

## IL-4 Serum Level Estimation in Myeloproliferative Neoplasm Patients

Ahmed Rushdi Abdullah

Medical Microbiology Department / Medical College / Al-Iraqia University / Baghdad - Iraq

Corresponding author: [rushdihoeif@gmail.com](mailto:rushdihoeif@gmail.com)

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### Abstract

**Back Ground:** Myeloproliferative neoplasm (MPN) is a long-term blood disease that has an excess production of mature hematopoietic pluripotent stem cells in the bone marrow. In the early fifties, W. Dameshek structured the Myeloproliferative disorders that are at present the World Health Organization (WHO) changed it to Myeloproliferative Neoplasms (MPNs). According to the Iraqi cancer registry, Chronic Myeloproliferative disorders in the male is 0.62% and the incidence rate is 0.36, in female Chronic Myeloproliferative disorders (45 case) is 0.31% and the incidence rate is 0.24. The *JAK2-V617F* genetic mutation is approximately seventy percent of the Myeloproliferative Neoplasm cases. Interleukin-4 plasma and serum levels are significantly increased in MPNs different types.

**Objectives:** The goal of this study is to estimate the IL-4 serum levels in the *JAK2-V617F* negative and positive mutation in the Iraqi MPNs patients.

**Materials and Methods:** Total of (60) patients screened by cohort prospective study of having MPN who are patients presented to the National Center of Hematology / Al-Mustansiriyah University. Depending on the *JAK2-V617F* genetic mutation we classified our MPNs cases into 3 groups: *JAK2-V617F* negative (N: 20), *JAK2-V617F* positive (N: 40) and control group (10). Blood sample (5) ml was obtained from each individual in each group, by venipuncture using disposable syringes for IL-4 serum estimation by Enzyme Linked ImmunoSorbent Assay (ELISA) technique.

**Results:** A clear indication of significant differences was observed between IL-4 serum level in *JAK2-V617F* negative samples and control samples ( $P < 0.05$ ).

**Conclusion:** The IL-4 serum level is high in MPNs patients, which is one of the immune evading mechanisms of the cancerous acting to imbalance the Th1/Th2 ratio and enhancing the anti-apoptotic activity inside those cells.

**Keywords:** Myeloproliferative Neoplasm (MPN), IL-4 serum levels, *JAK2-V617F* mutations.

### Introduction

Myeloproliferative neoplasm (MPN) is a long-term blood disease that has an excess production of mature hematopoietic pluripotent stem cells in the bone marrow. In MPN, there is unusual increase in the output of a specific cell kind. So, MPN includes an incorrect equilibrium in the output of various hematocytes kinds, also unusual output of any given blood cell kind (1). In the early fifties, W. Dameshek structured the Myeloproliferative disorders that are at present the World Health Organization (WHO) changed it to Myeloproliferative Neoplasms (MPNs). Philadelphia chromosome positive - Chronic myeloid leukemia (CML) and 3 Philadelphia chromosome negative: Primary Myelofibrosis (PMF), Essential Thrombocythemia (ET), and Polycythemia Vera (PV) are 4 classical kinds of Myeloproliferative Neoplasms (2).

In US, It is more common in males that suffer from 2.4 new cases / 100,000 while in females it's about

1.4 new cases / 100,000. The 5-year survival rate of MPNs patients is approximately 67.6%, and the fatality median age is approximately seventy seven years (3). According to Iraqi cancer registry, Chronic Myeloproliferative disorders in male is 0.62% with incidence rate of 0.36, while, in female the Chronic Myeloproliferative disorders (45case) is 0.31% and incidence rate is 0.24 (4).

Janus kinase (JAK) 2 is a protein kinase that can add a phosphate group to the signal transducer which will cause the activation of the JAK-STAT route, which ends with expression of several hematopoietic growth factor genes, its mutation cause the development of Myeloproliferative Neoplasms (5). The *JAK2-V617F* genetic mutation is approximately seventy percent of Myeloproliferative Neoplasm cases. This somatic mutation can cause changing of Valine to phenylalanine at codon 617 (*JAK2-V617F*) presented in pseudo kinase domain. The repetition of the *JAK2-V617F* genetic mutation can be presented

approximately ninety five percent in PV, fifty to seventy percent in ET, and forty to fifty percent in PMF. In five percent of *JAK2-V617F* negative individuals with PV, there is *JAK2* exon 12 genetic mutation; but, in ET and PMF there is no such mutation presented (6).

Interleukin 4 (IL-4) is an interleukin cause changing of the naive T helper cells (Th0 cells) to T helper 2 cells. Then T helper 2 cells output more this cytokine using a positive feedback mechanism. Basically the cells that produce IL-4 has not been recognized, but novel researches proposed that may be basophils are those cells. (7)

## Materials and Methods

### Sample collection

Sixty patients were screened by cohort prospective study of having MPN who are patients presented to the Al-Mustansiriyah University / National Center of Hematology, Patients were given their consent verbally, the age of the MPNs patients ranged from thirty to seventy two years old, thirty five males and twenty five females, the methods of diagnosis for MPNs patients including (PV, ET, PMF) depend

### Detection of IL-4 levels by ELISA

ELISA kit (RayBio® - P05112) was applied by using the manual of instructions. In short, the microtiter plate was previously covered with an antibody targeting IL-4 then standards and samples were added to the microtiter plates wells. A biotin-conjugated antibody prepared particularly to IL-4 and avidin conjugated to Horseradish peroxidase (HRP) was poured to every well. After incubation, 3, 3', 5, 5' tetramethyl-benzidine (TMB) substrate solution put in all wells. Specifically, the wells hold interleukine-4 biotin-conjugated antibody avidin going to show an alteration in the dye. The enzyme substrate reaction was stopped by adding (according to the manual), 3 M sulphuric acid solution then the dye alteration was measured by a spectrophotometer (ASYS, Australia) with a

IL-4 has several biological actions, like the activation of B-cell and T-cell proliferation, also the changing of B cells into plasma cells. It is the important organizer in both cellular and humoral immunity. Its cause B-cell class switching to IgE and stimulation of MHC class II production. IL-4 suppresses the outcome of macrophages, T helper 1 cells, IFN-gamma, dendritic cell and IL-12. Excessive amounts of IL-4 can be seen in allergic diseases (8). Many researchers found that Interleukin-4 serum and plasma level is significantly increased in different MPNs types (9)

The goal of this study is to estimate IL-4 serum levels in both *JAK2-V617F* negative and positive mutation in the Iraqi MPNs patients.

on; abdominal ultrasound, complete blood picture, blood film, biochemical, molecular (*JAK2-V617F* mutation), and bone marrow aspirate and biopsy investigations. Depending on the *JAK2-V617F* mutation, we classified the patients into 3 groups: *JAK2-V617F* negative (N: 20), *JAK2-V617F* positive (N: 40) and control group (N: 10). Blood sample (5) ml was obtained from each individual in each group, by venipuncture using disposable syringes for IL-4 serum estimation.

wavelength of 450 nm  $\pm$  2 nm. Finally, IL-4 concentration was estimated by matching the optical density of each sample to the standard curve.

### Data Analysis

SPSS were used as descriptive statistics in addition to differences tests using the t test, and the relationships were studied through correlation coefficient.

## Results

### Demographic Data

The age was ranged (30 - 72) years, with 35 men and 25 women, diagnosed as MPN patients including (PV, ET, PMF) as illustrated in Table 1.

Table 1: Demographic Data

Total No. of MPN cases	Age range	Sex		No. of JAK2 V617F positive Group	No. of JAK2 V617F negative Group	No. of control group
		Male	Female			
60	30 – 72	35	25	40	20	10

**Descriptive Statistics of the IL-4 serum level in all MPN groups and the control group**

In Table 2 the mean of IL-4 serum level in all MPN samples (1941.9833±4298.22256) while the

mean of the control samples was (143.0000±117.18077). Obviously, the dispersion data of IL4 serum level in all MPN samples was higher than that in the control samples.

Table 2: Descriptive statistics of IL-4 serum level in all MPN groups and the control group

Variable	n	Mean±SD	95% (C.I.) for Mean	
			Lower Bound	Upper Bound
IL-4 serum level in all MPN groups	60	1941.9833±4298.22256	831.6347	3052.3320
Control	10	143.0000±117.18077	59.1739	226.8261

**Measure the differences between IL-4 serum level in all MPN groups and the control group**

A t-test was used in the case of two independent samples to determine whether there was a difference between IL-4 serum level in all MPN samples and the control samples. Table 3 presents

the results of the test, where the value of t is 1.315 with significant level (P > 0.05). A clear indication was of no significant differences between IL-4 serum level in all MPN samples and the control samples.

Table 3: t test study between IL-4 serum level in all MPN groups and control group

Variable	Mean± SE	t	DF	Sig. (2-tailed)
IL-4 serum level in all MPN groups and control group	1798.98333±1367.59801	1.315	68	0.193

**Descriptive Statistics of IL-4 serum level in JAK2-V617F positive group and the control group**

In Table 4 the mean of IL-4 serum level in JAK2-V617F positive samples was

(2491.0750±5186.76229) while the mean of the control samples was (143.0000±117.18077). Obviously, the dispersion data of IL-4 serum level in JAK2-V617F positive samples was higher than of the control samples.

Table 4: Descriptive statistics of IL-4 serum level in JAK2-V617F positive group and the Control group

Variable	n	Mean±SD	95% (C.I.) for Mean	
			Lower Bound	Upper Bound
IL-4 serum level in JAK2-V617F positive group	40	2491.0750±5186.76229	832.2679	4149.8821
Control group	10	143.0000±117.18077	59.1739	226.8261

**Measure the differences between IL-4 serum level in JAK2-V617F positive group and the control group**

A t test was used in the case of two independent samples to determine whether there was a difference between IL-4 serum level in JAK2-

V617F positive samples and the control samples. Table 5 presents the results of the test where the value of t is 1.420 with significant level ( $P > 0.05$ ). A clear indication was of no significant differences between IL-4 serum level in JAK2-V617F positive samples and the control samples.

**Table 5: t test study between IL-4 serum level in JAK2-V617F positive group and the control group**

Variable	Mean± SE	t	DF	Sig. (2-tailed)
IL-4 serum level in JAK2-V617F positive group and the control group	2348.07500±1653.05998	1.420	48	0.162

**Descriptive Statistics of IL-4 serum level in JAK2-V617F negative group and the control group**

In Table 6 the mean of IL-4 serum level in JAK2-V617F negative samples was

(843.8000±493.67021) while the mean of the control samples was (143.0000±117.18077). Obviously, the dispersion data of IL-4 serum level in JAK2-V617F negative samples was higher than the control samples.

**Table 6: Descriptive statistics of IL-4 serum level in JAK2-V617F negative group and the control group**

Variable	n	Mean± SD	95% (C.I.) for Mean	
			Lower Bound	Upper Bound
IL-4 serum level in JAK2-V617F negative group	20	843.8000±493.67021	612.7552	1074.8448
Control Group	10	143.0000±117.18077	59.1739	226.8261

**Measure the differences between IL-4 serum level in JAK2-V617F negative group and the control group**

A t test was used in the case of two independent samples to determine whether there was a difference between IL-4 serum level in JAK2-

V617F negative samples and control samples. Table 7 presents the results of the test where the value of t is 4.391 with significant level ( $P < 0.05$ ). A clear indication was of significant differences between IL-4 serum level in JAK2-V617F negative samples and control samples.

**Table 7: t test study between IL-4 serum level in JAK2-V617F negative group and the Control group**

Variable	Mean± SE	t	DF	Sig. (2-tailed)
IL-4 serum level in JAK2-V617F negative group and Control group	700.80000±159.58782	4.391	28	0.000

**Measure the differences between IL-4 serum level in JAK2-V617F positive group and IL-4 serum level in JAK2-V617F negative group**

A t test was used in the case of two independent samples to determine whether there was a difference between IL-4 serum level in JAK2-V617F positive samples and IL-4 serum level in

JAK2-V617F negative samples. Table 8 presents the results of the test where the value of t is 1.411 with significant level ( $P > 0.05$ ). A clear indication was of no significant differences between IL-4 serum level in JAK2-V617F positive samples and IL-4 serum level in JAK2-V617F negative samples.

**Table 8: *t* test study between IL-4 serum level in JAK2-V617F positive group and IL-4 serum level in JAK2-V617F negative group**

Variable	Mean± SE	<i>t</i>	DF	Sig. (2-tailed)
IL-4 serum level in JAK2-V617F positive group and IL-4 serum level in JAK2-V617F negative group	1647.27500±1167.35118	1.411	58	0.164

### Discussion

Onco-inflammation indicates a relationship between tumor and its microenvironment proposing how much important this relation in the beginning and growing of tumors. (10,11) Actually MPNs generally characterized by modified activity of the immune system, expansion of myeloid-derived suppressor cells, increased monocyte/macrophage compartment, dysfunction of natural killer and T CD4+ cells, and abnormal frequency of regulatory T cells. (12)

Increased plasma levels of multiple interleukins and chemokines has been seen in all MPNs in contrast to control groups. That means an inflammatory mechanism might have a role in the physiopathology of MPNs, as chemokines and interleukins act in paracrine, autocrine and endocrine patterns, and may impact the hematopoietic microenvironment which manifested by increased level of IL-4 in all patient groups. (13) Which supported Also by Vaidya, *et al.* who showed by multiplex bead-based assaying and multivariable analysis, the increased plasma levels of thirteen interleukins like interleukin-4 was related to the decreased survival in a group of 127 PMF and 65 PV patients. (14)

All of the above studies supported our results, which showed obviously an increased mean of IL-4 serum level in All MPNs and both *JAK2-V617F* Negative and positive patients groups comparing to the control which are reported also in other researches. (15-18)

MPNs usually observed with a disorganization of the immune system, and tumor immune evading mechanisms which both collaborated in the evolution and development of the disease. (19)

In fact, cancer patients usually show an elevated Interleukin-4 level in the cancer microenvironment, and their lymphocytes. Peripheral blood lymphocytes or tumor infiltrating lymphocytes were generally

stimulated to produce other Th2 cytokines, as well as IL-4. Shurin, *et al.* abbreviated several clinical studies which inspected the Th2/ Th1 equilibrium in tumor cases. They discovered that interleukin-4 and other Th2 interleukins were generally up-regulated in cases of different kinds of tumors, for example non-small lung cancer, renal cell cancer, colon cancer, prostate cancer, breast cancer and other kinds of cancers (20). Onishi, *et al.* saw that the interleukin-4 quantities at tumor location were related to the grade and stage of the kidney cancer (21).

Yet lately, interleukin-4 was known to be engaged in tumor invasion and growth. Multiple actions have been characterized, for example the safeguard of cancer cells from programmed death by the stimulation of the anti-apoptotic proteins like survivin which is an apoptosis inhibitor protein (BIRC-5). BIRC-5 stimulated significantly in all three MPNs types. The high serum or plasma level of IL-4 in patients with MPNs may be the main participating element for lowering apoptosis by stimulating several anti-apoptotic factors, including survivin. (22,23) Also, IL-4 secreted by M2 macrophage which is well known that it's non-functional against the tumor cells. All these evidences may explain why IL-4 is serum level increased in our study.

In this study a significant differences seen between IL-4 serum level in *JAK2-V617F* negative samples and control samples which supported by many studies which explained that the prime interleukins are released separately of MPN-linked mutations with manifestation that *JAK2-V617F* might be delayed incident in MPN progression are stable assuming that long-term activation of myelopoiesis (via inflammation) can forego procurement of genetic mutation in the *JAK-2* (*CALR* and *MPL?*) genes in the types of MPNs cases. Also some researchers declared that in MPNs, an absence of engagement seen between the *JAK2-V617F* load and serum or blood estimations of those interleukins. Actually, so likely that it is only a part of those interleukins

is guided by JAK2-V617F such as interleukin 4, which plentiful released by other than hematopoietic (nonclonal and nonmutated) cells(24).

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### Conclusions

The IL-4 serum level is high in MPNs patients, which is one of the immune evading mechanisms of the cancerous acting to imbalance the Th1/Th2 ratio and enhancing the anti-apoptotic activity inside those cells. Increased IL-4 serum levels are independent of the JAK2 status because the JAK2-V617F mutation might be a delayed incident.

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## تقدير مستوى IL-4 في مصل مرضى الاورام التكاثرية النخاعية

أحمد رشدي عبد الله

فرع الاحياء المجهرية الطبية / كلية الطب / الجامعة العراقية/ بغداد -العراق

Corresponding author: [rushdihoief@gmail.com](mailto:rushdihoief@gmail.com)

## الملخص

خلفية عن الموضوع : ورم التكاثر النقوي (MPN) هو مرض دم طويل الأمد ينتج عنه زيادة في إنتاج الخلايا الجذعية الناضجة المكونة للدم في نخاع العظم. في أوائل الخمسينيات من القرن الماضي ، قام و. دمشق بتكوين اضطرابات تكاثر النخاع التي هي في الوقت الحاضر منظمة الصحة العالمية (WHO) غيرتها إلى الأورام التكاثرية النقوية (MPNs). وفقاً لسجل السرطان العراقي ، فإن معدل الإصابة باضطرابات التكاثر النقوي المزمن عند الذكور يبلغ 0.62% ومعدل الإصابة 0.36 ، في حالة الاضطرابات التكاثرية النقوية المزمنة لدى الإناث (45 حالة) 0.31% ومعدل الإصابة 0.24. تمثل الطفرة الجينية JAK2-V617F حوالي سبعين بالمائة من حالات الأورام التكاثرية النخاعية. حيث لوحظ زيادة مستويات البلازما والمصل للإنترلوكين 4 بشكل كبير في أنواع مختلفة من MPNs. الهدف من البحث: هدفت هذه الدراسة الى تقدير مستويات IL-4 في الطفرة السلبية والإيجابية للجين JAK2-V617F في مصل مرضى MPNs العراقيين.

المواد وطرق العمل: فحص ما مجموعه (60) مريضاً من خلال دراسة جماعية مستقبلية لوجود MPN من المرضى الذين قدموا إلى المركز الوطني لأمراض الدم / الجامعة المستنصرية. اعتماداً على الطفرة الجينية JAK2-V617F ، صنفت حالات MPNs تحت الدراسة إلى 3 مجموعات هي : JAK2-V617F سلبية (N: 20) ، JAK2-V617F إيجابية (N: 40) ومجموعة التحكم (N: 10). تم الحصول على عينة دم (5) مل من كل فرد في كل مجموعة ، عن طريق بزل الوريد باستخدام محاقن يمكن التخلص منها لتقدير مصل IL-4 بتقنية الفحص المناعي المرتبط بالإنزيم (ELISA).

النتائج: شوهد مؤشر واضح على وجود فروق ذات دلالة إحصائية بين مستوى مصل IL-4 في العينات السلبية للجين JAK2-V617F و عينات التحكم ( $P < 0.05$ ).

الاستنتاجات : مستوى المصل IL-4 مرتفع في مرضى MPNs ، وهو أحد آليات التهرب المناعي للسرطان الذي يعمل على عدم توازن نسبة Th1 / Th2 ويعزز النشاط المضاد للاستماتة داخل تلك الخلايا.

الكلمات المفتاحية: الاورام التكاثرية النقوية ، انترلوكين 4 ، الطفرة الجينية JAK2-V617F.