Original Article

Soluble CD163 Concentration in Chronic Lymphocytic Leukemia and its Correlation with Prognostic Parameters

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Abstract

Background: Chronic Lymphocytic Leukemia (CLL) is a clonal malignancy of mature B-lymphocytes characterized by significant clinical heterogeneity. Soluble CD163 (sCD163), a monocyte/macrophage-specific scavenger receptor, has been associated with disease severity and prognosis in several malignancies. However, its role in CLL remains unclear. While traditional staging systems like Rai and Binet remain foundational, emerging biomarkers offer enhanced prognostic precision. Among these, CD163, β2-Microglobulin (β2MG), and leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) have demonstrated clinical relevance. **Objectives:** To evaluate plasma levels of soluble CD163 at diagnosis in patients with CLL in comparison to healthy controls, correlate sCD163 levels with clinical staging, hematological parameters, and other prognostic parameters such as plasma B2MG and LAIR-1 expression. **Materials and methods:** This is A cross-sectional study was conducted over six months (December 2023 – May 2024), involving 88 individuals. Group I included 68 newly diagnosed CLL patients, and Group II consisted of 20 healthy controls. Diagnosis was confirmed via peripheral blood morphology and immunophenotyping using 8-color flow cytometry (BD FACS Canto II). Data collected included demographic and clinical features, hematological profiles, LAIR-1 expression, B2MG levels, and Binet clinical stage. **Results:** Significant difference for mean concentration of both soluble CD163 and B2MG between patients and control group with p value (0.022,0.003) respectively. No significant correlation was found between sCD163 and B2MG, hemoglobin levels, platelet counts, absolute lymphocyte count, smudge cell%, or LAIR-1 expression. Furthermore, sCD163 levels did not significantly differ across Binet stages (p = 0.704). **Conclusion:** Plasma CD163 levels are significantly reduced in CLL patients compared to healthy individuals, suggesting a potentially different role of macrophage-derived markers in CLL compared to other lymphomas. However, its lack of association with disease stage or other prognostic markers indicates limited utility as a standalone prognostic biomarker in CLL.

Keyword: Chronic Lymphocytic Leukemia, CD163 Soluble Biomarkers, B2-Microglobulin, LAIR-1, immunophenotyping

Introduction

Chronic Lymphocytic Leukemia (CLL) is a lymphoproliferative disorder characterized by the clonal expansion and accumulation of mature, typically CD5-positiveB lymphocytes in the peripheral blood, bone marrow, lymph nodes, and spleen. Clinical manifestations vary but often include lymphadenopathy, splenomegaly, and cytopenias as the disease advances [1,2]. Diagnosis requires a sustained lymphocyte count exceeding 5 × 10⁹/L in the peripheral blood for at least three months. Clonality of B cells must be confirmed by immunophenotyping, specifically through light chain restriction. On peripheral blood smears, CLL cells appear as small, mature lymphocytes with scant cytoplasm, dense chromatin, and no visible nucleoli [3]. The Rai and Binet staging systems remain standard tools for assessing prognosis and guiding treatment. However, they are limited in stratifying in

light of recent therapeutic advances. The CLL International Prognostic Index (CLL-IPI), which incorporates clinical, biological, and genetic data, has emerged as a more comprehensive model [4,5]. CD163 is a monocyte/macrophage-specific scavenger receptor belonging to the cysteine-rich (SRCR) family. It is considered a marker of alternatively activated (M2) macrophages, often associated with anti-inflammatory responses. Upon activation, CD163 is cleaved and released into the circulation, making it detectable in serum and cerebrospinal fluid [6]. The CD163 gene consists of 17 exons and 16 introns, with alternative splicing giving rise to multiple isoforms, including cytoplasmic, truncated, and extracellular variants [7]. Elevated plasma levels of soluble CD163 (sCD163) have been associated with disease severity in various malignancies, including Diffuse Large B-Cell Lymphoma, classical Hodgkin lymphoma, and colorectal cancer [8] . Prognostic markers such as sCD163 play a critical role in the clinical management of patients with CLL [9]. β2-Microglobulin (β2MG) is a non-polymorphic component of the MHC class I complex, essential for antigen presentation to CD8+ cytotoxic T cells. It is encoded by the B2M gene on chromosome 15. Deficiencies or mutations in this gene impair MHC class I surface expression, leading to immune dysfunction. In CLL, elevated serum β2MG levels are associated with higher tumor burden and advanced disease stage. As such, β2MG is widely recognized as a prognostic marker for disease progression and survival outcomes [11-12]. Leukocyte-Associated Immunoglobulin-Like Receptor-1 (LAIR-1, CD305) is an inhibitory transmembrane glycoprotein broadly expressed on immune cells. In CLL, LAIR-1 expression is higher in early disease stages and is significantly reduced in high-risk cases, including those with unmutated IGHV, CD38 positivity, or adverse cytogenetic abnormalities [13]. This study aimed to evaluate plasma levels of soluble CD163 at diagnosis in patients with CLL in comparison to healthy controls, correlate sCD163 levels with clinical staging, hematological parameters, and other prognostic parameters such as plasma B2MG and LAIR-1 expression.

Materials and Methods

This is a cross-sectional study included 88 participants, comprising 68 newly diagnosed CLL patients and 20 healthy individuals as controls. The study was conducted at the Hematology outpatient clinic of Baghdad Teaching Hospital over a six-month period from December 2023 to May 2024. Diagnosis of CLL was established through morphology and immunophenotyping using eight-color flow cytometry. Blood samples were collected and analyzed for complete blood count (CBC), reticulocyte count, and peripheral smear. Plasma was separated and stored at –80°C for subsequent measurement of soluble CD163 and β2MG levels using ELISA kits. Data of immunophenotyping profile were retrieved from the patient records.

Inclusion Criteria

Newly diagnosed patients with CLL prior to receiving treatment,Diagnosis of CLL confirmed through morphology and immunophenotyping, with a Mutates score of 4 or 5.

Exclusion Criteria

Patients currently undergoing chemotherapy or any other treatment for CLL Patients with other hematological or solid neoplasms, Patients with other hematological or solid neoplasms.

Statistical analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented

as frequencies and percentages. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. ANOVA test was used to compare means among three groups or more. Pearson correlation coefficient was used to assess relationship between two continuous variables. P value ≤ 0.05 was considered as significant relation.

Ethical considerations

All patients received verbal information explaining the aims of the study. Verbal consent was obtained from all the patients participating in the study. Ethical approval for the study was obtained from the ethical committee of the Department of Pathology and Council of the College of Medicine, University of Al-Mustansiriyah.

Results

Age groups and sex distribution

The study included 68 CLL patients with a mean age of (62.13 ± 10.70)years with the oldest patient being 83.0 years and youngest patient being 42.0 years. More than one third of patients (N= 23, 33.8%) presented with age group (60-69 years). Less than two third of patients (N=43, 63.2%) were males as illustrated in (**Figure 1 and Figure 2).**

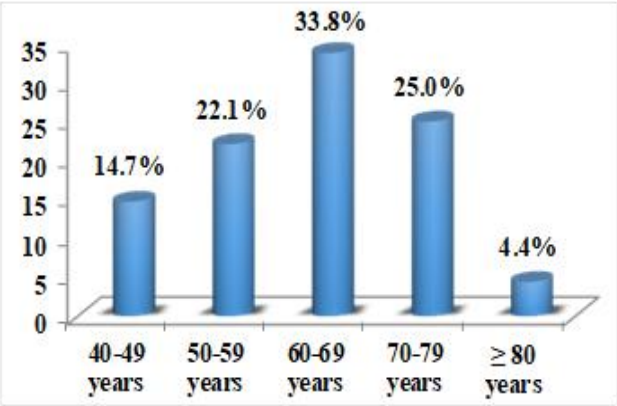

Figure 1: Distribution of patients with Chronic Lymphocytic Leukemia according to age (N=68)

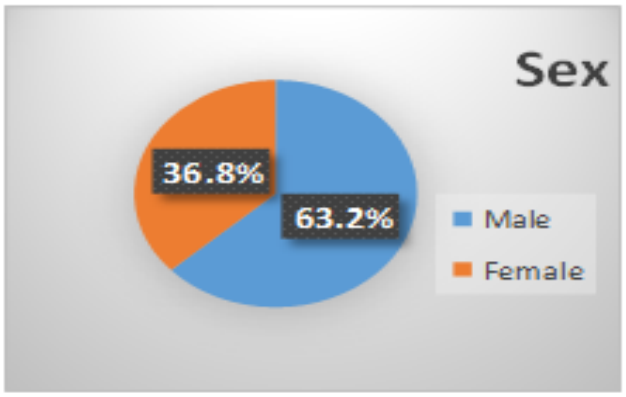

Figure 2: Distribution of patients with Chronic Lymphocytic Leukemia according to sex (N=68).

Distribution of CLL patients according to the Binet staging system

According to Binet staging, 42.6% were in stage A, 29.5% in stage B, and 27.9% in stage C As in **Table 1.**

Table 1: Distribution of patients with chronic lymphocytic leukemia according to Binet staging system of tumor (N=68)

Binet staging system of tumor	No.	%
Stage A	29	42.6%
Stage B	20	29.5%
Stage C	19	27.9%
Total	68	100.0%

Hematological parameters of the patient's group

Hematological findings showed a mean hemoglobin of (11.55 ± 2.50 g/L), platelet count of (199.72 ± 97.67 ×10⁹)/L, absolute lymphocyte count of (61.58 ± 55.86 ×10⁹)/L, and smudge cell % of (18.13 ± 6.54%). As in **Table 2.**

Table 2: Hematological parameters among patients with Chronic Lymphocytic Leukemia (N=68)

Study markers	N	Mean ± SD	Range
Hemoglobin (g/l)	68	11.55 ± 2.50	5.00- 16.40
Platelet count (*10^9/l)	68	199.72 ± 97.67	39.0- 518.0
Absolute lymphocytes count (*10^9 /l)	68	61.58 ± 55.86	8.40- 253.60
Smudge cell %	68	18.13 ± 6.54	6.0- 38.0

Comparison of the markers studied between patients and control groups

Statistically significant differences were observed in plasma levels of soluble CD163 (p = 0.022) and β2-Microglobulin (B2MG) (p = 0.003) in CLL patients compared to controls. As in **Table 3.**

Table 3: The comparison between two study groups according to CD163 concentration (N=88)

Study variable	Study group		P-value
	Patients (N=68) Mean ±SD	Control (N=20) Mean ±SD	
CD163 concentration (ng/ml)	1.34 ± 0.34	1.88 ± 0.97	0.022*
B2MG (ng/ml)	2.47 ± 0.95	1.80 ± 0.53	0.003*

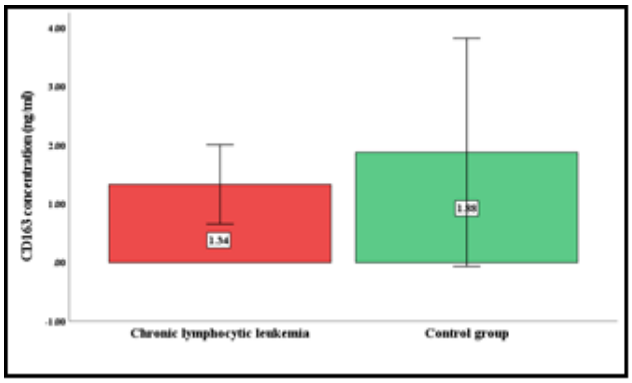

Figure 3: The comparison between two study groups according to the mean CD163 concentration (N=88)

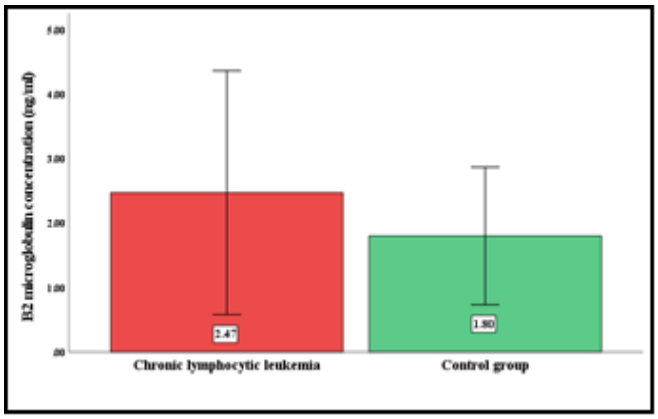

Figure 4: The comparison between two study groups (patients and control) according to the mean B2MG concentration

Comparison of studied markers across different stages of the disease

No significant differences in CD163 were found across disease stages (p = 0.704), B2MG levels differed significantly across Binet stages (p < 0.001), with highest values in stage C.As in **Table 4.**

Table 4: comparison of soluble CD163 and B2MG across disease stages

Study variables	Disease Stage	N	Mean ± SD	P-value
CD163 concentration (ng/ml)	A	29	1.31 ± 0.42	0.704
	B	20	1.39 ± 0.22	
	C	19	1.32 ± 0.31	
B2 Microglobulin concentration (ng/ml)	A	29	1.96 ± 0.58	<0.001*
	B	20	2.62 ± 0.82	
	C	19	3.10 ± 1.12	

*One way ANOVA

When Pearson correlation was used to explore any possible correlation between soluble CD163 concentrations and other hematological variables and B2MG, no significant correlation was established with any of the measured markers as seen in Table (5).

Table (5): The pearson correlation between CD163 concentration and study markers among patients with Chronic Lymphocytic Leukemia (N=68)

Study markers	CD163 concentration (ng/ml)	
	R	P-value
B2 Microglobulin concentration (ng/ml)	-0.147	0.232
Hemoglobin (g/l)	0.019	0.878
Platelet count (*10^9/l)	-0.075	0.543
Absolute lymphocytes count (*10^9 /l)	0.141	0.251
Smudge cell %	-0.056	0.648

LAIR-1 expression in patients group

No significant correlations were found between CD163 and B2MG or hematological parameters. LAIR-1 expression was positive in 16.2% of patients, with no significant difference in CD163 levels between LAIR-1 positive and negative groups (p = 0.143). **As in Figure 5**.

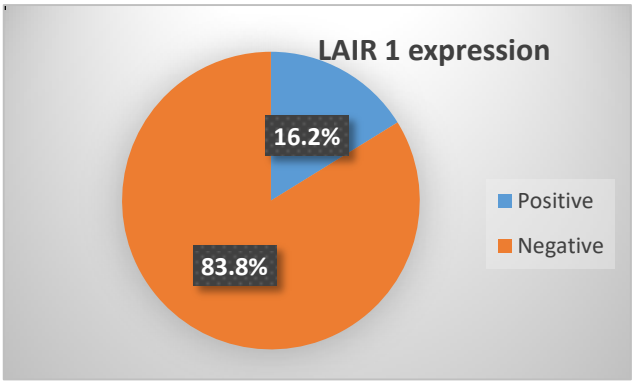

Figure 5: distribution of patient's group according to LAIR-1 expression

Discussion

Chronic lymphocytic leukemia (CLL) is characterized by marked clinical and biological heterogeneity. Therefore, the identification and assessment of prognostic indicators and risk factors are essential not only for establishing an accurate diagnosis but also for tailoring individualized treatment strategies. These prognostic markers contribute to predicting treatment response, disease progression, and overall survival [4]. In the current study, the mean age of CLL patients aligns with previous studies conducted in Iraq by Mahmood TI et al. 2021, [14] Muhammad SS et al.2021 [15], and Hasan KM,2018, [16] and was lower than that reported in Western studies, where the mean age is typically around 69 years [17,18]. These variations may be explained by differences in population structure, genetic predispositions, environmental factors, and life expectancy. The highest proportion of patients (33.8%) fell within the 60–69 years age group, which is consistent with findings from the Iraqi studies conducted in 2018 and 2021 [16,19]. Male predominance was observed in this study, with a male-to-female ratio of 1.7:1. This finding is consistent with global and regional studies [20,21], and the observed gender disparity may have a genetic basis, as suggested by Cantú et al. 2013 [22], who proposed sex-related genetic mechanisms contributing to disease susceptibility in males. The Binet staging system was applied in the clinical classification of CLL patients. The majority of patients (42.6%) were in stage A, followed by stage B (29.5%) and stage C (27.9%). This distribution corresponds with findings from Rashid et al.2021 [23] in Kurdistan, where approximately one-third of patients were also in stage C. Similarly, Ameen TM ,2022 [24] reported that 61% of patients in Baghdad were in stage A, whereas Hasan KM,2018[16] documented a higher percentage in stage C, suggesting possible regional differences in disease presentation or timing of diagnosis. Regarding hematological parameters, the mean Hemoglobin (Hb) level in our study was 11.55 ± 2.50 g/L, which is comparable to findings from previous Iraqi study[25]. However, it was higher than the Hb level reported by Al-Mudallal SS and Jasim HN.2012 [26], potentially due to the higher proportion of

early-stage (stage A) patients in the current study. Lymphocytosis is a hallmark of CLL, although the absolute lymphocyte count (ALC) may vary significantly among patients. In this study, the mean ALC was 61.58 ± 55.86 × 10⁹/L, which is higher than that reported in a Brazilian study (27 × 10⁹/L) [27], but lower than findings from the Egyptian study by Alrayes et al.2003 [28]. These differences may be influenced by disease stage, genetic diversity, or variations in diagnostic thresholds between populations. The mean platelet count in our study was 199.72 ± 97.67 × 10⁹/L, which was higher than values reported in other regional and international studies, including the Iraqi study by Al-Mudallal SS and Jasim HN,2012 [26], the Brazilian study (180 × 10⁹/L) [27], and the Egyptian study by Alrayes et al.2003 [28]. Nonetheless, the platelet count remained within the normal range. These discrepancies could result from differences in study sample sizes, laboratory methodologies, or disease severity. Lower platelet counts reported in other studies may reflect a more advanced disease state or marrow involvement. Overall, the demographic and hematological findings in this study are largely consistent with other Iraqi studies, yet show some variation when compared to international data. Such differences underscore the importance of understanding CLL in a population-specific context and highlight the need for regional guidelines and larger, multicenter studies. In the current study, no significant correlation was found between SCs% and disease parameters, which contrasts with findings from an Egyptian study in 2018 that highlighted a potential diagnostic role for SCs% in CLL patients [29]. Additionally, Nowakowski et al.2009[30] suggested that smudge cell formation is associated with the amount of vimentin, a cytoskeletal protein in leukemic cells, offering a biological explanation for inter-study variability. Our study showed a significant reduction in the mean level of soluble CD163 (sCD163) in patients with CLL compared to the control group. This result contradicts previous findings by Nederby et al.2014[9] who reported a higher mean concentration of sCD163 (2.085 mg/L) in CLL patients compared to controls (1.800 mg/L), although the difference was not statistically significant. The discrepancy could be attributed to the role of CD163 as a monocyte/macrophage-specific membrane marker, which may be influenced by cellular expression dynamics. Davis et al.2005[31] found an inverse relationship between soluble CD163 and its surface expression on monocytes and macrophages, suggesting that decreased serum levels may be due to increased membrane retention. Our results were also inconsistent with those of Ragab et al.2023 [32], who recently reported significantly elevated sCD163 levels in CLL patients relative to controls. Differences in methodology, sample size, or population characteristics may account for these divergent outcomes.Importantly, no significant association was found between sCD163 levels and disease stage in our study, implying that sCD163 may not serve as a reliable biomarker for disease progression in CLL. This observation contrasts with a previous study by Alrayes et al.2003[28], which found a highly significant positive correlation between sCD163 levels and Rai stage ($P < 0.001$). Another notable prognostic marker evaluated in this study was β2-microglobulin (β2MG). The results demonstrated higher levels of β2MG in patients at Binet stages B and C compared to stage A, aligning with previous findings that associate elevated β2MG with advanced disease and poor prognosis [33,34]. These findings support its utility in clinical staging and risk stratification. With respect to LAIR-1 expression, no statistically significant

difference was noted between patients with positive and negative expression, nor was there a clear association with disease parameters. This contrasts with the findings of Perbellini et al. 2014[13], who concluded that LAIR-1 expression independently predicted time to first treatment in newly diagnosed CLL patients. Their larger sample size (311 vs. 68 patients), along with the inclusion of other prognostic markers such as IGHV mutation status, may have contributed to more definitive conclusions. This study highlights a significant reduction in sCD163 levels in CLL patients compared to controls, measurable through a rapid and cost-effective ELISA-based method. Despite its diagnostic potential, the absence of correlation with disease stage suggests that sCD163 may have limited utility as a progression marker in CLL. Larger studies incorporating immunoph-enotyping and longitudinal follow-up are warranted to better understand the prognostic role of sCD163 in the context of CLL.

Conclusion

Plasma CD163 levels were significantly lower in patients with chronic lymphocytic leukemia (CLL) at the time of diagnosis compared to healthy controls. However, no significant correlation was observed between CD163 concentrations and other studied markers, including B2MG, absolute lymphocyte count (ALC), smudge cell%, or LAIR-1 expression.

Interest Conflicts

None**.**

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None.

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