IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Polycythemia Vera

Dr. Sri Ganesh Harinadh, G. RaviTeja, U. Tejaswini, K. Krupa Rani, B. Pushpa
Assistant professor pharm-D department of pharmacy practice
Adarsa College Of Pharmacy G. Kothapalli. Gokavaram Road, Andhra Pradesh India.

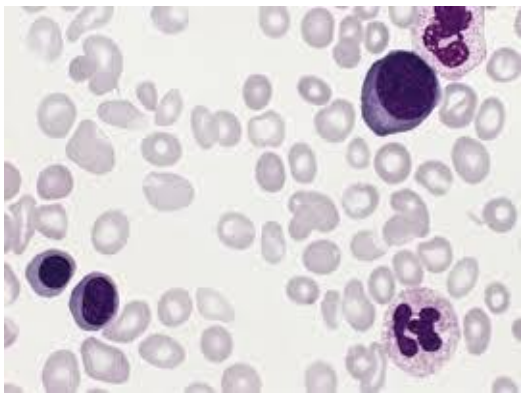
ABSTRACT: Polycythemia Vera (PV) is a chronic myeloproliferative disorder characterized by the overproduction of red blood cells, leading to increased blood viscosity and a heightened risk of thrombotic events. These patients are at risk for thrombosis due to the hyper viscosity of the blood that ensues. Patients with splenomegaly, increased hemoglobin or haematocrit, or portal venous thrombosis should be suspected of PV. pv should be suspected in patients with elevated haemoglobin or haematocrit, splenomegaly or portal venous thrombosis. secondary causes of increased red blood cell mass. ex: heavy smoking, chronic pulmonary disease, renal disease are more common than polycythemia vera and must be excluded diagnosis is made using criteria developed by the polycythmeia vera study group(PVSG) major criteria include elevated red blood cell mass, normal oxygen saturation, and palpable splenomegaly and treated patients may survive for 6 to 18 months ,whereas adequate treatment Phlebotomy with the potential inclusion of myelosuppressive medicines based on a risk assessment is part of a life extension to more than ten years of treatment. medicines under research for a stratified strategy include interferon alfa-2b, anagrelide, and aspirin consultation with a haematologist recommended.

Key Words: Myeloproliferative, Interferon, Polycythemia vera, Splenomegaly

INTRODUCTION:

Polycythemia Vera (PV) is an idiopathic myeloproliferative disorder characterized by an increased red blood cell mass (RCM), oreorythrocytosis which leads to hyperviscosity and an increased risk of thrombosis. First described by Louis Henri Vaquez in 1892, PV is characterized by the uncontrolled proliferation of red blood cells, platelets and white blood cells as well patients may present with complaints of pruritis after bathing, burning pains in the distal extremities (erythromelalgia), gastrointestinal disturbances, or nonspecific complaints such as weakness, headache, or dizziness. Patients with PV typically have a diagnosis at age 60, while it can affect people of all ages. pv occurs with slight predominance in men. a comprehensive reported incidents of pv to be 2.3 per 100,000 persons per year. therefore, a typical family physician can expect to make a diagnosis of pv once or twice during this or her career and will often have at least one patient in this or her patient panel who carries the diagnosis the seriousness of pv is underscored by the fact that the median

survival in untreated symptomatic patients after diagnosis is 6 to 18 months with treatment the median survival is more than 10 years.



TYPES OF POLYCYTHEMIA VERA:

1) Primary polycythemia vera.
2) Secondary polycythemia vera.
3) Relative polycythemia vera.
4) Spurious polycythemia vera.
5) Familial polycythemia vera.
6) Neoplasm associated polycythemia vera.

1.Primary Polycythemia (Polycythemia Vera):

Primary Polycythemia vera occurs when excess red blood cells are produced as a result of an abnormality of the bone marrow. Overproduction of platelets and white blood cells also occurs often. A genetic mutation of JAK2 gene leads to uncontrolled blood cell production.

Causes and Risk Factors:

Genetic mutation in the JAK2 gene (found in 95% of cases).

Family history.

Age (typically diagnosed after 60).

Sex (slightly more common in men)2.

2.secondary polycythemia vera:

Secondary polycythemia also known as secondary polycythemia vera is a condition where the body produces to many red blood cells in response to external factors, rather than a genetic mutation (as in primary polycythemia).

Caused by external factors:

chronic hypoxia (low oxygen levels).

kidney disease.

Testosterone replacement therapy.

Erythropoietin producing tumors.

3.Relative polycythemia vera:

Relative polycythemia vera (RPV) is a condition where there is a relative increase red blood cell count due to a decrease in plasma volume, rather than an absolute increase in red blood cell production. This is in contrast to primary polycythemia vera (PV), where there is an absolute increase in red blood cell production.

Causes:

Dehydration. Diuretic use. Burns. Gastrointestinal bleeding. Severe vomiting. Diarrhoea. Excessive sweating. Congestive heart failure.

4. Spurious Polycythemia vera (Gaisbock's Syndrome):

Spurious polycythemia vera (SPV), also known as Gaisbock's syndrome, is a rare condition where there is a false diagnosis of polycythemia vera (PV)due to laboratory errors are misinterpretation of results.

Causes: Laboratory errors. Pseudo polycythemia. Other conditions.

5. Familial Polycythemia:

Familial polycythemia vera (FPV)is a rare, inherited form of polycythemia vera (PV), characterized by an over production of red blood cells, white blood cells, and platelets. It is caused by genetic mutation that are passed down through families.

Causes:

Autosomal dominant inheritance pattern

Mutations in gene such as: JAK2, MPL, CALR, CSF3R

Familial cases often have younger age of onset and more severe disease

6.Neoplasm associated polycythemia vera:

Neoplasm associated polycythemia vera (NAPV) refers to the development of pv in association with another neoplasm(cancer) this can occur due to:

Paraneoplastic syndrome:

The cancer produces substance that stimulate red blood cell production.

Tumour related erythropoietin production:

The cancer produces erythropoietin, leading to increased red blood cell production.

Causes:

Renal cell carcinoma, Hepatocellular carcinoma, Uterine fibroids, Ovarian tumors &Testicular cancer

JAK-2 GENE MUTATION: The JAK2 protein plays an important role in controlling the production of blood cells from stem cells found in the bone marrow. The jak2 gene is responsible for the genetically coding the jak2 protein. This protein is a part of the JAK/STAT pathway which transmits signals to promote cell growth. Upon activation, the jak2 protein transmits a signal to the protein stat, which subsequently dimerizes by binding to another stat molecule. After entering the cell nucleus, this collection of chemicals activates genes that instruct the cells to divide and grow. The body's process of producing new cells is typically highly regulated. On the other hand, an overabundance of blood cells and uncontrollably high cell production result from any mutation in the jakstat system.

V617F MUTATION:

One base in the genetic code has changed, resulting in the V617F mutation. At position 617 in the JAK2 protein, this straightforward modification then changes the amino acid valine (V) to phenylalanine (F), changing the structure of the protein. This mutation causes signalling JAK2 to become activated, which is inactivated, and uncontrollably grows cells. Blood cancer results from this excessive blood cell production.

REASONS:

Named for a mutation at a specific position in the jak2 gene, JAK2V617F is the most prevalent jak2 mutation discovered in blood disorders. Mutations in JAK2V617F are acquired randomly instead of being inherited. Given that they arise in cells incapable of generating sperm or eggs, the mutation is not inherited by an individual's progeny.

PATHOPHYSIOLOGY:

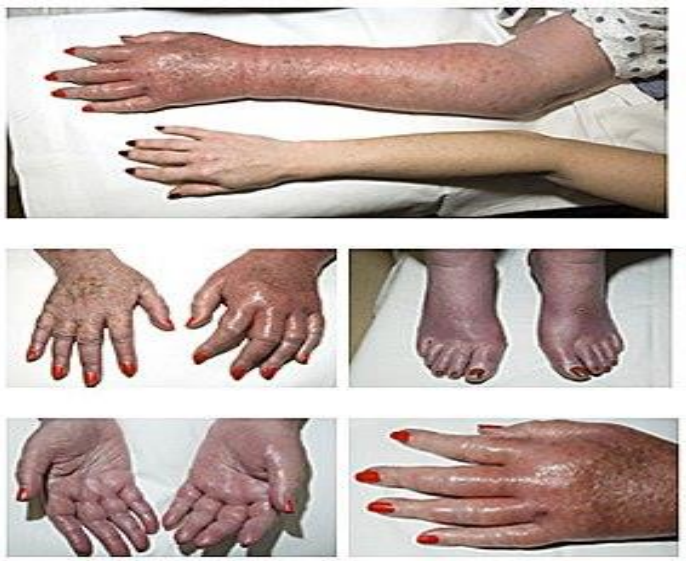
Patients with polycythemia vera (PV) have both normal and aberrant clonal stem cells in their bone marrow, which inhibit the growth and maturation of normal stem cells. Panmyelosis is brought on by unchecked neoplastic growth. PV is most likely caused by signaling disruptions caused by a mutation in JAK2 kinase. Constitutively active cytokine receptors result from a valine to phenylalanine alteration at position 617 of the JAK2 gene, or JAK2V617F. More than 90% of people with PV, 50% to 60% of patients with primary myelofibrosis, and 50% of patients with essential thrombocythemia had this mutation. This process leads to increased production of red blood cells and platelets with associated complications of thrombosis and bleeding.

EPIDEMOLOGY:

With no preference for one sex over another, polycythemia vera (PV) can affect anyone of any ethnicity, albeit men are slightly more likely than women to get it. Although it can strike people of any age, the usual diagnostic age is 60. In the US, between 0.6 and 1.6 persons per million are affected with PV. Japan has a lower incidence rate than either Europe or the US. While the frequency rises with age, polycythemia vera affects people of all ages. According to one study, the average age of diagnosis was 60 years old, however a Mayo Clinic study conducted in Olmsted County, Minnesota, indicated that individuals in their 70s to 79s had the highest frequency. The disease was more prevalent in Minnesota, where the overall incidence was 1.9 per 100,000 person-years in men than women. A cluster around a toxic site was confirmed in northeast Pennsylvania in 2008.

SYMPTOMS:

People with Polycythemia vera can be asymptomatic. Clinical signs of polycythemia vera are largely attributable to hyperviscosity of blood. Itching or pruritus is a classic sign of polycythemia vera, especially after being in warm water (such after a bath). This can be because of aberrant prostaglandin production or histamine release. Forty percent of people with polycythemia vera experience this type of irritation. Gouty Arthritis may be present in up to 20% of patients. Peptic is also common in patients with polycythemia vera; most likely due to increased histamine from mast cells, but may be related to an increased susceptibility to infection with the ulcer-causing bacterium H. pylori. Erythromegalia is a typical sign of polycythemia vera and essential thrombocythemia, a similar myeloproliferative illness. This is a searing ache in the hands or feet that is typically accompanied by bluish or reddish skin. Erythromelalgia is caused by an increased platelet count or increased platelet "stickiness" (aggregation), leading in the production of small blood clots in the capillaries of the extremity; it responds fast to treatment with aspirin. Some individuals may have palpable spleens as a result of splenomegaly, which has been linked by Lee et al. (2022) to the development of myelofibrosis and the V617F mutation.



DIAGNOSIS:

PV should be suspected when haemoglobin and/or haematocrit levels are elevated (i.e. haemoglobin level greater than 18 g per dL (180 g per L in white men and 16 g per dL 160 g per L in blacks and women, haematocrit level greater than 52 percent (0.52) in white men and 47 percent (0.47) in blacks and women). PV also should be suspected in patients with portal venous thrombosis and splenomegaly with or without thrombocytosis and leucocytosis. the physician must first exclude a secondary erythrocytosis. Major and minor criteria are combined to diagnose PV if a secondary etiology has been ruled out. Defined by the Polycythemia Vera Study Group (PVSG). Although new diagnostic modalities have been developed, these criteria remain the standard method to diagnose PV. Increased RCM, normal oxygen saturation, and splenomegaly are important diagnostic criteria. The test for RCM is a nuclear medicine study involving autologous infusion of radio-labelled red blood cells followed by serial phlebotomy to determine distribution. Physicians may refer patients to a specialty laboratory for this study. Changes to these diagnostic criteria have been proposed. For example, determinations of RCM, classically given in millilitres per kilogram (mL per kg), can be misleading if the patient is obese, because body fat is relatively avascular. The International Council for Standardization in Haematology (ICSH) has amended the RCM assessment, recommending the use of formulas incorporating body surface area, weight, gender, and plasma volume. 8-10 [level of evidence: C, con- sensus opinion Low oxygen saturation levels can occur in patients with PV because the condition can coexist with another hypoxic illness. Splenomegaly that is palpable is a significant physical finding and a key need. However, palpation is only 58 percent sensitive for diagnosis (i.e., if present, it will not be detected by examiners in 42 percent of cases). Specificity is much better. This lack of sensitivity has led to some discussion about the use of imaging techniques to answer the question, although such a finding by imaging might be relegated to the status of a minor criterion. 10 In addition, the minor criteria of leukocyte alkaline phosphatase (LAP) and serum vitamin B12 and B12 binding capacity may be dropped in the future because of inter-laboratory error regarding LAP and the unavailability of vitamin B12 binding capacity. 10 Furthermore, neither of these criteria is sensitive nor specific. Nonetheless, the PVSG criteria remain the diagnostic standard. Tests for PV have been suggested, including serum erythropoietin (EPO), bone marrow histology and karyotype, and the existence of endogenous erythroid colonies (EEC). Serum EPO levels in PV are low or normal because PV is an autonomous (i.e., EPO-independent) erythroid proliferation. Low serum EPO levels for pv have a sensitivity of 70% and a specificity of 90%.

Physiologically appropriate Chronic pulmonary or cardiac disease Decreased 2,3-diphosphoglycerate High oxygen affinity hemoglobinopathy Increased carboxyhaemoglobin (in smokers) and methaemoglobin Residence at high altitude.
Physiologically inappropriate Adrenal cortical hypersecretion Hydronephrosis Tumors producing erythropoietin or al abolic steroids
Relative (stress) Disorders associated with decreased plasma volume (e.g. Diarrhea, emesis, renal diseases)

Table: showing secondary causes of increased red cell mass (erythrocytosis)

MANAGEMENT AND TREATMENT:

here isn't just one PV treatment available. Most morbidity and mortality are caused by thrombosis, and the main objective of treatment is to avoid thrombotic episodes. Arterial and venous thrombosis, cerebrovascular accident, deep vein thrombosis, myocardial infraction, peripheral arterial occlusion, and pulmonary infarct are a few instances of thrombotic events. The symptomatic management of microvascular sequelae, including pruritus and distal extremity erythromelalgia, is also crucial for family doctors (Table 3). Since PV is an uncommon ailment, recruiting patients for carefully thought-out, long-term, randomized controlled trials has been challenging. Consequently, poorer quality data from case series and uncontrolled trials serves as the foundation for therapeutic The PVSG and Gruppo Italiano Studio Polycythemia (GISP) are two prospective trials that have unearthed a therapeutic dilemma regarding the two basic treatment approaches phlebotomy alone and phlebotomy plus myelosuppressive agents. A number of new therapeutic agents have been developed. In addition to interferon alfa-2b (Intron A) therapy agents that target platelet number (e.g., anagrelide Agrylin) and platelet function (e.g. Aspirin) are being investigate as potential therapies. Phlebotomy is the cornerstone of treatment for PV; the goal is to lower the venous haematocrit level to less than 45 percent (0.45) in white men and 42 percent (0.42) in black women and men in order to reduce hyperviscosity. The PVSG reported the best median survival, 12.5 years, for this type of treatment. Some

features of using phlebotomy alone are attractive, primarily because it is a simple procedure without many risks, except for the eventual development of iron deficiency. Experts have questioned the median survival results of the PVSG, pointing out that by the fifth year, up to 50% of patients receiving phlebotomy alone had to change to another treatment. After starting treatment, the PVSG discovered a statistically significant rise in the number of thrombotic events in the first three years. in contrast to the application of myelosuppressive drugs. But following this time, the rate of thrombosis for both treatment modalities didn't change Furthermore, the GISP found an added independent dupension to the risk of thrombosis-rates increase with age and a history of thrombotic events. Despite these concerns, a recent survey of physicians who were member sol the American Society of Haematology showed that 69 percent use phlebotomy as first-line therapy for PV The use of myelosuppressive agents such as radioactive phosphorus (P), chlorambucil (Leukeran), busulfan (MMeran), Pipo Broman (Verevte), madhydroxvurea (Hydrea). The non alkylating myelosuppressive agent hydroxyurea is widely used in the treatment of pv, because it is less leukemogenic the effectiveness of this drug as a bone marrow suppressor has been proven using PVSG data. Hydroxyurea patients had a decreased risk of thrombosis when compared to those who only receive phlebotomy. Recombinant interferon alfa-2b reduces myeloproliferation and splenomegaly and elevates the symptom of pruritus. One PVSG protocol found that 300mg of aspirin daily in conjunction with phlebotomy and dipyridamole was associated with increased risk of gastrointestinal bleeding. However, a small global information security policy (GISP) study randomized patients to low dose aspirin(40mg) per day the use of low dose aspirin being investigated by the European collaboration on low dose aspirin. Patients treated with phlebotomy alone benefit from low rates of malignancy but experience more thrombosis events during the first few years of treatment.

Table showing the risk stratification in polycythemia vera

Risk category	**Risk factors**
Low risk	Age younger than 60 years and no history of thrombocytosis And Platelet count lower than 150,000 per mm^3($1,500\times10^9$ per l)
Intermediate risk	Age younger than 60 years And either Platelet count higher than 150,000 per mm^3 Or

	Presence of cardiovascular risk factors
Higher risk	Age 60 years or older Or Positive history of thrombosis

Patients' treatment myelosuppressive agent and supplemental phlebotomy avoid this early thrombotic risk but in turn have significant rates of malignant transformation after above 6 years of therapy.

PROGNOSIS:

Poor prognostic features include age older than 60 years, history of thrombosis, leucocytosis, high JAK2 burden abnormal karyotype, and established cardiovascular risk factors such as smoking hypertension, diabetes, obesity, and hyperlipidaemia.

- Smoking cessation decreases the risk of thrombosis.
- Without treatment death typically occurs within two years mostly from thrombotic events.
- Median survival of patients with pv using standard-of-care treatment, including aspirin and hydroxy urea is 13.5 years.
- For those diagnosed before 60 years of age, median survival is 24 years.
- risk of blast transformation to acute myeloid leukaemia or myelodysplastic syndrome over 15 years is 5.5% to 18.7%.
- Progression to myelofibrosis over 15 years is 6% to 4% a practical tool to calculate survival has been developed.

CONCLUSION:

Polycythemia is an overabundance of red blood cells in the body. Physicians may find it during a normal blood test, or they may diagnose it after the patient begins to exhibit symptoms. The myeloproliferative neoplasm Polycythemia Vera is intricate and multifaceted, necessitating a thorough comprehension of its pathogenesis, clinical manifestation, and therapeutic approaches. Our capacity to identify and treat this illness has greatly increased because to recent developments in targeted medicines and molecular diagnostics. To maximize treatment results, lower the risk of thrombotic problems, and enhance the quality of life for PV patients, more research is yet required.

REFERENCES:

- Berk, P. D., Goldberg, J. D., Donovan, P. B., Fruchtman, S., Berlin, N. I., & Wasserman, L. R. (1986, April). Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. In *Seminars in hematology* (Vol. 23, No. 2, pp. 132-143).
- Streiff, M. B., Smith, B., & Spivak, J. L. (2002). The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of Hematology members' practice patterns. *Blood, The Journal of the American Society of Hematology*, *99*(4), 1144-1149.
- Policitemia, G. I. S. (1995). Polycythemia vera: the natural history of 1213 patients followed for 20 years. *Annals of Internal Medicine*, *123*(9), 656-664.
- Policitemia, G. I. S. (1995). Polycythemia vera: the natural history of 1213 patients followed for 20 years. *Annals of Internal Medicine*, *123*(9), 656-664.
- Stuart, B. J., & Viera, A. J. (2004). Polycythemia vera. *American family physician*, *69*(9), 2139-2144.
- Marchioli, R., Finazzi, G., Specchia, G., Cacciola, R., Cavazzina, R., Cilloni, D., ... & Barbui, T. (2013). Cardiovascular events and intensity of treatment in polycythemia vera. *New England Journal of Medicine*, *368*(1), 22-33.
- Spivak, J. L. (2018). Polycythemia vera. *Current treatment options in oncology*, *19*, 1-14.
- Barbui, T., & Finazzi, G. (1998). Treatment of polycythemia vera. *Haematologica*, *83*(2), 143-149.
- Michiels, J. J., & Juvonen, E. (1997, August). Proposal for revised diagnostic criteria of essential thrombocythemia and polycythemia vera by the Thrombocythemia Vera Study Group. In *Seminars in thrombosis and hemostasis* (Vol. 23, No. 04, pp. 339-347). Copyright© 1997 by Thieme Medical Publishers, Inc..
- Tefferi, A., Vannucchi, A. M., & Barbui, T. (2018). Polycythemia vera treatment algorithm 2018. *Blood cancer journal*, *8*(1), 3.
- Vannucchi, A. M. (2014). How I treat polycythemia vera. *Blood, The Journal of the American Society of Hematology*, *124*(22), 3212-3220.
- Grunwald, M. R., Kuter, D. J., Altomare, I., Burke, J. M., Gerds, A. T., Walshauser, M. A., ... & Mesa, R. (2020). Treatment patterns and blood counts in patients with polycythemia vera treated with hydroxyurea in the United States: an analysis from the REVEAL study. *Clinical Lymphoma Myeloma and Leukemia*, *20*(4), 219-225.
- Griesshammer, M., Gisslinger, H., & Mesa, R. (2015). Current and future treatment options for polycythemia vera. *Annals of hematology*, *94*, 901-910.
- Benevolo, G., Vassallo, F., Urbino, I., & Giai, V. (2021). Polycythemia vera (PV): update on emerging treatment options. *Therapeutics and clinical risk management*, 209-221.
- Ferrari, A., Carobbio, A., Masciulli, A., Ghirardi, A., Finazzi, G., De Stefano, V., ... & Barbui, T. (2019). Clinical outcomes under hydroxyurea treatment in polycythemia vera: a systematic review and meta-analysis. *Haematologica*, *104*(12), 2391.
- Lebowa, W. M., Ignatowicz, A., Ząber, J., & Sacha, T. (2024). Current status of hydroxyurea in treatment of polycythemia vera. *Acta Haematologica Polonica*, *55*(3).

- Ellis, M. H., Tadmor, T., Yekutiel, N., Chodick, G., Levy, M., Sharf, G., ... & Shavit, O. (2024). Clinical and Economic Implications of Hydroxyurea Intolerance in Polycythemia Vera in Routine Clinical Practice. *Journal of Clinical Medicine*, *13*(12), 3390.
- Lee, S. E., Hong, J., Bang, S. M., Park, J., Choi, C. W., Bae, S. H., ... & Kim, S. Y. (2024). Differences in Clinical Outcomes Between Hydroxyurea-Resistant and-Intolerant Polycythemia Vera Patients. *Journal of Korean Medical Science*, *39*(3).
- Yoon, S. Y., & Lee, S. E. (2024). Treatment with ropeginterferon alfa-2b in patients with hydroxyurea resistant or intolerant polycythemia vera in South Korea: one-year results from a phase 2 study. *Blood research*, *59*(1), 23.
- Chamseddine, R. S., Savenkov, O., Rana, S., Khalid, M., Silver, R. T., Kucine, N., ... & Abu-Zeinah, G. (2024). Cytoreductive therapy in younger adults with polycythemia vera: a meta-analysis of safety and outcomes. *Blood Advances*.
- Tahiraj, X., Bakalli, A., Krasniqi, X., Çitaku, H., Krasniqi, F., & Koçinaj, D. (2024). Acute myocardial infarction and polycythemia rubra vera: The double effect of treatment with hydroxyurea. *Radiology Case Reports*, *19*(8), 3386-3389.
- Visweshwar, N., Fletcher, B., Jaglal, M., Laber, D. A., Patel, A., Eatrides, J., ... & Manoharan, A. (2024). Impact of Phlebotomy on Quality of Life in Low-Risk Polycythemia Vera. *Journal of Clinical Medicine*, *13*(16), 4952.
- Martinez, J., Handa, S., Skorodinsky, A., & Kremyanskaya, M. (2024). The evolving landscape of polycythemia vera therapies. *Expert Opinion on Pharmacotherapy*, *25*(11), 1439-1452.
- Staff, T. O. (2024). Scott Evaluates Treatment Options for Hydroxyurea-Resistant Polycythemia Vera.
- Coltoff, A., Mesa, R., Gotlib, J., Shulman, J., Rampal, R. K., Siwoski, O., ... & Mascarenhas, J. (2020). Real-world outcomes of ruxolitinib treatment for polycythemia vera. *Clinical Lymphoma Myeloma and Leukemia*, *20*(10), 697-703.
- Alvarez-Larrán, A., Garrote, M., Ferrer-Marín, F., Pérez-Encinas, M., Mata-Vazquez, M. I., Bellosillo, B., ... & MPN Spanish Group (Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas). (2022). Real-world analysis of main clinical outcomes in patients with polycythemia vera treated with ruxolitinib or best available therapy after developing resistance/intolerance to hydroxyurea. *Cancer*, *128*(13), 2441-2448.
- Verstovsek, S., Pemmaraju, N., Reaven, N. L., Funk, S. E., Woody, T., Valone, F., & Gupta, S. (2023). Real-world treatments and thrombotic events in polycythemia vera patients in the USA. *Annals of Hematology*, *102*(3), 571-581.
- Parasuraman, S., DiBonaventura, M., Reith, K., Naim, A., Concialdi, K., & Sarlis, N. J. (2015). Patterns of hydroxyurea use and clinical outcomes among patients with polycythemia vera in real-world clinical practice: a chart review. *Experimental Hematology & Oncology*, *5*, 1-10.
- Chornenki, N. L. J., Chai-Adisaksopha, C., Leong, D. P., Siegal, D. M., & Hillis, C. M. (2018). The real-world outcomes of treating Polycythemia Vera: Physician adherence to treatment guidelines. *Leukemia Research*, *70*, 62-66.

- Palandri, F., Elli, E. M., Benevolo, G., Tiribelli, M., Bonifacio, M., Tieghi, A., ... & Latagliata, R. (2019). Clinical outcomes under hydroxyurea and impact of ELN responses in patients with polycythemia vera: a PV-NET real-world study. *Blood*, *134*, 4174.
- Mesa, R., Boccia, R. V., Grunwald, M. R., Oh, S. T., Colucci, P., Paranagama, D., ... & Stein, B. L. (2018). Patient-reported outcomes data from REVEAL at the time of enrollment (baseline): a prospective observational study of patients with polycythemia vera in the United States. *Clinical Lymphoma Myeloma and Leukemia*, *18*(9), 590-596.
- Coltoff, A., Tremblay, D., Kremyanskaya, M., Hoffman, R., & Mascarenhas, J. (2017). Real-world outcomes of ruxolitinib for polycythemia vera. *Blood*, *130*, 2926.
- Altomare, I., Parasuraman, S., Paranagama, D., Kish, J., Lord, K., Yu, J., & Colucci, P. (2021). Real-world dosing patterns of ruxolitinib in patients with polycythemia vera who are resistant to or intolerant of hydroxyurea. *Clinical Lymphoma Myeloma and Leukemia*, *21*(11), e915-e921.
- Verstovsek, S., Pemmaraju, N., Reaven, N. L., Funk, S. E., Woody, T., Valone, F., & Gupta, S. (2023). Real-world treatments and thrombotic events in polycythemia vera patients in the USA. *Annals of Hematology*, *102*(3), 571-581.
- Chornenki, N. L. J., Chai-Adisaksopha, C., Leong, D. P., Siegal, D. M., & Hillis, C. M. (2018). The real-world outcomes of treating Polycythemia Vera: Physician adherence to treatment guidelines. *Leukemia Research*, *70*, 62-66.
- Parasuraman, S., Yu, J., Paranagama, D., Shrestha, S., Wang, L., Baser, O., & Scherber, R. (2020). Elevated white blood cell levels and thrombotic events in patients with polycythemia vera: a real-world analysis of veterans health administration data. *Clinical Lymphoma Myeloma and Leukemia*, *20*(2), 63-69.
- Paranagama, D., Colucci, P., Evans, K. A., Bonafede, M., & Parasuraman, S. (2018). Are patients with high-risk polycythemia vera receiving cytoreductive medications? A retrospective analysis of real-world data. *Experimental Hematology & Oncology*, *7*, 1-6.
- Büyükaşık, Y., Ali, R., Turgut, M., Saydam, G., Yavuz, A. S., Ünal, A., ... & Tuğlular, T. (2020). Patterns of hydroxyurea prescription and use in routine clinical management of polycythemia vera: a multicenter chart review study. *Turkish Journal of Hematology*, *37*(3), 177.
- Gerds, A. T., Mesa, R. A., Burke, J. M., Grunwald, M. R., Stein, B. L., Scherber, R., ... & Oh, S. (2021). A real-world evaluation of the association between elevated blood counts and thrombotic events in polycythemia vera (analysis of data from the REVEAL study). *Blood*, *138*, 239.
- Grunwald, M. R., Zwicker, J. I., Gerds, A. T., Burke, J. M., Xue, Z., Crowgey, E. L., ... & Oh, S. (2023). A Real-World Evaluation of Risk Factors for Disease Progression in Patients with Polycythemia Vera (PV) Enrolled in REVEAL. *Blood*, *142*, 385.
- Parasuraman, S., Yu, J., Paranagama, D., Shrestha, S., Wang, L., Baser, O., & Scherber, R. (2020). Elevated white blood cell levels and thrombotic events in patients with polycythemia vera: a real-world analysis of veterans health administration data. *Clinical Lymphoma Myeloma and Leukemia*, *20*(2), 63-69.

- Komatsu, N., Jun, G., Yonezu, T., & Ohashi, Y. (2020). Real-world, retrospective study evaluating thromboembolic events, associated risk factors, and health-care resource utilization in Japanese patients with polycythemia vera. *International Journal of Hematology*, *112*(2), 176-184.
- Palandri, F., Elli, E. M., Benevolo, G., Tiribelli, M., Bonifacio, M., Tieghi, A., ... & Latagliata, R. (2019). Clinical outcomes under hydroxyurea and impact of ELN responses in patients with polycythemia vera: a PV-NET real-world study. *Blood*, *134*, 4174.
- Gerds, A. T., Mesa, R., Burke, J. M., Grunwald, M. R., Scherber, R., Yu, J., ... & Oh, S. T. (2022). P1062: A real-world evaluation of the association between elevated blood counts and thrombotic events in polycythemia vera: an analysis of data from the REVEAL study. *Hemasphere*, *6*, 952-953.
- Peters, S. P., Jones, C. A., Haselkorn, T., Mink, D. R., Valacer, D. J., & Weiss, S. T. (2007). Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. *Journal of Allergy and Clinical Immunology*, *119*(6), 1454-1461.
- Cazzoletti, L., Marcon, A., Janson, C., Corsico, A., Jarvis, D., Pin, I., ... & de Marco, R. (2007). Asthma control in Europe: a real-world evaluation based on an international population-based study. *Journal of allergy and clinical immunology*, *120*(6), 1360-1367.
- Haselkorn, T., Chen, H., Miller, D. P., Fish, J. E., Peters, S. P., Weiss, S. T., & Jones, C. A. (2010). Asthma control and activity limitations: insights from the Real-world Evaluation of Asthma Control and Treatment (REACT) study. *Annals of allergy, asthma & immunology*, *104*(6), 471-477.
- Gemma, A., Kusumoto, M., Sakai, F., Endo, M., Kato, T., Saito, Y., ... & Ohe, Y. (2020). Real-world evaluation of factors for interstitial lung disease incidence and radiologic characteristics in patients with EGFR T790M–positive NSCLC Treated with osimertinib in Japan. *Journal of Thoracic Oncology*, *15*(12), 1893-1906.
- Patorno, E., Schneeweiss, S., Gopalakrishnan, C., Martin, D., & Franklin, J. M. (2019). Using real-world data to predict findings of an ongoing phase IV cardiovascular outcome trial: cardiovascular safety of linagliptin versus glimepiride. *Diabetes care*, *42*(12), 2204-2210.
- Courtinard, C., Gourgou, S., Jacot, W., Carton, M., Guérin, O., Vacher, L., ... & Bellera, C. (2023). Association between progression-free survival and overall survival in women receiving first-line treatment for metastatic breast cancer: evidence from the ESME real-world database. *BMC medicine*, *21*(1), 87.
- Agboola, S., Hale, T. M., Masters, C., Kvedar, J., & Jethwani, K. (2014). "Real-world" practical evaluation strategies: a review of telehealth evaluation. *JMIR research protocols*, *3*(4), e3459.
- Ozaki, A. F., Choi, A. S., Le, Q. T., Ko, D. T., Han, J. K., Park, S. S., & Jackevicius, C. A. (2020). Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circulation: Cardiovascular Quality and Outcomes*, *13*(3), e005969.
- Suzuki, H., Ono, H., Hirasawa, T., Takeuchi, Y., Ishido, K., Hoteya, S., ... & Mizuguchi, Y. (2023). Long-term survival after endoscopic resection for gastric cancer: real-world evidence from a multicenter perspective cohort. *Clinical Gastroenterology and Hepatology*, *21*(2), 307-318.
- Dang, A. (2023). Real-world evidence: a primer. *Pharmaceutical medicine*, *37*(1), 25-36.

- Wang, W., Volkow, N. D., Berger, N. A., Davis, P. B., Kaelber, D. C., & Xu, R. (2024). Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nature medicine*, *30*(1), 168-176.
- Bakker, E., Plueschke, K., Jonker, C. J., Kurz, X., Starokozhko, V., & Mol, P. G. (2023). Contribution of real-world evidence in European medicines Agency's regulatory decision making. *Clinical Pharmacology & Therapeutics*, *113*(1), 135-151.
- Miyata, K., Izawa-Ishizawa, Y., Tsujinaka, K., Nishi, H., Itokazu, S., Miyata, T., ... & Ishizawa, K. (2024). Unveiling the association between fluoroquinolones and aortic diseases using real-world database analysis and pharmacological experiments. *Biomedicine & Pharmacotherapy*, *179*, 117418.
- Ferreira, P. C., Zhang, Y., Snitz, B., Chang, C. C. H., Bellaver, B., Jacobsen, E., ... & Karikari, T. K. (2023). Plasma biomarkers identify older adults at risk of Alzheimer's disease and related dementias in a real-world population-based cohort. *Alzheimer's & Dementia*, *19*(10), 4507-4519.
- Lazarus, J. V., Castera, L., Mark, H. E., Allen, A. M., Adams, L. A., Anstee, Q. M., ... & Tsochatzis, E. A. (2023). Real-world evidence on non-invasive tests and associated cut-offs used to assess fibrosis in routine clinical practice. *JHEP Reports*, *5*(1), 100596.
- Nagase, H., Suzukawa, M., Oishi, K., & Matsunaga, K. (2023). Biologics for severe asthma: The real-world evidence, effectiveness of switching, and prediction factors for the efficacy. *Allergology International*, *72*(1), 11-23.
- Goldman, A., Fishman, B., Twig, G., Raschi, E., Cukierman-Yaffe, T., Moshkovits, Y., ... & Maor, E. (2023). The real-world safety profile of sodium-glucose co-transporter-2 inhibitors among older adults (≥ 75 years): a retrospective, pharmacovigilance study. *Cardiovascular Diabetology*, *22*(1), 16.
- Tefferi, A., & Barbui, T. (2023). Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. *American journal of hematology*, *98*(9), 1465-1487.
- Moliterno, A. R., Kaizer, H., & Reeves, B. N. (2023). JAK2 V617F allele burden in polycythemia vera: burden of proof. *Blood*, *141*(16), 1934-1942.
- Kremyanskaya, M., Kuykendall, A. T., Pemmaraju, N., Ritchie, E. K., Gotlib, J., Gerds, A., ... & Hoffman, R. (2024). Rusfertide, a hepcidin mimetic, for control of erythrocytosis in polycythemia vera. *New England Journal of Medicine*, *390*(8), 723-735.
- Barbui, T., Vannucchi, A. M., De Stefano, V., Carobbio, A., Ghirardi, A., Carioli, G., ... & Rambaldi, A. (2023). Ropeginterferon versus standard therapy for low-risk patients with polycythemia vera. *NEJM evidence*, *2*(6), EVIDoa2200335.
- Waggoner, M. (2023). Polycythemia vera: thinking beyond the hematocrit. *Journal of the Advanced Practitioner in Oncology*, *14*(5), 405.
- Bewersdorf, J. P., How, J., Masarova, L., Bose, P., Pemmaraju, N., Mascarenhas, J., & Rampal, R. K. (2023). Moving toward disease modification in polycythemia vera. *Blood*, *142*(22), 1859-1870.
- Harrison, C. N., Nangalia, J., Boucher, R., Jackson, A., Yap, C., O'Sullivan, J., ... & Mead, A. J. (2023). Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. *Journal of Clinical Oncology*, *41*(19), 3534-3544.

- Verstovsek, S., Krečak, I., Heidel, F. H., De Stefano, V., Bryan, K., Zuurman, M. W., ... & Kiladjian, J. J. (2023). Identifying patients with polycythemia vera at risk of thrombosis after hydroxyurea initiation: the Polycythemia Vera—Advanced Integrated Models (PV-AIM) Project. *Biomedicines*, *11*(7), 1925.
- Verstovsek, S., Pemmaraju, N., Reaven, N. L., Funk, S. E., Woody, T., Valone, F., & Gupta, S. (2023). Real-world treatments and thrombotic events in polycythemia vera patients in the USA. *Annals of Hematology*, *102*(3), 571-581.