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# The Association Between Janus Kinase 2 and Factor V Leiden Mutations and Thrombotic Complications in Patients With Myeloproliferative Disorders: A Study From Saudi Arabia

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## Abstract

### Background

The Janus kinase 2 (JAK2) V617F mutations are related to increased thrombotic risk in patients with myeloproliferative disorders (MPDs). However, little is known about whether inherited thrombophilia represents an additive risk factor in mutated subjects. We addressed the association between combined mutations of JAK2 and factor V Leiden (FVL) and thrombotic complications in Saudi Arabian patients with MPDs.

### Methods

We studied 60 patients with MPDs, 32 with polycythemia vera (PV), 24 with essential thrombocythemia (ET), and four with primary myelofibrosis (PMF). All patients were examined for JAK2 V617F and FVL mutations.

### Results

The study included 50 (83.3%) males and 10 (16.7%) females, with a mean age of 44.23 ± 11.32 years. JAK2 was found positive among all (100%) of the studied patients. Thirty-eight patients out of 60 (63.3%) had thrombotic events. FVL was found positive in 12 (20%) patients. The patients with JAK2 and FVL mutations had a higher incidence of thrombotic events (11/38, 28.9%) than those with JAK2 but without FVL mutations (1/22, 4.5%). The relative risk ratios for increased risk for having thrombotic events were 2.1 (95% confidence interval (95% CI): 1.2-3.8, p=0.03) and 4.3 (95% CI: 2.1-9.5, p<0.001) for patients with *JAK2* mutations alone, and those with both JAK2 and FVL mutations, respectively.

### Conclusions

In the present study of patients with MPDs from Saudi Arabia, JAK2 mutations were found among all the studied patients, and FVL mutations were encountered in 20% of patients. The patients with both JAK2 and FVL mutations had a higher incidence of thrombotic events than those with JAK2 but without FVL mutations. The relative risk ratios for increased risk for thrombotic events among patients with MPDs were 2.1 and 4.3 for patients with JAK2 mutations alone and those with JAK2 and FVL mutations, respectively. Further larger prospective studies are warranted.

**Categories:** Genetics, Oncology, Hematology
**Keywords:** factor v leiden, incidence and prognosis, jak2, mutation, myeloproliferative disease, neoplasm, risk, saudi arabia, thrombophilia, thrombosis

## Introduction

Myeloproliferative neoplasms (MPNs) or myeloproliferative disorders (MPDs) are a group of rare blood cancers in which the bone marrow produces excess white blood cells (WBCs), red blood cells (RBCs), or platelets. The World Health Organization (WHO) classified MPNs as blood cancers [1]. As of 2016, the WHO lists the following subcategories of MPDs [2]: chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia (not otherwise specified), and MPN, unclassifiable (MPN-U).

Molecular and genetic studies have shown that the JAK2 V617F is one of the molecular markers of MPDs as

it has been detected in 31.3%-72.1% of patients with ET, 46.7%-100% of patients with PV, and 25.0%-85.7% of those with PMF [3-5]. The close relationship of the JAK2 V617F mutation with chronic MPD has led to the concept of considering it as an important criterion for diagnosing PV and ET [6]. Another interesting topic for the researchers was the role of JAK2 V617F mutations in thrombotic risk among patients with MPDs. This was particularly important as the most common causes of morbidity and mortality in those patients are thromboembolism and hemorrhage [7]. While the majority of evidence suggested that JAK2 V617F mutation increased the risk of thrombosis in patients with MPDs [8-10], some studies reported that the V617F mutation was not associated with increased thrombotic risk in those patients [11].

Factor V Leiden (FVL) is a variant (mutated form) of human factor V, which causes an increase in blood clotting [12]. Consequently, protein C, an anticoagulant protein that usually inhibits the activity of factor V, cannot bind to factor V, leading to a hypercoagulable state [13].

Given the rising prevalence of MPD and its effects on various demographic and ethnic groups worldwide, research for the correlation between the disease's incidence and the presence of two critical mutations (JAK2 and FVL) has become attractive. Previous studies have shown the association of JAK2 mutations alone [4,7,9] or FVL mutations alone [14] with the thrombotic risk among patients with MPD. However, few studies have investigated the effect of the dual burden of the JAK2 mutation and the inherited thrombophilia on the thrombotic in patients with MPDs [15].

Therefore, the present study addressed the association between combined mutations of JAK2 and FVL and thrombotic complications in well-defined Saudi Arabian patients with MPD.

# Materials And Methods

## Study design and population

This is a retrospective study of Saudi Arabian patients admitted to two hospitals (Armed Forces Hospital Southern Region (AFHSR) and Khamis Mushait General Hospital (KMGH), Saudi Arabia) diagnosed with MPD from February to September 2024.

## Data collection

Relevant sociodemographic data (age and gender) and hematological parameters (complete blood count) were retrieved from the electronic medical records. MPD diagnosis and subtyping were performed according to the 2016 WHO guidelines [2]. Key thrombotic events such as ischemic stroke, transient ischemia attacks, myocardial infarctions, angina pectoris, and deep vein thrombosis were reported.

## Procedures

Allele-specific polymerase chain reaction (PCR) was used to detect JAK2 V617F mutation, as shown by Baxter et al. [3]. The genomic DNA was amplified by PCR as per Wolanskyj's procedure [16]. The samples were analyzed, biotin-labeled markers and specialized primers were used for amplification and analysis via the Pyromark Q24 software, and the presence of mutation G to T positioning the V617 position in exon 12 was identified.

The identification of prothrombin (PT) G20210A and FVL polymorphisms was carried out as previously described [17,18]. All the assays were carried out blindly without knowing the patients' clinical backgrounds and diagnoses.

## Ethical considerations

The Armed Forces Hospital Southern Region (AFHSR) Ethical Approval Committee approved the study. The study participants gave written informed consent.

## Statistical data analysis

For nominal values, the chi-square test was used, whereas, for continuous variables, the t-test and ANOVA were utilized. Differences between groups were measured by the $x^2$ test, the Fisher’s exact test, and the Mann-Whitney test, whenever appropriate.

A 2x contingency table was used to identify the relative risk (RR) for thrombosis. The software Statistical Product and Service Solutions (SPSS, version 26; IBM SPSS Statistics for Windows, Armonk, NY) was used to analyze data. A p-value of <0.05 was considered significant.

# Results

## Demographic and clinical features

Sixty patients were enrolled in the study, 50 (83.3%) males and 10 (16.7%) females, aged 19-60, averaging

44.23 ± 11.32 years. PV was the most common disorder detected (53.3%), followed by ET and PMF (40% and 6.7%, respectively). PV and ET were more prevalent among males (50 and 33.3%) than females (3.3 and 6.7%) (Table 1).

| Disorder | Total, n (%) | Males | Females |
|---|---|---|---|
| Polycythemia vera (PV) | 32 (53.3%) | 30 (50%) | 2 (3.3%) |
| Essential thrombocythemia (ET) | 24 (40%) | 20 (33.3%) | 4 (6.7%) |
| Primary myelofibrosis (PMF) | 4 (6.7%) | 0 (0%) | 4 (6.7%) |

**TABLE 1: Myeloproliferative disorder distribution among the studied patients (n=60)**

## Hematological parameters among the studied patients

Table 2 shows the laboratory findings among the studied patients. The mean ± SD of WBCs was 8.51 ± 3.47 × $10^9$/L, ranging from 4.05 to 17.7 × $10^9$/L. The RBCs ranged from 3.28 to 6.9 x $10^{12}$/L, higher than the normal range for men and women.

| Index | Parameter | Statistics | Normal range |
|---|---|---|---|
| WBC (× $10^9$/L) | Mean ± SD | 8.51 ± 3.47 | 4.5 to 11.0 (× $10^9$/L) |
| | Range (Min-Max) | 4.05-17.7 | |
| RBC (x $10^{12}$/L) | Mean ± SD | 5.38 ± 0.87 | Male: 4.0-5.9 (x $10^{12}$/L), Female: 3.8-5.2 (x $10^{12}$/L) |
| | Range (Min-Max) | 3.28-6.9 | |
| PLT (× $10^9$/L) | Mean ± SD | 473.13 ± 246.91 | 150-400 (× $10^9$/L) |
| | Range (Min-Max) | 130-1046 | |
| HB (g/dL) | Mean ± SD | 15.47 ± 2.18 | Male: 13.8-17.2 (g/dL), Female: 12.1-15.1 (g/dL) |
| | Range (Min-Max) | 9.6-18.6 | |
| HCT (%) | Mean ± SD | 45.96 ± 6.39 | Male: 40-54 (%), Female: 36-48 (%) |
| | Range (Min-Max) | 27.4-56.4 | |

**TABLE 2: Hematological parameters among the studied patients (n=60)**

WBC; white blood cells, RBC; red blood cells, PLT; platelet, HB; hemoglobin, HCT; hematocrit

Significant differences were observed between PV, ET, and PMF patients in terms of WBC, platelets, Hb, and hematocrit. There were no significant differences between the patients' subgroups regarding RBCs.

## The prevalence of JAK2 and FVL mutations among MPN patients

JAK2 was found positive among all (100%) of the studied MPD. FVL was found positive in 12 (20%) MPD patients. There were highly significant statistical differences between +ve JAK2 vs -ve JAK2 and +ve FVL vs -ve FVL ($p<0.001$) (Figure 1).

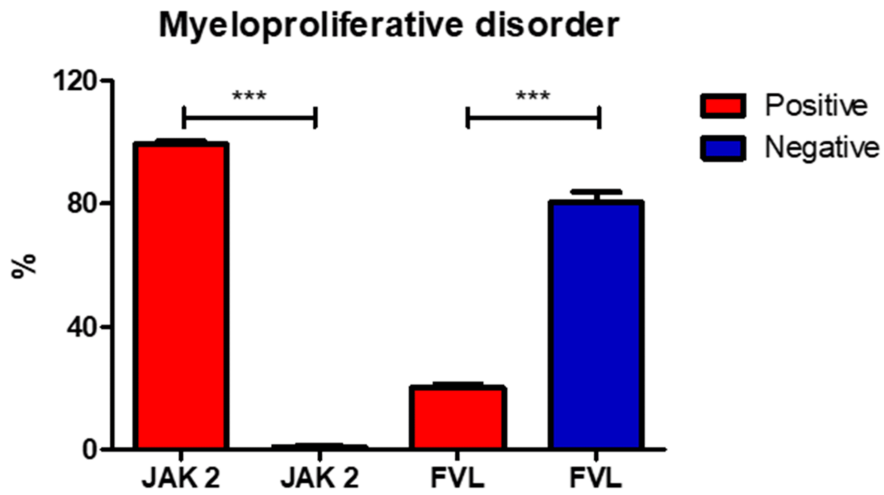


**FIGURE 1: The prevalence of +/- JAK2 and +/- FVL in myeloproliferative disorder patients (n=60)**

***: p<0.001; JAK2: Janus kinase 2; FVL: Factor V Leiden

## The prevalence of FVL among PV and ET patients

FVL was positive among 5% and 40% of PV and ET patients, respectively. There was a significant statistical difference between PV patients with and without FVL (p<0.001) and between ET patients with and without FVL (p<0.010) (Figure *2*).

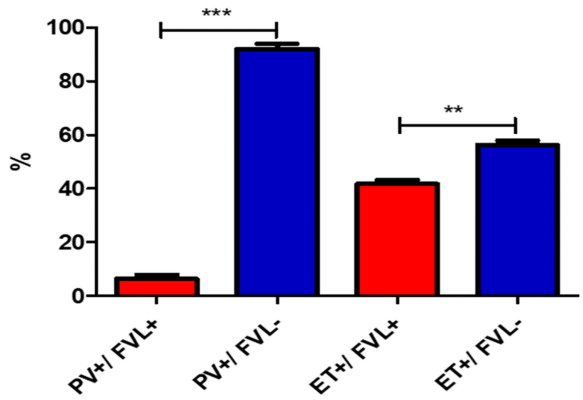


**FIGURE 2: Prevalence of FVL among PV and ET patients**

***: p<0.001; **: p=0.010; PV: Polycythemia vera; FVL: Factor V Leiden; ET: Essential thrombocythemia

## JAK2 and FVL mutations and thrombotic risk

Among patients with both JAK2 and FVL mutations (20% of the total), 11/12 (91.6%) experienced thrombotic events. Those patients had a higher incidence of thrombotic events (28.9%) than those with JAK2 but without FVL mutations (4.5%) (Table *3*).

| Characteristics | Total (n= 60) | Thrombotic event present (n = 38) | No thrombotic event (n = 22) | RR (95% CI) | P-value |
|---|---|---|---|---|---|
| JAK2 Mutation +ve | 60 (100%) | 38/38 (100%) | 22/22 (100%) | 2.1 (1.2-3.8) | 0.03 |
| Both JAK2 and FVL Mutations +ve | 12 (20%) | 11/38 (28.9%) | 1/22 (4.5%) | 4.3 (2.1-9.5) | <0.001 |

**TABLE 3: JAK2 and FVL mutations and thrombotic risk among patients with MPDs**

FVL: Factor V Leiden; JAK2: Janus kinase 2; MPDs: Myeloproliferative disorders; RR: Relative risk

Logistic regression analysis for thrombotic events risk revealed that the RR ratios for increased risk for having thrombotic events were 2.1 (95% confidence interval 1.2-3.8, p=0.03) for patients with JAK2 mutations alone compared to 4.3 (95% CI: 2.1-9.5, p<0.001), for those with both JAK2 and FVL mutations (Table *3*).

## Discussion

The current study is the first from Saudi Arabia to investigate the relationship between the JAK2 V617F and FVL mutation status and their combined effect on thrombotic risk among patients with MPDs.

We found the JAK2 V617F mutations in all MPD patients (100%). The study of Tevet and co-workers included 192 patients with MPDs: 42 with PV, 90 with ET, and 60 with PMF. The authors observed that the JAK2 V617F mutation was present in 62.8% of their cohorts, 54.5 % with ET, 97.6% with PV, and 53.44% patients with PMF [19].

The JAK2 gene mutations have been detected in up to 70% of patients with ET, 95% of patients with PV, and 40-50% of patients with PMF [20]. In the current study, the JAK2 mutations may be overestimated in patients with ET, or the procedures used for their estimation may differ from those used by other studies [20]. Further prospective studies in larger numbers of patients with ET are needed.

Prothrombin G20210A and FLV mutations were found to be the most frequent causes of inherited thrombophilia in the Caucasian populations. We observed that 20% of our cohorts had FVL mutation compared to the typical figures of 3-7% reported in the general populations; this relatively higher incidence of our results might be attributed to the small sample size that amplified the prevalence of this mutation and the fact that patients with MPDs in the current study were more likely to undergo genetic testing for thrombophilia, leading to a higher detection rate.

In this study, FVL was positive among 5% and 40% of PV and ET patients, respectively. There was a significant statistical difference between PV patients with and without FVL and between ET patients with and without FVL. The study of Ruggeri et al. [21] addressed the carriership of FVL mutation and venous thromboembolism (VTE) in 300 patients with PV and ET. The authors found that the prevalence of the FVL mutation in patients with PV and ET was comparable with that in the general population. They observed that FV Leiden mutation was a risk factor for VTE before and at the time of diagnosis and for VTE recurrences [21].

We observed significant WBC, platelets, Hb, and hematocrit differences between PV, ET, and PMF patients. There were no significant differences regarding RBC between the patients' subgroups. Similarly, Gulbay et al. [22] studied the mutational status of JAK2 V617F among 720 patients. They found a significant difference in WBC counts, hemoglobin values, hematocrit values, RBC distribution widths (RDW), and platelet counts in the JAK2 V617F-positive patients. No difference was observed in terms of RBC between JAK2 V617F-positive and negative cases in terms of RBCs.

Myeloproliferative diseases (except chronic myeloid leukemia (CML)) are characterized by thrombotic and hemorrhagic incidents that significantly impact the prognosis and quality of life of those patients. While it is rare in the proliferative stages of PMI, thrombosis is predominant in ET and PV. It was shown that the prevalence rates for significant thrombosis at diagnosis are 10-29% in ET, 34-39% in PV, and 4-7% in PMI. Notably, arterial events were more common than venous thrombotic events [19]. A prior history of thrombosis and advanced age were the most important risk factors for vascular complications [23].

Our results showed that patients with both JAK2 and FVL mutations had a higher incidence of thrombotic events (28.9%) than those with JAK2 but without FVL mutations (4.5%). The relative risks for increased risk for having thrombotic events were 2.1 and 4.3 for patients with JAK2 mutations alone and those with both

JAK2 and FVL mutations, respectively.

These results are in concordance with previous reports [19,24-26]. In the study by Tevet et al. [19], patients with mutations had an RR for thrombosis of 2.9 compared to those “wild-type” patients. In patients with both mutation and thrombophilia, the RR was 3.56 compared to patients with neither mutation nor thrombophilia. In an interesting meta-analysis of 2.436 patients with ET [24], the JAK2 V617F mutation was associated with an increased risk for thrombosis by 1.8-fold.

De Stefano et al. [25] evaluated 132 patients with ET and observed that, in younger patients, the thrombotic risk was higher in patients with JAK2 V617F mutations. The presence of inherited thrombophilia further increased this risk. In the study by Penka et al. [26], the JAK2 mutation was detected in 145 patients with MPN, 27.6% of whom had thrombosis, which was significantly higher than those without (8.0%, p=0.001). Among 78 patients with thrombosis, 25.6% had a positive thrombophilia status. The authors stated that the JAK2 mutation and the presence of additional thrombophilic markers predispose patients with MPN with thrombocythaemia to thrombosis [26]. On the other hand, our results disagree with those of Carobbio et al. [27], who found that the JAK2 V617F mutation did not influence the risk for thrombosis among a cohort of 657 patients with ET. It is to be noted that similarities and differences between these studies could be attributed to the differences in assessment procedures, as well as clinical and demographic characteristics of the studied cohorts and follow-up protocols.

The current study highlights that the combination of JAK2 and FVL mutations is associated with a disproportionately higher thrombotic risk, denoting the potential additive effect of FVL on thrombosis risk in JAK2-positive patients. This finding supports the hypothesis that FVL mutation significantly heightens thrombotic susceptibility in MPD patients already carrying the JAK2 mutation. This could justify further investigation into tailored thromboprophylaxis strategies for double-positive MPD patients for JAK2 and FVL. Notably, myeloproliferative diseases can make it more difficult to accurately determine the relationship between JAK2/FVL mutations and thrombotic events. Other thrombosis risk factors may also exist such as age, smoking, obesity, and comorbidities.

### Limitations

The current study has two limitations: first, it is a retrospective analysis, and second, it enrolled a small number of MPD patients. Therefore, multicenter studies with more significant numbers of MPD patients are warranted.

## Conclusions

In the present study of patients with MPDs from Saudi Arabia, JAK2 mutations were found among all the studied patients, and FVL mutations were encountered in 20% of patients. The patients with JAK2 and FVL mutations had a higher incidence of thrombotic events than those with JAK2 but without FVL mutations. The relative risk ratios for increased risk for having thrombotic events among patients with MPDs were 2.1 for patients with JAK2 mutations alone compared with 4.3 for those with both JAK2 and FVL mutations.

Here, it is to be mentioned that the results of the current study were obtained from enrolled relatively small numbers of cohorts carrying both inherited thrombophilia and the JAK2 V617F mutation. However, the following recommendations are to be advocated: (1) More comprehensive studies with larger patient cohorts need to be conducted to establish a robust association between JAK2 mutation, FVL mutation, and thrombotic risk in patients with MPDs. (2) Genetic testing of JAK2 V617F mutation among MPD patients could be beneficial in identifying any latent MPD in patients with different types of thrombosis. (3) No universal guidelines currently exist to recommend routine workups for thrombophilia in patients with MPDs. However, some clinical recommendations may suggest a targeted approach in specific cases, such as positive family history of thrombotic events, recurrent or unexplained thrombosis, and in women with MPDs who are planning a pregnancy or receiving oral contraceptives.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Acquisition, analysis, or interpretation of data:** Sherif Mohamed, Wafaa S. Sayed, Aws Al-Bayati, Mueed Alharthi

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**Critical review of the manuscript for important intellectual content:** Sherif Mohamed, Aws Al-Bayati, Lina G. Elzubair, Mueed Alharthi

**Supervision:** Sherif Mohamed, Wafaa S. Sayed

**Concept and design:** Wafaa S. Sayed, Lina G. Elzubair

## Disclosures

**Human subjects:** Consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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