JAK2 V617F Mutation in Patients with Thrombosis

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

**Background:** Thrombosis is a major disorder with serious complications. The JAK2 V617F mutation results in constitutive phosphorylation of JAK2 and activation of the cellular proliferation cascade. The present study aimed to clarify the prevalence of JAK2 V617F mutation in patients with thrombosis.

**Subjects and Methods:** This case-control study was conducted on 60 subjects subdivided into 2 groups: 30 healthy subjects as a control group (Group I) and 30 patients diagnosed with thrombosis (Group II). All subjects were subjected to full history taking, and clinical examination and investigated for Molecular detection of JAK2 V617F mutation, FV (Factor V Leiden) – PTH (Prothrombin), and MTHFR (Methylene tetrahydrofolate reductase).

**Results:** There was a statistically significant difference among the studied groups as regards the JAK2 V617F mutation (P value < 0.05, odds ratio = 41.216, 95% C.I. 95% = 2.302 - 738.034, relative risk = 25, 95% C.I. 95% = 1.547- 404.012). This mutation was more significantly associated with venous thrombosis than arterial thrombosis (P = < 0.05).

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**Conclusion:** This study showed a significant association between JAK2$^{V617F}$ mutation and thrombosis with more significant evidence in the venous than the arterial thrombosis.

Keywords: JAK2$^{V617F}$; mutation; thrombosis.

1. INTRODUCTION

"Thrombosis is a disease with multifactorial causes. Genetic and environmental risk factors increase the risk of developing blood clots. It is caused by the Virchow triad interaction (venous stasis, hypercoagulability, and endothelial injury)" [1].

"JAK2 is a cytoplasmic tyrosine kinase that has a role in the signal transduction of multiple hematopoietic growth factor receptors. In patients with splanchnic venous thrombosis, JAK2$^{V617F}$ mutation has been reported as a marker of occult myeloproliferative neoplasms (MPNs). Cytokine-independent myeloproliferative disorders, mobilization of blood cell progenitors, and spontaneous formation of endogenous erythroid colonies were linked to this mutation" [2].

"JAK2$^{V617F}$ is an acquired mutation located on the short arm of chromosome 9. It causes the substitution of valine by phenylalanine at position 617 of the pseudo kinase domain in the JAK2 protein. This mutation is present in polycythemia vera (95%), primary myelofibrosis, and essential thrombocythemia (50-60%)" [3].

This study aimed to clarify the prevalence of JAK2$^{V617F}$ mutation in patients with thrombosis and investigate how far it is added to the thrombophilia screen or not.

2. METHODS

This case-control study was conducted at the Clinical Pathology Department at Tanta University Hospitals, Egypt; between July 2021 to July 2022.

Sixty subjects were enrolled in this study and classified as; Group I: 30 healthy subjects as a control group (18 males and 12 females). Their ages range from (40 - 62) with a mean value of (49.33 ± 5.92). Group II: 30 patients with newly diagnosed venous and arterial thrombosis (20 males and 10 females). Their ages range from (42 - 66) with a mean value of (50.37 ± 5.82). They were selected from the Internal Medicine Department at Tanta University Hospitals, Egypt.

Thrombotic patients include; Venous thrombosis (8 cases with deep venous thrombosis (DVT), 8 cases with portal vein thrombosis (PVT), 4 cases with cerebral vein thrombosis (CVT), and 2 cases with mesenteric vein thrombosis (MVT), and Arterial thrombosis (8 cases with myocardial infarction (MI)). Subjects with hereditary thrombophilia and those with acquired risk factors for thrombosis, e.g., pregnancy, surgery, and immobilization were excluded.

2.1 All Subjects Undergo the Following

1. Full history taking.
2. Complete clinical examination.
3. Imaging studies for diagnosis of cases as follows:
   - Doppler ultrasound for deep venous thrombosis (DVT), and portal vein thrombosis (PVT) cases
   - Computed tomography scan (CT scan), abdominal for mesenteric vein thrombosis (MVT), and cranial for cerebral vein thrombosis (CVT)
   - Electrocardiography and echocardiography for myocardial infarction (MI) cases.
4. laboratory investigations
   - Routine investigation (Complete blood count, Prothrombin time (PT), and activated partial thromboplastin time (PTT))
   - Hereditary thrombophilia exclusion tests
     b- Protein C, protein S, and antithrombin III assays by automated coagulation analyzer [STAGO-CC3304A319].
   - Specific laboratory tests (Detection of JAK2 V617F mutation by real-time polymerase chain reaction by QuantStudio 5 Real-Time PCR System).

2.2 Specimen Collection

7 ml of venous blood was withdrawn under complete aseptic conditions from all participants and divided into two parts; each in a separate tube as follows:
1. 1.8 ml of blood was taken into plastic tubes containing tri-sodium citrate 1/9 by volume (0.1 ml citrate with 0.9 ml blood) for PT, PTT, protein C, protein S, and antithrombin III assays by automated coagulation analyzer [STAGO-CC3304A319].

2. 5 ml of blood was taken in EDTA (ethylenediaminetetraacetic acid) tube for the following:

3. 2 ml for complete blood picture by an automated blood cell counter (ERMA PCE-210 N cell counter), then for peripheral blood film examination.

4. 3 ml was used for DNA extraction for:
   - Molecular detection of JAK2\(^{V617F}\) mutation by real-time polymerase chain reaction (QuantiStudio 5 Real-Time PCR System).

For genotyping, genomic DNA was extracted using G-spin\textsuperscript{TM} total DNA extraction kit according to the manufacturer’s protocol [4]. DNA concentrations were determined by a Nanodrop spectrophotometer for measuring the absorbance at 260 nm (A260) using a quartz cuvette [5].

Molecular detection of JAK2\(^{V617F}\) mutation by real-time PCR for the extracted DNA after exclusion of hereditary thrombophilia was done using: (1) TaqMan Probes for JAK2\(^{V617F}\) mutation detection (Willowfort): Wild type; VIC-5'-TCTC-CACAGACACATA-3' BHQ, Mutant type; FAM-5'-TCCACAGAAACATAC3'-BHQ. (2) Primers flanking the mutant region: forward; 5'-AGCCTTCTCCACAGCATTGTTT-3', reverse; 5'-AGAAAGGATTAGAAAGCTGTAGTT-3'. (3) HERA qPCR Kit (Willowfort, WF1030200X) and deionized nuclelease-free water.

QuantStudio 5 Real-Time PCR System was used with a reaction mixture of 20 μl: [10 μl of HERA qPCR Master Mix, 1 μl of Primer (forward), 1 μl of Primer (reverse), TaqMan Probes: 0.5 μl of wild type and 0.5 μl of mutant type, 3 μl of DNA template (sample) and 4 μl of Nuclease free water]. It was programmed for Pre-cycling heat HERA enzyme activation of DNA polymerase at 95°C for 2 min, followed by 40 cycles of denaturation at 95°C for 10 seconds then annealing at 60°C for 30 seconds, and finally extension at 72°C for 30 seconds.

Hereditary Thrombophilia Screening: FV-PTH-MTHFR Strip Assay was done according to the manufacturer’s protocol by amplification of factor V, prothrombin, and MTHFR gene sequences in vitro from the pre-extracted genomic DNA. Plasma protein C and protein S and antithrombin III levels were assayed by the automated coagulation analyzer [STAGO-CC3304A319] by the colorimetric method for protein c [6] and antithrombin III [7] and by the immuno-turbimetric method for Protein S [6].

2.3 Statistical Analysis

In addition to the descriptive data, statistical analysis was done using IBM Statistical Package for the Social Sciences (SPSS) STATISTIC VERSION 21 PROGRAM. Data were expressed as Range, mean ± standard deviation (SD), and analyzed using the Chi-square (x2) test, the student’s t-test, and Fisher’s exact test to assess the significance of the difference between different parameters. P < 0.05 was accepted as significant.

3. RESULTS

Laboratory assessments of the measured parameters in the different submitted groups are presented in the following tables and figures.

- There was a statistically non-significant difference among the studied groups as regards age and sex (Fig. 1).
- There was a significant difference among the wild and mutant JAK2\(^{V617F}\) patients in the thrombotic group as regard hemoglobin (g/dl), total leukocyte count (10\(^3\)/mm\(^3\)), platelets (10\(^9\)/mm\(^3\)) count splenomegaly (P value = 0.0008, 0.0086, < 0.05and 0.0014) respectively, on the other hand, there was no effect of age and gender (P value = 0.765 and 0.114) respectively. It also showed that JAK2\(^{V617F}\) mutation was more significantly associated with venous thrombosis than arterial thrombosis (P value = < 0.05) (Table 1).
- The clinical data for patients with JAK2\(^{V617F}\) mutation, [30% heterozygous (9 cases) and 10% homozygous (3 cases)], there were higher levels of hemoglobin and platelets count in mutant homozygous patients if compared with mutant heterozygous patients, also there was a high prevalence of venous thrombosis (PVT) and splenomegaly in patients with JAK2\(^{V617F}\) mutation (both heterozygous and homozygous) (Table 2).
Fig. 1. Age and sex distribution among the studied groups

Table 1. Demographic and clinical characteristics of patients with thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Group II (No=30)</th>
<th>Chi-square (x²) test</th>
<th>Fisher exact test</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild type (No=18)</td>
<td>Mutant JAK2V617F (No=12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>1 (5.6%)</td>
<td>1 (8.3%)</td>
<td>0.09</td>
<td>0.765</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>17 (94.4%)</td>
<td>11 (91.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (77.8%)</td>
<td>6 (50%)</td>
<td>2.5</td>
<td>0.114</td>
</tr>
<tr>
<td>Female</td>
<td>4 (22.2%)</td>
<td>6 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15</td>
<td>1 (5.6%)</td>
<td>9 (75%)</td>
<td>15.63</td>
<td>0.00008</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>17 (94.4%)</td>
<td>3 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (10⁷/mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>8 (44.4%)</td>
<td>11 (91.7%)</td>
<td>6.91</td>
<td>0.0086</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>10 (55.6%)</td>
<td>1 (8.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (10⁹/m³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 300</td>
<td>5 (27.8%)</td>
<td>12 (100%)</td>
<td>0.0001</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&lt; 300</td>
<td>13 (72.2%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ve</td>
<td>3\18 (16.7%)</td>
<td>9\12 (75%)</td>
<td>10.21</td>
<td>0.0014</td>
</tr>
<tr>
<td>-ve</td>
<td>15\18 (83.3%)</td>
<td>3\12 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>10\18 (55.6%)</td>
<td>12\12 (100%)</td>
<td>0.01</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Arterial</td>
<td>8\18 (44.4%)</td>
<td>0\12 (0%)</td>
<td></td>
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</tr>
</tbody>
</table>
Table 2. Clinical data for patients with JAK2$^{V617F}$ mutation

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Venous</th>
<th>Spleno</th>
<th>Hb (gm/dl)</th>
<th>WBCs (X $10^3$)</th>
<th>Platelets (X $10^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutant Homozygous</td>
<td>52</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>20.5</td>
<td>19</td>
<td>590</td>
</tr>
<tr>
<td>Mutant Homozygous</td>
<td>50</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>18</td>
<td>11.5</td>
<td>666</td>
</tr>
<tr>
<td>Mutant Homozygous</td>
<td>55</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>17.5</td>
<td>13.5</td>
<td>609</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>48</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>17</td>
<td>18</td>
<td>400</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>66</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>15</td>
<td>15</td>
<td>490</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>49</td>
<td>♂</td>
<td>PVT</td>
<td>Venous</td>
<td>+ve</td>
<td>14.5</td>
<td>14.5</td>
<td>710</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>48</td>
<td>♂</td>
<td>MVT</td>
<td>Venous</td>
<td>+ve</td>
<td>14.8</td>
<td>19</td>
<td>660</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>43</td>
<td>♂</td>
<td>MVT</td>
<td>Venous</td>
<td>-ve</td>
<td>17</td>
<td>11.1</td>
<td>510</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>55</td>
<td>♂</td>
<td>CVT</td>
<td>Venous</td>
<td>-ve</td>
<td>14.2</td>
<td>20</td>
<td>430</td>
</tr>
<tr>
<td>Mutant Heterozygous</td>
<td>44</td>
<td>♂</td>
<td>CVT</td>
<td>Venous</td>
<td>-ve</td>
<td>15</td>
<td>8.5</td>
<td>457</td>
</tr>
</tbody>
</table>

There was a statistically significant difference among the studied groups as regards the JAK2$^{V617F}$ mutation (P value < 0.05) (Fig. 2).

The frequency distribution of JAK2$^{V617F}$ mutation among the thrombotic group (Group II) was 12 (40%) thrombotic patients with Mutant JAK2$^{V617F}$ [30% heterozygous and 10% homozygous] while 18 (60%) thrombotic patients were wild type (Fig. 3).

Table 3. Odds ratio (OR) and relative risk (RR) calculation

<table>
<thead>
<tr>
<th>Observation</th>
<th>95% Confidence Intervals</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (OR)</td>
<td>41.216</td>
<td>2.302</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>25</td>
<td>1.547</td>
</tr>
</tbody>
</table>

P value < 0.05 = significant
There was a 41.216 times higher likelihood of having the JAK2V617F mutation in patients with thrombosis compared to the control group (odds ratio = 41.216, 95% C.I. 95% = 2.302 – 738.034) with a significant level (p= 0.0115). Also, there was a relative risk of 25 meaning that people with JAK2V617F mutation would be twenty-fifth as likely to contract the disease (thrombosis) (relative risk = 25, 95% C.I. 95% = 1.547– 404.012) with a significant level (p= 0.024) (Table 3).

As regards the mean value for Hemoglobin level (g/dl), Hematocrit percent (%), Total Leukocyte Count (10^3/mm^3), and Platelets count (10^3/mm^3), the present study revealed a significant increase in the thrombotic patient group (Group II) if compared to the control group (Group I), P values = (0.0031, 0.0038, < 0.0001 and 0.0067) respectively (Fig. 4).

As regards the mean value for hemoglobin level (g/dl), hematocrit percent (%), total leukocyte count (10^3/mm^3), and the platelets count (10^3/mm^3), the present study revealed a significant increase in the mutant JAK2V617F thrombotic patients if compared to the wild type thrombotic patients, P values = (0.0030, 0.0035, 0.0037 and < 0.0001) respectively (Fig. 5).
Fig. 5. Comparison between the wild and mutant JAK2 V617F patients in the thrombotic group (Group II) with regard to the different laboratory parameters
Abbreviations: Hb = Hemoglobin, TLC = Total leukocyte count, INR = International Normalized Ratio, PTT = Partial Thromboplastin Time, PC = Protein C, PS = Protein S and AT III = Antithrombin III

4. DISCUSSION
The development of thrombosis occurs through the interaction of a combination of factors, such as platelet activation, changes in viscosity and shear stress, increased level of red blood cells, changes in inflammatory cytokines, and activation of white blood cells. The integrity of the endothelium and coagulation factors play a cornerstone in thrombus formation [8].

Janus kinase is a family that consists of 4 members: JAK1, JAK2, JAK3, and TYK2. The role of JAK2 in signal transduction may be disrupted by JAK2 alterations [9].

“The mutation in the JAK2 gene (V617F) has been detected in patients with unexplained thrombosis or thrombosis in unusual sites” [10]. “The identification of the JAK2 V617F mutation appears to be useful in diagnosing patients with idiopathic PVT and may overcome the difficulties of diagnosing MPN in this setting” [11].

The present study showed a statistically non-significant difference between the studied groups regarding sex and age. These results agreed with Ma [12] who stated that there were no significant differences between the age or sex distribution of the two groups in his study. Also, Li et al. [13] study agreed with the present study and stated that there was no significant difference found in the age between patients with and without thrombosis.

The current study showed that there was a statistically significant difference between the studied groups as regards the JAK2 V617F mutation (P value < 0.05), with significantly higher rates of the JAK2 V617F mutation among the thrombotic patients, suggesting that JAK2 V617F mutation may contribute to thrombosis.

In the present study clinical data for patients with JAK2 V617F mutation, [30% heterozygous (9 cases) and 10% homozygous (3 cases)], showed higher levels of hemoglobin and platelets count in mutant homozygous patients if compared with mutant heterozygous patients, also there were significantly high prevalence of venous thrombosis (PVT) more than with arterial thrombosis (P value = < 0.05) and splenomegaly in patients with JAK2 V617F mutation (both heterozygous and homozygous).

These results agreed with the study of González- Montero et al. [9] who mentioned that half of patients (60 cases) with mesenteric and/or portal venous thrombosis diagnosis over a 7-year period showed no secondary cause and had JAK2 V617F mutation.

Dentali et al. [14] agreed with the present work and stated that “there was a high prevalence of the JAK2 V617F mutation among patients with splanchic vein thrombosis. Patients with splanchic vein thrombosis that show no additional signs of hematologic disease other than the JAK2 V617F mutation at the time of
thrombosis have an overt MPN development rate that is high during the follow-up".

Also, the current study results agreed with Regina et al. [15] who concluded that “JAK2V617F mutation has been found in up to 40% of patients with splanchnic venous thrombosis. In contrast, the prevalence of the mutation has been reported to be low and did not exceed 1-5% in patients with non-splanchnic venous thrombosis and without overt MPNs”.

Li et al. [13] investigated “the correlation between the JAK2V617F mutation and thrombosis, their results agreed with current work and concluded that JAK2V617F is an important diagnostic standard in patients with MPN, and has an important clinical significance. We showed that the mutation was found in 44 of 68 patients with MPN (64.7%), including 24 ET, 17 PV, and 3 PMF patients. These results indicate the high incidence rate of the JAK2V617F mutation in patients with MPN. JAK2V617F participates in the development of MPN and is correlated with thrombotic disease in MPN patients”.

Finazzi et al. [16] reported that “the incidence of thrombus in patients with the JAK2V617F mutation is higher than that in patients without this mutation”. Kralovics et al. [17] also reported that “patients expressing the JAK2V617F mutation are more susceptible to complications such as thrombosis”.

“Thrombotic events could occur mainly through an increase of direct activation or endothelium adhesion of blood cells or an over-expression of the JAK2 mutation in endothelial cells” [18].

“There are many studies showing an association of high JAK2V617F allele burden in MPNs with thrombosis” [19,20,21,22].

“The prevalence of the JAK2V617F mutation in patients with venous thrombosis had focused on by several studies. Individuals lacking clinical evidence of MPN showed JAK2V617F positivity ranging from 12% to 74% in splanchnic vein thrombosis” [11,15,23-30].

Furthermore, JAK2V617F mutation was evaluated by other studies in patients with arterial thrombosis (acute myocardial infarction, ischemic stroke, and peripheral arterial thrombosis) and concluded absence or very low prevalence (0.7 – 1%) of JAK2V617F [31-35].

535 patients with arterial thrombosis were evaluated in six studies, and a very low prevalence of JAK2V617F was observed (1.1%; 95% CI, 0.40- 2.29%) [36]. So, the JAK2V617F mutation was not a risk factor for arterial thrombosis, and routine evaluation should not be done for these patients.

In the calculation of odds ratio and relative risk, the current study showed that there was a 41.216 times higher likelihood of having the JAK2V617F mutation in patients with thrombosis compared to the control group (odds ratio = 41.216, 95% C.I. 95% = 2.302 – 738.034) with a significant level (p= 0.0115). The current study also showed that there was a relative risk of 25 meaning that people with JAK2V617F mutation would be twenty-fifth as likely to contract the disease (thrombosis) (relative risk = 25, 95% C.I. 95% = 1.547– 404.012) with a significant level (p= 0.024).

A systematic review evaluated the prevalence of the JAK2V617F mutation (heterozygote and homozygote) in patients with venous thrombosis in usual and unusual sites. Twenty-four studies were included in the systematic review: six case-control studies and 18 retrospective cohort studies, with a total of 3508 patients. Lower limb deep venous thrombosis, splanchnic vein thrombosis, pulmonary embolism, retinal vein occlusion, and CVT were the thromboembolic events observed. The results of this meta-analysis were confined to 4 case-control studies and showed a strong association between JAK2V617F and splanchnic vein thrombosis (OR 53.98; 95% CI, 13.1-222.45) [14]. So, JAK2V617F is suggested as a strong predictor of the diagnosis of latent MPN in this situation. Considering that MPNs are among the most common acquired factors associated with splanchnic vein thrombosis [37], it seems reasonable to include JAK2V617F testing in the routine evaluation of patients with splanchnic vein thrombosis.

Splanchnic vein thrombosis (SVT) cases are thought to have what is frequently termed ‘latent’ or ‘masked’ MPD [15].

Speletas et al. [38] concluded that Homozygous JAK2V617F mutated patients showed significantly more complication and thrombotic risk than heterozygous JAK2V617F mutated patients.

In contrast to the current study results, Kumar et al. [3] conducted a prospective case-control study screening of JAK2V617F mutation and other thrombophilic risk factors on 52 cases of SVT,
and 40 controls. From the total of 52 patients; 2 had MVT, 10 had BCS, and 40 were PVT/EHPVO. The JAK2\textsuperscript{V617F} mutation was seen in two cases. JAK2\textsuperscript{V617F} mutation was observed in 3.8% of SVT patients (lower frequency of mutation).

Singh et al. [39] study, showed a lower prevalence of JAK2\textsuperscript{V617F} mutation (0.67%). This was in concordance with a few other studies worldwide which found that this mutation was either absent or was present at a very low frequency (1%-2%) in patients with thrombosis [32,33,40-42].

Also, Studies that evaluated the JAK2\textsuperscript{V617F} mutation in patients with venous thrombosis have found a very low prevalence (0.1-3%) of JAK2\textsuperscript{V617F} [15,25,32,33,41-44].

Another study found only 8 presented the mutation of 248 patients with CVT, with a mean prevalence of 2.57% (95% CI, 0.97 – 4.91%). Although these results did not reach statistical significance, they do suggest an association [14].

Some authors speculate that, given the rarity of this condition, the small number of patients included in the studies [45]. The most important reason for this variety could be the difference in sensitivity of the techniques used for the detection of JAK2\textsuperscript{V617F} mutation [38].

All these studies further added to the dilemma of whether to include the JAK2\textsuperscript{V617F} mutation screening test in routine thrombophilia screening or not [46,47].

The present study revealed a significant increase in hemoglobin level (g/dl), hematocrit percent (%), total leukocyte count (10\textsuperscript{3}/mm\textsuperscript{3}), and the Platelets count (10\textsuperscript{9}/mm\textsuperscript{3}) in the mutant JAK2\textsuperscript{V617F} thrombotic patients if compared to the wild type of thrombotic patients, with P values = (0.0015, 0.0018, 0.0019 and < 0.00001) respectively.

This agreed with Ma [12] who showed that the mean platelet count was significantly higher in patients with the JAK2\textsuperscript{V617F} mutation than in patients without the mutation with p-value = 0.013. At the same time, there were no significant differences in white blood cell count or hemoglobin levels between the two groups which were against the present work results at these points. JAK2\textsuperscript{V617F} mutation occurs frequently in CVST patients with thrombocytosis, approximately half (47.8%) of the CVST patients with thrombocytosis had the JAK2\textsuperscript{V617F} mutation, suggesting that this mutation is prevalent among these patients.

Edelmann et al. [48] also agreed with the present study and concluded that the JAK2\textsuperscript{V617F} mutation can lead to increased platelet count.

The present study results were also in agreement with Falanga et al. [49] who observed higher platelet and leukocyte activation in JAK2\textsuperscript{V617F}-positive patients. Also, Arellano-Rodrigo et al. and Passamonti et al. [50,51] suggest the association of JAK2\textsuperscript{V617F} with increased platelet and leukocyte activation. Hence, in clinical practice, physicians should be alert to patients with higher platelet counts. Clinical management of these patients may be facilitated by early detection of the JAK2\textsuperscript{V617F} mutation.

In contrast to the current work, Goodyer et al. [52] found a normal peripheral blood count in seven (44%) of 17 cases with JAK2\textsuperscript{V617F}-positive patients. Regina et al. [15] also stated that the two groups (patients and controls) were similar in regard to the peripheral blood count parameters. Thrombosis in JAK2\textsuperscript{V617F} mutation with an absence of erythrocytosis or thrombocytosis could potentially be caused by a possible JAK2-mediated effect with increased platelet and leukocyte activation [11].

5. CONCLUSION AND SUMMARY

The identification of JAK2\textsuperscript{V617F} has a special interest in studying patients with thrombosis, especially venous thrombosis.

This study showed that JAK2\textsuperscript{V617F} mutation was prevalent in 40% of patients with thrombosis and this is more evident in venous than arterial thrombosis.

The present work draws our attention to considering JAK2\textsuperscript{V617F} mutation as a risk factor of thrombosis especially in cases of venous thrombosis at unusual sites.

6. RECOMMENDATIONS

JAK2\textsuperscript{V617F} mutation in the routine investigation for thrombophilia is beneficial and recommended in patients with venous thrombosis at unusual sites.

Patients positive for JAK2\textsuperscript{V617F} mutation should be followed up for the development of myeloproliferative neoplasms (MPNs).
The use of targeted therapy directly against JAK2V617F mutation should be used and could be more effective than the current methods of medication for thrombosis.

ETHICAL APPROVAL AND CONSENT

The study was ethically approved by the Ethical Committee of the Faculty of Medicine, Tanta University (Approval code 36612/6/21). Written informed consent was obtained, and all participants of this study had code numbers to ensure their privacy.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


33. Sène D, Elalamy I, Ancri A, Cacoub P. JAK2V617F mutation is not associated with unexplained recurrent arterial and


51. Passamonti F, Rumi E, Pietra D, Porta MGD, Boveri E, Pascutto C, Cazzola M. Relation between JAK2V617F mutation status, granulocyte activation, and constitutive mobilization of CD34+ cells