COMPARISON OF HEMATOLOGICAL PARAMETERS OF JAK2 POSITIVE AND JAK2 NEGATIVE PATIENTS OF POLYCYTHEMIA VERA: A MINI-REVIEW

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ABSTRACT

Polycythemia vera (PV) is a malignant disorder with a different frequency based upon age and population. The present review aimed to determine the frequency of Janus Kinase-2 (JAK2) positive and JAK2 negative patients with PV and compare the hematological parameters. Operating polymerase chain reaction (PCR), studies found that mutations in the patients of JAK-2 V617F gene with low serum erythropoietin (EPO) and bone marrow depicted hypercellularity with increased red cell mass. PV is a subtype of myeloproliferative neoplasms (MPN), causing hyperviscosity and thrombotic complications. It's symptoms include fatigue, headache and pruritus. It's incidence ranges from 0.02 to 2.8 per 100,000. The JAK-STAT pathway mainly encompasses normal blood cell production and function, but irregularities can lead to disease conditions.

INTRODUCTION

Polycythemia Vera (PV), a hematopoietic stem cell clonal disorder marked by uncontrolled proliferation of granulocytes, erythrocytes and megakaryocytes, that follows hyperviscosity in the blood and thrombotic complications. The World Health Organization (WHO) defines PV as a type of chronic myeloproliferative disease [1]. Janus kinase 2 gene (JAK2-V617F) mutation affects part of JAK kinase known as pseudo kinase [2]. Firstly, it was reported in 1892 [3]. Further, polycythemia is split into two categories: primary polycythemia (Polycythemia vera), which is a multipotent hematopoietic stem cell

disorder; and secondary polycythemia, called erythrocytosis, which occurs due to the accumulation of the erythropoietin hormone [4]. Fatigue and itching, microvascular symptoms (such as migraines, dizziness, headaches, paresthesia, and unusual chest pain), and characteristics like splenomegaly, hyperviscosity, leukocytosis, thrombocytosis, thrombotic, and bleeding problems are among the clinical symptoms of PV. Acute myeloid leukemia or secondary myelofibrosis could develop from PV [5].

In 1903 and 1892, William Osler and Vasquez, respectively, showed rheumatism and stroke as clinical features of disease. Another scientist, Thomas Person, identified (famous for the phlebotomy technique) the use of leeches and bloodletting, which was a successful therapy for decades. A scientist from Framingham studied haemoglobin concentration and cerebral infraction, according to his study and stroke. 1972, man Hb ≥ 15 and female Hb ≥ 14 had twice as many cerebral infarctions [6].

This mini-review article explores the literature on the comparison between JAK2 positive and JAK2 negative patients of polycythemia vera, conducted at Khyber Medical University, Kohat, Pakistan, over a four-month period from February to May 2020. The studies on PV diagnosed cases and hematological parameters analysis were sourced from Google Scholar databases published between 1990-2023 in English language. The keywords used included “polycythemia”, “polycythemia vera”, “JAK2”, “hematological parameters” and “patients”.

Polycythemia can lead to several complications, each contributing to serious health risks. One of the potential complications is leukemia progression, with around 5% of cases progressing to acute myeloid leukemia (AML), a difficult-to-treat condition. The initiation of AML has been linked to certain medications like radioactive phosphorus, pipobroman, and chlorambucil [7]. Complications include recurrent nosebleeds and gastrointestinal bleeding, often due to iron deficiency anemia may complicate interpretation, particularly when assessing changes in bone marrow [8]. Thrombosis, a risk due to increased blood viscosity, increases the chances of venous and arterial clots, that may lead to to issues like cerebral ischemic infarctions and digital infarctions, and Budd-Chiari syndrome [9]. Additionally, polycythemia, can reduce oxygen delivery to tissues, due to compromised lung function that affects oxygen transfer, even with a high red blood cell count [5, 7]. Heart-related issues are prevalent including hypertension, heart failure, and an increased risk of stroke, which arise due to heightened blood viscosity and the additional strain placed on the heart [5]. These complications enhance the significance of closely monitoring and managing polycythemia to prevent further health risks.

The annual incidence of PV in European countries ranged from 0.4 to 2.8 per 100,000 people [10]. PV patients have approximately 90% mutations in JAK2V617F [11]. Recent studies from European countries depicts that polycythemia is the most common myeloproliferative disorder [12]. PV is a rare condition in

children, with a yearly incidence ranging from 0.02 to 2.8/100000 patients, increasing with age. The highest prevalence is between 70 and 79 years, with 1.6-fold higher mortality rates. JAK2, a cytoplasmic tyrosine kinase, has four groups in humans: JAK1, JAK2, JAK3, and TYK2.15. Its molecular weight is 120-140 kDa and irregularities in the JAK-STAT pathway can lead to disease conditions [13]. In 2007, V617F-negative patients with polycythemia vera showed multiple mutations in JAK 2's 12 axon, revealing that JAK2 12 axon 12 controls the erythropoietin channel [14]. About 80% of PV patients exhibit symptoms, including headaches, pruritus, fatigue, dyspnea, dizziness, visual changes, weight loss, and increased sweetness. The primary cause of morbidity and death in PV adult patients is thrombosis and bleeding [15].

The World Health Organization defines diagnostic criteria for erythroid colony formation, including two major criteria: high hemoglobin levels in men and women, the presence of a JAK2 mutation, and three minor criteria: bone marrow biopsy, low serum erythropoietin levels, and endogenous erythroid colony formation. Patients fulfilling the 2 major criteria and at least 1 minor criterion should be confirmed as diagnosed cases of polycythemia vera (PV) [16].

Cytogenetics is particularly useful in the diagnosis of myeloid disorders. It gives way or path in several pathogenic studies [17]. Since 2005, over 20 JAK2 gene mutations have been identified, with V617F being the most prevalent, accounting for 97% of PV patients, making it a crucial diagnostic criterion. [18].

In relation to comparative analysis of JAK2 positive and JAK2 negative patients**,** Akram et al.'s study found that hematological parameters of mutation-carrying individuals do not significantly differ from other PV patients. The 15-year survival rate for V617F positive patients is 76%, compared to 94% for wild type V617 patients. The clinical characteristics of PV patients are shown in Table 1 [18].

Table 1: Characteristics of Polycythemia Vera patients, including the detection of JAK2 V617F and exon 12 mutations.

Patient characteristics	**Patients n=24 (%)**	
Gender	Males	16 (66.7%)
	Females	8 (33.3%)
Median age (years)	57	
Platelet count (x10^9/L)	100-450	02 (8.3%)
	>450	22 (91.7)
Mean Platelet count (x10^9/L)	552±253	
Total leukocyte count (x10^9/L)	4-11	05 (20.8%)
	>11	19 (79.2%)
Mean TLC (x10^9/L)	17.6± 9.1	
Mean Hematocrit (%)	51.4±5.2	
Hemoglobin level in peripheral blood	>16g/dl	11 (45.8%)
Mean corpuscular Volume (MCV)	<77fl	18 (75.0%)
Mean MCV	77.2±13.0 fl	

Mean corpuscular Hemoglobin (MCH)	<27pg	20 (83.4%)
Mean MCH	25.6±3.9 pg	

Silver et al.'s study revealed that patients with PV diagnosis exhibit age-related hypercellularity due to pan-myelosis, characterized by a high number of megakaryocytic patients with cytologic pleomorphism and mild atypia [16]

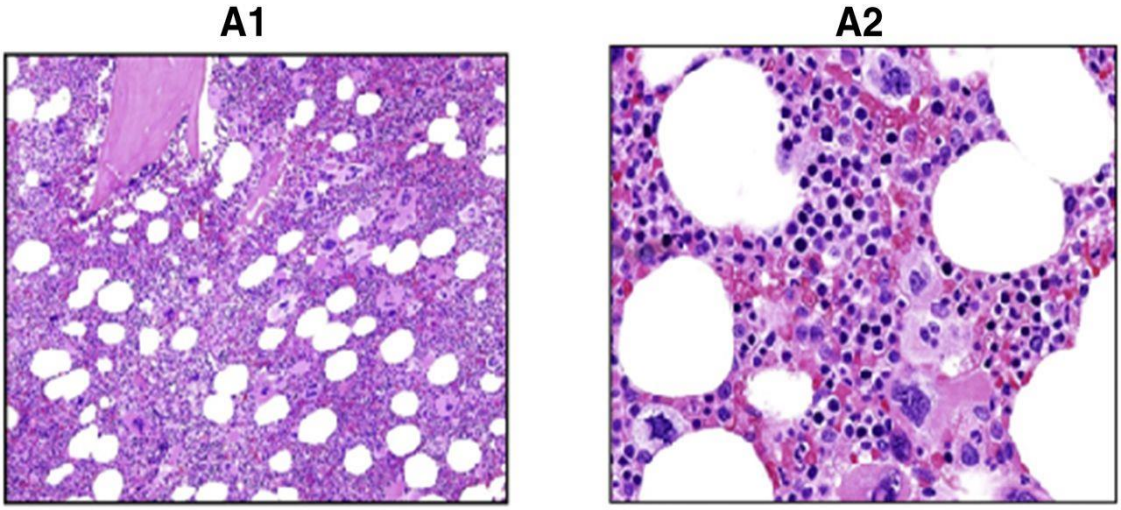

Figure 1: The hematoxylin and eosin sections of JAK2V617F positive study cases display typical PV morphology. (A1) The photo shows a hypercellular marrow with panmyelosis, with a 3200-magnification view (A2) The photo shows a 3400-magnification image of the same case, revealing pleomorphic megakaryocytes in loose clusters [16]

The study also showed that 28 patients diagnosed with PV found that only 7 met all the criteria for PV, including JAK2 positivity, increased red blood cell (RCM), hemoglobin, hematocrit, low serum EPO, and bone marrow. Only 10 and 20 met the elevated hemoglobin and hematocrit criteria, respectively (Table 2) [16].

Table 2: The diagnostic findings for the diagnosis of MPNs (n = 30)

Parameters						Number of patients	Final diagnosis
JAK2	RCM	HGB	HCT	BM biopsy result	EPO		
+	+	+	+	+	+	7	Polycythemia vera
+	+	–	+	+	+	7	Polycythemia vera
+	+	–	–	+	+	4	Polycythemia vera
+	+	–	+	+	–	2	Polycythemia vera
+	+	–	–	+	–	3	Polycythemia vera

+	+	+	+	+	*	3	Polycythemia vera
+	+	–	+	+	*	1	Polycythemia vera
+	+	–	–	+	*	1	Polycythemia vera
+	–	–	+	–†	+	1	Essential thrombocytopenia
+	–	–	–	–‡	–	1	Primary myelofibrosis

* EPO obtained 3 months after diagnosis

† (+ve for ET)| ‡ (+ve for PMF)| + (+ve for PV)| - (-ve for PV)

In another study done by Karkucak et al., it was found that 60% of patients (89 out of 148) diagnosed with polycythemia vera (PV) and essential thrombocytopenia (ET) had JAK2-V617F (+) mutations. JAK2 (+) patients had higher WBC (12.9×109/L) and Hb count (15.56 g/dL) and lower platelet count (683×10^9/L) than JAK2 (-) patients. Statistical significance tests showed that the group with the (+) mutation had significantly higher levels of WBCs, Hb and splenomegaly ($p = 0.021$, $p = 0.010$, $p = 0.014$). The differences between JAK2 positive and negative hematological parameters are displayed below (Table 3). [16]

Table 3: Characteristics stratified by JAK2-V617F mutation status patients of PV and ET [1]

Parameters	**JAK2-V617F (+) (n = 89)**	**JAK2-V617F (-) (n = 59)**
Gender (Male/Female)	36/53	26/33
Age	62.17 ± 12.85	50.03 ± 14.28
WBC ($\times10^9$/L)	12.9 ± 5.6	11.1 ± 3.8
Hb (g/dL)	15.56 ± 3.01	14.22 ± 3.07
Platelet ($\times10^9$/L)	683(124–2763)	968(155–2900)

A study done by Vera showed that reducing cardiovascular (CV) risk factors including hypertension, smoking, diabetes, hypercholesterolemia, and obesity can lead to better management among PV patients [19].

Treatments should be focused on normalizing Hb, Hct, and leukocytosis as well as lowering cardiovascular risk factors like obesity, diabetes, hypertension, dyslipidemia, and smoking in order to lower the risk of thrombotic events. Above all, hypertension and its treatment play a major part. In fact, recent research indicates that angiotensin converting enzyme inhibitors (ACEIs) may also help lower erythrocytosis [20]. According to Berlin et al., the initial treatment of PV is accomplished via phlebotomy, myelosuppression using radioactive phosphorus ^{32}P or other myelosuppressive chemotherapeutic drugs, hydroxyurea and interferon [15]. Since decades ago, polycythemia vera (PV) has been treated using

interferons (IFNs). Clinical trials evaluating IFN in patients with PV showed significant hematological and molecular response rates, suggesting that IFN may have disease-modifying effects. Ropeginterferon alfa-2b, or ROPEG, is an isoform-specific monopegylated IFN that differs from earlier IFNs in terms of dose frequency and tolerability. Due to its enhanced pharmacokinetic and pharmacodynamic qualities, ROPEG can be administered on a monthly basis throughout the maintenance phase and at longer intervals of every two weeks [21].

Therapeutic phlebotomy is a popular method to reduce hematocrit levels and thromboembolic risk. However, increasing hepcidin and using antisense oligonucleotides against Tmprss6 mRNA can also achieve similar results. Tmprss6-ASO, administered less frequently, may improve compliance and reduce side effects at injection sites [22]. Passamonti highlighted aspirin as the primary antiplatelet drug in PV treatment, but withdrawing it if bleeding occurs is advised, especially in patients over 60 years old, severe thrombosis, or splenomegaly. The first-line treatment for cytoreductive therapy in PV is hydroxyurea [23].

Patients with PV requiring cytoreductive therapy must use oral antimetabolites to inhibit ribonucleoside reductase, preventing DNA synthesis [24].

CONCLUSION

PV is a subtype of MPN, a hematopoietic stem cell disorder causing hyperviscosity and thrombotic complications. Its frequency varies regionally and age-wise, with 5% diagnosed annually in patients under 40. The highest incidence is between 70 and 79 years old. PV's clinical features include headache, pruritus, and fatigue. Morbidity and death in adult patients are due to thrombosis and bleeding. Diagnosis is based on JAK2-positive patients with low EPO levels, increased RCM, and hypercellularity. Aspirin is commonly used in PV antiplatelet therapy.

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