High proportion of circulating CD8+CD28- T cells predicts inferior prognosis in AIDS-related non-Hodgkin lymphoma

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Background: Tumor cells and the immune system interact in dynamic and intricate ways, but the precise immune cell types influencing AIDS-related non-Hodgkin lymphoma (AR-NHL) prognosis remain elusive. Furthermore, the disparities in circulating lymphocyte subsets between AR-NHL and HIV-negative NHL patients are poorly understood.

Methods: This observational, longitudinal cohort study enrolled 31 newly diagnosed adult AR-NHL patients and 52 matched HIV-negative NHL populations. Peripheral lymphocyte immunophenotyping was dynamically assessed during immunochemotherapy using flow cytometry. Multivariate survival analysis was performed with the Cox regression model. Linear correlation analysis and the Mann–Whitney U test were used to examine the relationship between immune indices and clinical characteristics.

Results: In our study, AR-NHL patients exhibited comparable overall survival and progression-free survival to those observed in HIV-negative NHL individuals. Compared to HIV-seronegative NHL cohorts, AR-NHL patients tended to be younger with elevated levels of β2-microglobulin (β2-MG), erythrocyte sedimentation rate, and EBV-encoded RNA (EBER). At diagnosis, AR-NHL populations demonstrated decreased counts of CD4+ T cells and CD4/CD8 ratio, along with reduced percentages of Treg cells, naive CD45RA+, and memory CD45RO+ CD4+ T cells. Conversely, they displayed increased proportions of Tregs/CD4, CD8+, CD8+CD28+, and CD8+CD28- T cells. Additionally, these alterations in Treg cells, CD4+, memory CD45RO+ CD4+, CD8+, CD8+CD28+, and CD8+CD28- T cells persisted throughout immunochemotherapy. Notably, multivariate analysis revealed that a heightened presence of initial CD8+CD28- T cells independently predicted an unfavorable prognosis in AR-NHL patients. This subset of T cells was strongly correlated with aggressive clinical indicators, including elevated β2-MG, decreased albumin levels, diminished CD4/CD8 ratio, high International Prognostic Index score, and positivity for EBER.

Keywords: AIDS-related non-Hodgkin lymphoma; Immunophenotype; CD8+CD28- T cells; Prognostic factor; Immunosenescence

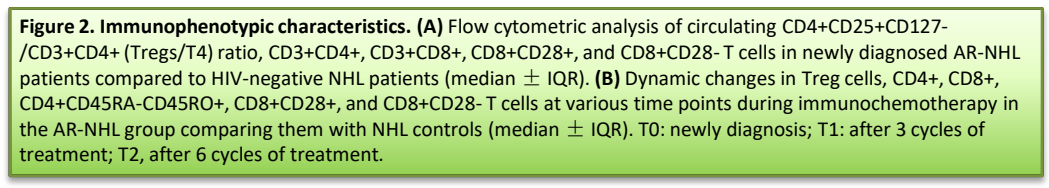


Figure 2. Immunophenotypic characteristics. (A) Flow cytometric analysis of circulating CD4+CD25+CD127-/CD3+CD4+ (Tregs/T4) ratio, CD3+CD4+, CD3+CD8+, CD8+CD28+, and CD8+CD28- T cells in newly diagnosed AR-NHL patients compared to HIV-negative NHL patients (median ± IQR). **(B)** Dynamic changes in Treg cells, CD4+, CD8+, CD4+CD45RA-CD45RO+, CD8+CD28+, and CD8+CD28- T cells at various time points during immunochemotherapy in the AR-NHL group comparing them with NHL controls (median ± IQR). T0: newly diagnosis; T1: after 3 cycles of treatment; T2, after 6 cycles of treatment.

Table 1. Cox regressions analysis for progression-free survival in AR-NHL patients (n = 31).

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Male	1.593 (0.356–7.126)	0.543		
Age > 60 years	2.064 (0.569–7.496)	0.271		
Ann Arbor stage III/IV	27.197(0.060–12250.370)	0.289		
Extra-nodal involvement ≥ 2	2.119 (0.588–7.631)	0.251		
LDH > ULN	2.521 (0.701–9.061)	0.157		
ECOG PS ≥ 2	1.262 (0.421–3.782)	0.677		
B symptoms (Yes)	2.813 (0.977–8.093)	0.055		
Bulky tumor (Yes)	2.370 (0.817–6.876)	0.112		
EBER (Positive)	1.200 (0.416–3.458)	0.736		
LMR < 2.12	5.409 (1.479–19.546)	**0.010**	3.819 (0.802–18.189)	0.092
PLR ≥ 204.82	0.943 (0.331–2.690)	0.913		
ALB < 35.70 g/L	6.330 (1.745–22.294)	**0.005**	2.495 (0.527–11.808)	0.249
CD4 count < 200 cells/μL	1.911 (0.533–6.854)	0.320		
CD4/CD8 < 0.31	1.870 (0.645–5.421)	0.249		
HIV-1 RNA ≥ 100 000 copies/mL	1.668 (0.576–4.830)	0.346		
CD3+ ≥ 77.10%	1.961 (0.655–5.873)	0.229		
CD3+CD4+ < 17.10%	1.870 (0.645–5.421)	0.249		
CD3+CD8+ ≥ 57.30%	2.869 (0.897–9.181)	0.076		
CD3-CD16+CD56+ ≥ 12.50%	1.028 (0.360–2.938)	0.958		
CD4+CD25+CD127-/CD3+CD4+ ≥ 12.85%	1.664 (0.573–4.831)	0.349		
CD8+CD28- ≥ 30.48%	4.827 (1.336–17.432)	0.016	5.365 (1.427–20.167)	**0.013**
CD8+CD28+ ≥ 26.67%	0.595 (0.206–1.719)	0.337		
CD8+CD28-/CD8+CD28+ ≥ 1.113	1.565 (0.542–4.515)	0.408		

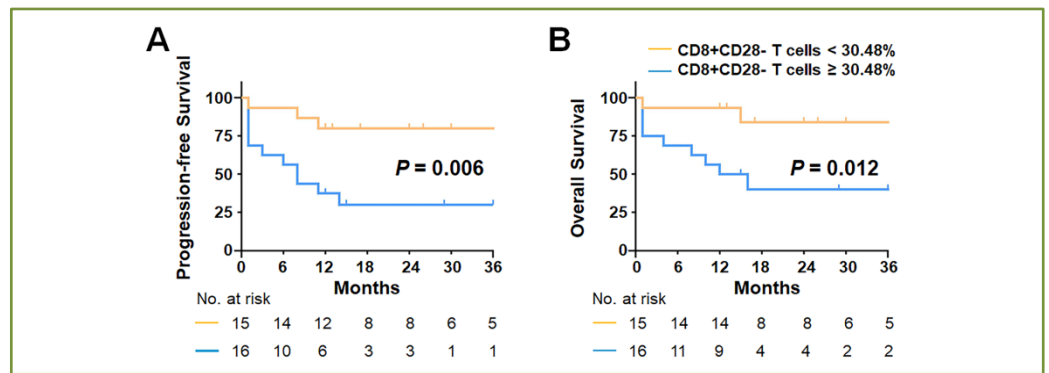


Figure 3. Prognostic significance based on independent predictor in AR-NHL patients. Kaplan–Meier survival analyses depicting progression-free survival **(A)** and overall survival **(B)** stratified by CD8+CD28- T cells.

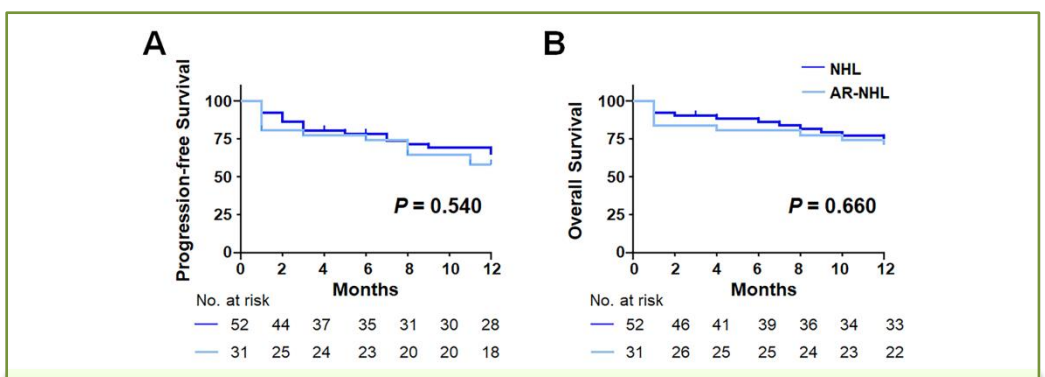
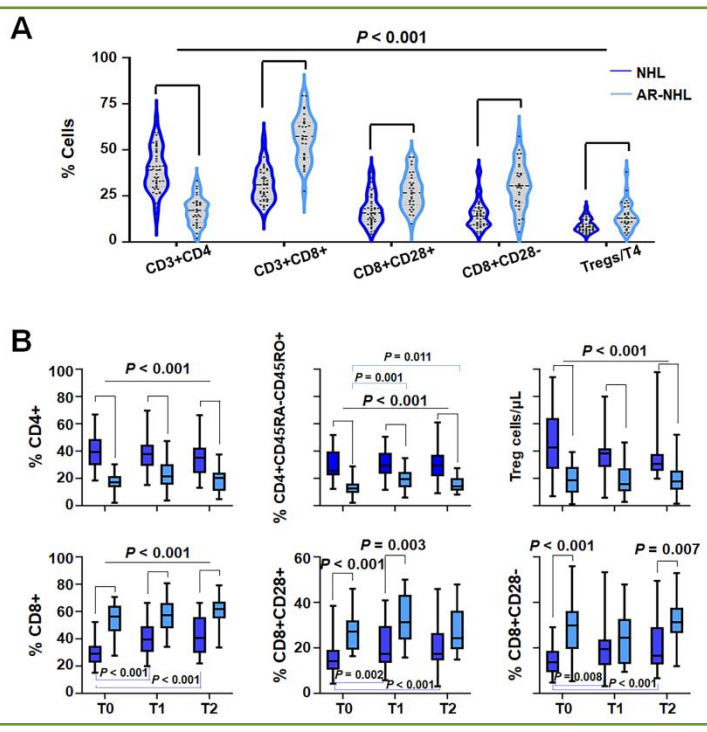


Figure 1. Survival analysis. Kaplan–Meier survival curves illustrating the 1-year progression-free survival **(A)** and overall survival **(B)** for 31 patients with AIDS-related non-Hodgkin lymphoma (AR-NHL) compared to 52 HIV-negative NHL individuals.



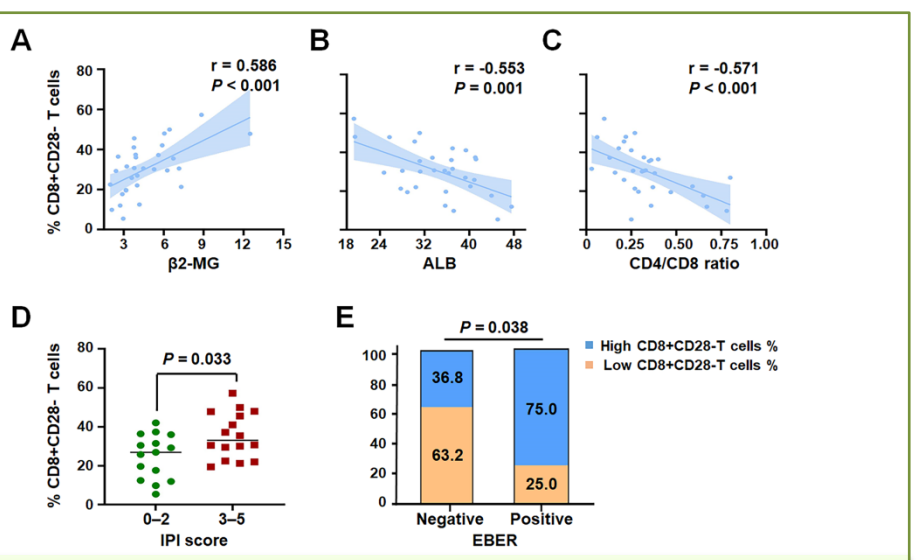


Figure 4. Correlation of CD8+CD28- T cells with clinical variables in AR-NHL patients. (A-C) The percentages of CD8+CD28- T cells in relation to β2-microglobulin (β2-MG), albumin (ALB), and CD4/CD8 ratio quantification. **(D)** The average levels of CD8+CD28- T cells across different International Prognostic Index (IPI) score groups. **(E)** The proportions of CD8+CD28- T cells in Epstein-Barr virus (EBV)-encoded RNA (EBER) groups.

Conclusions

The prognosis of AR-NHL patients significantly improved with high-intensity chemotherapeutic regimens in the combined antiretroviral therapy era, becoming comparable to that of the general NHL population. AR-NHL individuals exhibited distinct premature immunosenescence phenotypes compared to HIV-negative patients. A high proportion of circulating CD8+CD28- T cells served as an independent biomarker for predicting outcomes in AR-NHL, potentially associated with heightened viral exposure and chronic immune activation.

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