

Research Paper

Lymphocyte/Monocyte Ratio is a Novel Predictor for Early Stage Extranodal Natural Killer/T-cell Lymphoma, Nasal Type

Qiao-xuan Wang^{1,2*}, Shao-hua Li^{1,3*}, Bao-yan Ji⁴, Han-yu Wang^{1,2}, Yi-yang Li⁵, Ling-ling Feng^{1,2}, Kai Chen^{1,2}, Yun-fei Xia^{1,2}, Yu-jing Zhang^{1,2}

1. State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, P. R. China;
2. Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, P. R. China;
3. Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, Guangzhou, P. R. China;
4. Department of Oncology, Qinghai Province People's Hospital;
5. Department of Oncology, the First Affiliated Hospital of Guangdong Pharmaceutical University.

* These authors contributed equally to this work.

✉ Corresponding authors: Yu-jing Zhang, M.D., Tel: 0086-020-87343702; Fax: 0086-020-87343392; E-mail: yujing_zhang1969@163.com. Kai Chen, M.D., Tel: 0086-020-87343702; Fax: 0086-020-87343392; E-mail: chenkaai@sysucc.org.cn.

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Abstract

Objective: Great heterogeneity exists in clinical behavior and survival outcome in patients with stage IE/IIIE extranodal natural killer/T-cell lymphoma, nasal type (ENKTL). In this study, we proposed lymphocyte/monocyte ratio (LMR) as a new prognostic factor for these early stage ENKTL.

Methods: We retrospectively examined the LMR as a prognostic variable in a cohort of 379 patients with newly diagnosed stage IE/IIIE ENKTL. The relationship between the LMR and clinicopathologic variables were analyzed in Kaplan-Meier log-rank survival analysis, and the Cox proportional hazards model was used to determine the survival significance of the LMR for both progression-free survival (PFS) and overall survival (OS).

Results: Patients were categorized into two different groups based on the LMR using cut-off value of 2.0. The 5-year PFS rates in the low and high LMR group were 43.9% and 62.7%, respectively, and the 5-year OS rates in the two groups were 59.1% and 77.7%, respectively. In multivariate analysis, low LMR at diagnosis was associated with worse PFS (hazard ratio 1.611, 95% confidence interval: 1.027-2.525, $P=0.038$) independent of age ($P=0.033$) and treatment stratagem ($P<0.001$), and indicated worse OS (hazard ratio 2.003, 95% confidence interval: 1.124-3.569, $P=0.018$) independent of age ($P=0.007$), LDH level ($P=0.042$), local tumor invasiveness ($P=0.008$), and treatment stratagem ($P<0.001$).

Conclusion: The LMR is an independent prognostic factor for both DFS and OS in patients with stage IE/IIIE ENKTL, and provides additional prognostic value beyond standard clinicopathological parameters.

Key words: extranodal natural killer/T-cell lymphoma, lymphocyte/monocyte ratio, prognosis

Introduction

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL), is a distinct histopathologic subtype of non-Hodgkin's lymphoma according to the new World Health Organization (WHO)

Classification, characterized by vascular damage and destruction, obvious necrosis, cytotoxic phenotype, and related to Epstein-Barr virus (EBV)[1]. Although it is quite rare in western populations, ENKTL is more

prevalent in East Asia and makes up approximately 5–10% of all lymphomas in the Chinese population[2].

Patients who presented with ENKTL are staging using the Ann Arbor staging system for non-Hodgkin's lymphoma. Stage IIIE/IVE ENKTL exhibited more aggressive tumor behavior and poorer prognosis compared with patients of stage IE/IIIE. However, there were quite a lot of cases with stage I/II ENKTL who had poor prognosis because of rapid disease progression and recurrence, and the Ann Arbor stage failed to predict survival differences between stage IE and stage IIE in some studies[3]. The International Prognostic Index (IPI)[4] was also used for assessing the prognosis of patients with ENKTL. Though validated in many subtypes of non-Hodgkin's lymphoma, the prognostic impact of IPI has been controversial in ENKTL, for most patients diagnosed with ENKTL were in the low-risk IPI group [5]. Ergo, clinical challenges still exist in treatment selection due to the inability to predict the heterogeneous clinical behaviors of stage IE/IIIE ENKTL.

Efforts have been made to find out new prognostic indicators for ENKTL. Recently, it has been demonstrated that proinflammatory chemokines and cytokines in the tumor microenvironment contribute to proliferation and survival of malignant cells, angiogenesis, metastasis, subversion of adaptive immunity, reduced response to chemotherapeutic agents, thus affecting survival[6]. Markers of inflammation such as lymphocytes[7], monocytes[8], C-reactive proteins (CRP)[9] had been previously studied in ENKTL patients and were found to have a prognostic value.

Lymphocyte-to-monocyte ratio (LMR), as a converted inflammatory response related biomarker, has been demonstrated to have potential prognostic significance in patients with various types of malignancies[10-14]. However, none of the previous studies looked into the effects of LMR on ENKTL patients. The purpose of this study was to assess the value of the LMR as a predictor of survival in early stage ENKTL patients.

Materials and Methods

Patient Selection

This was a retrospective study of an unselected cohort of all newly diagnosed patients with histologically proven ENKTL who were treated at Sun Yat-sen University Cancer Center (Guangzhou, China) between January 1996 and April 2012. The study was performed following approval by the ethic committee of Sun Yat-Sen University Cancer Center. All patients provided written informed consent for

the collection and publication of their medical information at the first visit to our center, which was filed in their medical records, and the ethics committees approved this consent procedure. The inclusion criteria were as follows: (1) pathologically confirmed diagnosis of upper aerodigestive tract ENKTL, based on the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues[1]. (2) Ann Arbor stage IE/IIIE. (3) Previously untreated patients. (4) No previous or concomitant malignancies. (5) A complete set of clinical information and follow-up data. (6) Patients with blastic NK-cell lymphoma/leukemia, aggressive NK-cell lymphoma/leukemia, or peripheral T-cell lymphoma, unspecified, were excluded. (7) Patients with any clinical evidence of acute infection or chronic active inflammatory disease, such as rheumatoid arthritis and virus hepatitis, were also excluded. All pathologic specimens were reviewed and reclassified by central review according to the WHO criteria for pathologic diagnosis. Antibodies to the following antigens were used for immunophenotype analysis: CD3, CD56, TIA-1, Granzyme-B, CD45RO, CD20, CD79a, CD30, Ki67 and the anaplastic large cell lymphoma kinase. In situ hybridization was used for the detection of EBV-encoded RNA.

Data collection

The data were collected at diagnosis, including patient demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), primary site, involved sites, systemic B symptoms, complete blood count, serum LDH, Ann Arbor stage, bone marrow status, nuclear magnetic resonance scan of the head and neck and computed tomography scans of the thorax, abdomen and pelvic cavity. All patients were staged using the Ann Arbor staging system. ENKTL was classified into two subsets based on the anatomic distribution of the tumor at presentation [15]. Upper aerodigestive tract NK/T-cell lymphoma was defined as a primary tumor involving the nasal cavity, nasopharynx and upper aerodigestive tract. Only these patients were included in analysis. Local tumor invasiveness was defined as bony invasion or destruction or tumor invasion of the skin or paranasal involvement. Absolute lymphocyte count and absolute monocyte count in peripheral blood were derived from the standard automated complete blood counts which were done at diagnosis. LMR was calculated using the equation $LMR = \text{absolute lymphocyte count} / \text{absolute monocyte count}$.

Response criteria

Tumor response was assessed radiologically after every two cycles of chemotherapy or before and

after radiotherapy on the basis of standardized response criteria for non-Hodgkin lymphoma[16]. After completion of treatment, patients were followed up every 3 months in the first 2 years, then every 6 months for the next 3 years and annually thereafter.

Statistical analyses

All statistical analyses were performed using Statistical Package for the Social Sciences program (SPSS Inc. Chicago, IL, version 15.0 for Windows). Progression-free survival (PFS) was defined as the interval between the date of diagnosis and the date of first relapse, progression, death from any cause, or the last date at which patients were censored. Overall survival (OS) was defined from the date of diagnosis until either the time of death from any cause or the last date at which patients were censored. Categorical characteristics were compared using the chi-square test or Fisher's exact test. Continuous biologic variables were dichotomized. Survival functions were estimated by the Kaplan-Meier method and compared by log-rank test. Multivariate analysis was performed according to the Cox proportional hazards model. Significance was set at $P < 0.05$.

Results

Patient characteristics

All patients' characteristics were shown in Table 1. In this cohort of 379 patients with ENKTL, 256 patients (67.5%) were men and the mean age was 43.0 years (range, 9– 80years). More patients were in Ann Arbor stage I (61.4%) than in stage II. B symptoms were present in 170 patients (45.0%), and serum LDH levels were elevated in 85 patients (22.8%). The present of local tumor invasiveness was common (66.2%). The median absolute lymphocyte count at diagnosis was $1.5 \times 10^9/L$ (range 0.1–5.3), while the median absolute monocyte count was $0.5 \times 10^9/L$ (range, 0.1–2.2). For most patients, the absolute lymphocyte count (90.8%) and absolute monocyte count (94.2%) levels were within the normal range at diagnosis.

Identification of the optimal cut-off value for defining LMR

The differences in the PFS and OS rates obtained when the patients were stratified into high or low LMR groups using various cut-off values were shown in Table 2. The largest difference was obtained using a cut-off of 2.0 for PFS, and this cut-off point also had significant predictive value for OS. Therefore, this was used to define the low and high LMR groups in subsequent analyses.

Table 1. Baseline clinical characteristics of patients by LMR levels at diagnosis.

Variable	No. (%)	Low LMR group (LMR \leq 2.0)	High LMR group (LMR $>$ 2.0)	P value
Age				
\leq 60	321	86	235	0.505
$>$ 60	58	18	40	
Gender				
Male	256	77	179	0.097
Female	123	27	96	
B symptoms				
+	170	49	121	0.553
-	207	54	153	
Ann Arbor stage				
Stage I	233	50	183	0.001
Stage II	146	54	92	
LDH				
Normal	288	75	213	0.298
Elevated	85	27	58	
Local tumor invasiveness				
Yes	223	66	257	0.593
No	114	26	88	
Treatment				
Chemotherapy	80	37	43	0.000
Radiotherapy/ radiotherapy plus chemotherapy	299	67	232	
Absolute lymphocyte count				
$\leq 1.5 \times 10^9/L$	194	86	108	0.000
$> 1.5 \times 10^9/L$	185	18	167	
Absolute monocyte count				
$\leq 0.5 \times 10^9/L$	190	21	169	0.000
$> 0.5 \times 10^9/L$	189	83	106	

Table 2. Differences in the PFS and OS for patients with ENKTL dichotomized using different cut-off values for the pretreatment LMR.

Cut-off, g/L	number of patients, low/high	PFS		OS	
		chi-square	P value	chi-square	P value
1.8	69/310	14.804	0.000	17.230	0.000
1.9	84/295	13.064	0.000	10.768	0.001
2.0	104/275	15.665	0.000	14.112	0.000
2.1	109/270	15.456	0.000	13.434	0.000
2.2	132/247	9.852	0.002	6.982	0.008
2.3	140/239	8.997	0.003	6.719	0.01
2.4	152/227	7.678	0.006	6.624	0.01
2.5	167/212	5.890	0.015	4.853	0.028

Association of LMR with the clinical characteristics

Baseline clinical characteristics of patients with $LMR \leq 2.0$ at diagnosis were compared with those with $LMR > 2.0$ (Table 1). No significant between-group difference was observed for age, gender, present of B symptoms and local tumor invasiveness, and LDH levels, though the proportion of patients classified as Ann Arbor stage II was higher in the low LMR group compared to the high LMR group.

Treatment modalities and response

The primary treatment modalities were as follows: (1) chemotherapy alone (80 cases) and (2) radiotherapy alone (9 cases) and (3) both chemotherapy and radiotherapy (290 cases). Radiation therapy was given with daily fractions of 1.8-2.0Gy and five fractions per week using a linear accelerator (6-8 MV). The median radiation dose to the primary tumor site and lymph node negative neck area were 55.4Gy and 46Gy, respectively. Chemotherapy was given over a median of four cycles (range, 1-9 cycles). The regimens of chemotherapy in the initial treatment included: CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), CHOPL (CHOP and asparaginase), GELOX (gemcitabine, oxaliplatin and asparaginase), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) and several other regimens used at the discretion of the treating physician. In total, 37.2% patients received the asparaginase-based regimens. More patients received only chemotherapy in the low LMR group.

In the initial treatment modality, complete remission was achieved in 156 patients (41.2%), partial remission in 141 patients (37.2%), stable disease in 51 patients (13.5%), and progressive disease in the remaining 31 patients (8.2%), resulting in an objective response rate (ORR) of 78.4%. The ORR after the initial treatment in patients with $LMR \leq 2.0$ was 69.8%, significantly lower than that in patients with $LMR > 2.0$ (83.0%, $p=0.000$).

Survival and prognostic factors

During a median follow-up time of 28.8 months, 240/379 patients (63.3%) experienced tumor progression after treatment (figure 1A). By the end of follow-up, 85/379 patients (22.4%) had died (figure 1B), including 82 (96.5%) who died of ENKTL and 3 (3.5%) who died of other causes. The 2-year and 5-year PFS rates for the whole cohort were 67.9%, and 57.7%, respectively, while the 2-year and 5-year OS rates were 78.5%, and 72.9%, respectively.

Table 3 and 4 showed the results of univariate and multivariate analysis. LMR at diagnosis was significant predictor for both PFS and OS. Demonstrated in figure 2A, patients in the high LMR group had significantly better PFS than those in the low LMR group (5-year PFS rate: 62.7% vs. 43.9%). As shown in figure 2B, patients in the high LMR group also had significantly better OS than those in the low LMR group (5-year OS rate: 77.7% vs. 59.1%).

In univariate analysis, clinical features such as age, Ann Arbor stage, local tumor invasiveness, treatment modality and regimens of chemotherapy, laboratory features such as the LDH level, absolute

lymphocyte count and LMR were all significant predictors for PFS. Prognostic factors for OS were age, Ann Arbor stage, LDH level, local tumor invasiveness, treatment modality, regimens of chemotherapy, absolute lymphocyte count and LMR. In multivariate analysis, LMR retained its predictive power for both PFS and OS. Age, treatment modality and regimens of chemotherapy were also identified as independent predictive factors for both PFS and OS, while local tumor invasiveness was proved to be an independent predictive factor merely for OS.

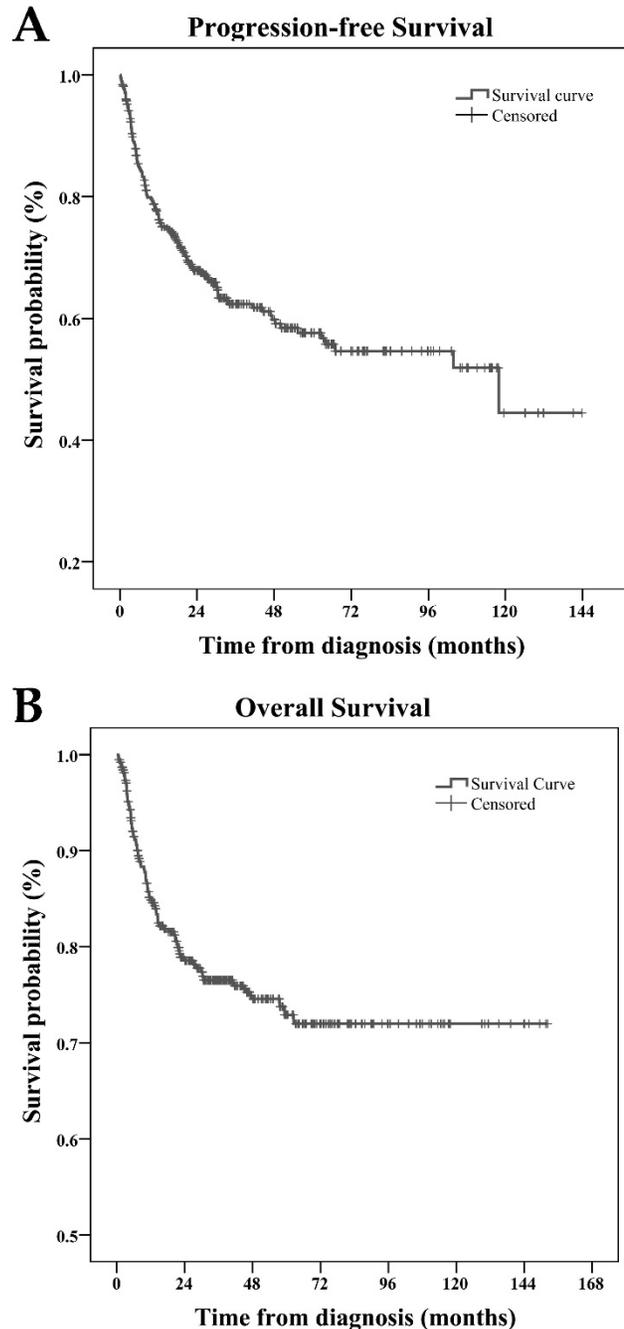


Figure 1. Progression-free survival (A) and overall survival (B) of 379 patients with extranodal natural killer/T-cell lymphoma, nasal type (ENKTL).

Table 3. Univariate and multivariate analysis of prognostic factors for PFS.

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95%CI)	P value	
Age (>60 vs. ≤60)	0.004	2.031 (1.288-3.203)	0.002	
Gender (male vs. female)	0.586	1.158 (0.786-1.707)	0.459	
B symptoms (yes vs. no)	0.803	1.303 (0.882-1.925)	0.183	
Ann Arbor stage (II vs. I)	0.032	1.354 (0.908-2.018)	0.137	
LDH (elevated vs. normal)	0.030	1.246 (0.792-1.961)	0.341	
local tumor invasiveness (yes vs. no)	0.028	1.298 (0.861-1.956)	0.212	
Treatment (chemotherapy vs. radiotherapy or both)	0.000	2.746 (1.842-4.091)	0.000	
Regimens of chemotherapy (asparaginase-based vs. others)	0.000	2.367 (1.468-3.818)	0.000	
Absolute lymphocyte count (≤1.5×10 ⁹ /L vs. >1.5×10 ⁹ /L)	0.035	1.005 (0.667-1.514)	0.981	
Absolute monocyte count (≤0.5×10 ⁹ /L vs. >0.5×10 ⁹ /L)	0.152	1.045 (0.689-1.585)	0.837	
LMR (≤2.0 vs.>2.0)	0.000	1.763 (1.119-2.777)	0.014	

Table 4. Univariate and multivariate analysis of prognostic factors for OS.

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95%CI)	P value	
Age (>60 vs. ≤60)	0.001	2.711 (1.536-4.787)	0.001	
Gender (male vs. female)	0.173	1.494 (0.881-2.534)	0.137	
B symptoms (yes vs. no)	0.760	1.320 (0.810-2.151)	0.265	
Ann Arbor stage (II vs. I)	0.005	1.348 (0.818-2.222)	0.241	
LDH (elevated vs. normal)	0.001	1.725 (0.998-2.982)	0.051	
local tumor invasiveness (yes vs. no)	0.001	2.252 (1.246-4.071)	0.007	
Treatment (chemotherapy vs. radiotherapy or both)	0.000	2.172 (1.287-3.667)	0.004	
Regimens of chemotherapy (asparaginase-based vs. others)	0.000	3.952 (1.984-7.871)	0.000	
Absolute lymphocyte count (≤1.5×10 ⁹ /L vs. >1.5×10 ⁹ /L)	0.010	0.963 (0.567-1.637)	0.890	
Absolute monocyte count (≤0.5×10 ⁹ /L vs. >0.5×10 ⁹ /L)	0.925	1.631 (0.950-2.801)	0.076	
LMR (≤2.0 vs.>2.0)	0.000	2.230 (1.237-4.018)	0.008	

Discussion

Although ENKTL is a distinctive disease entity with poor prognosis, most of the patients were categorized as low risk based on IPI score, especially for the early stage patients, and standard treatment strategy for this disease has not yet been established.

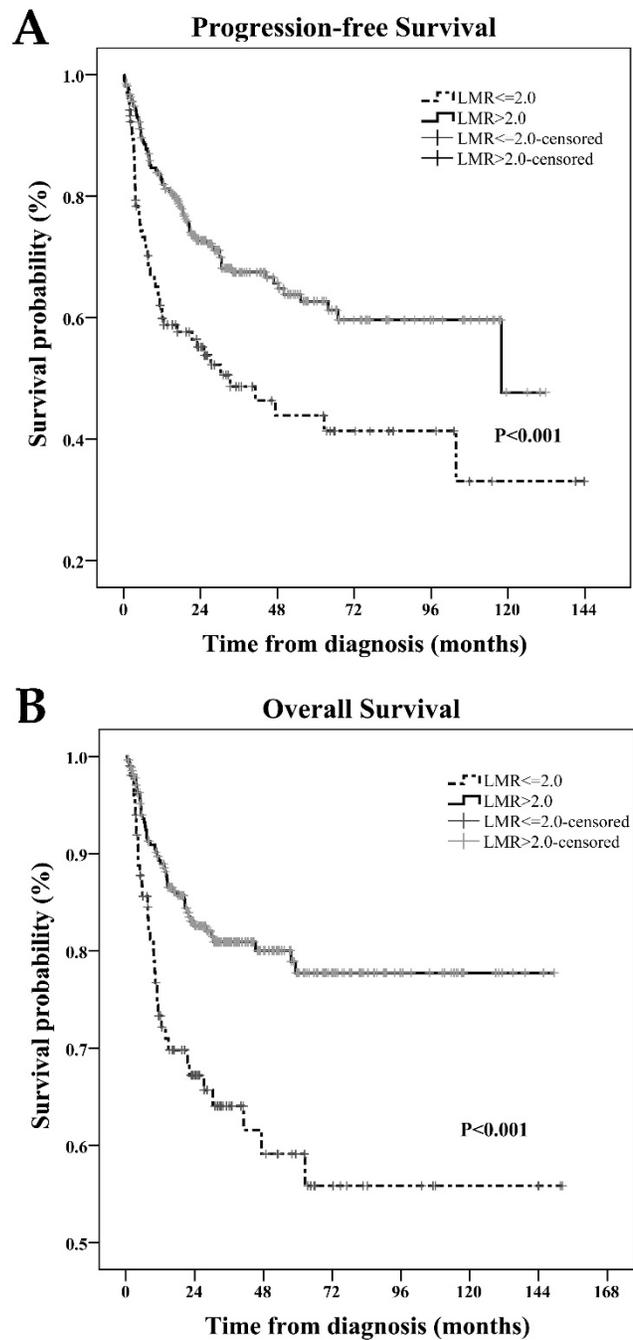


Figure 2. Progression-free survival (A) and overall survival (B) of patients according to lymphocyte/monocyte ratio (LMR) ≤2.0 and >2.0 at diagnosis.

For early stage ENKTL, radiation therapy is usually administered. Chemotherapy has been applied in some cancer centers to reduce local relapse and systemic failure [17,18]. However, adding chemotherapy or not remains controversial for early stage ENKTL. Study showed that chemotherapy after radiation therapy did not significantly decrease the systemic failure rate nor improve survival[19]. Meanwhile, there were quite a lot of cases with stage I/II ENKTL who had poor prognosis because of rapid disease progression and recurrence, and intensive

systemic therapy may be needed for these patients. Therefore, these so called early stage patients need to be subdividing, for predicting the prognosis precisely and guiding the clinical practice appropriately, and multiple new prognostic indicators were proposed for this purpose.

LMR, as an integrated biomarker, has been demonstrated as an independent prognostic indicator in various malignancies[10-14]. However, until now, there has been limited data regarding the role of LMR in the prognosis of ENKTL, and this is the first study to investigate the relationship between LMR and ENKTL to our knowledge. The main finding of this study was that pretreatment LMR is an independent predictor of both OS and PFS in early stage ENKTL patients. Although the low LMR group was associated with advanced Ann Arbor stage and more patients in this group were given only chemotherapy, the prognostic value of LMR remained significant after adjusting for these confounders.

Previous studies reported that asparaginase-based regimens were significantly superior to anthracycline-based regimens for ENKTL in terms of CR rate and long-term survival outcomes[20]. In this study, we also showed that regimen without asparaginase was an adverse factor for survival. However, after adjusting for this confounder, LMR was still proven to be an independent prognostic factor.

The relationship between chronic inflammation and cancer has been studied for decades. It has been observed that inflammatory diseases increase the risk of developing many types of cancer and that inflammatory cells, chemokines and cytokines are present in the microenvironment of all tumors in experimental animal models and humans from the earliest stages of development[6]. The two pathways connecting inflammation and cancer are elucidated as: the extrinsic pathways, in which inflammatory conditions facilitate cancer development; and the intrinsic pathways driven by oncogenes or tumor suppressor genes that activate the expression of inflammation-related programmers[6]. Previous studies have revealed the link between markers of inflammation such as lymphocytes[7], monocytes[8], platelet lymphocyte ratio[21], CRP[9] and survival in ENKTL patients, and this is synonymous to the association of LMR to ENKTL. There are several potential explanations why chronic inflammation plays such an important role in ENKTL. First, ENKTL is frequently characterized by necrosis and inflammation, and inflammatory cytokines has been shown to be increased in ENKTL[1]. Second, EBV infection is associated with ENKTL. The whole blood EBV DNA load correlates well with treatment

response and the increase of EBV DNA load indicates adverse outcome in ENKTL. EBV infection may induce a consistent expression of viral immunogenic proteins, leading to a potent immune response[22]. However, the mechanism by which a systemic inflammatory response might influence survival in ENKTL patients remains unclear.

Inflammation plays an important role in cancer progression and metastasis, which are also influenced by host immunity[23]. Lymphocyte is a key mediator of immunosurveillance, and lymphocyte infiltration into the tumor microenvironment is a prerequisite to an immunologic antitumor reaction[24]. Lymphocytes, including natural killer cells, are important mediators of antibody-dependent cell-mediated cytotoxicity [25], and CD 8+ and CD 4+ T-lymphocytes play an essential role in anti-tumor reaction of the immune system by inducing tumor cell apoptosis[26,27]. Therefore, lymphopenia is considered a surrogate marker of host immunological incompetence. Observation study showed that lymphopenia is an adverse prognostic factor in NHL of various subtypes, including ENKTL [7]. In this study, lymphopenia was associated with impaired PFS and OS in univariate analysis.

Monocyte has also been reported to be associated with adverse prognosis in various malignancies, mostly due to the tumor-associated macrophages (TAMs)[28,29], which are derived from circulating monocyte populations. Mounting evidence showed that TAMs exert activity that is primarily protumoral including promotion of metastasis, immunosuppression, and tumor angiogenesis[29]. Monocyte has also been found to induce the proliferation of natural killer (NK)/T lymphoma cells, and NK/T-cell lymphoma cells can produce the IP-10 (a major chemoattractant of human monocytes) which increase monocyte infiltration of the tumor microenvironment[30]. Therefore, there is a positive feedback relationship between monocytes and lymphoma cells in the microenvironment of NK/T-cell lymphoma [30].

In this study, we showed that absolute lymphocyte count was also related to survival outcomes in NKTCL. However, our multivariate analysis showed that only LMR was a prognostic factor for OS and PFS. LMR, as a parameter represented both immunosurveillance and immunosuppression, was shown to outperform the absolute lymphocyte count in the prediction of survival outcome, and this is in line with previous report[10]. Because pre-treatment absolute lymphocyte count and monocyte count are routinely tested in clinical practice, calculation of LMR is easily accessed compared with other parameters. And we

suggest that LMR should be calculated more often in clinical practice.

However, the appropriate cutoff point for LMR still needs to be investigated. Previous studies have used different cutoff points, ranged from 1.0 to ≥ 4 , and 89% of these studies have reached a general conclusion that lower LMR group was associated with adverse outcome[31]. Whether there exists a perfect cutoff point for LMR is an important question for its use in clinic and further study may be needed to answer this question.

Other limitations in the current study include: (1) this is a single-institution retrospective study and is therefore limited by the bias inherent in this type of analysis; (2) some patients were treated in the 1990s and received only chemotherapy which may led to inferior survival.

In conclusion, this study demonstrated that LMR at diagnosis is a valuable prognostic indicator of clinical outcome in early stage ENKTL patients. Large prospect study is required to validate this finding, to find out a perfect cutoff point and to provide a better understanding of the mechanisms underlying the association between low LMR level and the adverse clinical outcomes.

Abbreviations

ENKTL: extranodal natural killer/T-cell lymphoma, nasal type; WHO: World Health Organization; EBV: Epstein-Barr virus; IPI: International Prognostic Index; CRP: C-reactive proteins; LMR: absolute lymphocyte count/absolute monocyte count ratio; LDH: lactate dehydrogenase; PFS: progression-free survival; OS: overall survival; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; CHOPL: CHOP and asparaginase; GELOX: gemcitabine, oxaliplatin and asparaginase; EPOCH: etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone; ORR: objective response rate.

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Competing Interests

The authors have declared that no competing interest exists.

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