ORIGINAL RESEARCH

Study of Patients with Polycythemia Vera in JAK2V617F and Mutated and Unmutated Status along with their Anxiety and Worried Thoughts: A Single-center Experience from Eastern India

Rishu Vidhatri[1], Sandeep Saha[2], Abhishek Sharma[3], Shuvra Neel Baul[4], Tuphan Kanti Dolai[5]

Received on: 13 August 2024; *Accepted on:* 11 October 2024; *Published on:* 09 December 2024

Abstract

Background: Polycythemia vera (PV) is associated with the gain of a function point mutation in Janus 2 tyrosine kinase (JAK-2), leading to an increase in the activity of JAK2V617F. The anxiety associated with PV is mostly incidentally detected post diagnosis.

Aim: To study the impact of JAK2V617F mutation status on the PV phenotype in terms of clinical and laboratory features. The mental anxiety of patients with PV was assessed at diagnosis and subsequently.

Material and methods: A retrospective study was done on 50 patients with PV for the last 5 years. For the measurement of anxiety among patients, a self-administered questionnaire was used as a screening tool and severity measure for generalized anxiety disorder questionnaire and scores were used and graded accordingly.

Results: On analysis of our 50 patients with PV. There was a significant statistical difference in terms of median age at presentation (61 vs 44.5 years; $p = 0.002$), median hemoglobin (Hb) at time of presentation (20.7 vs 17.5 gm/dL; $p = 0.001$), median total leukocyte count (TLC) at time of presentation (15,700 vs 8,100 µL; $p = 0.001$), median platelet counts at the time of presentation (3,20,000 vs 1,90,000 µL; $p = 0.044$) and low serum erythropoietin (EPO) level ($p = 0.00$) between JAK2 mutated and unmutated group. At one year when anxiety levels were checked in PV patients, it was found that none of the patients was severely anxious about their disease entity and few were moderately anxious.

Conclusion: The age of patients and laboratory parameters such as (Hb, TLC, platelet counts, and serum EPO levels) showed a statistically significant difference between JAK2 mutated and Unmutated group. Thrombosis was also more common in JAK2V617F mutated patients. With the passage of time gradually the stress and anxiety declined among patients with PV.

Keywords: Anxiety, JAK2V617F, Mutated, Unmutated, Polycythemia vera.

Bengal Physician Journal (2024): 10.5005/jp-journals-10070-8068

Introduction

A Philadelphia-negative myeloproliferative neoplasm (MPN) with pan-myelosis is referred to as Polycythemia vera (PV). It differs from other MPNs in terms of elevated hematocrit/red cell mass and subnormal erythropoietin (EPO) level. Polycythemia vera is linked to point mutations in Janus 2 tyrosine kinase (JAK-2) that result in a gain of function and increased JAK-2 activity.[1,2] Usually, JAK-2V617F mutation has been observed in 90–95% cases of PV and 50–60% cases of primary myelofibrosis as well as Essential Thrombocythemia.[3,4] JAK-2V617F mutation status and allele burden are also known to affect the clinical phenotype of PV patients.[5] The clinical behavior of JAK-2V617F mutation status among PV patients in an Eastern Indian population was examined in this study. The anxiety associated with PV, which is usually present, was also assessed in this study. The investigation aims to examine prevalent anxiety symptoms in PV patients.

Materials and Methods

A retrospective study was executed on 50 patients who suffered from PV between July 2018 and August 2023. In 2016, the World Health Organization (WHO) issued updated guidelines for PV diagnosis. The criteria consist of three major and one minor criterion. A diagnosis is established when all three major criteria or two major criteria along with one minor criterion are satisfied.[5]

Major Criterion

- Hemoglobin (Hb) exceeding 16.5 gm/dL or hematocrit (HCT) surpassing 49% in males, and Hb exceeding 16 gm/dL or HCT surpassing 48% in females, or red blood cell mass exceeding 25% above the mean normal predicted value.

[1–5]Department of Hematology, N.R.S. Medical College and Hospital, Kolkata, West Bengal, India

Corresponding Author: Shuvra Neel Baul, Department of Hematology, N.R.S. Medical College and Hospital, Kolkata, West Bengal, India, Phone: +91 9062015351; e-mail: shuvraneelb@gmail.com

How to cite this article: Vidhatri R, Saha S, Sharma A, *et al*. Study of Patients with Polycythemia Vera in JAK2V617F and Mutated and Unmutated Status along with their Anxiety and Worried Thoughts: A Single-center Experience from Eastern India. Bengal Physician Journal 2024;11(3):116–119.

Source of support: Nil

Conflict of interest: None

- A bone marrow biopsy reveals tri-lineage growth (panmyelosis) with hypercellularity for age, accompanied by pleomorphic, mature megakaryocytes (differences in size) and prominent erythroid, megakaryocytic, and granulocytic proliferation.
- Presence of JAK2 V617F or JAK2 exon 12 mutation.

Minor Criterion

- The level of serum EPO is below the normal reference range.

These criteria must be utilized for diagnosis solely upon eliminating polycythemia's secondary causes. In all patients, meticulous clinical examinations were done. A complete hemogram was performed using the five-part differential cell counter SYSMEX XN-1000 for all study patients, and bone marrow aspiration, as well as biopsy, were conducted for each participant. Mutation screening for JAK2V617F and EXON-12 was conducted for all patients arriving at the hematology OPD with suspected PV by RT-PCR and Sanger sequencing respectively from venous blood, which were outsourced to a reference laboratory. Serum EPO levels were also outsourced and it was done by Chemiluminescence assay. Bone marrow aspiration and biopsy slides for microscopy were stained with Giemsa.

For assessment of anxiety among patients with polycythemia post diagnosis, a self-administered patient questionnaire was employed as a screening tool and severity was assessed with a GAD-7 (generalized anxiety disorder) questionnaire and scores were used and graded accordingly.

0–4: minimal anxiety;

5–9: mild anxiety;

10–14: moderate anxiety;

15–21: severe anxiety.

In all study, patients were treated with phlebotomy to bring the hematocrit to less than 45 percent and medications like hydroxyurea, ecosprin, and allopurinol were prescribed as oral medication and were monitored as outpatients only. All patients with PV were also instructed to drink at least 3 liters of water every day. All patients in our study gave their informed consent for all interventions and therapy.

The sample size for the above study was calculated using Slovin's formulae for estimation and the formulae are $N/(1 + N \times e^2)$.

N = population size, e = margin of error

Statistical Analysis

The mean ± standard deviation was used to express numerical data. Fisher's exactor Chi-square test and Mann–Whitney test were used to establish a correlation between non-parametric and parametric data, respectively. Tests with p-values less than 0.05 were considered statistically significant.

Results

A retrospective analysis of 50 individuals who visited Hematology OPD between July 2018 and February 2023 who were diagnosed with PV based on WHO criteria was conducted. Patient characteristics of JAK-2V617F mutated and unmutated were examined. 52 years was the median age of presentation. The ratio of male to female patients was 5:1. Of the 50 patients, 34 (68%) had a mutation in JAK2V617F, while 16 (32%) did not. No significant association with respect to gender was revealed through statistical comparison between JAK2V617F mutated and unmutated, incidence of thrombosis (18.75 vs 11.76%; $p = 0.396$), bleeding manifestations (6.25 vs 8.82%; $p = 0.617$), pruritus (18.75 vs 8.82%; $p = 0.285$), transformation to myelofibrosis (0 vs 2.94; $p = 0.680$), as well as high-risk disease (56.25 vs 32.3%; $p = 0.097$). Nevertheless, a significant statistical difference among JAK-2V617F mutated as well as unmutated PV patients have been observed, with median age (61 vs 44.5 years; $p = 0.002$), median Hb (20.7 vs 17.5 gm/dL; $p = 0.001$), median total leukocyte count (TLC) (15,700 vs 8100 µL; $p = 0.001$), median platelet count at the time of presentation (3,20,000 vs 1,90,000 µL; $p = 0.044$), and low serum EPO level ($p = 0.00$) (Table 1).

Table 1: Clinical phenotype of JAK2V617F mutated vs unmutated patients

Clinical and laboratory parameters of diagnosed PV patients (N = 50)	*JAK2V617F Mutated (N = 34)*	*JAK2V617F Unmutated (N = 16)*	*p-value*
Median age at presentation (years)	61	44.5	$p = 0.002$
Median hemoglobin at presentation (gm/dL)	20.7	17.5	$p = 0.001$
Median TLC at presentation (/µL)	15,700	8,100	$p = 0.001$
Median platelet at presentation (/µL)	3,20,000	1,90,000	$p = 0.044$
Low serum EPO (%)	62.5	100	$p = 0.00$
Incidence of thrombosis (%)	18.75	11.76	$p = 0.396$
Incidence of bleeding (%)	6.25	8.82	$p = 0.617$
Incidence of pruritis (%)	18.75	8.82	$p = 0.285$
High-risk disease (%)	56.25	32.3	$p = 0.097$
Transformation to myelofibrosis (%)	0	2.94	$p = 0.680$
Transformation to acute leukemia	0	0	–

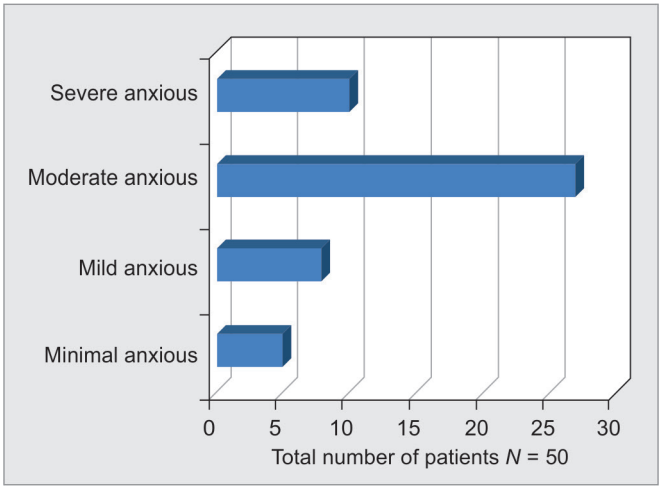

Fig. 1: Distribution of patients showing anxiety at diagnosis

Distribution of patients with anxiety levels at diagnosis of PV as depicted in (Fig. 1) shows that the majority of study patients showed a moderate level of anxiety and few were severely anxious considering the phlebotomy procedure and associated risks of deep venous thrombosis besides long-term risks for progression toward myelofibrosis using the generalized anxiety disorder (GAD-7 questionnaire.

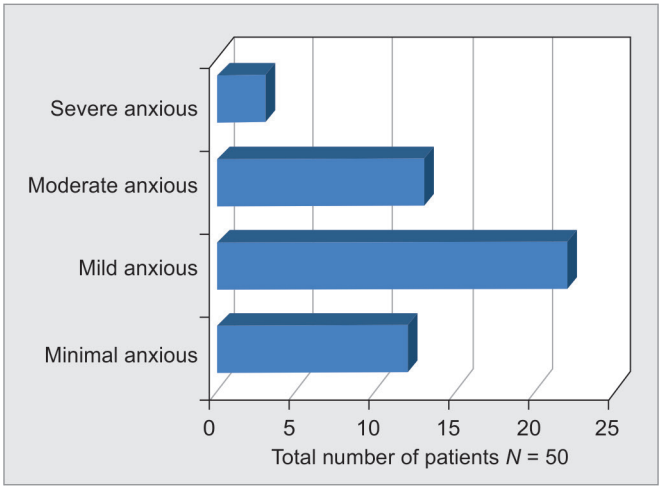

Fig. 2: Distribution of patients showing anxiety at six months

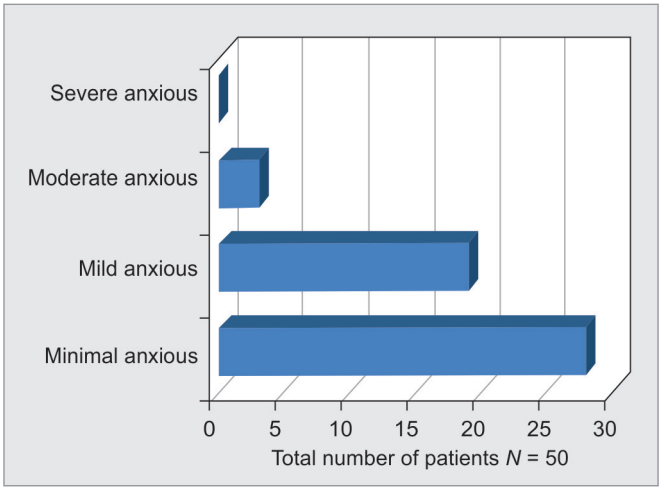

Fig. 3: Distribution of patients showing anxiety at one year

However at six months, after initiation of therapy and on assessment of anxiety scores it was found that the majority of patients showed mild and minimal levels of anxiety compared to moderate and severe anxiety levels at baseline (Fig. 2).

At one year, when anxiety levels were again assessed in the study patients, it was found that none of the patients were severely anxious about their disease entity and few were moderately anxious. Almost all were mild and minimally anxious, and they were actively involved with their daily livelihoods (Fig. 3).

Discussion

The presence of mutated JAK2V617F is an essential diagnostic criterion required in diagnosing Philadelphia-negative MPNs. Published literature has shown that the JAK2V617F allele burden positively correlates with systemic symptoms as well as the risk of disease progression.[6,7] In this study, we assessed whether the absence or presence of mutated JAK2V617F is correlated with the phenotype of disease in PV patients. We observed that there was no significant difference with respect to gender, risk of thrombosis, bleeding manifestations, pruritus, high-risk disease, and disease progression. However, the median age at diagnosis was higher in JAK2 mutated patients, and median Hb, TLC, as well as platelet count at presentation, were higher in JAK2 positive patients. Also, JAK2-positive PV patients had lower serum EPO levels. Vannucchi et al.[7, 8,9] suggested that the presence of JAK2V617F mutation was significantly related to thrombosis. According to Passamonti et al.,[10] no significant correlation had been exhibited with the risk of thrombosis among Italian PV patients.

At the beginning of diagnosis, it was found that most patients were anxious related to subsequent complications like the risk of thrombosis and the remote chance of transformation to myelofibrosis. Another important implication is bone marrow procedure which incites needful stress and anxiety among patients with all hematological diseases. However, at 6 months, most patients gradually get accustomed as their symptoms and hematocrit level come down with needful therapy and routine phlebotomy is seldom required. At one year none of the patients were seriously anxious and most returned to their routine activities of daily living; however, a query for a definite disease-modifying agent is always there from patients with PV.

The study by Gibek et al. emphasized the significance of identifying somatic disorders, depression, anxiety, and other associated symptoms in patients receiving interferon-alpha treatment who have MPNs as well as those receiving alternative therapies. None of our study patients received interferon alpha that has unique side effects. The study included all categories of MPN patients but our study was only concerned with patients with PV only.[10,11]

The therapeutic landscape of patients with PV is with a lot of unmet needs. The concurrent administration of low aspirin dose (81 mg/day) and phlebotomy to attain a target hematocrit below 45% is commonly employed in clinical practice.[12] This combination is suitable to be employed in conjunction with cytoreductive therapy for individuals in high-risk groups and is the first-line treatment choice for individuals having low risk.[13] The application of ruxolitinib is presently restricted to PV patients who exhibit resistance to hydroxyurea or demonstrate intolerance to it.[14]

The limitation of our study was the lack of usage of Interferon alfa in our patients with PV. It was also not possible to use ruxoltinib in some resistant patients because of its fancy cost issues; however, one waits for MDM2 inhibitors and HDAC inhibitors that are required in certain pilot studies, and more research should be done before they form part of patient care.[15]

Conclusion

The study evaluated the influence of the JAK2V617F mutation state over the phenotype of PV in relation to clinical as well as other laboratory characteristics. Despite the absence of variation in the majority of clinical characteristics between mutated and unmutated groups, the age of diagnosis as well as other laboratory parameters, such as TLC, Hb, platelet counts, and serum EPO levels, exhibited a statistically significant difference. Thrombosis was more prevalent in patients with JAK2V617F mutation. With the passage of time gradually the stress and anxiety decline among patients with PV and can lead to a near normal life.

Ethics

This article's work adheres to the World Medical Association's Code of Ethics (Declaration of Helsinki) for human experiments, EU Directive 2010/63/EU for animal experiments, and the Uniform Requirements for manuscripts submitted to biomedical journals.

Orcid

Shuvra Neel Baul https://orcid.org/0000-0002-9911-4985

References

1. James C, Ugo V, Le Couédic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434(7037):1144–1148. DOI: 10.1038/nature03546.
2. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med 2005;352(17):1779–1790. DOI: 10.1056/NEJMoa051113.
3. 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(4):387–397. DOI: 10.1016/j.ccr.2005.03.023.
4. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005;365(9464):1054–1061. DOI: 10.1016/S0140-6736(05)71142-9.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–2405. DOI: 10.1182/blood-2016-03-643544.
6. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–1097. DOI: 10.1001/archinte.166.10.1092.
7. Moliterno AR, Kaizer H, Reeves BN. JAK2 V617F allele burden in polycythemia vera: Burden of proof. Blood 2023;141(16):1934–1942. DOI: 10.1182/blood.2022017697.
8. Vannucchi AM, Pieri L, Guglielmelli P. JAK2 allele burden in the myeloproliferative neoplasms: Effects on phenotype, prognosis and change with treatment. Ther Adv Hematol 2011;2(1):21–32. DOI: 10.1177/2040620710394474.
9. Vannucchi AM. JAK2 mutation and thrombosis in the myeloproliferative neoplasms. Curr Hematol Malig Rep 2010;5:22–28. DOI: 10.1007/s11899-009-0038-x.
10. Passamonti F, Rumi E, Pietra D, et al. A prospective study of 338 patients with polycythemia vera: The impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. Leukemia 2010;24:1574–1579. DOI: 10.1038/leu.2010.148.
11. Gibek K, Sacha T, Cyranka K. Comparison of depressive, anxiety, and somatic symptoms in patients with essential thrombocythemia, polycythemia vera, and myelofibrosis treated with interferon alpha. Acta Haematol Polonica 2022;54:18–30. DOI: 10.5603/AHP.a2022.0058.
12. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004;350:114–124. DOI: 10.1056/NEJMoa035572.
13. Barbui T, Carobbio A, Ghirardi A, et al. No correlation of intensity of phlebotomy regimen with risk of thrombosis in polycythemia vera: Evidence from European Collaboration on low-dose aspirin in polycythemia vera and cytoreductive therapy in polycythemia vera clinical trials. Haematologica 2017;102:e219–e221. DOI: 10.3324/haematol.2017.165126.
14. McMullin MF, Harrison CN, Ali S, et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. Br J Haematol 2019;184:176–191. DOI: 10.1111/bjh.15648.
15. Arya Y, Syal A, Gupta M, et al. Advances in the treatment of polycythemia vera: Trends in disease management. Cureus 2021;13(3):e14193. DOI: 10.7759/cureus.14193.