple-negative cases displayed higher platelet counts; the latter was even more pronounced in type-2/like (median 1044/923 $\times$ 10^9/L) versus type-1/like (median 890/780 $\times$ 10^9/L) *CALR* mutations (Mayo/Florence cohorts); median hemoglobin levels in the Mayo patient cohort for *JAK2/CALR/MPL/triple-negative* cases were 14/13.6/13.8/13.3 g/dL, leukocyte counts 8.9/8.0/7.4/7.8 $\times$ 10^9/L, and platelet counts 705/955/802/905 $\times$ 10^9/L. The respective readings in the Florence cohort were 14.2/13.8/13.1/13.7 g/dL for hemoglobin, 8.7/8.0/7.7/8.0 $\times$ 10^9/L for leukocyte count, and 671/826/838/725 $\times$ 10^9/L for platelet count.[45,46]

4 | DEMOGRAPHICS AND PRESENTING CLINICAL CHARACTERISTICS

According to the recently published Mayo-Florence study of 2000 patients with ET,[45,46] median age (range) at diagnosis for the Mayo cohort was 58 years (18–90) and for the Florence cohort 59 years (18–95); the corresponding percent female patients were 63% and 65%. At presentation, patients with ET might be asymptomatic or display a spectrum of symptoms including microvascular disturbances (headaches, lightheadedness, visual symptoms such as blurring and scotomata, palpitations, chest pain, erythromelalgia, and distal paresthesias), splenic discomfort associated with splenomegaly, superficial thrombophlebitis, minor mucocutaneous bleeding, or overt thrombosis or bleeding. Erythromelalgia is the most dramatic vasomotor symptom, characterized by erythema, warmth, and pain in distal extremities;[47] the underlying pathology of erythromelalgia might include abnormal platelet-endothelium interactions.[48] In the aforementioned Mayo/Florence studies,[45,46] presenting characteristics included median hemoglobin values of 13.9/14 g/dL, leukocyte count of 8.5/8.5 $\times$ 10^9/L, and platelet counts of 777/715 $\times$ 10^9/L. The percentages of patients with leukocytosis (leukocyte count >11 $\times$ 10^9/L) were 20%/16%, extreme thrombocytosis (platelet count ≥1000 $\times$ 10^9/L) 26%/16%, cardiovascular (CV) risk factors 54%/52%, palpable splenomegaly 12%/13%, abnormal karyotype 6%/10%, microvascular symptoms 29%/29%, major arterial thrombosis at or prior to diagnosis 14%/13%, major venous thrombosis at or prior to diagnosis 10%/6%, and major hemorrhage at or prior to diagnosis 8%/4%.

5 | DIAGNOSIS

There are currently two classification systems for MPN: ICC[3] and WHO, 5th edition.[7] The current review operates on the ICC, which enlists several subcategories of MPN, including ET, PV, PMF, MPN-U, chronic myeloid leukemia (CML), chronic neutrophilic leukemia, and chronic eosinophilic leukemia, not otherwise specified (Table 1).[3] Among these clinicopathologic entities, ET, PV, PMF, and MPN-U share similar genetic characteristics, especially in regard to their close association with *JAK2/CALR/MPL* mutations, and are, therefore, referred to as *JAK2* mutation-prevalent MPN. Diagnosis of ET should be based on a composite assessment of clinical, morphological, and laboratory features (Table 2). In this regard, it should be noted that the overwhelming majority of thrombocytosis cases in routine clinical practice are non-clonal in nature and associated with a spectrum of unrelated conditions such as infections, inflammation, post-surgical state, splenectomy, and iron deficiency. On the contrary, while the detection of *JAK2*V617F, *CALR*, or *MPL* mutations confirms the presence of an underlying MPN, their absence does not rule out the possibility of ET since up to 20% of patients might be triple-negative (i.e., negative for all three mutations; Figure 1). It is also important to note that other *JAK2/CALR/MPL*-mutated MPN (or MDS/MPN) can mimic ET in their presentation; these include prefibrotic PMF and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).[49] However, in the presence of *JAK2/CALR/MPL* mutation, the main distinction is with prefibrotic PMF (Figure 2).[3]

Bone marrow (BM) examination is necessary to make an accurate morphologic diagnosis of ET and distinguish it from other myeloid neoplasms, especially from prefibrotic PMF (Figure 2). BM morphology in ET is often normocellular with increased number of megakaryocytes that are mostly large to giant in size, hyperlobulated, and distributed in "loose" clusters; dense megakaryocyte clusters are infrequent.[3] By contrast, megakaryocytes in prefibrotic PMF display abnormal maturation with hyperchromatic and irregularly folded nuclei and form tight clusters; megakaryocytic atypia seen in prefibrotic PMF includes increased nuclear to cytoplasmic ratio, irregular chromatin clumping, and bulbous appearance, often associated with increased "background" granulocytic proliferation, and increased reticulin fibrosis.[50] Figure 2 also includes other ET versus prefibrotic PMF distinguishing features including serum LDH level, red cell indices, and peripheral blood smear.[50] A large international study confirmed the

TABLE 2 International Consensus Classification diagnostic criteria for essential thrombocythemia and post-essential thrombocythemia (ET) myelofibrosis (see text for references).

Essential thrombocythemia (diagnosis requires meeting all four major criteria or the first three major and one minor criteria)	Post-essential thrombocythemia myelofibrosis (diagnosis requires meeting both major criteria and at least 2 minor criteria)
Major criteria: 1. Platelet count ≥450 × 10^9/L 2. BM megakaryocyte proliferation with mature cytology, hyperlobulated nuclei, and in loose clusters, BM fibrosis absent or ≤grade 1 3. Not meeting ICC criteria for other myeloid neoplasms, including PV, prefibrotic MF, and CML 4. *JAK2*-, *CALR*-, or *MPL*-mutated	Major criteria: 1. Prior documentation of ICC-defined ET 2. BM fibrosis grade ≥2
Minor criteria: 1. Other clonal marker present 2. No evidence of reactive thrombocytosis	Minor criteria: 1. Anemia combined with a ≥2 g/dL decrease in hemoglobin from baseline 2. A leukoerythroblastic blood smear 3. Increase in palpable splenomegaly of >5 cm from baseline or new palpable splenomegaly 4. Increased serum lactate dehydrogenase 5. Development of constitutional symptoms[a]

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; ICC, International Consensus Classification; MF, myelofibrosis; PV, polycythemia vera.
[a]Any two of the following three: >10% weight loss in 6 months, drenching night sweats, unexplained fever of >37.5 degrees centigrade.

prognostic relevance of distinguishing ET from prefibrotic PMF.[51] In the absence of *JAK2*/*CALR*/*MPL* mutations, the possibility of CML is readily addressed by *BCR-ABL1* mutation screening;[52] BM megakaryocytes in CML are much smaller compared to those seen in ET (Figure 2). The diagnosis of post-PV or post-ET MF should adhere to criteria published by the International Working Group for MPN Research and Treatment (Table 2).[4]

6 | LIFE EXPECTANCY

A Surveillance, Epidemiology, and End Results Registry US data involving 10 725 patients with PV, 8768 with ET, and 3689 with PMF reported 5-year relative survival rates of 88.3%, 88.7%, and 44.9%, respectively.[53] The corresponding median survivals were 11.9, 12.1, and 4.0 years, respectively.[53] In another population-based study from Sweden, outcome for 9285 patients with MPN was compared to that of 35 769 matched controls; in patients with MPN, the hazard ratios for death from hematologic malignancies and infections were 92.8 and 2.7, respectively, and patients with MPN had an overall higher mortality rate than that of matched controls.[54] The same study showed increasing survival over time. However, overall survival in PV and other MPNs remained inferior to that of age- and sex-matched general population.[54,55]

General survival estimates in MPN have also been sourced from single institutional retrospective studies. Among 826 Mayo Clinic patients with ET, PV, or PMF, the respective median survivals were ca. 20 years for ET, 14 years for PV, and 6 years for PMF;[18] the corresponding values for patients younger than age 60 years were 33, 24, and 15 years. The particular study also showed that life expectancy in ET was inferior to that of the sex- and age-matched US population and that survival in ET was superior to that of PV, regardless of mutational status.[18] In another Mayo Clinic study of 1952 patients seen between 2000 and 2017 (444 with PV, 551 with ET, and 957 with PMF) and followed for a median of 5.3 years, median survival was 12.7 years for PV, 14.9 years for ET, and 4.4 years for PMF.[53] A more recent Mayo Clinic review of 3023 patients with MPN, seen between 1967 and 2017, included 1076 patients with ET; after a median follow-up of 10 years (some followed up to 47 years), 43% deaths, 4% leukemic transformations, and 13% fibrotic progressions were recorded. Median overall survival in ET was significantly longer at 18 years versus 15 years for PV and 4.4 years for PMF, and significantly shorter than the age- and sex-matched control population.[56]

7 | RISK FACTORS FOR OVERALL, LEUKEMIA-FREE, AND MYELOFIBROSIS-FREE SURVIVAL

Age is by far the most important risk factor for survival in ET; in a Mayo Clinic study of 361 young (age ≤40 years) patients with MPN including 291 with ET, 79 with PV, and 63 with PMF, median survival in young patients was 37 years for PV, 35 for ET, and 20 for PMF (Figure 3); the corresponding values, applied to the larger database of 3023 patients of all ages, were 22, 22, and 8 years for ages 41–60 years and 10, 11, and 3 years for ages >60 years ($P < .01$).[57] In an international study of over 1104 patients with ET ($N = 891$) or prefibrotic PMF ($N = 180$), 10/15-year overall survival rates were 89%/76% and 80%/59%, respectively, leukemic transformation rates 0.7%/2.1% and 5.8%/11.7%, and overt myelofibrosis (MF) progression rates 0.8%/9.3% and 12.3%/16.9%.[51] Multivariable analysis in the particular study[51] identified prefibrotic morphology, age >60 years, leukocyte count >10 × 10^9/L, anemia, and thrombosis

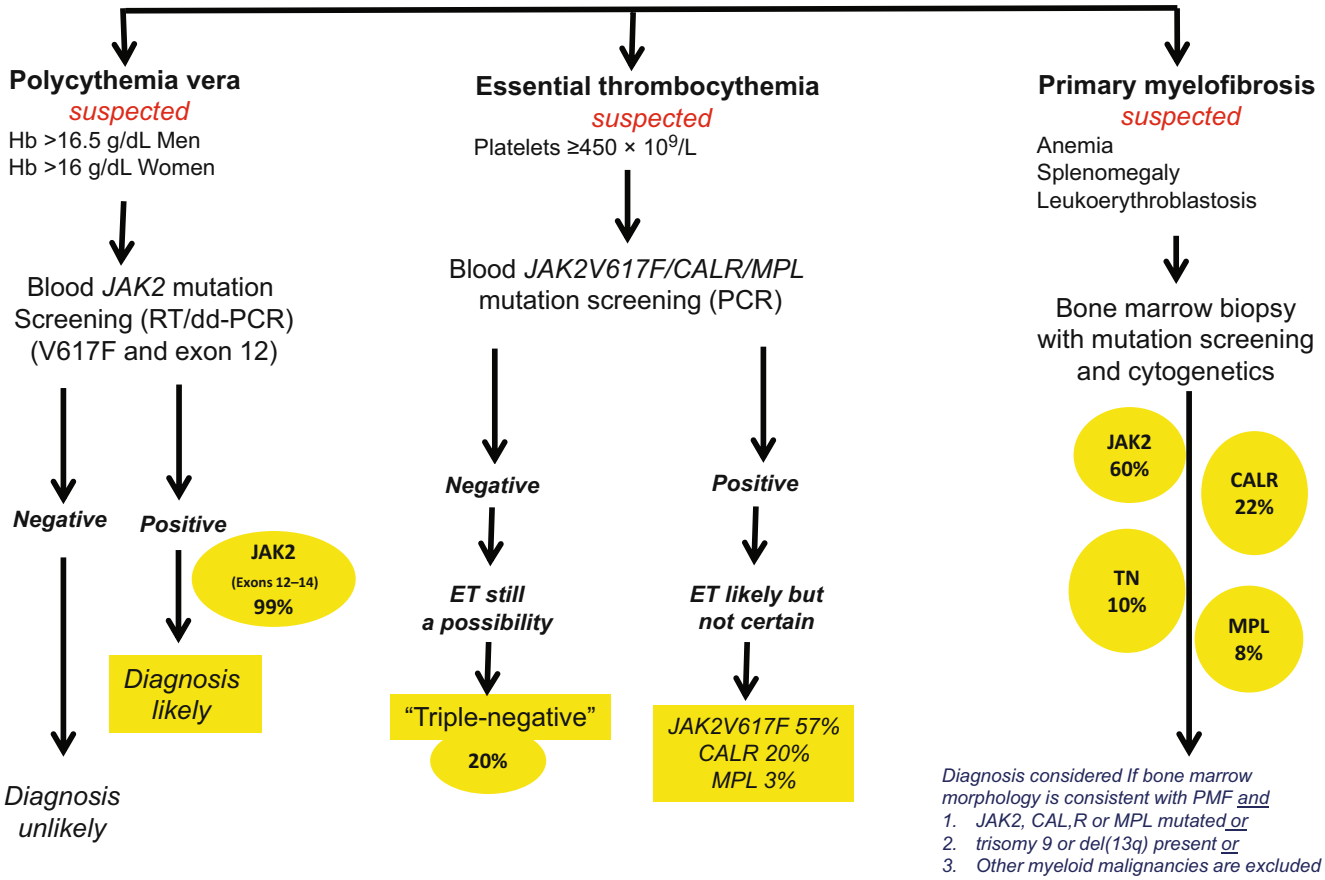

FIGURE 1 Practical diagnostic algorithm for myeloproliferative neoplasms.

history as independent risk factors for overall survival; risk factors for leukemia-free survival were prefibrotic PMF morphology, thrombosis, and extreme thrombocytosis (platelets >1000 × 10^9/L) and for MF-free survival prefibrotic PMF morphology, advanced age, and anemia; the presence of *JAK2*V617F was associated with a lower risk of fibrotic transformation.[51] In a subsequent international study limited to 867 patients with WHO-defined ET, independent risk factors for survival included age ≥60 years, leukocyte count ≥11 × 10^9/L, and history of thrombosis.[58]

Most recently, we have reported on 2000 patients with ET, recruited from the Mayo Clinic, USA ($N = 1000$), and University of Florence, Italy ($N = 1000$).[45,46] Among the Mayo Clinic cases, median overall survival was close to 21 years with 10-year, 20-year, and 30-year survival rates of 81%, 52%, and 25%, respectively; furthermore, median overall survival was not reached and 20-year survival rate 80% in younger patients (age <50 years) without neutrophilia (absolute neutrophil count [ANC] <8 × 10^9/L) and with absolute lymphocyte count (ALC) ≥1.7 × 10^9. Similarly, the risk of leukemic transformation in the Mayo Clinic study was reported at only 3% with 10-year and 20-year risk rates of 1.5% and 7.6%, respectively. In the University of Florence cohort, median overall survival was 27.1 years with 10-year, 20-year, and 30-year survival rates of 86%, 64%, and 43%, respectively, and risk of leukemic transformation 2% overall. In general, overall survival did not appear to be affected by the specific driver mutation associated, in both the Mayo and Florence patient series.

Multivariable analysis applied to the Mayo Clinic patient cohort of the above-mentioned Mayo-Florence study[45,46] identified abnormal karyotype and extreme thrombocytosis (platelet count ≥1000 × 10^9/L) as independent risk factors for leukemia-free survival with 20-year risk of leukemic transformation at only 3% in the absence of both risk factors and close to 13% in the presence of at least one risk factor. Interestingly, the association between extreme thrombocytosis and leukemic transformation appeared to be limited to patients with *JAK2* mutation and did not affect triple-negative cases. In regard to MF-free survival, multivariate analysis of Mayo Clinic cases identified *MPL* mutation and ANC ≥8 × 10^9/L as independent risk factors and the latter's impact was again limited to *JAK2* mutated cases; risk figures ranged from 12% to 49% in the absence of both risk factors and presence of at least one risk factor, respectively. Similar multivariable analyses in the Florence cohort identified advanced age as a risk factor for leukemia-free survival and male gender, *CALR-1* and *MPL* mutations for MF-free survival.

Of particular note, observations from the above-mentioned Mayo-Florence study[45,46] identify triple-negative driver mutational status as an all-around favorable risk factor in ET while *CALR-1* and *MPL* mutated cases ran a higher risk of fibrotic progression. In the Florence study, the risk of fibrotic progression was significantly less in triple-negative disease (2%) and more in *MPL*/*CALR-1* (16%/20%)-mutated disease

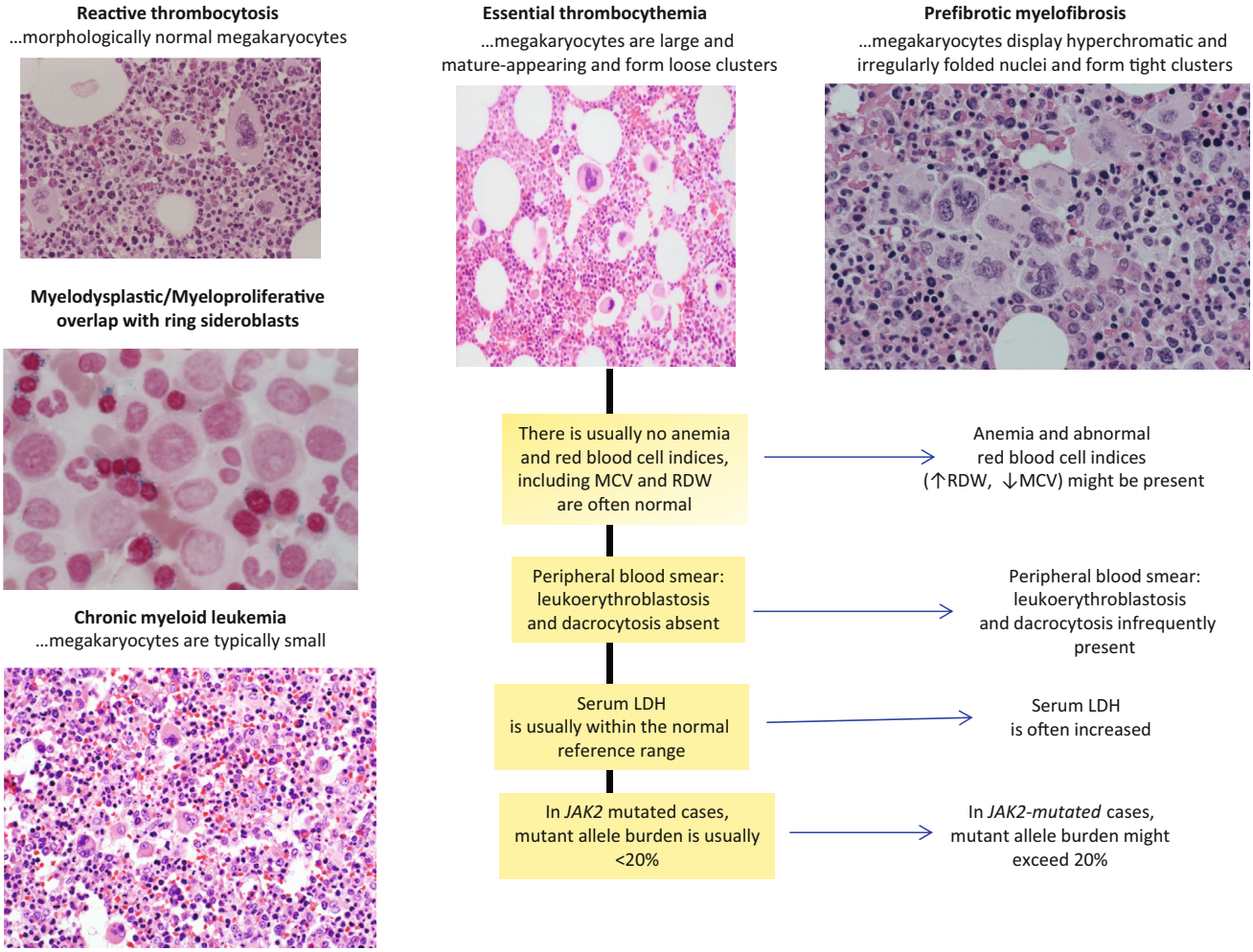

FIGURE 2 Morphologic and laboratory features of essential thrombocythemia and other causes of thrombocytosis, especially prefibrotic myelofibrosis. Dacrocytes, "teardrop" cells; LDH, lactate dehydrogenase; leukoerthyroblastosis, presence of immature myeloid cells and nucleated red cells; MCV, mean corpuscular volume; RDW, red cell distribution width. *Source*: Adapted from Tefferi and Pardanani.[50]

(confirmed by multivariate analysis). Also in the Florence study, triple-negative and *CALR-2*-mutated disease displayed significantly lower (vs. *JAK2*) risk of both arterial and venous thrombosis and non-significantly lower risk of leukemic transformation (0% in triple-negative vs. 0% in *CALR-2* vs. 2% in *JAK2* vs. 3% in *CALR-1* vs. 4% in *MPL* mutated disease). In the Mayo Clinic study, triple-negative driver mutational status was associated with a lower risk of blastic transformation (0% vs. 3%/3%/6%/3% for *JAK2/CALR-1/CALR-2/MPL*; *P* not significant), fibrotic progression (10% vs. 10%/20%/15%/27% for *JAK2/CALR-1/CALR-2/MPL*; *P* significant vs. *CALR-1*), and arterial/venous thrombosis risk (6%/2% vs. 14%/8% for *JAK2*, 11%/6% for *CALR-1*, 12%/9% for *CALR-2*, and 13%/0% for *MPL*; *P* significant vs. *JAK2* and *CALR-1*, for both arterial and venous thrombosis).

In earlier reports, we described the occurrence and prognostic relevance of DNA sequence variants/mutations other than *JAK2/CALR/MPL* in both PV and ET.[59,60] Next-generation sequencing revealed 53% percent of 133 Mayo Clinic patients with PV and 53% of 183 with ET harbored one or more sequence variants/mutations, other than *JAK2/CALR/MPL*; the most frequent were *TET2* and *ASXL1*. "Adverse variants/mutations," in terms of overall, leukemia-free, or fibrosis-free survival, in PV included *ASXL1*, *SRSF2*, and *IDH2* and in ET *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, and *EZH2*; combined prevalence was 15% and 15%, respectively. Adverse variants/mutations were associated with inferior survival in both PV and ET, and the effect was independent of conventional prognostic models; these observations were validated in 215 Italian patients with PV and 174 with ET. In both Mayo Clinic and Italian cohorts, leukemic or fibrotic progression was also predicted by adverse variants/mutations. Number of mutations did not provide additional prognostic information.[59]

8 | SURVIVAL RISK MODELS IN ET

There are currently three risk models for survival that are considered in ET (Table 3). The international prognostic score for ET (IPSET)[58] considers 3 variables (age ≥60 years with two points, leukocyte count ≥11 × 10^9/L with one point, and prior thrombosis with one point),[58] in order to delineate high- (median survival 13.8 years), intermediate- (median 24.5 years), and low- (median not reached) risk groups (Table 3). The second survival model in ET incorporates mutations and

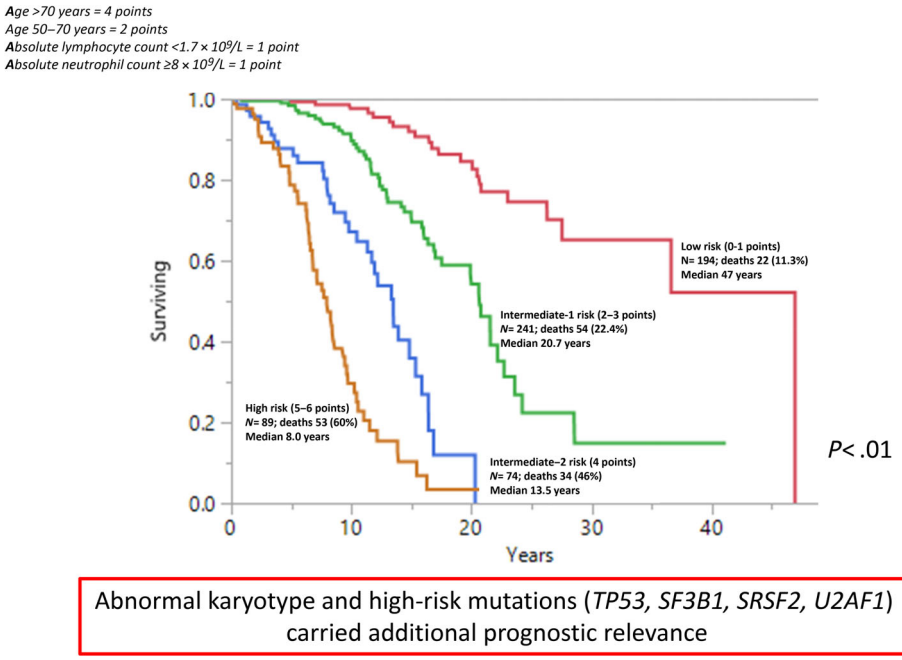

FIGURE 3 Triple A (AAA) survival model in essential thrombocythemia. Overall survival data among 598 Mayo Clinic patients stratified by Age, Absolute neutrophil count, and Absolute lymphocyte count, median follow-up 8.4 years.

TABLE 3 Current prognostic models for overall survival in essential thrombocythemia.

Models	Variables	Risk categories			
		Low	Intermediate-1	Intermediate-2	High
AAA Triple A survival model	Age >70 years (4 points) Age 50–70 years (2 points) ANC ≥8 × 10^9/L (1 point) ALC <1.7 × 10^9/L (1 point)	(0–1 points) 47 years	(2–3 points) 20.7 years	(4 points) 13.5 years	(5–6 points) 8 years
IPSET International prognostic score for essential thrombocythemia	Age ≥60 years (2 points) WBC ≥11 × 10^9/L (1 point) Thrombosis history (1 point)	(0 points) not reached	(1–2 points) 24.5 years		(3–4 points) 13.8 years
MIPSS-ET Mutation-enhanced international prognostic system for essential thrombocythemia	Age >60 years (4 points) Male gender (1 point) WBC ≥11 × 10^9/L (1 point) Adverse mutations (2 points) (*SF3B1/SRSF2/U2AF1/TP53*)	(0–1 points) 34.4 years	(2–5 points) 14.1 years		(≥6 points) 7.9 years

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; WBC, white blood cell (leukocyte) count.

is referred to as the mutation-enhanced international prognostic system for ET (MIPSS-ET; Table 3).[60] MIPSS-ET considers 4 variables (age >60 years with four points, male gender with one point, leukocyte count ≥11 × 10^9/L with one point, and adverse mutations including *SF3B1*, *SRSF2*, *U2AF1*, *TP53* with two points), in order to delineate high- (≥6 points; median survival 7.9 years), intermediate- (2–5 points; median 14.1 years), and low- (0–1 points; median 34.4 years) risk groups (Table 3). Genetic risk factors for overall survival in ET, according to MIPSS-ET, included *SF3B1* and *SRSF2* mutations; for MF-free survival *U2AF1* and *SF3B1* mutations; and for leukemic transformation *TP53* mutations. The incidence of these adverse mutations in ET was estimated at 10% and their prognostic relevance was independent of age >60 years, male sex, and leukocytosis.

The most recently introduced new survival model in ET is referred to as the triple A (AAA) survival risk model and is based on Age, ANC, and ALC (Figure 3).[61] In developing the AAA survival model in ET, we examined the individual prognostic contribution of ANC, ALC, and absolute monocyte count (AMC), on overall, leukemia-free, and MF-free survival, in 598 informative cases; multivariable analysis resulted in HR (95% CI) of 16.5 (9.9–27.4) for age >70 years, 3.7 (2.3–6.0) for age 50–70 years, 2.4 (1.7–3.3) for ANC ≥8 × 10^9/L, and 1.9 (1.4–2.6) for ALC <1.7 × 10^9/L. The corresponding HR-based scores were 4, 2, 1, and 1, resulting in a new four-tiered AAA (triple A) risk model: high (5–6 points; median survival 8 years; HR 30.1, 95% CI 17.6–54), intermediate-2 (four points; median 13.5 years; HR 12.7, 95% CI 7.1–23.0), intermediate-1 (2–3 points; median 20.7 years; HR 3.8, 95% CI 2.3–6.4), and low (0–1 points; median 47 years). The AAA model (AIC 621) performed better than IPSET (AIC 647) and was subsequently validated by an external University of Florence ET cohort ($N = 485$). Adverse mutations ($P < .01$) and karyotype ($P < .01$) displayed additional prognostic value without disqualifying the prognostic integrity of the AAA model.

The AAA model was recently applied to a recently published Mayo-Florence study of 2000 patients with ET;[45,46] among 653 informative cases from the Mayo Clinic series, HR-weighted scoring allocated four adverse points for age >70 years, two adverse points for age 50–70 years, one adverse point each for ANC ≥8 × 10^9/L, and, ALC <1.7 g/dL: low (0–1 point; $n = 194$), intermediate-1 (2–3 points; $n = 277$), and high/intermediate-2 (4–6 points; $n = 182$), with respective median survival (20-year rate) of not reached (80%), 21.3 years (60%), and 10.6 (7%) years ($P < .0001$). The AAA survival distributions for the Florence series were median 10.1 years for high-risk, 12.7 years for intermediate-2-risk, 26.2 years for intermediate-1-risk, and median not reached for low-risk disease. Additional AAA-independent risk factors for overall survival included male gender in both the Mayo and Florence patient cohorts and arterial thrombosis history and hypertension, in the Mayo patient cohort.

Most recently, additional analysis of an international database of patients with ET have suggested the probability of death in ET patients with intermediate thrombosis to be higher than in those without thrombosis.[62] Another recent development regards variant allele frequency (VAF) of MPN driver mutations; in a retrospective study of 1607 patients with WHO-defined ET, independent risk factors for MF-free survival, in the discovery patient cohort, were age >60 years, male sex, palpable splenomegaly, *CALR-1* or *MPL* mutation, and *JAK2*V617F VAF >35%.[63] Similarly, a *CALR* VAF of >60% in ET was recently shown to be associated with a higher risk of progression to MF.[64]

9 | RISK FACTORS FOR THROMBOSIS AND BLEEDING

Current treatment-relevant risk stratification in ET, designated as the revised-IPSET-thrombosis,[65] is designed to estimate the likelihood of thrombosis and includes four risk categories (Figure 4): very low risk (age ≤60 years, no thrombosis history, *JAK2* wild-type), low risk (age ≤60 years, no thrombosis history, *JAK2* mutated), intermediate risk (age >60 years, no thrombosis history, *JAK2* wild-type), and high risk (thrombosis history or age >60 years with *JAK2* mutation).[65] The original IPSET-thrombosis was developed in the context of an international study of 891 patients with WHO-defined ET and identified age >60 years, thrombosis history, CV risk factors, and JAK2V617F, as independent risk factors for thrombosis, which subsequently led to a 3-tiered prognostic model:[66] low-, intermediate-, and high-risk disease with respective thrombosis risk of 1.03% of patients/year, 2.35% of patients/year, and 3.56% of patients/year. The subsequently developed revised-IPSET-thrombosis considered 1019 patients with WHO-defined ET and revealed limited enhancement of thrombosis risk by *JAK2* mutation or CV risk factors, in traditionally-assigned high-risk disease with thrombosis history, while *JAK2* mutation affected thrombosis risk in high-risk disease assigned by older age alone.[65] According to revised IPSET-thrombosis, risk of thrombosis was remarkably low at 1.05% patients/year in very low-risk disease with and 0.44% patients/year without CV risk factors.[65] By contrast, the thrombosis risk rates in low-risk disease ranged from 1.59% to 2.57% patients/

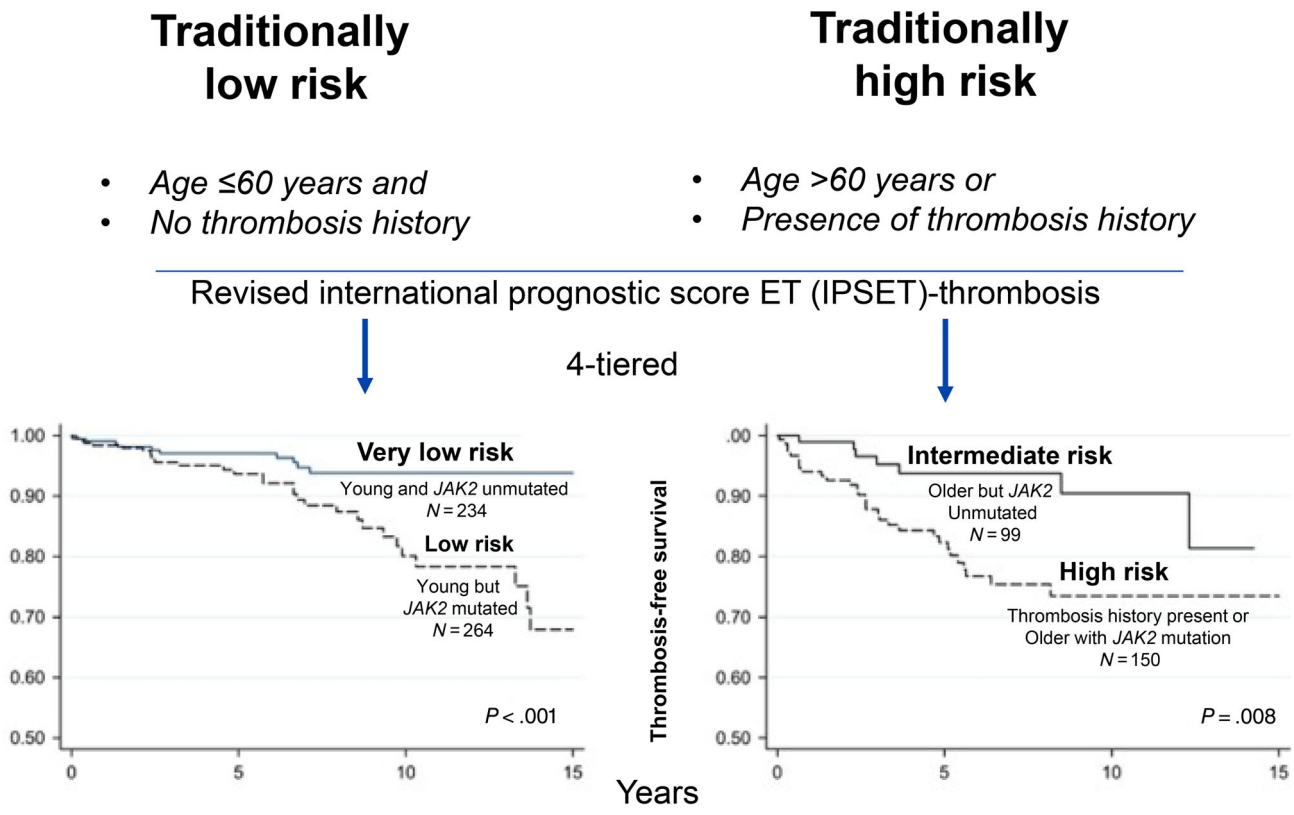

FIGURE 4 Thrombosis risk stratification in essential thrombocythemia (ET). *Source*: Adapted from Barbui et al.[65]

year in the presence of *JAK2* mutation alone or in association with CV risk factors, respectively.[65] The thrombosis risk rates in intermediate- and high-risk disease were 1.44%–1.64% and 2.36%–4.17% patients/year, respectively.[65] The revised IPSET-thrombosis has been validated by multiple subsequent studies[67,68] while the original IPSET-thrombosis score performed better in prefibrotic MF.[69]

Separate analysis of arterial and venous thrombosis was performed on the IPSET database of 891 patients with WHO-defined ET;[70] after a median follow-up of 6.2 years, 109 (12%) patients experienced arterial ($n = 79$) or venous ($n = 37$) thrombosis. In multivariable analysis, predictors of arterial thrombosis included age >60 years, thrombosis history, CV risk factors including tobacco use, hypertension, or diabetes mellitus, leukocytosis (>11 $\times$ 10^9/L), and presence of *JAK2*V617F.[70] By contrast, only male gender predicted venous thrombosis. Interestingly, platelet count more than 1000 $\times$ 10^9/L was associated with a lower risk of arterial thrombosis. Mutant *CALR* (vs. *JAK2*) was associated with lower incidence of thrombotic events without necessarily affecting risk assessed by IPSET-thrombosis.[71] In a more recent Mayo Clinic study, risk factors for recurrent venous thrombosis in ET included age >60 years, splanchnic vein thrombosis (SVT) history, and *JAK2* mutation.[72] In the aforementioned Mayo-Florence study of 2000 patients with ET who were mostly managed according to current standard of care,[45,46] multivariate analysis, in the Florence cohort, identified *JAK2* mutation as a risk factor for both arterial and venous thrombosis-free survival and older age for arterial thrombosis-free survival. A similar analysis on the Mayo Clinic cohort identified advanced age, male gender, *JAK2* mutation, hypertension, and arterial thrombosis history as independent risk factors for arterial thrombosis-free survival, whereas male gender and venous thrombosis history predicted venous thrombosis. Aspirin therapy appeared to mitigate both arterial and venous thrombotic events, in the Mayo cohort, while a similar protective role was apparent for cytoreductive therapy, in the Florence cohort. Taken together, these observations generally support our current antithrombotic treatment approach in ET (detailed in the next section)[73–75] with room for improvement in both event prediction[63,72,76–78] and optimal prevention of thrombosis.[79,80]

Extreme thrombocytosis, operationally defined as a platelet count of ≥1000 $\times$ 10^9/L, has been associated with acquired von Willebrand syndrome (AvWS) and excess bleeding, especially in the presence of aspirin therapy.[81] The mechanism behind the particular phenomenon is believed to be related to increased degradation of VWF multimers, mediated by ADAMTS13 and correctable with cytoreductive therapy.[82,83] In a recent study, 64 patients with ET or PV were studied for AvWS and loss of VWF high-molecular-weight multimers was documented in 51.4% of patients with PV and 55.6% ET and correlated with increased platelet and leukocyte counts.[84] In current practice, several diagnostic tools are applied in order to measure VWF activity including ristocetin-induced binding (VWF:RCo), ristocetin-independent binding to mutant GP1ba (VWF:GP1bM), and immobilized collagen (VWF:CB). In the aforementioned study,[84] a VWF:GP1bM/Ag ratio of 0.8 was shown to serve as an optimal screening tool and it performed better, in that regard, against VWF:CB/Ag. At the Mayo Clinic, we use both VWF:RCo and latex immunoassay[85] for screening and we consider VWF:RCo level of 20% as the actionable target. In a Mayo-Florence study of 2000 patients with ET,[45,46] additional risk factors for hemorrhage included older age, leukocytosis, but not treatment with aspirin.

10 | TREATMENT

10.1 | Overview

Median survival in young patients with ET and PV exceeds 35 years and is not that much worse for older patients.[56,57] Therefore, it is very important to avoid non-evidence-based therapeutic adventures that might shorten life expectancy and increase the rate of fibrotic or leukemic transformations, as has been previously reported with chlorambucil,[86] radiophosphorus,[87] pipobroman,[88] and anagrelide.[89,90] To date, drug therapy has not been shown to improve survival or prevent leukemic/fibrotic transformation in either ET or PV; therefore, treatment is instead directed at preventing thrombotic complications. In this regard, the decision to institute drug therapy should take into consideration individual risk of thrombosis, availability of controlled evidence of value, and potential harm to patient, both short-term and long-term. In the latter regard, drug-induced alteration of host immunity and impact on clonal evolution are particularly highlighted in the context of opportunistic infections, induction of second malignancies, and leukemic or fibrotic transformation.

Figure 5 outlines our general treatment approach in ET, which starts with thrombosis risk stratification: very low (age ≤60 years, no thrombosis history, *JAK2* wild-type), low (same as very low but *JAK2* mutation present), intermediate (age >60 years, no thrombosis history, *JAK2* wild-type), and high (thrombosis history present or age >60 years with *JAK2* mutation). Thrombosis risk in very low risk patients with triple-negative driver mutational status is too low to warrant the need for any form of therapy, but once-daily aspirin therapy is advised in the presence of either CV risk factors or *CALR-1/MPL* mutations.[45,46] Once- or twice-daily aspirin is strongly advised in low-risk patients, in the absence or presence of CV risk factors, respectively (Figure 5). Twice-daily aspirin is also our current treatment choice for intermediate-risk disease, but combination of a cytoreductive drug with once-daily aspirin is a reasonable alternative in intermediate-risk patients with CV risk factors (Figure 5).

In high-risk patients, first-line cytoreductive drug of choice is currently hydroxyurea (HU), a practice based on the results of randomized[89,91] and carefully designed single-arm cohort studies.[91–94] Efforts to improve upon HU as first-line therapy for ET have not materialized as yet and instead have suggested harmful effects for some of the alternative drugs.[89] Second-line drugs of choice in high-risk ET or PV, based on single-arm cohort studies with adequate follow-up and documentation of long-term safety, are pegylated interferon-α (IFN- α) and busulfan. Concerns about drug leukemogenicity involving HU or busulfan, which we do not share, are largely based on anecdotes rather than properly executed controlled studies and their safety in this regard has been affirmed by large retrospective studies (subject

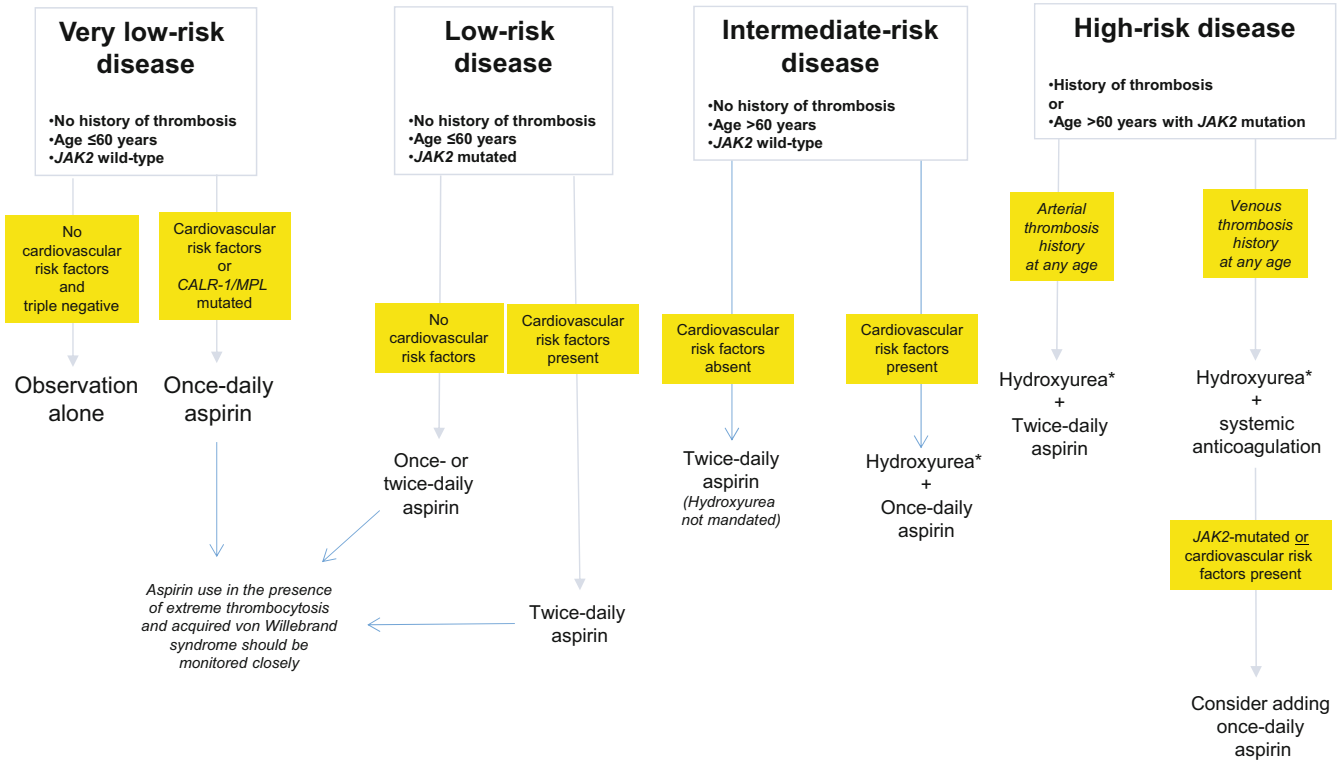

FIGURE 5 Current treatment algorithm for essential thrombocythemia. *Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN-α or busulfan.

discussed below in more details).[51,55] There are no controlled studies that have compared new drugs against currently established second-line drugs, including busulfan and IFN-α, in HU non-responsive or intolerant patients; instead, ruxolitinib, JAK1/2 inhibitor, was compared to HU, in such a setting and showed superior response in control of hematocrit, splenomegaly, and symptoms in PV;[95] however, the particular study did not target the appropriate health outcome as study endpoints, such as thrombosis, survival, and leukemic/fibrotic disease transformation rates.

10.2 | More on risk-adapted therapy: very low or low risk with or without extreme thrombocytosis

Very low-risk patients with ET might not require any therapy, unless in the presence of CV risk factors or *CALR-1/MPL* mutations, where once-daily low-dose aspirin is advised (Figure 5).[96] Such a treatment strategy is not necessarily modified by the presence of extreme thrombocytosis, unless it is associated with AvWS, where the use of aspirin needs careful monitoring. In two recently published retrospective studies comprising 2000 patients with ET,[45,46] triple-negative disease was associated with the lowest risk of thrombosis, which supports our observation alone treatment approach in such patients, especially in the absence of CV risk factors (Figure 5). On the contrary, we recommend the use of low-dose aspirin (81 mg/day; range 40–100 mg/day) in all patients with low-risk *JAK2*-mutated ET, provided there are no major contraindications; the latter include clinically significant VWF:RCo <20% associated with bleeding complications.

We have recently addressed the issue of extreme thrombocytosis (platelet count ≥1000 × 10^9/L) in very low/low-risk ET by examining the medical records of 710 Mayo Clinic patients with ET;[96] the incidence of platelet count ≥1500 × 10^9/L was 6% and significantly higher (15%) in patients <40 years of age; additional correlations included *CALR* mutation, lower hemoglobin level, leukocytosis, and major hemorrhage, at presentation; there were no significant associations with arterial or venous thrombosis or microvascular symptoms. More importantly, extreme thrombocytosis was not associated with higher risk of thrombosis or hemorrhage.[96] Among 24 patients with very low/low-risk disease and platelet count ≥1500 × 10^9/L, 5 were under observation alone while aspirin alone ($N = 5$), cytoreductive treatment alone ($N = 7$), or aspirin + cytoreductive drug ($N = 7$) was implemented in the rest; at a median follow-up of 15.3 years, only 2 arterial events were recorded and both occurred in patients on cytoreductive therapy alone without aspirin; a single venous event in a patient under observation alone treatment strategy was observed.[96] In other words, none of the 12 patients initiated on aspirin therapy at diagnosis experienced any thrombosis. In the same study,[61] two patients experienced major hemorrhage after diagnosis and none were on aspirin therapy during the incident.

Based on the above, we do not recommend cytoreductive therapy in very low/low-risk ET patients, including those aged 40–60 years.[97] On the contrary, based on our experience elaborated

above, as well as that of others,[98] and the experience in PV,[99] we are in favor of using low-dose aspirin in both very low-and low-risk ET. Furthermore, a previously published study tested the hypothesis that increased platelet turnover in ET and PV might compromise durable (i.e., over 24-h period) inhibition of platelet cyclo-oxygenase (COX-1); accordingly, three aspirin dosing regimens were investigated and BID/TID dosing was more effective, compared with QD dosing, in reducing platelet activation, measured by serum thromboxane B2 level.[79] Low-dose aspirin therapy has also been shown to be effective in alleviating vasomotor (microvascular) disturbances associated with ET or PV.[100] In the presence of aspirin-resistant symptoms, it is reasonable to utilize a twice-daily rather than once-daily regimen of low-dose aspirin or alternative antiplatelet agents such as clopidogrel (75 mg/day) alone or in combination with aspirin,[101] as long as patients are monitored closely for drug side effects. One might also consider platelet-lowering agents (e.g., HU) in aspirin-refractory cases, but the target platelet count in this instance should be the level at which relief of symptoms is observed, and not necessarily 400 $\times$ 10^9/L.

Bleeding diathesis in ET or PV is currently believed to be multifactorial in etiology.[102] Laboratory evidence of AvWS occurs in the majority of patients with ET or PV and, as elaborated in a previous section, is characterized by the loss of large von Willebrand factor multimers, linked to their increased proteolysis by the ADAMTS13 cleaving protease, in a platelet count-dependent fashion. This results in a functionally more relevant defect that may not be apparent when measuring VWF:Ag and FVIII levels alone and requires the use of assays that assess VWF function (e.g., ristocetin cofactor activity; VWF:RCoA). Other causes of platelet dysfunction in ET or PV include acquired storage pool deficiency, increased platelet activation, decreased adrenergic receptor expression, impaired response to epinephrine, and decreased platelet membrane glycoprotein receptor expression.[102] Regardless, in the presence of platelets >1000 $\times$ 10^9/L, screening for ristocetin cofactor activity is advised and consideration given to withhold aspirin therapy if the result shows <20% activity. Furthermore, clinically-relevant AvWS can occur even when the platelet count is below 1000 $\times$ 10^9/L and laboratory evaluation of AvWS must be performed in the presence of abnormal bleeding, regardless of platelet count.[103]

10.3 | More on risk-adapted therapy: high- or intermediate-risk disease

In addition to low-dose aspirin, high-risk patients with ET should receive HU, as first-line cytoreductive drug of choice, in order to minimize their risk of thrombosis (starting dose 500 mg BID). These recommendations are based on both controlled[89,91] and carefully designed prospective and retrospective studies (see detailed discussion in the section below);[104] we also consider the experience in PV, with HU, as additional layer of evidence for the use of HU in high-risk ET (Figure 5).[91–94,105–109] The dose of HU is titrated to keep platelet count in the normal range. However, it is to be noted that the recommended platelet target is not based on controlled evidence. ET patients who are either intolerant or resistant to HU are effectively managed by IFN-α (pegylated preparations preferred) or busulfan.[110,111] Among these 2 s-line drugs, we prefer the use of IFN-α for patients younger than age 65 years and busulfan in the older age group, although there is no controlled evidence to support or refute such a strategy. Busulfan is started at 2–4 mg/day, withheld in the presence of platelets <200 $\times$ 10^9/L or white blood cell <3 $\times$ 10^9/L, and the dose is reduced to 2 mg/day when treatment is resumed after withholding.

We usually start subcutaneous pegylated IFN-α at 45 mcg once-a-week (or ropeginterferon 100 mcg every 2 weeks) and titrate up to 180 mcg once-a-week (300 mcg ropeginterferon), if tolerated. We also believe it is reasonable to use twice-daily aspirin in patients with arterial thrombosis if they are older or harbor *JAK2* mutations or in the presence of CV risk factors (Figure 5).[79] In patients with venous thrombosis, systemic anticoagulation is advised and the addition of once-daily low-dose aspirin, in the presence of *JAK2* mutation or CV risk factors, is reasonable. The therapeutic role of direct oral anticoagulants is currently being investigated and has been suggested in retrospective studies,[112] as well as in those with SVT, where recurrence might[113] or might not[114] be secured with the use of vitamin K-antagonists (VKA). Cytoreductive therapy is not mandatory in intermediate-risk patients with ET (age >60 years but without *JAK2* mutation and without history of thrombosis), and treatment approach in such cases should be individualized.

10.4 | Clinical trials that support the use of cytoreductive therapy

In one of the very few controlled studies in ET, Cortelazzo et al. randomized 114 mostly high-risk patients to HU ($n = 56$) or not ($n = 58$).[91] After 27 months of follow-up, the incidences of thrombotic complications were 3.6% for HU and 24% for no HU, although the "thrombotic" episodes in two patients in the non-HU arm constituted superficial thrombophlebitis. In a more recent study, 382 low-risk ET patients aged 40–59 and without extreme thrombocytosis were randomized to aspirin therapy with or without HU; after a median follow-up of 73 months, there was no significant difference between the two arms in regards to vascular events, disease transformation rates, or overall survival.[97]

Two randomized studies in ET compared HU with anagrelide. In the earlier study,[89] 809 high-risk patients were given low-dose aspirin plus either anagrelide or HU. HU was better in terms of reducing the risk of arterial thrombosis, major bleeding, and fibrotic progression. Anagrelide performed better in preventing venous thrombosis. In addition, adverse dropout rate was significantly higher in the anagrelide arm. In the second study,[115] anagrelide was compared with HU in 259 high-risk ET patients; during the total observation time of 730 patient-years, there was no significant difference between the anagrelide and HU group regarding incidences of major arterial (7 vs. 8) and venous (2 vs.6) thrombosis, severe bleeding events (5 vs. 2), minor arterial (24 vs. 20) and venous (3 vs. 3) thrombosis and minor

bleeding events (18 vs. 15), or discontinuation rates (adverse events 12 vs. 15 or lack of response 5 vs. 2); incidences of leukemic or fibrotic transformations were not reported. It should be noted that WHO diagnostic criteria were strictly adhered to in the latter study[115] and not in the former.[89]

In a randomized phase-3 study,[116] HU ($n = 86$) was compared with peg-IFN-α ($n = 82$) in 168 treatment-naive, high-risk patients with ET ($n = 81$) or PV ($n = 87$). After a median treatment duration of 81 weeks for HU and 95 weeks for peg-IFN-α, complete hematologic response (CR; defined as a platelet count <400 × 10^9/L, hematocrit <45% without phlebotomy for patients with PV, leukocyte count <10 × 10^9/L, resolution of splenomegaly, resolution of disease-related symptoms, and BM histologic remission), after 12 months of treatment, was documented in 37% and 35% of patients treated with HU or peg-IFN-α, respectively; the corresponding overall response rates (same as CR but not requiring histologic remission) were 70% for HU and 78% for peg-IFN-α. Among evaluable cases with a spleen size ≥13 cm by imaging at baseline, 4/37 (11%) receiving HU, and 6/36 (17%) receiving peg-IFN-α attained normal spleen size; among evaluable cases, 23% on HU versus 5% on peg-IFN-α achieved BM histologic response; pre- and post-treatment cytogenetic studies showed no significant difference between HU and peg-IFN-α treated cases regarding infrequent losses or gains of abnormalities. Treatment with peg-IFN-α led to a greater reduction in *JAK2*V617F allele burden at 24 months, but histopathologic responses were more frequent with HU. Thrombotic events and disease progression were infrequent in both arms, whereas grade 3/4 adverse events were more frequent with peg-IFN-α (46% vs. 28%).[116] Ruxolitinib (JAK1/2 inhibitor) has also been compared with best available therapy in HU unresponsive/intolerant high-risk ET, in a randomized phase-2 study;[117] the 1-year complete response rates, which were not associated with molecular responses, were similar in the two study arms as were the 2-year rates of thrombosis, hemorrhage, and leukemic/fibrotic transformation.

10.5 | More on interferon and busulfan therapy in ET

It is now well established that IFN-α can control erythrocytosis or thrombocytosis in the majority of patients with PV or ET. A similar degree of benefit is appreciated in terms of reduction in spleen size or relief from pruritus. Two earlier studies of pegylated IFN-α (~90 μg SC weekly) in PV and ET reported hematologic remissions of ~80% accompanied by decreases in *JAK2*V617F allele burden (complete molecular remission rate of 5%–10%).[118,119] In one of the two studies,[118] 77 cases were evaluable after a median follow-up of 21 months and 76% and 70% of patients with ET or PV, respectively, achieved a complete hematologic remission, mostly in the first 3 months; side effects were recorded in 96% of the patients and 22% had discontinued treatment. Pegylated IFN has also shown activity in patients with PV or ET who were resistant or intolerant to HU; responses in ET were higher in the presence of *CALR* mutation.[110] More recently, a newer form of pegylated IFN (ropeginterferon) has shown efficacy and safety profile similar to that of other pegylated IFNs.[120,121] Controlled studies are needed to clarify the advantage (or disadvantage) of IFN therapy in ET or PV, compared with HU therapy in high-risk disease and phlebotomy/aspirin alone in low-risk disease; such studies are currently ongoing in both high-[122] and low-[121,123–125] risk PV, but their follow-up time is too short to fully appreciate their value in terms of long-term survival or disease transformation rates. IFN therapy was also associated with significant reduction in mutant *CALR* allele burden in ET,[126] whereas drug-induced *JAK2*V617F allele burden reduction has also been demonstrated with busulfan use in PV.[127] There are currently several phase-2 and phase-3 studies of ropeginterferon in ET (ClinicalTrials.gov).

The safety and efficacy of busulfan treatment in ET was recently underlined by a long-term study of 36 patients above age 60 years of age;[128] no instances of AML or other malignancies were documented after a median follow-up of 72 months. In a more recent study of over 1500 patients with PV, the use of busulfan was not correlated with leukemic transformation.[55] Most recently, the use of busulfan in HU-resistant PV produced over 80% complete hematologic response and molecular remission in about a third of the patients.[111]

10.6 | The issue of drug leukemogenicity

There are, to date, no controlled studies that implicate either HU or busulfan as being leukemogenic in either ET or PV. Similarly, the two largest non-controlled studies in ET[104] and PV[105] do not support the concern that leukemia might arise from the use of HU and there is additional evidence to that effect from long-term studies of patients receiving HU for sickle cell disease.[129] The evidence for busulfan leukemogenicity in the context of treatment for PV or ET is equally weak and inappropriately extrapolated from older patients with advanced phase disease and exposed to multiple cytoreductive drugs. The recurrent flaw in data interpretation, when it comes to examining the relationship between leukemic drugs and leukemic transformation, is best illustrated by the largest prospective/retrospective study, to date, in PV ($n = 1638$).[105] At a median follow-up of 8.4 years from diagnosis, only 1.3% of the patients developed AML. When the authors compared the patients who transformed to those who did not, the former were older and more likely to have leukocytosis (known risk factor for leukemic transformation) at time of diagnosis or registration to the central database. They also had significantly longer disease duration and were more likely to have been treated with multiple drugs. In other words, exposure to alkylating agents other than HU selects patients who are at a higher risk of leukemic transformation because of older age, longer disease duration, and intrinsic aggressive disease biology. This is the reason for the apparent association in some studies between leukemic transformation and drug therapy in PV or ET. Our impression is further supported by a recent International Working Group study of 1545 PV patients in which cumulative hazard of leukemic transformation, with death as a competing risk, was 2.3% at 10 years and 5.5% at 15 years;[55] risk factors

for leukemic transformation were older age, abnormal karyotype, and leukocytes ≥15 × 10^9/L. Leukemic transformation was associated with treatment with pipobroman, P32, or chlorambucil but not with HU or busulfan.[55] Whether or not the same holds true for second cancers developing in patients with MPN remains to be clarified.[130]

11 | TREATMENT STRATEGIES IN SPECIFIC CONTEXTS

11.1 | Management during pregnancy

Platelet counts in general decline in all pregnancies and revert back to baseline postpartum;[131] potential underlying biologic mechanisms have recently been entertained.[132] The same is true for pregnant women with ET, with an average percent decline, at nadir (time of delivery), of 43% from baseline;[133] platelet counts increased back to baseline postpartum with 75% recovery within 1 month. Both pregnancy and MPN impart a hypercoagulable state, conferring a heightened risk for thrombosis. Bleeding is an additional risk at the time of delivery and in the postpartum phase, especially in the context of treatment with aspirin and/or low molecular weight heparin (LMWH). Besides maternal complications, resultant fetal consequences beyond fetal loss such as intra-uterine growth retardation (IUGR) from preeclampsia or placental insufficiency need special considerations. In general, the assessment of risk during pregnancy is based on an extrapolation of known risk factors for thrombosis in MPN, including prior thrombosis, presence of *JAK2* mutation, and CV risk factors.

Almost all information regarding pregnancy outcome in ET or MPN is sourced from retrospective studies,[134] with few exceptions.[135] As such, it is difficult to discern the specific circumstances or treatments that might have influenced outcome. Based on a number of retrospective studies published over the years, it is reasonable to expect increased risk of first-trimester miscarriages and premature delivery with pregnancy in ET, while rates of stillbirth, preeclampsia, and other maternal complication of thrombosis and bleeding might be similar to those expected in the general population.[134,136,137] In a recent large population-based Swedish study,[137] 342 pregnancies in 229 women with MPN and had reached gestational week 22–28 were considered and compared with controls matched 1:1 for age, calendar year, and parity; MPN patients had higher risk of preterm birth (14% vs. 2%) and low birth weight; by contrast, stillbirth, maternal thrombotic complications, and bleeding events were infrequent and not significantly different from the matched control group, although more likely to occur in the MPN group.[137]

We have previously reviewed the published literature on pregnancy in MPN, spanning over two decades, including four select independent series with ET comprising 100 or more pregnancies each, with a total 493 pregnancies; live birth, maternal thrombosis, and hemorrhage rates were 70.2%, 3.5%, and 4.5%, respectively.[134] Incidence figures for outcome events displayed marked variation across these studies with live birth rates ranging from 41% to 90% and spontaneous first-trimester miscarriage rates 25%–50%.[74] In our own experience with 95 pregnancies in 55 women with ET,[138] live birth rate was 62%, fetal loss in general 38% and first trimester 35%. Maternal complications were infrequent and included postpartum hemorrhage in five (9%) women, thrombosis 5%, preeclampsia 5%, and placental abruption 4%.[138] Our observations in the latter study[138] included identification of prior history of fetal loss as a risk factor for subsequent pregnancy loss and the beneficial role of aspirin in reducing the risk of fetal loss with rates of 27% versus 60% with and without aspirin therapy, respectively. On the contrary, MPN driver mutational status did not impact fetal loss.[138]

Observations from other studies were consistent to those of our own, as elaborated above, and recently reviewed.[134] In a previous study from Boston, USA, including 121 pregnancies in 52 women with ET, live birth rate was 69%, fetal loss 32%, spontaneous abortion 26%, preterm delivery 7.4%, thrombosis/hemorrhage during pregnancy 2.5%/5.8%, preeclampsia 3.3%, and intra-uterine growth retardation 2.5%.[133] Also in this Boston study,[77] prior pregnancy loss conferred an increased risk of subsequent pregnancy complication, whereas aspirin use was beneficial in that regard; MPN driver mutational status was once again not significantly correlated with pregnancy outcomes.[51] Similar observations were apparent in a large retrospective multi-institutional study from 11 Italian centers comprised of 237 pregnancies in 158 women with ET; fetal loss rate was 29% (88% of which was in the 1st trimester), and maternal complication rate 7%; also in this study, *JAK2* mutation did not impact pregnancy outcome with fetal loss rates of 35% versus 27% among *JAK2* mutated versus unmutated cases. On the contrary, other studies had previously suggested increased risk of complications in *JAK2*-mutated ET and no therapeutic benefit from aspirin.[139] Such discord in observations across studies is even more apparent in regard to treatment experience regarding IFN therapy and use of LMWH.[134]

The therapeutic impact of aspirin, LMWH, and IFN-α on fetal and maternal outcome, in pregnant women with ET, must be interpreted cautiously, and there are no controlled studies that allow an informed strategy. In one systematic review of 22 studies reporting on 1210 pregnancies in 767 women with MPN,[140] live birth rate was 71.3% (71.1% for ET) and use of aspirin and IFN were associated with higher odds of live birth; the addition of heparin to aspirin did not improve the odds of live birth; 59.1% of spontaneous abortions occurred during the 1st trimester and 24.9% in the 2nd.[140] Also in the particular study,[140] IFN use with or without aspirin or heparin increased the odds of live birth; however, in a more detailed analysis of studies in which patients received both IFN-α and aspirin (nine patients) versus aspirin alone (32 patients), there was no difference in live births; maternal complications remained similar among patients managed with aspirin or aspirin combined with LMWH versus observation or IFN-α.[140] In yet another systematic review of 756 pregnancies in 504 women with ET,[141] live birth rate was 74% and 1st trimester fetal loss rate 19%; antepartum risk of venous thromboembolism (VTE) was 1.3% (0% in the presence of LMWH use vs. 2.5% otherwise) while VTE incidence was similar in the presence or absence of aspirin use and favored IFN use (0% vs. 2%). Postpartum VTE occurred in 1.8% of

cases and LMWH use appeared to be fully protective;[141] interestingly, bleeding risk did not appear to be enhanced by use of LMWH.

Taken together, we recommend that all women of childbearing age, with ET, should undergo counseling regarding risk of early fetal loss, premature delivery, and other complications, especially those with prior pregnancy loss or history of thrombosis. We recommend treatment with low-dose aspirin in all women with ET who are or wish to be pregnant, based on the above elaborated retrospective data regarding protection from first-trimester fetal losses.[133,138] In the absence of history of thrombosis or prior pregnancy loss, we do not recommend additional therapy, either antepartum or postpartum, unless otherwise dictated by other circumstances. In low-risk patients with prior history of pregnancy loss, the use of IFN therapy or LMWH should be individually addressed. We recommend cytoreductive therapy with IFN in patients with prior vascular events and consider adding LMWH, in case of venous thrombosis history; the value of LMWH during pregnancy or postpartum, in the absence of venous thrombosis history, is uncertain, and not mandatory. We do not advise the use of HU or warfarin because of their teratogenic potential. Despite the safety and efficacy of direct oral anticoagulants in MPN, their use during pregnancy is not recommended.

11.2 | Management of SVT

Although it is well known that SVT frequents patients with MPN, including MPN-U, there remains a significant knowledge gap regarding its management. As a background on SVT in general, in one population-based study of 1915 patients,[142] the affected veins were portal in 78%, hepatic in 11%, and mesenteric in 11%; risk was similar between the two sexes and the respective incidence rates were 21, 3, and 3/100 000 persons per year. In the study,[142] comorbidities included recent surgery (40%), liver cirrhosis (11%), pancreatitis (11%), gastrointestinal cancer (9%), extraintestinal cancer (10%), and MPN (1.2%). The incidence of MPN as a comorbid condition was higher in another study (8%).[143]

In a recent retrospective study, 518 patients with MPN-SVT were compared with 1628 otherwise unselected MPN cases;[113] the former were more likely to be younger, females, and *JAK2*V617F-mutated (90%). The study included 192 (37%) patients with PV (median age 45 years; 53% females) and 178 (34%) with ET (median age 39 years; 71% females; 85% *JAK2* mutated) and affected veins included portal (67%), hepatic (25%), splenic (29%), and mesenteric (24%).[113] A concomitant hypercoagulable disorder was documented in 39% of the cases. SVT recurrence rate was 1.6 per 100 patient-years and significantly improved by treatment with VKA but not cytoreductive therapy. Bleeding complications did not appear to be influenced by VKA therapy but were more likely to occur in patients with esophageal varices. Overall survival of PV patients in the study[113] was not affected by SVT; furthermore, there was little evidence of disease progression in patients with MPN-U with SVT ($n = 55$). The potential value of systemic anticoagulation in SVT, in the setting of noncirrhotic chronic portal vein thrombosis, was recently underlined in a controlled study of 111 patients where the recurrent thrombosis rate was 0 per 100 person-years in patients treated with rivaroxaban versus 19.71 per 100 person-years in those not receiving such treatment; after a median follow-up of 30.3 months, major bleeding occurred in two patients receiving rivaroxaban and in one patient not receiving anticoagulation.[144]

Currently, there are no reliable predictors of first-event or recurrent SVT in MPN, including ET. A retrospective report looked into risk factors for adverse outcome in 80 patients with MPN-SVT (mostly PV);[145] at a median follow-up of 11 years, 13% of the patients experienced an adverse outcome and were enriched for cases with ≥50% *JAK2*V617F allele burden, and additional mutations (spliceosome or *TP53*); MPN-SVT patients with at least one of the latter two risk factors displayed inferior event-free (81% vs. 100%) and overall (89% vs. 100%) survival at 10 years. Regardless, along with observations from other studies,[114,146] it is reasonable to expect survival in MPN-SVT to be primarily influenced by the underlying MPN.[114,145] The therapeutic value of systemic anticoagulation (and the choice between VKA and DOAC)[113] or cytoreduction (and the choice between HU and IFN)[147,148] requires further examination, in a controlled setting. A small study of ruxolitinib therapy in patients with MPN-SVT did not indicate salutary effect on esophageal varices or mesenteric circulation,[149] which is consistent with lack of evidence for its value in reducing thrombosis risk.[150]

In patients with ET/MPN-associated SVT, we recommend an aggressive treatment approach in order to prevent thrombosis extension, promote vascular recanalization, prevent bowel ischemia, preserve liver function, minimize complications from portal hypertension including ascites, and reduce risk of recurrence. This requires a multidisciplinary approach that includes coagulation clinic, vascular medicine, interventional radiology, and liver transplantation. In the acute setting, based on prospective but non-randomized treatment data,[151] we recommend immediate treatment with LMWH for 1–3 months followed by long-term anticoagulation with VKA or DOAC, based on renal and liver function status, intestinal absorption capacity, bleeding risk, and patient preference. We also recommend initial cytoreductive therapy with HU, but this can subsequently be modified based on other factors.[147,148]

11.3 | Perioperative management

It is important to consider the possibility of increased risk of thrombosis or hemorrhage in ET patients undergoing surgery, in lieu of their underlying *JAK2*-mutated MPN as well as the expected post-surgical risk of thrombosis and bleeding. There are currently limited data for guidance regarding optimal pre- and perioperative management of patients with ET or PV. In a 1963 report by Wasserman and Gilbert,[152] 62 major surgical operations in patients with PV were analyzed and revealed fatal and non-fatal complication rates of 83% versus 21%, in hematologically uncontrolled versus controlled disease, respectively. More recent studies have suggested more favorable outcome; in one such study,[153] 255 patients with PV or ET were analyzed

for a total of 311 surgical interventions, including 25 emergency procedures; antithrombotic prophylaxis included subcutaneous heparin in 54% and antiplatelet therapy in 15% of the patients; in addition, 74% of patients were on cytoreductive therapy before surgery; 3-month post-operative course was uneventful in more than 80% of the cases, whereas arterial or venous events were documented in 12 patients, each, with the former being more frequent in ET and the latter in PV; major bleeding complications occurred in 23 cases and deaths in 5; platelet count and hematocrit level at time of surgery were not predictive of vascular events and the value of pre-procedure prophylactic therapy was not apparent. The lack of a standardized approach to perioperative care in patients with MPN was recently underlined by a pan-Canadian physician survey.[154] Our current practice regarding perioperative management in ET is based more on intuition rather than evidence and includes keeping platelet count below 450×10^9/L, before and at least 1 week after surgery; platelet count control in low-risk patients might require a short course of treatment with HU; in addition to cytoreductive therapy, careful use of LMWH is advised in high-risk patients.

11.4 | Management of post-ET MF and leukemic transformation

The diagnosis of post-ET-MF requires documentation of an antecedent WHO/ICC-defined ET[3,7] that progressed into a PMF-like phenotype with grade ≥2 BM fibrosis, as well as at least two of the following minor criteria: (i) anemia associated with ≥2 g/dL decrease from baseline hemoglobin level, (ii) a leukoerythroblastic peripheral blood smear, (iii) increasing splenomegaly, (iv) increased LDH above reference level, and (v) development of constitutional symptoms.[4] Compared to that of PMF,[155] current information on the natural history of post-ET or post-PV-MF is relatively limited and is derived mostly from the MF secondary to PV and ET (MYSEC) project.[156] Unfortunately, specific interpretation of phenotype, genotype, and outcome analyses from the MYSEC project is confounded by inclusion of patients with both post-ET and post-PV MF. Among 333 patients with post-ET-MF reported by the MYSEC group,[156] median age at time of diagnosis was 64 years (males 50%) and the median time from diagnosis of ET to that of post-ET-MF was 10.3 years;[156] driver mutation distribution was 54% *JAK2*, 31% *CALR*, 9% *MPL*, and 6% triple-negative. The study also showed 27% incidence of abnormal karyotype, 37% constitutional symptoms, and 8% circulating blasts ≥3%; median palpable spleen size was 4 cm (range 0–27), platelet count 379×10^9/L (range 40–1908), hemoglobin level 10.7 g/dL, and leukocyte count 7.8×10^9/L. After a median follow-up of 3.1 years, incidence/100 patients-year were 2.3 for leukemic transformation, 2.4 for thrombotic events, and 5.5 for deaths.[156]

The MYSEC survival risk model,[156] which lumped patients with post-PV and post-ET MF together, considers older age (scored 0.15 points/year), hemoglobin <11 g/dL (two points), circulating blasts ≥3% (two points), absence of *CALR* mutation (two points), platelets $<150 \times 10^9$/L (one point), and constitutional symptoms (one point), as risk factors for survival; risk categories included low (<11 points; median survival not reached), intermediate-1 (11–14 points; median 9.3 years), intermediate-2 (>14 and <16 points; median 4.4 years), and high (≥16 points; median 2 years). By contrast, the mutation-enhanced international prognostic scoring system (IPSS) for PMF, version 2.0 (MIPSS*v2*) is a genetically more robust model and utilizes non-driver mutations and karyotype, in addition to other clinical risk factors including anemia, constitutional symptoms, and circulating blasts.[157] In other words, MIPSSv2 captures risk variables listed for MYSEC and provides additional prognostic information derived from cytogenetic and next-generation sequencing studies.

MIPSS*v2* utilizes nine components, including five genetic and four clinical;[157] the five genetic variables include very high risk (VHR; single or multiple abnormalities of −7, inv (3)/3q21, i(17q), 12p−/12p11.2, 11q−/11q23, autosomal trisomies other than +9 or + 8) karyotype (four points), unfavorable (neither VHR or favorable; the latter being normal karyotype or sole abnormalities of 20q-, 13q-, +9, chromosome 1 abnormalities including 1q duplication, loss of Y chromosome, or other sex chromosome abnormality) karyotype (three points), ≥2 high-molecular-risk mutations (three points), presence of one high-molecular-risk mutation (two points), and absence of type 1/like *CALR* mutation (two points); the four clinical variables in MIPSS*v2* include constitutional symptoms (two points), severe anemia, defined by hemoglobin levels of <8 g/dL in women and <9 g/dL in men (two points), moderate anemia, defined by hemoglobin levels of 8–9.9 g/dL in women and 9–10.9 g/dL in men (one point), and circulating blasts ≥2% (one point). MIPSS*v2* includes five risk categories: VHR (≥9 points), high risk (5–8 points), intermediate risk (3–4 points), low risk (1–2 points), and very low risk (zero points); in patients aged 70 years or younger, the corresponding median survivals (10-year survival rates) were 1.8 years (<5%), 4.1 years (13%), 7.7 years (37%), 16.4 years (56%), and "median not reached" (92%).

From a practical standpoint, we believe that both MIPSS*v2* and MYSEC-PM adequately serve their main purpose in identifying high-risk patients with post-ET MF who should be referred for allogeneic hematopoietic stem cell transplant sooner than later. However, the utilization of two separate risk models in primary versus secondary MF is both redundant and unnecessary and we prefer to use MIPSS*v2* for both MF variants. Our contention is consistent with more recent reports from the MYSEC group in identifying the additional prognostic value for karyotype[158] and other mutations,[159] as well as another recent report from Japan, where Dynamic IPSS (DIPSS)-plus was shown to be superior to MYSEC-PM, in its predictive performance, among 272 patients with post-PV/ET-MF.[160] Similarly, a previously published Mayo Clinic study had shown similar applicability of risk models used in PMF for patients with post-PV/ET MF, including the IPSS, dynamic DIPSS, and karyotype-enhanced DIPSS (DIPSS-plus).[161] Non-transplant therapies for post-ET-MF are similar to those of PMF and are mostly palliative.[155] Similarly, leukemic transformation is diagnosed and managed the same way as blast phase MPN, which is covered under our recently published annual update series on PMF.[155]

12 | NEW DRUGS UNDER INVESTIGATION

Unlike the case with MF and PV, there are only a handful of new drugs currently being investigated for the treatment of ET and include Lysine-specific demethylase-1 (LSD1; histone demethylase specific for H3K4) inhibitor (bomedemstat)[162] and a monoclonal antibody treatment targeting mutant CALR.[163] The latter, identified as INCA033989, involves a human monoclonal antibody that selectively targets mutant CALR and subsequently disrupts thrombopoietin receptor dimerization and oncogenic signaling. Pre-clinical studies showed that INCA033989 binds to human $CD34^+$ cells expressing mutant *CALR* and inhibits their proliferation, in a dose-dependent manner. In an in vivo MPN model, a 10-week treatment with INCA033989 prevented the development of mutant *CALR*-driven thrombocytosis and lowered the percentage of *CALR*-mutated precursor cells. Whether or not the value of such treatment extends beyond simple lowering of platelet count remains to be shown in patients with *CALR*-mutated ET or MF.

LSD1 is believed to be important for the self-renewal of malignant myeloid cells and maturation of megakaryocytes. Bomedemstat is an orally active LSD1 inhibitor. In a phase-2 study of high-risk ET patients ($N = 73$) considered intolerant or refractory to conventional therapy (NCT04254978),[162] >6 months of therapy resulted in 94% of patients achieving a platelet count response of $\leq 400 \times 10^9$/L, at a median time of 8 weeks, with the majority sustaining their response for 3 months. The drug was equally effective in reducing leukocyte counts without significant impact on hemoglobin and improvement on symptom burden was also noted. Common side effects of bomedemstat included dysgeusia (43%), constipation (27%), fatigue (23%), thrombocytopenia (23%), arthralgia (21%), contusion (16%), and diarrhea (15%). Treatment discontinuation rate was relatively high at 20%.[162] The primary endpoint used in this latter study might not be clinically meaningful in terms of risk for thrombosis or survival. In other words, the unmet need in ET is not necessarily control of platelet count but prevention of thrombosis, fibrotic progression, leukemic transformation, or death. Considering the remarkably indolent course of the disease in ET, one might have to demonstrate not only convincing evidence of disease-modifying activity, but also a broad safety profile, in order to justify large scale exposure of study patients to a candidate new drug.

13 | CONCLUDING REMARKS

There is currently a limited number of controlled clinical trials in ET.[89,91,97,116,164] This is not surprising considering the indolent course of the disease making it challenging to design a clinical trial with survival or leukemic transformation as a primary endpoint. Similarly, attempts in the past to use thrombosis as clinical trial endpoint have not always produced outcomes that justify changing current treatment paradigms,[89,97,164] with some exceptions.[91] If anything, some of these studies have revealed long-term adverse consequences from new drugs, in the absence of value in terms of meaningful health outcome.[90,165]

The aforementioned Mayo-Florence studies of 2000 patients with ET, although retrospective in design, provide important observations that are both confirmatory and novel, and useful. The two studies were concordant in their identification of triple-negative driver mutational status as a particularly favorable risk group, in terms of both thrombosis and disease transformation, and *MPL* and *CALR-1* mutations as risk factors for fibrotic transformation. Accordingly, it is reasonable to recommend a highly conservative treatment approach in triple-negative ET that is devoid of cytoreductive drugs while prefibrotic MF should be seriously considered, as an alternative diagnosis, in *MPL/CALR-1*-mutated disease. The outstanding prognosis in triple-negative ET makes it difficult to subject such patients to clinical trials with drugs devoid of demonstrable disease-modifying activity. The same can be said about low-risk ET, in general, while an argument can be made for innovative clinical trials to target ET patients with increased ANC or abnormal karyotype. Furthermore, controlled studies in ET should aspire to use primary endpoints that reflect meaningful health outcomes, such as thrombosis and progression-free or overall survival, rather than parameters of dubious clinical relevance, such as platelet count.[96,166]

AUTHOR CONTRIBUTIONS

All authors contributed to the design and discussion of the manuscript content and framework. AT wrote the paper.

CONFLICT OF INTEREST STATEMENT

None of the authors declare conflict of interest regarding the current work.

DATA AVAILABILITY STATEMENT

Data availability by email request.

ORCID

Ayalew Tefferi https://orcid.org/0000-0003-4605-3821
Alessandro Maria Vannucchi https://orcid.org/0000-0001-5755-0730
Tiziano Barbui https://orcid.org/0000-0003-2747-6327

REFERENCES

1. Thiele J, Kvasnicka HM, Orazi A, et al. The International Consensus Classification of myeloid neoplasms and acute leukemias: myeloproliferative neoplasms. *Am J Hematol*. 2023;98:166-179.
2. Thiele J, Kvasnicka HM, Orazi A, et al. The International Consensus Classification of myeloid neoplasms and acute leukemias: myeloproliferative neoplasms. *Am J Hematol*. 2023;98:544-545.
3. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140:1200-1228.
4. Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the international working Group for Myelofibrosis Research and Treatment. *Leukemia*. 2008; 22:437-438.
5. Orazi A, Hasserjian RP, Cazzola M, Döhner H, Tefferi A, Arber DA. International Consensus Classification for myeloid neoplasms at-a-glance. *Am J Hematol*. 2023;98:6-10.
6. Arber DA, Hasserjian RP, Orazi A, et al. Classification of myeloid neoplasms/acute leukemia: global perspectives and the International Consensus Classification approach. *Am J Hematol*. 2022;97: 514-518.

7. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36:1703-1719.
8. Hultcrantz M, Ravn Landtblom A, Andreasson B, et al. Incidence of myeloproliferative neoplasms - trends by subgroup and age in a population-based study in Sweden. *J Intern Med*. 2020;287:448-454.
9. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7:387-397.
10. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434:1144-1148.
11. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med*. 2005;352:1779-1790.
12. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365:1054-1061.
13. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356:459-468.
14. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med*. 2013;369:2391-2405.
15. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369:2379-2390.
16. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006;3:e270.
17. Pardanani A, Lasho TL, Finke C, Hanson CA, Tefferi A. Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. *Leukemia*. 2007;21:1960-1963.
18. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124:2507-2513.
19. Broseus J, Park JH, Carillo S, et al. Presence of calreticulin mutations in JAK2-negative polycythemia vera. *Blood*. 2014;124:3964-3966.
20. Pardanani A, Lasho TL, Finke CM, Tefferi A. Infrequent occurrence of MPL exon 10 mutations in polycythemia vera and post-polycythemia vera myelofibrosis. *Am J Hematol*. 2011;86:701-702.
21. Tefferi A. Myeloproliferative neoplasms: a decade of discoveries and treatment advances. *Am J Hematol*. 2016;91:50-58.
22. Alimam S, Villiers W, Dillon R, et al. Patients with triple-negative, JAK2V617F- and CALR-mutated essential thrombocythemia share a unique gene expression signature. *Blood Adv*. 2021;5:1059-1068.
23. Broseus J, Lippert E, Harutyunyan AS, et al. Low rate of calreticulin mutations in refractory anaemia with ring sideroblasts and marked thrombocytosis. *Leukemia*. 2014;28:1374-1376.
24. Steensma DP, Caudill JS, Pardanani A, McClure R, Lasho TL, Tefferi A. MPL W515 and JAK2 V617 mutation analysis in patients with refractory anemia with ringed sideroblasts and an elevated platelet count. *Haematologica*. 2006;91:ECR57.
25. Vainchenker W, Kralovics R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. *Blood*. 2017;129:667-679.
26. Dupont S, Masse A, James C, et al. The JAK2 617V>F mutation triggers erythropoietin hypersensitivity and terminal erythroid amplification in primary cells from patients with polycythemia vera. *Blood*. 2007;110:1013-1021.
27. Lasho TL, Finke CM, Tischer A, Pardanani A, Tefferi A. Mayo CALR mutation type classification guide using alpha helix propensity. *Am J Hematol*. 2018;93:E128-E129.
28. Constantinescu SN, Vainchenker W, Levy G, Papadopoulos N. Functional consequences of mutations in myeloproliferative neoplasms. *Hema*. 2021;5:e578.
29. Pecquet C, Papadopoulos N, Balligand T, et al. Secreted mutant calreticulins as rogue cytokines in myeloproliferative neoplasms. *Blood*. 2023;141:917-929.
30. Balligand T, Achouri Y, Pecquet C, et al. Knock-in of murine Calr del52 induces essential thrombocythemia with slow-rising dominance in mice and reveals key role of Calr exon 9 in cardiac development. *Leukemia*. 2020;34:510-521.
31. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis. *Blood*. 2014;123:e123-e133.
32. Constantinescu SN, Girardot M, Pecquet C. Mining for JAK-STAT mutations in cancer. *Trends Biochem Sci*. 2008;33:122-131.
33. Tefferi A. Challenges facing JAK inhibitor therapy for myeloproliferative neoplasms. *N Engl J Med*. 2012;366:844-846.
34. Vainchenker W, Constantinescu SN. JAK/STAT signaling in hematological malignancies. *Oncogene*. 2013;32:2601-2613.
35. Benlabiod C, Cacemiro MDC, Nedelec A, et al. Calreticulin del52 and ins5 knock-in mice recapitulate different myeloproliferative phenotypes observed in patients with MPN. *Nat Commun*. 2020;11:4886.
36. Toppaldoddi KR, da Costa CM, Bluteau O, et al. Rare type 1-like and type 2-like calreticulin mutants induce similar myeloproliferative neoplasms as prevalent type 1 and 2 mutants in mice. *Oncogene*. 2019;38:1651-1660.
37. Tiedt R, Hao-Shen H, Sobas MA, et al. Ratio of mutant JAK2-V617F to wild-type Jak2 determines the MPD phenotypes in transgenic mice. *Blood*. 2008;111:3931-3940.
38. Prick J, de Haan G, Green AR, Kent DG. Clonal heterogeneity as a driver of disease variability in the evolution of myeloproliferative neoplasms. *Exp Hematol*. 2014;42:841-851.
39. Li J, Kent DG, Godfrey AL, et al. JAK2V617F homozygosity drives a phenotypic switch in myeloproliferative neoplasms, but is insufficient to sustain disease. *Blood*. 2014;123:3139-3151.
40. Chen E, Beer PA, Godfrey AL, et al. Distinct clinical phenotypes associated with JAK2V617F reflect differential STAT1 signaling. *Cancer Cell*. 2010;18:524-535.
41. Chen E, Schneider RK, Breyfogle LJ, et al. Distinct effects of concomitant Jak2V617F expression and Tet2 loss in mice combine to promote disease progression in myeloproliferative neoplasms. *Blood*. 2014;123:1126-1335.
42. Rampal R, Ahn J, Abdel-Wahab O, et al. Genomic and functional analysis of leukemic transformation of myeloproliferative neoplasms. *Proc Natl Acad Sci U S A*. 2014;111:E5401-E5410.
43. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371:2477-2487.
44. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371:2488-2498.
45. Gangat N, Karrar O, Al-Kali A, et al. One thousand patients with ET: Mayo Clinic series. *Blood Cancer J*. 2024;14:11.
46. Loscocco GG, Gesullo F, Capecchi G, et al. One thousand patients with ET: the florence-CRIMM series. *Blood Cancer J*. 2024;14:10.
47. van Genderen PJ, Michiels JJ. Erythromelalgia: a pathognomonic microvascular thrombotic complication in essential thrombocythemia and polycythemia vera. *Semin Thromb Hemost*. 1997;23:357-363.
48. Michiels JJ, Abels J, Steketee J, van Vliet H, Vuzevski VD. Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis in thrombocythemia. *Ann Intern Med*. 1985;102:466-471.

49. Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis: "2019 update on diagnosis, risk-stratification, and management". *Am J Hematol*. 2019;94:475-488.
50. Tefferi A, Pardanani A. Essential thrombocythemia. *N Engl J Med*. 2019;381:2135-2144.
51. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *J Clin Oncol*. 2011;29:3179-3184.
52. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2018;93:442-459.
53. Smith CJ, Thomas JW, Ruan G, et al. A population-based study of outcomes in polycythemia vera, essential thrombocythemia, and primary myelofibrosis in the United States from 2001 to 2015: comparison with data from a Mayo Clinic single institutional series. *Am J Hematol*. 2021;96:E464-E468.
54. Hultcrantz M, Wilkes SR, Kristinsson SY, et al. Risk and cause of death in patients diagnosed with myeloproliferative neoplasms in Sweden between 1973 and 2005: a population-based study. *J Clin Oncol*. 2015;33:2288-2295.
55. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27:1874-1881.
56. Szuber N, Mudireddy M, Nicolosi M, et al. 3023 Mayo Clinic patients with myeloproliferative neoplasms: risk-stratified comparison of survival and outcomes data among disease subgroups. *Mayo Clin Proc*. 2019;94:599-610.
57. Szuber N, Vallapureddy RR, Penna D, et al. Myeloproliferative neoplasms in the young: Mayo Clinic experience with 361 patients age 40 years or younger. *Am J Hematol*. 2018;93:1474-1484.
58. Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the international working group on Myelofibrosis research and treatment. *Blood*. 2012;120:1197-1201.
59. Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. *Blood Adv*. 2016;1:21-30.
60. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. *Br J Haematol*. 2020;189:291-302.
61. Tefferi A, Loscocco GG, Farrukh F, et al. A globally applicable "triple a" risk model for essential thrombocythemia based on age, absolute neutrophil count, and absolute lymphocyte count. *Am J Hematol*. 2023;98:1829-1837.
62. Carobbio A, Vannucchi AM, Rumi E, et al. Survival expectation after thrombosis and overt-myelofibrosis in essential thrombocythemia and prefibrotic myelofibrosis: a multistate model approach. *Blood Cancer J*. 2023;13:115.
63. Loscocco GG, Guglielmelli P, Gangat N, et al. Clinical and molecular predictors of fibrotic progression in essential thrombocythemia: a multicenter study involving 1607 patients. *Am J Hematol*. 2021;96:1472-1480.
64. Guglielmelli P, Szuber N, Gangat N, et al. Calr variant allele frequency in essential thrombocythemia: molecular associations and impact on disease phenotype and outcome. *Blood*. 2023;142:6328.
65. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. *Blood Cancer J*. 2015;5:e369.
66. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an international prognostic score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120:5128-5133; quiz 5252.
67. Haider M, Gangat N, Lasho T, et al. Validation of the revised international prognostic score of thrombosis for essential thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients. *Am J Hematol*. 2016;91:390-394.
68. Alvarez-Larran A, Cuevas B, Velez P, et al. Application of IPSET-thrombosis in 1366 patients prospectively followed from the Spanish registry of essential thrombocythemia. *Hema*. 2023;7:e936.
69. Guglielmelli P, Carobbio A, Rumi E, et al. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. *Blood Cancer J*. 2020;10:21.
70. Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. *Blood*. 2011;117:5857-5859.
71. Finazzi G, Carobbio A, Guglielmelli P, et al. Calreticulin mutation does not modify the IPSET score for predicting the risk of thrombosis among 1150 patients with essential thrombocythemia. *Blood*. 2014;124:2611-2612.
72. Gangat N, Singh A, Szuber N, et al. Site-specific venous thrombosis in essential thrombocythemia: impact on subsequent vascular events and survival. *J Thromb Haemost*. 2022;20:2439-2443.
73. Guglielmelli P, Vannucchi AM. Current management strategies for polycythemia vera and essential thrombocythemia. *Blood Rev*. 2020;42:100714.
74. Vannucchi AM, Guglielmelli P, Tefferi A. Polycythemia vera and essential thrombocythemia: algorithmic approach. *Curr Opin Hematol*. 2018;25:112-119.
75. Vannucchi AM, Guglielmelli P. What are the current treatment approaches for patients with polycythemia vera and essential thrombocythemia? *Hematology Am Soc Hematol Educ Program*. 2017;480-488:2017-2488.
76. Karrar OS, Abdelmagid M, Vannucchi AM, Barbui T, Tefferi A, Gangat N. ABO blood group type and risk of venous thrombosis in essential thrombocythemia. *Br J Haematol*. 2023;202:699-703.
77. Farrukh F, Guglielmelli P, Loscocco GG, et al. Deciphering the individual contribution of absolute neutrophil and monocyte counts to thrombosis risk in polycythemia vera and essential thrombocythemia. *Am J Hematol*. 2022;97:E35-E37.
78. Guglielmelli P, Gangat N, Coltro G, et al. Mutations and thrombosis in essential thrombocythemia. *Blood Cancer J*. 2021;11:77.
79. Rocca B, Tosetto A, Betti S, et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. *Blood*. 2020;136:171-182.
80. De Stefano V, Rocca B, Tosetto A, et al. The aspirin regimens in essential thrombocythemia (ARES) phase II randomized trial design: implementation of the serum thromboxane B(2) assay as an evaluation tool of different aspirin dosing regimens in the clinical setting. *Blood Cancer J*. 2018;8:49.
81. van Genderen PJ, van Vliet HH, Prins FJ, et al. Excessive prolongation of the bleeding time by aspirin in essential thrombocythemia is related to a decrease of large von Willebrand factor multimers in plasma. *Ann Hematol*. 1997;75:215-220.
82. Kubo M, Sakai K, Hayakawa M, et al. Increased cleavage of von Willebrand factor by ADAMTS13 may contribute strongly to acquired von Willebrand syndrome development in patients with essential thrombocythemia. *J Thromb Haemost*. 2022;20:1589-1598.
83. Lancellotti S, Dragani A, Ranalli P, et al. Qualitative and quantitative modifications of von Willebrand factor in patients with essential thrombocythemia and controlled platelet count. *J Thromb Haemost*. 2015;13:1226-1237.
84. Janjetovic S, Rolling CC, Budde U, et al. Evaluation of different diagnostic tools for detection of acquired von Willebrand syndrome in patients with polycythemia vera or essential thrombocythemia. *Thromb Res*. 2022;218:35-43.

85. Chen D, Tange JI, Meyers BJ, et al. Validation of an automated latex particle-enhanced immunoturbidimetric von Willebrand factor activity assay. *J Thromb Haemost*. 2011;9:1993-2002.
86. Berk PD, Goldberg JD, Silverstein MN, et al. Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. *N Engl J Med*. 1981;304:441-447.
87. Berk PD, Wasserman LR, Fruchtman SM, et al. Treatment of polycythemia vera: a summary of clinical trials conducted by the polycythemia vera study group. In: Wasserman LR, Berk PD, Berlin NI, eds. *Polycythemia Vera and the Myeloproliferative Disorders*. W.B. Saunders; 1995:166-194.
88. Kiladjian JJ, Chevret S, Dosquet C, Chomienne C, Rain JD. Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980. *J Clin Oncol*. 2011;29:3907-3913.
89. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353:33-45.
90. Tefferi A, Szuber N, Vallapureddy RR, et al. Decreased survival and increased rate of fibrotic progression in essential thrombocythemia chronicled after the FDA approval date of anagrelide. *Am J Hematol*. 2019;94:5-9.
91. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995;332:1132-1136.
92. Carobbio A, Finazzi G, Antonioli E, et al. Hydroxyurea in essential thrombocythemia: rate and clinical relevance of responses by European LeukemiaNet criteria. *Blood*. 2010;116:1051-1055.
93. Finazzi G, Ruggeri M, Rodeghiero F, Barbui T. Efficacy and safety of long-term use of hydroxyurea in young patients with essential thrombocythemia and a high risk of thrombosis. *Blood*. 2003;101:3749.
94. Barbui T, Vannucchi AM, Finazzi G, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. *Am J Hematol*. 2017;92:1131-1136.
95. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372:426-435.
96. Gangat N, Szuber N, Jadoon Y, et al. 1.5 million platelet count limit at essential thrombocythemia diagnosis: correlations and relevance to vascular events. *Blood Adv*. 2022;6:3835-3839.
97. Godfrey AL, Campbell PJ, MacLean C, et al. Hydroxycarbamide plus aspirin versus aspirin alone in patients with essential thrombocythemia age 40 to 59 years without high-risk features. *J Clin Oncol*. 2018;36:3361-3369.
98. Alvarez-Larran A, Cervantes F, Pereira A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. *Blood*. 2010;116:1205-1210; quiz 1387.
99. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350:114-124.
100. Michiels JJ, Berneman Z, Schroyens W, et al. Platelet-mediated erythromelalgic, cerebral, ocular and coronary microvascular ischemic and thrombotic manifestations in patients with essential thrombocythemia and polycythemia vera: a distinct aspirin-responsive and coumadin-resistant arterial thrombophilia. *Platelets*. 2006;17:528-544.
101. Kayacioglu I, Gunay R, Saskin H, et al. The role of clopidogrel and acetylsalicylic acid in the prevention of early-phase graft occlusion due to reactive thrombocytosis after coronary artery bypass operation. *Heart Surg Forum*. 2008;11:E152-E157.
102. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. *Br J Haematol*. 2005;128:275-290.
103. Tefferi A, Smock KJ, Divgi AB. Polycythemia vera-associated acquired von Willebrand syndrome despite near-normal platelet count. *Am J Hematol*. 2010;85:545.
104. Gangat N, Wolanskyj AP, McClure RF, et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. *Leukemia*. 2007;21:270-276.
105. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera. An analysis of 1,638 patients enrolled in a prospective observational study. *Blood*. 2005;105:2664-2670.
106. Donovan PB, Kaplan ME, Goldberg JD, et al. Treatment of polycythemia vera with hydroxyurea. *Am J Hematol*. 1984;17:329-334.
107. Kaplan ME, Mack K, Goldberg JD, Donovan PB, Berk PD, Wasserman LR. Long-term management of polycythemia vera with hydroxyurea: a progress report. *Semin Hematol*. 1986;23:167-171.
108. West WO. Hydroxyurea in the treatment of polycythemia vera: a prospective study of 100 patients over a 20-year period. *South Med J*. 1987;80:323-327.
109. Fruchtman SM, Mack K, Kaplan ME, Peterson P, Berk PD, Wasserman LR. From efficacy to safety: a polycythemia vera study group report on hydroxyurea in patients with polycythemia vera. *Semin Hematol*. 1997;34:17-23.
110. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood*. 2019;134:1498-1509.
111. Alvarez-Larran A, Martinez-Aviles L, Hernandez-Boluda JC, et al. Busulfan in patients with polycythemia vera or essential thrombocythemia refractory or intolerant to hydroxyurea. *Ann Hematol*. 2014;93:2037-2043.
112. Serrao A, Breccia M, Napolitano M, et al. A multicenter real-life study on anticoagulant treatment with direct Oral anticoagulants in patients with Ph negative myeloproliferative neoplasms. *Am J Hematol*. 2020;95:E329-E332.
113. Sant'Antonio E, Guglielmelli P, Pieri L, et al. Splanchnic vein thromboses associated with myeloproliferative neoplasms: an international, retrospective study on 518 cases. *Am J Hematol*. 2020;95:156-166.
114. Lavu S, Szuber N, Mudireddy M, et al. Splanchnic vein thrombosis in patients with myeloproliferative neoplasms: the Mayo clinic experience with 84 consecutive cases. *Am J Hematol*. 2018;93:E61-E64.
115. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared to hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET study, a randomized controlled trial. *Blood*. 2013;121:1720-1728.
116. Mascarenhas J, Kosiorek HE, Prchal JT, et al. A randomized phase 3 trial of interferon-alpha vs hydroxyurea in polycythemia vera and essential thrombocythemia. *Blood*. 2022;139:2931-2941.
117. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. *Blood*. 2017;130:1889-1897.
118. Quintas-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol*. 2009;27:5418-5424.
119. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112:3065-3072.
120. Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, et al. Ropeginterferon alfa-2b, a novel IFNalpha-2b, induces high response rates with low toxicity in patients with polycythemia vera. *Blood*. 2015;126:1762-1769.
121. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon versus standard therapy for low-risk patients with polycythemia vera. *NEJM Evid*. 2023;2(6). doi:10.1056/EVIDoa2200335

122. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol*. 2020;7:e196-e208.
123. Barbui T. Phase II randomized clinical trial comparing ropeginterferon versus phlebotomy in low-risk patients with polycythemia vera. Results of the pre-planned interim analysis. Absract from EHA 2020 EHA library. Barbui T. 06/14/20; 303391; LB2602. 2020.
124. Barbui T, Carobbio A, De Stefano V, et al. Ropeginterferon phase 2 randomized study in low-risk polycythemia vera: 5-year drug survival and efficacy outcomes. *Ann Hematol*. 2023. Published online on Decemeber 7.
125. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (low-PV study): a multicentre, randomised phase 2 trial. *Lancet Haematol*. 2021;8:e175-e184.
126. Cassinat B, Verger E, Kiladjian JJ. Interferon alfa therapy in CALR-mutated essential thrombocythemia. *N Engl J Med*. 2014;371:188-189.
127. Kuriakose ET, Gjoni S, Wang YL, et al. JAK2V617F allele burden is reduced by busulfan therapy: a new observation using an old drug. *Haematologica*. 2013;98:e135-e137.
128. Shvidel L, Sigler E, Haran M, et al. Busulphan is safe and efficient treatment in elderly patients with essential thrombocythemia. *Leukemia*. 2007;21:2071-2072.
129. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood*. 2010;115:2354-2363.
130. Marchetti M, Ghirardi A, Masciulli A, et al. Second cancers in MPN: survival analysis from an international study. *Am J Hematol*. 2020; 95:295-301.
131. Reese JA, Peck JD, Deschamps DR, et al. Platelet counts during pregnancy. *N Engl J Med*. 2018;379:32-43.
132. Yang Z, Hu L, Zhen J, et al. Genetic basis of altered platelet counts and gestational thrombocytopenia in pregnancy. *Blood*. 2023.
133. How J, Leiva O, Bogue T, et al. Pregnancy outcomes, risk factors, and cell count trends in pregnant women with essential thrombocythemia. *Leuk Res*. 2020;98:106459.
134. Gangat N, Tefferi A. Myeloproliferative neoplasms and pregnancy: overview and practice recommendations. *Am J Hematol*. 2021;96: 354-366.
135. Alimam S, Bewley S, Chappell LC, et al. Pregnancy outcomes in myeloproliferative neoplasms: UK prospective cohort study. *Br J Haematol*. 2016;175:31-36.
136. Sant'Antonio E, Borsani O, Camerini C, et al. Philadelphia chromosome-negative myeloproliferative neoplasms in younger adults: a critical discussion of unmet medical needs, with a focus on pregnancy. *Blood Rev*. 2022;52:100903.
137. Landtblom AR, Andersson TM, Johansson ALV, et al. Pregnancy and childbirth outcomes in women with myeloproliferative neoplasms-a nationwide population-based study of 342 pregnancies in Sweden. *Leukemia*. 2022;36:2461-2467.
138. Gangat N, Joshi M, Shah S, et al. Pregnancy outcomes in myeloproliferative neoplasms: a Mayo Clinic report on 102 pregnancies. *Am J Hematol*. 2020;95:E114-E117.
139. Passamonti F, Randi ML, Rumi E, et al. Increased risk of pregnancy complications in patients with essential thrombocythemia carrying the JAK2 (617V>F) mutation. *Blood*. 2007;110:485-489.
140. Maze D, Kazi S, Gupta V, et al. Association of Treatments for myeloproliferative neoplasms during pregnancy with birth rates and maternal outcomes: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2:e1912666.
141. Skeith L, Carrier M, Robinson SE, Alimam S, Rodger MA. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. *Blood*. 2017;129:934-939.
142. Sogaard KK, Darvalics B, Horvath-Puho E, et al. Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study. *Thromb Res*. 2016;141:1-7.
143. Ageno W, Riva N, Schulman S, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. *JAMA Intern Med*. 2015;175:1474-1480.
144. Plessier A, Goria O, Cervoni JP, et al. Rivaroxaban prophylaxis in non-cirrhotic portal vein thrombosis. *NEJM Evid*. 2022;1:EVIDoa2200104.
145. Debureaux PE, Cassinat B, Soret-Dulphy J, et al. Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses. *Blood Adv*. 2020;4:3708-3715.
146. Alvarez-Larran A, Pereira A, Magaz M, et al. Natural history of polycythemia vera and essential thrombocythemia presenting with splanchnic vein thrombosis. *Ann Hematol*. 2020;99:791-798.
147. Mascarenhas J, Kosiorek H, Prchal J, et al. A prospective evaluation of pegylated interferon alfa-2a therapy in patients with polycythemia vera and essential thrombocythemia with a prior splanchnic vein thrombosis. *Leukemia*. 2019;33:2974-2978.
148. De Stefano V, Rossi E, Carobbio A, et al. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases. *Blood Cancer J*. 2018; 8:112.
149. Pieri L, Paoli C, Arena U, et al. Safety and efficacy of ruxolitinib in splanchnic vein thrombosis associated with myeloproliferative neoplasms. *Am J Hematol*. 2017;92:187-195.
150. Masciulli A, Ferrari A, Carobbio A, Ghirardi A, Barbui T. Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis. *Blood Adv*. 2020;4:380-386.
151. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology*. 2010;51:210-218.
152. Wasserman LR, Gilbert HS. Surgery in polycythemia vera. *N Engl J Med*. 1963;269:1226-1230.
153. Ruggeri M, Rodeghiero F, Tosetto A, et al. Postsurgery outcomes in patients with polycythemia vera and essential thrombocythemia: a retrospective survey. *Blood*. 2008;111:666-671.
154. Szuber N, Toliopoulos P, Busque L, et al. Perioperative management of myeloproliferative neoplasms: a pan-Canadian physician survey and international expert opinion. *Am J Hematol*. 2022;97:E466-E469.
155. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98:801-821.
156. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31:2726-2731.
157. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ version 2.0: mutation and karyotype-enhanced international prognostic scoring system for primary Myelofibrosis. *J Clin Oncol*. 2018;36:1769-1770.
158. Mora B, Giorgino T, Guglielmelli P, et al. Value of cytogenetic abnormalities in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a study of the MYSEC project. *Haematologica*. 2018;103:e392-e394.
159. Loscocco GG, Guglielmelli P, Mannelli F, et al. SF3B1 mutations in primary and secondary myelofibrosis: clinical, molecular and prognostic correlates. *Am J Hematol*. 2022;97:E347-E349.
160. Shide K, Takenaka K, Kitanaka A, et al. Nationwide prospective survey of secondary myelofibrosis in Japan: superiority of DIPSS2 plus to MYSEC-PM as a survival risk model. *Blood Cancer J*. 2023;13:110.
161. Tefferi A, Saeed L, Hanson CA, Ketterling RP, Pardanani A, Gangat N. Application of current prognostic models for primary myelofibrosis in the setting of post-polycythemia vera or post-essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31:2851-2852.

162. Gill H, Palandri F, Ross DM, et al. A phase 2 study of the LSD1 inhibitor bomedemstat (IMG-7289) for the treatment of essential thrombocythemia (ET). *Blood*. 2022;140:1784-1787.
163. Reis E, Buonpane R, Celik H, et al. Discovery of INCA033989, a monoclonal antibody that selectively antagonizes mutant calreticulin oncogenic function in myeloproliferative neoplasms (MPNs). *Blood*. 2022;140:14-15.
164. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET study, a randomized controlled trial. *Blood*. 2013;121:1720-1728.
165. Bieniaszewska M, Sobieralski P, Leszczynska A, et al. Anagrelide in essential thrombocythemia: efficacy and long-term consequences in young patient population. *Leuk Res*. 2022;123:106962.
166. Barbui T, Vannucchi AM, Guglielmelli P, de Stefano V, Rambaldi A. An agenda for future research projects in polycythemia vera and essential thrombocythemia. *Haematologica*. 2020;105:1999-2003.

How to cite this article: Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2024;99(4):697-718. doi:10.1002/ajh.27216