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Interplaying Correlation of Some Genetic and Inflammatory Factors among Patients with Polycythemia Vera

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ABSTRACT

Background: Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by the overproduction of red blood cells. A key feature of PV is the dysregulation of cytokine networks, with elevated levels of various pro-inflammatory cytokines contributing to disease progression. The JAK2 mutation, a common genetic driver of PV, stimulates the production of these cytokines, leading to increased cell proliferation, inhibited apoptosis and inflammation. Estimation of IL-12 and IL-21 Level and study the correlation between of theses cytokine with JAK2 V617F and hematological parameters.

Methods: This study investigated 60 patients diagnosed with polycythemia vera (PV) at the National Center of Hematology between January 2023 and July 2024. The patient group consisted of 33 females and 27 males, with ages ranging from 18 to 75 years. Detection JAK2 V617F using Poly chain reaction (PCR) as well as estimation of IL-12 and IL-21 by sandwich ELISA technique.

Result: In this Study 31 of PV patients detected as JAK2 V 617F Negative while 29 patients were positive. Also, this study examined the role of IL-12 and IL-21 in polycythemia vera (PV). Patients with the JAK2 V617F mutation had significantly higher IL-12 levels, suggesting a strong association. However, no significant differences were found in IL-21 levels between groups. Additionally, WBC count and platelets count were positively correlated with IL-21.

Key words: Il-12, Il-21, Jak2 V617f, Polycythemia vera.

INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by hyperproliferation of erythroid progenitors. Mutation in the JAK2 gene is a common genetic driver of PV, leading to constitutive activation of downstream signaling pathways. The clinical manifestations of PV include thrombotic complications, symptoms associated with increased blood viscosity, disease progression to secondary myelofibrosis or acute leukemia (Barbui *et al*., 2023; Tefferi *et al*., 2021). The incidence rate of PV is higher in women than men, with a rate of o.68-2.6 cases per 100000 people per year. PV is uncommon people younger than 60 and the average life expectancy after diagnosis is 14 years (Cacemiro *et al*., 2020; Spivak *et al*., 2014). PV is considered an onco-inflammatory disease bec ause PV patients exhibit augmented levels of several pro-inflammatory cytokines (Cacemiro *et al*., 2020). He bones marrow microenvironment serves as a milieu to produce cytokines and growth factors, which significantly impact the regulation of cellular survival, proliferation, differentiation and immune responses (Jahandideh *et al*., 2020; Abass *et al*., 2025). The understanding of cytokine function has not only led to the development of supportive therapies, such as Erythropoietin (EPO), but also plays a crucial role in the diagnosis of certain hematopoietic disorders. For instance, the subnormal serum EPO level is one of the minor criteria for polycythemia vera (PV) according to the WHO 2008 classification. This suggests that the dysregulation of cytokines can be a valuable biomarker in the identification of these disorders (Vardiman *et al*., 2010).

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Elevated levels of inflammatory cytokines have been reported in all entities of classical MPN and could be consider as prognostic factor for survival patient IL-8, IL-2R, IL-12 and IL-15 (Tefferi *et al*., 2011; Vaidya *et al*., 2012). Furthermore, cytokine levels in myelofibrosis have been shown to predict response to treatment with pomalidomide (Pourcelot *et al*., 2014; Pardanani *et al*., 2011) and JAK inhibitor therapy-induced down regulation of

pro-inflammatory cytokines has been correlated with response in constitutional symptoms (Rentschler *et al*., 2022; Verstovsek *et al*., 2010). Number of cytokines have been studied in patients with myeloproliferative neoplasms (MPNs). Among these, several have shown potential connections to the progression of all types of MPN or have been linked to prognosis. These include IL-1β, TNF-α, IL-6, IL-8, VEGF, PDGF, IFNs and TGF-β. While other cytokines like IL-1α, IL-2Ra, IL-11 and MIP-1 have been investigated, their role in MF progression or prognosis is less clear (Wang *et al*., 2019). The equilibrium between pro-inflammatory and anti-inflammatory cytokine effects is crucial for maintaining no rmal physiological functions. Imbalances can le ad to organdys function or diseases. In the context of myelopro liferative neoplasms (MPN), abnorm alities in cytokine networks have been documented, highlighting their critical role in disease pathology (Hoe rmann *et al*., 2015). In polycythemia vera, there is an observed elevation in various cytokines, including IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL17, EGF,etoxin, FGF-b, GM-CSF, IFNγ, MCP1, PDGF-BB, TNFα, VEGF, HGF and erythropoietin (EPO). This complex cytokine profile under scores the intricate network of immune responses involved in the patho physiology of the disease (Holdsworth *et al*., 2015). JAK2-mutated hematopoietic progenitor and stem cells (HPSCs) secrete IL1β, TNFα, IL-12 and IFNγ, among other proinflammatory cytokines, which provide a survival advantage to the mutated HPSCs and serve as promoters of mutagenesis (Waksal *et al*., 2024). Understanding the role of cytokine network dys regulation in PV is essential for developing effective therapeutic strategies. Targeting specific cytokines or their signaling pathways may offer promising avenues for treating these complex disorders.

MATERIALS AND METHODS

Subjects

Sixty myeloproliferative (MP) patients diagn osed with polycythemia vera (PV) were clinically and laboratory diag nosed at the National Centre of Hematology, Mustansiriyiah University, between January 2023 and July 2024. Among these patients, 33 were female and 27 were male, with ages ranging from 18 to 75 years. The diagnosis was based on the 2008 World Health Organ ization classification Vardiman *et al*. (2009). Additionally, 30 healthy individuals served as the control group. This study designed as case control.

Inclusion criteria

Patients diagnosed with PV, age between 18 to 75, JAK2V617F positive and Negative.

Exclusion criteria

Other MPN patients, Age under 18 and pregnant women.

Sample collection

Peripheral blood samples from each patient and control group were collected by venipuncture using a disposable 10 ml syringe and it was drawn into two tubes, one of EDTA tubes for CBC, Blood picture and DNA extraction and other of plan tubes which subjected to centrifugation (2000 rpm for 15 minutes) to collect sera that were employed in IL-12, IL- 21 and EPO assessments.

DNA Extraction

EDTA blood sample was used to extract genomic DNA according to the manufacturer's instruction of Promega Corporation/USA; by using wizard genomic DNA purification kit.

Polymerase chain reaction (PCR)

To detect the *JAK2* V617F (499 pb) mutation, DNA was amplified in exon 14 by using ARMS-PCR technique (Table 1 and 2).

Assessment of IL-12, IL-21 and EPO

The level of IL-12 and EPO (R&D/USA) and IL-21 (Elabscience/China) were determined by an enzyme-linked immunosorbent assay (ELISA). The principal method was Sandwich ELISA and the concentrations of Cytokines were determined with a standard curve derived from known amounts of the relevant cytokine using absorbance readings at 450 nm on a spectrophotometer (ELISA reader) (Mindray/China) .

Statistical analysis

The statistical analysis was conducted using the software package SPSS IBM Corp., Released 2021. IBM SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY). Demographic data were characterized

Table 1: The JAK2 V617F primers sequences (IDT, Korea).

Primer name	Primers sequence 5′ to 3′	Tm	pmol/µg
Forward outer (FO)	TCCTCA GAACGTTGATGGCAG	54.2	230
Reverse outer (RO)	ATTGCTTTCCTTTTTCACAAGAT	48	228
Forward inner wild type (Fwt)	GCATTTGGTTTTAAATTATGGAGTATATG	52.9	197
Reverse inner mutant (Rmt)	GTTTTACTTACTCTC	55.1	338

Table 2: Thermal cycler condition for PCR amplification to detection JAK2 V617F using thermal cycler (Bio-Rad C1000 , USA).

Gene	Initial denaturation	Denaturation	Annealing	Extension	Final extension
		Repeat cycle 40 more times			
JAK2 V617F	94C°/6 min	94C°/40sec	56 C°/40sec	72 C°/50 sec	72 C°/10min

using descriptive statistics, mean, percentage, ratio and T-test. Estimated p-values<0.05 were considered significant.

RESULTS AND DISCUSSION

Finally, the amplified PCR products were to electrophoresis using 1% agarose gel with red safe (0.5 µg/ml) (Promega/ USA) for 30 minutes (10 Volts/cm^2) using gel electrophoresis instrument (Media/korea). A100 bp DNA ladder (Promega/ USA) was employed to assess the PCR product size. The products were Visualized under UV light at 336 nm using UV documentation (Germany).

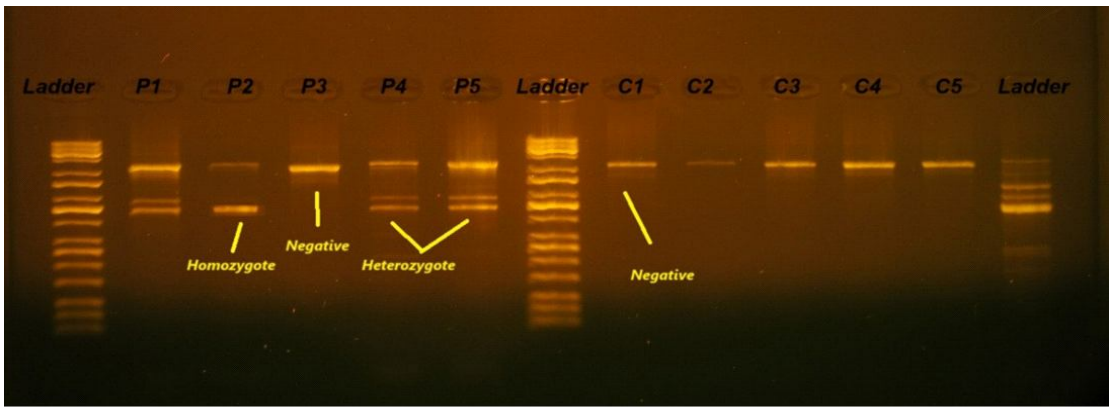
This study is conducted on 60 patients with PV, after detection of JAK2 V617 F mutation, 31 (51.67%) patients of them were negative JAK2 617F, while the rest 29 (48.33%) patients were positive Fig 1, along with those patients, 30 healthy looking persons are enrolled to act as control group with matched age and gender. The age mean showed non-significant differences between control group (51±14 year) and patients (50.42±313.4). Also, female to male ratio in PV patients is 1.22, thus the distribution of female to male ratio in control group (1.3) is conducted to be matched with that in patients and with non-significant difference Table 3.

Estimation levels of IL-12 , IL-21 and EPO

In this study comparing the level of IL-12 and IL-21 between control and JAK2 V617F positive and negative groups, significant differences were found. The control group (n=30) had IL-12 levels of 92.9±12.6, while the positive group (N=29) and negative group (N=31) had markedly higher level 262±109.1 and 266±135.9 respectively, with p-value <0.001. Similarly, IL-21 level were 329.4±56.9 in the control group, 348.5±128.9 in the positive group and 413±176.4 in the negative group, also with p-value 0.116. These findings suggest a strong correlation between JAK2 V617F mutation and increased IL-12 while no correlation with IL-21 levels. The EPO levels are significantly lower in the JAK2 V617F-positive group (2.7±1.20) compared to both the JAK2 V617F-negative group (19.8±7.56) and the control group (10.8± 2.8). This difference is statistically significant with a p-value of less than 0.001.

In summary, the JAK2 V617F-positive group exhibits significantly lower EPO levels than the other two groups. Table 4.

The study included 60 participants, 31 of whom were negative for the JAK2 V617F mutation. Among the 29 positive individuals, IL-12 levels were found to be 266.3±135.9, also



The upper band of 279 bp showing the presence of the mutation. The second band of 229 bp confirms the presence of amplifiable DNA. (P) patient (C) control. The Lane P1,2,4,5, showed JAK2 mutation. Lane P3, C1 to C5 are non-mutated, using 1% agarose for 30 min at 5 volt /cm.

Fig 1: Detection of the JAK2V617F mutation in peripheral blood of polycythemia vera.

Table 3: Baseline characteristic of study groups.

Characteristic	PV		Control		p-value
Number (%)	60		30		
Age (mean±SD)	50.42±13.4		51±14		0.825
JAK2V617F negative	31 (51.67%)	Ratio	30		
JAK2V617F positive	29 (48.33%)	1.07			
Female	33 (55%)	Ratio			
Male	27 (45%)	1.22	17 (56%)	Ratio	
			13 (44%)	1.3	
WBC × 10^9 /L Mean ±SD	12.6±5.0		7.6±2.2		<0.001
Platelets × 10^9 /L Mean±SD	313±171		248±49.4		0.089
Hb g/dl	16.3±2.6		13.6±1.2		<0.001
HCT %	49.6±8.7		41.3±3.7		<0.001

IL-21 levels were non significantly differences at 348.5±128.9 compared to the negative group (262.1±109.1 and 413±176.4, respectively). The p-value for IL-12 and IL-21 was 0.897, 0.145 respectively, indicating no significant difference. The level of EPO shows significant differences between JAK2 V617F positive and Negative groups (p<0.001) (Table 5).

In comparison the levels of IL-12, IL-21 and EPO between a treated group (n=23) and an untreated group (n=37). The mean IL-12 level in the treated group was 290±123.2, while in the untreated group it was 250.5±121.4. This difference was not statistically significant (p=0.23). The mean IL-21 level in the treated group was 367.6±123.6 and in the untreated group it was 387.2±178.4. This difference was also not statistically significant (p=0.06). In order to EPO, the mean EPO level in the treated group was 12.7±8.72 and in the untreated group it was 10.6±9.71. This difference was also not statistically significant (p=0.459) (Table 6).

The study examined the relationship between blood parameters (WBC, HB, HCT and platelets) and the cytokines IL-12 and IL-21. While WBC levels were weakly positively correlated with IL-12 (r = 0.346, p = 0.640), they were significantly positively correlated with IL-21 (r = 0.289, p = 0.026). Hemoglobin and hematocrit levels showed no significant associations with either cytokine. Interestingly, platelet levels were positively correlated with IL-21 (r = 0.813, p = 0.001) but not with IL-12 (r = 0.085, p = 0.522). The cytokines themselves, IL-12 and IL-21, were not significantly correlated (r = 0.119, p = 0.368). The correlation between EPO and WBC is not statistically significant (r = 0.247, p = 0.059), while the correlation between EPO and HB is statistically highly significant correlation (r = 0.34, p = 0.008). Also the correlation between EPO and HCT and Platelets are statistically significant correlation (r = 0.281, p = 0.031; r = 0.320, p = 0.014). Finally there were no statistically significant correlation among EPO, IL12 and IL21 , (Table 7).

JAK2 V617F is associated with clonal hematopoiesis, genomic variation, dysfunction in hemostasis and immune response. JAK2 V617F Variant is a high frequency in PV, leading to constitutive activation of the JAK-STAT signaling pathway and increased proliferation of hematopoietic cells (hasan *et al*., 2024; Hameed *et al*., 2024; Alyasiri *et al*., 2024). Several studies have reported elevated levels of various cytokines, including IL-6, IL1-2, IL-17, IL-18, VEGF, TNF-α and TGF-β, in PV patients. These cytokines may contribute to the development of thrombotic complications and disease progression(Patterson *et al*., 2023).IL-12 and IL-21: These cytokines play important roles in immune regulation and inflammation. IL-12 is a potent inducer of Th1 cell differentiation and IFN-γ production (Ullrich *et al*., 2020; Yahya *et al*., 2024). while IL-21 is involved in B-cell and T-cell activation (Biewenga *et al*., 2022). The findings of this study provide valuable insights into the complex interplay between genetic factors, cytokine dysregulation and clinical manifestations in PV. The increased IL-12 levels in both JAK2 V617F-positive and negative patients suggest that this cytokine may play a broader role in the pathogenesis of PV than previously recognized. Previous studies illustrated that IL-12 are potential biomarker of onco-inflammatory cytokine and may contributes to disease development and progression (Jain *et al*., 2021; Cattaneo *et al*., 2021; Al-Maliki *et al*., 2024). The lack of a significant association between IL-21 levels and JAK2 V617F mutation status suggests that IL-21 may not be a primary driver of

Table 4: Comparison of IL-12, IL-21 and EPO levels among control, JAK2 V617F-Positive and JAK2 V617F-Negative Groups.

Parameters	JAK2 V617F N=60		Control N=30	P-value
	Negative N=31	Positive N=29		
IL-12	266.3±135.9	262.1±109.1	92.9±12.6	<0.001
IL-21	413±176.4	348.5±128.9	329.4±56.9	0.116
EPO	19.8±7.56	2.7±1.20	10.8±2.8	<0.001

Table 5: Comparison of IL-12 , IL-21 and EPO levels between JAK2 V617F-Positive and JAK2 V617F-Negative Groups.

Parameters	JAK2 V617 F N=60		P-value
	Negative N=31	Positive N=29	
IL-12	266.3±135.9	262.1±109.1	0.897
IL-21	413±176.4	348.5±128.9	0.145
EPO	19.8±7.56	2.7±1.20	<0.001

Table 6: Comparison of IL-12, IL-21 and EPO Levels between treated and untraded groups.

Parameters	Polycythemia vera N=60		P-value
	Treated N=23	Untreated N=37	
IL-12	290±123.2	250.5±121.4	0.23
IL-21	367.6±123.6	387.2±178,4	0.06
EPO	12.7±8.72	10.6±9.71	0.459

Table 7: Relationship among study parameters.

Parameter		IL12	IL21	EPO
WBC	Pearson correlation	0.346	0.289*	0.247
	p-value	0.64	0.026	0.059
HB	Pearson correlation	0.151	0.126	0.340**
	p-value	0.254	0.343	0.008
HCT	Pearson correlation	0.076	0.134	0.281*
	p-value	0.565	0.311	0.031
Platelets	Pearson correlation	0.085	0.813**	0.320*
	p-value	0.522	0.001	0.014
IL-12	Pearson correlation	1	0.119	0.184
	p-value		0.368	0.163
EPO	Pearson correlation	0.184	0.03	1
	p-value	0.163	0.79	

*. The correlation is significant at the 0.05 level.**. Correlation is significant at the 0.01 level.

have indicated that *in vitro* differentiated human megakaryocytes express the receptor for IL-21 (IL-21R), an immunostimulatory cytokine associated with inflammatory disorders and currently under evaluation in cancer therapy. It is possible that IL-21 may have a role in regulating megakaryopoiesis or platelet function (Pesce *et al*., 2020: Behrens *et al*., 2018). In current study the level of EPO in JAK2 V617F positive group lower than JAK2 617F Negative group with significant result ($p<0.001$). Cells carrying the JAK2 V617F mutation exhibit increased sensitivity to erythropoietin (EPO), a hormone that stimulates red blood cell production (Benbarche *et al*., 2017; Dupont *et al*., 2007). In some cases, cells with the JAK2 V617F mutation can become independent of EPO, meaning they can proliferate and differentiate into red blood cells even in the absence of EPO. This further contributes to the overproduction of red blood cells in PV patients. This heightened sensitivity leads to excessive red blood cell production (Lanikova *et al*., 2016). As a result of the increased red blood cell mass and the autonomous proliferation of erythroid cells, the body's demand for EPO decreases. This leads to lower serum EPO levels in PV patients, which can be used as a diagnostic marker for the disease (Yoon *et al*., 2024). The lack of a significant impact of treatment on cytokine levels suggests that current therapies may not effectively target the underlying inflammatory processes in PV. Future studies should explore novel therapeutic strategies aimed at modulating cytokine production or signaling pathways to improve clinical outcomes. Targeting cytokine signaling pathways may offer a novel therapeutic approach for PV. For example, JAK inhibitors, such as ruxolitinib, have shown efficacy in reducing disease burden and improving clinical outcomes in PV patients (Verstovsek *et al*., 2012: Braun *et al*., 2010).

CONCLUSION

This study provides indication for the involvement of IL-12 in the pathogenesis of polycythemia vera, regardless of JAK2 V617F mutation status. Further research is needed to elucidate the accurate mechanisms by which IL-12 promotes disease development and progression. Additionally, the potential role of IL-21 in regulating platelet function permits further investigation. The lower EPO levels in JAK2 V617F-positive patients are consistent with the known mechanisms of JAK2 V617F-mediated EPO hypersensitivity and independence. The lack of significant impact of treatment on cytokine levels highlights the need for novel therapeutic strategies that target underlying inflammatory processes.

Conflict of interest

All authors declared that there is no conflict of interest.

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