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ORIGINAL ARTICLE

The combined prognostic value of pretreatment neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio in stage IE/IIE extranodal natural killer/T-cell lymphoma

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Abstract

Objective This study aimed to explore the combined prognostic value of pretreatment neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) in newly diagnosed IE/IIE extranodal natural killer/T-cell lymphoma (ENKTL) treated with a P-Gemox regimen combined with radiotherapy or radiotherapy alone.

Methods A total of 132 patients from 2009 to 2017 at the Sichuan Cancer Hospital were enrolled in the study. The cutoff values of NLR, LMR, and PLR using overall survival (OS) rate as an endpoint were obtained by the receiver operating curve.

Results The cutoff value of NLR was 3.5. Patients with high NLR had significantly shorter progression-free survival (PFS) ($P < 0.001$) and OS ($P < 0.001$) than those with low NLR. Similarly, the cutoff value of LMR was 3.0. The high LMR group had significantly longer PFS ($P=0.001$) and OS ($P < 0.001$) than the low LMR group. Similarly, the cutoff value of PLR was 191.7. The high PLR group was significantly associated with poor PFS ($P < 0.001$) and OS ($P < 0.001$) than the low PLR group. Furthermore, combining NLR, LMR, and PLR to build a new model to stratify patients into low-, intermediate-, intermediate-high-, and high-risk groups, there were also significant differences in PFS ($P < 0.001$) and OS ($P < 0.001$). The univariate analysis showed that presenting B symptoms, stage IIE, local tumor invasion, Eastern Cooperative Oncology Group score ≥ 2, elevated lactate dehydrogenase level, elevated NLR, decreased LMR, and elevated PLR were significantly associated with poor survival. The multivariate analysis demonstrated that PLR was an independent prognostic factor for both PFS (hazard ratio [HR] = 2.073, 95% confidence interval [CI] = 1.080–3.981, $P = 0.028$) and OS (HR = 2.127, 95% CI = 1.102–4.107, $P = 0.025$).

Conclusion Elevated pretreatment PLR was a novel simple predictor of poor survival in patients with stage IE/IIE ENKTL. Combining NLR, LMR, and PLR could provide additional stratification.

Key words: extranodal natural killer/T-cell; neutrophil-to-lymphocyte ratio; lymphocyte-to-monocyte ratio; platelet-to-lymphocyte ratio; prognosis

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Extranodal natural killer/T-cell lymphoma (ENKTL) of the nasal type, is a rare type of non-Hodgkin lymphoma (NHL) with a highly heterogeneous and invasive disease characterized by "lethal midline granuloma" and more commonly observed in Asia than Western countries [1]. Its main histologic changes are shown as obvious vascular destruction, tissue necrosis, and cytotoxic phenotype and closely associated with Epstein-Barr virus infection [2]. Although most patients with ENKTL were diagnosed with stage IE/IIE, previous studies confirmed that quite a few cases were correlated with unsatisfactory treatment outcomes because of highly aggressive biological behavior, rapid disease progression, and recurrence [3–5]. So far, unified treatment strategies have not yet been established for this disease. Though the International Prognostic Index (IPI) and Korean Prognostic Index (KPI)

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have been proved to assess prognosis in patients with ENKTL, the prognostic value remained controversial [6–7] because IPI and KPI scores were based on patients treated with anthracycline-based regimens. Recently, the prognostic index of natural killer/T-cell lymphoma (PINK) [8] was validated to predict prognosis in patients with ENKTL, but a number of patients diagnosed with ENKTL were categorized into low-risk group due to unbalanced distribution, and it may be further modified by other laboratory parameters. Therefore, great efforts have been made to establish a novel predictor for patients with ENKTL.

Recently, emerging evidence [9–12] has revealed the relationship between inflammation and tumor progression. The results have suggested that inflammation mediators (e.g., chemokines, cytokines, free radicals) in the tumor microenvironment created a favorable condition for tumor cells to promote tumor cell growth, proliferation, progression, and metastatic dissemination, as well as treatment resistance and poor prognosis. Presently, meta-analyses have demonstrated that inflammation-based markers, such as neutrophil-to-lymphocyte ratio (NLR) [13], lymphocyte-to-monocyte ratio (LMR) [14], and platelet-to-lymphocyte ratio (PLR)[15], are significantly correlated with poor survival in solid tumors. Meanwhile, the results of clinical studies have also proved that lymphocytes [16], monocytes [17], LMR [18], and PLR [19] are prognostic factors in patients with ENKTL. Until now, no study has been performed to evaluate the combined prognostic value of NLR, LMR, and PLR in patients with ENKTL. Therefore, we retrospectively conducted this study to evaluate the combined prognostic value of NLR, LMR, and PLR in patients with ENKTL treated with P-Gemox regimen combined with radiotherapy or radiotherapy alone.

Material and methods

Patients

A total of 132 patients with upper aerodigestive tract ENKTL at Sichuan Cancer Hospital from 2009 to 2017, who were histologically diagnosed based on the 2016 World Health Organization criteria [20] and clinical stage according to the Ann Arbor staging system [21], were recruited. All patients included in this study met the following criteria: (1) new diagnosis of pathologically and immunohistochemically confirmed ENKTL; (2) clinical stage classified as stage I/IIE; (3) no current antitumor therapy; and (4) available clinical follow-up data. Patients with infection or symptoms of inflammation were excluded. We collected the following pretreatment information for the analysis: age, sex, Eastern Cooperative Oncology Group (ECOG) score, B symptoms, and serum lactate dehydrogenase (LDH), neutrophil, lymphocyte, monocyte, and platelet levels. Moreover, to evaluate the stage, bone marrow examination, magnetic resonance imaging or computed tomography (CT) of the head and neck, and CT of the chest and whole abdomen were performed. Peripheral blood sample was collected from each patient using an ethylenediamine tetraacetic acid-treated tube, and calculation of neutrophil, lymphocyte, monocyte, and platelet levels was conducted using the automated hematology system Mindray BC5800 (Mindray, Shenzhen, China).

Treatments

The treatment strategies for all patients are as follows: 49 patients received P-Gemox sandwich radiotherapy (defined as two or three cycles of chemotherapy followed by radiotherapy and then two or three cycles of original chemotherapy), 42 patients received P-Gemox regimen sequential radiotherapy (defined as two or three cycles of chemotherapy followed by radiotherapy), and 41 patients were treated with radiotherapy alone. P-Gemox (PEG-asparaginase 2500 IU/m^2 intramuscular injection on day 1 + gemcitabine 800–1000 mg/m^2 intravenous drip on days 1 and 8 + oxaliplatin 130 mg/m^2 intravenous drip on day 1). Radiotherapy for the involved field was performed using 6-MeV linear accelerator, intensity modulated radiotherapy, with a dose range of 50–60 Gy (median dose, 56 Gy) for gross tumor volume in daily fractions of 1.8–2.0 Gy, 5 days per week.

Statistical analysis

Progression-free survival (PFS) was defined as the time interval from the disease diagnosis to the first documented disease progression, or relapse, or death, or until the last follow-up visit. Overall survival (OS) was defined as the time interval from the disease diagnosis to death from any cause or the last follow-up visit. NLR was defined as the neutrophil count to the lymphocyte count ratio; LMR was defined as the lymphocyte count to the mononuclear count ratio; and PLR was defined by the platelet count to the lymphocyte count ratio. The receiver operating curve (ROC) and Youden index (maximum [sensitivity+specificity-1]) were used to determine the optimal cutoff values for NLR, LMR, and PLR. The chi-square test was used to compare the differences between the groups. The Kaplan-Meier method was performed in the survival curve analysis, and the log-rank test was conducted in the univariate analysis. When the *P*-value was < 0.05, the corresponding factor was added into the multivariate analysis. A multivariate analysis was conducted using the Cox regression model. All data were analyzed using SPSS software version 17.0 (SPSS Inc., Chicago, IL). A *P*-value <0.05 was considered statistically significant, and all *P*-values correspond to two-sided significance tests.

Results

Optimal cutoff values for NLR, LMR, and PLR

Using OS as an endpoint, stratification based on the NLR, LMR, and PLR was conducted by analyzing the ROC and area under curve (AUC). The optimal cutoff values were 3.5 for NLR (AUC = 0.617, sensitivity = 49.1%, specificity = 77.2%), 3.0 for LMR (AUC = 0.665, sensitivity = 57.0%, specificity = 75.5%), 191.7 for PLR (AUC = 0.652, sensitivity = 52.8%, specificity = 79.7%) (Fig. 1).

Patient characteristics

The baseline characteristics of 132 patients are shown in Table 1. This study included 92 men and 40 women (ratio, 2.3:1). The median age was 46 years (range, 15–86 years), and 26 patients (19.7%) were aged > 60 years. Of the patients, 77 (58.3%) had stage IE, 35.6% had elevated serum LDH level, 61.4% presented with B symptoms, and 48.5% had local tumor invasion. The majority of patients (75.0%) had an ECOG score of 0–1, and 77.3% had a PINK score of 0. Moreover, 66.7% of patients were assigned to the low NLR group (NLR < 3.5), and the remaining patients (33.3%) were assigned to the high NLR group (NLR ≥ 3.5). Of the patients, 56.1% were categorized into the low LMR group (LMR < 3.0), and 43.9% patients into the high LMR group (LMR ≥ 3.0). Furthermore, 67.4% of the patients were classified as the low PLR group (PLR < 191.7), and the remaining patients (32.6%) as the high PLR group (PLR ≥ 191.7). Forty-nine patients (37.1%) received P-Gemox sandwich radiotherapy, 42 (31.8%) received P-Gemox regimen sequential radiotherapy, and 41 (31.1%) received radiotherapy alone.

Survival analysis

In 132 patients, follow-up was conducted until March 2019. The median OS was 37 months (range, 3–114 months). In all patients, the 3-year PFS was 59.9% (Fig. 2a), and the 3-year OS was 67.1% (Fig. 2b).

All patients were divided into the low NLR (< 3.5) and high NLR (≥ 3.5) groups by ROC. The 3-year PFS for the two NLR groups were 69.8% and 39.8%, respectively,

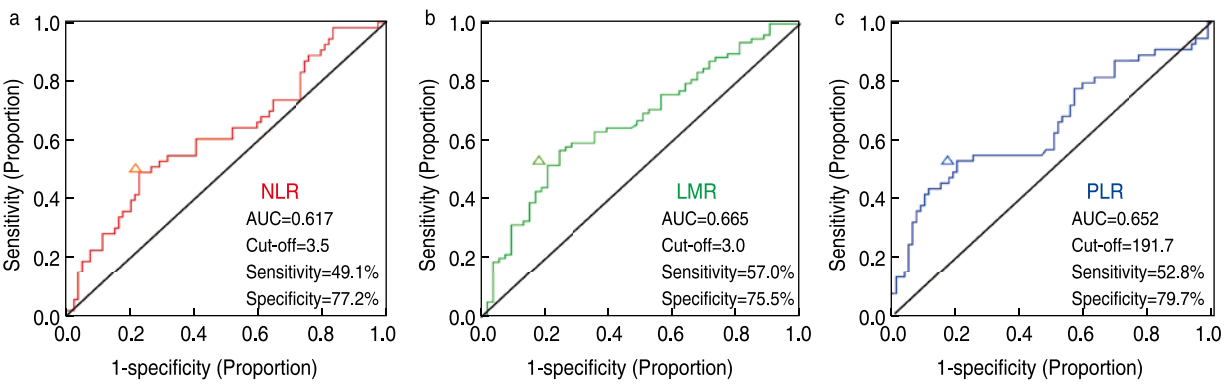

Fig. 1 The cutoff values of NLR, LMR, PLR obtained by the receiver operating curve using overall survival as endpoint. (a) ROC of NLR; (b) ROC of LMR; (c) ROC of PLR

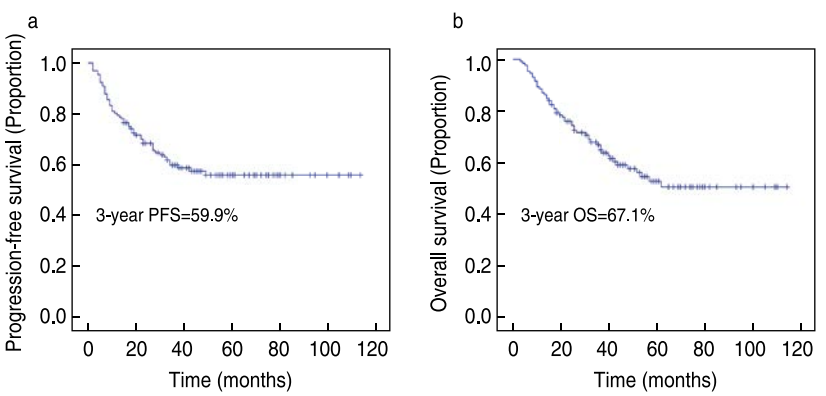

Fig. 2 Survival curve of the whole patients for PFS and OS. (a) PFS; (b) OS

Table 1 Baseline clinical characteristics of patients

Clinical characteristics	No. of patients (n = 132)	Percentage (%)
Gender		
Male	92	69.7
Female	40	30.3
Age (years)		
≤ 60	106	80.3
> 60	26	19.7
Ann Arbor stage		
IE	77	58.3
IIE	55	41.7
LDH (U/L)		
≤ 240	85	64.4
> 240	47	35.6
B symptoms		
No	51	38.6
Yes	81	61.4
Local tumor invasion		
No	68	51.5
Yes	64	48.5
ECOG		
0–1	99	75.0
≥ 2	33	25.0
PINK score		
0	102	77.3
≥ 1	30	22.7
Pretreatment NLR		
< 3.5	88	66.7
≥ 3.5	44	33.3
Pretreatment LMR		
< 3.0	58	43.9
≥ 3.0	74	56.1
Pretreatment PLR		
< 185	88	66.7
≥ 185	44	33.3
Treatment modalities		
P-Gemox sandwich radiotherapy	49	37.1
P-Gemox sequential radiotherapy	42	31.8
Radiotherapy alone	41	31.1

and the 3-year OS were 76.8% and 47.0%, respectively. The Kaplan-Meier curve revealed that patients with high NLR had significantly poorer PFS (χ^2 = 12.854, P < 0.001, Fig. 3a) and OS (χ^2 = 14.141, P < 0.001, Fig. 3b). Similarly, all patients were classified into the low LMR (< 3) and high LMR (≥ 3) groups. The 3-year PFS for the two LMR groups were 46.5% and 77.1%, respectively, and the 3-year OS were 58.1% and 78.6%, respectively. Patients with low LMR had significantly shorter PFS (χ^2 = 12.009, P = 0.001, Fig. 3c) and OS (χ^2 = 12.180, P < 0.001, Fig. 3d). All patients were categorized into the low PLR (< 191.7) and high PLR (≥ 191.7) groups. The 3-year PFS for the two PLR groups were 71.6% and 35.2%, respectively, and the 3-year OS were 76.2% and 48.2%, respectively. Patients with high PLR tend to have worse PFS (χ^2 = 18.096, P < 0.001, Fig. 3e) and OS (χ^2 = 19.109, P < 0.001, Fig. 3f) than those with low PLR.

Survival analysis of combining NLR, LMR, and PLR

Furthermore, combining NLR, LMR, and PLR to establish a new prognostic model (patients with low NLR, high LMR, or low PLR were allocated a score of 0; those with high NLR, low LMR, or high PLR were allocated a score of 1) to stratify patients into the low-risk group (score, 0), intermediate-risk group (score, 1), intermediate-high risk group (score, 2), and high-risk group (score, 3). The 3-year PFS of the four groups were 81.9%, 62.4%, 48.7%, and 23.9%, respectively, and the 3-year OS were 84.0%, 72.4%, 54.6%, and 40.4%, respectively. There were statistically significant difference in PFS (χ^2 = 25.353, P < 0.001, Fig. 4a) and OS (χ^2 = 26.368, P<0.001, Fig. 4b) among the four groups.

Subgroup survival analysis

In the subgroup analysis, when the cutoff values of NLR, LMR, and PLR were added to the group (PINK score 0, 102 patients), patients with high NLR, low LMR, or high PLR had significantly shorter PFS (NLR, χ^2 = 11.648, P = 0.001, Fig. 5a; LMR, χ^2 = 10.336, P = 0.001, Fig. 5c; PLR, χ^2 = 13.640, P < 0.001, Fig. 5e) and OS (NLR, χ^2 = 12.330, P < 0.001, Fig. 5b; LMR, χ^2 = 10.732, P = 0.001, Fig. 5d; PLR, χ^2 = 15.440, P < 0.001, Fig. 5f).

Prognostic factors for PFS

The results of the univariate and multivariate analyses are presented in Table 2. The univariate analysis showed that B symptoms (χ^2 = 4.572, P = 0.032), stage IIE (χ^2 = 4.324, P = 0.038), local tumor invasion (χ^2 = 5.773, P = 0.016), ECOG score (χ^2 = 28.229, P < 0.001), LDH level (χ^2 = 19.053, P < 0.001), NLR (χ^2 = 12.854, P < 0.001), LMR (χ^2 = 12.009, P = 0.001), and PLR (χ^2 = 18.096, P < 0.001) were significantly associated with PFS. The multivariate analysis demonstrated that ECOG score (HR = 3.371, 95% CI = 1.906–5.961, P<0.001), LDH level (HR = 2.298, 95% CI = 1.279–4.128, P = 0.005), and PLR (HR = 2.073, 95% CI = 1.080–3.981, P = 0.028) were independent prognostic factors for PFS.

Prognostic factors for OS

The results of the univariate and multivariate analyses are shown in Table 3. The univariate analysis demonstrated that B symptoms (χ^2 = 5.018, P = 0.025), stage IIE (χ^2 = 4.248, P = 0.039), local tumor invasion (χ^2 = 5.500, P = 0.019), ECOG score (χ^2 = 29.734, P < 0.001), LDH level (χ^2 = 17.792, P < 0.001), NLR (χ^2 = 14.141, P < 0.001), LMR (χ^2 = 12.180, P < 0.001), and PLR (χ^2 = 19.109, P <

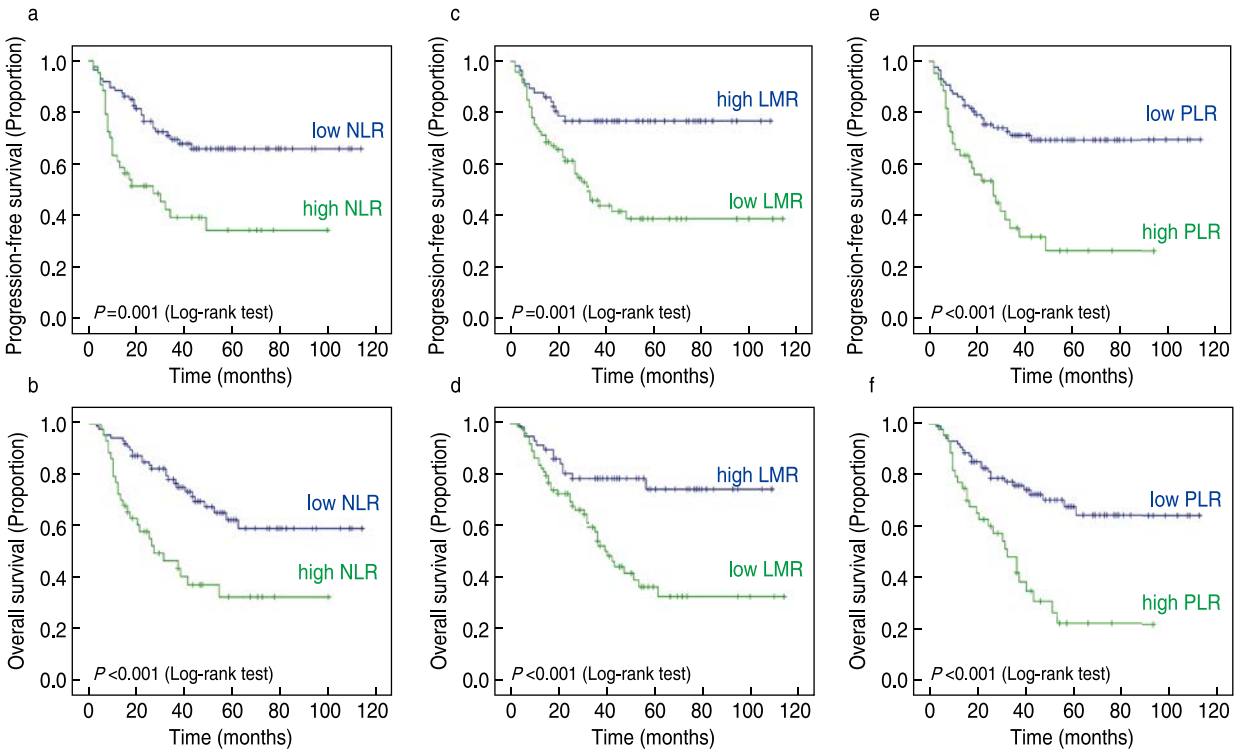

Fig. 3 Survival curve of the whole patients for NLR, LMR, PLR. (a) PFS curve of ENKTL patients in the two NLR groups (< 3.5 vs ≥ 3.5); (b) OS curve of ENKTL patients in the two NLR groups (< 3.5 vs ≥ 3.5); (c) PFS curve of ENKTL patients in the two LMR groups (< 3.0 vs ≥ 3.0); (d) OS curve of ENKTL patients the two LMR groups (< 3.0 vs ≥ 3.0); (e) PFS curve of ENKTL patients in the two PLR groups (< 191.7 vs ≥ 191.7); (f) OS curve of ENKTL patients in the two PLR groups (< 191.7 vs ≥ 191.7).

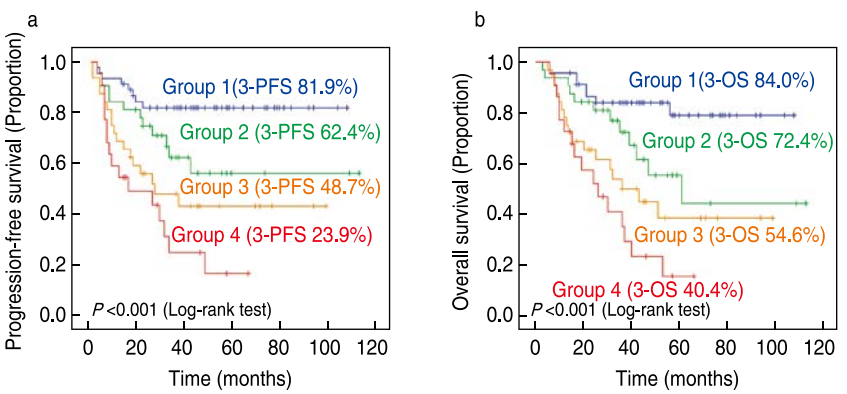

Fig. 4 Survival curve of combining NLR, LMR and PLR to build a new prognostic model to stratify patients into the low risk group (score 0), intermediate risk group (score 1), intermediate-high group (score 2) and high risk group (score 3). (a) PFS of ENKTL patients in the four groups; (b) OS of ENKTL patients in the four groups

0.001) were significantly related to OS. The multivariate analysis showed that ECOG score (HR = 3.521, 95% CI = 1.984–6.248, P<0.001), LDH level (HR = 2.139, 95% CI = 1.197–3.821, P = 0.010), and PLR (HR = 2.127, 95% CI = 1.102–4.107, P = 0.025) were independent prognostic factors for OS.

Discussion

To our knowledge, ENKTL is a distinct subtype of NHL and is frequently characterized by a prominently heterogeneous disease with poor prognosis. Recently, there are improvements in the validated benefit

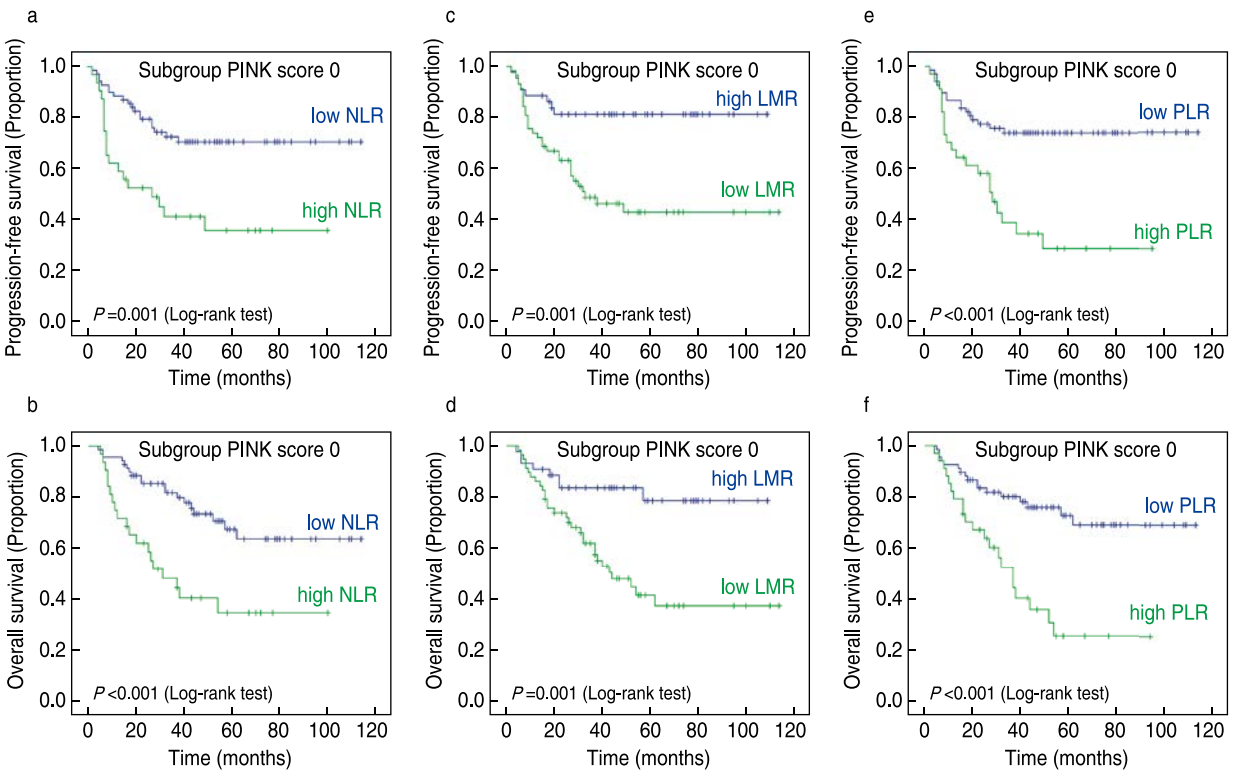

Fig. 5 Subgroup survival analysis of combining NLR, LMR and PLR to PINK score 0 group. (a) PFS curve of patients with PINK score 0 in the two NLR groups (<3.5 vs ≥3.5); (b) OS curve of patients with PINK score 0 in the two NLR groups (<3.5 vs ≥3.5); (c) PFS curve of patients with PINK score 0 in the two LMR groups (<3.0 vs ≥3.0); (d) OS curve of patients with PINK score 0 in the two LMR groups (<3.0 vs ≥3.0); (e) PFS curve of patients with PINK score 0 in the two PLR groups (<191.7 vs ≥191.7); (f) OS curve of patients with PINK score 0 in the two PLR groups (<191.7 vs ≥191.7)

Table 2 Prognostic factors analysis of progression free survival

Clinical characteristics	No. of patients				
	Univariate		Multivariate		
	χ^2	*P*	HR	95%CI	*P*
Gender (male *vs.* female)	0.067	0.795	–	–	–
Age (≤ 60 years *vs.* > 60 years)	2.043	0.153	–	–	–
Stage (IE *vs.* IIE)	4.324	0.038	1.021	0.481–2.166	0.957
LDH (≤ 240 U/L *vs.* > 240 U/L)	19.053	< 0.001	2.344	1.306–4.205	0.004
B symptoms (no *vs.* yes)	4.572	0.032	0.899	0.433–1.869	0.776
Local tumor invasion (no *vs.* yes)	5.773	0.016	1.328	0.595–2.963	0.488
ECOG score (0–1 *vs.* ≥2)	28.229	< 0.001	3.299	1.869–5.821	< 0.001
PINK score (0 *vs.* ≥1)	1.724	0.189	–	–	–
NLR (< 3.5 *vs.* ≥3.5)	12.854	< 0.001	1.195	0.594–2.404	0.618
LMR (< 3.0 *vs.* ≥3.0)	12.009	0.001	1.636	0.835–3.202	0.151
PLR (< 191.7 *vs.* ≥191.7)	17.226	< 0.001	1.973	1.018–3.824	0.044

of L-asparaginase-based regimens combined with radiotherapy in patients with early stage ENKTL [22–24]. However, there is still quite a large proportion of patients with stage IE/IIE ENKTL with unappealing outcomes due to disease recurrence or metastasis [3–5]. Therefore, intensive systemic therapy is necessary to prolong survival and improve prognosis in these patients. Previous studies have reported that IPI and KPI scores were initially used to estimate the prognosis of patients with ENKTL but these scores were based on non-asparaginase regimens, and most patients were classified into the low-risk group [6–7]. Recently, the PINK score [8] based on L-asparaginase

Table 3 Prognostic factors analysis of overall survival

Clinical characteristics	OS				
	Univariate		Multivariate		
	χ^2	*P*	HR	95%CI	*P*
Gender (male *vs.* female)	0.104	0.747	–	–	–
Age (≤ 60 years *vs.* > 60 years)	3.324	0.068	–	–	–
Stage (IE *vs.* IIE)	4.248	0.039	0.923	0.438–1.947	0.834
LDH (≤ 240 U/L *vs.* > 240 U/L)	17.792	< 0.001	2.171	1.216–3.873	0.009
B symptoms (no *vs.* yes)	5.018	0.025	1.115	0.557–2.231	0.759
Local tumor invasion (no *vs.* yes)	5.500	0.019	1.177	0.532–2.604	0.688
ECOG score (0–1 *vs.* ≥ 2)	29.734	< 0.001	3.464	1.955–6.136	< 0.001
PINK score (0 *vs.* ≥ 1)	3.132	0.077	–	–	–
NLR (< 3.5 *vs.* ≥ 3.5)	14.141	< 0.001	1.381	0.684–2.787	0.368
LMR (< 3.0 *vs.* ≥ 3.0)	12.180	< 0.001	1.517	0.776–2.969	0.223
PLR (< 191.7 *vs.* ≥ 191.7)	18.525	< 0.001	2.059	1.059–4.002	0.033

chemotherapy showed good prognostic value but this model was mainly based on clinical features and does not completely comprehensively reflect the biological behavior of patients with ENKTL. Therefore, a novel powerful marker to precisely predict the prognosis of patients with ENKTL and appropriately guide the clinical practice is needed.

A mounting body of work [9–12] had been devoted to elucidating the close link between systemic inflammation response and tumor development. The potential explanations that inflammatory cells, proinflammatory cytokines, and chemokines in the tumor microenvironment participated in different pathways of tumor development through facilitated angiogenesis, growth, proliferation, metastasis, and inhibited apoptosis of the malignant cell, leading to worse treatment response, shorter survival, and poorer prognosis. Several studies [13–15] have also confirmed that inflammatory markers such as elevated NLR or PLR and decreased LMR were associated with poor survival in various solid tumors, including ENKTL [18–19]. However, the specific mechanism behind poor tumor prognosis, which might be influenced by NLR, LMR, or PLR, remained completely unclear. Several potential explanations might account for this as follows:

Neutrophil, an inflammatory cell, is an important component of the inflammatory response, and is capable of defense against microorganisms. A high neutrophil count is classically associated with the process of tumor development and likely reflects an increased inflammatory reaction and decreased antitumor immune response [25]. A study by Tecchio *et al* [26] confirmed that production of cytokines by neutrophils (including transforming growth factor-β, oncostatin M) was involved in promoting tumor cell growth and proliferation, as well as invasion. Moreover, accumulating evidence [27–28] showed that neutrophils could promote angiogenesis of tumor cells due to the release of several angiogenic factors (e.g., vascular endothelial growth factor, fibroblast growth factor-2, and angiopoietin-1). Recently, the study conducted by Szczerba *et al* [29] also reported that neutrophils help circulating tumor cells to act on cell cycle progression, resulting in a more efficient metastasis. As already discussed, this might partially indicate why neutrophils have been associated with tumor development. Lymphocytes, a key part in immune response, are responsible for immunosurveillance to remove tumor cells. A series of studies [30–33] have shown that lymphocytes could suppress tumor progression by producing various cytokines (e.g., interferon, tumor necrosis factor, and interleukin-2). Thus, lymphopenia, a reduction in the ability to respond against tumors, is regarded as an indicator of immunosuppression. Therefore, based on these findings and knowledge, it is not surprising that low lymphocyte levels were an independent risk factor for unsatisfactory survival in patients with ENKTL [34–35].

Monocyte is also a type of inflammatory cell from the peripheral blood. Many studies have indicated that tumor-associated macrophages are considered relevant with unfavorable prognosis in tumors, which could secrete monocyte chemoattractant protein-1 to promote tumor angiogenesis, progression, growth, invasion, and distant metastasis through the production of cytokines, chemokines, and proteases (tumor necrosis factor-α, interleukin-1, and interleukin-6) [36–38]. Therefore, monocytes, which play an opposite role to that of lymphocytes, are likely to stimulate and mediate tumor development. A study conducted by Huang *et al* [39] showed that increased monocyte levels were considered as a poor prognostic factor in patients with ENKTL. Platelets, another population of proinflammatory cells

in charge of blood coagulation functions, directly or indirectly participate in the inflammatory response. Thus, thrombocytosis might represent a nonspecific response. Some studies have revealed that activated platelets released a variety of growth factors, chemokines, adhesion molecules, proangiogenic regulatory proteins, and microparticles within the tumor microenvironment to compromise the antitumor ability of natural killer cells and promote tumor cell angiogenesis, growth, proliferation and invasion, and metastasis [40–43]. Moreover, Buergy *et al* [44] reported that increased pretreatment platelet levels were correlated with unfavorable prognosis in different types of tumors.

In this way, inflammation-based markers such as NLR, LMR, and PLR were significant predictors of survival in various types of cancer [13–15]. It was considered that elevated NLR or PLR and decreased LMR were often caused by an imbalance between two types of cells, violating antitumor immune response and tumor-promoting inflammation. Undoubtedly, they may have an impact on survival of patients with cancer patients by affecting the tumor microenvironment and immune system. Meanwhile, NLR, LMR, and PLR, as the ratio of absolute counts between two types of cells, have more relative stability than one type of cell alone. Therefore, in this study, our results also confirmed that a relatively elevated NLR or PLR and decreased LMR were associated with short survival in patients with ENKTL, consistent with the findings of a previous study [18–19]. We further combined NLR, LMR, and PLR to establish a new prognostic model to stratify patients into four risk groups, and there were significant differences in PFS and OS. This might partially explain that, in patients with ENKTL with elevated NLR or PLR and decreased LMR, the balance was tipped toward tumor-promoting inflammation, promoting tumor cell growth, proliferation, and metastasis, compromising the antitumor ability, and resulting in poor treatment outcome and prognosis. Our results are consistent with those of a previous study that increased PLR was an independent risk factor for ENKTL [19]. However, our study indicated that both NLR and LMR were not independent prognostic factors, which was not concluded in the previous study [18]. This may be because, with the simultaneous addition of NLR, LMR, and PLR in the multivariate analysis, PLR might have an influence on NLR or LMR, or the impact of the interaction among the three factors or the confounding effect of other factors could not be completely abolished. Efforts are needed to determine the underlying mechanism. Therefore, NLR or LMR may be a complement prognostic factor for PLR in patients with ENKTL. It is important to note that the cutoff values for LMR and PLR in the ROC of our study were 3.0 and 191.7, respectively, and were different from those of other studies [18–19] (LMR = 3.5, PLR = 185). This variation may be explained by the nature of NLR, LMR, and PLR as nonspecific markers or different treatment regimens, inclusion criteria, or sample sizes. Thus, a consensus on cutoff values for NLR, LMR, and PLR is still to be determined.

Previous studies showed that ECOG score, LDH level, B symptoms, stage, and local tumor invasion were independent prognostic markers in patients with ENKTL [6–8, 16–19]. As expected, our results showed that ECOG score, LDH level, B symptoms, stage, and local tumor invasion were associated with poor prognosis, consistent with the findings of previous studies. Based on previous studies, the multivariate analysis revealed that ECOG score and LDH level remained to be independent prognostic indicators for both PFS and OS. However, it is worth noting that B symptoms, stage, and local tumor invasion were not independent prognostic factors. The reasons for this might be the diagnosis of early stage ENKTL in all patients, retrospectively small sample size, and short-term follow-up. Surprisingly, in the univariate analysis of the current study, no statistical significance was observed in age in the prediction of survival. This might be because all patients with localized lesions had favorable general health status, could develop toxicities with P-Gemox regimens, and were also sensitive to radiotherapy. Although the PINK score was an important prognostic model in patients with ENKTL, our study found that it was not correlated with survival because of the unbalanced distribution, resulting in classification of most patients into the low-risk group. This might partially explain why the PINK score was inapplicable to patients with stage I/IIE. Moreover, we determine whether a new prognostic model is equivalent or superior to other validated prognostic models. We further performed s subgroup analysis. When the cutoff value of NLR, LMR, or PLR was added to the group with PINK score of 0, NLR, LMR, and PLR enabled us to statistically significantly distinguish patients who belong to the “low-risk group”. Therefore, patients with early stage ENKTL needed to be further subdivided to accurately predict the prognosis and appropriately guide the clinical practice. Thus, NLR, LMR, and PLR are useful complements to patients with PINK score 0 to make discrimination of patients into the low-risk group possible. Meanwhile, NLR, LMR, and PLR have the advantage of low cost and ease of access in routine blood examination in clinical practice.

Conclusion

This study was a single-center, retrospective analysis, and the sample size was small. Despite these limitations, PLR appeared to be a promising marker for early stage ENKTL. NLR and LMR were useful complements to PLR. In the future, large-scale prospective studies are necessary to fully verify the utility of PLR in a clinical setting.

Conflicts of interest

The author declare no potential conflicts of interest.

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