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## A Review On All Aspects Of Essential Thrombocythemia

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### ABSTRACT

Essential thrombocythemia is a rare genetic disorder that affects platelets, the blood cells that controlled bleedings which occurs in the body. It is a rare blood disease in which the bone marrow produces too many platelets. People with this condition develop many blood clots. This increase in the level of stroke and heart attack. High numbers of platelets may lead to thrombus, a blood clot that forms in a blood vessel. This can cause serious health problems such as a stroke, heart attack or pulmonary embolism. The cause of this disorder is unclear. It often appears to be connected to changes in certain genes. The criteria for diagnosis were reviewed in 2016 by WHO. The incidence varies from 0.2 to 2.5:100000 people per year, with a prevalence of 38 to 57 cases per 100000 people. Essential thrombocythemia (ET) is a rare chronic blood cancer (myeloproliferative neoplasm) characterised by the overproduction of platelets (thrombocytes) by megakaryocytes in the bone marrow. It is a type of myeloproliferative neoplasm (blood cancers) where in the body makes too many white or red, or platelets. This may results in the rarely developed myeloid acute leukaemia or myelofibrosis (rarely developed bone marrow disorder). The two other types of blood cells are red blood cells, which carry oxygen to all tissues in the body, and white blood cells, which help to fight infections. Red blood cell numbers (often measured as a percentage of whole blood, called a hematocrit) are generally normal in ET, while white blood cell numbers are normal or slightly elevated in ET. [1-3] [13-15]

**KEYWORDS:** Essential thrombocythemia [ET], Myeloproliferative neoplasm [MPN], blood cancers, Polycythemia vera (PV), Acute leukemia.

## INTRODUCTION THROMBOCYTHEMIA

Thrombocythemia is a disease in which bone marrow makes too many platelets. It is a condition of high platelet (thrombocyte) count in the blood. Normal platelet count is in the range of  $150 \times 10^9$  to  $450 \times 10^9$  platelets per litre of blood. Having too many platelets may cause serious conditions. This can cause clotting or not enough clotting.<sup>[4]</sup>

### CAUSES

1. Thrombocythemia is mostly caused by genes or genetics (mutations).
2. Mutations or changes in the genes that control the formation of platelets in the bone marrow which may cause thrombocythemia.
3. It is caused by defects in the bone marrow's platelet-making cells.<sup>[35-39]</sup>

### SYMPTOMS OF THROMBOCYTHEMIA INCLUDE

- Blood clots in arteries and veins, mostly occurred in the hands, feet, and brain
- Bruising easily
- Bleeding from the nose, gums, and GI tract
- Bloody stools
- Bleeding after injury or surgery
- Weakness
- Headache and dizziness
- Swollen lymph nodes<sup>[1]</sup>

### TREATMENT MAY INCLUDE

- **Chemotherapy.** This is given with an oral chemotherapy medicine (hydroxyurea), or with interferon alpha.
- **Plateletpheresis.** This is a procedure that is used to remove extra platelets from your blood.<sup>[7] [34]</sup>

### THE ESSENTIAL THROMBOCYTHEMIA (ET)

It is a Chronic Philadelphia-negative Myeloproliferative Neoplasm (MPN) which is characterized by a survival curve. The main characteristics of ET are the marked thrombocytosis and the high frequency of thrombosis. Thrombotic and hemorrhagic risk and constitutional symptoms. Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are the classic Philadelphia chromosome-negative chronic Myeloproliferative neoplasms (MPNs). ET is a chronic myeloproliferative disorder with an annual cases up to 1.2 to 3.0 per 100,000 population. Although it is a disease of the elderly, usually affecting patients between the ages of 55 and 65 years, it also develops in adults. The people who are younger than 40 years in 20% of cases. Women are mostly affected than men.

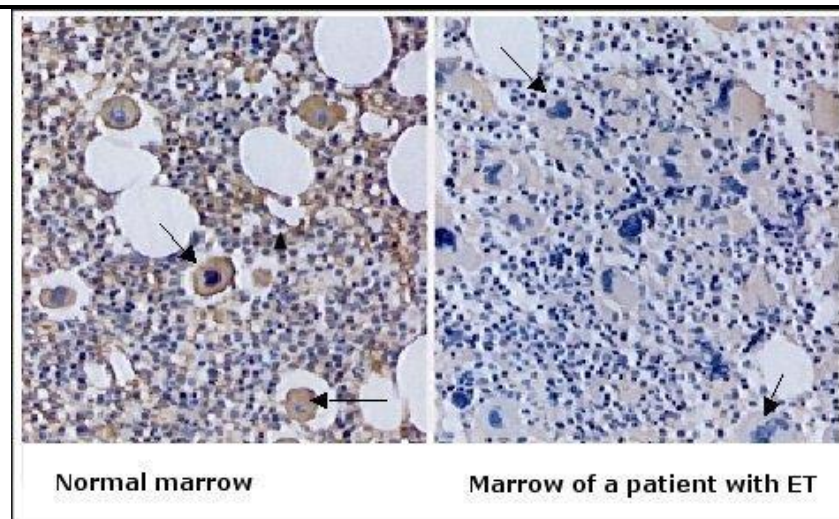


**Figure 1: Bone marrow - normal vs patient with ET.**

ET is an elevated by thrombocyte count in the peripheral blood, acknowledge by excessive megakaryopoiesis in the bone marrow. Essential thrombocythemia is not curable but treatment may reduce the risk of developing serious complications.<sup>[1][3][7]</sup>

### SYNONYMS

- Essential hemorrhagic thrombocythemia.
- Essential thrombocytosis.
- ET idiopathic thrombocythemia.
- Idiopathic thrombocytosis.
- Primary thrombocythemia.<sup>[60]</sup>

### HOW DOES THIS DISORDER AFFECTS BODY

Bone marrow produces megakaryocytes along with erythrocytes and leukocytes. Normally, bone marrow acts like a factory supervisor, usually monitoring supply and demand of enough platelets to slow or stop bleeding. Essential thrombocythemia affects platelets, the tiny & sticky blood cells, if blood vessels rupture from injury or disease because platelets are sticky, they quickly form cluster that may plug holes in the damaged blood vessels. In essential thrombocythemia, bone marrow produces more platelets than body required. The abnormal platelets are also larger than normal and notable shaped. Excess inventory that takes up space in already-crowded storage areas, the abnormal platelets make blood clots that crowd into blood vessels and block blood flow of that specific part of body. Essential thrombocythemia can cause blood clots in body, specific areas like (brain, hands and feet). Those women who are pregnant or planning to become pregnant have additional risk of developing blood clots during pregnancy.<sup>[26]</sup>

### CLINICAL PRESENTATION

In the clinical course of ET, patients have various signs and symptoms. In many cases, it is an acute onset of complications and emergencies that leads to a diagnosis of this rare condition. Vascular complications are usually often in ET and can develop in both systems like, the venous and arterial systems, although the arterial system is 3 times more likely to be afflicted. Microcirculatory disturbances due to small-vessel occlusions can occur in any part of the body and contaminate quality of life. Involvement of the CNS may

lead to headaches, dizziness, visual disturbances, or a complete loss of vision (if the ophthalmic vessels are occluded). Occlusions in vessels of the peripheral limbs can result in erythromelalgia (redness in arms, feet, hands), ischemia, or peripheral paresthesia<sup>[42]</sup>. Erythromelalgia can affect the skin of both the lower and upper limbs and presents as red, painful hot spots. If it is untreated, acrocyanosis, necrosis, or gangrene of the toes and fingers can occur (serious and rare condition). While studying this disorder, 14 patients who had ET with ischemic strokes were assessed. In these, 14 had atherosclerotic risk factors. Both studies highlighted that cardiovascular risk factors of stroke & possibility of leukemia in patients with pre-existing ET.<sup>[43]</sup>

### GOALS OF CARE

The goal of treatment of ET is to prevent thrombotic and hemorrhage complications. (Eg:- headache, dizziness, visual disturbances, burning dysesthesia). The treatment that are available in the market are non-curative and it neither shown a prolong survival nor prevent disease transformation to acute myeloid leukemia (AML) or post-ET myelofibrosis.<sup>[26]</sup>

### POSSIBILITY OF CANCER CELL FORMATION

Essential thrombocythemia is an example of a myeloproliferative neoplasm(MPN). The formation of excessive blood cells or platelets that cause harm to body and results in the formation of blood cancer cells. It may possible and formation of cancer cells occurred.<sup>[27]</sup>

### THE DIFFERENCE BETWEEN ESSENTIAL THROMBOCYTHEMIA AND THROMBOCYTOSIS

If any person having essential thrombocythemia (rarely occurred condition), they have a high platelet count that isn't related to another medical condition or disease. If a person having reactive thrombocytosis, then platelet count is high because of another disease or condition. Thrombocytosis is more common than thrombocythemia.<sup>[8]</sup>

### DIAGNOSIS

Diagnosis of essential thrombocythemia requires blood testing. A complete blood count measures both blood cells and platelets. Normal platelet levels are between 150,000 to 400,000 platelets per microliter ( $\mu\text{L}$ ) of blood. Consistently high platelet levels than normal may be a sign of essential thrombocythemia. Bone marrow megakaryocytic proliferation, and presence of JAK2, CALR, or MPL mutation are the main diagnostic criteria for ET. PMF is characterized by bone marrow megakaryocytic proliferation, reticulin and/or collagen fibrosis, and presence of JAK2, CALR, or MPL mutation. Elevation in the platelet count may result physiologic or pathologic mechanisms. Essential thrombocytosis must be separate from secondary thrombocytosis which may be due to an inflammatory state, iron deficiency or recent surgery or to an underlying solid tumor or hematologic neoplasm. A patient who has ET with complications or an emergency should start with an extensive medical history. The history should cover cardiovascular risk factors such as hypertension, diabetes, smoking, and hyperlipidemia. The diagnosis of ET includes secondary and reactive thrombocytosis, prefibrotic MDF, PV, and PMF, for which a bone marrow biopsy is useful. Although the detection of JAK2 V617F, CALR, or MPL mutations confirms the presence of MPN, their absence does not affect because 20% of ET cases can be triple-negative.<sup>[51]</sup> A fraction of patients with PV

may present with increased thrombocyte counts.<sup>[52]</sup> Therefore, a bone marrow examination is necessary to make an accurate morphologic diagnosis of ET and distinguish it from prefibrotic PMF and PV.<sup>[6-7][58][62]</sup>

### KEY DIAGNOSTIC FACTORS

- Erythromelalgia
- Splenomegaly
- Arterial and venous thrombosis
- Bleeding<sup>[63]</sup>

### OTHERS DIAGNOSTIC FACTORS

- Age 50 to 70 years.
- Female gender.
- Headache.
- No symptoms<sup>[63]</sup>

### RISK FACTORS

- Unknown risk factors
- Genetic mutations (e.g., JAK2, CALR, or MPL) □ Being 60 years and older.
- Being a woman or a person assigned female at birth or pregnant women.
- Having a history of blood clots.

### TESTING

1. CBC (complete blood count). This test measures the amount of red blood cells, white blood cells, and platelets in blood.
2. Blood smear. This test checks platelets.
3. Bone marrow aspiration or biopsy. This may be done to see if bone marrow is healthy.
4. Genetic testing: Providers may analyse your blood, looking for changes in the genes that may affect platelet production.<sup>[10][32]</sup>

### THERAPY

ET is an indolent (slowly grown) disease, and the life expectancy of patients with ET does not show an abnormal symptom that is different from the general population. Because the 15-year survival has been reported to be 80% and the 10-year risk of transformation to AML or MF is less than 1%, treating every patient with ET is not advisable or not supported. Current available treatment in ET to prevent thrombotic complications, which can occur in only 10% to 20% of patients, and to prevent bleeding. Although treatment has focused on preventing complications or abnormal symptoms to reduce morbidity and mortality, very few data is available on the management of complications and emergencies of ET.<sup>[58]</sup>

## SIGNS AND SYMPTOMS

- Chronic or long-term headache.
- Dizziness.
- Burning or throbbing feeling in the palms of your hands and soles of your feet.
- Numbness or red hands and feet.
- Changes in your pattern of speech.
- Migraines.
- Seizures.
- Pain or discomfort in your upper body, including your arms, back, neck, jaw or belly (abdomen).
- Nausea
- Shortness of breath.
- Chest pain
- Weakness.
- Enlarged spleen
- Nose bleeds (epistaxis).
- Bleeding gums.
- Blood in your poop (stool).
- Blood in your pee (urine) □ Bruising more easily.
- Heavy menstrual periods.<sup>[5]</sup>

## CAUSES

Essential thrombocythemia is an acquired genetic disorder. It happens when genes inside the specific cells mutate or change. In this case, the genes that mutate affect stem cells in bone marrow that make blood cells. Those genes are JAK2, CALR and MPL.

- JAK2 stands for Janus kinase 2. The JAK2 gene tells cells how to make the JAK2 protein. This protein helps to control how stem cells produce blood cells.<sup>[38]</sup>
- The CALR gene provides instruction on making the calreticulin protein. Researchers believe calreticulin helps to control gene activity, how cells grow and divide and when cells die.<sup>[39]</sup>
- MPL stands for myeloproliferative leukemia virus. The MPL gene is an oncogene. Oncogenes are genes can cause cancer.<sup>[40]</sup>

When these cells mutate these drives on an excessive production of cells or platelets in body.

The over production of platelets can cause ET.

## THERAPIES

Treatment consists of various suggestions. That are meant to be cured the signs and symptoms of ET. The main aim is to control the blood clotting. Mostly Hematologist are preferred. Hematologists are the doctors that are that specialize in the diagnosis, recovery or treatment of the blood disorder. Patients who had a clotting event in the past are at high risk for succeeding events. Less significant risk factors for clots are tobacco use, high blood pressure, diabetes, and the presence of the JAK2 mutation that was discussed above (causes). For most patients with ET, a low dose of aspirin (usually 81-100 mg daily) is recommended to reduce the risk of clots. Aspirin may not be recommended for some patients who are at a very low risk for blood clots, or who may be at a higher risk for bleeding (a side-effect of aspirin), or in those with an allergy or other sensitivity against aspirin. Therefore, aspirin may not be recommended for patients on other medications such as blood thinners that increase the risk of bleeding. The most common type of chemotherapy doctors uses to treat ET is hydroxycarbamide. It is a tablet. There may be a small increase in risk or possibility of developing a leukaemia if you take hydroxycarbamide for a long time.<sup>[35][58]</sup>

### FOR ACUTE TREATMENT

Thrombosis or bleeding

### FOR ONGOING TREATMENT

1. Nonpregnant: very low-, low-, or intermediate-risk
2. Nonpregnant: high risk
3. Pregnant: very low- or low-risk
4. Pregnant: intermediate-risk
5. Pregnant: high-risk<sup>[30-33]</sup>

### Current Treatment Algorithm in Essential Thrombocythemia

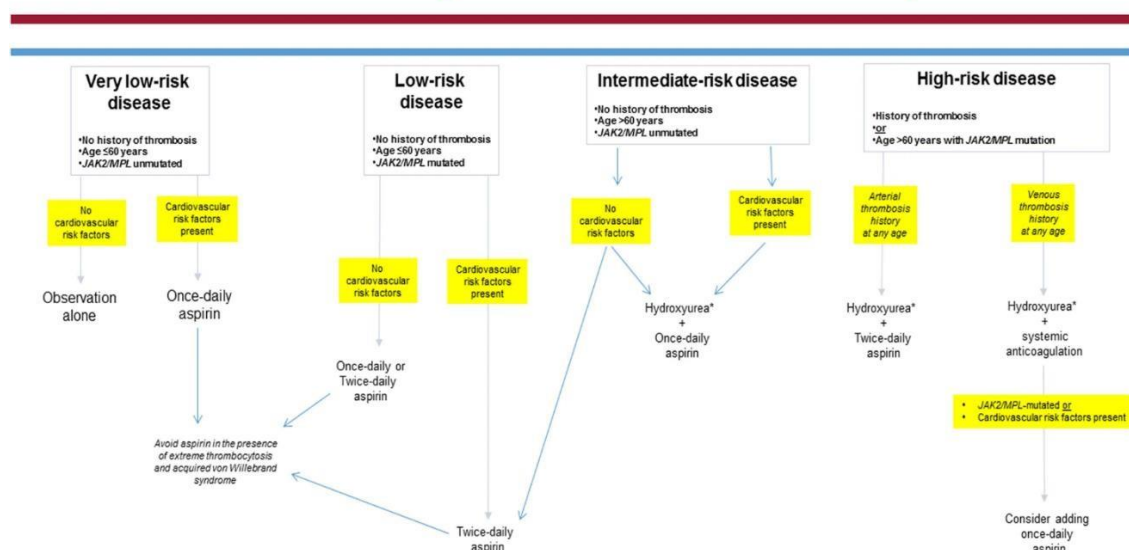


Fig. Shows algorithms of treatment.

Fewer than 1 in 100,000 people are diagnosed with ET in any year (the most recent estimates range from 0.38 to 1.7 per 100,000). Women are more likely to be diagnosed with ET than men. The average age of onset is mid-fifties, but the range is wide, and it includes women in their childbearing years (the ability to get

pregnant), which makes up an important subset of ET patients with special therapeutic contemplations. In children ET is very rare an inherited genetic disorder. In adults, the genetic mutations identified in ET are not inherited, and instead are acquired genetic accidents that happen during an individual's lifetime.[12-16]

## PREVENTION

People with essential thrombocythemia have an increased risk of developing blood clots and/or bleeding more than normal. Reduce the risk by:-

- Not smoking cigarettes: People who smoke are more likely to develop blood clots than usual.
- Avoid smoking, which may increase blood clots.
- Control other health conditions such as high cholesterol, high blood pressure, and diabetes.
- Avoid things that may increase bleeding, including medicines such as aspirin.<sup>[10]</sup>

## CONCLUSION

clinical experience show that ET is a chronic myeloproliferative neoplasm (MPN) with a relatively benign prognosis- slowly grown and do not spread, with overall survival data appearing similar or slightly lower than that of the age-matched healthy general population. Essential thrombocythemia is non curable disease but the treatment must be taken because it effects the mutational status of patient may lead to generate higher risk and treatment can helps to reduce the pain sensation that is occur during the significant ET. The mutational status and the thrombotic risk critically influence therapeutic choices. Besides, the introduction of advanced molecular biology techniques has greatly improved the understanding of the pathogenesis and the ability to make diagnosis and estimate prognosis. Despite this improvement, unfortunately, many diagnoses of ET are still performed after the thrombotic event. Early detection of ET may minimize the risk of thrombotic events and globally improve prognosis.

## REFERENCES

1. Rodrick Babakhanlou, MD, MSc ,Lucia Masarova, MD, Srdan Verstovsek, MD, “A review on essential thrombocythemia and its complications”, Clinical Advances in Hematology & Oncology, February 2023; 21(2), PhD Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas
2. Ayalew Tefferi, Alessandro M. Vannucchi, Tiziano Barbui essential thrombocythemia treatment algorithm 2018, Blood Cancer Journal, 10 Jan 2018; 8.
3. Vincenzo Accurso, Marco Santoro, Salvatrice Mancuso, Mariasanta Napolitano, Melania Carlisi, Marta Mattana, Chiara Russo, Alessandro Di Stefano, Davide Sirocchi, and Sergio Siragusa. The Essential Thrombocythemia in 2020: What We Know and Where We Still Have to Dig Deep. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
4. Toddd Gersten, MD, Heamatology/oncology, “a review on primary thrombocythemia”

Florida cancer specialists & Research institute, Wellington, FL

5. Genetic and Rare Disease Information Center. Essential Thrombocythemia. (<https://rarediseases.info.nih.gov/diseases/6594/essential-thrombocythemia>) Accessed 8/17/2022.
6. Beer, PA; Green, AR. "Pathogenesis and management of essential thrombocythemia". Hematology, 2009; 621–8.
7. Fu, R; Zhang, L; Yang, R. "Paediatric essential thrombocythaemia: clinical and molecular features, diagnosis and treatment". British Journal of Haematology, November 2013; 163(3): 295–302.
8. Ma X, Vanasse G, Cartmel B, et al. Prevalence of polycythemia vera and essential thrombocythemia. Am J Hematol, 2008; 83: 359–362. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
9. Mesa RA, Silverstein MN, Jacobsen SJ, et al. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County study, 1976–1995. Am J Hematol, 1999; 61: 10–15. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
10. Cortelazzo S, Viero P, Finazzi G, et al. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol, 1990; 8: 556–562. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
11. Fenaux P, Simon M, Caulier MT, et al. Clinical course of essential thrombocythemia in 147 cases. Cancer. 1990;66:549–556. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]  
Tefferi A, Fonseca R, Pereira DL, et al. A long-term retrospective study of young women with essential thrombocythemia. Mayo Clin Proc., 2001; 76: 22–28. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
12. Epstein E, Goedel A. Hämorrhagische thrombocythämie bei vasculärer schrumpfmilz. Virchows Arch path Anat., 1934; 292: 233–248. [Crossref], [Google Scholar]
13. Fanger H, Cella LJ, Jr, Litchman H. Thrombocythemia; report of three cases and review of literature. N Engl J Med., 1954; 250: 456–461. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
14. Ozer FL, Truax WE, Miesch DC, et al. Symposium on leukemia primary hemorrhagic thrombocythemia. Am J Med. , 1960;2 8: 807–823. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
15. Murphy SI, H, Rosenthal D, Laszlo J. Essential thrombocythemia: an interim report from the polycythemia vera study group. Semin Hematol, 1986; 23: 177–182. [PubMed], [Web of Science ®], [Google Scholar]
16. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet, 2005; 365: 1054–1061. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
17. 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. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
18. James C, Ugo V, Le Couedic J-P, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature, 2005; 434: 1144–1148. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
19. 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. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

20. Pardanani AD, Levine RL, Lasho T, et al. Mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. *Blood.*, 2006; 108: 3472–3476. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
21. 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. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
22. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. *Blood.*, 2014; 123: 3714–
23. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med.*, 2013; 369: 2379–2390. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
24. 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. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
25. Adamson JW, Fialkow PJ, Murphy S, et al. Polycythemia vera: stem-cell and probable clonal origin of the disease. *N Engl J Med.*, 1976; 295: 913–916. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
26. Fialkow PJ, Faguet GB, Jacobson RJ, et al. Evidence that essential thrombocythemia is a clonal disorder with origin in a multipotent stem cell. *Blood*, 1981; 58: 916–919. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
27. Accurso V, Santoro M, Mancuso S, Napolitano M, Carlisi M, Mattana M. The Essential Thrombocythemia in 2020: What We Know and Where We Still Have to Dig Deep. (<https://pubmed.ncbi.nlm.nih.gov/33447121/>) Clin Med Insights Blood Disord. 2020; Accessed 8/17/2022.
28. MPN Research Foundation. Essential Thrombocythemia (ET). (<https://www.mpnresearchfoundation.org/essential-thrombocythemia-et/>) Accessed 8/17/2022.
29. National Cancer Institute. Chronic Myeloproliferative Neoplasms Treatment (PDQ ®). (<https://www.cancer.gov/types/myeloproliferative/patient/chronic-treatmentpdq>) Accessed 8/17/2022.
30. National Heart, Lung and Blood Institute. Platelet Disorders - Thrombocythemia and Thrombocytosis (<https://www.nhlbi.nih.gov/health/thrombocythemiathrombocytosis>) Accessed 8/17/2022.
31. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. (<https://pubmed.ncbi.nlm.nih.gov/32974939/>) Am J Hematol, Dec, 2020; 95(12): 15991613. Accessed 8/17/2022.
32. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med.*, 1996; 2: 561-6.
33. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med.*, 1995; 332: 1132-6.

34. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.*, 2001; 344: 1031-7.
35. Nowell PC, Hungerford DA. Chromosome studies on normal and leukemic human leukocytes. *J Natl Cancer Inst*, 1960; 25: 85-109.
36. Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood*, 1951; 6: 372-5.
37. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*, 2005; 434: 1144-8.
38. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med.*, 2005; 352: 1779-90.
39. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell.*, 2005; 7: 387-97.
40. Kittur J, Knudson RA, Lasho TL, et al. Clinical correlates of JAK2V617F allele burden in essential thrombocythemia. *Cancer*, 2007; 109: 2279–2284. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
41. Cheung B, Radia D, Pantelidis P, et al. The presence of the JAK2 V617F mutation is associated with a higher haemoglobin and increased risk of thrombosis in essential thrombocythaemia. *Br J Haematol*, 2006; 132: 244–245. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
42. Zhang S, Qiu H, Fischer BS, et al. JAK2 V617F patients with essential thrombocythemia present with clinical features of polycythemia vera. *Leuk Lymphoma*, 2008; 49: 696–699. [Taylor & Francis Online], [Web of Science ®], [Google Scholar]
43. Toyama K, Karasawa M, Yamane A, et al. JAK2-V617F mutation analysis of granulocytes and platelets from patients with chronic myeloproliferative disorders: advantage of studying platelets. *Br J Haematol*, 2007; 139: 64–69. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
44. Wong RSM, Cheng C-K, Chan NPH, et al. JAK2 V617F mutation is associated with increased risk of thrombosis in Chinese patients with essential thrombocythaemia. *Br J Haematol*, 2008; 141: 902–904. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
45. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. *Lancet*, 2005; 366: 1945–1953. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
46. Rumi E, Pietra D, Ferretti V, et al. CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood*, 2014; 123: 1544–1551. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
47. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood*, 2014; 123: 1552–1555. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

48. Pietra D, Rumi E, Ferretti VV, et al. Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms. *Leukemia*, 2016; 30: 431–438. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
49. Cabagnols X, Favale F, Pasquier F, et al. Presence of atypical thrombopoietin receptor (MPL) mutations in triple-negative essential thrombocythemia patients. *Blood.*, 2016; 127: 333–342. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
50. Milosevic Feenstra JD, Nivarthi H, Gisslinger H, et al. Sequencing identifies novel MPL and JAK2 mutations in triple-negative myeloproliferative neoplasms. *Blood*, 2016; 127: 325–332. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
51. Yamamoto Y, Iba S, Abe A, et al. Elongation of MPL transmembrane domain is a novel activating-mutation in essential thrombocythemia. *Blood.*, 2015; 126: 1628–1628. [Crossref], [Web of Science ®], [Google Scholar]
52. Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. *Leukemia*, 2010; 24: 1128–1138. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

