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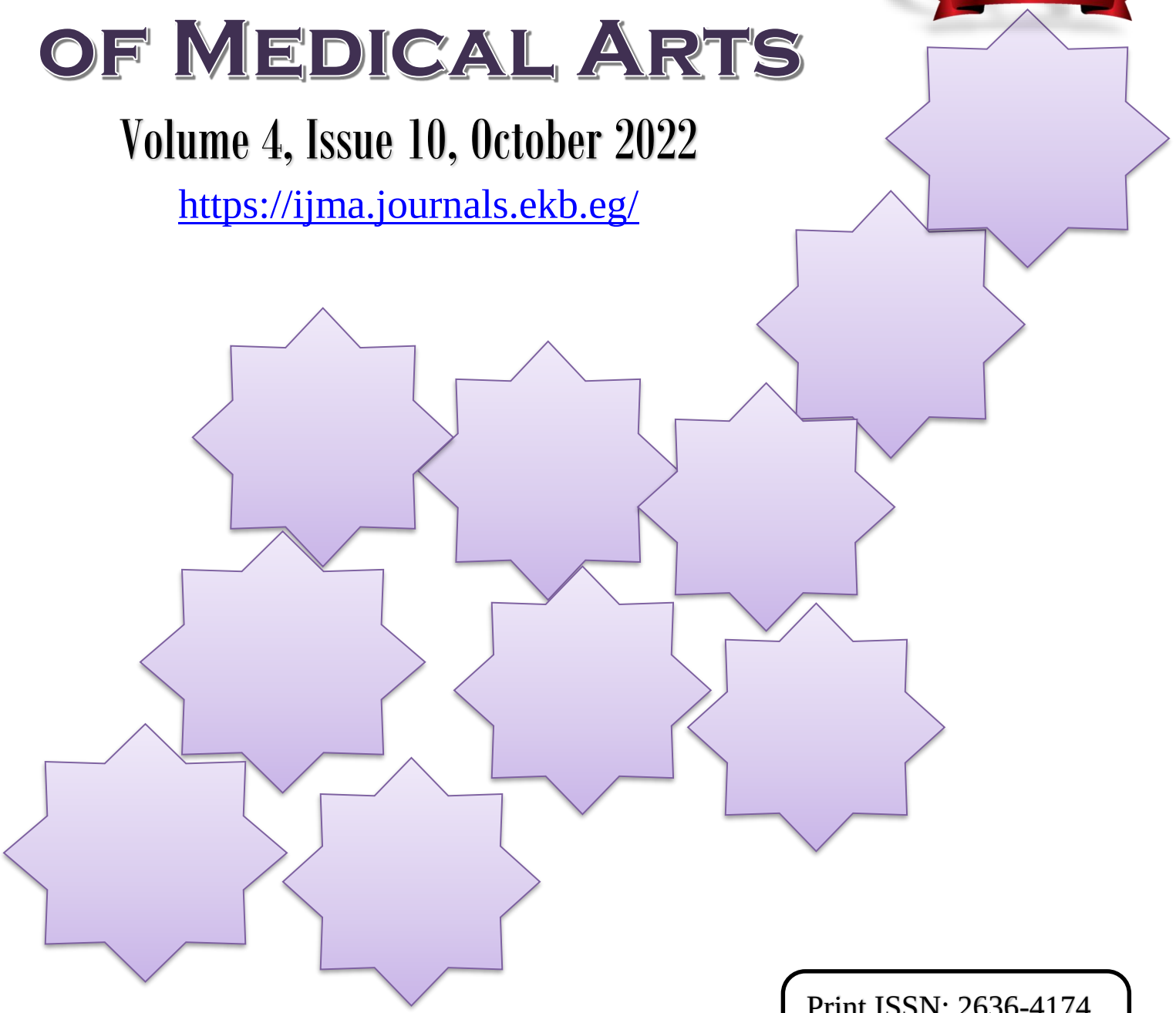

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## Original Article

# Assessment of IL6 and TNF α in Chronic Lymphocytic Leukemia

**Mohamed Abd-El-Haleem Abd-El-Razik Mousa *[1], Ibrahim El-Sayed Ibrahim Eweis [1], Salem Soliman Ahmed [2], Abdullah Mostafa Gaafar [1]**

[1] Departments of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

[2] Departments of Internal Medicine, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

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*Corresponding author

**Email:** drmoht5@gmail.com

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## ABSTRACT

**Background:** Among the cytokines and inflammatory markers, Interleukin 6 [IL6] and TNF α are the most common markers in the practice of medicine. Many studies determine the values of these two markers among the patients with chronic lymphocytic leukemia [CLL] in comparison to the healthy population which may help in correlation of their levels in relation to the severity of CLL.

**Aim of the work:** To assess IL6 and TNF α in Patients with chronic lymphocytic leukemia and correlate its results with the stage of the disease.

**Patients and methods:** This study was carried out at the Clinical Pathology Department, Al-Azhar University. The study included 40 patients suffering from CLL, who attended to the National Cancer Institute in Cairo during the period from January 2021 to July 2022.

**Results:** In our study, there were significant increase in TNF α levels and IL6 between cases of CLL patients and control groups. After classification of the patients in two groups according to modified Rai staging system, 21/40 [52.5%] at stages I, II [intermediate risk] and 19/40 [47.5%] at stages III, IV [high risk], there were no statistical significant difference [p-value = 0.205] between intermediate group and high-risk group as regard TNF α and also as regard Interleukin 6.

**Conclusion:** Serum levels of IL6 and TNF α were significantly elevated in newly diagnosed CLL patients compared to control group. However, there were no significant difference in serum levels of IL6 and TNF α were observed in high risk groups than the intermediate risk group. Therefore, our study suggests that these markers cannot be used to differentiate between different CLL stages.

**Keywords:** Markers of apoptosis; Chronic lymphocytic leukemia; IL6; TNF

## INTRODUCTION

A mutant clone of mature B lymphocytes proliferates and accumulates in the bone marrow, blood, lymph nodes, and spleen resulting in chronic lymphocytic leukemia [CLL], a hematologic malignancy. CLL is a cancer that grows very slowly and is linked to apoptosis failure [1].

As CLL cells accumulate in the bone marrow, normal hematopoiesis finally becomes suppressed. This raises the danger of bleeding and infection, all of which can be fatal, and also causes anemia, thrombocytopenia, and/or neutropenia. Additionally, the immunological incompetence of CLL cells increases the risk of infection and can cause autoimmune cytopenias [2].

Numerous prognostic factors have been identified for CLL treatment, response and survival. The best characterized and most significant prognostic markers are CD38, Zeta-associated protein 70 [ZAP-70], immunoglobulin heavy chain variable region [IgVH] mutational status, and chromosomal abnormalities [3].

Intercellular short acting soluble mediators known as cytokines play a role in the development of cancer. Cytokines may be used as a marker of immune status and/or prognosis in cancer since they can be produced by or have effects on neoplastic or reactive cells [4].

Interleukin 6 is a multifunctional cytokine that regulates a variety of cellular processes, including proliferation, apoptosis, angiogenesis, differentiation, and immune response regulation. It has also been linked to the pathogenesis of a number of lympho-proliferative disorders, which suggests a critical role for IL6 in the persistence of CLL cells. Higher IL6 levels in CLL patients are typically associated with more severe illnesses [5]. The plasma level of IL6 varies significantly among different stages of patients with CLL; some studies indicated that IL6 plays a role in the development of lymphoma and elevated level of IL6 correlates with bad prognosis in patients with lymphoma and CLL [6].

Tumor necrosis factor-alpha [TNF α] was initially thought to be a product only of macrophages, T-cells, B-cells and monocytes. TNF α has now been shown to be produced by a wide variety of tumor cells, including those of CML, B-Cell lymphoma, and many other kinds of tumors. It was first isolated as an anticancer cytokine, where TNF α can mediate a wide variety of diseases, including cancer [7].

Among the cytokines and inflammatory markers, IL6 and TNF α are the most common employed markers in the practice of medicine. In the wake of the COVID 19 outbreak, their use has grown more widespread. Numerous researches compare the values of these two markers between CLL patients and the general population in order to establish how these two markers relate to the severity of CLL [8].

## THE AIM OF THE WORK

The aim of the present study was to assess IL6 and TNF α in Patients with chronic lymphocytic leukemia and correlate its results with the stage of the disease.

## PATIENTS AND METHODS

This study was carried out at the Clinical Pathology Department, Al-Azhar University. The study included 40 patients suffering from chronic lymphocytic leukemia [CLL], who attended to the National Cancer Institute in Cairo during the period from January 2021 to July 2022 with appropriate consent to participate in this study after explanation to patients how much it is helpful in diagnosis and treatment.

The study included 40 patients, and 20 healthy control matched with age and sex, patients were classified into 2 groups according to modified **Rai system** [9]:

**Group 1 [intermediate risk patients]:** 21 patients had intermediate risk CLL [lymphocytosis plus one or more of: enlarged lymph nodes, enlarged liver, enlarged spleen]. They were 10 males and 11 females, their ages [57.8 ± 8.7 years].

**Group 2 [high risk patients]:** 19 patients had high risk CLL [lymphocytosis plus anemia "Hb < 11 g/dl" and/or thrombocytopenia "Platelets < 100 × $10^3$ / mm3"]. They were 13 males and 6 females, their ages [64.9 ± 9.2 years].

**Control group:** 20 healthy control matched with age and sex.

**Table [1]:** Rai clinical staging system with survival according to stage [9, 10]

| Original Rai [10] | Revised Rai [9] | Description | Median survival |
|---|---|---|---|
| **Stage 0** | Low risk | Lymphocytosis only | Normal |
| **Stage I** | Intermediate risk | Lymphocytosis plus enlarged lymph nodes | 101 months |
| **Stage II** | | Lymphocytosis plus enlarged liver &/or spleen | 71 months |
| **Stage III** | High risk | Lymphocytosis plus anemia [hemoglobin <11 g/dL] | 19 months |
| **Stage IV** | | Lymphocytosis plus thrombocytopenia [Platelets < 100 $\times 10^9$ /L] | 19 months |

**Inclusion criteria:** Any patient who was newly diagnosed by flowcytometry to have CLL was included in our research.

**Exclusion criteria:** Any patients suffering from lymphocytosis due to causes other than CLL e.g. polyclonal lymphocytosis due to viral infections, was excluded from our research.

**All patients were subjected to the following:**

I. Full history and clinical examination stress on lymphadenopathy and organomegaly [Liver and spleen]

II. Peripheral blood samples [5 mL: 1 mL on EDTA vacutainer for CBC and flow-cytometry and 5 mL on plain vacutainer].

**Samples were submitted to the following:**

1. Complete blood picture [CBC]: using CELL-DYN RUBY HEMATOLOGY auto analyzer, Abbott Park, Illinois, U.S.A.

2. Immunophenotyping by flow cytometry [Becton Dickenson /BD FACS Canto] using chronic lymphocytic leukemia CD3, CD5, CD10, CD19, CD20, CD22/CD79b, CD23, sIgM, kappa, lambda and FMC7.Cells were considered positive for a marker when > 20% of the cells expressed that marker [3].

3. Specific laboratory investigations: [A] Serum TNF α measurement by ELISA. [B] Serum IL6 measurement by Chemilumine-scence.

**Interleukin 6 Method:** The Roche Elecsys IL6 assay is a non-competitive [sandwich] chemiluminescent immunoassay. Range of detection: 1.5 – 5,000 pg/ml.

**TNF-α:** TNF-α levels were assayed using enzyme-linked immunosorbent assay [Sandwich-ELISA] [Elabscience Human TNF α Immunoassay]. Range of detection: 7.81-500 pg/ml.

**Statistical analysis:** Version 24 of the Statistical Program for Social Science [SPSS] was used to analyze the data. Quantitative information was presented as mean±SD [for normally distributed data] and median [IQR] [for abnormally distributed data]. Frequency and percentage were used to express qualitative data. When comparing two means, the independent-samples t-test was employed [for normally distributed data]. The mean [average] is the middle value in a set of discrete numbers; it is the sum of values divided by the total number of values. The measure of a set of values' dispersions is the standard deviation [SD]. As opposed to a high SD, which shows that the values are dispersed over a greater range, a low SD implies that the values tend to be close to the established mean. Median is the value separating the higher half from the lower half of data. The basic advantage of median comparing to mean is that the median is not skewed so much by small proportion of extremely large or small values. IQR [inter-quartile range] is the measure of statistical dispersion, being equal to the difference between 75th and 25th percentile. Mann–Whitney [u] test was employed to compare two means [for abnormal distributed data]. The Chi-square test was employed to compare non-parametric data. Cutoff value, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV] were all determined using the ROC curve [Receiver Operating Characteristic Curve]. The likelihood that a test result will be positive when the disease is present is known as sensitivity. Specificity is the likelihood that a test will come back negative when the disease is absent. The likelihood that a disease will be present when a test is positive is known as positive predictive value. The likelihood that the disease is not present when the test is negative is known as the negative predictive value. Accuracy: overall probability that a patient will be correctly classified. P value < 0.05 was considered significant.

## RESULTS

Table [2] shows non-significant difference [p-value = 0.209] between studied groups as regard age [61.3 ± 9.5 years] when compared with control group [58.4 ± 4.6 years]. No statistically significant difference [p-value = 0.853] between studied groups regarding sex. There were 23 males [57.5%] and 17 females [42.5%] in patients' group while there were 12 males [60%] and 8 females [40%] in control group. There was statistically significant [p < 0.001] increased WBCs in patients' group [90.5 ± 72.8] when compared with control group [6.7 ± 1.8]. There was statistically significant [p < 0.001] decrease of Hb in patients' group [10.4 ± 1.9] when compared to control group [14.5 ± 1.3]. There was statistically significant [p < 0.001] decrease of PLTs in patients' group [159.5 ± 57.3] when compared with control group [299.5 ± 83]. There was statistically significant [p < 0.001] increased IL6 in patients' group [Median = 13.3, IQR = 6.0 – 35.6] when compared with control group [Median = 3.1, IQR = 1.9 – 4.4]. There was statistically significant [p < 0.001] increased TNF α in patients' group [Median = 16.3, IQR = 14.8 – 18] when compared to control group [Median = 7.4, IQR = 6 – 9].

Using ROC curve, it was shown that serum IL6 can be used to differentiate between patients and control at a cutoff level of > 5.55, with 80% sensitivity, 90% specificity, 88.9% PPV and 81.8% NPV [AUC = 0.85 & p-value < 0.001]. Serum TNF α can be used to differentiate between patients and control at a cutoff level of > 11.5, with 97.5% sensitivity, 90% specificity, 90.7% PPV and 97.3% NPV [AUC = 0.95 & p-value < 0.001] [Table 3].

Table [4] shows description of staging in patients' group. It was intermediate in 21 patients [52.5%] and high in 19 patients [47.5%].

Table [5] show statistically significant [p-value = 0.017] increased age in high stage patients [64.9 ± 9.2 years] when compared with intermediate stage patients [57.8 ± 8.7 years]. No statistically significant difference [p-value = 0.853] between high stage and intermediate stage patients as regard sex. There were 10 males [47.6%] and 11 females [52.4%] in high stage patients while there were 13 males [68.4%] and 6 females [31.6%] in low stage patients. There was statistically significant [p-value < 0.001] decreased Hb in high stage patients [9.2 ± 1.2] when compared with intermediate stage patients [11.6 ± 1.7]. No statistically significant difference [p-value = 0.436] between intermediate and high stage patients as regard WBCs. The median WBC count was 76 with IQR of 50 – 95 in intermediate stage patients while the median WBC count was 100 with IQR of 40 – 122 in high stage patients. No statistically significant difference [p = 0.238] between intermediate and high stage patients as regard PLTs. It was 169.7 ± 55.4 in intermediate stage patients while it was 148.1 ± 58.6 in high stage patients. No statistically significant difference [p-value = 0.144] between intermediate and high stage patients as regard IL6. The median IL6 was 10.6 with IQR of 3.8–32.9 in intermediate stage while the median IL6 was 20.8 with IQR of 8.3 – 46.4 in high stage. No statistically significant difference [p = 0.205] between intermediate and high stage patients as regard TNF. The median TNF was 16 with IQR of 13.9 – 17.2 in intermediate stage while the median TNF was 17.1 with IQR of 14.8 – 19.2 in high stage.

**Table [2]:** Comparison between studied groups as regard age, gender, CBC and studied markers

| | | Patients [n = 40] | Control [n = 20] | Test | P-value |
|---|---|---|---|---|---|
| **Age [years]** | Mean ± SD | 61.3 ± 9.5 | 58.4 ± 4.6 | t = 9.2 | 0.209 |
| **Gender** | Male<br>Female | 23 [57.5%]<br>17 [42.5%] | 12 [60%]<br>8 [40%] | $X^2$ = 0.03 | 0.853 |
| **WBCs [x10³/ul]** | Mean ± SD | 90.5 ± 72.8 | 6.7 ± 1.8 | 5.1 | < **0.001** |
| **Hb [g/dl]** | Mean ± SD | 10.4 ± 1.9 | 14.5 ± 1.3 | 8.7 | < **0.001** |
| **PLTs [x10³/ul]** | Mean ± SD | 159.5 ± 57.3 | 299.5 ± 83.0 | 7.6 | < **0.001** |
| **IL6 [pg/mL]** | Median [IQR] | 13.5 [6.0–35.6] | 3.1 [1.9–4.4] | 112.5 | < **0.001** |
| **TNF α [pg/mL]** | Median [IQR] | 16.3 [14.8-18] | 7.4 [6–9] | 40 | < **0.001** |

**Table [3]:** Diagnostic performance of serum IL6 and TNF in discrimination of studied groups

| | Cut off | AUC | Sensitivity | Specificity | PPV | NPV | p-value |
|---|---|---|---|---|---|---|---|
| **IL6** | > 5.55 | 0.85 | 80% | 90% | 88.9% | 81.8% | < **0.001** |
| **TNF** | > 11.5 | 0.95 | 97.5% | 90% | 90.7% | 97.3% | < **0.001** |

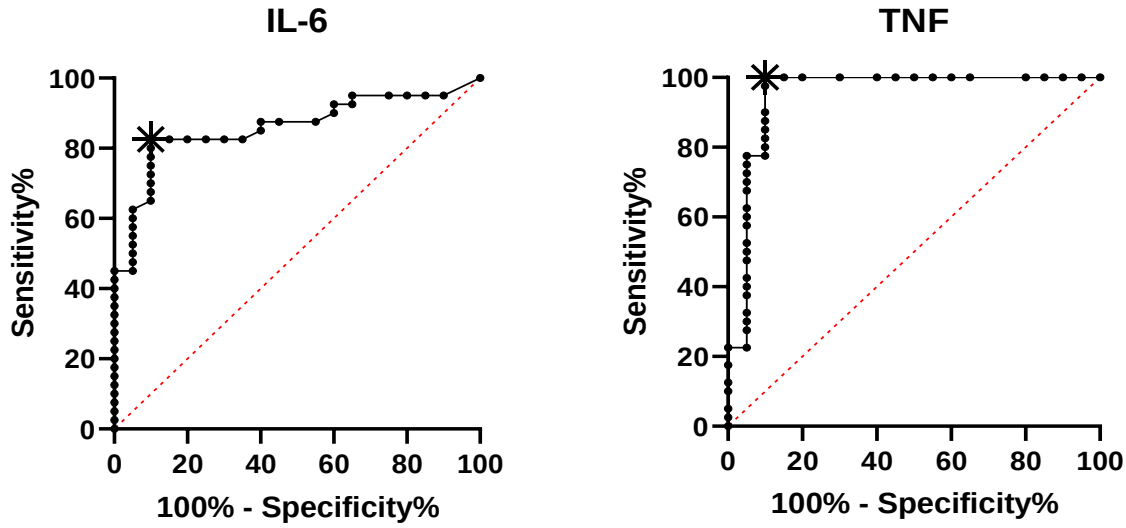



**Figure [1]:** ROC curve between patients and control as regard serum IL6 and TNF

**Table [4]:** Description of staging in the patient group

| | | Patients [n = 40] | |
|---|---|---|---|
| **Staging** | **Intermediate** | **21** | **52.5%** |
| | **High** | **19** | **47.5%** |

**Table [5]:** Comparison between studied stages as regard age, gender, CBC and studied markers

| | | Stage | | Test | P-value |
|---|---|---|---|---|---|
| | | **Intermediate [n = 21]** | **High [n = 19]** | | |
| **Age [years]** | Mean ± SD | 57.8 ± 8.7 | 64.9 ± 9.2 | t = 2.5 | **0.017** |
| **Gender** | Male<br>Female | 10 [47.6%]<br>11 [52.4%] | 13 [68.4%]<br>6 [31.6%] | $X^2$ = 1.76 | 0.184 |
| **WBCs [x10/ul]** | Median [IQR] | 76 [50 – 95] | 100 [40–122] | MW = 170.5 | 0.436 |
| **Hb [g/dl]** | Mean ± SD | 11.6 ± 1.7 | 9.2 ± 1.2 | t = 5.05 | **< 0.001** |
| **PLTs [x10³/ul]** | Mean ± SD | 169.7 ± 55.4 | 148.1 ± 58.6 | t = 1.19 | 0.238 |
| **IL6 [pg/mL]** | Median [IQR] | 10.6 [3.8 – 32.9] | 20.8 [8.3 – 46.4] | 128 | 0.144 |
| **TNF [pg/mL]** | Median [IQR] | 16 [13.9 – 17.2] | 17.1 [14.8 – 19.2] | 152 | 0.205 |

Examples of peripheral blood films and flowcytometry of the patients included in our work are shown in the following figures:

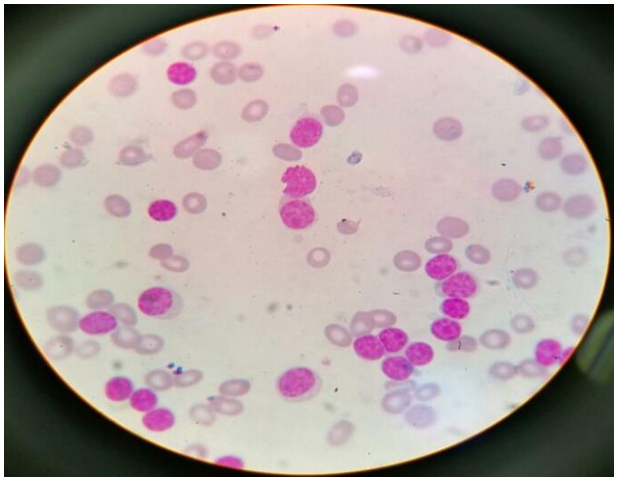


**Figure [2]:** Peripheral blood film of patient with high risk CLL showing many small mature looking lymphocytes, one smudge cell is shown, RBCs & platelets counts are decreased

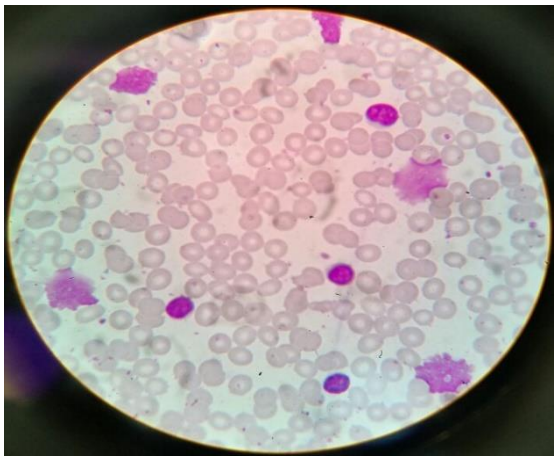


**Figure [3]:** Peripheral blood film of a CLL patient showing many small mature looking lymphocytes, many smudge cells and low platelet count

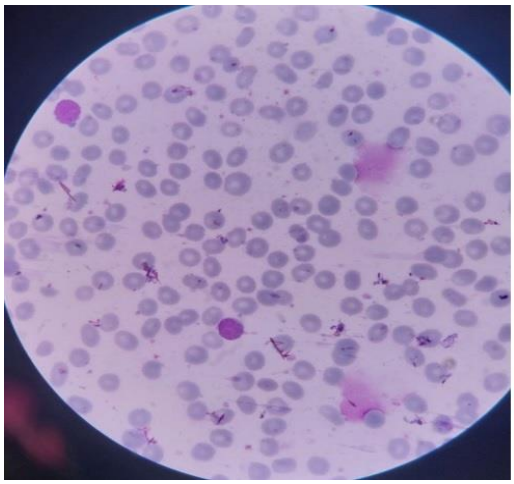
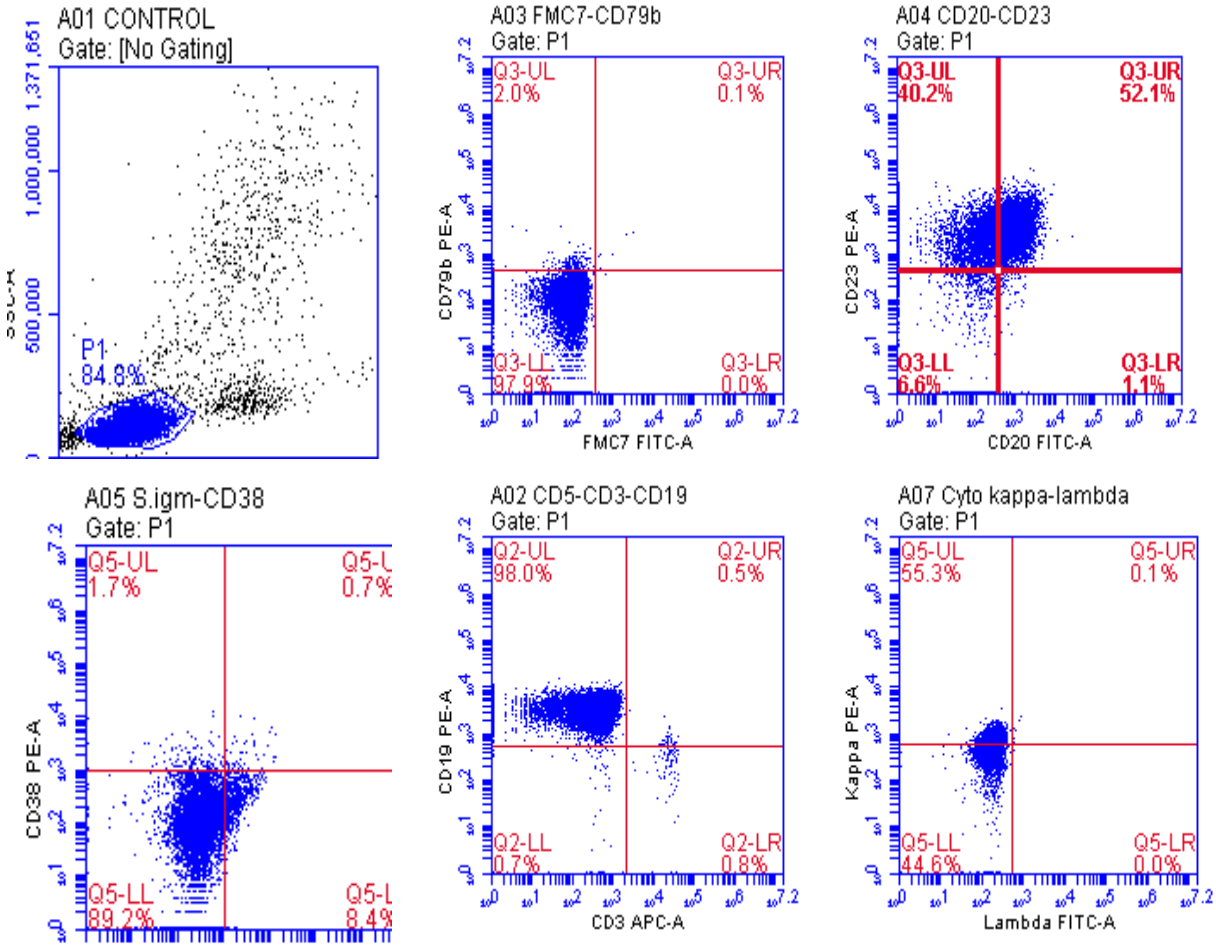


**Figure [4]:** Peripheral blood film of a CLL patient showing: - Red blood cells show moderate normocytic normochromic anemia. - White blood cells show mild total leukocytosis with marked absolute lymphocytosis [small mature looking lymphocytes] and many smudge cells are seen



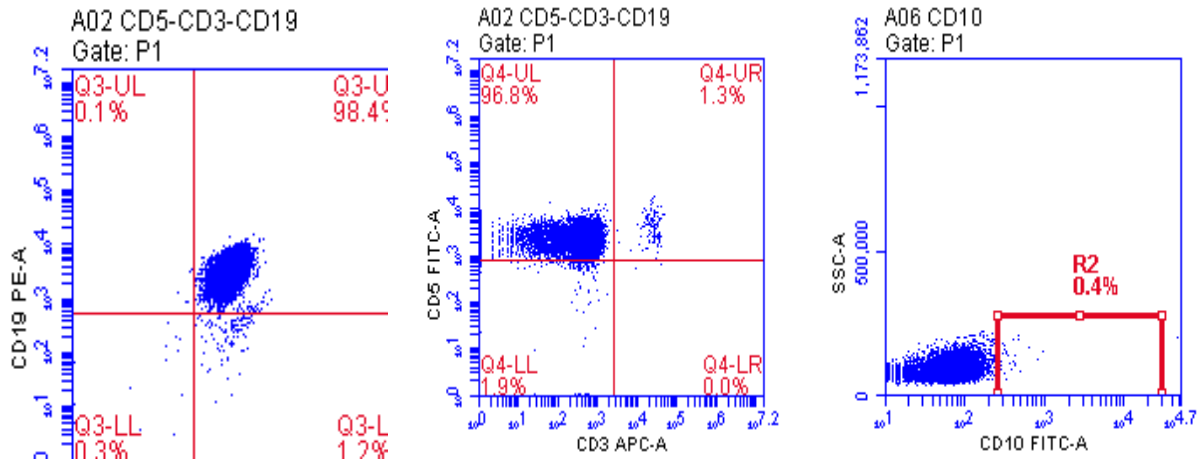



**Figure [5]:** Immunophenotyping analysis of PB lymphocytes revealed presence of B lymphoid clone with positive expression of CD5, CD19, coexpression of CD5/CD19 [dual CD5/19=99.4%], CD23 and CD 20 [dim expression]. This B clone is dim kappa light chain restricted. There was negative expression of CD79b, FMc7, SIg, lambda light chain and the prognostic marker CD38 is negative. Residual T lymphocytes is depressed and constitute 1.3% of whole lymphocytes population

## DISCUSSION

Numerous researches focused on finding surrogate markers with prognostic value for CLL whose expression could be easily evaluated. For instance, it has been demonstrated that the expression of CD38, immunoglobulin M [IgM], and IgD heavy chain in CLL associated with a poor prognosis [4]. There is a need to the establishment of prognostic markers in chronic lymphocytic leukemia for good prognosis and thereby approve the therapeutic decision [11].

There have been higher quantities of tumour necrosis factor [TNF] and its receptors [TNFR] found in the sera of CLL patients, and since high TNF α levels are indicative of an aggressive disease, this raises the possibility that they may play a role in CLL progression [8].

Among the cytokines and inflammatory markers, IL6 and TNF α are the most common employed markers in the practice of medicine. In the wake of the COVID 19 outbreak, their use has grown more widespread. Numerous researches compare the values of these two markers between CLL patients and the general population in order to establish how these two markers relate to the severity of CLL [8].

Our study was done to assess IL6 and TNF α in patients with chronic lymphocytic leukemia and correlate its results with the stage of the disease.

In the present study, total leucocytic count ranged from 17.7 to 163.3 x $10^9$ /l. These results were going hand in hand with those previously reported by **Ibrahim *et al.*** [12]. Similar to our result, **El-Khawanky *et al.*** [13] reported that TLC ranged between 10-215 x $10^9$/l.

In this study, hemoglobin level ranged from 8.5 to 12.3 g/dl and the platelet count ranged from 102.2 to 216.8 x $10^9$/l. Important prognostic factors for CLL include anemia and thrombocytopenia, which are included in the data used for staging. Heavy lymphocytic infiltration causes bone marrow failure in advanced CLL [14].

In our study, there was significant increase in TNF α mean levels [pg/mL] [16.3 vs. 7.4, P-value < 0.001] between cases of CLL patients and control groups. Our findings were in line with **Ferrajoli *et al.*** [15] who determined a similar higher value of TNF-α in cases with CLL as compared to control population. Also, **Alrayes and Abd Albaset** [16] reported significant elevation of serum TNF α level in patients having B-CLL when compared with the control group [P=0.000], they suggested that TNF α was involved in the progression of CLL.

Overall, the results indicated that serum TNF α levels are increased among the patients with CLL compared to control. On ROC, both the parameters had significant discriminatory power to predict CLL cases [< 0.001] at cutoff point of > 11.5, with 97.5% sensitivity, 90% specificity, 90.7% PPV and 97.3%.

In this study, modified Rai staging system [9] was used for CLL patients' classification as it was the most suitable staging system matched with the few numbers of CLL patients and statistical analysis. According to this system, 21/40 [52.5%] were at stages I, II [intermediate risk] and 19/40 [47.5%] were at stages III, IV [high risk]. After classification of the cases in two groups, no significant difference [P= 0.205] between intermediate and high stage patients as regard TNF-α. On the other hand, **Ferrajoli *et al.*** [15] reported that TNF α plasma levels correlated significantly with stage of the disease. Patients with Rai stage III or IV disease had higher TNF α level.

The plasma level of IL6 varies significantly among different stages of patients with CLL, some studies indicated that IL6 plays a role in the development of malignant lymphoma and elevated level of IL6 correlates with bad prognosis in patients with lymphoma and CLL [6].

In our study, there was significant increase in IL6 levels [pg/mL] [P-value < 0.001] between cases of CLL patients and control groups. Our findings were in line with **Albanaa *et al.*** [4], and also **Ahmed** [17] who determined a similar higher value of IL6 in cases with CLL as compared to control population. Also, **Al-Dahery *et al.*** [18] reported that plasma level of IL6 and IL10 were significantly elevated in newly diagnosed CLL patients compared to controls. Several investigators have suggested that IL6 in CLL inhibits proliferation but prolongs survival by suppressing apoptosis of CLL cells [19].

**Hadi *et al.*** [5] demonstrated that the serum level of IL6 was significantly higher in NHL patients than in healthy control and suggested that the level of IL6 from both the lymphoma cells themselves and reactive lymphocytes in lymph nodes can produce IL6.

Overall, the results indicated that serum IL6 levels are increased among the patients with CLL as compared to the healthy control. On ROC, both the parameters had significant discriminatory power to predict CLL cases [P< 0.001] at cutoff point of > 5.55, with 80% sensitivity, 90% specificity, 88.9% PPV and 81.8% NPV.

In this study, no statistically significant difference [p = 0.144] between intermediate and high stage patients as regard IL6. The median IL6 was 10.6 with IQR of 3.8-32.9 in intermediate stage while the median IL6 was 20.8 with IQR of 8.3-46.4 in high stage. Our findings were in line with **Hadi *et al.*** [5] which revealed that there was no significant relation between IL6 level and malignant grade. In contrast to other studies that found the IL6 plasma levels elevated significantly in patients with CLL with advanced stage of the disease [Rai stage III /IV] [4, 20]. **Lai *et al.*** [21] observed that IL6 plasma levels increase in patients with advanced stage of disease.

**Fayad *et al.*** [22] found that, in CLL, Serum IL6 measurement may help to identify a subgroup of patients whose disease is beginning to evolve to a more aggressive form even though morphologic evidence of transformation is not yet evident. High serum IL6 levels were found to correlate with unfavorable phenotypic features of the disease, such as advanced Rai stage, and also revealed that IL6 levels are more frequently elevated in the more aggressive lymphomas. Additionally, they discovered that Richter transformation and development to prolymphocytic leukemia were considerably more frequent in CLL patients who had elevated levels of at least one cytokine [IL6 and/or IL10] than in those who did not. This indicates that plasma levels of IL6 and TNF α are not a sensitive signal in determining the prognosis of the CLL disease.

**Conclusion:** We conclude that serum levels of IL6 and TNF α were significantly elevated in newly diagnosed CLL patients compared to control group. However, no significant difference in serum levels of IL6 and TNF α were observed in high risk groups than the intermediate risk group. Therefore, our study suggests that these markers cannot be used to differentiate between different CLL stages.

**Conflict of interest and Financial Disclosure:** None

## REFERENCES

1. Uchiyama T, Yokoyama A, Aoki S. Measurable residual disease in the treatment of chronic lymphocytic leukemia. J Clin Exp Hematop. 2020 Dec 15;60[4]:138-145. doi: 10.3960/jslrt. 20014.
2. Del Giudice I, Raponi S, Della Starza I, De Propris MS, Cavalli M, De Novi LA, *et al.* Minimal Residual Disease in Chronic

Lymphocytic Leukemia: A New Goal? Front Oncol. 2019 Aug 29;9:689. doi: 10.3389/fonc. 2019.00689.

3. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, *et al*. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018 Jun 21;131[25]:2745-2760. doi: 10.1182/blood-2017-09-806398.
4. Albanaa AM, Almudalal SS, Almamoori HS. Evaluation of CD69 Expression and Plasma Interleukin-6 in Chronic Lymphocytic Leukemia. J Pharm Sci Res. 2019 Mar 1;11[3]:935-41.
5. Hadi DA, Shani WS, Khalaf AA, Abed AH. Serum levels of interleukin-6 and interleukin-10 in adult newly diagnosed Iraqi Non Hodgkin's lymphoma patients. Eur J Exp Biol. 2013;3[5]:441.
6. Ali IS, Al-Ani GA, Taher YM, Alwan AF. Prognostic values of β2 microglobulin, interleukin-4, and interleukin-6 in patients with different stages of chronic lymphocytic leukemia. Iraq J Hematol. 2020 Jan 1;9[1]:47.
7. Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nat Rev Immunol. 2003 Sep;3[9]:745-56. doi: 10.1038/ nri1184.
8. Saxena D, Dawson L, Gera R. Study of serum cytokines [interleukin-6 and tumor necrosis factor-alpha] in acute leukemias. J Rad Cancer Res. 2022 Apr 1;13[2]:74. doi: 10.4103/jrcr.jrcr_ 48_21
9. Rai K. A critical analysis of staging in CLL. Chronic Lymphocytic Leukemia, Recent Progress and Future Directions. 1987:253-64.
10. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46[2]:219-234.
11. Hamblin TJ. Autoimmune complications of chronic lymphocytic leukemia. Semin Oncol. 2006 Apr;33[2]:230-9. doi: 10.1053/j. seminoncol.2006.01.011.
12. Ibrahim S, Keating M, Do KA, O'Brien S, Huh YO, Jilani I, *et al*. CD38 expression as an important prognostic factor in B-cell chronic lymphocytic leukemia. Blood. 2001 Jul 1;98[1]:181-6. doi: 10.1182/blood.v98.1.181.
13. El-Khawanky MM, Morsy MH, Elnaggar AM, Hussin OA, Zaewer MM, Khalifa NA. CD14 as a potential prognostic factor and Bcl-2 as a therapeutic target in egyptian B-Cell chronic lymphocytic leukemia patients. J App Hematol. 2019 Jan 1;10[1]:23-28. doi: 10.4103/joah. joah_5_19
14. Hoffbrand AV, Higgs DR, Keeling DM, Mehta AB, editors. Postgraduate haematology. John Wiley & Sons; 2016 Jan 19.
15. Ferrajoli A, Keating MJ, Manshouri T, Giles FJ, Dey A, Estrov Z, *et al*. The clinical significance of tumor necrosis factor-alpha plasma level in patients having chronic lymphocytic leukemia. Blood. 2002 Aug 15;100[4]:1215-9. PMID: 12149200.
16. Alrayes MH, Abd Albaset HH. Significance of tumor necrosis factor-α and B2 microglobulin in patients having chronic lymphocytic leukemia. Egy J Hosp Med. 2003 Apr 1;12[1]:28-37.
17. Ahmed NS. Expression of Cytokine of Chronic Lymphocyte Leukemia from Baghdad/Iraq Population. Iraqi J Cancer Med Genet. 2014; 7[2]:140-145.
18. Al-Dahery HS, Alwan AF, Muslit HS. Estimation of zeta-chain-associated protein 70, interleukin-6 and interleukin-10 levels in sera of Iraqi newly diagnosed chronic lymphocytic leukemia. Iraqi J Hematol. 2016 Jul 1;5[2]:173-177. doi: 10.4103/2072-8069.198123
19. Aderka D, Maor Y, Novick D, Engelmann H, Kahn Y, Levo Y, Wallach D, Revel M. Interleukin-6 inhibits the proliferation of B-chronic lymphocytic leukemia cells that is induced by tumor necrosis factor-alpha or -beta. Blood. 1993 Apr 15;81[8]:2076-84. PMID: 8386026.
20. Burger R. Impact of interleukin-6 in hematological malignancies. Transfus Med Hemother. 2013 Oct;40[5]:336-43. doi: 10.1159/ 000354194.
21. Lai R, O'Brien S, Maushouri T, Rogers A, Kantarjian H, Keating M, Albitar M. Prognostic value of plasma interleukin-6 levels in patients with chronic lymphocytic leukemia. Cancer. 2002 Sep;95[5]:1071-5. doi: 10.1002/cncr.10772.
22. Fayad L, Keating MJ, Reuben JM, O'Brien S, Lee BN, Lerner S, Kurzrock R. Interleukin-6 and interleukin-10 levels in chronic lymphocytic leukemia: correlation with phenotypic characteristics and outcome. Blood. 2001 Jan 1; 97[1]:256-63. doi: 10.1182/blood.v97.1.256.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