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Lymphocyte Subset Distribution can Predict the Efficacy of First-line Treatment in Patients with Non-Hodgkin Lymphoma

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KEYWORDS

Non-Hodgkin's Lymphoma;
Diffuse Large B-Cell Lymphoma;
Nasal NK/T-Cell Lymphoma;
Lymphocyte Subsets;
Flow Cytometry;
Tumor-Specific Growth Factor (TSGF);
Lactate Dehydrogenase (LDH);
Ki67

ABSTRACT

Objective: To investigate the predictive value of pretreatment peripheral blood lymphocyte subset distribution and other laboratory indices for the efficacy of first-line chemotherapy in patients with diffuse large B-cell lymphoma (DLBCL) and nasal natural killer/T-cell lymphoma (ENKTL).

Methods: A retrospective analysis was conducted on 110 newly diagnosed lymphoma patients, comprising 63 cases of DLBCL and 47 cases of ENKTL. Demographic characteristics, disease stage, treatment regimens, and efficacy evaluations were collected, along with pretreatment levels of peripheral blood lymphocyte subsets (T cells, CD4+, CD8+, B cells, NK cells, CIK cells), tumor-specific growth factor (TSGF), lactate dehydrogenase (LDH), and Ki-67 expression. Univariate and multivariate logistic regression analyses were performed, with a significance threshold of $P < 0.05$.

Results: The DLBCL group predominantly presented with stage III–IV disease, while the ENKTL group mainly had stage I disease, demonstrating a statistically significant difference in stage distribution ($P < 0.001$). Multivariate analysis revealed that in DLBCL patients, disease stage (stage III: OR = 0.07, P = 0.043), elevated CD8+ T cell proportion (OR = 0.94, P = 0.047), and increased LDH levels (OR = 1.00, P = 0.021) were independent risk factors for poor treatment efficacy. In ENKTL patients, disease stage (stage II: OR = 0.03, P = 0.042; stage IV: OR = 0.00, P = 0.033) and elevated total T cell proportion (OR = 0.74, P = 0.049) emerged as independent predictors of unfavorable outcomes.

Conclusion: Pretreatment peripheral blood lymphocyte subset distribution is closely correlated with the efficacy of first-line chemotherapy in DLBCL and ENKTL patients. Elevated CD8+ T cell proportion indicates poorer outcomes in DLBCL, while increased total T cell proportion is associated with adverse treatment responses in ENKTL. Integrating lymphocyte subset testing with disease stage and LDH levels serves as a robust tool for individualized efficacy prediction, providing valuable insights for adjusting clinical treatment strategies.

Introduction

Lymphoma is the most common malignant tumor of the lymphohematopoietic system. The World Health Organization (WHO) classifies lymphoma into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), the latter originating from B cells or T cells/natural killer

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(NK)cells [1,2]. Diffuse large B-cell lymphoma (DLBCL) is the most common and aggressive type of B-cell lymphoma in adults, accounting for 30%–40% of NHL in China. DLBCL has great heterogeneity in clinical manifestations and prognosis [1]. Nasal NK/T-cell lymphoma (ENKTL) is a unique pathological subtype of non-Hodgkin lymphoma [3], which is highly aggressive, has poor response to treatment, and is prone to relapse [4]. ENKTL accounts for a relatively high proportion of head and neck lymphomas (about 22%), and occurs more frequently in the head and neck than lymphomas in other parts of the body [5]. Studies have found that nasal and sinus ENKTL and DLBCL have similar clinical symptoms, including nasal congestion, headache, and eye symptoms, which can easily lead to misdiagnosis. Clinically, it is necessary to combine other laboratory tests to improve the accuracy of diagnosis of the two [6]. Therefore, it is very meaningful to seek simple, readily avail-able, fast and accurate laboratory indicators to differentiate between the two.

Lymphocytes maintain dynamic balance in the body, thereby playing the functions of immune defense, immune surveillance and immune homeostasis. In the tumor state, the body's immune function is suppressed, which may lead to tumor proliferation, metastasis and spread, while peripheral blood lymphocyte subsets can reflect the immune function status of tumor patients and are related to the patient's prognosis [7]. Lactate dehydrogenase (LDH) has been included in the DLBCL international prognostic index scoring system, and is used in combination with age, Ann Arbor stage, performance status score and whether there is extranodal invasion to identify low, medium and high risk patients [1,2]. Tumor-specific growth factor (TSGF) is a protein produced by tumor cells during their formation. It is closely related to tumor growth and has relative specificity for tumors. Therefore, it has a strong ability to diagnose tumors before treatment and to evaluate the efficacy of treatment after recurrence [8]. Ki67 is a nuclear protein that has been widely used in clinical practice as a marker of proliferating cells. Its expression level is closely related to the degree of tumor cell proliferation, differentiation, malignancy (infiltration, metastasis) and patient prognosis [9]. Therefore, this study analyzed the distribution of lymphocyte subsets and the relationship between the expression of LDH, TSGF and Ki67 and the survival status and treatment effect of DLBCL and ENKTL, in order to find a more sensitive and reliable marker that can improve the diagnostic accuracy of DLBCL and ENKTL and predict the treatment effectiveness of both.

Materials and Methods

General Information

From August 2015 to December 2017, the patient sought medical treatment at Hunan Cancer Hospital and was diagnosed with DLBCL or ENKTL were included. Clinical data such as patient gender, age and time of diagnosis, disease stage (Ann Arbor staging), treatment regimen, and efficacy evaluation were collected. Patients were followed up to collect data on their survival status and survival time. Pre-treatment lymphocyte subsets (T, CD4, CD8, B, NK, CIK), TSGF, LDH, and Ki67 test results were retrieved and recorded.

Inclusion Criteria

1) Diagnosed as DLBCL or ENKTL (diagnostic classification 1 or 2);
2) Survival time is assessable (>1 month);
3) The results of the tests for T, CD4, CD8, B, NK, CIK, TSGF, LDH, and Ki67 are complete.

Peripheral Blood Lymphocyte Subset Analysis

EDTA-anticoagulated peripheral blood sample was collected from the patient. The flow cytometer used was a Beckman Coulter FC500 (USA); All flow cytometry reagents were manufactured by Beckman Coulter. Antibodies were as follows: a quadruple antibody of T lymphocyte subset: CD45-FITC/CD4-PE/CD8-ECD/CD3-PC5; a quadruple antibody of B lymphocyte subset: CD45- FITC/CD56-PE/ CD19-ECD/CD3-PC5 and standalone CD16-PE; quality control was IMMUNO-TROL ™ Cells whole blood quality control; red blood cell lysis buffer: Optilyse. The percentages of CD3+ T cells, CD4+ T cells, CD8+ T cells, CD19+ B cells, and CD3 - CD16+CD56+ NK cells, as well as the CD4+/CD8+ ratio, were analyzed using the FC500's built-in software.

Treatment Plan and Efficacy Evaluation

Treatment regimens included R-CHOP regimens (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), GELOXD regimens (gemcitabine + asparaginase + oxaliplatin + dexamethasone), and others. Efficacy was evaluated according to the 2014 Lugano criteria, categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) was the sum of the CR and PR rates. In this study, response was defined as CR / PR; ineffectiveness as SD /PD.

Follow-Up

All patients were followed up through outpatient services and telephone at Hunan Cancer Hospital, with the follow-up deadline being June 30, 2023. Progression-free survival (PFS) refers to the time from diagnosis to disease recurrence/ progression or death from any cause, or the last follow-up.

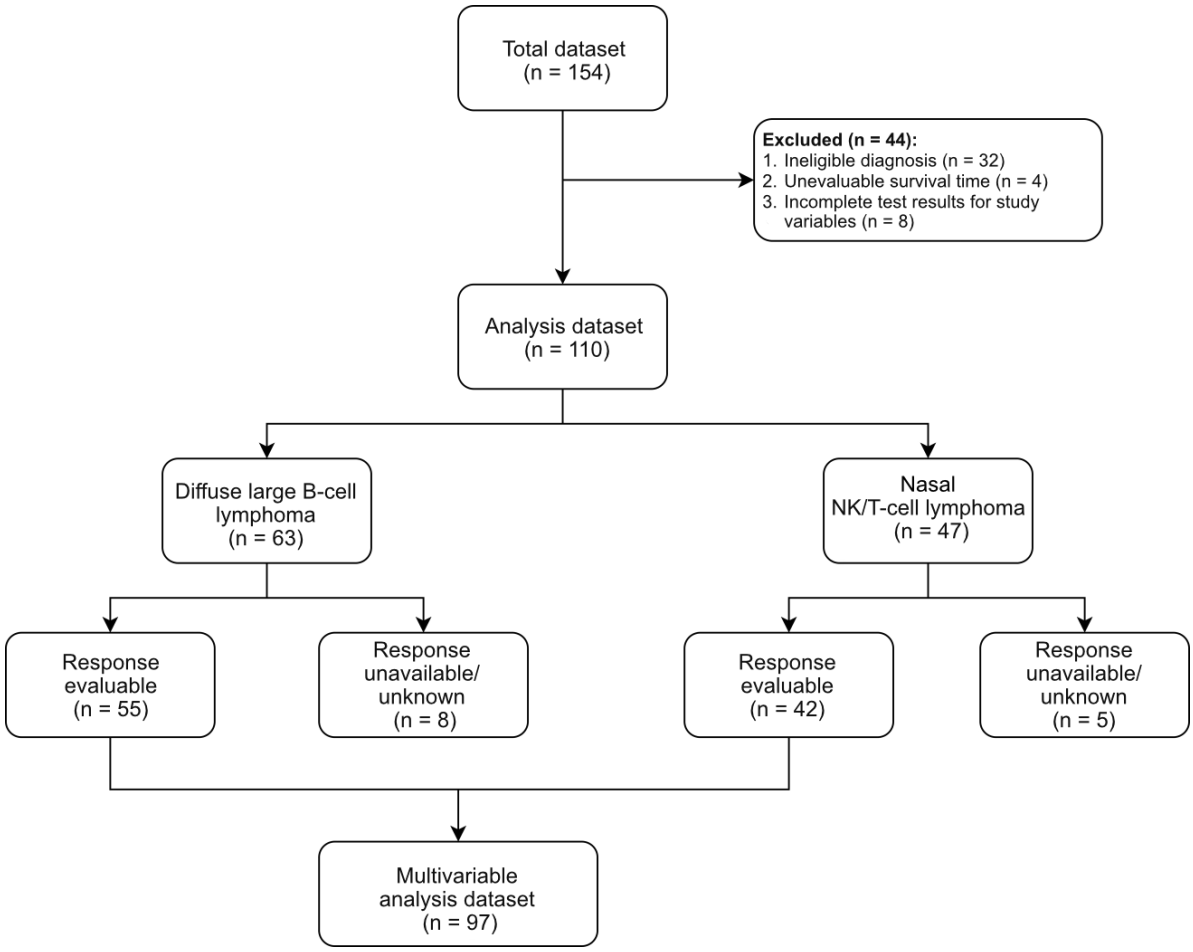

Figure 1 | Screening and group inclusion process flowchart

Flowchart of participant screening and group allocation in the study. The total initial dataset comprised 154 cases. From this, 44 cases were excluded for three reasons: ineligible diagnosis (n = 32), unavailable survival time (n = 4), or incomplete test results for study variables (n = 8). This yielded an analysis dataset of 110 cases, which was then stratified into two pathological subtypes: diffuse large B - cell lymphoma (n = 63) and nasal NK/T - cell lymphoma (n = 47). Within each subtype, cases were categorized by response assessability: "response evaluable" and "response unavailable/unknown". Specifically, for diffuse large B - cell lymphoma, 55 cases were response evaluable and 8 were response unavailable/unknown; for nasopharyngeal NK/T - cell lymphoma, 42 cases were response evaluable and 5 were response unavailable/unknown. Finally, a total of 97 cases across both subtypes were included in the multivariable analysis dataset.

Overall survival (OS) refers to the time from diagnosis to death from any cause, or the last follow-up.

Statistical Methods

Data analysis was performed using IBM SPSS 26.0 statistical software. Qualitative and ordinal data, including patient baseline characteristics (including gender, age, disease stage (Ann Arbor stage), treatment regimen, efficacy evaluation, survival time, and survival status), were compared using chi-square tests or Fisher's exact tests. Normality tests were performed on quantitative data. If the data followed a normal or approximately normal distribution, t-tests were used to compare the means; if the data did not follow a normal distribution, nonparametric methods were used to compare central tendency (median). Kaplan-Meier analysis was used for PFS and OS. Uni-variate and multivariate analyses were performed using Cox proportional hazards regression models. A p-value < 0.05 was considered statistically significant.

Results

Patient Baseline Information

Data Cleaning

Patients with evaluable survival time (>1 month) and complete pre-treatment lymphocyte subset (T, CD4, CD8, B, NK, CIK), TSGF, LDH, and Ki67 test results were included in the study. After data screening and filtering, 110 cases were included in the study; among them, 63 patients were diagnosed with DLBCL, and 47 patients were diagnosed with ENKTL. (The screening and enrollment process flowchart is shown in **Figure 1**).

Baseline Data Statistical Analysis

As shown in **Table 1**, the baseline distribution of DLBCL and ENKTL was as follows: there was no significant difference in gender between DLBCL and ENKTL patients; the majority of patients in both cases were under 60 years old

Table 1 | Population baseline data analysis (n%)

Factor		Diffuse large B-cell lymphoma n=63	Nasal NK/T-cell lymphoma n=47	Total population n=110	X^2 test, *P*
Gender	male	37 (58.73%)	26 (55.32%)	63 (57.27%)	X^2 = 0.128 , *P* = 0.721
	female	26 (41.27%)	21 (44.68%)	47 (42.73%)	
Age	<60	45 (71.43%)	44 (93.62%)	89 (80.91%)	X^2 = 8.580 , *P* = 0.003
	>=60	18 (28.57%)	3 (6.38%)	21 (19.09%)	
Disease staging	I	11 (17.46%)	26 (55.32%)	37 (33.64%)	X^2 = 22.928 , P = 0.000
	II	18 (28.57%)	13 (27.66%)	31 (28.18%)	
	III	9 (14.29%)	1 (2.13%)	10 (9.09%)	
	IV	22 (34.92%)	4 (8.51%)	26 (23.64%)	
	Unknown	3 (4.76%)	3 (6.38%)	6 (5.45%)	
Treatment plan	Contains CHOP	48 (76.19%)	13 (27.66%)	61 (55.45%)	X^2 = 60.986 , P = 0.000
	Includes GELOXD (excluding CHOP)	0 (0.00%)	32 (68.09%)	32 (29.09%)	
	other	15 (23.81%)	2 (4.26%)	17 (15.45%)	
Therapeutic effect assessment	CR	18 (28.57%)	30 (63.83%)	48 (43.64%)	X^2 = 14.996 , *P* = 0.005
	PR	22 (34.92%)	7 (14.89%)	29 (26.36%)	
	SD	2 (3.17%)	0 (0.00%)	2 (1.82%)	
	PD	13 (20.63%)	5 (10.64%)	18 (16.36%)	
	Unknown	8 (12.70%)	5 (10.64%)	13 (11.82%)	
Survival time	Lost to visit	3 (4.76%)	1 (2.13%)	4 (3.64%)	X^2 = 1.497 , *P* = 0.473
	<60 months	23 (36.51%)	22 (46.81%)	45 (40.91%)	
	>=60 months	37 (58.73%)	24 (51.06%)	61 (55.45%)	
Survival status	Lost to visit	3 (4.76%)	1 (2.13%)	4 (3.64%)	X^2 = 2.754 , *P* = 0.252
	Survival	39 (61.90%)	36 (76.60%)	75 (68.18%)	
	die	21 (33.33%)	10 (21.28%)	31 (28.18%)	

Note: Data in red font indicate statistically significant differences (P < 0.05); the statistical software used was IBM SPSS 26.0.

Appendix 1 | Normality test of quantitative indicators (according to diagnostic classification)

Factor	Diagnostic classification	Kolmogorov - Sminov (V)a			Shapiro Wilke		
		statistics	Degrees of freedom	Significance	statistics	Degrees of freedom	Significance
Age	B cells	0.103	63	0.093	0.968	63	0.099
	NK/T cells	0.103	47	0.200*	0.978	47	0.497
T	B cells	0.086	63	0.200*	0.985	63	0.620
	NK/T cells	0.090	47	0.200*	0.969	47	0.250
CD4	B cells	0.061	63	0.200*	0.975	63	0.229
	NK/T cells	0.065	47	0.200*	0.991	47	0.975
CD8	B cells	0.101	63	0.178	0.962	63	0.050
	NK/T cells	0.067	47	0.200*	0.979	47	0.546
CD4/CD8	B cells	0.102	63	0.099	0.943	63	0.006
	NK/T cells	0.210	47	0.000	0.791	47	0.000
B	B cells	0.087	63	0.200*	0.948	63	0.010
	NK/T cells	0.122	47	0.078	0.935	47	0.012
NK	B cells	0.143	63	0.003	0.942	63	0.005
	NK/T cells	0.103	47	0.200*	0.947	47	0.034
CIK	B cells	0.265	63	0.000	0.518	63	0.000
	NK/T cells	0.208	47	0.000	0.753	47	0.000
TSGF	B cells	0.144	63	0.002	0.910	63	0.000
	NK/T cells	0.102	47	0.200*	0.966	47	0.193
LDH	B cells	0.279	63	0.000	0.538	63	0.000
	NK/T cells	0.247	47	0.000	0.751	47	0.000
Ki67	B cells	0.118	63	0.029	0.945	63	0.007
	NK/T cells	0.147	47	0.013	0.963	47	0.143

** This is the lower bound for true significance.*
a. Reilly significance correction

Appendix 2 | Normality test of quantitative indicators (population)

Category	Kolmogorov - Sminov (V)a			Shapiro Wilke		
	statistics	Degrees of freedom	Significance	statistics	Degrees of freedom	Significance
Age	0.090	110	0.028	0.979	110	0.080
T	0.058	110	0.200*	0.984	110	0.198
CD4	0.034	110	0.200*	0.990	110	0.586
CD8	0.054	110	0.200*	0.985	110	0.253
CD4/CD8	0.146	110	0.000	0.860	110	0.000
B	0.067	110	0.200*	0.956	110	0.001
NK	0.125	110	0.000	0.947	110	0.000
CIK	0.233	110	0.000	0.642	110	0.000
TSGF	0.102	110	0.006	0.939	110	0.000
LDH	0.281	110	0.000	0.463	110	0.000
Ki67	0.131	110	0.000	0.957	110	0.001

** This is the lower bound for true significance.*
a. Reilly significance correction

Table 2 | Analysis of pathological markers in two types of non-Hodgkin's lymphoma (t-test for all variables) (mean (95 CI))

Factors/Indicators	Diffuse large B-cell lymphoma n=63	Nasal NK/T-cell lymphoma n = 4 7	Total population n=110	*t* -test, *P*
Age	53.27 (50.42, 56.12)	42.79 (39.19, 46.38)	48.79 (46.38, 51.21)	t=4.640, P=0.000
T	71.34 (68.50, 74.19)	75.18 (72.46, 77.89)	72.98 (70.98, 74.99)	t=1.899, P=0.060
CD4	36.09 (33.64, 38.54)	36.12 (33.14, 39.09)	36.10 (34.24, 37.96)	t=0.016, P=0.988
CD8	30.76 (28.35, 33.18)	31.90 (28.92, 34.88)	31.25 (29.40, 33.10)	t=0.600, P=0.550
B	7.28 (5.96, 8.61)	7.72 (6.41, 9.04)	7.47 (6.54, 8.40)	t=0.464, P=0.643

Note: Data in red font indicate statistically significant differences (P < 0.05); the statistical software used was IBM SPSS 26.0.

Table 3 | Analysis of pathological markers in two types of non-Hodgkin's lymphoma (non-parametric test) (median (Q25, Q75))

Factors/Indicators	Diffuse large B-cell lymphoma n=63	Nasal NK/T-cell lymphoma n = 4 7	Total population n=110	Mann - Whitney U test, *P*
CD4/CD8	1.21(0.86,1.65)	1.08 (0.82, 1.52)	1.18(0.82,1.64)	U=1376.50, P=0.530
NK	17.70 (11.30, 26.80)	15.10 (9.20, 21.80)	16.10 (10.13, 23.75)	U=1156.00, P=0.050
CIK	1.90 (0.70, 3.70)	3.80 (0.80, 6.30)	2.25(0.70,5.55)	U=1788.50, P=0.063
TSGF	67.80 (53.70, 74.55)	55.70 (41.95, 66.90)	61.91 (47.46, 72.41)	U=1062.50, P=0.012
LDH	262.90 (183.30, 463.10)	209.10 (183.90, 250.90)	227.75 (183.75, 330.38)	U=1159.50, P=0.052
Ki67 (%)	70.00 (50.00, 80.00)	70.00 (50.00, 80.00)	70.00 (50.00, 80.00)	U=1411.00, P=0.671

Note: Data in red font indicate significant differences (P < 0.05); data in bold black font indicate marginally significant differences (P approximately 0.05). Statistical software used was IBM SPSS 26.0 .

Table 4 | Analysis of pathological markers in two types of non-Hodgkin's lymphoma (ANOVA) (mean (95 CI))

Factors/Indicators	Diffuse large B-cell lymphoma n=63	Nasal NK/T-cell lymphoma n = 4 7	Total population n=110	F-test, *P*
age	53.27 (50.42, 56.12)	42.79 (39.19, 46.38)	48.79 (46.38, 51.21)	F=21.529, P=0.000
T	71.34 (68.50, 74.19)	75.18 (72.46, 77.89)	72.98 (70.98, 74.99)	F=3.607, P=0.060
CD4	36.09 (33.64, 38.54)	36.12 (33.14, 39.09)	36.10 (34.24, 37.96)	F=0.000, P=0.988
CD8	30.76 (28.35, 33.18)	31.90 (28.92, 34.88)	31.25 (29.40, 33.10)	F=0.360, P=0.550
CD4/CD8	1.33 (1.17, 1.49)	1.37 (1.10, 1.64)	1.35 (1.20, 1.49)	F=0.071, P=0.791
B	7.28 (5.96, 8.61)	7.72 (6.41, 9.04)	7.47 (6.54, 8.40)	F=0.216, P=0.643
NK	19.48 (16.82, 22.14)	15.69 (13.19, 18.18)	17.86 (15.99, 19.72)	F=4.077, P=0.046
CIK	3.29 (2.01, 4.57)	4.98 (3.33, 6.64)	4.01 (3.00, 5.03)	F=2.712, P=0.103
TSGF	61.84 (57.54, 66.15)	53.67 (47.90, 59.43)	58.35 (54.84, 61.86)	F=5.420, P=0.022
LDH [a]	440.53 (305.30, 575.77)	237.12 (205.99, 268.24)	353.62 (273.67, 433.56)	F=6.540, P=0.012
Ki67	64.86 (60.22, 69.49)	42.79 (39.19, 46.38)	64.23 (60.71, 67.74)	F=0.168, P=0.683

Note: Data in red font indicate statistically significant differences (P < 0.05). The statistical software used was IBM SPSS 26.0 . α indicates unequal variances; in this case, the F-test results are for reference only.

(P = 0.003); DLBCL had more advanced (III-IV) cases, while ENKTL had more early (I) cases (P = 0.000); DLBCL was mainly treated with CHOP-containing regimens, while ENKTL was mainly treated with GELOXD regimens (P = 0.000); DLBCL was mainly characterized by PR, while ENKTL was mainly characterized by CR. ENKTL had a better prognosis (P = 0.005). Therefore, the statistical analysis was determined to focus on "efficacy assessment" as the primary outcome indicator.

Analysis and Comparison of Pathological Indicators in Two Types of Non-Hodgkin Lymphoma

Normality Test of Quantitative Indicators

As shown in Appendices 1 and 2, the normality test results indicate that age, T, CD4, CD8, and B follow an approximately normal distribution (**Appendix 1**). The t-test will be used to compare the means (**Table 2**). CD4/CD8, NK, CIK, TSGF, LDH, and Ki67 do not follow a normal distribution (**Appendix 2**). Nonparametric methods will be used to com-pare the central tendency (median, **Table 3**). Furthermore, this study also used ANOVA (Analysis of Variance) to further validate the above results (**Table 4**).

Comparison of Pathological Markers Between Two Types of non-Hodgkin's Lymphoma

As shown in **Tables 2, 3 and 4**, the differences in age, NK and TSGF between DLBCL and ENKTL were statistically significant ($P<0.05$), LDH showed a marginally significant difference ($P\approx0.05$), while the differences in the other 7 indicators were not statistically significant ($P>0.05$).

KM Survival Analysis of Two Types of non-Hodgkin Lymphoma

As shown in **Figure 2**, the survival curves of DLBCL and ENKTL highly overlap, with no significant difference in survival time and survival rate. Based on this, the direction of statistical analysis was determined again: "efficacy assessment" was used as the main outcome indicator.

Evaluation of the Efficacy of DLBCL and Nasal ENKTL

Evaluation of the Efficacy of DLBCL

Logistic regression analysis was performed first, using univariate regression analysis. Cases with a p-value < 0.10 in univariate regression were then included in multivariate regression analysis. Because CD4/CD8 is a known interaction variable with other factors (CD4, CD8), if CD4 or CD8 was already included in multivariate regression, CD4/ CD8 was not included. A p-value < 0.05 was considered statistically significant in multivariate regression. The analysis results showed that stage, CD8, and LDH were independent risk factors for the efficacy of first-line treatment in diffuse large B-cell lymphoma (higher values indicated poorer outcomes) (**Table 5**). ANOVA analysis showed that CD8, CD4/CD8, and LDH may be associated with the efficacy of first-line treatment for diffuse large B-cell lymphoma; this was consistent with the results of logistic regression analysis (**Table 6**).

Evaluation of the Efficacy of Nasal ENKTL

Logistic regression analysis was performed first, with univariate regression analysis conducted. Cases with a p-value < 0.10 in univariate regression were then included in multivariate regression analysis. Because CD4/CD8 is a known interaction variable with other factors (CD4, CD8), if CD4 or CD8 was already included in multivariate regression, CD4/ CD8 was not included. A p-value < 0.05 was considered statistically significant in multivariate regression. The analysis results showed that stage and total T cell proportion were risk factors for the efficacy of first-line treatment for nasal NK/T-cell lymphoma (higher values indicated poorer outcomes) (**Table 7**). ANOVA analysis showed no factors associated with the efficacy of first-line treatment for nasal NK/T-cell lymphoma. Total T cell proportion showed marginal significance. This may be due to differences between univariate and multivariate analyses; in this case, the results of logical regression were considered definitive (**Table 8**).

Discussion

DLBCL is the most common type of NHL. In China, it accounts for about 40 % of adult NHL cases. The median age of onset is 50 to 70 years, with males slightly more affected than females [10]. In this study, the average age of onset for DLBCL patients was 53 years, which is close to the results of a retrospective analysis of DLBCL patients from the Cancer Hospital of the Chinese Academy of Medical Sciences from 2005 to 2018 (median age of onset was 54 years). The majority of patients were under 60 years old (71.43 %), which is earlier than the median age of onset for patients in the United States during the same period (63 years). The basic treatment for DLBCL is targeted therapy combined with chemotherapy. Rituximab combined with CHOP is the standard first-line treatment regimen (R-CHOP) [11]. In this study, there were more advanced (III-IV) DLBCL cases. 76.19% of DLBCL patients used the R- CHOP regimen, and the CR+PR rate reached 63.49%. Studies have reported that the standard first-line R-CHOP regimen can cure about 60% of DLBCL patients [12].

In China, ENKTL is the most common peripheral T-cell lymphoma, with an incidence rate of approximately 28.16% [10]. ENKTL is more common in men and has a lower age of onset. In this study, the median age of onset for ENKTL was approximately 42.8 years, with a slightly higher rate in men. The tumor is often confined to the nasal cavity or directly invades adjacent structures or tissues. Stage I-II patients ac-

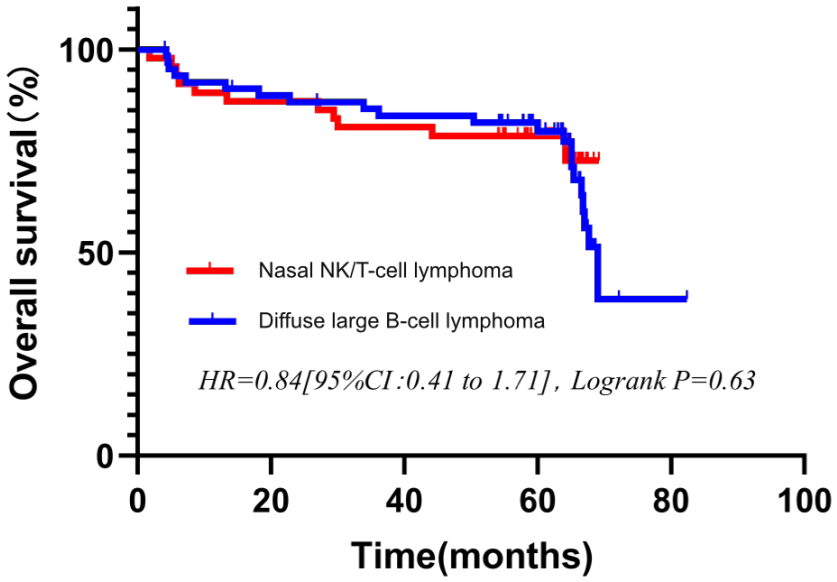

Figure 2 | Kaplan-Meier curves for overall survival in two types of lymphoma

Kaplan - Meier survival curves for overall survival in patients with nasal NK/T - cell lymphoma and diffuse large B - cell lymphoma. The red line represents nasal NK/T - cell lymphoma, and the blue line represents diffuse large B - cell lymphoma. The hazard ratio is 0.84 with a 95% confidence interval of 0.41 to 1.71. The Logrank test gives a value of 0.63, which indicates that there is no statistically significant difference in overall survival between the two groups of lymphoma. The survival curves were plotted using GraphPad Prism 8.0.

Table 5 | Evaluation of treatment efficacy in diffuse large B-cell lymphoma - logistic regression analysis (N=55)

factor	Univariate OR (95% CI)	Single-factor P	Multifactorial OR (95% CI)	Multifactor-P
Gender	0.85 (0.26-2.78)	0.782		
Disease staging (Reference: Stage I)				
Phase II	0.11 (0.01-0.99)	0.049	0.13 (0.01-1.22)	0.074
Phase III	0.05 (0.00-0.59)	0.017	0.07 (0.01-0.92)	0.043
Phase IV	0.07 (0.01-0.58)	0.014	0.20 (0.02-2.11)	0.178
Unknown	0.02 (0.00-0.29)	0.004	0.02 (0.00-0.35)	0.006
age	1.02 (0.96-1.08)	0.491	-	-
T	0.99 (0.94-1.05)	0.709	-	-
CD4	1.05 (0.98-1.12)	0.142	-	-
CD8	0.92 (0.86-0.99)	0.016	0.94 (0.88-1.00)	0.047
CD4/CD8	4.13 (1.12-15.21)	0.033	-	-
B	1.08 (0.95-1.23)	0.221	-	-
NK	1.00 (0.95-1.06)	0.942	-	-
CIK	1.00 (0.90-1.12)	0.957	-	-
TSGF	0.98 (0.94 - 1.02)	0.302	-	-
LDH	1.00 (0.99-1.00)	0.032	1.00 (0.99-1.00)	0.021
Ki67	0.05 (0.00-2.10)	0.115	-	-

Table 6 | Diffuse large B-cell lymphoma - pathological marker analysis

Factors/Indicators	S D or P D n=15	P R or CR n=40	Total population n=55	*F* -test, *P*
age	50.73 (45.53, 55.93)	52.90 (49.43, 56.37)	52.31(49.49,55.13)	F=0.466, P=0.498
T	73.31 (66.04, 80.59)	72.08 (68.82, 75.35)	72.42(69.46,75.38)	F=0.135, P=0.714
CD4	32.97 (26.78, 39.16)	37.54 (34.44, 40.64)	36.29 (33.53, 39.05)	F=2.233, P=0.141
CD8	36.62 (30.86, 42.38)	29.28 (26.51, 32.04)	31.28 (28.67, 33.88)	F=7.048, P=0.010
CD4/CD8	1.00 (0.73, 1.28)	1.43 (1.22, 1.64)	1.32 (1.14, 1.49)	F=5.237, P=0.026
B	5.49 (2.90, 8.08)	7.40 (5.72, 9.08)	6.88 (5.49, 8.26)	F=1.526, P=0.222
NK	18.58 (11.61, 25.55)	18.81 (15.71, 21.90)	18.75 (15.93, 21.56)	F=0.005, P=0.943
CIK	3.31(1.34,5.27)	3.39 (1.50, 5.29)	3.37 (1.92, 4.82)	F=0.003, P=0.958
TSGF	66.63 (56.75, 76.51)	61.66 (56.85, 66.46)	63.01 (58.73, 67.29)	F=1.077, P=0.304
LDH	756.75 (275.98, 1237.53)	278.26 (226.29, 330.24)	408.76 (270.72, 546.80)	F=11.429, P=0.001
Ki67	0.70 (0.59, 0.81)	0.61(0.55,0.67)	0.64 (0.59, 0.69)	F=2.599, P=0.113

Note: Data in red font indicate statistically significant differences (P < 0.05); the statistical software used was IBM SPSS 26.0.

Table 7 | Evaluation of treatment efficacy for nasal NK/T-cell lymphoma Logistics regression analysis (N=42)

factor	Univariate OR (95% CI)	Single-factor P	Multifactorial OR (95% CI)	Multifactor-P
Gender	NR	0.998		
Disease staging (Reference: Stage I)				
Phase II	0.13 (0.01-1.43)	0.095	0.03 (0.00-0.88)	0.042
Phase III	NR	NR	NR	NR
Phase IV	0.09 (0.00-1.98)	0.126	0.00 (0.00-0.59)	0.033
Unknown	NR	NR	NR	NR
age	0.92 (0.82-1.02)	0.121	-	-
T	0.89 (0.78-1.02)	0.088	0.74 (0.56-1.00)	0.049
CD4	0.94 (0.85-1.03)	0.184	-	-
CD8	0.99 (0.91-1.08)	0.792	-	-
CD4/CD8	0.60 (0.28-1.33)	0.209	-	-
B	1.05 (0.84-1.31)	0.658	-	-
NK	1.16 (0.97-1.38)	0.109	-	-
CIK	0.95 (0.83-1.09)	0.478	-	-
TSGF	0.99 (0.94-1.04)	0.642	-	-
LDH	1.00 (0.99-1.01)	0.885	-	-
Ki67	0.68 (0.01-85.97)	0.875	-	-

Note: The logistic regression statistical analysis software used is IBM SPSS 26.0 ; NR indicates that the numerical value cannot be specifically calculated (the denominator in the proportion is 0).

Table 8 | Nasal Cavity NK/T Cell Lymphopathological Indicators Analysis

Factors/Indicators	S D or P D n=5	P R or CR n=37	Total population n=42	*F* -test, *P*
Age	50.40 (44.22, 56.58)	41.46 (37.50, 45.42)	42.52 (38.90, 46.15)	F=2.715, P=0.107
T	82.10 (72.18, 92.03)	74.18(71.17,77.19)	75.12(72.25,77.99)	F=3.459, P=0.070
CD4	41.90 (20.36, 63.44)	35.21(32.14,38.29)	36.01 (32.76, 39.26)	F=1.848, P=0.182
CD8	33.18 (10.58, 55.78)	31.86 (28.67, 35.05)	32.02 (28.71, 35.33)	F=0.067, P=0.798
CD4/CD8	1.92 (-0.19, 4.03)	1.31 (1.03, 1.59)	1.39 (1.08, 1.69)	F=1.750, P=0.193
B	7.12 (3.86, 10.38)	8.08 (6.48, 9.68)	7.96 (6.54, 9.39)	F=0.188, P=0.667
NK	9.52 (-2.09, 21.13)	16.27 (13.62, 18.92)	15.47 (12.88, 18.06)	F=3.059, P=0.088
CIK	6.74 (-5.34, 18.82)	4.76 (3.01, 6.50)	4.99 (3.18, 6.80)	F=0.507, P=0.481
TSGF	56.87 (38.47, 75.26)	52.51(45.69,59.34)	53.03 (46.86, 59.20)	F=0.209, P=0.650
LDH	227.84 (191.79, 263.89)	235.12 (197.41, 272.84)	234.26 (201.09, 267.42)	F=0.020, P=0.888
Ki67	0.64 (0.43, 0.85)	0.63 (0.56, 0.69)	0.63 (0.57, 0.69)	F=0.023, P=0.879

Note: Data in red font indicate statistically significant differences (P < 0.05); the statistical software used was IBM SPSS 26.0 .

count for 70%-90%, and Stage III-IV patients account for 10%-30% [13, 14]. The results of this study are consistent with this, with Stage I-II accounting for 82.98%. Studies have reported that although the disease is mainly localized (Stage I and II) at onset, its efficacy is poor and the overall prognosis is bad. In this study, the survival rate of cases with a survival time of more than 5 years reached more than 50%. The recommended treatment for ENKTL is chemotherapy regimens based on L-asparaginase or pegaspargase, including the P-GemOx regimen (gemcitabine + pegaspargase + oxaliplatin), the DDGP regimen (cisplatin + dexamethasone + gemc-itabine + pegaspargase), the dose-adjusted SMILE regimen (methotrexate + leucovorin + ifosfamide + mesna + dexam-ethasone + etoposide + L- asparaginase)and the AspaMetDex regimen (pegaspargase + high-dose methotrexate + dexam-ethasone), etc. [10]. In this study, most ENKTL patients used the GELOXD regimen (68.09%), which was similar to the P-GemOx regimen. The study showed that this regimen was more effective, less toxic, and more tolerable than chemo-therapy regimens such as SMILE, Hyper-CVAD, and Hy-per- CCVP [15]. In this study, ENKTL patients were mainly CR.

DLBCL and ENKTL include factors such as age, distant lymph node invasion, stage, primary extranasal tumor, and LDH. This study newly included lymphocyte subsets and TSGF, indicators that are reported in the literature to be closely related to tumor prognosis, in order to discover more sensitive and reliable prognostic biomarkers or supplement existing prognostic factors. Studies have found that the occurrence and development of tumors are related to changes in peripheral blood lymphocyte subsets [16-18]. Lymphocyte subsets can reflect the body's immune status, have certain

value in the diagnosis of benign and malignant tumors, and are related to clinicopathological features such as lymph node metastasis, clinical stage, and molecular subtyping [19-21]. Studies have reported that lymphocyte subsets can predict the response to neoadjuvant chemoimmunotherapy in NSCLC [22]. Therefore, monitoring lymphocyte subsets in vivo is helpful for the auxiliary diagnosis and disease analysis of cancer in clinical practice.

In this study, the proportion of NK cells, TSGF, and LDH expression were all higher in DLBCL than in ENKTL. Ki67 expression showed no significant difference. Since there was no significant difference in survival time and survival rate between DLBCL and ENKTL in this study, we further analyzed the correlation between various factors and disease treatment efficacy. The results showed that stage, CD8+ T cell proportion, and LDH were independent risk factors for first-line treatment efficacy in DLBCL; stage and total T cell proportion were risk factors for first-line treatment efficacy in ENKTL. Stage and LDH, as classic prognostic factors, have been widely reported and included in guidelines [10,23]. Lymphocyte subsets can serve as new prognostic markers to supplement existing models.

Conclusion

The distribution of peripheral blood lymphocyte subsets is closely related to the efficacy of first-line treatment for DLBCL and nasal ENKTL. By detecting the distribution of peripheral blood lymphocyte subsets before treatment, the efficacy of first-line treatment for DLBCL and nasal ENKTL can be predicted, thereby guiding doctors to adjust the treatment plan.

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