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Evaluation of the relevance of serum level of interleukin-8 in chronic lymphocytic leukemia

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Abstract:

BACKGROUND: Chronic lymphocytic leukemia (CLL) is the most common leukemia affecting the elderly. It is characterized by monoclonal B-cell proliferation expressing CD5 and CD23. Interleukin-8 (IL-8) has been found to induce the proliferation of malignant cells and make them resistant to apoptosis. Thus, IL-8 could be implicated in disease progression.

OBJECTIVE: The objective of the study was To determine the clinical significance of serum IL-8 levels in CLL patients and to evaluate its potential as a biomarker for disease progression.

MATERIALS AND METHODS: A cross-sectional study was conducted on 30 CLL patients and 30 normal individuals (control). Participants were recruited from October 2024 and continuing until August 2025 at The National Center of Hematology/Mustansiriyah University. Patients' demographics were collected using a special form. Blood samples were collected and analyzed for IL-8 levels using ELISA in addition to complete blood count.

RESULTS: The mean serum IL-8 level for CLL patients was 28.83 ± 12.68 pg/mL, which is higher than that of the control group 10.20 ± 1.008 pg/mL, with no statistical significance (P = 0.1483). It was concluded that a statistically significant difference in IL-8 levels existed across all stages of CLL (P = 0.0193). The highest median level was 16.28 pg/mL in Stage A, whereas the median levels in Stages B and C were 7.476 pg/mL and 7.608 pg/mL, respectively. The receiver operating characteristic curve showed that IL-8 powerful in distinguishing between Stage A and C, with a sensitivity of 81.82%, and a specificity of 72.73% at a cutoff of 10.07 pg/mL. IL-8 does not show a significant correlation with other variables.

CONCLUSION: As an autocrine growth and apoptosis resistance factor, higher level of IL-8 among CLL patients may be related to the disease persistence, with higher levels among earlier stages of CLL in comparison to later stages, which may be related to immune system exhaustion. Thus, it could be useful in monitoring disease status.

Keywords:

Biomarker, chronic lymphocytic leukemia, chronic lymphocytic leukemia stages, interleukin-8

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Introduction

Chronic lymphocytic leukemia is the most common leukemia affecting the elderly. It is characterized by monoclonal B-cell proliferation expressing CD5 and CD23.[1] In addition, the disease involves disruption of cytokine profiles in the form of raised pro-inflammatory cytokines such as tumor necrosis factor, inteleukin-6 (IL-6), IL-8, and IL-17, as well as anti-inflammatory cytokines such as IL-10, IL-13, IL-4, and transforming growth factor -beta (TGF-β).[2]

IL-8, which is also known as a pro-inflammatory chemokine, is generated by a variety of cell types, including but not

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limited to fibroblasts, keratinocytes, endothelial cells, neutrophils, mast cells, monocytes, macrophages, and megakaryocytes.[3]

IL-8 is a cytokine that is important in the defensive mechanism of the body due to its effects on the activity of neutrophils.[4] However, an ongoing and continuous presence of IL-8 in circulation in response to inflammatory conditions may result in tissue damage of varying severity. Furthermore, it has been found that IL-8 acts as a catalyst for the mitogen-activated protein kinase (MAPK) and tyrosine phosphorylation of proteins that are found in cells.[5]

IL-8 is a significant mediator in acute inflammation. It functions as a strong chemoattractant and activator of neutrophils by activating CXCR1 and CXCR2.[6]

The malignant B-cells of individuals with chronic lymphocytic leukemia (CLL) always express IL-8 and IL-8 receptors. The addition of exogenous IL-8 to *ex vivo* cultures leads to an increase in IL-8 expression and an extension of leukemia cell survival, in part due to the elevated expression of Bcl-2. IL-8 may serve as an autocrine growth and apoptosis resistance factor in chronic lymphocytic leukemia. The beginning of leukocyte infiltration and neovascularization, which both come before metastasis and invasion, are the most important effects of IL-8.[7]

The regulation of angiogenesis, cell motility, immune cell infiltration, cell growth, and survival in the microenvironment, and modulation of local antitumor immune responses may be the underlying mechanism that allows for the advancement of this tumor.[8] The purpose of this study is to investigate the clinical significance of serum IL-8 levels in patients with CLL and to determine if these levels might be useful as a biomarker for predicting disease progression.

Materials and Methods

Research strategy and environment

Starting in October of 2024 and continuing until August 2025, a comparative cross-sectional research was carried out at The National Center of Hematology/Mustansiriyah University.

There were a total of sixty individuals that were recruited and split up into two groups. Thirty adult patients (≥18 years) with a confirmed diagnosis of CLL.

Thirty seemingly healthy volunteers who have been matched on age and gender make up the control group.

Ethics approval was granted from the scientific ethical committee of The National Center of Hematology/Mustansiriyah University (Reference: nchh-erc-21-4), and this study was performed in line with the principles of the Declaration of Helsinki. Informed consent is obtained from each participant before enrollment in this study.

Criteria for diagnosis and qualification

Diagnosis of chronic lymphocytic leukemia

The standardized criteria that were set by the International Workshop on Chronic Lymphocytic Leukemia were used to determine the diagnosis of CLL patients.[9]

The criteria for inclusion in the CLL group were as follows: patients were required to be adults who were at least 18 years of age, had a confirmed diagnosis of CLL by multicolor flow cytometry of a peripheral blood sample, and had complete clinical and laboratory data available. This data included disease stage according to the Binet classification,[9] as well as a comprehensive treatment history, such as whether they had never been treated for the disease or had been treated previously.

Exclusion criteria

Participants were eliminated from both the CLL and control groups if they exhibited any of the following conditions at the time that their blood was sampled: active infection, an autoimmune illness or a chronic inflammatory disease, previous diagnosis of any other type of cancer.

Gathering a sample group and collecting data

After participants provide their informed consent, blood samples will be taken from their peripheral blood under standardized settings. By utilizing a standardized data collecting form, pertinent clinical and laboratory information will be collected from the medical records of the patients.

The blood samples, which each contained 5 ml, were collected at the time of sampling from both the patients and the controls. In order to determine blood count indices, 2 ml were administered in a tube containing EDTA, and the values were then acquired and computed by using an automated blood count analyzer. Following this, 3 ml were administered in a tube containing gel, and then they were centrifuged for a duration of ten minutes at a speed of 4000 revolutions per minute. Subsequent to that, the serum sample was taken and preserved at a temperature of twenty degrees below zero Celsius till the analysis of the IL8 level was carried out. The quantitative sandwich enzyme-linked immunosorbent assay (ELISA) technique was used to evaluate the levels of IL-8 in accordance with the manufacturer's instructions for the IL-8 kit (R and D Systems, USA). The outcome was expressed in picograms per milliliter (pg/ml) in terms of concentration.

The data were analyzed statistically with the use of GraphPad Prism software, version 6.0. The probability was computed using the unpaired *t*-test for parametric data and the Mann–Whitney and Kruskal–Wallis tests for nonparametric data. Dunn's correction for multiple comparisons was included in the analyses that were conducted *post hoc*. In order to determine the probability for categorical data, Fisher's exact test was utilized. The Spearman correlation test was used to determine the degree of correlation between the parameters. If $P < 0.05$, then the difference is deemed to be statistically significant.

Results

Thirty CLL patients included with a mean age (55.23 ± 9.276) years ranged between (40 and 80) years, and thirty matched age and gender healthy volunteers were considered as a control group, ranging between (17 and 67) years, with a mean 51.23 ± 7.421 years. The male: female ratio among the CLL patients was (2:1), and the control group was (1:1). Both the CLL patients groups and the control group were genders matched without significant differences ($P = 0.2949$), as shown in Table 1. Regarding blood indices analyses of studied groups, including hemoglobin level, WBCs count, platelets count, and lymphocyte percentage are shown in Table 1. Furthermore, results showed an elevated level of IL-8 among CLL patients with a mean ± SE (28.83 ± 12.68 pg/ml) compared to the control group with a mean ± SE (10.20 ± 1.008 pg/mL), although it was not significant ($P = 0.1483$).

Regarding disease stages results showed that the median level of IL-8 in serum was higher among CLL patients in Stage (A) (16.28 pg/mL) compared to Stage (B) (7.476) and Stage (C) (7.608 pg/ml) with a significant difference ($P = 0.0193$) among the three groups, as shown in Table 2.

Table 1: The general characteristics of chronic lymphocytic leukemia patients and control groups

	Control	Patients	*P*
Number	30	30	
Sex			
Male	15	20	0.2949
Female	15	10	
Hb (g/dL), mean±SE	14.03±0.2919	11.54±0.3211	<0.0001
WBC (10^3/µL), median (range)	7.75 (5–10)	54.5 (22–197)	<0.0001
PLT (10^3/µL), median (range)	312 (198–485)	154.5 (45–265)	<0.0001
Lymphocyte (%), mean±SE	29.62±0.9221	72.05±2.903	<0.0001
IL-8 (pg/mL), mean±SE	10.20±1.008	28.83±12.68	0.1483**

**Unpaired *t*-test. SE: Standard error, WBC=White blood cell, PLT=Platelet count, IL-8=Interleukin-8, Hb=Hemoglobin

The correlation between different studied parameters shown in Table 3, no considerable correlation between IL-8 and all parameters.

In terms of age groups, >60 years and ≤ 60 years old the findings of IL-8 and hematological parameters didn't show a significant difference as shown in Table 4.

In terms of gender, findings of IL-8 and hematological parameters did not show a significant difference, as shown in Table 5.

The receiver operating characteristic (ROC) curve analysis of IL-8 was showed a good prediction of the area under the curve value when predicting the CLL patients in stage (A) from stage (C), with 81.82% sensitivity and 72.73% specificity, comparisons for CLL vs control, A vs. B, and B vs. C showed poor discriminatory value with no significance as shown in Table 6 and Figure 1

Discussion

Finding and then confirming features that suggest a high chance of a positive reaction to treatment and illness-free survival rates, as well as overall survival

Table 2: Distribution of serum interleukin-8 levels among chronic lymphocytic leukemia patients according to disease stage

Stage of disease	IL-8 (pg\mL)median (range)	Adjusted *P* values		
		Stage of disease	A	B	C
A (*n*=11)	16.28 (7.695–381.1)	A		0.1322	0.0232
B (*n*=8)	7.476 (5.882–107.6)	B	0.1322		>0.999
C (*n* =11)	7.608 (5.392–36.5)	C	0.0232	>0.999	

P value of Kruskal–Wallis test before multiple comparison is 0.0193.
IL-8: Interleukin-8

Table 3: Correlations between different studied parameters

	IL-8	Age	HGB	WBC	PLT	Lymphocyte (%)
IL-8		0.268	0.228	0.216	0.345	−0.087
Age	0.268		0.113	0.027	0.060	0.141
HGB	0.228	0.113		0.292	0.151	−0.285
WBC	0.216	0.027	0.292		0.040	0.157
PLT	0.345	0.060	0.151	0.040		−0.429*
Lymphocyte (%)	−0.087	0.141	−0.285	0.157	−0.429*	

Significance (two-tailed)=*$P \leq 0.05$, $P \leq 0.01$, $P \leq 0.001$, $P \leq 0.0001$. Numbers represent (*r*) value of Pearson correlation. When *r*=0.9 to 1 (very high positive correlation), *r*=0.7 to 0.9 (high positive correlation), *r*=0.5 to 0.7 (moderate positive correlation), *r*=0.3 to 0.5 (low positive correlation), *r*=0 to 0.3 (negligible positive correlation). When *r*=−0.9 to −1 (very high negative correlation), *r*=−0.7 to −0.9 (high negative correlation), *r*=−0.5 to −0.7 (moderate negative correlation), *r*=−0.3 to −0.5 (low negative correlation), *r*=0 to −0.3 (negligible negative correlation). WBC=White blood cell, PLT=Platelet count, IL-8=Interleukin-8, Hb=Hemoglobin

Table 4: Interleukin-8 serum levels and hematologic parameters in participants as categorized according to age groups: <60 years, >60 years

	Parameters				
	IL-8 (pg/mL), median (range)	WBC (×10³/µL), median (range)	Hb (g/dL), mean±SE	PLT (×10³/µL), mean±SE	Lymphocyte (%) median (range)
≤60 years	8.028 (5.4–381)	46 (22–197)	11.48±0.3739	157.3±13.27	75 (40–90)
>60 years	8.824 (7.7–40.8)	60 (53–91)	11.73±0.6661	146.1±30.02	85 (50–97)
P	0.19	0.2207	0.7522	0.7039	0.2397

WBC=White blood cell, PLT=Platelet count, IL-8=Interleukin-8, SE=Standard error, Hb=Hemoglobin

Table 5: Interleukin-8 serum levels and hematologic parameters in participants as categorized according to gender

	Parameters					
	IL-8 (pg/mL), median (range)	Age (years), mean±SE	WBC (×10³/µL), median (range)	Hb (g/dL), mean±SE	PLT (×10³/µL), mean±SE	Lymphocyte (%), mean±SE
Male	8.271 (5.9–381)	55.45±2.379	74 (34–197)	11.60±0.421	152.3±14.81	74.66±3.19
Female	9.4 (5.4–108)	54.80±1.948	37.5 (22–59)	11.43±0.496	159.6±22.09	66.84±5.828
P	0.4888	0.8601	0.0001	0.8134	0.7804	0.21

WBC=White blood cell, PLT=Platelet count, IL-8=Interleukin-8, SE=Standard error, Hb=Hemoglobin

Table 6: The receiver operating characteristic curve for interleukin-8 for chronic lymphocytic leukemia diagnostic performance

IL-8 comparison groups	AUC	Explanation	95% CI of AUC	*P*	Optimum cut-off value	Sensitivity (%)	Specificity (%)
CLL versus control	0.5678	Poor	0.42–0.716	0.3672	8.343 pg/mL	50	50
A versus B	0.75	Fair	0.49–1.015	0.0693	11.06	75	72.73
A versus C	0.851	Good	0.68–1.019	0.00528	10.07	81.82	72.73
B versus C	0.534	Poor	0.25–0.816	0.8044	7.576	45.45	50

AUC=Area under the curve, CI=Confidence interval, CLL=Chronic lymphocytic leukemia, IL-8=Interleukin-8

rates, could help us better understand the biological and pathophysiological aspects of CLL.

CLL cells' growth and survival in their natural environment depend on a lot of different signals, including cytokines like IL-8. A study found that IL-8 is always made in CLL cells and acts as an autocrine growth and apoptosis resistance factor.[10]

The mean IL-8 in CLL patients was higher than that of healthy controls, although it was not statistically significant (P = 0.1483). This finding suggests that IL-8 may have some role in the disease; however, as the IL-8 level difference was not that much, the statistical analysis did not exhibit significance. This could be attributed to the high standard error (SE) of IL-8 in patients which denoted high variation in IL-8 serum levels among patients; a finding that has been reported by several studies.[11-13] In addition, one research has highlighted the significant fluctuation of IL-8 serum levels per patient across the disease course.[12] Altogether, these variations were attributed to variations of tumor microenvironment from one patient to another and in each patient over time.[14]

The most interesting thing we found was that IL-8 levels changed a lot at different stages of the disease (P = 0.0193). Contrary to the expectation that IL-8 levels would be elevated in the advanced stages of the disease, it was found that the early stage exhibited the highest median level of IL-8 (Stage A: 16.28 pg/mL).

These findings are in line with these of[15] which reflects active microenvironment signaling. Another study has pointed out that IL-8 secretion is strongly stimulus dependent on other signaling molecules (e.g., CD40 L, BCR signaling). Since in early disease the pathways of these signals are more active, this would be translated to higher IL-8 levels.[12]

Conversely, Il-8 levels decline in advanced disease due to chronic stimulation of the immune system, which leads to immune exhaustion and finally diminished IL-8 production. Moreover, the tumor microenvironment becomes immunosuppressive by the domination of IL-10, TGF-β, and regulatory T-cells, which they add further suppressing effect on IL-8 levels. Furthermore, patients in advanced cases may have been subjected to therapy that affects IL-8 release. In addition, the tumor microenvironment in those patients has been overwhelmed by tumor cells, making unable to release IL-8.[16]

Taken together, our data delineate an IL-8 pattern where IL-8 exhibits high serum levels in early disease, while late disease manifests with low levels.

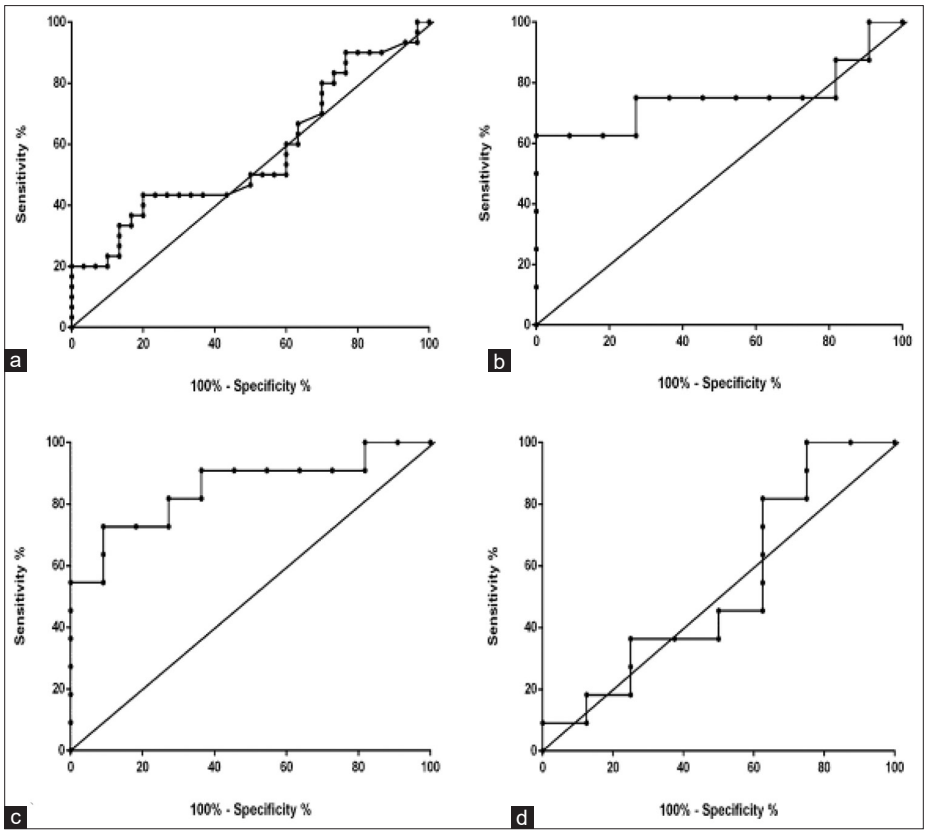

Figure 1: CLL versus Control groups receiver operating characteristic curve for interleukin-8: Presents the discriminatory power of: (a) CLL versus control comparison (area under the curve [AUC] =0. 567) showing poor performance. (b) A versus B groups (AUC = 0.75) showing poor performance. (c) A versus C groups (AUC = 0.851) showing best performance. (d) B versus C groups (AUC = 0.534) showing poor performance

This reflects the vital role of IL-8 in CLL development and progression as IL-8 plays a key role in cell proliferation in early disease. Conversely, it declines in advanced cases due to genetic changes or altered signaling mechanisms from the tumor microenvironment which eventually leads to lower blood vessels in stage B or C.[17]

The ROC curve study strongly supports this idea as it shows that IL-8 was a very good predictor of Stage A versus Stage C illness.

The implementation of IL-8 as a diagnostic marker for CLL should follow a careful, concise approach. IL-8 could be a useful promising marker in diagnosing patients with early disease; however, its role and value decline as the disease advances.

A study conducted by[13] concluded that IL-8 can be implemented as a prognostic marker. Furthermore, IL-8 serves as a monitoring tool as it changes with disease status in terms of remission or relapse it would be useful for monitoring disease progression, remission, and response to therapy.[10]

There is no association between IL-8 levels and other factors such as age, hemoglobin, white blood cell count, platelet count, and lymphocyte percentage. This finding is in accordance with other studies that have highlighted the importance of IL-8 as an independent prognostic marker.[18]

Conclusion

Il-8 could be utilized as a promising prognostic factor in patients with early CLL disease. Nevertheless, it can be of value to monitor disease progression during patient follow-up and monitoring prior to treatment.

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Conflicts of interest

There are no conflicts of interest.

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