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# Impact of JAK2 V617F allele burden on clinical and laboratory parameters in polycythemia vera

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## ABSTRACT

**Aims:** To investigate the association between the JAK2 V617F allele burden and clinical and laboratory parameters in polycythemia vera (PV) patients, focusing on its association with thrombotic events, disease severity, and systemic inflammatory markers.

**Methods:** This retrospective study included 71 patients with PV. Data were collected from medical records, including demographics, laboratory values, spleen size, and thrombotic history. Patients were stratified by JAK2 V617F allele burden into subgroups for comparative analysis. Quantitative polymerase chain reaction (PCR) was used to measure allele burden. Statistical analyses were performed using the Mann-Whitney U test, Kruskal-Wallis test, and Spearman correlation, with a significance level of $p<0.05$.

**Results:** The median JAK2 V617F allele burden was significantly higher in women than in men (9.53% vs. 2.00%, p=0.003). Patients with platelet counts ≥400×10$^9$/L had a significantly higher allele burden than those with counts <400×10$^9$/L (8.94% vs. 1.33%, p=0.019). There was no significant association between allele burden and thrombotic events (p=0.549) or splenomegaly (p=0.191).

**Conclusion:** JAK2 V617F allele burden is associated with certain laboratory parameters, including platelet count, and varies by gender in patients with PV. Although not significantly associated with thrombotic events or splenomegaly in this cohort, allele burden remains a potentially valuable biomarker for disease monitoring and individualised treatment.

**Keywords:** Polycythemia vera, janus kinase 2, alleles

## INTRODUCTION

Polycythemia vera (PV) is the most common subtype among myeloproliferative neoplasms, characterized by the clonal proliferation of hematopoietic stem cells. The disease presents with an increase in red blood cell mass, leukocytosis, thrombocytosis, and an increased risk of thrombotic and hemorrhagic complications. The diagnosis is supported by findings such as increased blood cell production, the presence of JAK2 mutations, and bone marrow biopsy results (**Table 1**).[1,2] The pathogenesis and natural course of PV have been better elucidated through understanding the genetic and biological factors associated with disease progression.

PV is driven by constitutive activation of the JAK-STAT signaling pathway due to the JAK2 V617F mutation.[1,2] This pathway activation promotes clonal hematopoiesis and inflammatory cytokine production, contributing not only to myeloproliferation but also to disease related complications. Over time, chronic myeloproliferation may lead to stem cell exhaustion, clonal evolution, and epigenetic alterations, increasing the risk of post-polycythemic myelofibrosis and, less frequently, transformation to acute myeloid leukemia.[1,2]

**Table 1.** Diagnostic criteria for polycythemia vera

| Criterion type | Criteria | Diagnostic thresholds |
|---|---|---|
| Major criteria 1 | Elevated hemoglobin, hematocrit, or red cell mass | - Hemoglobin: >16.5 g/dl (male), >16.0 g/dl (female)<br>- Hematocrit: >49% (male), >48% (female)<br>- Red cell mass: >25% above the predicted normal value |
| Major criteria 2 | Presence of JAK2 mutation | JAK2 V617F or JAK2 exon 12 mutation |
| Major criteria 3 | Hypercellular bone marrow biopsy showing trilineage proliferation (erythroid, granulocytic, and megakaryocytic) without atypia | Not required in cases with hemoglobin >18.5 g/dl (male) or >16.5 g/dl (female) and hematocrit >55.5% (male) or >49.5% (female) with JAK2 mutation |
| Minor criteria | Serum erythropoietin level | Below the normal range |
| Diagnostic requirements | - All major criteria must be met, or<br>- The first two major criteria and the minor criterion must be met | |

The JAK2 V617F mutation, is detected in over 95% of cases and serves as a critical biomarker in diagnosis.[1-3] JAK2 V617F

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allele burden has been linked with both clinical features and prognosis of the disease.[3]

This study aims to investigate the relationship between JAK2 V617F allele burden and clinical and laboratory parameters in PV in greater detail. By focusing on the correlation of allele burden with thrombotic events, disease severity, and systemic inflammatory markers, the study seeks to evaluate the potential role of this biomarker in disease management and prognosis.

## METHODS

This study included 71 patients diagnosed with PV. The diagnostic and clinical data of the patients were retrospectively collected from medical records. The study was approved by the Clinical Researches Ethics Committee of Gazi Yaşargil Training and Research Hospital. (Date: 27.12.2024, Decision No: 283), and informed consent was obtained from all participants. All procedures were followed with ethical guidelines and the tenets of the Declaration of Helsinki. Patients with JAK2 exon 12 mutations were excluded from the study. The diagnosis of PV was made according to the most recent WHO criteria (**Table 1**). At diagnosis, white blood cell count (WBC), neutrophil, lymphocyte, monocyte, hemoglobin (Hb), and platelet (PLT) counts and serum erythropoietin levels were recorded. Spleen size was assessed by abdominal ultrasonography, with lengths over 120 mm considered splenomegaly. A detailed history of thrombosis, including arterial and venous events, was obtained.

The JAK2 V617F mutation was detected and quantified using a Quantitative polymerase chain reaction (PCR)-based method. Genomic DNA was extracted from peripheral blood and PCR amplification was performed using specific primers. Mutation burden was calculated by comparing mutant and total allele products via a standard curve.

### Statistical Analysis

The data analyses were conducted using SPSS Version 25.0. Categorical variables were summarized as frequencies (%), and continuous variables as medians (min–max). The Mann–Whitney U and Kruskal–Wallis tests were used for group comparisons. Correlations were assessed using Spearman's rho, and categorical comparisons with Pearson's Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

## RESULTS

The study included 71 patients with a mean age of 58 years (range: 20–90). Of these, 32 (45.1%) were female, and 39 (54.9%) were male. The median JAK2 V617F allele burden among all patients was 14.42%, which was used as the cutoff value for subgroup comparisons. The median JAK2V617F allele burden was 9.53% (range: 0.5–54%) in females and 2.00% (range: 0.01–25%) in males, a statistically significant difference (p=0.003).

Patients were grouped by age: 46 patients (64.8%) were ≤60 years old, and 25 patients (35.2%) were >60 years old. The median JAK2V617F allele burden in patients >60 years of age was 9.98% (range: 0.01–22.69%), compared to 4.96% (range: 0.01–54.00%) in those ≤60 years of age, a statistically significant difference (p=0.039). Gender distribution did not differ significantly between age groups.

Based on Hb levels, patients were categorized into two groups: 9 patients (12.7%) with Hb <17 g/dl and 62 patients (87.3%) with Hb≥17 g/dl. The median JAK2V617F allele burden was 5.55% (range: 0.50–22%) in patients with Hb <17 g/dl and 8.39% (range: 0.01–54%) in those with Hb≥17 g/dl (p=0.653).

The median WBC count for all patients was $11\times10^9$/L (range: 5.8–$21\times10^9$/L). Patients were divided into two groups: 37 patients (52.1%) with WBC<$10\times10^9$/L and 34 patients (47.9%) with WBC≥$10\times10^9$/L. The median JAK2V617F allele burden was 5.60% (range: 0.01-33.40%) in patients with WBC<$10\times10^9$/L and 8.75% (range: 0.01–54%) in those with WBC ≥$10\times10^9$/L (p=0.180).

The median PLT count for all patients was $528\times10^9$/L (range: 161–$1.134\times10^9$/L). Patients were classified into two groups: 26 patients (36.6%) with PLT <$400\times10^9$/L and 45 patients (63.4%) with PLT ≥$400\times10^9$/L. The median JAK2V617F allele burden was 1.33% (range: 0.01–25%) in patients with PLT <$400\times10^9$/L and 8.94% (range: 0.03–54%) in those with PLT ≥$400\times10^9$/L, a statistically significant difference (p=0.019).

Spleen size was assessed in all patients. Splenomegaly was absent in 55 patients (77.5%) and present in 16 patients (22.5%). The median JAK2V617F allele burden was 9% (range: 0.05–20.25%) in patients with splenomegaly and 4.48% (range: 0.01–54%) in those without splenomegaly (p=0.191). Male patients had significantly larger spleens compared to females (p=0.003), with a mean difference of approximately 4.66 mm.

During the course of the disease, 15 patients (21.1%) had a history of thrombosis, while 56 patients (78.9%) did not. The median JAK2V617F allele burden was 9.09% (range: 0.01–33.4%) in patients with a history of thrombosis and 6.70% (range: 0.01–54%) in those without (p=0.549). Comparison of clinical and laboratory parameters by median JAK2 allele burden is shown in **Table 2**.

## DISCUSSION

The clinical course varies of PV due to genetic and phenotypic heterogeneity. While some patients have a stable disease course, others are at risk of serious complications such as thrombosis, cardiovascular events, myelofibrosis or transformation into acute leukaemia. This variability necessitates personalised disease management and treatment strategies.

In recent years, JAK2 V617F allele burden has emerged as a critical biomarker for understanding the impact of PV on laboratory and clinical parameters. Higher allele burden has been associated with an increased risk of thrombosis, splenomegaly, myeloproliferation, and poor prognosis.[4-6,10] However, the mechanisms underlying these associations and their implications for clinical management remain incompletely understood. A better understanding of the relationship between JAK2 allele burden and clinical and laboratory parameters is essential to improve risk stratification and optimise treatment strategies.

**Table 2.** Comparison of clinical and laboratory parameters by median JAK2 allele burden

| Variables | JAK2 median (min-max) | p |
|---|---|---|
| **Gender, n (%)** | | |
| Female | 9.53 (0.50-54.00) | 0.003 |
| Male | 2.00 (0.01-25.00) | |
| **Age, n (%)** | | |
| ≤60 | 4.96 (0.01-54.00) | 0.039 |
| >60 | 9.98 (0.01-22.69) | |
| **Hb, n (%)** | | |
| <16 | 5.55 (0.50-22.00) | 0.653 |
| ≥16 | 8.39 (0.01-54.00) | |
| **WBC, n (%)** | | |
| <10 | 5.60 (0.01-33.40) | 0.180 |
| ≥10 | 8.75 (0.01-54.00) | |
| **PLT, n (%)** | | |
| <400 | 1.33 (0.01-25.00) | 0.019 |
| ≥400 | 8.94 (0.03-54.00) | |
| **Epo, n (%)** | | |
| <5 | 8.58 (0.01-54.00) | 0.135 |
| ≥5 | 1.92 (0.01-33.40) | |
| **Spleen, n (%)** | | |
| ≤120 | 4.48 (0.01-54.00) | 0.191 |
| >120 | 9.00 (0.05-20.25) | |
| **Thrombosis, n (%)** | | |
| Absent | 6.70 (0.01-54.00) | 0.549 |
| Present | 9.09 (0.01-33.40) | |

Mann-Whitney U test; p<0.05 is considered statistically significant. Min: Minimum, Max: Maximum, Hb: Hemoglobin, WBC: White blood cell count, PLT: Platelet

Studies have demonstrated correlations between JAK2 V617F allele burden and Hb, WBC, and PLT levels. Higher allele burden is generally associated with higher Hb and WBC levels, although the relationship with PLT counts varies across studies. In our study, the median allele burden was 14.42% and we observed a trend suggesting higher Hb levels might be associated with increased allele burden, although the result did not reach statistical significance. Similarly, Vannucchi et al.[4] reported a positive correlation between allele burden and Hb levels. Guglielmelli et al.[5] also found significantly higher Hb levels in patients with increased mutation burden.

Regarding WBC counts, Larsen[6] and Guglielmelli[5] found statistically significant differences in allele burden across different WBC levels. In our study, patients with WBC<$10\times10^9$/L had a lower median JAK2 V617F allele burden compared to those with WBC ≥$10\times10^9$/L, although the difference was not statistically significant. This lack of significance may be attributed to the relatively small sample size in our cohort.

In the analysis of PLT levels, we found that patients with PLT levels <$400\times10^9$/L had significantly lower JAK2 V617F allele burden compared to those with PLT levels ≥$400\times10^9$/L. This finding contrasts with studies by Larsen[6] and Guglielmelli,[5] who reported lower PLT counts in patients with higher allele burdens. Differences in patient populations and disease duration may account for these discrepancies.

Stein et al.[7] investigated the relationship between JAK2 V617F allele burden and gender in chronic myeloproliferative neoplasms, identifying gender as an independent factor influencing allele burden variability. Females were reported to have lower allele burdens than men, potentially due to less frequent mitotic recombination events in females. Similarly, Karantanos et al.[8] and Larsen et al.[6] found that women had lower allele burdens than males, suggesting sex-specific differences in disease biology. Interestingly, in our study, women exhibited significantly higher median JAK2 V617F allele burdens than men (p=0.003). This discrepancy highlights the variability of results between cohorts and underlines the need for careful interpretation. Factors such as sample size, genetic background, and disease duration may contribute to these differences.

Splenomegaly, present in approximately 36% of PV patients at diagnosis, is a significant clinical feature that influences prognosis and treatment decisions.[9] Vannucchi et al.[4] demonstrated a strong association between higher JAK2 V617F allele burden and the presence of splenomegaly, particularly in patients with allele burden >50%. Similarly, Guglielmelli et al.[5] found that palpable splenomegaly was more common in patients with allele burden >50%. In our study, patients with splenomegaly had a higher median allele burden (9.00%) compared to those without splenomegaly (4.48%), although the difference was not statistically significant (p=0.191).

Cardiovascular and thromboembolic events are leading causes of morbidity and mortality in PV. Current treatment strategies aim to prevent thrombotic complications through phlebotomy, low-dose aspirin, and cytoreductive therapy for high-risk patients.[1] Despite adherence to these treatments, thrombotic risk persists. Recent studies have focused on the impact of JAK2 V617F allele burden on thrombosis risk. Guglielmelli et al.[5] reported a higher incidence of venous thrombosis in patients with allele burden >50% compared to those with ≤50%. Similarly, Vannucchi et al.[4] found that an allele burden >75% increased thrombotic event risk. In our study, patients with thrombosis had higher allele burden than those without, although the difference was not statistically significant (p=0.549). The small sample size and the low proportion of patients with a high allele burden may explain this finding.

## Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective design may introduce selection bias. Second, the relatively small sample size, particularly the small number of patients with high JAK2 allele load, may have reduced the statistical power to detect meaningful associations. Additionally, the lack of multivariate analysis prevented the adjustment for potential confounding factors such as age, gender, or treatment status. Finally, the absence of long-term data limits the ability to draw conclusions about prognostic value.

## CONCLUSION

This study highlights the importance of JAK2 V617F allele burden in shaping the phenotypic variability of PV. The results suggest that allele burden may serve as a useful biomarker for predicting disease progression. However, larger cohorts and further research are needed to clarify the relationships between allele burden and clinical outcomes. Future studies should also include gender-specific analyses to improve our understanding of this complex disease.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was approved by the Clinical Researches Ethics Committee of Gazi Yaşargil Training and Research Hospital. (Date: 27.12.2024, Decision No: 283).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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