Documenta Haematologica -
Revista Romana de Hematologie | 2024, Vol. 2, Nr. 3

https://doi.org/10.59854/dhrrh.2024.2.3.125

– REVIEW –

Diagnosis and Management of Essential Thrombocythemia: A Comprehensive Review

Sandra LAZAR[1,2], Despina Calamar POPOVICI[1,2,3]*, Oana SARAU[1,2], Hortensia IONITA[2], Claudiu Octavian IONITA[4], Dacian Nicolae OROS[1,2,3], Ioana IONITA[1,2,3]

Abstract

Myeloproliferative neoplasms, including essential thrombocythemia, are characterized by clonal proliferations of hematopoietic stem cells, leading to an increase in mature myeloid lineage cells. Essential thrombocythemia is a rare condition, with an incidence of 1-5 cases per 100,000 population, and it is more prevalent in females and older individuals. The JAK2 mutation was a key diagnostic factor in the 2008 World Health Organization classification for BCR-ABL negative myeloproliferative neoplasms, with the JAK2V617F mutation identified in over 50% of ET patients, while CALR, MPL, and "triple-negative" mutations are reported in 10% of ET patients. This review provides a comprehensive summary of the key factors related to the diagnosis and management of essential thrombocythemia, including considerations for specific patient populations.

Keywords: *Myeloproliferative neoplasms; Essential thrombocythemia; Platelets; JAK2 mutation; CALR gene; MPL gene;*

[1] Department V of Internal Medicine I, Discipline of Hematology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania,

[2] Department of Hematology, Emergency Municipal Hospital Timisoara, Romania,

[3] Multidisciplinary Research Center for Malignant Hematological Diseases (CCMHM), Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

[4] Department IX of Surgery I, Discipline Surgical Semiology I and Thoracic Surgery, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania,

Corresponding author:
* **Despina Calamar Popovici,** Department of Hematology, Emergency Municipal Hospital Timisoara, Gheorghe Dima Street 5, Timis County, Romania
email: calamar.despina@umft.ro

Introduction

Myeloproliferative neoplasms (MPNs) are characterized as a clonal proliferation of hematopoietic stem/progenitor cells, which cause an increase in one or more mature myeloid lineage cells. MPNs consist of multiple subgroups: chronic myeloid leukemia (CML); polycythemia vera (PV); essential thrombocythemia (ET); prefibrotic primary myelofibrosis (PMF); overt PMF; chronic neutrophilic leukemia (CNL); chronic eosinophilic leukemia (CEL); and unclassifiable MPN, not otherwise specified [1].

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN)c characterized by an elevated platelet count, resulting from clonal expansion of

megakaryocytes. ET is a member of the BCR-ABL negative myeloproliferative neoplasms, which share a common pathophysiology marked by acquisition of a JAK-STAT signaling mutation in the hematopoietic stem cell, leading to excessive proliferation of one or more mature myeloid cell lineages [2].

The JAK2V617F mutation is the most common disease-causing mutation in MPN, including ET. This mutation leads to constitutive JAK-STAT signaling and increased gene expression. While JAK2V617F is present in over 95% of polycythemia vera cases, it is found in only around 50% of ET patients. Approximately one-third of ET patients have a CALR gene mutation, which encodes the calreticulin protein. Mutations in the MPL gene, which encodes the TPO receptor, are reported in less than 5% of ET patients, often in older individuals. Roughly 10% of ET patients lack identifiable JAK-STAT driver mutations and are considered "triple-negative" [3]

Epidemiology and natural history

Essential thrombocythemia is a rare disease, with an estimated incidence of around 1-5 cases per 100,000 population and a prevalence of 38-57 per 100,000. The disease is more common in females. ET typically affects older individuals, with an onset between 50-60 years of age. However, a substantial cohort of younger patients are also diagnosed with ET. Compared to the general population, overall survival in ET patients is mildly reduced. Nevertheless, the prognosis in ET is more favorable than in other myeloproliferative neoplasms, such as polycythemia vera or primary myelofibrosis. Notably, younger ET patients, particularly those under 60 years old and with a platelet count less than 1500 × 10^9/L, seem to have a more indolent disease course. Moreover, these younger ET patients exhibit a thrombotic risk comparable to the general population and better overall survival [4].

Genetic and molecular pathways

Mutations in JAK2, MPL, and CALR are frequently observed in BCR-ABL negative MPN, and detecting these driver mutations has become crucial for diagnosis. Comprehensive genetic analyses have identified additional mutations associated with prognosis in these disorders. Single-cell studies have provided insights into the effects of mutation order and the pathogenesis of BCR-ABL negative MPNs. Furthermore, overexpression of CREB3L1 has been observed in the megakaryocytes and platelets of these patients [5].

The JAK2 mutation was a key diagnostic factor in the 2008 World Health Organization (WHO) classification for BCR-ABL negative MPN. Since then, mutations in MPL and CALR have also been identified as important diagnostic markers, leading to a revised 2022 WHO classification that relies on detecting these three driver gene mutations. However, some patients with ET and PMF lack mutations in all three genes and are considered "triple-negative." [6] For these triple-negative cases, excluding non-cancerous causes of high blood cell counts is important, and a bone marrow (BM) biopsy is needed to confirm the MPN diagnosis based on the characteristic BM features. ET, along with PV and PMF, make up the classical Philadelphia-negative MPNs, which share common clinical and molecular traits. While ET generally has a good prognosis, it can be variable, and some patients may progress to more serious conditions like myelofibrosis or acute leukemia [4,7].

Clinical Characteristics

ET reflects the transformation of a multipotent hematopoietic stem cell, but its precise molecular pathogenesis remains unclear. It is a rare, heterogeneous neoplasm with the potential to progress to MF or leukemic transformation, presenting with a wide spectrum of symptoms ranging from asymptomatic thrombocytosis to increased thrombotic and hemorrhagic conditions [8].

In under a half of ET patients, the most frequent symptoms are asthenia, weight loss, fever and early satiety. The onset and/or progression of ET may be complicated by thrombotic events and/or the progression to myelofibrosis and/or acute myeloid leukemia (AML). The most common arterial events reported in ET are stroke (10.7%) and acute coronary syndromes (6.1%), whereas the most frequent venous events are deep vein (3.4%), pulmonary (0.9%), splanchnic (1.4%) and cerebral (0.7%) thrombosis, respectively. The prevalence of hemorrhagic events in ET is evaluated at 7.3% (5.3–10.0), the most common being cutaneous/mucosal and/or gastrointestinal bleedings [1,9].

Thrombotic risk estimation is based on the history of thrombosis, presence of the JAK2 V617F mutation, age, and cardiovascular risk [9].

The risk of progression to MF at 15 years varies between 4 and 11%, and that to AML varies between 2 and 5% [10].

Diagnostic Criteria and Testing

Thrombocytosis, defined by a persistently elevated platelet count ≥450 × 10^9/L, may be due to a wide range

of conditions with divergent management strategies, expected clinical courses, and prognoses. The accurate diagnosis and appropriate management of ET require an integrated, comprehensive approach [11]. This involves addressing both the major and minor criteria outlined in the WHO diagnostic guidelines, as well as thoroughly excluding secondary causes of thrombocytosis [1].

The diagnostic workup for ET typically includes a detailed medical history, complete blood count, peripheral blood smear analysis, assessment of iron status, C-reactive protein levels, and genetic testing to detect driver mutations such as JAK2V617F, CALR, and MPL. If these initial investigations fail to identify a secondary cause for the thrombocytosis, further evaluation with bone marrow aspiration and biopsy is warranted. In cases where the JAK2V617F, CALR, or MPL mutations are not detected, it is important to perform a more comprehensive myeloid gene panel to assess for the presence of clonal markers in other, non-JAK-STAT pathway genes [12,13]. This multifaceted diagnostic approach is crucial for ensuring accurate classification, appropriate risk stratification, and the development of an optimal management plan for patients with suspected ET.

A comparison between the diagnostic criteria for ET from the British Society of Hematology and WHO is summarized in Table 1.

BSH (2014 Modification of 2010 Criteria)		**WHO 2016**	
A 1	Sustained platelet count ≥ 450 × 109 /L	Major criteria	Platelet count ≥ 450 × 109 /L
A 2	Presence of an acquired pathogenic mutation (JAK2/CALR/MPL)		BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
A 3	No other myeloid malignancy		Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasms
A 4	No reactive cause for thrombocytosis and normal iron stores		Presence of JAK2, CALR, or MPL mutation
A 5	Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)	Minor criteria	Presence of a clonal marker (eg, abdominal karyotype) or absence of evidence for reactive thrombocytosis
Diagnosis requires A1-A3 Or A1+ A3-A5		Diagnosis requires all 4 major, or first 3 major and one minor criteria	

Table 1. *Diagnostic Criteria for Essential Thrombocythemia According to the BSH and WHO.*

BM = bone marrow; BSH = British Society of Haematology; CML = chronic myeloid leukemia; MDS = myelodysplastic syndrome; PMF = primary myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

Differential diagnosis

Investigation of reactive causes for thrombocytosis requires a comprehensive assessment, including the full blood count, blood film, iron status, C-reactive protein, and bone marrow trephine biopsy, which may reveal features such as increased macrophage activity and few or no megakaryocytes with typical ET morphology [11].

ET must be differentiated from other MPN that can mimic it, such as PV, PMF, BCR-ABL1-positive CML, myelodysplastic/myeloproliferative neoplasm (MDS/MPN) overlap syndromes, and MDS with isolated del(5q) or chromosome 3 abnormalities, all of which can present with thrombocytosis.

Iron deficiency, a feature of PV, can mask the elevated hemoglobin and hematocrit levels of PV in a patient presenting with normal red cell indices and an elevated platelet count, thus mimicking ET [14,15]. This MPN subtype, known as "masked PV," has been reported to have a higher risk of myelofibrotic transformation and thrombosis than ET, and its management includes maintaining a hematocrit below 45% [16]. The 2016 WHO criteria adjusted the hemoglobin range to better identify these cases when diagnosing PV [6].

Risk Stratification

Vascular complications, including arterial and venous thrombosis, are the primary drivers of morbidity and mortality in patients with ET. Thrombosis can be the presenting symptom that leads to the diagnosis of ET. The incidence of thrombosis in ET is estimated to be around 14% at 10 years, with a prevalence at diagnosis of 10%-35%. Additionally, microvascular complications are observed, manifesting as symptoms such as erythromelalgia, migraine, and paresthesia [17–19].

Hemorrhagic episodes may occur in ET, particularly in cases with extreme thrombocytosis. The bleeding in these patients is primarily due to an acquired von Willebrand syndrome (vVWS), a complex and not fully understood condition. The proposed mechanism involves the loss of high molecular weight multimers of von Willebrand factor (vWF), which can occur through increased proteolysis by the enzyme ADAMTS-13 and/or increased adsorption of vWF onto the surface of the elevated number of platelets. This platelet count-dependent depletion of functional vWF leads to impaired platelet adhesion and increased bleeding risk in these patients [20]. The development of this acquired vVWS is a key factor contributing to the hemorrhagic complications observed in ET, particularly when the platelet count is markedly elevated [21,22].

Risk stratification is crucial in ET to identify patients at higher risk of thromboembolic events, which significantly contribute to morbidity and mortality.

The conventional risk stratification approach for ET relies on a system that categorizes patients as either high-risk or low-risk, as derived from the landmark study by Cortelazzo et al [23]. This risk assessment takes into account factors such as age and prior thrombosis. Moreover, the presence of the JAK2 V617F mutation, one of the most common driver mutations in BCR-ABL-negative myeloproliferative neoplasms, has been shown to independently increase the risk of vascular events in ET, underscoring the importance of molecular profiling in the comprehensive evaluation and management of these patients [17,23].

Recent studies suggest that factors such as mutation type, leukocytosis, and anemia may also influence prognosis, outcomes, and survival in ET. Around 50% of ET patients experience systemic manifestations that can negatively impact their quality of life, despite some being asymptomatic [24]. Common symptoms include constitutional symptoms and those associated with microvascular complications, such as headache, dizziness, and erythromelalgia [24].

Additionally, a multivariable retrospective analysis led to the development of the International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET), which incorporates several factors into a single prognostic score for thrombosis risk [25,26]. This model classified patients into 3 risk groups based on age >60 years (1 point), cardiovascular risk factors including tobacco use, hypertension, and diabetes mellitus (1 point), previous thrombosis (2 points), and JAK2 V617F positivity (2 points). Patients with 2 points are considered high risk (thrombosis risk 3.56% of patients per year). A revised IPSET-thrombosis score leading to a 4-tier model where patients were classified as very low risk (no thrombosis, age 60, JAK2 unmutated), and high risk (thrombosis history; or age >60 and JAK2 mutated); cardiovascular risk factors were no longer a part of the model. The revised IPSET-thrombosis score has been validated by Haider et al and its use has been adopted by European Leukemia Net and National Comprehensive Cancer Network guidelines [25–27].

Therapeutic options

Therapeutic strategies

Individualized management is essential for patients with ET.

Contemporary therapies for ET, such as antiplatelet agents and cytoreductive therapies aimed at reducing the platelet count, primarily target the management of thrombotic risk [24]. However, these approaches do not fully address the risk of disease progression, such as the potential transformation to more advanced MPD like myelofibrosis or acute leukemia. Therefore, treatment decisions for patients with ET require a careful consideration of various factors. These include the specific mutation profile of the disease, the patient's overall prognosis, their personal preferences and priorities, the potential drug toxicity profiles, the mode of drug administration, the impact on

the patient's quality of life, and the management of fertility concerns, particularly in younger individuals [28]. By incorporating these comprehensive clinical, molecular, and patient-centered perspectives, clinicians can develop an optimal management plan to address the complex needs of patients with ET.

Conventional Cytoreductive Therapies

Hydroxycarbamide (HC) is the cytoreductive agent recommended by expert consensus for ET. As the most widely utilized cytoreductive therapy, HC is particularly preferred for the treatment of elderly patients, who constitute the majority of the ET population [28,29].

However, HC may not be the optimal choice for all patients. Some literature data argue that the use of HC should be approached with caution. Therefore, alternative cytoreductive therapies, such as interferon-alpha (INF-a) or anagrelide, may be more suitable for certain elderly ET patients, as they can provide effective platelet reduction with potentially fewer adverse effects. The choice of cytoreductive agent should be carefully considered based on the individual patient's risk factors, comorbidities, and overall prognosis [30].

Cytoreductive treatment is recommended for high-risk ET patients, such as those aged 60 or older, with a history of thrombosis or bleeding, or with a platelet count of 150 × 10^9/L or higher. Cytoreductive treatment may also be appropriate for some low-risk ET patients with persistent symptoms [30].

The results of clinical trials have demonstrated that treatment with HC in combination with low-dose aspirin is superior to treatment with anagrelide plus low-dose aspirin in reducing the risk of thrombotic events in patients with ET. Patients treated with anagrelide had similar rates of thrombosis compared to those on other cytoreductive agents, but they experienced higher rates of hemorrhage and progression to myelofibrosis. Therefore, anagrelide is more frequently and appropriately utilized in the second-line setting, rather than as a first-line therapy.

In the context of the emergence of novel targeted therapies for myeloproliferative neoplasms, the European LeukemiaNet has defined the specific criteria for resistance and intolerance to hydroxyurea, which are crucial in guiding treatment decisions for patients with essential thrombocythemia [29–33]. (Table 2).

1.	Platelets exceeding 600,000/mmc after 3 months of hydroxyurea therapy at a minimum dose of 2g/day
2.	Platelets above 400,000/mmc with leukocyte count less than 25,000/mmc at any hydroxyurea dose
3.	Platelets over 400,000/mmc combined with hemoglobin less than 10 g/dL at any hydroxyurea dose
4.	Development of ulcers or other unacceptable mucocutaneous side effects at any hydroxyurea dose
5.	Fever attributed to hydroxyurea administration.

Table 2*. ELN definitions for HC resistance/intolerance in TE patients [31]*

The management of intermediate-risk ET lacks clear evidence, and the majority of these patients may not benefit from cytoreductive treatment. For younger patients, consideration of an alternative first-line agent, such as INF-a, is recommended. Excellent responses have been observed in patients treated with pegylated-interferon-alpha-2a (PEG-INF-2a). Although older INF preparations had tolerability issues, the appearance of pegylated formulations has improved this issue [34].

Targeted Molecular Therapies

The first clinically approved JAK1/JAK2 inhibitor, Ruxolitinib (RUX), has shown promise in the treatment of ET as well. RUX is currently approved for the management of patients with symptomatic MF and with PV, where it has demonstrated excellent responses in terms of a reduction in spleen size, achievement of hematocrit control, and improvements in patients' symptoms and quality of life. Building on these successes, RUX has also been investigated in clinical trials for patients with ET who are HC-resistant or HC-intolerant, or as a potential third-line therapy option for this condition[35]. The results of these trials suggest that RUX may offer an effective targeted treatment approach for certain subsets of ET patients, particularly those who have

limited options due to resistance or intolerance to conventional cytoreductive therapies [36].

Non-cytoreductive treatment

Antiplatelet therapy is considered a cornerstone of ET management and is widely adopted as the standard of care. However, there are certain exceptions where antiplatelet agents may not be appropriate, such as in patients with adverse reactions or young individuals deemed to have a low thrombotic risk, where the risks may outweigh the benefits. Additionally, antiplatelet treatment is contraindicated in certain situations, when an increased bleeding risk attributed to acquired von Willebrand syndrome is possible [24]. Aspirin, an irreversible COX-1 inhibitor, has demonstrated efficacy in reducing the risk of thrombotic events and mitigating vasomotor symptoms in ET. Consequently, low-dose aspirin is recommended for the management of most ET risk groups, with some exceptions.

Interestingly, a retrospective study reported an increased bleeding risk in low-risk CALR-mutated ET patients, without a corresponding reduction in thrombotic risk. In the second-line setting, various targeted therapeutic approaches are currently under investigation in ET, with promising emerging signals [37].

Considerations for specific populations

Young Patients

The driver mutation profile observed in the younger cohort of ET patients was notably distinct from the more typical pattern seen in older ET patients. This younger group exhibited a significantly higher prevalence of CALR and MPL mutations, along with a larger proportion of triple-negative cases. Interestingly, the JAK2V617F mutation, which is the most common driver in ET overall, was present in only 31.7% of these younger patients, markedly lower than the proportion typically observed in the broader ET population [38].

This unique mutational landscape observed in younger ET patients suggests that the underlying molecular pathogenesis may differ from that of their older counterparts. The specific driver mutations present can have important implications for disease behavior, thrombotic risk, and response to targeted therapies. Given the rarity of ET in younger individuals, the optimal management approach to effectively prevent thrombotic complications in this patient subgroup remains uncertain [39].

The majority of these younger ET patients would be classified as low-risk according to current risk-stratification guidelines, and may not require intensive cytoreductive treatment [38]. However, a recent comprehensive review found that over 60% of the younger ET patients included were managed with cytoreductive therapies, despite most not meeting high-risk criteria. This disparity highlights the need for further research and the development of tailored risk-stratification and treatment strategies that account for the distinct molecular and clinical features observed in younger ET patients. Elucidating the precise drivers of disease in this population and understanding their impact on thrombotic risk and therapeutic responsiveness will be crucial to optimizing management and improving outcomes for these individuals [38–40].

Triple-Negative Thrombocytosis

This subgroup of ET patients with distinct clinicopathological features warrants further investigation to elucidate the presumptive underlying pathophysiology. They are characterized by a younger age and increased prevalence in females. Before confidently assigning a triple-negative molecular status, it is important to consider the possibility of inherited or reactive etiologies [41]. While hereditary thrombocytosis is rare, it has been described in families with mutations in JAK-STAT signaling genes. Exploring the potential presence of low-level driver mutations, noncanonical JAK-STAT signaling mutations, or non-JAK-STAT driver clonal markers may be warranted in this patient subgroup. Long-term follow-up of these triple-negative patients will be interesting to determine their outcomes and whether intervention is ever required for modest thrombocytosis without complications [11].

Given the increased incidence ET in women, including those of reproductive age, understanding the potential complications of ET during pregnancy and implementing appropriate clinical management strategies is crucial. Maternal morbidity and pregnancy complications are elevated in ET, including thrombosis, hemorrhage, miscarriage, stillbirth, intrauterine growth restriction, preeclampsia, and premature labor. However, successful pregnancies occur more often in ET patients than in those with PV. Importantly, the JAK2V617F mutation status has not been associated with pregnancy complications or outcomes. Low-dose aspirin is considered safe in pregnancy and has been shown to reduce rates of preeclampsia and fetal mortality. In the setting of ET, aspirin use is associated with improved maternal and fetal

outcomes without increased bleeding, either alone or in combination with heparin. Low-molecular weight heparin is widely used for thromboprophylaxis in pregnancy when the risk of venous thromboembolism is greater than 3%. If cytoreductive therapy is required, interferon is the only safe option, and observational data suggest it may be associated with a higher live birth rate [42]. Management strategies for thrombosis and bleeding in the context of ET and pregnancy are also discussed.

Conclusion

While ET is a relatively indolent MPN, the disease can be associated with significant morbidity and mortality due to thrombotic and hemorrhagic complications. Accurate diagnosis, comprehensive molecular profiling, and risk-adapted management strategies are essential to optimizing outcomes for patients with ET. Treatment is primarily focused on reducing the risk of thrombotic events, and the selection of specific cytoreductive and antiplatelet therapies should be informed by individualized risk assessment based on factors such as age, prior thrombosis, cardiovascular risk factors, and the presence of driver mutations like JAK2 V617F. Emerging therapies, including novel targeted agents, hold promise for expanding the therapeutic arsenal and further improving the care and quality of life for patients with ET [43–45]. Moreover, a multidisciplinary approach involving close collaboration between hematologists, primary care providers, and other relevant specialists is crucial for providing comprehensive, patient-centered care for this complex condition.

No funding for this study

Conflicts of interest

All the authors of this papper certify that there is no financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

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