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RESEARCH ARTICLE

Serum Homocysteine, Hepcidin, IL-22 and IL-33 as Critical Biomarkers in Chronic Lymphocytic Leukemia Patients

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Abstract

Introduction: Chronic lymphocytic leukemia (CLL) is a diverse hematologic malignancy marked by considerable genetic and clinical heterogeneity. Therefore. The present study investigated the roles of interleukin IL-22 and IL-33 along with their relation with iron levels, and inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in progression of CLL disease, aiming to identify prospective biomarkers for enhanced risk evaluation and focused therapy approaches. **Materials and Methods:** A total of 60 individuals with CLL and 40 healthy control were enlisted. Blood samples were collected from all participants to evaluate the ESR, while the serum of participants was used to detect homocysteine, hepcidin, iron levels, IL-22, IL-33 and CRP by using enzyme-linked immunosorbent assay (ELISA). **Results:** demonstrated markedly elevated homocysteine levels in CLL patients (20.98 ± 0.62 nmol/ml) in compared to control (7.6 ± 0.48 nmol/ml, $P < 0.0001$). Iron levels were also much lower in CLL patients (41.38 ± 1.46 µg/dL) than the control (97.44 ± 4.6 µg/dL, $P < 0.0001$). Both IL-22 and IL-33 were considerably enhanced in CLL patients; IL-22 increased from 3.55 ± 0.45 pg/ml in control to 51.7 ± 3.2 pg/ml in patients ($P < 0.0001$), while IL-33 rose from 12.77 ± 1.3 pg/ml to 59.9 ± 2.9 pg/ml ($P < 0.0001$). Also, CRP and ESR levels were very high in CLL patients. Correlation analysis revealed significant connections among iron levels, IL-22, IL-33, and inflammatory markers, illustrating the intricate interplay of metabolic and inflammatory processes in CLL. **Conclusion:** These results provide light on the abnormal clinical manifestations of CLL and indicate that monitoring biochemical and inflammatory biomarkers may improve risk assessment and guide targeted therapy.

Keywords: Chronic lymphocytic leukemia- Homocysteine- Hepcidin- IL-22 and IL-33- iron- CRP and ESR

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults, particularly in Western countries, accounting for approximately 25–30% of all leukemia cases. In 2019, an estimated 100,000 new cases of CLL were reported worldwide, with nearly 40,000 associated deaths [1]. The disease is characterized by the progressive accumulation of long-lived, functionally incompetent lymphocytes that exhibit resistance to apoptosis [2]. The pathogenesis of CLL is multifactorial, involving genetic, immunological, and environmental determinants.

A key feature of CLL is the presence of a persistent inflammatory state, which plays a crucial role in disease progression and immune dysregulation. This chronic inflammatory environment promotes tumor survival, proliferation, and resistance to therapy [3]. In this context, metabolic alterations have gained increasing attention, particularly the role of homocysteine, a sulfur-containing amino acid involved in methionine metabolism. Elevated homocysteine levels (hyperhomocysteinemia) have been associated with adverse clinical outcomes in various malignancies, including CLL. Mechanistically, homocysteine contributes to oxidative stress, endothelial dysfunction, and immune imbalance, all of which may enhance leukemic progression. Additionally, disruptions in homocysteine metabolism are linked to DNA damage and epigenetic alterations, further supporting its potential role as a biomarker for disease activity and prognosis [4, 5].

Hepcidin, a peptide hormone synthesized by the liver, is a significant element in the inflammatory mechanisms

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linked to CLL. Hepcidin is pivotal in maintaining iron homeostasis by binding to ferroportin, the iron exporter, resulting in its degradation and thereby diminishing iron outflow from cells. Dysregulation of hepcidin is frequently noted in chronic lymphocytic leukemia (CLL), primarily attributable to chronic inflammation and the overproduction of cytokines, especially interleukin-6. Increase hepcidin levels lead to the retention of iron in macrophages, causing functional iron deficiency and anemia of chronic illness, a prevalent consequence in CLL patients [6, 7]. Furthermore, hepcidin's function in an immune response regulation and tumor microenvironment modulation indicates its potential direct contribution to leukemic cell proliferation, rendering it a significant factor in CLL pathogenesis [8]. The relationship between homocysteine and hepcidin in CLL is intricate and multifaceted and An epigenome-wide DNA methylation analysis in CLL patients revealed key modulators associated with drug sensitivity and survival post-treatment, illustrating the impact of epigenetic dynamics on therapeutic outcomes,including vitamin B12, vitamin D3 and other essential nutrients. This deficiency can impair the re-methylation of homocysteine to methionine, resulting in elevated homocysteine levels [9-11].

Besides these metabolic variables, interleukins including IL-33 and IL-22 are essential in modulating inflammation and tumor advancement in CLL. Interleukin-33, a constituent of the IL-1 cytokine family, is a powerful stimulator of Th2 immune responses. In chronic lymphocytic leukemia (CLL), interleukin-33 (IL-33) engages the ST2 receptor on immune cells, initiating an inflammatory cascade that facilitates the survival and multiplication of leukemic cells. This cytokine facilitates immune evasion by inhibiting T-cell and NK-cell function, hence promoting the persistence of CLL (11). Interleukin-22, predominantly synthesized by Th17 and Th22 cells, plays a role in tissue healing and inflammation. In the context of CLL, IL-22 exacerbates the inflammatory milieu by enhancing leukemic cell viability and treatment resistance [8]. The interleukins, together with other inflammatory markers, highlight the significance of chronic inflammation in the pathogenesis of CLL. Moreover, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often elevated inflammatory markers in chronic lymphocytic leukemia (CLL) that can provide valuable clinical information. While CRP is linked to poor prognosis and disease activity, ESR reflects the systemic inflammatory burden; both act as predictors of clinical outcomes in CLL patients [12, 13]. The relationships between homocysteine, hepcidin, IL-33, IL-22, and various inflammatory markers provide a comprehensive view of the metabolic-inflammatory axis in CLL. These biomarkers allow for the assessment of illness progression and could also serve as targets for treatment [14]. Therefore, the present study aims to investigate the roles of interleukin-22 (IL-22) and interleukin-33 (IL-33) and to evaluate their association with iron levels, as well as inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), in patients with chronic lymphocytic leukemia

Materials and Methods

Study Design and Subjects

This case–control study was conducted on patients diagnosed with chronic lymphocytic leukemia (CLL) who attended Medical City Hospital in Baghdad, Iraq, between December 2023 and April 2024. The diagnosis of CLL was established by consultant hematologists according to internationally recognized criteria, including the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines, based on clinical presentation, peripheral blood lymphocytosis ($\geq 5 \times 10^9$/L), and immunophenotyping. A total of 60 patients with confirmed CLL were enrolled, alongside [20-70 years] age- and sex-matched to 40 healthy subjects used as control group.Patients were classified according to disease stage using the Rai staging system to provide clinical context for disease progression. Inclusion criteria encompassed adult patients aged ≥18 years, without prior chemotherapy or radiotherapy. Exclusion criteria included patients with concomitant acute infection, autoimmune diseases other than CLL-associated autoimmunity, liver or renal impairment, or any condition known to affect serum homocysteine, hepcidin, or inflammatory markers.

Demographic and Clinical Classification

Participants were categorized by age (20–37 years, n=31; 38–54 years, n=14; 55–71 years, n=15), sex (male, female), and hereditary background (patients with or without a family history of hematologic malignancies in first-degree relatives: n=18 and n=42, respectively).

Blood Sample Collection and Processing

Venous blood samples (5 mL) were collected from each participant under aseptic conditions. For biochemical assay, 3 mL of blood was allowed to clot at room temperature and centrifuged at 3000 × g for 10 minutes to obtain serum, which was aliquoted and stored at –80°C until analysis. The remaining 2 mL was collected into EDTA tubes for complete blood count ESR measurement.

Measurement of Serum Homocysteine and Hepcidin

Serum homocysteine levels were quantified using the Human HCY (Homocysteine) ELISA Kit (MyBioSource, Catalog No. MBS766119), following the manufacturer's protocol. Briefly, standards and samples were added to wells pre-coated with anti-HCY antibodies, followed by incubation with biotin-conjugated detection antibodies and avidin-HRP conjugate. After substrate addition and color development, absorbance was measured at 450 nm using a microplate reader (BioTek ELx800, USA). Serum hepcidin concentrations were determined using the Human Hepcidin ELISA Kit (MyBioSource, Catalog No. MBS1601481) according to the provided instructions. The assay employs a sandwich ELISA format with high specificity and sensitivity for human hepcidin, with results expressed in ng/mL.

Measurement of Inflammatory Markers (CRP and ESR)

Serum C-reactive protein (CRP) levels were assessed

using the High Sensitivity Human CRP ELISA Kit (MyBioSource, Catalog No. MBS2021863). Samples and standards were processed according to the kit protocol, and CRP concentrations were expressed in mg/L. The erythrocyte sedimentation rate (ESR) was determined using the Westergren method, in which anticoagulated whole blood was drawn into a standardized Westergren tube (BD Vacutainer®, USA), and the distance of red blood cell sedimentation after 1 hour was recorded in mm/h.

Measurement of Immunological Markers (IL-22 and IL-33)

Serum IL-22 and Serum IL-33levels were measured using the Human IL-22 and Human IL-33 ELISA Kit (MyBioSource, Catalog No. MBS824726 and MBS283905), respectively. The procedure was carried out according to the manufacturer's instructions. Both samples and standards were processed as per the provided protocol, and the IL-22 and IL-33 concentrations were expressed in pg/mL.

Ethical Considerations

The Ethics Committee of the Department of Biology, College of Science, University of Baghdad, gave their permission for this work. reference no. CSEC/1023/0077, on October 28, 2023.

Statistical analysis

Statistical analysis was performed using the Statistical Analysis System (SAS) software (2018). Data were expressed as mean ± standard error (SE). The independent samples t-test was used to compare differences between two groups (CLL patients and controls), while one-way analysis of variance (ANOVA) was applied for comparisons involving more than two subgroups (e.g., age groups or disease stages).

Pearson correlation analysis was conducted to evaluate relationships among continuous variables. Cohen's d was calculated to estimate the effect size of differences between group means, providing a measure of the magnitude of observed effects rather than association. A p-value of ≤0.05 was considered statistically significant.

Results

Comparison of Metabolic Markers

The results showed that homocysteine levels were significantly elevated in CLL patients (20.98 ± 0.62 pmol/mL) compared to controls (7.6 ± 0.48 pmol/mL; $p < 0.0001$, Cohen's d = 3.2). Hepcidin levels were also markedly higher in patients (179.8 ± 8.99 µg/dL) versus controls (36.08 ± 1.5 µg/dL; $p < 0.0001$, Cohen's d = 2.6). Conversely, serum iron was significantly reduced in patients (41.38 ± 1.46 µg/dL) compared to controls (97.44 ± 4.6 µg/dL; $p < 0.0001$, Cohen's d = -2.72), indicating disrupted iron homeostasis (Table 1).

Comparison of Immunological Markers

IL-22 was significantly higher in CLL patients (51.7 ± 3.2 pg/mL) compared to controls (3.55 ± 0.45 pg/mL; $p < 0.0001$, Cohen's d = 2.45). Similarly, IL-33 levels were elevated in patients (59.9 ± 2.9 pg/mL) versus controls (12.77 ± 1.3 pg/mL; $p < 0.0001$, Cohen's d = 2.63) (Table 2).

Comparison of Inflammatory Markers

The ESR was significantly elevated in patients (46.45 ± 1.98 mm/h) compared to controls (16.88 ± 1.5 mm/h), and CRP levels were higher in patients (4.71 ± 0.4 mg/dL) versus controls (0.687 ± 0.071 mg/dL; $p < 0.0001$) (Table 3).

Table 1. Comparison of Homocysteine, Hepcidin, and Iron between Patients with CLL and the Control Group

	Mean ± SE			
Parameters	Control	Patients with CLL	P-value	Cohen's d
Homocysteine (pmol/ml)	7.6 ± 0.48	20.98 ± 0.62	0.0001	3.2
Hepcidin (ug/dl)	36.075 ± 1.5	179.8 ± 8.99	0.0001	2.6
Iron (µg/dL)	97.44 ± 4.6	41.38 ± 1.46	0.0001	-2.72

Table 2. Comparison of Immunological Markers (IL-22 and IL-33) between Patients with CLL and the Control Group.

	Mean ± SE			
Parameters	Control	Patients with CLL	P-value	Cohen's d
IL-22 pg/ml	3.55 ± 0.45	51.7 ± 3.2	0.0001**	2.45
IL-33 Pg/mL	12.77 ± 1.3	59.9 ± 2.9	0.0001**	2.63

Table 3. Comparison of Inflammation Markers (CRP and ESR) between Patients with CLL and the Control Group

	Mean ± SE			
Parameters	Control	Patients with CLL	P-value	Cohen's d
CRP (mg/dl)	0.687 ± 0.071	4.71 ± 0.4	0.0001**	1.647
ESR (mm/h)	16.88 ± 1.5	46.45 ± 1.98	0.0001**	2.219

Subgroup Analysis

Age groups

Homocysteine levels varied significantly among age groups (P = 0.040), with the middle-aged group showing the highest mean value. Iron levels decreased significantly with age (P = 0.005), while hepcidin levels showed a non-significant increasing trend (P = 0.071). Gender and hereditary history: No significant differences in any parameters were observed between males and females, or between patients with and without family history of hematologic malignancies. The results of Table 4 showed that homocysteine (Hcy) levels a statistically significant variation in homocysteine levels was noted among distinct age groups (P-value = 0.040). The youngest group (20-37 years) exhibited a mean homocysteine content of 19.6 pmol/ml, which escalated in the middle-aged group (38-54 years) to 23.3 pmol/ml. The oldest group (55-71 years) exhibited a marginally reduced mean homocysteine level of 21.6 pmol/ml. Iron levels were noted to be a significant diminished in older age group, with the youngest group exhibiting 45.74 µg/dL, the middle-aged group 38.07 µg/dL, and the oldest group 35.47 µg/dL. Despite a trend of rising hepcidin levels with age, the difference was not statistically significant. The levels of IL-22 and IL-33 did not differ significantly between groups of different age of CKD patients (Table 4). Also, no significant difference in the level of inflammation markers (CRP and ESR) among different age groups of CLL patients was observed (Table 4). The results presented in Table 4 indicate non- significant difference in all parameters studies among the CLL patients based on gender. Moreover, similar results were observed with history of hereditary diseases among all parameters studies (Table 4).

Correlation Analysis

Positive correlation between homocysteine and hepcidin (r = 0.271, P = 0.036).Negative correlation between IL-22 and IL-33 (r = -0.283, P = 0.028). Iron negatively correlated with homocysteine (r = -0.315, P =0.014) and hepcidin (r = -0.764, P < 0.001). IL-33 negatively correlated with iron (r = -0.283, P = 0.028) (Table 5).

Discussion

The present study demonstrates significant metabolic and inflammatory alterations in CLL patients compared to healthy controls, highlighting the complex interplay between immune dysregulation, iron metabolism, and systemic inflammation in disease progression.

Metabolic Alterations

Seruma Serum homocysteine levels were markedly elevated in CLL patients, reflecting disruptions in one-carbon metabolism and DNA methylation pathways [15]. Accumulation of homocysteine contributes to oxidative stress, genomic instability, and impaired methylation, potentially supporting leukemic cell survival. Vitamin B12 deficiency may further hinder homocysteine metabolism, amplifying these effects. These findings suggest that homocysteine plays a role in leukemic cell persistence and tumor biology.

Elevated hepcidin levels in CLL patients indicate a disturbance in iron homeostasis, likely driven by chronic inflammation. Hepcidin reduces intestinal iron absorption and promotes macrophage iron sequestration, leading to decreased serum iron and anemia of chronic disease, a common complication in CLL. The concurrent elevation of homocysteine and hepcidin suggests a coordinated metabolic-inflammatory response, where oxidative stress and inflammatory signaling jointly modulate iron and cellular metabolism.

Inflammatory Markers

Inflammatory indicators, including CRP and ESR, were significantly increased in CLL patients, confirming the presence of systemic inflammation. Chronic low-grade inflammation may facilitate immune evasion, enhance the stromal microenvironment, and support leukemic cell persistence, contributing to disease progression [16].

Table 4. Distribution of Parameters Studies According to Age, Gender, and Hereditary Diseases.

	Mean ± SE						
Age categories (Years)	Hcy (pmol/ml)	Hepcidin (ug/dl)	Iron (µg/dL)	IL-22 (pg/ml)	IL-33 (Pg/mL)	CRP (mg/dl)	ESR (mm/h)
20-37 (31)	19.5932 ± 083	160.048 ± 8.8	45.74 ± 1.7	52.7 ± 4.77	58.9 ± 4.5	5.5 ± 0.6	44.19 ± 2.4
38-54 (14)	23.345 ± 1.3	197.36 ± 20.13	38.07 ± 1.24	52.57 ± 6.5	59.5 ± 5.32	3.32 ± 0.79	48.79 ± 4.8
55-71 (15)	21.64 ± 1.14	204.25 ± 23.33	35.47 ± 3.55	48.87 ± 6.3	62.27 ± 5.31	4.39 ± 0.70	48.93 ± 4.4
P-value	0.040*	0.071 NS	0.005**	0.885 NS	0.894 NS	0.082 NS	0.508 NS
			Gender				
Female	20.74 ± 0.97	183.18 ± 13.2	40.2 ± 1.97	48.28 ± 3.98	60.9 ± 4.14	5.3 ± 0.62	45.8 ± 2.8
Male	21.22 ± 0.77	176.43 ± 12.4	40.2 ± 1.97	55.12 ± 5.13	59.62 ± 32	4.13 ± 0.5	47.1 ± 2.9
P-value	0.705 NS	0.711NS	0.423 NS	0.297NS	0.7841 NS	0.147 NS	0.148 NS
			Hereditary diseases				
Yes (18)	19.94 ± 0.93	166.22 ± 16.08	40.2 ± 1.97	48.28 ± 3.98	60.9 ± 4.14	4.33 ± 0.72	43.22 ± 2.98
No (42)	21.42 ± 0.78	185.62 ± 10.84	42.57 ± 2.16	55.12 ± 5.13	59.62 ±	4.88 ± 0.49	47.83 ± 2.51
P-value	0.275 NS	0.327 NS	0.423 NS	0.297NS	0.7841 NS	0.533 NS	0.290 NS

Table 5. Pearson Correlation Analysis among Some Parameters Studies (Homocysteine, Hepcidin, Iron, IL-22 and IL-33).

		Pearson correlation			
		Homocysteine	Hepcidin	IL-22	IL-33
	Sig. (2-tailed)	0.052	0.001	0.559	0.792
	Sig. (2-tailed)	0.185	0.563	0.386	0.562
	Sig. (2-tailed)	0.222	0.231	0.518	0.304
	Sig. (2-tailed)	0.696	0.819	0.486	0.992
Homocystein	Pearson Correlation	1	0.271	-.176-	0.012
	Sig. (2-tailed)		0.036	0.177	0.929
Hepcidin	Pearson Correlation	0.271	1	-.166-	0.121
	Sig. (2-tailed)	0.036		0.205	0.357
IL-22	Pearson Correlation	-.176-	-.166-	1	-.283-
	Sig. (2-tailed)	0.177	0.205		0.028
IL-33	Pearson Correlation	0.012	0.121	-.283-	1
	Sig. (2-tailed)	0.929	0.357	0.028	
	Sig. (2-tailed)	0.198	0.944	0.027	0.477
Iron	Pearson Correlation	-.315-	-.764-	0.216	-.059-
	Sig. (2-tailed)	0.014	0	0.098	0.652

Cytokine Involvement

Cytokines IL-22 and IL-33 were elevated in CLL patients, consistent with their roles in tumor-immune interactions. IL-22 can promote leukemic cell viability via STAT3 signaling and modulation of tissue repair, whereas IL-33, as an alarmin, is released in response to cellular stress and supports immune polarization and inflammatory processes [17, 18]. The observed negative correlation between IL-22 and IL-33 may indicate a regulatory balance within the immune milieu.

Demographic Considerations

Age-related variations in biomarkers may reflect cumulative disease burden and immunosenescence. Aging is associated with a pro-inflammatory state ("inflammaging") that may exacerbate metabolic and immunological dysregulation in CLL [19]. No significant differences were observed between male and female patients for homocysteine, hepcidin, cytokines, or inflammatory markers, suggesting that disease-driven metabolic and inflammatory processes may override natural hormonal influences . Family history did not significantly affect biomarker levels, indicating that systemic metabolic and inflammatory alterations are primarily disease-driven rather than genetically inherited [20, 21].

Correlations

Correlation analysis revealed a positive association between homocysteine and hepcidin, supporting a link between metabolic stress and inflammation-mediated iron regulation. Hepcidin was inversely correlated with serum iron, confirming its key role in iron homeostasis [17]. Homocysteine showed no significant correlation with IL-22 or IL-33, suggesting that metabolic dysregulation and cytokine-mediated immune responses operate via distinct mechanisms.

Limitations

This study has several limitations. The sample size was relatively small, which may affect the generalizability of the findings. Clinical staging of CLL (e.g., Rai or Binet classification) was not included, limiting interpretation in relation to disease severity. Additionally, potential confounding factors, such as nutritional status, vitamin B12, and folate levels, were not controlled, which could influence homocysteine measurements. Future studies with larger cohorts, clinical stratification, and control of confounding variables are recommended.

Overall, these findings provide a comprehensive perspective on the interplay between metabolic, inflammatory, and immunological pathways in CLL and suggest that integrated evaluation of these markers may enhance understanding of disease mechanisms and progression.

In conclusion, the present study demonstrates that chronic lymphocytic leukemia is characterized by significant metabolic and inflammatory dysregulation, reflected by alterations in homocysteine, hepcidin, inflammatory markers, and immunomodulatory cytokines. Elevated homocysteine and hepcidin levels highlight the contribution of disrupted methylation pathways and iron homeostasis to disease pathophysiology. Persistent systemic inflammation, evidenced by CRP and ESR, further underscores the role of inflammatory signaling in leukemic progression. Demographic factors such as age, sex, and family history showed limited influence on biomarker expression, suggesting that disease-related mechanisms predominate. Correlation analysis confirmed the interconnected nature of metabolic and inflammatory pathways in CLL. These findings support the potential utility of combined metabolic and inflammatory biomarkers in understanding disease mechanisms and guiding future therapeutic interventions.

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Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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