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Frequency, Risk stratification, Complications and Outcome of Polycythemia Vera: A Single Institute Experience

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Abstract

Objectives: To evaluate the frequency of PV among patients with high hemoglobin and hematocrit, risk stratification, complications, and long-term outcomes of PV patients in a single institute tertiary care setting.

Methodology: This retrospective cohort study is conducted at Aga Khan University Hospital, Karachi, duration from January 2020 to December 2024. Sixty nine patients were diagnosed with PV based on WHO 2022 criteria and molecular testing out of 450 who presented with erythrocytosis. Data was extracted from electronic medical records and analyzed using SPSS.

Results: The prevalence of JAK2-positive PV was 15.3% (n=69) among patients presented with erythrocytosis. Cohort showed a male predominance (66.7%) with a mean age of 58.5 years. Hypertension (56.5%) and headache (55.1%) were the most common comorbidity and symptom assessed, respectively. High-risk patients constituted 63.8% of cases. Pre-treatment thrombotic events observed exclusively in the high-risk group (52.3%). Post-treatment complications (including arterial/venous events, leukemic transformation, and secondary malignancies) were observed in 20.5% of high-risk patients, however low-risk patients experienced no complications. The overall 5-year mortality rate was 8.7%, entirely in the high-risk group. 65.2% of the total cohort remained alive at the final follow-up.

Conclusion: Significant thrombotic morbidity and mortality were observed in high risk patients of PV in this South Asian cohort. These findings emphasize the inevitability of early molecular diagnosis, risk-adapted cytoreductive therapy, and structured long-term monitoring to improve clinical outcomes.

Key Words: Lupus Anticoagulants, Systemic Lupus Erythemotosis, Miscarriages, Venous Thrombosis

Introduction

Polycythemia vera (PV) is a chronic Philadelphia chromosome–negative myeloproliferative neoplasm. It is driven by clonal hematopoiesis, most commonly due to JAK2 mutations, leading to constitutive activation of the JAK–STAT signaling pathway, this results in erythropoietin-independent overproduction of red blood cells, often accompanied by leukocytosis and thrombocytosis.[1]

Its incidence is estimated to be around 2 cases per 100,000 individuals per year worldwide ([2]). In Asia, PV is documented to be predominant in males, age those above 50 years old and those with a high JAK2V617F allele burden.[3,4]

The 2022 World Health Organization (WHO) diagnostic major criteria include 1) elevated hemoglobin concentration (>16.5 g/dL in men; >16.0 g/dL in women, or elevated hematocrit > 49% in men; >48% in women), [2] bone Marrow biopsy showing age-adjusted hypercellularity with trilineage growth including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic mature megakaryocytes, and 3) presence of JAK2 V617F or JAK2 exon 12 mutation with minor criteria including subnormal serum erythropoietin level. [2,5]

Frequency of JAK2 mutations positivity in Polycythemia vera is approximately 95 to 100 %, in which exon 14 comprises around 95 to 97%.[6]. JAK2 positivity with sensitivities of 94.7% of the total 100%.[7] Exon 12 mutations are identified in a subset of patients who lack the V617F mutation.

Exclusion of secondary causes is needed, which includes cystic disease of the kidney, renal artery stenosis, unilateral hydronephrosis, SGLT2 inhibitors, chronic hypoxia or tumors and other disorders with JAK2 positivity (example: CMML).[8–10] Serum erythropoietin (EPO) also serves as a predictive marker.[11] A common issue encountered in the outpatient primary care setting

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that is often undiagnosed or inappropriately worked up.[12,13]

Complications and survival of polycythemia vera depend on the allele burden of JAK2V617F.[4,14] Polycythemia treatment commenced on a risk stratification basis, characterized as high and low risk.[15] Mortality among high risk patients are more observed. [16]

The literature shows a paucity of new driver mutations in polycythemia vera (PV) especially in Asia. Our purpose is to improve diagnostic accuracy, differentiate from secondary causes, stratify risk, control symptoms and improve quality of life, surveillance for disease transformation. Additionally, these mutations also open opportunities for targeted therapies, potentially reducing side effects and complications while enhancing treatment efficacy.

Methodology

A retrospective cohort study was conducted at Aga Khan University Hospital in Karachi, Pakistan, from January 2020 till December 2024. The study included a total of 450 patients, of whom 69 patients were diagnosed with Polycythemia Vera associated with molecular driver mutations. The patient data was extracted using the electronic medical record numbers of the institute. Ethical approval for the study was given by the ethical review committee (ERC #: 2024-10100-30097) of Aga Khan University Hospital, Pakistan.

Study variables include the patient's demographical characteristics, history, physical examination, routine complete blood count, baseline workup, erythropoietin levels, JAK2V617F, and myeloproliferative neoplasm panel.

Sample size we calculated using the Openepi software. Data was collected using a pre-structured questionnaire encompassing demographic information, comorbidities and hematological parameters. Patients' charts were reviewed for response assessment. Statistical analysis was conducted for Polycythemia Vera using SPSS, with descriptive statistics such as means, standard deviations, frequencies, and percentages.

Inclusion Criteria:

Patients above 18 years of age with high hemoglobin and hematocrit levels with positive JAK2 mutations.

Exclusion Criteria:

Patients with secondary and idiopathic erythrocytosis and those who met WHO diagnostic criteria for primary myelofibrosis, essential thrombocythemia, chronic myeloid leukemia or other myeloid neoplasms were excluded.

Operational Definitions:

1. JAK2 V617F mutation: refers to a specific change in the Janus kinase 2 (JAK2) gene, where the amino acid valine (V) is substituted with phenylalanine (F) at codon 617.
2. MPN panel: includes JAK2V617F, JAK2 exon 12, CALR mutations, MPL, and C-Kit.
3. Low-risk patients were ≤60 years of age and no history of thrombosis.
4. High-risk patients were those >60 years of age or with a history of thrombosis

Results

In our study, a total of 450 patients were tested for polycythemia vera (PV), of whom 69 (15.3%) were positive for the JAK2V617F mutation (figure 1). Among the PV-positive patients, the proportion of male patients was twice that of females (46 vs. 23), with a mean age of 58.5 years (median: 60 years, range: 27 to 90 years). Geographical distribution included residents of Karachi (56.5%), followed by Quetta (29.0%), Interior Sindh (13.0%), and Punjab (1.4%). (Figure 1)

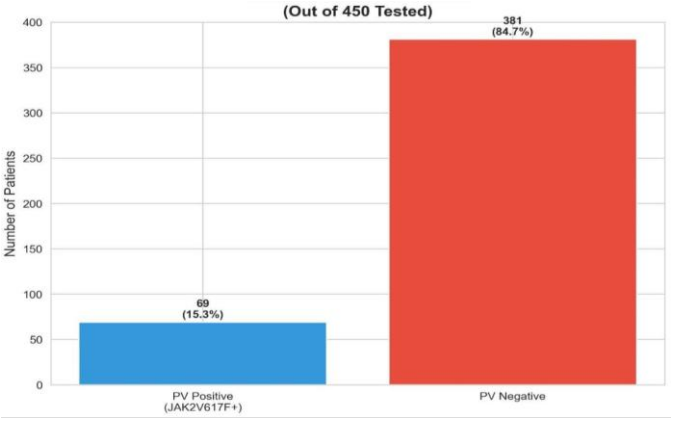

Figure 1. Mutation status distribution.

Table I: Patients Characteristics.		
Characteristic	(n=69)	(%)
Gender		
Male	46	66.7%
Female	23	33.3%
Age (Years)		
Median (Range)	60.0	(27–90)
Risk Stratification		
High Risk	44	63.8%
Low Risk	25	36.2%
Clinical Features		
Headache	38	55.1%
Chest Pain	10	14.5%
Pruritus	7	10.1%
Visual Disturbance	7	10.1%
Burning Pain (Erythromelalgia)	4	5.8%
Abdominal Fullness	2	2.9%
Asymptomatic	1	1.4%
Mutation		
JAK2 negative	381	84.7%
JAK2 V617F (Exon 14)	67	14.8%
JAK2 (Exon 12)	2	0.4%
Serum Erythropoietin (EPO)		
Sub-normal	37	53.6%
Normal	32	46.4%
Ultrasound Abdomen		
Normal scan	45	
Splenomegaly: Low risk High risk	7 2 5	
Not performed	7	

Hypertension was the most common comorbidity, observed in 39 patients (56.5%) of the cohort, followed by diabetes in 14 patients (20.3%), smoking in 3 patients (4.3%), cancer in 1 patient (1.5%), and other conditions in 12 patients (16.3%) others. The most frequent presenting symptoms included headache in patients 38 (55.1%) of patients, chest pain in 10 (14.5%), pruritus and visual disturbances in 7 (10.1%) each, burning pain in 4 (5.8%), and abdominal fullness in 2 patients (2.9%), while 1 patient (1.4%) reported no symptoms.

Of the confirmed PV cases, patients categorized as high risk were almost twice as much as the low-risk group (44 vs. 25) (Table I).

Before initiating treatment, thrombotic complications were documented mainly in the high-risk category i.e. 23 patients, which includes venous thromboembolism (VTE), stroke, and myocardial infarction (MI), observed in 6 (13.6%), 8 (18.2%), and 9 (20.5%) patients, respectively, amounting to a total of 52.3% pre-treatment thrombotic events in this group. However, none of the low-risk patients experienced any thrombotic event.

Screening via the Myeloproliferative Neoplasm (MPN) panel confirmed JAK2 mutations in 69 subjects. The majority of these cases (n=67, 14.8%) were positive for the JAK2 V617F mutation, whereas exon 12 variants were rare (n=2, 0.4%). A negative result was recorded for 381 patients (84.7%).

According to minor criteria, serum erythropoietin levels were also assessed; results were subnormal in the majority of patients. Abdominal ultrasound was also advised on presentation; 45 patient's scans showed no significant findings, and 7 patients did not perform. However, splenomegaly was observed in 7 patients; of them 2 patients were in low-risk category, while 5 patients were in the high risk. Bone marrow trephine at the time of diagnosis was performed in only 10 patients; findings were consistent with polycythemia vera.

Regarding treatment patterns, the low-risk group was mainly treated with aspirin and phlebotomies to maintain hematocrit <45% in 16 patients (68.0%), followed by aspirin and hydroxyurea in 8 patients (32.0%) these patients required multiple therapeutic phlebotomies and subsequent escalation of therapy. Cytoreductive therapy was required in 79.5% (n=35) of high-risk patients; 34 patients received hydroxyurea, and one patient was treated with Peg interferon alpha, in addition to the baseline regimen of aspirin and phlebotomy. However, 2

Table II: Treatment Modalities by Risk Group.			
Risk Category	Treatment Regimen	Number of Patients	Percentage (%)
Low Risk (n = 25)	Aspirin + Periodic Phlebotomy	16	68.0%
	Aspirin + Phlebotomy + Hydroxyurea	8	32.0%
High Risk (n = 44)	Aspirin + Phlebotomy + Hydroxyurea	34	77.2%
	Aspirin + Phlebotomy + Peg Interferone	1	2.3%
	Aspirin + Phlebotomy + Hydroxyurea + Ruxolitinib	2	4.5%
	Aspirin alone	6	13.6%
	Non-compliant	1	2.3%

patients (4.5%) received Ruxolitinib along with the above, 6 patients (13.6%) received aspirin alone and 1 patient (2.3%) was non-complaint to medicines (Table II).

Initially, therapeutic phlebotomies were required in 14 low-risk and 23 high-risk patients, with an average duration of approximately one year and a mean frequency of three phlebotomies per year in both groups. A subset of patients subsequently required escalation of therapy due to recurrent need for therapeutic phlebotomies. High-risk patients who developed venous thrombosis were treated with aspirin in combination with anticoagulation, administered either for three months or long-term, depending on individual clinical assessment. Some high-risk patients were started on aspirin alone without cytoreductive therapy due to delay in establishing the diagnosis, early death at presentation, or subsequent loss to follow-up.

Post-treatment complications occurred exclusively in high-risk patients, affecting 9 patients (20.5%). These included arterial events in 2 patients (4.5%), venous events in 3 patients (6.8%), and four patients in the cohort experienced disease progression, including transformation to acute leukemia, post-polycythemia myelofibrosis, and 2 patients of them develop second malignancy in a median duration of 2 years, accounting for a total of 9% of cases, whereas 79.5% experienced no complications, including low-risk patients. In combined risk-and-treatment analysis, no complications occurred in any low-risk subgroup, while among high-risk patients, complications developed in 2 patients treated with aspirin alone, 5 patients of those receiving hydroxyurea plus ascard, 1 patient of those on Ruxolitinib, and the single not appropriately treated patient (Table III).

Table III: Clinical Complications and Disease Progression.

Risk Category	Complication Type	(n)	(%)
Low Risk	Total without complications	25	100%
High Risk	Total without complications With complications	35 9	79.5% 20.5%
	Thrombotic Events		
	— Venous Event	3	6.8%
	— Arterial Event	2	4.5%
	Disease Transformation		
	— Acute Myeloid Leukemia (AML)	1	2.25%
	— Post-Polycythemia Myelofibrosis	1	2.25%
	Other		
	— Second Malignancy	2	4.5%

With regard to clinical outcomes, 21 patients (84.0%) of low-risk patients were alive at last follow-up and 4 patients (16.0%) were lost to follow-up. Among high-risk patients, 24 patients (54.5%) were alive, 15 patients (31.8%) were lost to follow-up, and 5 patients (13.6%) had died. Considering all PV-positive patients collectively, 65.2% were alive, 26.1% were lost to follow-up, and 8.7% was the mortality rate in a duration of 5 years. The cause of mortality mainly was ischemic stroke; however, two patients died due to secondary malignancy and transformation to acute leukemia, respectively (Table IV).

Table IV: Patient Outcomes and Survival Status.

Risk Category	Outcome Status	(n)	(%)
Low Risk	Alive	21	84.0%
	Lost to Follow-up	4	16.0%
High Risk	Alive	24	54.5%
	Lost to Follow-up	15	31.8%
	Death	5	13.6%
Total Study	5-Year Overall Mortality Rate	—	8.7%

Discussion

This single center study conducted in a South Asian population provides insight regarding the epidemiology, clinical presentation, and survival outcomes of patients diagnosed with PV. Out of the 450 participants tested, the proportion of 15.3% patients testing positive for JAK2 mutations is in line with the well identified reliance on JAK2 mutations for diagnosing PV, which has a crucial contribution in its pathophysiology through the activation of the JAK-STAT signaling pathway.[17] This highlights the diagnostic role of molecular testing for PV and to rule out other causes of erythrocytosis.

Cohort shows male predominance with mean age of 58.5 years that is consistent with international data, indicating that PV in the South Asian population reflects global demographic trends.[18,19] Most of the patients were from Karachi, followed by Quetta and interior Sindh, likely showing disparities in healthcare access, diagnostic responsiveness, and referral designs.[20] Limited availability of molecular testing access in remote areas may lead to underestimat prevalence of PV, highlighting the need to expand diagnostic services to better define the true disease burden in Pakistan.

The portion of cardiovascular comorbidity has a clinical significance, as these increase the risk of thrombotic complications, which impacts morbidity and mortality in PV.[21,22] The most common presenting symptoms, headache, chest pain, visual disturbances, and pruritus are well documented in abundant literature[23,24] and are associated with hyperviscosity and microvascular dysfunction that characterizes PV. Minority of patients presented with abdominal fullness likely suggests splenomegaly[25], which usually corresponds to a longer duration of the disease or an advanced stage.

As for molecular description, JAK2-positive patients were included, indorsing this mutation as the predominant driver of PV and supporting its continued global diagnostic use.[26–28] Using conventional risk stratification, nearly two-thirds of patients were classified as high risk based on age >60 years or prior thrombosis[29], suggesting delayed diagnosis and presentation at a later disease stage. Notably, one-third of patients had pre-treatment thrombotic events, consistent with existing literature implicating hyperviscosity, platelet activation impaired, fibrinolytic activity, leukocyte activation, and endothelial damage in PV-related vascular complications.[30,31,32]

The therapeutic approach in our study was consistent with standard global practice, with high-risk patients predominantly receiving aspirin with periodic phlebotomies along with hydroxyurea, reflecting the efficacy of cytoreductive therapy in reducing thrombotic risk[33] Low-risk patients were mainly managed with aspirin plus periodic phlebotomies

to control hematocrit, given its established role in preventing cardiovascular and thrombotic events.[34] Post-treatment complications occurred exclusively in the high-risk group, most commonly venous and arterial thrombosis [35], followed by transition to myelofibrosis[36] and secondary malignancies[37] consistent with earlier studies. The low transformation rate in our study supports the effectiveness of appropriate monitoring and therapy, although the occurrence of secondary malignancies underscores the need for vigilant long-term surveillance.The limited use of ruxolitinib in local practice showed variable outcomes, highlighting the necessity to better define its role, particularly in hydroxyurea-intolerant or resistant patients. [38–40]

The study shows 8.7% mortality rate exclusively in the high-risk group, emphasizing that age and thrombotic history are key determinants of survival.[22,41] Loss to follow-up, limited long-term outcome assessment, highlighting the need for vigilant in planned clinic visits and patient assessment. Overall, the findings were similar as in international literature while providing regional data from the South Asian population, to achieve favorable outcomes in risk-adapted management and emphasizing the need for increased physician awareness and timely relevant testing.[42,43]

The limitations of this study include its retrospective, single-center design and small sample size. A short follow-up period and significant loss to follow-up may have underrated long-term complications and survival differences. Nevertheless, the study provides valuable baseline epidemiologic and outcome data from Pakistan, serving as a benchmark for future prospective and multicenter research.

Conclusion

1. This study demonstrates a wide spectrum of clinical manifestations associated with positive LA1/LA2 ratios in a cross-section of the Pakistani population.
2. Venous thrombosis was the most common clinical presentation.
3. A subset of individuals with weakly positive LA ratios remained asymptomatic, highlighting the necessity of excluding transient or false-positive LA results through clinical correlation and follow-up.
4. These findings reinforce the importance of individualized risk assessment and cautious interpretation of LA positivity in clinical practice.

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