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ELEVENTH ANNUAL MEETING

THE EFFECT OF T-LYMPHOCYTE SUBGROUPS AT DIAGNOSIS ON THE PROGNOSIS OF CHRONIC LYMPHOCYTIC LEUKEMIA

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INTRODUCTION

Studies have reported **increased CD4 and CD8 T-lymphocyte counts in CLL patients**. However, their effect of leukemic B-lymphocytes is controversial.

AIM

This study aims **to examine the prognostic significance and effect of T-lymphocyte subgroups at diagnosis on CLL prognosis and survival**.

METHOD

Patient Selection:

- **83 previously untreated** patients
- September 1998-2019

Study Design:

- **Retrospective Cohort**
- CD4, CD8, and CD7 T-lymphocyte ratios on flow cytometry
- T-cells/Malignant B-Cells (MBC): CD5+CD19+ B-lymphocytes

Main Outcomes:

- Progression-free survival (PFS)
- Overall survival (OS)

RESULTS

Patient characteristics at diagnosis

Characteristics	n = 83 (%)
Age at diagnosis, years	61.9 ± 10.6 (40-84)*
Follow-up time, months	73.7 ± 58.6 (1-243)*
Gender	
Male	51 (61.4 %)
Female	32 (38.6 %)
Rai Stage	
0	40 (48.2 %)
I+II	38 (45.8 %)
III+IV	5 (6 %)
Binet Stage	
A	58 (69.9 %)
B	20 (24.1 %)
C	5 (6 %)
β-2 microglobulin, mg/L	3.93 ± 2.66 (0.95-14.9)*
High > 3.5 mg/dL	26 (31.3 %)
Low < 3.5 mg/dL	19 (22.9 %)
n/a	38 (45.8 %)
Progression-free survival time, months	50.9 ± 53.0 (0-242, median: 31.0)*
Non-progressive disease	44 (53 %)
Progressive disease	39 (47 %)
Overall survival time, months	88.7 ± 58.5 (1-263, median: 91.0)*
Alive	63 (75.9 %)
Exitus	20 (24.1 %)

*-mean ± s.d. (range), n/a-not available

- **No difference** in T-lymphocyte parameters **according to age, gender, or disease stages.**
- **Lower** CD4 (*P* .048) and CD7 (*P* .020) percentages, CD4/MBC (*P* .021), CD8/MBC (*P* .035), and CD7/MBC (*P* .012) values **in progressive patients**.
- **Lower** CD3 (*P* .001), CD4 (*P* .001), CD8 (*P* .005), and CD7 (*P* .007) percentages **in deceased patients**.

T-Lymphocyte subgroups according to prognostic factors

	Rai Low-Risk	Rai Intermediate and High Risk	p	Binet A	Binet B-C	p	β2 Microglobulin ≤ 3.5	β2 Microglobulin > 3.5	p
	mean ± s.d.	mean ± s.d.		mean ± s.d.	mean ± s.d.		mean ± s.d.	mean ± s.d.	
CD3 %	18.43 ±14.49	14.18 ±11.11	0.229	16.83 ±12.84	14.84 ±13.37	0.290	16.33 ±10.30	10.45 ±6.91	***0.046***
CD4 %	10.47 ±7.64	8.67 ±6.46	0.247	9.85 ±7.21	8.82 ±6.81	0.430	10.14 ±6.27	6.23 ±3.89	***0.022***
CD8 %	11.32 ±12.59	7.43 ±5.99	0.264	9.91 ±10.83	7.88 ±7.21	0.323	9.79 ±11.81	5.72 ±4.41	0.083
CD7 %	23.36 ±16.75	18.32 ±13.75	0.269	23.01 ±16.78	15.88 ±10.49	0.122	19.69 ±11.33	17.01 ±16.96	0.218
ATC %	6.22 ±5.17	4.93 ±3.16	0.641	6.04 ±4.78	4.79 ±3.60	0.403	5.27 ±2.92	4.03 ±2.48	0.374
CD4 #	2372.42 ±2635.65	2163.70 ±2117.06	0.708	2269.40 ±2339.61	2269.70 ±2535.54	0.733	2169.35 ±2331.77	2066.57 ±1697.41	0.877
CD8 #	2357.63 ±3380.83	1842.88 ±2148.73	0.791	2235.41 ±2934.67	1777.83 ±2603.39	0.295	2177.58 ±2932.80	1680.95 ±1834.44	0.700
CD7 #	5402.67 ±6610.26	4004.82 ±4719.57	0.110	5027.22 ±5812.74	3948.96 ±5648.94	0.093	4799.63 ±5508.45	3741.56 ±4213.59	0.305
CD4/MBC	0.20 ±0.19	1.45 ±7.75	0.337	0.18 ±0.18	2.32 ±10.01	0.878	0.19 ±0.18	2.64 ±10.82	0.103
CD8/MBC	0.24 ±0.41	0.42 ±1.84	0.343	0.20 ±0.35	0.64 ±2.38	0.667	0.22 ±0.45	0.69 ±2.57	0.133
CD7/MBC	0.43 ±0.41	1.12 ±4.83	0.314	0.40 ±0.37	1.57 ±6.06	0.667	0.36 ±0.35	1.87 ±6.74	0.318
CD4/CD8	1.35 ±0.79	1.46 ±1.23	0.884	1.39 ±1.08	1.44 ±0.96	0.878	1.42 ±0.80	1.36 ±0.80	0.713

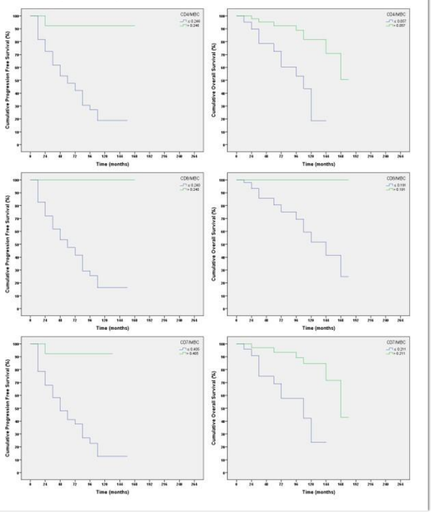
% indicates percentage; #, absolute value; ATC, Activated T-Cells (CD7+HLA-DR+) and MBC, Malignant B-Cells (CD5+CD19+).

Cox regression models for PFS and OS

	Progression Free Survival				Overall Survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
Gender (Male)	1.450 (0.733, 2.866)	0.286			2.175 (0.780, 6.065)	0.137		
Age (≥ 65 years)	1.181 (0.601, 2.321)	0.630			3.906 (1.579, 9.660)	***0.003***		
Gamma globulin	1.348 (0.442, 4.110)	0.599			0.487 (0.102, 2.324)	0.367		
Beta-2 Microglobulin	1.281 (1.115, 1.472)	***<0.001***			1.398 (1.158, 1.687)	***<0.001***		
Rai (Intermediate+High)	3.047 (1.558, 5.960)	***0.001***	3.546 (1.516, 8.295)	***0.004***	3.336 (1.273, 8.739)	***0.014***	4.404 (1.561, 12.425)	***0.005***
Binet (B+C)	4.256 (2.066, 8.767)	***<0.001***			2.808 (1.141, 6.914)	***0.025***		
CD3 %	0.960 (0.930, 0.992)	***0.014***			0.875 (0.808, 0.947)	***0.001***		
CD4 %	0.929 (0.877, 0.984)	***0.012***			0.816 (0.723, 0.920)	***0.001***		
CD8 %	0.938 (0.889, 0.989)	***0.019***			0.830 (0.730, 0.945)	***0.005***		
CD4/CD8	1.014 (0.709, 1.452)	0.938			1.118 (0.702, 1.780)	0.640		
CD4/MBC	0.009 (0.001, 0.267)	***0.007***			0.001 (0.001, 0.098)	***0.007***		
CD8/MBC	0.015 (0.001, 0.482)	***0.018***			0.001 (0.001, 0.012)	***0.005***	0.001 (0.001, 0.001)	***0.002***
CD7/MBC	0.054 (0.007, 0.401)	***0.004***	0.069 (0.005, 0.881)	***0.040***	0.001 (0.001, 0.341)	***0.008***		
HLA-DR %	1.027 (1.001, 1.054)	***0.048***			1.113 (1.044, 1.187)	***0.001***		
CD7 %	0.946 (0.913, 0.980)	***0.002***			0.949 (0.903, 0.998)	***0.040***		
ATC %	0.982 (0.838, 1.149)	0.817			0.847 (0.676, 1.062)	0.150		
CD38 %	1.007 (0.964, 1.053)	0.745			0.716 (0.444, 1.156)	0.171		
Treatment (Yes)	13.930 (5.664, 34.257)	***<0.001***	8.406 (2.825, 25.010)	***0.001***	2.062 (0.821, 5.180)	0.123		

HR, Hazard Ratio; CI, Confidence Interval; %, percentage; #, absolute value; ATC, Activated T-Cells; MBC, Malignant B-Cells.

PFS and OS using cut-off values for T-lymphocyte/MBC ratios determined with ROC analysis and Kaplan-Meier tests.



COX-REGRESSION

Factors Effecting PFS and OS in Cox-Regression Analysis		
	Progression-free Survival (PFS)	**Overall Survival (OS)**
Univariate Analysis	Treatment status (Yes)	Age (≥ 65 years)
	• T-lymphocyte percentage • T-lymphocyte/MBC rates • HLA-DR percentage • Rai stage (Intermediate-High Risk) • Binet stage (B+C) • Beta-2 microglobulin level	
Multivariate Analysis*	▪ Rai stage (Intermediate-High Risk) ▪ Treatment status (Yes) ▪ **CD7/MBC** [A single unit of increase **decreased the risk of progression by 93.1%** (95% CI: .005-.881, *P* .040)] *PFS (χ^2=41.470, *P* < .001)	▪ Rai stage (Intermediate-High Risk) ▪ **CD8/MBH** [A single unit of increase **decreased the mortality risk by 99.99%** (95% CI: .001-.001, *P* .002)] *OS (χ^2=9.237, *P* .010)

CONCLUSION

- **Low T-lymphocyte percentages and low T-lymphocyte/MBC ratios at diagnosis were associated with poor prognosis, progressive disease, and decreased survival.**
- The role of T-lymphocytes in CLL prognosis could be revealed in more detail with prospective studies evaluating naive T-lymphocyte and differentiated T-lymphocyte subgroups, as well as functional T-lymphocyte markers such as HLA-DR and PD-1.

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