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Original Research Article

Deciphering the Relationship Between Janus Kinase -2 (Jak-2) Mutation and Thrombocytopenia

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Abstract: *Hematological parameters, including white blood cells (WBCs), haemoglobin (HB), hematocrit (HCT), and platelet (PLT) levels, play a crucial role in assessing overall health and disease conditions. Understanding their relationships with various influencing factors is essential for refining diagnostic and prognostic evaluations.* **Objective:** *This study aimed to explore the relationships between various haematological parameters, including white blood cells (WBCs), haemoglobin (HB), hematocrit (HCT), and platelet (PLT) levels, and their respective influencing factors. The correlation coefficients (r-values) and p-values were analyzed to determine the strength and statistical significance of these associations.* ***Methods:*** *A correlation analysis was conducted on the haematological parameters. The R-values were calculated to assess the strength and direction of relationships, while the p-values determined the statistical significance. The parameters studied included WBC, HB, HCT, and PLT. The duration of the study was from April 2024 to September 2024.* ***Results:*** *- WBC analysis yielded an R-value of 0.05 and a p-value of 0.034, indicating a positive correlation with statistical significance.- HB analysis showed an r-value of -0.055 and a p-value of 0.604, reflecting a negative correlation that was not statistically significant. - HCT analysis that was also not statistically significant. - PLT analysis produced an R-value of 0.037 and a p-value of 0.727, indicating a negative correlation that was also not statistically significant.* ***Conclusion:*** *The analysis revealed that while the WBCs and AGE showed a statistically significant positive correlation, the other parameters—HB, HCT, and PLT—did not exhibit statistically significant correlations with the variables studied. These findings suggest that the factors investigated have minimal or no meaningful impact on the haematological parameters, warranting further research to identify more significant associations.*

Keywords: White blood cells, Hemoglobin, Hematocrit, Platelets, Correlation analysis, Statistical significance

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Introduction

Myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are clonal hematopoietic stem cell disorders characterized by overproduction of mature myeloid blood cells (1). A key discovery was the JAK2V617F mutation, present in a majority of MPN patients, which constitutively activates downstream signalling pathways, leading to cytokine-independent proliferation (2). The JAK2V617F mutation is found in most patients with polycythemia vera and about half of those with essential thrombocythemia or primary myelofibrosis (3). Thrombocytopenia, defined as a platelet count below 150,000 per microliter, is a common and clinically significant complication in MPNs (4). Thrombocytopenia in MPNs can arise from various mechanisms, including splenic sequestration, increased platelet destruction, or decreased production due to bone marrow fibrosis, often exacerbated by the presence of the JAK2V617F mutation and disease progression (5). JAK2 inhibitors have shown efficacy in treating MPNs by reducing the production of blood cells, but thrombocytopenia remains a significant clinical challenge (6). Understanding the mechanisms driving thrombocytopenia in the context of JAK2-mutated MPNs is crucial for developing targeted therapeutic strategies that improve patient outcomes. The identification of the JAK2 V617F mutation as the primary cause of polycythemia vera (PV) has prompted the creation of various targeted therapies aimed at inhibiting JAK2. These JAK2 inhibitors have shown significant efficacy in patients with myelofibrosis (MF). For patients with PV who do not respond to or cannot tolerate hydroxyurea (HU) or interferon (IFN), or who are suffering from persistent itching, severe systemic symptoms, or pronounced splenomegaly, treatment with a JAK inhibitor may provide substantial benefits compared to traditional therapies.(7)

Patients with thrombocytopenia (low platelet count) may have myelofibrosis (MF), one of the MPNs fibrous tissue, which hinders the production of myelofibrosis often have the JAK2 V617F mutation, which is linked to more pronounced splenomegaly and an increased risk of thrombocytopenia as the disease worsens.

Patients with JAK2 mutations may occasionally experience treatment-related thrombocytopenia or develop it as a result of secondary causes such as splenomegaly, which can sequester platelets. Thrombocytopenia may also be present in patients receiving cytoreductive therapy for MPNs or in patients developing blast-phase disease. Increased bone marrow fibrosis in MPN patients has been associated with the JAK2 V617F mutation; this can have a direct effect on platelet production. This fibrosis may result in thrombocytopenia due to inefficient hematopoiesis.

Methodology

This experimental cross-sectional study utilized non-probability purposive sampling to collect samples from 90 patients with a prescription request for JAK2 (V617F) mutation testing at the Armed Forces Institute of Pathology (AFIP) between April 2024 and September 2024. Inclusion criteria were age 18-90 years and willingness to provide details and family history (consent). Exclusion criteria included other

haematological disorders (e.g., myelodysplastic syndrome, leukaemia) and recent chemotherapy or radiation therapy (within the last 6 months). Data were collected via questionnaires and lab reports. Statistical analysis was performed using SPSS version 25. Descriptive statistics, frequencies, and Pearson's correlation analysis were employed. Phlebotomy was performed following standard procedures, including informed consent, PPE, and sterile technique. DNA was extracted from peripheral blood using an automated extractor (Thermofisher GeneJet Genomic DNA Purification kit). Real-time PCR was performed using SYBRGreen/AVA green dye (Thermo Fisher) with V617F-specific primers.

Forward Primer: 5'-AGCATTTGGTTTTAAATTATGGAGTATATT 3'

Reverse Primer 5'- CTGAATAGTCCTACAGTGTTTTCAGTTTCA 3'

Each PCR batch included positive, negative (NTC), and water blank controls to prevent contamination. Thermal cycling conditions comprised 40 cycles of denaturation at 95°C for 10 minutes, 15 seconds at 95°C, and primer annealing at 60°C.

Results

A total of 90 patients were included in this study. Then Patients were divided into five groups according to their age. In group 15–30 years 23.3% (n = 21), in group 31–45 years 21.1% (n = 19), in group 46–60 years, 28.9% (n = 26), in group 61-75 years, 16.7 %(n=15) and in a group of 76-90 years,10%(n=9). The studied sample was divided into two groups based on gender, consisting of 57.8% (n = 52) males and 42.2% (n = 38) females.

The studied patients were also divided into 7 groups according to their clinical findings: fatigue, shortness of breath, bone pain, flushed skin, headache, hepatosplenomegaly, and night sweats. The highest percentage of patients fell into fatigue (45.46%), headache (21.11%) and shortness of breath (16.67).

Pearson's correlation analysis was performed to measure the direction and strength between the independent variable and dependent variables of this study. The results are shown in table 5.5.

Independent Variable (IV) of this study:

- JAK-2

Dependent Variables (DV) of this study:

- WBCs, Age, Hct, Platelets and, Hemoglobin.

The correlation analysis revealed a significant strong positive correlation between JAK-2 mutation and Age (r = 0.273**, p= 0.009). The relationship between these variables was statistically significant at the 0.01 level. The sample consisted of 90 participants for both variables.

The correlation analysis revealed a positive significant correlation between JAK-2 mutation and WBCs (r = 0.05, p= 0.034). Even though the correlation (r-value) between variables is very weak, the relationship is statistically significant due to the low p-value.

Since the r-value is very close to zero (r= -0.055) and the p-value is not statistically significant (p= 0.604), there is a negative significant correlation between the jak-2 mutation and haemoglobin.

There is a positive significant correlation between the jak-2 mutation and hematocrit as (r=0.115) and (p=0.281).

The correlation between jak-2 mutation and platelets is extremely weak, and the high p-value (p=0.727) suggests that the correlation is not statistically significant.

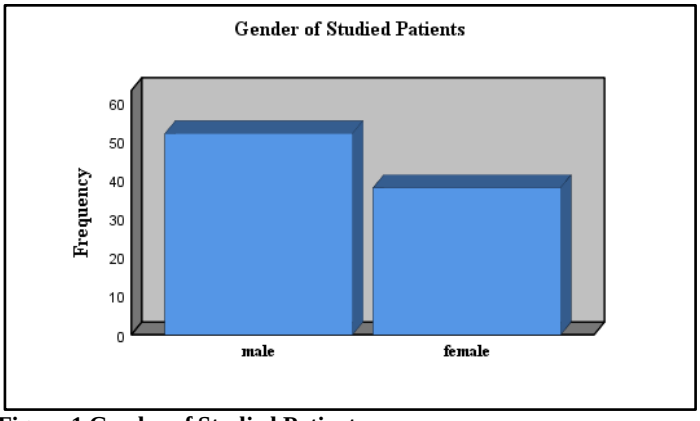

Figure 1 Gender of Studied Patients

Table 1 Age of the Studied Patients

Age Group	Frequency n=90	Percentage%
15-30	21	23.3%
31-45	19	21.1%
46-60	26	28.9%
61-75	15	16.7%
76-90	9	10%
Total	90	100%

Table 2 Clinical Findings of Studied Patients

Clinical findings	Frequency	Percentage
Fatigue	41	45.56%
Shortness of Breath	15	16.67%
Headache	19	21.1%
Bones Pain	4	4.4%
Flushed Skin	3	3.3%
Hepatosplenomegaly	1	1.1%
Night Sweats	7	7.8%
Total	90	100%

Table 3 Correlation Analysis of Continuous Variables

Parameters	N	JAK-2 r-value	Jak-2 P- Value
Age	90	0.01	0.009
WBCs	90	0.05	0.034
HB	90	-0.055	0.604
HCT	90	0.115	0.281
PLT	90	0.037	0.727

Note: n= total number of patients, r = Pearson's Correlation p = Significance value, JAK-2 = Janus Kinase-2, WBCs = White Blood Cells, Hb = Hemoglobin, HCT = Hematocrit, PLT = Platelets

Discussion

The JAK-2 mutation occurs in approximately 0.1-0.2% of the general population. However, the clinical significance of this mutation remains unclear for the individuals who carry it but don't exhibit any obvious signs of a myeloproliferative neoplasm. The study of Neilson, C, Bojesen, S.E., Nordesgaard *et al.* 2014.

The frequency of the JAK2 V617F genetic alteration in individuals with low platelet counts in Pakistan has been examined in different situations, especially when looking at myeloproliferative neoplasms (MPNs) like essential thrombocythemia (ET) and primary myelofibrosis (PMF). An investigation involving 21 individuals with ET found that **61.9%** of them had a JAK2 V617F mutation. This research underscored the significance

of looking for this mutation to distinguish between reactive and clonal thrombocytosis.

Although few detailed research efforts concentrate only on thrombocytopenia linked to JAK2 gene changes in people from Pakistan, the current studies suggest that thrombocytopenia might happen together with these gene changes, especially in more severe types of myeloproliferative neoplasms (MPNs) such as PMF.

In this study, 90 patients were undergone through JAK-2(V617F) mutation test of which 52 were males (57.8%) and 48 were females (42.2%). Out of 90 patients, 17 patients (18.8%) were found positive. Furthermore, the examination of the relationship between JAK2 mutation and various haematological parameters yields noteworthy insights. The association between JAK2 and age indicates a significant positive correlation ($r = 0.0273$, $p = 0.009$), suggesting that the prevalence of JAK2 mutation may slightly increase with advancing age, though the strength of this correlation is minimal. In contrast, no significant correlation is observed between JAK2 and haemoglobin levels, as evidenced by an r-value of -0.055 and a p-value of 0.604, indicating that the mutation does not have a meaningful effect on haemoglobin levels. Additionally, JAK2 shows a statistically significant positive correlation with white blood cell (WBC) count ($r = 0.05$, $p = 0.034$), suggesting a potential link between the mutation and elevated WBC counts, although the strength of this association remains modest. The correlation between JAK2 and hematocrit is positive ($r = 0.115$) but not statistically significant ($p = 0.281$), indicating no reliable connection between the mutation and hematocrit levels in this dataset. Finally, the relationship between JAK2 and platelet count is non-significant ($r = 0.037$, $p = 0.727$), suggesting that JAK2 mutations likely do not exert a significant effect on platelet levels. In summary, while some statistically significant correlations exist between JAK2 mutation and age or WBC count, the mutation does not appear to have a substantial impact on other parameters such as haemoglobin, hematocrit, or platelets. These findings highlight the need for further research with larger sample sizes to validate or demonstrate the observed relationships. This study shows that there is no meaningful significance between JAK-2 mutation and thrombocytopenia as it is also found by Stephen E. Langabeer, Karl Haslam *et al*. 2016.

While this study identified a statistically significant association between JAK2 mutation and both age and WBC count, the observed correlations were weak, suggesting that JAK2 mutation status explains only a small portion of the variability in these parameters. Furthermore, we found no statistically significant relationship between JAK2 mutation and haemoglobin, hematocrit, or platelet levels. These results may reflect the influence of additional, unmeasured factors on haematological parameters in MPNs. The study's cross-sectional design prevents us from establishing causality, and the lack of stratification by disease subtype or other biomarkers limits our ability to assess the JAK2 mutation's impact within specific MPN subgroups.

Conclusion

The analysis indicates a notable yet weak relationship between JAK2 mutations and both age and white blood cell (WBC) count. In contrast, haemoglobin, hematocrit, and platelet levels do not exhibit statistically significant correlations with the JAK2 mutation. The observed weak correlations among these variables imply that the JAK2 mutation may not consistently influence these haematological parameters within the studied population, or that additional co-factors could be affecting the variability of these results. Subsequent research could aim to stratify the population based on disease subtype, severity, or other biomarkers to investigate potential subgroups where the effects of the JAK2 mutation may be more significant.

RECOMMENDATION

It is crucial to conduct longitudinal studies to better understand causal relationships and changes over time, as this would provide a more comprehensive view of the phenomena under investigation. Increasing the sample size is also essential; larger and more diverse samples can enhance the generalizability of the findings and reduce the impact of potential biases. Additionally, employing random sampling techniques can help ensure a more representative population, allowing for more robust conclusions. Future studies should also consider utilizing mixed-method approaches, incorporating qualitative data to gain deeper insights into participants' perspectives. Finally, researchers should be mindful of the timing of data collection and consider factors that may influence responses, which could improve the relevance and applicability of the findings. By implementing these recommendations, future research can expand upon the findings of this study and provide a more comprehensive understanding of the subject.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRBEC-HMCAD-0399-24)

Consent for publication

Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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