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Study of CD24 in Chronic Lymphatic Leukemia Patients: Relation to Disease Characteristics

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ABSTRACT

Background: In the adult population, chronic lymphocytic leukemia (CLL) is the leading form of leukemia. Over the past decade, the treatment paradigm has shifted dramatically with the adoption of potent targeted therapies. Markers like CD38, ZAP-70, and cytogenetic/molecular changes serve as important prognostic indicators. CD24, a maturation-linked B-cell marker, may also intersect with apoptotic signaling. **Objective:** This study aimed to evaluate CD24 expression in de novo CLL and examine its relationship with key disease characteristics.

Materials and methods: We quantified CD24 by flow cytometry in peripheral blood obtained from 60 newly diagnosed CLL cases and 30 age- and sex-matched healthy controls at the Medical Research Institute, Alexandria University, and Tanta University Hospitals (Egypt).

Results: CD24 expression was found to be significantly higher in CLL than in controls and was enriched among patients meeting criteria for therapy. CD24 correlated positively with established prognostic markers. **Conclusion:** CD24 showed promise as an independent prognostic indicator in untreated CLL and may help anticipate disease progression.

Keywords: CD24, Chronic Lymphatic Leukemia, CD38, ZAP-70.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) chiefly affects older adults and exhibits marked heterogeneity in clinical behavior. Pathologically, it consists of clonal expansions of mature, CD5-positive B lymphocytes that accumulate within blood, marrow, lymph nodes, and spleen [1-2]. Early cytogenetic lesions, notably del(13q), del(11q), and trisomy 12, are frequently implicated and are often followed by additional genetic mutations that fuel progression [3].

Approximately 80% of patients are found, through cytogenetic assessment, to carry one of the major aberrations: del(13q14.3), del(11q), del(17p), or trisomy 12. Whole-exome and whole-genome studies have outlined a broader mutational landscape, characterized by recurrent lesions and copy-number alterations [4]. Genes commonly involved include NOTCH1, MYD88, TP53, ATM, SF3B1, FBXW7, POT1, CHD2, RPS15, IKZF3, ZNF292, ZMYM3, ARID1A, and PTPN11 [4-7].

Immunophenotypically, CLL cells co-express CD5 with B-cell markers (CD19, CD20 & CD23). Relative to normal B cells, they show characteristically low surface immunoglobulin, diminished CD20 and CD79b, and light-chain restriction to κ or λ [8-10].

Risk stratification is commonly performed using the Rai system, which classifies patients into low risk (lymphocytosis only), intermediate risk (presence of organomegaly and/or lymphadenopathy), and high risk (anemia with Hb <11 g/dL or thrombocytopenia with platelets $<100 \times 10^9$/L). Alternatively, the Binet system stages disease as A, B, or C, according to the number of sites involved and the presence of cytopenias [11].

Per iwCLL guidance, treatment is reserved for active/symptomatic disease; asymptomatic, early-stage patients (Rai 0, Binet A) are generally observed [2]. In those considered for therapy, age, performance status, del(17p)/TP53 status, and IGHV mutation status help personalize management; reassessment of TP53/del(17p) and IGHV is recommended before subsequent lines [12, 13].

Current first-line strategies increasingly favor targeted agents irrespective of age or del(17p)/TP53 status, including second-generation BTK inhibitors (acalabrutinib & zanubrutinib) with or without anti-CD20 antibodies, or venetoclax with obinutuzumab [14].

CD24 is a GPI-anchored, heavily glycosylated surface molecule expressed across developing and mature immune and neural cells. In B-cell biology, its dynamic expression tracks maturation; functionally,

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CD24 engagement can trigger apoptosis in immature B cells and modulate proliferation in later stages [15].

Despite advances in elucidating the prognostic landscape of CLL, much of the current knowledge focuses on established biomarkers like CD38, ZAP-70, cytogenetic abnormalities, and molecular mutations. However, the role of CD24 in CLL remains insufficiently defined, despite its recognized importance in B-cell maturation, apoptosis, and regulation of proliferation. Only limited data are available regarding its potential as a prognostic biomarker or its correlation with clinical staging and disease progression. This lack of clarity highlights the need for further investigation into CD24 expression in CLL patients to determine whether it may serve as an independent predictor of disease course or therapeutic response. So, we conducted this research to assess CD24 expression in newly diagnosed CLL and explore its correlation with clinical and laboratory parameters.

MATERIALS AND METHODS

This study enrolled 60 newly diagnosed CLL patients, stratified into two equal groups—watchful waiting versus treatment-indicated per iwCLL criteria—alongside 30 matched healthy controls. Participants were recruited from the Hematology Department, Medical Research Institute (Alexandria University), and Tanta University Hospital, Egypt.

Exclusion criteria, Rational and specifications

Inclusion Criteria: Eligibility followed WHO diagnostic criteria for CLL, requiring a persistent peripheral blood B-lymphocyte count $\geq 5 \times 10^9$/L for at least three months. Clonality was verified by flow-cytometric light-chain restriction. On blood smears, leukemic cells typically appeared as small mature lymphocytes with scant cytoplasm, condensed chromatin, and absent conspicuous nucleoli [2, 11].

The characteristic immunophenotype comprised CD5 co-expression with CD19, CD20, and CD23, reduced surface immunoglobulin, CD20 and CD79b, and κ/λ light-chain restriction. A consensus panel of CD19, CD5, CD20, CD23, and κ/λ is commonly adequate to establish a definitive diagnosis [2, 11].

Exclusion criteria: Patients with an active second malignancy.

Clinical and laboratory assessment

All patients underwent systematic baseline work-up comprising clinical examination, a complete blood count (CBC), examination of the peripheral blood film, immunophenotyping of peripheral blood and contrast-enhanced CT. Patients were staged according to Rai and Binet classifications.

At diagnosis, investigations included reticulocyte count, LDH, direct antiglobulin test (DAT), β2-microglobulin, platelet-to-lymphocyte ratio (PLR), and expression of ZAP-70, CD38, and CD24. Bone marrow examination was performed when clinically indicated.

Study design and population characteristics: Design and setting: A cohort study conducted at two tertiary hematology centers in Egypt (Tanta University Hospitals and the Medical Research Institute—Alexandria University). The cohort comprised 60 de novo CLL cases (30 treatment-indicated; 30 watchful waiting) and 30 healthy controls.

Data collection:

For each participant, detailed medical history and comprehensive physical examination were obtained. CBC with peripheral smear review was performed, and bone marrow aspiration/examination was undertaken when required to confirm the diagnosis.

Ethical approval: The study was granted by the Faculty of Medicine, Tanta University. Written informed consent was secured from each participant after explanation of the study aims and procedures. Follow-up began at diagnosis and included serial CBCs, and marrow assessments as clinically indicated, continuing for up to 36 months or until death, the prespecified study endpoint. The study followed The Declaration of Helsinki through its execution.

For hematology assays, 2.5 mL of whole blood was collected in EDTA tubes and analyzed immediately on a Sysmex XN-550 analyzer for hemoglobin, platelet count, total and differential leukocyte counts; PLR and DAT were calculated/recorded accordingly. Peripheral blood films were stained with Giemsa, and reticulocytes were assessed using brilliant cresyl blue.

An additional 3 mL sample was drawn into plain tubes, left to clot for 30 minutes at room temperature, and subsequently centrifuged at 1,500×g for 10 minutes to separate serum. Serum aliquots were used to measure LDH, DAT, and β2-microglobulin.

Flow cytometry: Diagnostic immunophenotyping was performed for all CLL patients, and CD24, CD38, and ZAP-70 were assessed in both patients and controls. Analyses were run on a BD FACSCanto II (BD Biosciences, San Jose, CA, USA). Antibodies were organized as follows: Tube I: CD23-PE, CD19-PE-Cy7, CD5-PerCP-Cy5.5, CD200-APC & CD20-V450. Tube II: CD7-FITC, CD79b-PE & FMC-7-V450. Tube III: κ-FITC, λ-PE, CD19-PE-Cy7; plus CD38-APC-

H7, ZAP-70-PE & CD24-FITC (all from BD Biosciences).

Sample preparation: Leukocyte concentration was adjusted to 1×10^6 cells/tube. Fluorochrome-conjugated monoclonal antibodies were added per titrated volumes, gently vortexed, and left to incubate for 25 minutes at room temperature in darkness.

Red cell lysis was achieved by adding 1 mL lysing solution, vortexing, and incubating for 20 minutes in the dark at room temperature. Samples were then properly washed with 0.5 mL PBS and centrifuged at 2,500 rpm for 3 minutes; the wash step was repeated. Cell pellets were subsequently resuspended in 300 µL PBS for acquisition.

For intracellular ZAP-70, cells were fixed and permeabilized with 250 µL of fixation/permeabilization buffer for 10 minutes at room temperature in the dark before antibody staining. Data acquisition included 10,000 events with lymphocyte gating. Positivity thresholds were 30% for B-CLL markers and 20% for ZAP-70. Data were analyzed using BD FACSDiva software (BD Biosciences).

Radiological staging comprised chest radiography, abdominal ultrasonography, and either contrast-enhanced CT or PET-CT to evaluate extranodal involvement. Bone marrow aspiration was routinely performed according to institutional protocols.

Statistical analysis

Data were processed using SPSS version 27 and R v4.2.1. Normality of continuous variables (age, CD24, CD38, ZAP-70, PLR, Hb & ALC) was assessed and results were reported in form of mean ± SD or median (IQR) and categorical variables as counts/percentages. Comparisons between groups employed ANOVA or Kruskal–Wallis tests for continuous variables, and Chi-square or Fisher's exact tests for categorical variables. Correlations were examined with Pearson or Spearman coefficients. ROC analysis with Youden index determined cutoffs and diagnostic performance. Predictors were evaluated via logistic regression (ORs, 95% CI) with collinearity checks (VIF >5). Time-to-treatment (TTT) was analyzed by Kaplan–Meier and Cox proportional hazards models with time-dependent ROC. Random-forest ranking appraised variable importance, latent class analysis explored subgroups and propensity-score matching (SMD <0.1) addressed imbalance. Missing data were imputed using MICE. Significance was set at $p \leq 0.05$.

RESULTS

60 de novo CLL patients—equally split between treatment-indicated and watchful-waiting groups—and 30 healthy controls. Median age was 62 years with a male predominance, aligning with international epidemiology. As expected, treatment-indicated cases exhibited more advanced iwCLL-defined disease (Table 1).

Table (1): Baseline sociodemographic and clinical characteristics

Characteristic		Treatment-Indicated (n=30)	Non-Treatment-Indicated (n=30)	Controls (n=30)	p-value
Age (years), median (IQR)		63 (55–70)	61 (53–68)	60 (52–67)	0.412*
Gender, n (%)	**Male**	19 (63.3%)	17 (56.7%)	16 (53.3%)	
	Female	11 (36.7%)	13 (43.3%)	14 (46.7%)	
Binet Stage, n (%)	**A**	2 (6.7%)	18 (60.0%)		
	B	13 (43.3%)	9 (30.0%)		
	C	15 (50.0%)	3 (10.0%)		
Coombs Test, n (%)				N/A	0.006†
Positive		12 (40.0%)	3 (10.0%)		
Negative		18 (60.0%)	27 (90.0%)		
Hepatomegaly, n (%)		6 (20.0%)	1 (3.3%)	0 (0%)	0.012†
Splenomegaly, n (%)		12 (40.0%)	4 (13.3%)	0 (0%)	<0.001†
Lymphadenopathy, n (%)		20 (66.7%)	12 (40.0%)	0 (0%)	<0.001†
Platelets (x10³/µL), Mean ± SD		115,00±28,10	185,00±45,97	250,00 ± 30,00	<0.001*
Hb (g/dL), mean ± SD		8.3±2.0	12.0±2.2	13.5±1.5	<0.001*
ALC (x10³/µL), median (IQR)		55,000 (35,000–160,000)	18,000 (10,000–38,000)	2,000 (1,500–2,50(	<0.001‡
TLC (x10³/µL), median (IQR)		65,000 (45,000–190,000)	28,000 (15,000–48,000)	6,000 (4,500–7,500)	<0.001‡

*ANOVA; †Chi-square test; ‡Kruskal-Wallis test. Hb: hemoglobin; ALC: absolute lymphocyte count; TLC: total leukocyte count; N/A: not applicable.

Expression of CD24 was markedly higher among treatment-indicated patients than in watchful-waiting patients and controls, paralleling elevations in CD38 and ZAP-70. Conversely, PLR values were lower in the treatment-indicated group, consistent with marrow infiltration (Table 2).

Table (2): Expression of Prognostic Markers in CLL Patients and Controls

Marker	Treatment-Indicated (n=30)	Non-Treatment-Indicated (n=30)	Controls (n=30)	p-value
CD24 (%), mean ± SD	67.8 ± 24.5	26.2 ± 14.8	9.8 ± 3.0	<0.001*
CD38 (%), mean ± SD	58.4 ± 21.2	24.6 ± 14.3	4.9 ± 2.1	<0.001*
ZAP-70 (%), mean ± SD	47.1 ± 19.3	19.8 ± 11.9	3.5 ± 1.7	<0.001*
PLR, median (IQR)	2.5 (1.4–3.8)	9.5 (6.5–13.0)	14.8 (12.5–17.5)	<0.001‡

*ANOVA; ‡Kruskal-Wallis test. PLR: platelet-to-lymphocyte ratio.

CD24 showed strong positive correlations with CD38 (r=0.65, p<0.001), ZAP-70 (r=0.61, p<0.001), and absolute lymphocyte count (ALC) (r=0.64, p<0.001), supporting its association with markers of disease activity and proliferation. Negative correlations were observed with platelet-to-lymphocyte ratio (PLR) (r=-0.48, p<0.001) and hemoglobin (Hb) (r=-0.42, p=0.001). Heatmap displaying Spearman correlations between CD24 and prognostic markers (CD38, ZAP-70, PLR, absolute lymphocyte count [ALC] & hemoglobin [Hb]) in 60 CLL patients. CD24 showed strong positive correlations with CD38 (r=0.65), ZAP-70 (r=0.61) & ALC (r=0.64) and negative correlations with PLR (r=-0.48) and Hb (r=-0.42, all p≤0.001). Stronger correlations are represented by more intense colors, with positive values in red and negative in blue as Illustrated in table (3) and figure (1).

Table (3): Correlation matrix of CD24 with prognostic markers

Prognostic Marker	Correlation with CD24 (r)	p-value
CD38	0.65	<0.001
ZAP-70	0.61	<0.001
PLR	-0.48	<0.001
ALC	0.64	<0.001
Hb	-0.42	0.001

Spearman correlation coefficients are reported.

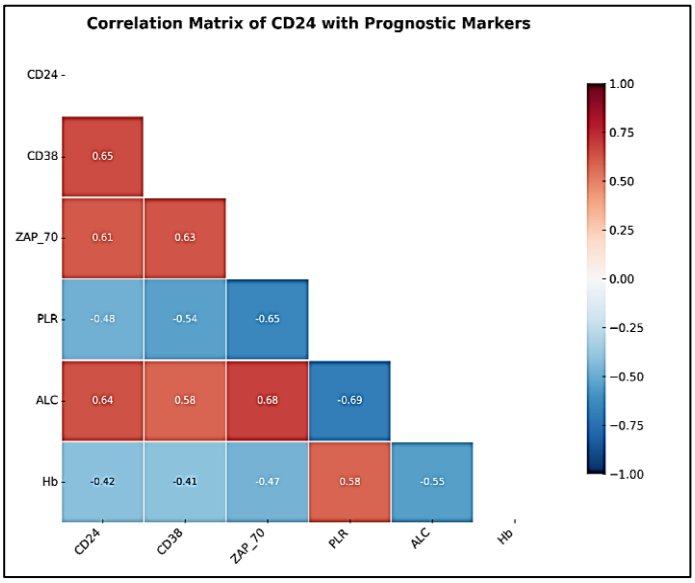


Figure (1): Correlation matrix of CD24 with prognostic markers.

Multivariable logistic regression identified high CD24 expression (OR=1.07 per 1% increase, p<0.001), high CD38 (OR=1.06, p=0.003), positive Coombs test (OR=3.80, p=0.003), and low PLR (OR=0.82, p=0.005) as independent predictors of treatment indication. There was a significant interaction between CD24 and the Coombs test (p=0.04) (Table 4).

Table (4): Multivariable Logistic Regression for treatment indication

Predictor	OR (95% CI)	*p*-value
CD24 (%)	1.07 (1.04–1.11)	<0.001
CD38 (%)	1.06 (1.02–1.10)	0.003
ZAP-70 (%)	1.03 (0.99–1.07)	0.12
Coombs Test (Positive)	3.80 (1.60–9.00)	0.003
PLR	0.82 (0.72–0.94)	0.005
Age	1.03 (0.98–1.07)	0.28
Gender (Male)	1.50 (0.60–3.80)	0.39
CD24 × Coombs Test	1.04 (1.00–1.08)	0.04

OR: odds ratio; CI: confidence interval.

Correlations between CD24 and prognostic markers (CD38, ZAP-70, PLR, ALC & Hb) in 60 CLL patients; stronger associations are rendered with greater color intensity (Table 5 & figure 2).

Table (5): Cox Proportional Hazards Model for time to treatment

Variable	HR (95% CI)	*p*-value
CD24 (≥30% vs. <30%)	2.80 (1.80–4.40)	<0.001
CD38 (%)	1.04 (1.01–1.07)	0.003
ZAP-70 (%)	1.02 (0.99–1.05)	0.15
Binet Stage C (vs. A/B)	2.40 (1.50–3.90)	<0.001

HR: hazard ratio; CI: confidence interval.

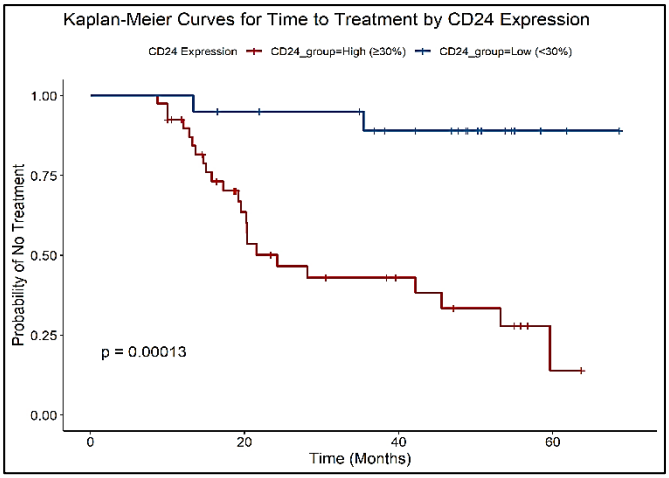


Figure (2): Kaplan-Meier Curves for Time to Treatment by CD24 Expression, correlations between CD24 and prognostic markers (CD38, ZAP-70, PLR, ALC & Hb) in 60 CLL patients; stronger associations are rendered with greater color intensity.

CD24 provided the highest discriminative accuracy for treatment indication (AUC = 0.88), exceeding CD38 (AUC = 0.80) and ZAP-70 (AUC = 0.73). At a 30% cutoff, sensitivity and specificity were 82% and 78% respectively, with PPV of 84% and NPV of 76%, underscoring potential clinical utility (Tables 6 & 7 and figures 3 & 4).

Table (6): Diagnostic Accuracy of Prognostic Markers

Prognostic Marker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CD24	0.88 (0.78–0.98)	82	78	84	76
CD38	0.80 (0.69–0.91)	75	70	23	71
ZAP-70	0.73 (0.61–0.85)	68	65	68	65

PPV, positive predictive value; **NPV,** negative predictive value.

Table (7): Time-Dependent ROC Analysis for TTT

Time Point	AUC (95% CI)	Sensitivity (%)	Specificity (%)
12 months	0.85 (0.75–0.95)	80	76
24 months	0.82 (0.71–0.93)	78	74
36 months	0.80 (0.69–0.91)	76	72

Receiver Operating Characteristic (ROC) curves for CD24, CD38 and ZAP-70 in predicting treatment indication in 60 CLL patients. CD24 demonstrated the highest accuracy (AUC=0.88, 95% CI: 0.78–0.98, 82% sensitivity, 78% specificity at 30% cutoff) compared to CD38 (AUC=0.80) and ZAP-70 (AUC=0.73) (Figure 3).

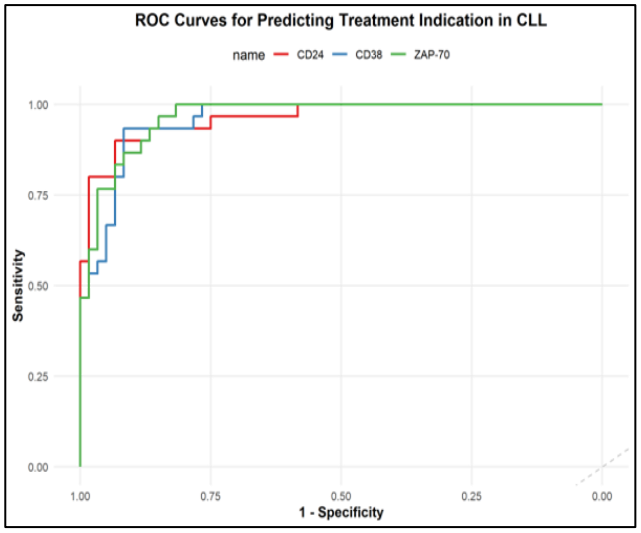


Figure (3): ROC Curves for Predicting Treatment Indication in CLL.

Time-dependent Receiver Operating Characteristic (ROC) curves assessing CD24's predictive accuracy for time to treatment (TTT) at 12, 24, and 36 months in 60 CLL patients. AUCs were 0.85 (95% CI: 0.75–0.95, 12 months), 0.82 (0.71–0.93, 24 months), and 0.80 (0.69–0.91, 36 months), indicating sustained prognostic value (Figure 4).

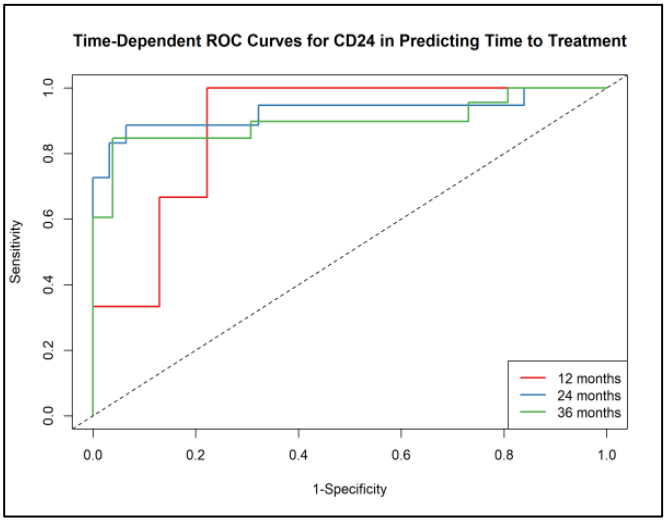
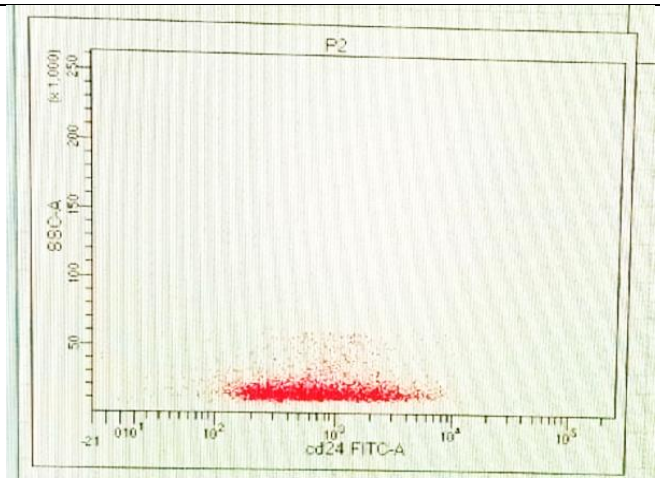


Figure (4): Time-Dependent ROC Curves for CD24 in Predicting Time to Treatment.

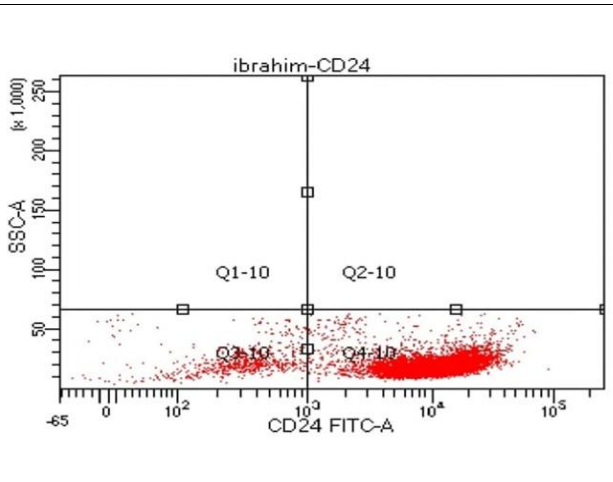
Random forest modeling ranked CD24 as the most important predictor of treatment indication (mean decrease in Gini=36.5), followed by CD38 (mean decrease in Gini=30.2) and PLR (mean decrease in Gini=27.8) (Table 7).

Table (7): Random Forest Variable Importance

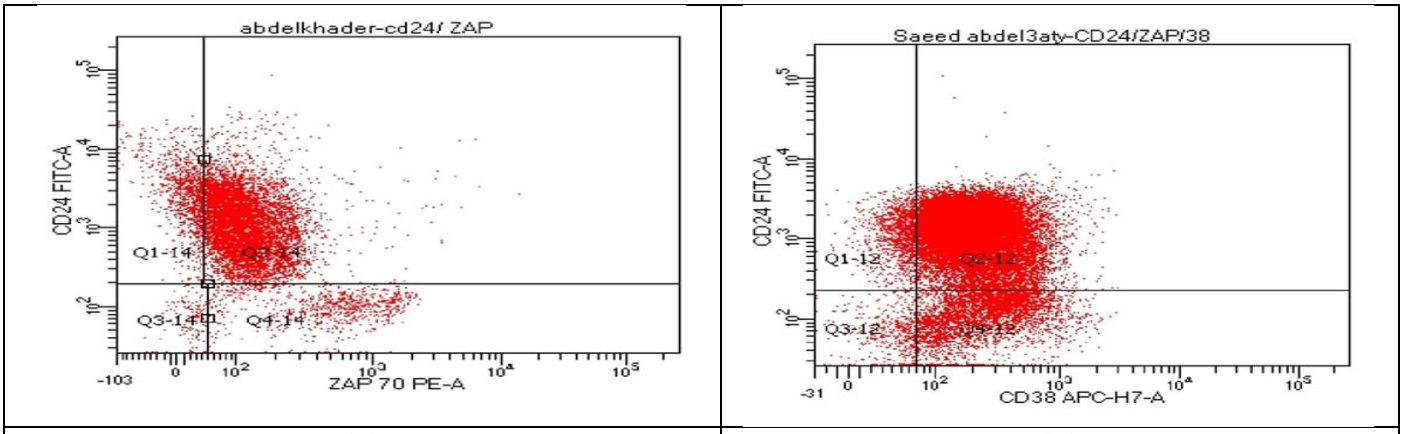
Prognostic Marker	Mean Decrease in Gini
CD24	36.5
CD38	30.2
PLR	**27.8**
ZAP-70	22.4



(A)



(B)



(C) (D)

Figure (5): Representative Flow-cytometry plots: (A) CLL with low CD24, (B) CLL with high CD24, (C) dual CD24/ZAP-70 positivity and (D) dual CD24/CD38 positivity.

DISCUSSION

Attia *et al.* [16] and **Fathy *et al.*** [17] reported that Egyptian CLL cohorts present at a younger age. Our median of 62 years coincides with their observations. In contrast, **Mukkamalla *et al.*** [18] and **Eichhorst *et al.*** [19] described Western populations with median ages around the seventh decade, which we do not mirror. Taken together, these patterns likely reflect demographic and referral differences rather than fundamental biological divergence.

D'Arena *et al.* [20] demonstrated that combined ZAP-70/CD38 positivity delineates more aggressive disease. Our results agree with both CD38 and ZAP-70, which were significantly higher in Binet C and in the treatment-indicated group. Conversely, **Abdelgader *et al.*** [21] reported no significant association comparing these markers and clinical stage. Our data disagree with that report, a discrepancy plausibly explained by methodological differences (cut-offs, antibody clones & gating) or stage mix at enrollment.

Popova *et al.* [22] noted that several flow markers may be negative early and later shift with progression. This concept aligns with our stratified findings, where marker burden clustered among patients requiring therapy, supporting stage-contingent immunophenotypic evolution.

El-Ashwah *et al.* [23] linked low PLR and high PDW to adverse features and survival, whereas **Bakouny *et al.*** [24] reported no independent prognostic value for PLR after adjustment. In our cohort, PLR was lower in treatment-indicated patients (consistent with marrow involvement), which coincides directionally with **El-Ashwah *et al.*** [23] and helps explain conflicting literature when cohorts, eras, and covariate structures differ.

Huang *et al.* [25] showed that surface phenotypes (including CD24) distinguish progressive from stable CLL. Our data agree and extend this by quantifying strength of association where CD24 correlated positively with CD38 ($r = 0.65$), ZAP-70 ($r = 0.61$), and ALC ($r = 0.64$), and inversely with PLR ($r = -0.48$) and hemoglobin ($r = -0.42$) (all $p \leq 0.001$, Hb $p = 0.001$). Importantly, CD24 remained an independent predictor of treatment indication (OR 1.07 per 1% increase; $p < 0.001$), and CD24 $\geq$ 30% predicted shorter time-to-treatment (HR 2.80; $p < 0.001$). For discriminating treatment need, CD24 achieved AUC 0.88 (sensitivity 82%, specificity 78% at 30%), outperforming CD38 (AUC 0.80) and ZAP-70 (AUC 0.73) in our dataset.

Aroldi *et al.* [26] provided translational support for the biological relevance of CD24, reporting that interrupting CD24-mediated signaling (often alongside CD47) may augment antibody-dependent cytotoxicity. Our observation showed that higher CD24 was associated with earlier treatment and progression coincided with this adverse biology and highlighted CD24 as a prognostic and potentially actionable axis.

Crespo *et al.* [27] established ZAP-70 as a surrogate for IGHV mutation status. Our finding that ZAP-70 clusters with treatment indication and advanced stage agrees with the adverse biology captured by ZAP-70. Notably, CD24 added independent prognostic information in our multivariable models, suggesting complementary utility alongside canonical markers (ZAP-70/IGHV, CD38).

Strengths of our study include standardized, same-timepoint immunophenotyping at diagnosis, convergence across multiple markers and linkage to time-to-treatment.

Limitations include single-country recruitment, moderate sample size, and fixed cut-offs. Future multi-center validation should determine whether CD24 delivers decision-changing value beyond TP53/del(17p), IGHV, and conventional flow panels, and whether CD24-directed combinations can be rationally integrated into the current BTK/BCL2 inhibitor era.

CONCLUSION

In summary, CD24 expression aligns with established adverse markers (CD38, ZAP‑70) and higher lymphocyte counts while inversely related to PLR and hemoglobin. These findings support CD24 as an independent prognostic biomarker and a potential therapeutic target in de novo CLL.

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No conflict of interest.

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