Original Article

The Association of High-Sensitive C-reactive Protein with Clinical Parameters in Chronic Lymphocytic Leukemia and Diffuse Large B-Cell Lymphoma

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is the most prevalent form of leukemia in the Western world, although it is less common in Asia. According to the annual report of cancer disease in Iraq in 2013, the incidence rate for all subtypes of leukemia in Iraq is 4.43 cases per 100,000, with CLL accounting for 5.34% of cases. **Objective:** The objective of this study was to assess the usefulness of high-sensitivity C-reactive protein (hsCRP) level against other clinical and laboratory parameters in both CLL and diffuse large B-cell lymphoma (DLBCL). We assessed the prognostic significance of pretreatment C-reactive protein (CRP) concentration in CLL and DLBCL patients. **Patient and Methods:** A hospital-based cohort study was conducted over the period of fifteen months from September 2019 to November 2020. This study was conducted in the hematology centers in Baghdad. We prospectively reviewed 30 patients with newly diagnosed CLL and 30 patients with DLBCL. hsCRP was estimated using immunoassay for both CLL and DLBCL patients. **Results:** The mean value of hsCRP for CLL was 5.47 ± 5.96 mg/L ranged from 0.3 to 28 and the mean value for DLBCL was 24.28 ± 24.59 mg/L ranged from (2.5 to 96). There was a significant statistical difference of pretreatment hsCRP between CLL and DLBCL patients (P = 0.0001). There was no association between pretreatment hsCRP concentration and the presence of Binet stage B/C disease (P = 0.081) and albumin concentration (P = 0.893), there was moderate association with lactate dehydrogenase (LDH) concentration (P = 0.046), whereas in DLBCL, there was no association between pretreatment high-sensitive CRP concentration and presence of advanced Ann Arbor stage of disease (P = 0.064) and LDH concentration (P = 0.136). An increased hsCRP concentration was significantly associated with the high IPI (P = 0.009). Increased hsCRP concentration was not associated with poorer outcomes than those patients with low CRP concentration whereas in DLBCL, the elevated level of pretreatment hsCRP was significantly associated with poorer outcomes (P = 0.064 and P = 0.001, respectively). **Conclusion:** Monitoring of hsCRP May not be valuable in CLL patients' assessment or follow-up, however, if it get an increase, there may be other causes rather than the disease itself like coinfection or secondary malignancy. Unlike DLBCL where hsCRP is attributed to disease progression and advanced IPI scoring. Disease outcome had not found to be associated with hsCRP in CLL but the reverse in DLBCL with the significant association.

Keywords: Chronic lymphocytic leukemia, C-reactive protein, diffuse large B-cell lymphoma

Introduction

Chronic B-cell lymphoproliferative disorders are a biologically heterogeneous group of malignancies characterized by clonal proliferation of different stages of mature B lymphocytes in the bone marrow (BM), peripheral blood, and lymphoid tissue. Chronic lymphocytic leukemia (CLL) is characterized by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, BM, lymph nodes, and spleen.[1]

CLL is the most common type of leukemia in Western countries. With an age-adjusted incidence of 4.1/100 000 inhabitants in the United States.[2]

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In Iraq, the incidence rate for all subtypes of leukemia is 4.43 cases per 100,000 of which 5.34% of cases are CLL according to the Annual Report of Cancer Disease in Iraq 2013. The median age at diagnosis lies between 67 and 72 years. More male than female patients (1.7:1) are affected.[2]

Causation is unknown and no association exists with exposure to environmental or industrial toxins and neither is it more common in those with immunodeficiency syndromes. In contrast, a correlation with hepatitis C has been reported.[3]

Corresponding data with respect to Epstein–Barr or cytomegalovirus infection are lacking. Currently, it is considered that genetic or familial factors are predisposing since a two-to-seven-fold excess risk in first-degree relatives is noted.[4]

Within CLL cells, the surface antigen CD5 is co-expressed with the antigens of B-cell CD19, CD20, and CD23. The surface immunoglobulin, CD20, and CD79b concentrations are characteristically small relative to those found on normal B-cells.[5] In borderline cases, markers such as CD43, CD79b, CD81, CD200, CD10, or ROR1 may help to refine the diagnosis.[6]

A marrow aspirate and biopsy generally are not required for the diagnosis of CLL. However, a marrow biopsy and aspirate can help evaluate for factors that might contribute to cytopenias (anemia and thrombocytopenia) that may or may not be directly related to leukemia-cell infiltration of the marrow.[7]

Deletions on the long arm of chromosome 13, specifically involving band 13q14 (del[13q14]), constitute the single most frequently observed cytogenetic aberration in CLL, occurring in about 55 percent of all cases. An isolated del(13q14) features a benign course of the disease.[8] Additional frequent chromosomal aberrations include trisomy of chromosome 12, deletions in the long arm of chromosomes 11 (del[11q]) or 6 (del[6q]), or in the short arm of chromosome[9] (del[17p]).

The leukemia cells express immunoglobulin that may or may not have had somatic mutations in the variable region genes of the immunoglobulin heavy chain (IgVH genes); the result of patients with leukemia cells using an unmutated IgVH gene is lower than that of patients with leukemia cells using a mutated IgVH gene. Leukemia cell expression of ZAP-70 or CD38 was found to correlate with the expression of unmutated IgVH genes and to predict a poor prognosis.[9]

C-reactive protein (CRP) is a classic acute phase protein produced by hepatocytes, especially interleukin-6 (IL6), in response to inflammatory cytokines.[10]

High-sensitivity C-reactive protein (hsCRP) measures trace amounts of CRP in the blood. Traditional testing measures CRP within the range of 10–1000 mg/L, whereas hs-CRP values range from 0.5 to 10 mg/L. Serum CRP levels are also commonly elevated in a variety of lymphoproliferative disorders, including non-Hodgkin's and Hodgkin's lymphoma, higher levels are common in more aggressive histological subtypes of lymphoma, in patients with B-symptoms, advanced stage, bulky disease, and high international prognostic index scores and have been shown to correlate with survival.[11,12] The risk of developing future solid tumors by more than fourfold, especially lung and colorectal cancers.[13-15]

The study was conducted aiming to measure the value of CRP level and its association with other readily available clinical and laboratory "bedside" parameters (lactate dehydrogenase [LDH]) and demonstrate if there is any correlation with disease stage, and the need to treatment compared that with patients of diffuse large B-cell lymphoma (DLBCL).

Patient and Methods

Within the Hematology Department in Al-Imamian Al Kadhimian Medical City, Baghdad Medical City, and National Hematology Center/Al Mustansiriyah University, a prospective cohort study was conducted over 15 months from September 2019 to November 2020.

Thirty patients were diagnosed to have CLL on the basis of clinical manifestation and laboratory work up, the patients collected were 20 new cases, five in remission, and five on long-term follow-up. The collected data included age, gender, date of CLL diagnosis, complete blood count, Binet clinical stage, and date of first treatment.

All of them have been followed over a median period of 6 months by monitoring their disease control and outcome. The patients were excluded from our study were those who have an infection, viral hepatitis, atypical CLL, and rest of other lymphoproliferative diseases.

The control cohort was chosen from the patients collected at the Hematology department in Al-Imamian Al Kadhimian Medical City, Baghdad Medical City, and National Hematology Center/Al Mustansiriyah University, having DLBCL diagnosed on the basis of tumor histology and immunehistochemistry all of them was new cases not receiving chemotherapy a total 30 patients were collected over 15 months from September 2019 to December 2020 and followed up over median period of 6 months (range: 1–15 months).

The demographic data collected from each patient included age, gender, date of CLL diagnosis, complete blood count including the absolute lymphocyte count (ALC), hemoglobin (HB) and platelet count (the latter two were incorporated into the disease staging), Binet clinical stage, date of first treatment, the duration of disease, the previous lines, and the laboratory data that includedCBC, hsCRP, LDH, and Coombs test.

Blood sample (2–3 ml) was directly collected from each patient by gel tube and labeled by case number and name, then transferred into the private laboratory for processing and investigations at the

same day. Plasma samples were collected in gel tube, centrifuged at 3000 rpm for 10 min at room temperature, aliquoted, labeled, and stored at +2°C to +8°C before the study. The time between collection of the sample and storage was a period of 1 h. Relevant information (e.g. date of collection, identification code, and *t* data) was entered for each patient. An assay is based on the principle of particle-enhanced immunological agglutination and is performed on Latex enhanced immunoturbidimetric assay (Randox) at the private laboratory in short, anti-CRP antibodies coupled to latex microparticles react with CRP in the sample to form an antigen/antibody complex that induces turbidity of the reaction mixture to agglutinate, the extent of which is measured as the amount of light absorbed at 570 nm. By constructing a standard curve from the absorbance of the standards, the CRP concentration of the sample can be determined. The range of this assay is approximately 0.5–10.0 mg/l. In the event of a rerun, the upper limit is extended to approximately 25.0 mg/l. Antigen excess effects are not noted with concentrations in excess of 500 mg/l. LDH and serum albumin were done for all patients in our study at the same time of hsCRP measuring, to correlate them with our result.

Analysis of data was carried out using the available statistical package of SPSS-27 (Statistical Packages for Social Sciences-version 27, SPSS Inc., Chicago, IL, USA). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of the difference of different means (quantitative data) was tested using Student's-*t*-test for the difference between two independent means or the ANOVA test for differences among more than two independent means. The significance of the difference of different percentages (qualitative data) was tested using Pearson Chi-square test (Chi-square-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the $P \leq 0.05$.

Ethics approval

This study was approved by the ethical committee of haematology department in Al-Imamian Al Kadhimian Medical City Baghdad, Iraq, on 28th of September 2019.

Verbal consent was obtained from the participants before filling the questionnaire. Participants were informed that their participation in this study is voluntary, no incentives or compensations will be offered in return, and that they have the right to withdraw from the study at any stage.

All the participants' information was kept private by keeping it in a secured folder in a password-protected computer owned by the study investigators. No information was shared with any other individuals or entities.

Results

A total of 30 patients with newly diagnosed CLL treated with different protocols were enrolled in this study [Table 1].

Table 1: Clinical and demographic parameters in chronic lymphocytic leukemia patients

CLL	*n* (%)
Age (years)	
<60	16 (53.3)
≤60	14 (46.7)
Mean±SD (range)	56.3±10.4 (33–76)
Gender	
Male	18 (60.0)
Female	12 (40.0)
Stage (Binet staging)	
A	6 (20.0)
B	17 (56.7)
C	7 (23.3)
Treatment response	
Complete response	5 (16.7)
Partial response	17 (56.7)
No response	8 (26.7)

CLL: Chronic lymphocytic leukemia, SD: Standard deviation

Table 2: The-distribution of normal and abnormal laboratory

CLL	*n* (%)
hsCRP (mg/L)	
Normal (0.5–5)	21 (70.0)
High (>5)	9 (30.0)
Mean±SD (range)	5.47±5.96 (0.3–28)
LDH (IU/L)	
Normal (130–280)	21 (70.0)
High (>280)	9 (30.0)
Mean±SD (range)	338.0±383.38 (135–2000)
Serum albumin (g/dL)	
Normal (3.5–5.5/dL)	27 (90.0)
Low (<3.5 g/dL)	3 (10.0)
Mean±SD (range)	3.82±0.32 (3.2–4.5)

CLL: Chronic lymphocytic leukemia, SD: Standard deviation, hsCRP: High-sensitivity C-reactive protein, LDH: Lactate dehydrogenase

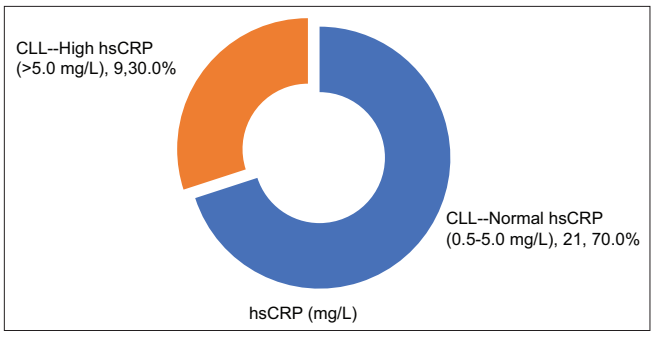

Figure 1: The distribution of high-sensitivity C-reactive protein level in chronic lymphocytic leukemia patients

The median follow-up was 6 months (range: 1–15 months). Male-to-female ratio was 1.5:1 (18:12) and the mean age of patients at diagnosis was 56.3 ± 10.4 years old (range: 33–76 years). Sixteen patients (53.3%) were <60 years and nine (30%)

patients only showed an increased LDH concentration [Table 2]. According to Binet classification, 6 (20%) patients were stage A, 17 (56.7%) were stage B, and the other 7 (23.3) were stage C. The mean concentration of pretreatment hsCRP was 5.47 ± 5.96 mg/l (range from 0.3 to 28 mg/l).

Among these 30 patients, 9 (30%) had increased hsCRP concentration (>5 mg/l), while the other 21 (70%) had normal hsCRP concentration (<5 mg/l) [Figure 1].

The laboratory data revealed that the HB level ranged from 6.6–15 g/dL. The mean was (11.55 ± 2.37 12 g/dL), which had a statistically significant relationship (P = 0.006). The mean level of white blood cell (WBC) in our study was 114.803 ± 97.474 × 10^3/mL ranged from (3.1 to 487 × 10^3), as shown in Table 3.

A total of 30 patients with newly diagnosed DLBCL treated with different protocols were enrolled in this study [Table 4]. The median follow-up was 6 months (range: 1–15 months). Male-to-female ratio was 2.75:1 (22: 8) and the mean age of patients at diagnosis was 52.8 ± 11.4 years old (range: 30–69 years). Twenty patients (66.7%) were <60 years; fifteen patients (50%) had an increased LDH concentration. As for the Ann Arbor stage, 8 (26.7%) patients were early stage (stage 1A-2A), the other 22 (73.3%) were advanced stage (2B-4). The mean concentration of pretreatment hsCRP was 24.28 ± 24.59 mg/l (range from 2.5 to 96 mg/l) [Tables 4 and 5].

By reviewing of many previous studies, the hsCRP levels of more than 20 mg/L were considered pathological values, as shown in Table 6 and Figure 2.

Among these 30 patients, 18 (60%) had increased hsCRP concentration (>20 mg/l), while the other 12 (40%) had low hsCRP concentration (<20 mg/l). The associations between pretreatment CRP concentration and baseline characteristics are presented in Table 7. There was no significant difference in age between the two groups (P = 0.866). There was no association between pretreatment hsCRP concentration and the presence of advanced Ann Arbor stage of disease (P = 0.064) and LDH concentration (P = 0.136). However, an increased hsCRP concentration was significantly associated with the IPI (P = 0.009).

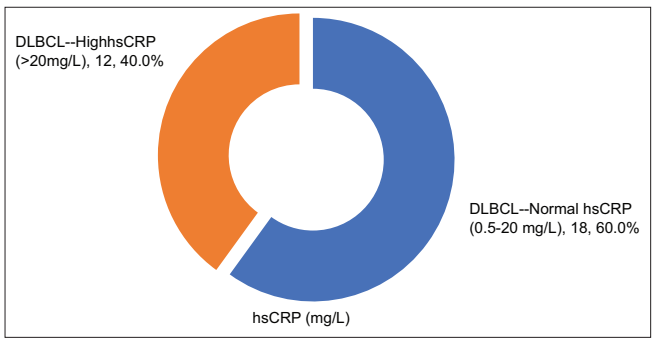

Figure 2: Distribution of high-sensitivity C-reactive protein level among diffuse large B-cell lymphoma patients

Among these 30 patients, 15 (50%) had complete response, 9 (30%) had partial response while the other 6 (20%) had

Table 3: The mean value of laboratory parameters in chronic lymphocytic leukemia patients

CLL	Mean±SD (range)
WBC (×10^3)/mL	114.803±97.474 (3.1–487)
Hb (g/dL)	11.55±2.37 (6.6–15)
Platelets (×10^3)/mL	171.10±60.90 (55–283)
LDH (IU/L)	338.0±383.38 (135–2000)
Serum albumin (g/dL)	3.82±0.32 (3.2–4.5)

CLL: Chronic lymphoid leukemia, WBC: White blood cell, LDH: Lactate dehydrogenase, Hb: Hemoglobin, SD: Standard deviation

Table 4: Clinical and demographic parameters in diffuse large B-cell lymphoma patients

DLBCL	*n* (%)
Age (years)	
<60	20 (66.7)
≥60	10 (33.3)
Mean±SD (range)	52.8±11.4 (30–69)
Gender	
Male	22 (73.3)
Female	8 (26.7)
DLBCL	
Early	8 (26.7)
Advanced	22 (73.3)
Outcome	
Complete response	15 (50.0)
Partial response	9 (30.0)
No response	6 (20.0)
IPI score	
Early (0–1)	13 (43.3)
Intermediate (2–3)	13 (43.3)
High (4–5)	4 (13.3)

DLBCL: Diffuse large B-cell lymphoma, SD: Standard deviation, IPI: International Prognostic Index

Table 5: Laboratory parameters in diffuse large B-cell lymphoma patients

DLBCL	*n* (%)
hsCRP (mg/L)	
Normal (0.5–5)	2 (6.7)
High (>5)	28 (93.3)
Mean±SD (range)	24.28±24.59 (2.5–96)
LDH (IU/L)	
Normal (130–280)	15 (50.0)
High (>280)	15 (50.0)
Mean±SD (range)	338.0±383.38 (135–2000)
Serum albumin (g/dL)	
Normal (3.5–5.5/dL)	23 (76.7)
Low (<3.5 g/dL)	7 (23.3)
Mean±SD (range)	3.83±0.45 (3.0–4.7)

DLBCL: Diffuse large B-cell lymphoma, SD: Standard deviation, hsCRP: High-sensitivity C-reactive protein, LDH: Lactate dehydrogenase

complete response. The study showed that patients with increased hsCRP concentration had a significant statistical association with poor outcomes than those with low CRP concentration ($P = 0.012$) [Table 7].

The laboratory data revealed that the mean level of WBC in our study was 10.780 ± 14.834 × 10^3/mL ranged from 2.4 to 88 × 10^3. There was no statistically significant association between WBC count and hsCRP ($P = 0.388$). HB level ranged from (9.5 to 16 g/dL), which had statistically no relationship ($P = 0.209$). The platelet count ranged from 114 to 411 × 10^3/mL with the mean level was 235.33 ± 99.78 × 10^3/mL, with also no statistical relationship was observed ($P = 0.285$) [Tables 8 and 9].

Table 6: High-sensitivity C-reactive protein cut off value in diffuse large B-cell lymphoma patients

DLBCL	*n* (%)
hsCRP (mg/L)	
Normal (0.5–20)	18 (60.0)
High (>20)	12 (40.0)
Mean±SD (range)	24.28±24.59 (2.5–96)

DLBCL: Diffuse large B-cell lymphoma, SD: Standard deviation, hsCRP: High-sensitivity C-reactive protein

Table 7: Association of high-sensitivity C-reactive protein with clinical and laboratory parameters in diffuse large B-cell lymphoma patients

DLBCL	hsCRP (mg/L)		*P*
	Low (0.5–20), *n* (%)	High (>20) *n* (%)	
Age (years)			
<60	12 (66.7)	8 (66.7)	-
≥60	6 (33.3)	4 (33.3)	
Gender			
Male	13 (72.2)	9 (75.0)	0.866
Female	5 (27.8)	3 (25.0)	
LDH (IU/L)			
Normal (130–280)	11 (61.1)	4 (33.3)	0.136
High (>280)	7 (38.9)	8 (66.7)	
Serum albumin (g/dL)			
Normal (3.5–5.5)	14 (77.8)	9 (75.0)	0.860
Low (<3.5)	4 (22.2)	3 (25.0)	
Stage			
Early	7 (38.9)	1 (8.3)	0.064
Advanced	11 (61.1)	11 (91.3)	
Outcome			
Complete response	13 (72.2)	2 (16.7)	0.012*
Partial response	3 (16.7)	6 (50.0)	
No response	2 (11.1)	4 (33.3)	
IPI score			
Early (0–1)	11 (61.1)	2 (16.7)	0.009
Intermediate (2–3)	7 (38.9)	6 (50.0)	
High (4–5)	-	4 (33.3)	

*Significant difference between percentages using Pearson Chi-square test at 0.05 level. DLBCL: Diffuse large B-cell lymphoma, hsCRP: High-sensitivity C-reactive protein, LDH: Lactate dehydrogenase, IPI: International Prognostic Index

High-sensitivity C-reactive protein levels in chronic lymphocytic leukemia patients in compare with diffuse large B-cell lymphoma

The mean value of hsCRP for CLL was 5.47 ± 5.96 mg/L ranged from (0.3 to 28) and the mean value for DLBCL 24.28 ± 24.59 mg/L ranged from (2.5 to 96). There was a significant statistical difference of pretreatment hsCRP between CLL and DLBCL patients ($P = 0.0001$), as shown in Table 10 and Figure 3.

Discussion

CRP identified as a prognostic factor in a number of solid and hematological malignancies such as NK/T-cell lymphoma and multiple myeloma as described by Li *et al*. and Najjar and Al Tameemi respectively.[16,17] To our knowledge, there is a paucity of reports studied the prognostic value of pretreatment CRP concentrations in newly diagnosed CLL.

In the current study, the pretreatment hsCRP levels at the time of CLL diagnosis were relatively low. The level of hsCRP is higher in the lymphoma group than in the CLL group, with a strong significant association with disease burden ($P = 0.0001$). There are many potential mechanisms whereby CRP is increased in DLBCL. It could indicate the rate at which the tumor is progressing.[18] Tumor growth with overlying inflammation can boost IL-6 activity, which is the master regulator of liver CRP production. Tumor-associated mononuclear cells produce higher levels of IL-6 as part of the immune cytokine response to tumor growth and progression in DLBCL patients which in turn increase CRP production.[18,19] It is still unclear whether CRP plays a causal role in the pathogenesis of DLBCL or if elevated CRP levels are simply a DLBCL marker. A retrospective study done by Herishanu *et al*. reviewed the records of 107 consecutive treatment naïve patients with CLL, and a control group also showed near

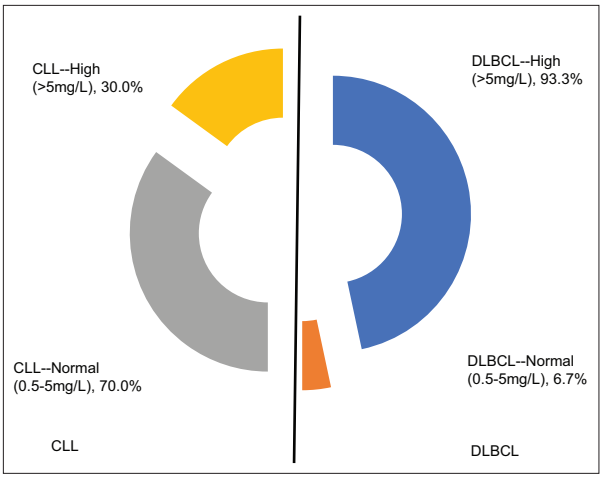

Figure 3: Distribution of high-sensitivity C-reactive protein level among chronic lymphocytic leukemia and diffuse large B-cell lymphoma patients

Table 8: The mean value of laboratory parameters in diffuse large B-cell lymphoma patients

	DLBCL
WBC (×10³/mL)	10.780±14.834 (2.4–88)
Hb (g/dL)	13.08±1.52 (9.5–16)
Platelets (×10³)/mL	235.33±99.78 (114–411)
LDH (IU/L)	387.1±348.45 (130–1800)
Serum albumin (g/dL)	3.83±0.45 (3.0–4.7)

Hb: Haemoglobin, WBC: White blood cell, LDH: Lactate dehydrogenase, DLBCL: Diffuse large B-cell lymphoma

Table 9: Association of high-sensitivity C-reactive protein with mean hematological parameters in diffuse large B-cell lymphoma patients

	DLBCL				*P*
	hsCRP normal (0.5–20)		High (>20 mg/L)		
	n	Mean±SD	*n*	Mean±SD	
WBC (×10³/mL)	18	12.728±19.039	12	7.858±2.094	0.388
Hb (g/dL)	18	12.79±1.72	12	13.52±1.10	0.209
Platelets (×10³/mL)	18	251.50±110.71	12	211.08±78.96	0.285

Hb: Haemoglobin, WBC: White blood cell, DLBCL: Diffuse large B-cell lymphoma, SD: Standard deviation

Table 10: The difference in high-sensitivity C-reactive protein level between chronic lymphocytic leukemia and diffuse large B-cell lymphoma

hsCRP (mg/L)	DLBCL	CLL	*P*
Normal (0.5–5 mg/L)	2 (6.7)	21 (70.0)	0.0001*
High (>5 mg/L)	28 (93.3)	9 (30.0)	
Mean±SD (range)	24.28±24.59 (2.5–96)	5.47±5.96 (0.3–28)	0.0001#

*Significant difference between percentages using Pearson Chi-square test at 0.05 level, #Significant difference between two independent means using Student's-*t*-test at 0.05 level. DLBCL: Diffuse large B-cell lymphoma, SD: Standard deviation, hsCRP: High-sensitivity C-reactive protein, CLL: Chronic lymphoid leukemia

normal CRP in CLL patients, which is consistent with our findings.[20] Pavlidis *et al*. retrospectively reviewed 50 patients with the newly diagnosed lymphoproliferative disease, 34 NHL and 16 CLL, and 25 age- and sex-matched normal control and showed agreement with these reports of significant differences in CRP levels between low-, intermediate-, and high-grade lymphoproliferative disease ($P < 0.001$ and $P < 0.05$, respectively).[21]

In the present research, there is no statistically significant link between hsCRP and patient age or gender of the patients ($P = 0.523$ and $P = 0.636$, respectively). In comparison, Herishanu *et al*., also discovered that the hsCRP is not related to the age and gender in CLL patients.[20] Despite the fact that the majority of the patients in this study were in stage B (56.7%), they have no statistically relevant relationship with the elevation of hsCRP ($P = 0.081$). Herishanu *et al*. also did not find any association between the advanced stage of the disease and elevation of CRP level.[20] Elevation of CRP during the progression of CLL may be due to cellular damage and clonal turnover that take place during tumor progression lead to the release of naked nuclear material. This repeated, low-level, T-cell-independent activation of toll-like receptor 7 (TLR7) on CLL cells may result in enhanced tumor growth,[22] which in turn stimulate stromal cells to produce and release high levels of IL-6 (which is responsible for Acute phase protein synthesis by the liver particularly CRP) that stimulate MIRNA17,19 production which in turn inhibit RNA synthesis of TLR7 and act as antitumor activity.[22] It did not demonstrated in statistical terms here due to the limited number of patients also the relation between the level of CRP and IL6 was actually studied in NHL not CLL which made this difference in the present study.

In the present research, serum LDH is found to be elevated in those with elevated hsCRP ($P = 0.042$). In NHL, Legouffe *et al*. studied 39 patients with NHL treated by the same group in Montpellier, France, and 25 normal volunteers. He found a significant relationship between CRP and LDH levels ($P < 0.042$).[23]

Concerning hematological parameters, patients with elevated hsCRP does not have higher level of mean WBC count ($P = 0.165$). Herishanu *et al*. also observed that there is no significant relationship between high ALC and elevation of hsCRP.[20] Low level of the mean HB is significantly associated with higher level of hsCRP ($P = 0.006$). We could not observe any association between thrombocytopenia and hsCRP level in our analysis ($P = 0.443$), no literature data to support this relation but clearly the anemia and thrombocytopenia indicated an advanced stage of disease and initially, in our study, we did not find any correlation with hsCRP.

Patients with elevated hsCRP concentrations had no significant poorer outcome ($P = 0.064$) than patients with usual CRP concentrations in the current study. In fact, the IL-6 (which induces CRP production from the liver) acts as a tumor suppressor in CLL by inhibiting TLR signaling and tumor necrosis factor-alpha.[22,24] Actually, we do not know whether the correlation between the level of IL6 and CRP in CLL is the same as in NHL, so the correlation between CRP and IL6 in CLL has to be studied in the future to approve this finding.

Unlike the finding of Herishanu *et al*., where the CRP concentrations before treatment were independently predictive of poor outcomes.[20] The difference could be due to the small number of patients in the current study and the short period of follow-up so that the OS and PFS cannot be reached. Consequently, data on cytogenetic aberrations and IGHV mutations were also available for a limited number of patients and not included in the research which influenced the current findings.

The results of this study in DLBCL patients treated with different protocols found that there is no statistically significant

link between hsCRP and the age of the patients ($P = 0.866$). In comparison, Wang *et al*. and Pavlidis *et al*. discovered that the hsCRP is also not related to age in DLBCL patients.[21,25] Despite the fact that the majority of the patients in this study were in the advanced stage (73.3%), they have no statistically relevant relationship with the elevation of hsCRP ($P = 0.064$). In line with our results, Legouffe *et al*. also discovered that advanced stage and hsCRP elevation had no relationship.[23] In contrast to Troppan *et al*. and Pavlidis *et al*. who discovered a significant association between them.[21,26] This variance in the findings may be due to the limited number of patients and also due to the disparity in hsCRP cutoff values between the current research and the previous studies.

Regarding IPI scores, those with an early score accounted for 43.3%, those with a moderate score accounted for 43.3%, and those with a high score accounted for 13%. The statistical relationship between hsCRP and IPI score was highly significant ($P = 0.009$). Previous research by Wang *et al*., Cao *et al*., and Troppan *et al*. found similar findings, demonstrating a statistically significant relationship between CRP value and IPI score ($P = 0.0001$, 0.003, and 0.001, respectively).[25-27]

The level of LDH has no association with the existence of pretreatment hsCRP levels ($P = 0.136$). Wang *et al*. and Legouffe *et al*., on the other hand, discovered a correlation between them ($P = 0.000$, $P = 0.042$).[23,25] Eventually, the limited number of patients in the current study and the difference in hsCRP cutoff values between the current research and the previous studies may be an explanation for this discrepancy.

In this analysis, there was no evidence that differences in the mean levels of hematological parameters (WBC, HB, and platelet count) had an effect on the elevation of hsCRP ($P = 0.388$, 0.209, and 0.285). Unlike Adams *et al*., who discovered a correlation between a low HB level and elevation in hsCRP of the advanced stages of the disease,[28] we do not find such a link in our research. The relationship between hematological parameters clearly reflects the advanced stage of the disease (BM infiltration). However, it was not demonstrated statistically here, which may be attributable to the small number of patients in Ann Arbor stage 4 (only 3 patients), which may explain the difference in the present analysis.

Patients with elevated hsCRP concentrations have significant poorer outcome ($P = 0.012$) than patients with usual hsCRP concentrations. In the current study, we select 20 mg/l as the optimal cutoff point of CRP concentration.[21,25] The cause of the generally poor prognosis linked to higher CRP levels is unknown. Yang *et al*. found that CRP enhances cell proliferation under stress and protects myeloma cells from chemotherapy drug-induced apoptosis by binding to activating Fc receptors, activating the PI3K/Akt, ERK, and NF-kappaB pathways, and inhibiting Caspase cascade activation in myeloma cells, whether these or other mechanisms may have a role in DLBCL has to be clarified.[29]

Thus, the results in the present study show that a high pretreatment CRP concentration is a significantly independent predictor of worse outcomes in DLBCL patients. In line with our results, Wang *et al*. demonstrated the same prognostic value of increased pretreatment CRP concentrations in Chinese patients with newly diagnosed DLBCL treated with RCHOP therapy.[25] Furthermore, a study by Adams *et al*.[28] in 104 RCHOP-treated DLBCL patients demonstrated that pretreatment CRP concentrations are significantly associated with poor outcomes in DLBCL patients in the rituximab era. Increased CRP concentrations were defined as 10 mg/L in their study. Patients with increased CRP concentrations had a significantly poorer OS ($P = 0.036$) and PFS ($P = 0.040$) than patients with normal CRP concentrations. Troppan *et al*. retrospectively reviewed 477 patients with newly diagnosed DLBCL at 2 Austrian centers. Increased CRP concentrations were defined as 15 mg/l. Patients with increased CRP concentrations had a significantly inferior OS ($P < 0.001$) and disease-free survival ($P < 0.001$) than patients with normal CRP concentrations.[26] The results of their retrospective study were consistent with our findings that show pretreatment CRP concentrations to be independently predictive of survival at current analyses.

Measurement of serum CRP concentrations is easily applicable and relatively inexpensive in daily clinical practice. Thus, CRP concentrations may be measured routinely in patients with DLBCL as a further prognostic indicator of survival.

Conclusion

Monitoring of hsCRP may not be valuable in CLL patients' assessment or follow-up, however, if it get an increase, there may be other causes rather than the disease itself such as coinfection or secondary malignancy. Unlike DLBCL where hsCRP is attributed to disease progression and advanced IPI scoring thus pretreatment hsCRP measuring have prognostic value on the outcome and should be done for every patient with newly diagnosed DLBCL. Disease outcome had not found to be associated with hsCRP in CLL but the reverse in DLBCL with significant association, neither clinical nor laboratory parameters had associated with pretreatment hsCRP in CLL and DLBCL, and lastly, Serum LDH was statistically associated with hsCRP in CLL but not in DLBCL.

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Conflicts of interest

There are no conflicts of interest.

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