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An Analysis of 100 Patients with Chronic Lymphocytic Leukemia in Kerbala, Iraq: A Comprehensive Immunophenotypic and Genetic Study

Conflict of interest: nothing to declare.

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Abstract

Introduction. Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults. It is caused by the buildup of mature but dysfunctional B-lymphocytes in the blood, bone marrow, and lymphoid organs.
Purpose. This study examines immunophenotypic markers (CD5, CD19, CD38, LAIR1) and genetic changes (17p, 11q, 13q deletions) in a group of CLL patients from Kerbala, Iraq. Flow cytometry using BD/FACS LYRICS and FISH was performed, and the results from the lab were compared to the clinical findings.
Materials and methods. This retrospective study evaluated 100 treatment-naïve CLL patients diagnosed at Al-Mujtaba Hospital for Hematological Diseases and Bone Marrow Transplantation. The diagnosis was confirmed following the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, immunophenotypic confirmation via flow cytometry.
Results. The most recent study found that 68% of patients had elevated LAIR1, which is linked to rapid disease progression ($p<0.001$). Additionally, 17p deletion (18%) combined with CD38+ was associated with worse survival (median PFS: 14 months). A new high-risk profile was identified: CD38+/LAIR1+/17p del (3-year OS: 42%).
Conclusion. This study shows that LAIR1 and 17p deletion are crucial for predicting outcomes in Iraqi CLL patients.
Keywords: CLL, immunophenotyping, 17p deletion, LAIR1, CD38

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Анализ данных 100 пациентов с хроническим лимфоцитарным лейкозом в Кербеле, Ирак: комплексное иммунофенотипическое и генетическое исследование

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Резюме

Введение. Хронический лимфоцитарный лейкоз (ХЛЛ) – наиболее распространенный тип лейкемии у взрослых. Он вызывается накоплением зрелых, но дисфункциональных В-лимфоцитов в крови, костном мозге и лимфоидных органах.
Цель. В данном исследовании изучаются иммунофенотипические маркеры (CD5, CD19, CD38, LAIR1) и генетические изменения (делеции 17p, 11q, 13q) в группе пациентов с ХЛЛ из Кербелы, Ирак. Была проведена проточная цитометрия с использованием BD/FACS LYRICS и FISH, а результаты лабораторных исследований сравнивались с клиническими данными.
Материалы и методы. В этом ретроспективном исследовании были оценены данные 100 пациентов с ХЛЛ, ранее не получавших лечения, которым был поставлен диагноз в больнице гематологических заболеваний и трансплантации костного мозга Аль-Муджтаба. Диагноз был подтвержден в соответствии с критериями Международного рабочего совещания по хроническому лимфоцитарному лейкозу (IWCLL), а также иммунофенотипически подтвержден с помощью проточной цитометрии.
Результаты. В последнем исследовании было установлено, что у 68% пациентов наблюдался повышенный уровень LAIR1, что связано с быстрым прогрессированием заболевания ($p<0,001$). Кроме того, делеция 17p (18%) в сочетании с CD38+ была связана с худшей выживаемостью (медиана выживаемости без прогрессирования 14 месяцев). Был выявлен новый профиль высокого риска: CD38+/LAIR1+/делеция 17p (3-летняя общая выживаемость 42%).
Заключение. Данное исследование показывает, что LAIR1 и делеция 17p имеют решающее значение для прогнозирования исходов у иракских пациентов с ХЛЛ.
Ключевые слова: ХЛЛ, иммунофенотипирование, делеция 17p, LAIR1, CD38

■ INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults in Western countries, affecting 4 to 5 out of every 100,000 people each year. It is caused by the buildup of mature but dysfunctional B-lymphocytes in the blood, bone marrow,

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and lymphoid organs. Most people with this condition are older, with a median age of 70 when they are diagnosed. CLL has a very varied clinical course, with some cases being so mild that they don't need treatment for years and others being so aggressive that they need therapy right away [1, 2].

Immunophenotyping is used to make a diagnosis, but cytogenetic abnormalities and mutational status are used to help choose the best treatment [1]. Targeted therapies like Bruton tyrosine kinase (BTK) inhibitors and BCL-2 antagonists have made a big difference in how well patients do [3]. Genetic problems, epigenetic changes, and interactions with the microenvironment that help leukemic cells survive and grow are all part of the etiology [4].

The clinical profile shows that CLL mostly affects older adults, with a small male-to-female ratio of about 1.7:1 [5]. Approximately 25% of patients exhibit no symptoms upon diagnosis, and standard blood tests inadvertently uncover them [6].

Certain immunophenotypes (CD5+/CD19+/CD23+) determine the diagnostic criteria. Recent data highlights both prognostic indicators: CD38: A transmembrane glycoprotein linked to aggressive illness [7], and LAIR1 as an immune checkpoint molecule that suppresses T-cell responses [8]. Genetic anomalies Deletion of 17p (loss of TP53) predicts resistance to chemotherapy [4], but isolated deletion of 13q is associated with a favorable prognosis [9].

Although there are potential regional variations in disease biology, no prior studies have comprehensively evaluated these markers in Iraqi CLL patients. Immunophenotypic markers (CD38, LAIR1), genetic aberrations (17p, 11q deletions), and microenvironment interactions all contribute to the variable clinical behavior of chronic lymphocytic leukemia (CLL) [10].

This underscores the necessity of developing prognostic models capable of forecasting disease progression, treatment timelines, and survival outcomes in this heterogeneous condition. The Rai and Binet staging systems were established in the late 1970s to early 1980s. Patients were categorized into distinct stages according to clinical features and test results. Although these basic staging methods remain in use, additional prognostic indicators are necessary for personalized evaluation. Recent advancements in genomic techniques have enhanced the molecular understanding of CLL, resulting in the emergence of novel prognostic markers [11].

Established prognostic factors:

- Rai and Binet staging systems (0–III) [12, 13].
- Serum markers (β2M and HLA class I complex microglobulin, TK) [14, 15].
- IGHV somatic hypermutation status [16].
- TP53 mutations [17, 18].
- Cytogenetic changes in CLL are Del17(p) [deletions of the short arm of chromosome 17 (del[17p]) [19, 20], deletions in chromosome 11 (11q23) [4, 14], Trisomy 12 [21], PI3K protein [22], NOTCH1 mutations [22, 23] and SF3B1 mutations [24].

CLL treatment has evolved significantly over the past few years, with new drugs like BTK, BCL-2, chemoimmunotherapy and PI3K inhibitors being used [25].

Developing a region-specific predictive model, the interaction between genetic anomalies and surface indicators, and the prevalent immunophenotypes in Iraqi CLL patients are some of the topics covered in this work.

■ MATERIALS AND METHODS

Patient Selection and Study Design

This retrospective study evaluated 100 treatment-naïve CLL patients diagnosed at Al-Mujtaba Hospital for Hematological Diseases and Bone Marrow Transplantation, Karbala, Iraq, between 2022 and 2024. The diagnosis was confirmed following the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria, which include peripheral blood lymphocytosis (≥5×10^9/L B-lymphocytes sustained for ≥3 months), immunophenotypic confirmation via flow cytometry (CD5+/CD19+/CD23+ with weak surface immunoglobulin).

CLL immunophenotypic analysis by flow cytometry, which is validated by multiple methods. So, the following antibody panel was utilized with a 10-color BD FACS LYRICS flow cytometer:

- B-cell markers include sIgM (weak), CD19, CD20 (dim), and CD23.
- T-cell/NK markers include CD3 (T-cell control) and CD5 (co-expression on B-cells).
- Prognostic indicators: LAIR1 (CD305) and CD38.
- Additional markers include kappa/lambda light chains (which measure clonality), CD43, CD31, CD10 (which excludes other lymphomas), and CD11c (which excludes hairy cell leukemia).

Positive threshold values

These values are obtained by results which promoted 30% of leukemic cells have the CD38 gene and LAIR1 has an expression level of at least 20% (7, 8).

For the purpose of identifying genetic aberrations, fluorescence in situ hybridization (FISH) was carried out on samples of peripheral blood using Vysis probes, which were manufactured by Abbott Molecular: both 17p13 (a loss of TP53) and 11q22.3 (a deletion of ATM), 13q14 and the loss of D13S25 and RB1, and trisomy 12 (the CEP12 probe).

Clinical data collection and follow-up are conducted based on demographics (age, sex, Rai/Binet stage), laboratory parameters (hemoglobin, platelet count, LDH, β2-microglobulin, and therapy response), and progression-free survival (PFS) and overall survival (OS).

Inclusion criteria

- Age ≥18 years.
- Recently diagnosed, undergoing treatment-naïve chronic lymphocytic leukemia.
- Readiness to provide informed consent.

Exclusion criteria

- Previous therapy aimed at chronic lymphocytic leukemia (CLL).
- Simultaneous active malignancies.
- Infection with HIV or HTLV-1.

Data analysis

For quantitative data, we used the mean + SD, ranges, percentages, and frequencies tools in SPSS (Statistical Package for the Social Sciences) version 26. For qualitative data, we utilized the frequency function. Survival analysis was conducted using the Kaplan-Meier curve, with comparisons were conducted with the log-rank test. Multivariate

Cox regression analysis was conducted to ascertain independent predictive variables, adjusting for age, stage, CD38, LAIR1, and 17p deletion. A p-value below 0.05 was deemed statistically significant.

■ RESULTS

This group of predominantly male CLL patients (median age: 62 years) had a statistically significant number of advanced-stage illnesses (Rai III–IV: 23% [p-value<0.001], Binet C: 22% [p-value=0.002]). Even though universal lymphocytosis confirmed the diagnostic criteria, splenomegaly (47% [p-value=0.04]) and lymphadenopathy (63% [p-value=0.01]) were both prevalent. Because 65% of the people were male, the sex distribution was not statistically significant (p-value=0.12) (Table 1).

Flow cytometry showed that CD5 and CD19 were expressed in all cells (100%). There was a strong link between the level of LAIR1 (68%) and the condition of the sickness (p<0.001), as well as the level of CD28 (42%; p=0.003). There was a lot of CD23 expression (92%), but it wasn't statistically significant (p=0.21). IgM expression was low (38%; p=0.08), although the number of people with Stage C illness (88%) did not have a statistically significant relationship (p=0.15) (Table 2).

Table 1
Patient characteristics

Parameter	%	p-value
Median Age	62 years (45–80)	–
Sex (male : female)	65:35	0.12
Rai Stage		
Stage 0 (low risk)	32	–
Stage I–II (intermediate)	45	0.03
Stage III–IV (high risk)	23	<0.001
Binet Stage		
Stage A	40	–
Stage B	38	0.08
Stage C	22	0.002
Lymphocytosis (≥5×10^9/L)	100	–
Splenomegaly	47	0.04
Lymphadenopathy	63	0.01

Table 2
Expression of principal immunophenotypic markers

Parameter	%	p-value of disease status
CD 5	100	–
CD 19	100	–
CD 23	92	0.21
CD 28	42	0.003
LAIR1	68	<0.001
sIgM	38	0.08
Stage C	88	0.15

Table 3
Prevalence of cytogenetic abnormalities by FISH

Genetic Abnormality	%	OS (months)	PFS (months)	p-value
17p deletion (TP53 loss)	18	28	14	<0.001
11q deletion (ATM loss)	22	42	22	0.01
13q deletion (sole)	35	None	60	0.002
Trisomy 12	15	55	36	0.08
Normal FISH	10	72	48	–

Table 4
Comparison high-risk with low-risk

Parameter	High-risk (n=12)	Low-risk (n=35)	p-value of disease status
3-Year OS (%)	42%	89%	<0.001
Median PF	14	48	
Treatment failure	83%	12%	

Note: high-risk: CD38+/LAIR1+/17p del, low-risk: CD38-/LAIR1-/normal FISH.

FISH testing showed that 18% of patients had a deletion on 17p (TP53 loss), which was linked to a worse prognosis (OS: 28 months, PFS: 14 months [p-value<0.001]). The 11q deletion (22%) similarly indicated bad results (overall survival: 42 months, progression-free survival: 22 months [p-value=0.01]). The solitary 13q deletion was the most common problem, affecting 35% of people. It was linked to a 60-month progression-free survival rate [p-value=0.002]. Trisomy 12 (15%) had an intermediate survival rate that was not statistically significant (overall survival: 55 months, progression-free survival: 36 months; [p-value=0.08]). Patients who did not have chromosomal abnormalities (10%) had a very good chance of surviving (overall survival: 72 months, progression-free survival: 48 months) (Table 3).

Patients with high-risk CLL (n=12) did much worse than patients with low-risk CLL (n=35). This was shown by a lower 3-year overall survival rate (42% vs. 89% [p<0.001]), a shorter median progression-free survival rate (14 vs. 48 months [p<0.001]), and a higher rate of treatment failure (83% vs. 12% [p<0.001]). BTK inhibitors improved progression-free survival in people with 17p deletions (p=0.02), however chemoimmunotherapy didn't work in 83% of high-risk individuals. These results support risk-stratified therapy methods and support personalized treatments for illnesses with a high hereditary risk (Table 4).

■ DISCUSSION

The progressive proliferation and accumulation of mature lymphocytes that are functionally incompetent are the hallmarks of CLL, a monoclonal disorder. In the image below, the histologic sample illustrates the morphology of these lymphocytes [26]. CLL is the most prevalent form of leukemia for adults in Western countries. It is not uncommon for patients to succumb to complications from CLL within a few years of their diagnosis; however, the majority of patients survive for a minimum of five years [27].

In order to diagnose CLL, it is necessary to conduct a microscopic examination of the peripheral blood and a flow cytometry analysis of the lymphocytes to confirm clonality

and molecular expression [1]. A modest blood sample is sufficient to perform both procedures [28]. A flow cytometer instrument is capable of analyzing the expression of molecules on individual cells. This necessitates the utilization of specific antibodies that target fluorescent markers on cell-surface molecules that exhibit recognition by the instrument [29]. In CLL, the lymphocytes are genetically identical due to their descent from the same B cell lineage. CLL cells have the ability to express both conventional B-cell markers, such as CD19 and CD20, and aberrant surface markers, such as CD5 and CD23 [30].

Because of the significant clinical variability of CLL, reliable prognostic markers are essential for directing risk-adapted treatment. Our study offers the first thorough examination of genetic (17p, 11q, 13q deletions) and immunophenotypic (CD38, LAIR1) markers in Iraqi CLL patients, presenting a number of important discoveries with biological and therapeutic ramifications. With male predominance (65%), consistent with global CLL epidemiology [1]. Also, with high-risk Rai stages (III–IV) in 23%, similar to Western cohorts [4].

Our research revealed LAIR1 overexpression in 68% of patients, markedly exceeding the 30-45% documented in European populations (8, 44). This gap may indicate ethnic or microenvironmental variations within Middle Eastern people. LAIR1 (Leukocyte-Associated Immunoglobulin-Like Receptor 1) is an immunological checkpoint protein that suppresses T-cell activation, perhaps facilitating immune evasion in CLL [8]. LAIR1 interaction with collagen in the lymph node microenvironment transmits inhibitory signals that diminish cytotoxic T-cell responses, hence promoting leukemia cell survival [31]. Our findings that LAIR1+ patients exhibited markedly worse progression-free survival (18 vs. 48 months, $p<0.001$) corroborate recent research indicating LAIR1 as an autonomous predictor of aggressive illness. The findings indicate that LAIR1 testing ought to be integrated into standard CLL prognostication, especially for high-risk individuals [32].

The current study detected 17p deletion in 18% of patients, consistent with global reports [1, 4]. However, the poor survival in our cohort (median OS: 28 months vs. 32–36 months in Western studies) may reflect delayed access to targeted therapies (e.g., BTK inhibitors) in Iraq. Notably, CD38+/17p del patients had the worst outcomes (3-year OS: 42%), reinforcing the concept that CD38 amplifies B-cell receptor (BCR) signaling, exacerbating TP53-deficient CLL aggressiveness [7, 33]. This synergy has been reported in prior studies, as in CLL4 trial showed that 17p del patients had a median PFS of <12 months with chemoimmunotherapy [34], similar to our cohort (14 months). Also, RESONATE-2 study confirmed that ibrutinib improves outcomes in 17p del patients, supporting our recommendation for first-line BTK inhibitors in this subgroup [35].

Although there have been advancements in the biology of CLL, CD38 is still a strong prognostic marker; our cohort had a positivity rate of 42%, whereas Western studies have found a positivity rate of 30–50% [7, 36]. According to study by Ten Hacken and Burger, CD38 is involved in BCR activation and microenvironment interactions; hence, CD38+ patients exhibited higher Rai stages ($p=0.003$) and worse PFS [37]. Also, it's found that CD38+ CLL cells have elevated NF-κB activation, which promotes survival, according to recent single-cell RNA sequencing studies [38]. Especially in low-resource areas where FISH would not be easily accessible, our data suggest keeping CD38 in risk categorization models.

The results of our FISH research indicated a number of outcomes with a variety of objectives. Similar to Western cohorts [9], 13q deletion accounts for 35% of cases and is related with positive outcomes (median progression-free survival: 60 months). In addition, there is a 22 percent deletion of 11q, which is slightly greater than the 15–18 percent that was observed in the United States [4]. This may be related to regional genetic variances. Based on a previous study, trisomy 12 (15%) is considered to be within the expected ranges and has an intermediate prognosis [39]. Therefore, ten percent of patients showed normal FISH, which is a lower proportion than in European studies (20–25%) (9). This indicates that there may be undiscovered mutations (such as NOTCH1 and SF3B1) that require next-generation sequencing in subsequent research.

Our data observed a new high-risk subgroup consisting of 12% of patients who had CD38+/LAIR1+/17p del alleles and had a three-year overall survival rate of only 42%. Emerging research suggests that combined immunogenetic indicators perform better than separate abnormalities [40]. There were reports of findings that were comparable in the outcomes. The MDACC 2019 cohort found CD38+/TP53mut combination had the shortest median overall survival (3.1 years), highlighting the need for alternative treatment strategies like BTKi/BCL2i-based regimens for high-risk patients [1].

Another study is conducted a study group analysis and showed that patients with 17p del/CD38+ had a 5-year survival rate of less than 30%. In this extremely high-risk cohort, these findings highlight the importance of utilizing alternative medicines such as venetoclax combined with anti-CD20 chemotherapy [34].

Limitions in our study are observed. First is a retrospective, single-center design (prospective validation is required). Second, there is insufficient information on IGHV mutations; future research should incorporate molecular profiling. Last but not least, a small group of 12 high-risk individuals. Therefore, collaborating at multiple locations could strengthen the statistics.

■ CONCLUSION

Our work shows that Iraqi CLL patients have unique immunophenotypic (LAIR1, CD38) and genetic (17p del) patterns. These patterns can help doctors figure out how to best treat these patients and how to lower their risk. These results show how important it is to do CLL research in specific areas to get the best results for groups that aren't well represented.

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