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JAK2 mutation, a potential cause of increasing Hemoglobin levels in symptomatic aged women

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Abstract

Background: Polycythemia Vera (PV) is a myeloproliferative neoplasm (MPN) characterized by the overactivity of erythroid progenitors, leading to excessive red blood cell (RBC) production. More than 90% of PV cases harbor a Janus kinase 2 (JAK2) gene mutation. This study aimed to assess the prevalence of JAK2 mutations in individuals with elevated hemoglobin (Hb) levels referred to the laboratory by physicians.

Methods: In this descriptive cross-sectional study, genomic DNA from 72 patients was analyzed for JAK2 mutations using a TaqMan-specific probe.

Results: Of the 72 patients, 24 (33.3%) were women and 48 (66.6%) were men. JAK2 mutations were detected in 33 cases (45.5%), while 39 (54.2%) were negative. Notably, 15 of 24 female patients (62.5%) tested positive for the JAK2 mutation, compared to 18 of 48 male patients (37.5%).

Conclusion: Our findings suggest that screening for JAK2 mutations is particularly important in women with above-normal Hb levels.

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Introduction

Erythrocytosis, defined as an elevated red blood cell (RBC) count, is classified into relative erythrocytosis (Caused by reduced plasma volume/hemoconcentration) or absolute erythrocytosis (Characterized by increased RBC mass) (1). Absolute erythrocytosis may arise from a clonal bone marrow disorder, such as Polycythemia Vera (PV), which has an incidence of 0.84%, or secondary causes (e.g., physiologic or pathologic factors), with a prevalence of 6%-8% (2).

PV is a chronic myeloproliferative neoplasm (MPN) marked by clonal expansion of myeloid lineage cells, predominantly erythrocytes, necessitating differentiation from other MPNs (3). Diagnostic criteria for PV have evolved: the 2008 World Health Organization (WHO) guidelines used hemoglobin (Hb) thresholds of >18.5 g/dL (Men) and >16.5 g/dL (Women) as surrogates for elevated RBC mass (4). The 2016 revision lowered these thresholds to >16.5 g/dL (Men) and >16 g/dL (Women), with additional hematocrit cutoffs (>49% for men, > 48% for women) (5).

A pivotal advancement in PV understanding came in 2005 with the discovery of the somatic JAK2 V617F mutation. The *JAK2* gene, located on 9p24, encodes a non-receptor tyrosine kinase critical for the JAK-STAT signaling pathway. This pathway regulates erythropoiesis, influencing proliferation, differentiation, and apoptosis of erythroid progenitors (6,7). The *V617F* mutation causes constitutive JAK2 activation, leading to erythropoietin (EPO)-independent erythroid growth, uncontrolled proliferation, and subsequent Hb elevation (8).

In this study, we investigated the prevalence of JAK2 mutations in individuals with age- and gender-adjusted elevated Hb levels, referred to our laboratory for clinical evaluation.

Methods

This descriptive cross-sectional study investigated JAK2 mutations in 60 patients exhibiting elevated hemoglobin levels according to WHO criteria (5), with an initial clinical suspicion of polycythemia vera (PV). The patients, referred by oncologists for laboratory analysis, were enrolled after approval by Islamic Azad University, Gorgan Branch (Registration code: 162474677). Approximately 4 mL of whole blood was collected in EDTA tubes from each participant, and a complete blood count (CBC) was performed using an automated Sysmex KX-21N analyzer (Sysmex, Japan) to assess key hematological parameters, including white blood cell (WBC) count, platelet (PLT) count, Hb level, and hematocrit (Hct). Demographic data were recorded for all patients, and written informed consent was obtained before inclusion in the study. Genomic DNA was extracted from the samples using the AccuPrep® Genomic DNA Extraction Kit (Bioneer, Korea) following the manufacturer's instructions, and the purified DNA was stored at 4°C until further analysis. To detect the JAK2 V617F mutation, allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) was performed using a reaction mixture containing 20–200 ng of template DNA, 20 µM master mix, 5 µM forward control primer (FC), 5 µM forward-specific primer (FS), 5 µM reverse primer, 5 U/µL Taq DNA polymerase, and nuclease-free distilled water. The primer sequences and PCR amplification conditions are provided in Tables 1 and 2, respectively.

The amplification conditions include initial denaturation at 95°C for 10 min, followed by 14 cycles of denaturation (94°C for 20 sec), annealing (65°C, 60 sec), and extension (72°C for 60 sec). These cycles were followed by a final extension step at 72°C for 5 min. The results were analyzed by Lightcycler96 (Roche, Germany) (Figure 1)

Table 1. Allele-specific oligonucleotide-polymerase chain reaction primers

Primer	Sequences (5' → 3')
Forward control	ATC TAT AGT CAT GCT GAA AGT AGG AGA AAG
Forward specific	AGC ATT TGG TTT TAA ATT ATG GAG TAT ATT
Reverse primer	CTG AAT AGT CCT ACA GTG TTT TCA GTT TCA

Table 2. Patient population information without considering JAK-2 mutation incidence

Gender		Age	WBC	RBC	Hb	PLT*1000
Female	Mean	44.13	9.711	5.378	14.125	629
(No: 24)	SD	17.578	4.4536	1.7982	4.1664	556
Male	Mean	38.94	8.239	5.782	16.325	363
(No: 48)	SD	17.699	2.9808	1.0141	2.3185	282

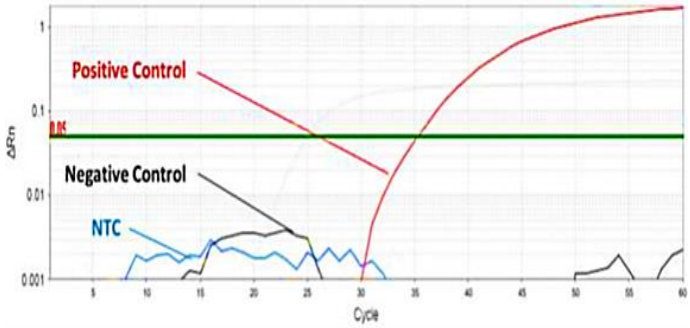

Figure 1. The result of PCR. The green line shows the threshold between Positive and Negative results. The red line revealed a positive result, and the black line shows a negative result for the JAK2 mutation

Results

Out of 72 patients, 24 were women (33.3%) and 48 (66.6%) were men; among them, 39 (54.2%) were negative and 33 (45.5%) were positive for the JAK2 mutation. The data also showed that 15 out of 24 female patients (62.5%) had a positive JAK2 mutation, while in the male patients, 18 out of 48 (37.5%) had the mutation present (p=0.013).

Table 2 shows the information of the patient population by gender without considering the incidence of JAK-2 mutation. The results indicated that there was no significant difference between men and women in any of the investigated parameters. However, the comparison of these parameters without considering the gender and only based on the occurrence of JAK-2 mutation showed that only in the age parameter, there was a significant difference between the two groups; men and women, and with increasing age, the incidence of this disease increases (p=0.024) (Table 3)

Investigations based on the occurrence of JAK2 mutation in the female population also showed that the age parameter in positive and negative groups for the mutation had been significant (p=0.029), so that the age of the negative group was 28.13 ± 13.7 and in positive group it was 53.8 ± 11.8, and in other parameters in female group was not significant (Table 4). However, in the male population, the age of JAK2 positive patients was higher than Negative patients, but there was no significant difference in age and other factors (Table 4). Also, the comparison of all parameters in JAK2 positive mutation patients showed that there was no significant difference in the studied parameters in men and women (Table 5).

Table 3. Comparison of these parameters without gender discrimination based on the occurrence of the JAK2 mutation

Variable	JAK2 Mutation	Mean	Std. Deviation	P-Value
Age	Negative	33.46	18.035	0.024
	Positive	49.18	12.766	
WBC	Negative	8.085	3.1692	0.339
	Positive	9.492	3.8905	
RBC	Negative	5.378	0.8668	0.28
	Positive	5.965	1.6690	
Hb	Negative	15.223	2.7980	0.545
	Positive	16.027	3.6078	
PLT	Negative	368615.38	247101.713	0.319
	Positive	539000.00	541274.607	

Table 4. Comparison of parameters of patients by gender based on the presence or absence of mutation

Gender	JAK2 Mutation		Age	WBC	RBC	Hb	PLT
Female	Negative	Mean	28	9.217	4.927	13.067	441000
		Std. Deviation	13.748	2.4744	0.8593	3.166	273040.29
	Positive	Mean	53.8	10.008	5.648	14.76	716000
		Std. Deviation	11.584	5.5996	2.2462	4.9013	710397.776
	P-Value		0.029	0.829	0.622	0.617	0.554
Male	Negative	Mean	35.1	7.745	5.513	15.87	346900
		Std. Deviation	19.462	3.3876	0.8658	2.4891	250149.933
	Positive	Mean	45.33	9.062	6.23	17.083	391500
		Std. Deviation	13.397	2.1678	1.162	1.9671	353253.309
	P-Value		0.277	0.411	0.179	0.328	0.319

Table 5. Comparison of blood parameters of JAK2-positive patients according to gender

Variable	Gender	N	Mean	Std. Deviation	P-Value
Age	Female	15	53.80	11.584	0.297
	Male	18	45.33	13.397	
WBC	Female	15	10.008	5.5996	0.710
	Male	18	9.062	2.1678	
RBC	Female	15	5.648	2.2462	0.529
	Male	18	6.230	1.1620	
Hb	Female	15	14.760	4.9013	0.312
	Male	18	17.083	1.9671	
PLT	Female	15	716000.00	710397.776	0.349
	Male	18	391500.00	353253.309	

Discussion

The influence of gender on the occurrence of PV has been widely discussed in the literature, though findings remain contradictory. Our study revealed a higher prevalence of PV in women (62.5%) compared to men (37.5%), aligning with reports by Godferi et al. (2013) (9) and Payzin (2014) (10). However, conflicting data exist; for instance, Hamid et al. observed a higher mutation rate in men, with a statistically significant correlation between JAK2 V617F and male gender (11). Conversely, Deadmond et al. reported that PV risk was consistently lower in women across all age groups (12). Some studies further suggest that myeloid disorders are more common in younger females, whereas older males exhibit higher susceptibility (13,14). These discrepancies highlight the need to consider gender-specific differences in genotype-phenotype correlations among JAK2-positive patients, particularly in diagnosis, prognosis, and complication management. Given that gender may influence clonal expansion and JAK2 allele burden variability, future research should explore factors driving mitotic recombination events.

The mean age of JAK2-positive cases in our cohort was 45 years for men and 53 years for women, reinforcing the role of age in PV manifestation, as noted in prior studies (11,15). Notably, women with PV exhibited age-dependent susceptibility, with older patients and elevated hemoglobin (Hb) levels being more prone to the disease (Mean age: 53.8 vs. 28 years in unaffected women). In contrast, male patients presented across a broader age range, suggesting divergent pathogenic mechanisms.

Hematological parameters-including WBC, RBC, Hb, and platelet counts-were significantly elevated in JAK2-positive patients, correlating strongly with the mutation. These findings align with Gulbay et al. (16), who reported marked differences in WBC, Hb, HCT, RDW, and PLT between JAK2 V617F-positive and negative individuals.

Conclusion

Our findings suggest that women with Hb levels above the normal range may be at higher risk for PV, underscoring the importance of early screening in this demographic. Additionally, younger men with elevated Hb should also be monitored for PV. These insights could enhance diagnostic accuracy and prognostic stratification in clinical practice.

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Ethical statement

This study was conducted following the approval of the ethics code (RI.IAU.CHALUS.REC.1401.009) by the Ethics Committee of Islamic Azad University, Chalus branch.

Conflicts of interest

The Authors had no Conflicts of interest

Author contributions

Zeinab Siahmargoie Performing the test; Mohammad Taher Hojjati Supervision, Final validation of the article; Hadi Bazzazi Writing draft of the article and Data analysis; Khodaberdi Kalavi, Data interpretation and technical consultant; Mana Zakeri Writing draft of the article and Statistical analysis; Hadi Joshaghani Clinical consultant and Writing draft of the article.

Data availability statement

All data produced or analyzed during this study are contained within this published article.

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