# Estimation of the level of serum IL-40 and IL-41 in Chronic Myeloid Leukemia of Iraqi Patients

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**Abstract**

**Background:** Chronic Myeloid Leukemia (CML) is a type of cancer that affects the blood and bone marrow. It is characterized by the overproduction of myeloid cells and is often associated with a specific genetic mutation known as the Philadelphia chromosome.

**Objective:** Determine the levels of IL-40 and IL-41 in the serum of Iraqi patients with CML disease and their function in determining disease severity.

**Methods:** The quantified ELISA was used to assess the levels of IL-40 and IL-41 in serum from 35 persons in Baghdad, Iraq, who had been diagnosed with CML. In addition, control samples from thirty healthy individuals were taken for comparison purposes

**Results:** Serum IL-40 and Serum IL-41 were significantly higher in the CML group compared to control 6.95±0.57 pg/ml *vs* 2.94±0.45pg/ml for serum IL-40, and 60.37±3.91pg/ml *vs* 35.59±6.29pg/ml for serum IL-41. A significant correlation appeared between IL-40 and IL-41in serum with $r = 0.90$; $p < 0.001$. Both tests showed excellent performance with 100% Sensitivity, Specificity, Accuracy, and area under the curve.

**Conclusion:** Patients with CML showed high serum levels of IL-41 and IL-40, which may correlate with disease severity and act as biomarkers for chronic myeloid leukemia.

**Keywords:** Cytokines, Chronic myeloid leukemia, IL-40; IL-41, Immune response.

## Introduction

Is a myeloproliferative disorder arising in the haemopoietic stem cell (HSC) compartment (1). This disease is characterized by a reciprocal t(9;22) chromosomal translocation, resulting in the formation of the Philadelphia (Ph) chromosome containing the BCR-ABL1 gene (2). CML most commonly manifests in a chronic phase of the disease with neutrophilic leukocytosis, and the demonstration of the Philadelphia chromosome is the ultimate confirmation of the diagnosis (3). The BCR-ABL1 protein is a constitutively active tyrosine kinase activity that forges the pathogenesis of CML (4). This aberrant kinase signaling activates downstream targets that reprogram the cell to cause uncontrolled proliferation and result in myeloid hyperplasia and 'indolent' symptoms of chronic phase CML (1). Patients with CML may present with constitutional symptoms including fatigue, weight loss, and night sweats. Splenomegaly is fairly common and can result in abdominal pain and fullness (5). Hepatomegaly may be present and

splenomegaly reflects extramedullary hematopoiesis. In developed countries, more and more patients are diagnosed incidentally, when an abnormal complete count blood (CBC) obtained for an unrelated reason leads to a diagnostic workup (2). Blast crisis (BC) remains the major challenge in the management of chronic CML. The sequel of continued BCR-ABL activity leads to genetic instability, DNA damage, and impaired DNA repair (6).

Cytokines are small secreted proteins (<40 kDa), produced by nearly every cell to regulate and influence immune response. The release of pro-inflammatory cytokines will lead to the activation of immune cells and the release of further cytokines (8).

However, recent research indicates that a simultaneous release of pro- and anti-inflammatory cytokines is mandatory in any immune response (9). There are two newly focused cytokines, IL-40 and 41. Interleukin 40 is a proinflammatory cytokine produced by the C17orf99 gene (RF) (10). It is an identified cytokine associated with B cells that were first introduced by Catalan et al. in 2017 (11) This cytokine has several roles in the body, including functions in the formation of B cells in the bone marrow, IgA production, and expression in the intestinal microbiome (10) Moreover, IL-40 appears to be involved in numerous autoimmune and inflammatory conditions, such as rheumatoid arthritis, systemic lupus erythematosus, primary Sjogren's syndrome, ankylosing spondylitis, type 2 diabetes, Graves' disease, and hepatic cell carcinoma (12) Our understanding of this molecule is quite restricted due to its novelty. However, because of its inflammatory characteristics, there is a high probability that it contributes to a variety of inflammatory disease complications (10)

Interleukin (IL-41) is expressed in tissues such as mucosa, skin, adipose tissue, respiratory tract, and macrophages, it is associated with several immune and metabolic diseases (14). Numerous studies have shown that IL-41 is associated with psoriasis, itchy nodular rash, actinic keratosis, and rheumatoid arthritis (RA) (14), it is decreased in inflammatory bowel disease, Graves' disease and is elevated in Kawasaki disease, gout, psoriatic arthritis, and RA. These findings suggest the potential role of IL-41 in abnormal immune responses. An increase of IL-41 in the serum is also associated with the disease activity of RA (16)

Previous studies have shown that immune cells produce IL-4 and IL-17A, which stimulate macrophages to produce IL-41, while IFN-γ inhibits IL-41 production. This suggests that IL-41

may be involved in Th1, Th2, and Th17 immune responses (15) Recent studies have shown that IL-41 is closely associated with several metabolic, inflammatory, and autoimmune diseases. Jung found that IL-41 can alleviate inflammation and insulin resistance through AMP-activated protein kinase or proliferator-activated receptor δ-dependent signal pathways in skeletal muscle (17) The inflammatory response plays a significant role in HUA, and several authors have reported that IL-41 exerts anti-inflammatory effects in various disease states (14)

Because little is known about the role of IL40 and 41 in CML. This study aimed to determine serum levels of IL-40 and IL-41 in a sample of Iraqi patients with CML was analyzed to find their role in disease severity. Furthermore, the relationship between IL-40 and IL-41 levels in patients according to the clinical baseline and laboratory data was evaluated. This investigation may clarify the functions of IL-40 and IL-41 in the CML pathophysiology.

## Methods

The case-control subjects of this study were conducted between July /2024 and October/ 2024, to investigate the potential role of IL-40 and IL-41 and their serum level. Participants were recruited from a private hospital in Baghdad. A total of 30 participants were included in the study, diagnosed with CML by consultant hematologists based on several laboratory tests. Along with 30 healthy controls denoted as (Control)/(CO) for brevity. Also, the group was not sex-matched, they were matched based on age. They were queried using the Health Activity Index, HFAI (Health-Friendly Activity Index). Consent was obtained and participants provided information about their family medical history, outlining risk and general information

## Collection of Sample

Venous blood samples (3mL) were collected from diagnosed CML patients and control subjects after obtaining a comprehensive medical history. The blood samples were transferred to a gel tube and centrifuged at 3000 rpm for 10 min. Subsequently, the serum was placed in 1.5mL Eppendorf tubes and stored in the freezer at –20°C. The serum was then analyzed for the serum-aimed markers in the International Center for Training and Development, utilizing the Enzyme-Linked Immunosorbent Assay (ELISA) technique.

## Outcome measurements

The levels of IL-40 and IL-41 in the blood of both patients and healthy people were determined using sandwich ELISA kits from BT LAB/China. These kits are intended for the quantitative measurement of human IL-40 and IL-41.

**Statistical analysis**

The data was analyzed statistically using IBM's SPSS v27 software. The results are reported as mean±standard error (SE); after data processing, the Duncan test was performed to establish statistical significance (i.e., when the p-value was less than 0.05).

**Results**

CML disease affects all age groups; here, the youngest patient was eight years old, while the oldest was 63. de la Fuente et al., (2014) (20) found that chronic myeloid leukemia in children and young people is a relatively rare form of leukemia that shows increased incidence with age. Some evidence suggests that the molecular basis differs from that in adults.

The randomly collected leukemia group included 32 patients, of whom 27 % were males and 73% were females. The mean age for the patient group was 24.26 years. The control group comprised 53 participants, of whom 60 % were males and 40 % were females, its mean age was 25.71 years.

Based on the findings, the total occurrence of CML was significantly greater in females than males. The results of this study were in disagreement with Radivoyevitch et al., (2014) as they proposed that males have a higher risk of developing CML or a shorter latency from initiation to diagnosis of CML (21). Also, in a series of diagnosed CML patients reported by Rohrbacher and Hasford, (2009)) (22), they found that the proportion of Philadelphia (Ph)/BCR-ABL-positive chronic myeloid leukemia (CML), was more frequent in males than in females.

**Determination of IL40 levels in the serum of group specimens**

Although, little research has evaluated the level of IL-40 and IL-41 in chronic myeloid leukemia. The present study result in Table 1 revealed statistically significant differences between the studied groups < 0.001. The mean concentration of IL 40 in the leukemia group was 6.95±0.57 pg/ml, while in the control group 2.94±0.45 pg/ml, and there are

**Table 1. Illustrates the descriptive statistics value of serum IL-40.**

| Marker | Leukemia | Control | P Value |
|---|---|---|---|
| | mean± SD | mean± SD | |
| IL-40 | 6.95±0.57 | 2.94±0.45 | < 0.001 |
| Median | 6.82 | 2.98 | |
| 75 % Percentiles | 7.37 | 3.30 | |
| 25 % Percentiles | 6.42 | 2.63 | |

On the other hand, the predication curve Figure 1 indicates the association of this interleukin with this disease through the following output; the serum IL-40 presents excellent performance with a cutoff of 4.90, Sensitivity of 100%, Specificity of 100%, true positive predictive value of 100%, true negative predictive value of 100%, AUC of 1.00, accuracy of 100%, and P value < 0.001.

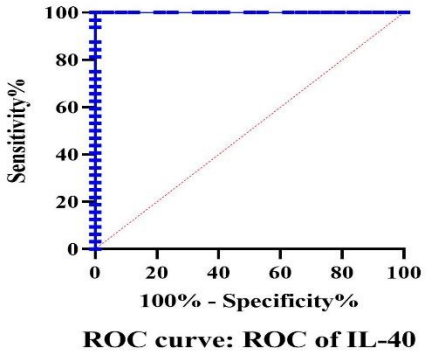


**Figure 1: Reciprocal Operation Curve of Interleukin-40**

**Determination of IL41 levels in the serum of group specimens**

The results in **Table 2** show the significant descriptive statistics ($p \leq 0.001$) of serum IL-41 level, the mean concentration in the leukemia group was 60.37±3.91 pg/ml, while in the control group 35.59±6.29 pg/ml.

**Table 2. Illustrates the descriptive statistics value of serum IL-41.**

| **Serum IL-41** | **Leukemia** | **Control** | **P value** |
|---|---|---|---|
| **Mean±SD** | 60.37±3.91 | 35.59±6.29 | < 0.001 |
| **Median** | 60.83 | 33.72 | |
| **75 % Percentiles** | 61.87 | 35.90 | |
| **25 % Percentiles** | 59.91 | 32.82 | |

On the other hand, the predication curve Figure 2 indicates the association of interleukin 41 with this disease through the following data; the serum IL-41 presents excellent performance with a cutoff of 56.9, Sensitivity of 96.6 %, Specificity of 96%, true positive predictive value of 100%, true negative predictive value of 100%, AUC of 0.973, accuracy of 98.3%, and P value < 0.001.

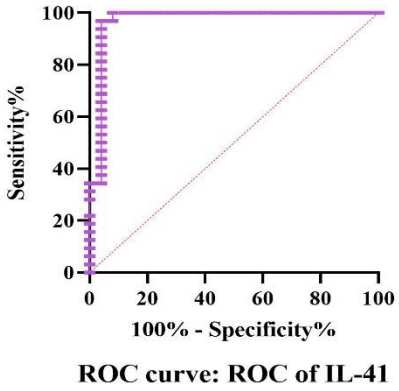


**Figure 2: Reciprocal Operation Curve of Interleukin-41**

Thus**,** the predication curve data indicated the strong relation of IL-41 with chronic myeloid leukemia

**Determination of the Correlation between IL-40 and 41:**

The result of the correlation between Serum IL-40 and serum IL-41 shows a significant strong positive correlation between them with a correlation coefficient r = 0.90; p < 0.001. Figure 3.

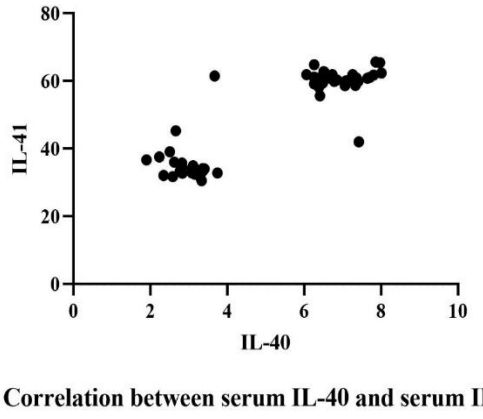


**Figure 3: Correlation between serum IL-40 and serum IL-41.**

IL-40 and 41 may be a new potential biomarker that can help physicians estimate treatment effectiveness and predict patient responses.

**Disscusion**

This result is different from that recorded in the case of AML by Mustafa and Ad'hiah(2024)(23) who found that this interleukin expression exhibited down-regulated levels in the blood of AML patients. At the same time, DNA methylation was up-regulated. Despite that, increased expression of IL-40 has been established in some autoimmune and inflammatory diseases (Navrátilová et al., 2021)(24).

Giuliana *et al.,* (2023)(25) reported that IL-40 is a new B-cell-related cytokine.T cells can also produce it. Its production is raised by IL-4 and altering growth factor-β1. furthermore, human B cell lymphomas can produce and express IL-40. The upregulation of IL-40 has been described in several inflammatory diseases such as rheumatoid arthritis. They confirm the upregulation of IL-40 in primary Sjögren syndrome. Additionally, IL-40 stimulates the release of proinflammatory cytokines from immune cells and promote NETosis in this disease. Remarkably, they detected a strong expression of IL-40 in linked non-Hodgkin's lymphoma. Also, Jovani and his colleagues (2017)(26) concluded that IL40 plays a significant role in humoral immune responses and may also have a role in B cell progress. As well as this interleukin is also secreted by activated B cells and by some B cell lymphomas. They suggested that it may have a role in the pathogenesis of certain human inflammatory diseases.

Thus, it can be suggested that the recent results confirmed that documented by other researchers indicated the role of IL40 in severe inflammatory diseases such as CML.

Different research indicates increasing the serum level of several pro-inflammatory cytokines such as IL-6 increased in CML, which is well known to play a role in the activation of B cells (27). This increase is not limited to IL-6 which, but also TGF-β as its known role in supporting leukemogenesis. Guggino et al.,(2023)(28) showed that TGF-β is a crucial factor for increasing the expression of IL-40 in activated B cells, but it seems that other factors could also enhance its

expression that has not been discovered yet (13). In addition to the role of IL-40 in CML appears to be a pro-inflammatory as (Navrátilová et al., 2021) ( 29 ) indicated that some immune cells treated with IL-40 in vitro released pro-inflammatory cytokines, specifically interferon-γ from B cells and T-CD8+ and tumor necrosis factor-α and IL-17 from both T-CD4+ and T-CD8+ ), the dysregulation of various cytokines is indicated to the malignant transformation of hematopoietic stem cells(30).

**Determination of Serum IL-41 in chronic myeloid leukemia**

Interleukin (IL-41) is a recently discovered secreted protein expressed in various tissues. It is associated with several immune and metabolic diseases (14). However, some studies show some relatedness in terms of markers in the case of autoimmune where they found a significant elevation in serum IL-41 compared to control.

The present study sheds light on the potential role of IL-41 and its biological activity in mediating inflammation in leukemic patients. It is essential to know the role of IL-41 in inflammation and its effectiveness in CML, as IL-41 is newly discovered and described.

(Bridgewood et al., 2019) (31) Study investigated IL-41 protein expression in synovial tissue in Rheumatoid Arthritis, Psoriatic Arthritis, and Osteoarthritis patients and evaluated IL-41 production from healthy enthesis samples, as the enthesis represents the primary inflammatory site in Psoriatic Arthritis the result is that entheseal stromal cells were the dominant producer of IL-41 from the enthesis. Moreover, stromal-derived IL-41 could be further induced by IL-17A and/or F and TNF. They concluded that IL-41 is expressed in Psoriatic Arthritis synovium and is present and inducible at the enthesis. Also, Gong et al., (2023) (32) and Jocić et al., (2024)(33) (15) found serum IL-41 concentrations were higher in Rheumatoid Arthritis patients than in Hepatocellular carcinoma.

While, Li et al., (2024) (34) demonstrated that Interleukin-41 is a novel serum marker for alpha-fetoprotein-negative hepatocellular carcinoma. The serum expression of IL-41 was highest in AFP-negative HCC patients and significantly higher than in AFP-positive HCC and metastatic cancer patients. A negative significance correlation was recorded between elevated serum IL-41 and the clinicopathological features. High serum expression of IL-41 suggests poorer survival and earlier recurrence after resection, and IL-41 is upregulated in patients with early recurrence and

death. Whereas Cen et al., (2023) (35) investigated the ability of IL-41 to protect against CS-induced lung inflammation in vivo. They found that IL-41 pre-treatment alleviated pulmonary inflammatory infiltration and lung tissue lesions. IL-41 pre-treatment also limited CS-induced weight loss in lower numbers of macrophages in the bronchoalveolar lavage fluid and lower percentages of neutrophils and monocytes in the blood. Moreover, pre-treatment with IL-41 was associated with higher levels of IL-10 in the bronchoalveolar lavage fluid and lung tissues of CS-exposed animals and lower production of tumor necrosis factor-α, IL-6, and IL-1β in the serum and lung tissues.

Additionally, (Zhou et al., 2023) (36) determined the expression of IL-41 in the serum of gout patients. Serum IL-41 concentrations in acute gout patients were higher than those in HCs and there was no significant difference in serum IL-41 levels between remission gout patients and HCs. In addition, IL-41 was positively correlated with white blood cell count, erythrocyte sedimentation rate, and C-reactive protein and serum amyloid A concentrations, while it was negatively correlated with triglyceride levels.

Therefore it can be suggested that a significant increase in the levels of serum IL-41 in a group of patients with CML suggests a potential role in the pathogenesis of the CML. Several studies have demonstrated that IL-41 is diffusely activated in macrophages. Various cytokines can trigger IL-41 production and indirectly control other chemokines and cytokines. When bone marrow macrophages are stimulated by IL-4, IL-6, IL-12, IL-17α, and TNF-α, they can produce IL-41, with TNF-α being the most potent inducer as (37) mentioned. IL-6 plays a critical role in the survival and proliferation of CML stem and progenitor cells, contributing to the disease's progression (38), As IL-6 levels are elevated in patients with chronic myeloid leukemia (CML) (39). The strong significant correlation can be attributed to the involvement of IL-41 in affecting the production of some cytokines like IL-6 the latter is an activator of B cells which is the producer of IL-40 so these two cytokines act synergistically and as proinflammatory cytokines. The role of serum IL-41 in CML might contribute to the inflammatory milieu associated with CML, potentially promoting the survival and proliferation of leukemic cells.

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## Conclusion

The current study suggests that the severity of the disease was positively correlated with an increase in IL-40 and IL-41 levels in the serum of patients with CML. Furthermore, IL-41 has the potential function as a biomarker for chronic infection with CML and may be essential to the immunopathological mechanism of CML.

**Acknowledgments**

The author thanks the College of Science, University of Baghdad for supporting the study. Also, we thanks all medical staff, patients, and volunteers for their help during sample collection.

**Conflict of interests**

No conflict of interests was declared by the author.

**Funding source**

The author did not receive any source of fund.

**Data sharing statement**

Supplementary data can be shared with the corresponding author upon reasonable request.

**References**

1- CHEREDA, B. & MELO, J. V. 2015. Natural course and biology of CML. Annals of Hematology, 94, 107-121.
2- OSMAN, A. E. G. & DEININGER, M. W. 2021. Chronic Myeloid Leukemia: Modern therapies, current challenges and future directions. Blood Rev, 49, 100825.
3- VARDIMAN, J. W. 2009. Chronic Myelogenous Leukemia, BCR-ABL1+. American Journal of Clinical Pathology, 132, 250-260.
4- GOLDMAN, J. M. & MELO, J. V. 2008. BCR-ABL in Chronic Myelogenous Leukemia – How Does It Work? Acta Haematologica, 119, 212-217.
5- WILLIAMS, L. A., AULT, P., CLEELAND, C. S., REYNOLDS, R. J., SHAH, N. A., SHAH, P. K. & CORTES, J. E. 2010. Symptom burden in chronic myeloid leukemia (CML). Journal of Clinical Oncology, 28, 6133-6133.
6- CALABRETTA, B. & PERROTTI, D. 2004. The biology of CML blast crisis. Blood, 103, 4010-4022.
7- HEHLMANN, R. 2012. How I treat CML blast crisis. Blood, 120, 737-747.

8- RAMANI, T., AULETTA, C. S., WEINSTOCK, D., MOUNHO-ZAMORA, B., RYAN, P. C., SALCEDO, T. W. & BANNISH, G. 2015. Cytokines:The Good, the Bad, and the Deadly. International Journal of Toxicology, 34, 355-365.

9- KANY, S., VOLLRATH, J. T. & RELJA, B. 2019. Cytokines in Inflammatory Disease. Int J Mol Sci, 20.

10- CATALAN-DIBENE, J., VAZQUEZ, M. I., LUU, V. P., NUCCIO, S.-P., KARIMZADEH, A., KASTENSCHMIDT, J. M., VILLALTA, S. A., USHACH, I., PONE, E. J., CASALI, P., RAFFATELLU, M., BURKHARDT, A. M., HERNANDEZ-RUIZ, M., HELLER, G., HEVEZI, P. A. & ZLOTNIK, A. 2017. Identification of IL-40, a Novel B Cell–Associated Cytokine. The Journal of Immunology, 199, 3326-3335.

11- DABBAGH-GORJANI, F. 2024. A Comprehensive Review on the Role of Interleukin-40 as a Biomarker for Diagnosing Inflammatory Diseases. Autoimmune Diseases, 2024, 3968767.

12- AG AL GHURAIBAWI, Z., SHARQUIE, I. K. & GORIAL, F. I. 2022. Diagnostic potential of interleukin-40 (IL-40) in rheumatoid arthritis patients. The Egyptian Rheumatologist, 44, 377-380.

13- MOHAMMADNEZHAD, L., LO PIZZO, M., LENTINI, V. L., DI LIBERTO, D., LA BARBERA, L., RAIMONDO, S., SHEKARKAR AZGOMI, M., URZì, O., BERARDICURTI, O., CAMPISI, G., ALESSANDRO, R., GIACOMELLI, R., DIELI, F. & CICCIA, F. 2023. Possible role for IL-40 and IL-40-producing cells in the lymphocytic infiltrated salivary glands of patients with primary Sjögren's syndrome. RMD Open, 9, e002738.

14- ZHANG, H. & DHALLA, N. S. 2024. The Role of Pro-Inflammatory Cytokines in the Pathogenesis of Cardiovascular Disease. International Journal of Molecular Sciences, 25, 1082.

15- JOCIĆ, J., LUČIĆ, A. T., JOVANOVIĆ, I., JURIŠEVIĆ, M., STANISAVLJEVIĆ, I., STAMENKOVIĆ, B. & PAVLOVIĆ, S. 2024. Interleukin 41 As A Potential Predictor of Bio-Therapy Efficacy In Patients With Rheumatoid Arthritis: A Prospective Observational Study. Int J Med Sci, 21, 2518-2524.

16- GONG, L., HUANG, G., WENG, L., XU, J., LI, Y., CUI, W. & LI, M. 2022. Decreased serum interleukin-41/Metrnl levels in patients with Graves' disease. Journal of Clinical Laboratory Analysis, 36, e24676.

17- CAI, X., LI, K., LI, M., LU, Y., WU, J., QIU, H. & LI, Y. 2023. Plasma interleukin-41 serves as a potential diagnostic biomarker for Kawasaki disease. Microvascular Research, 147, 104478.

18- GAO, X., LEUNG, T. F., WONG, G. W., KO, W. H., CAI, M., HE, E. J.,CHU, I. M., TSANG, M. S., CHAN, B. C., LING, J., FAN, X., LU, L., LAM, C. W. & WONG, C. K. 2022. Meteorin-β/Meteorin like/IL-41 attenuates airway inflammation in house dust mite-induced allergic asthma. Cell Mol Immunol, 19, 245-259.

19- ONUORA, S. 2019. Novel cytokine, IL-41, linked with PsA. Nature Reviews Rheumatology, 15, 636-636.

20- DE LA FUENTE, J., BARUCHEL, A., BIONDI, A., DE BONT, E., DRESSE, M.-F., SUTTORP, M., MILLOT, F. & COMMITTEE, I. B. G. S. G. C. M. L. 2014. Managing children with chronic myeloid leukaemia (CML). British Journal of Haematology, 167, 33-47.

21- RADIVOYEVITCH, T., JANKOVIC, G. M., TIU, R. V., SAUNTHARARAJAH, Y., JACKSON, R. C., HLATKY, L. R., GALE, R. P. & SACHS, R. K. 2014. Sex differences in the incidence of chronic myeloid leukemia. Radiation and Environmental Biophysics, 53, 55-63.

22- ROHRBACHER, M. & HASFORD, J. 2009. Epidemiology of chronic myeloid leukaemia (CML). Best Practice & Research Clinical Haematology, 22, 295-302.

23- Mustafa A. Bashi and Ali H. Ad'hiah(2024)Molecular landscape of the interleukin-40 encoding gene, C17orf99, in patients with acute myeloid leukemia. Gene ;Volume 904, 30 April 2024, 148214.

24- NAVRáTILOVá, A., BEČVáŘ, V., HULEJOVá, H., TOMČíK, M., ŠTOLOVá, L., MANN, H., RŮŽIČKOVá, O., ŠLEGLOVá, O., ZáVADA, J., PAVELKA, K., VENCOVSKý, J., ŠENOLT, L. & ANDRES CEREZO, L. 2023. New pro-inflammatory cytokine IL-40 is produced by activated neutrophils and plays a role in the early stages of seropositive rheumatoid arthritis. RMD Open, 9, e00.

25- Giuliana Guggino, Chiara Rizzo, Leila Mohammadnezhad,Marianna Lo Pizzo,Vincenzo Luca Lentini, Diana Di Liberto,Lidia La Barbera, Stefania Raimondo, Mojtaba Shekarkar Azgomi,Ornella Urzì, Onorina Berardicurti, Giuseppina Campisi, Riccardo Alessandro, Roberto Giacomelli , Francesco Dieli,Francesco Ciccia(2023)Possible role for IL-40 and IL-40-producing cells in the lymphocytic infiltrated salivary glands of patients with primary Sjögren's syndrome. Sjögren's syndrome. RMD Open 2023;9:e002738. doi:10.1136/ rmdopen-2022-002738.

26- Jovani Catalan-Dibene; Monica I. Vazquez; Van Phi Luu; Sean-Paul Nuccio, Alborz Karimzadeh;Jenna M. Kastenschmidt;S. Armando Villalta;Irina Ushach;Egest J. Pone; Paolo Casali ;Manuela Raffatellu; Amanda M. Burkhardt; Marcela Hernandez-Ruiz;Gina Heller;Peter A. Hevezi ;Albert Zlotnik (2017)Identification of IL-40, a Novel B Cell–Associated Cytokine. J Immunol (2017) 199 (9): 3326–3335. https://doi.org/10.4049/jimmunol.1700534.

27- HASHWAH, H., BERTRAM, K., STIRM, K., STELLING, A., WU, C. T., KASSER, S., MANZ, M. G., THEOCHARIDES, A. P., TZANKOV, A. & MULLER, A. 2019. The IL‐6 signaling complex is a critical driver, negative prognostic factor, and therapeutic target in diffuse large B‐cell lymphoma. EMBO Molecular Medicine, 11, e10576.

28- Giuliana Guggino, Chiara Rizzo, Leila Mohammadnezhad,Marianna Lo Pizzo,Vincenzo Luca Lentini, Diana Di Liberto,Lidia La Barbera, Stefania Raimondo, Mojtaba Shekarkar Azgomi,Ornella Urzì, Onorina Berardicurti, Giuseppina Campisi, Riccardo Alessandro, Roberto Giacomelli , Francesco Dieli,Francesco Ciccia(2023)Possible role for IL-40 and IL-40-producing cells in the lymphocytic infiltrated salivary glands of patients with primary Sjögren's syndrome. Sjögren's syndrome. RMD Open 2023;9:e002738. doi:10.1136/ rmdopen-2022-002738.

29- Adela Navrátilová , Lucie Andrés Cerezo , Hana Hulejová , Viktor Bečvář , Michal Tomčík , Martin Komarc , David Veigl , Dana Tegzová , Jakub Závada, Marta Olejárová, Karel Pavelka, Jiří Vencovský , Ladislav Šenolt(2021)IL-40: A New B Cell-Associated Cytokine Up-Regulated in Rheumatoid Arthritis Decreases Following the Rituximab Therapy and Correlates With Disease Activity, Autoantibodies, and NETosis. Front Immunol; 12:745523. doi: 10.3389/fimmu.2021.745523.

30- MOHAMMADNEZHAD, L., LO PIZZO, M., LENTINI, V. L., DI LIBERTO, D., LA BARBERA, L., RAIMONDO, S., SHEKARKAR AZGOMI, M., URZì, O., BERARDICURTI, O., CAMPISI, G., ALESSANDRO, R., GIACOMELLI, R., DIELI, F. & CICCIA, F. 2023. Possible role for IL-40 and IL-40-producing cells in the lymphocytic infiltrated salivary glands of patients with primary Sjögren's syndrome. RMD Open, 9, e002738.

31- BRIDGEWOOD, C., RUSSELL, T., WEEDON, H., BABOOLAL, T., WATAD, A., SHARIF, K., CUTHBERT, R., WITTMANN, M., WECHALEKAR, M. & MCGONAGLE, D. 2019. The novel cytokine Metrnl/IL-41 is elevated in Psoriatic Arthritis synovium and inducible from both entheseal and synovial fibroblasts. Clinical Immunology, 208, 108253.

32- GONG, L., ZHOU, Y., SHI, S., YING, L., LI, Y. & LI, M. 2023. Increased serum IL-41 is associated with disease activity in rheumatoid arthritis. Clin Chim Acta, 538, 169-174

33- JOCIĆ, J., LUČIĆ, A. T., JOVANOVIĆ, I., JURIŠEVIĆ, M., STANISAVLJEVIĆ, I., STAMENKOVIĆ, B. & PAVLOVIĆ, S. 2024. Interleukin 41 As A Potential Predictor of Bio-Therapy Efficacy In Patients With Rheumatoid Arthritis: A Prospective Observational Study. Int J Med Sci, 21, 2518-2524.

34- LI, Y., WANG, H., REN, D., LI, J., MU, Z., LI, C., HE, Y., ZHANG, J., FAN, R., YIN, J., SU, J., HE, Y. & YAO, B. 2024. Interleukin-41: a novel serum marker for the diagnosis of alpha-fetoprotein-negative hepatocellular carcinoma. Front Oncol, 14, 1408584.

35- CEN, T., MAI, Y., JIN, J., HUANG, M., LI, M., WANG, S. & MA, H. 2023. Interleukin-41 diminishes cigarette smoke-induced lung inflammation in mice. International Immunopharmacology, 124, 110794.

36- ZHOU, Y., SHI, S., MENG, S., ZHAO, H., WU, X., LI, M. & LI, Y. 2023. Potential clinical value of serum interleukin-41 levels in patients with acute gout. International Immunopharmacology, 122, 110621.

37- ELENKOV, I. J., IEZZONI, D. G., DALY, A., HARRIS, A. G. & CHROUSOS, G. P. 2005. Cytokine Dysregulation, Inflammation and Well-Being. Neuroimmunomodulation, 12, 255-269.

38- NIEVERGALL, E., REYNOLDS, J., KOK, C. H., WATKINS, D. B., BIONDO, M., BUSFIELD, S. J., VAIRO, G., FULLER, K., ERBER, W. N., SADRAS, T., GROSE, R.,

YEUNG, D. T., LOPEZ, A. F., HIWASE, D. K., HUGHES, T. P. & WHITE, D. L. 2016. TGF-α and IL-6 plasma levels selectively identify CML patients who fail to achieve an early molecular response or progress in the first year of therapy. Leukemia, 30, 1263-72.

39- PAVLOVSKY, C., VASCONCELOS CORDOBA, B., SANCHEZ, M. B., MOIRAGHI, B., VARELA, A., CUSTIDIANO, R., FERNANDEZ, I., FREITAS, M. J., VENTRIGLIA, M. V., BENDEK, G., MARIANO, R., MELA OSORIO, M. J., PAVLOVSKY, M. A., DE LABANCA, A. G., FONCUBERTA, C., GIERE, I., VERA, M., JUNI, M., MORDOH, J., SANCHEZ AVALOS, J. C., CUETO, G., MIRANDA, S., LEVY, E. M. & BIANCHINI, M. 2023. Elevated plasma levels of IL-6 and MCP-1 selectively identify CML patients who better sustain molecular remission after TKI withdrawal. J Hematol Oncol, 16, 43.