

Increased serum levels of interleukin-15 correlate with negative prognostic factors in extranodal NK/T cell lymphoma

Hua Wang · Jia-yu Zhu · Cheng-cheng Liu ·
Meng-yuan Zhu · Jing-hua Wang · Qi-rong Geng ·
Yue Lu

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Abstract Interleukin-15 (IL-15) is a proinflammatory cytokine involved in the proliferation, survival, and activation of multiple lymphocyte lineages. However, the prognostic significance of IL-15 for extranodal NK/T cell lymphoma (ENKTL) has not been well established. We retrospectively analyzed 112 patients with newly diagnosed ENKTL. Baseline serum IL-15 levels were determined using sandwich enzyme-linked immunosorbent assays. Patients with high IL-15 (>3.94 mg/L) at diagnosis tended to have more adverse clinical features. Patients with low IL-15 (≤ 3.94 mg/L) at diagnosis had better progression-free survival (PFS; $P < 0.001$) and overall survival (OS; $P < 0.001$) and achieved higher complete remission rates ($P = 0.001$). Multivariate analysis revealed independent prognostic factors for PFS. Similarly, high IL-15

levels ($P = 0.009$), no CR after chemotherapy ($P = 0.001$), Stage III/IV ($P = 0.048$), and elevated serum EBV-DNA ($P = 0.038$) were independently predictive of shorter OS. Using the International Prognostic Index or Korean Prognostic Index for nasal NK/T cell lymphoma, the majority of patients were in the low-risk category (with no or one adverse factor). Serum IL-15 was helpful to differentiate the low-risk patients with different survival outcomes ($P < 0.001$). Our data suggest that serum IL-15 at diagnosis is a novel, powerful predictor of prognosis for ENKTL, which suggests a role for IL-15 in the pathogenesis of this disease and offers new insight into potential therapeutic strategies.

Keywords Extranodal NK/T cell lymphoma · Serum IL-15 · ELISA · Prognosis

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H. Wang · C. Liu · M. Zhu · J. Wang · Q. Geng · Y. Lu
State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong, People's Republic of China

H. Wang · C. Liu · M. Zhu · J. Wang · Q. Geng · Y. Lu (✉)
Department of Hematological Oncology, Sun Yat-sen University Cancer Center, Guangzhou 510060, Guangdong, People's Republic of China
e-mail: dr_luyue@sina.com

H. Wang · Y. Lu
Collaborative Innovation Center of Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou 510060, Guangdong, People's Republic of China

J. Zhu
Department of Obstetrics and Gynecology, Nan Fang Hospital of Southern Medical University, Guangzhou 510515, Guangdong, People's Republic of China

Introduction

Extranodal NK/T cell lymphoma (ENKTL) is relatively more common in Asia than in Western countries [1, 2]. Based on a recent large survey [3], it is the second most prevalent lymphoma subtype and accounts for 5–10 % of all types of lymphomas in China. ENKTL is characterized by angiodestruction, obvious necrosis, and association with Epstein–Barr virus (EBV). Multiple studies have demonstrated that elevated cytokines levels are associated with these pathological changes, for instance, CXCL9, CXCL10 [4, 5], and interleukin-9 (IL-9) [6].

Interleukin-15 (IL-15) is a proinflammatory cytokine referred to the proliferation, survival, and activation of multiple lymphocyte lineages via various kinds of signaling pathways [7, 8]. Recently, many studies have demonstrated that IL-15 can endow neoplastic cells with a

selective growth advantage initiating and promoting certain types of malignancies [9, 10]. As regards the clinical significance of IL-15 in hematopoietic malignancies, several studies have suggested that IL-15 may enhance cellular proliferation and was associated with poor prognosis, in particular, relapse-free survival in adult acute lymphoblastic leukemia [11, 12]. Baldassarre et al. [13] also reported that chronic stimulation with IL-15 gives rise to the development of NK lymphoma in a mouse model. In a study with small sample sizes, the serum levels of IL-15 were increased significantly in ENKTL patients than in healthy individuals [14]. The same team of researchers found that the supplementation with exogenous interleukin-15 can promote proliferation and inhibit apoptosis of NK-92, an NK-cell lines (CD3–CD56+TCR–), in vitro [14]. These results indicate that IL-15 can play an important role in the pathogenesis of ENKTL. We hypothesize that IL-15 levels are associated with poor prognosis for ENKTL.

In ENKTL, the prognostic value of Korean Prognostic Index (KPI) was verified by clinical studies. More than 50 % of the patients with ENKTL are in the low KPI risk group, but some of these patients still have a poor clinical outcome [15]. Therefore, the identification of specific risk factors remains an important issue. In this study, we characterized the serum levels of IL-15 and evaluated its impact on the outcome in ENKTL.

Materials and methods

Ethics statement

This study was approved by the Institutional Review Board and ethics committees of Sun Yat-Sen University Cancer Center. Written informed consent for blood samples and medical information were obtained from all patients and healthy volunteers. The study was performed in agreement with the guidelines of the Declaration of Helsinki.

Eligibility criteria

We conducted a retrospective study of 112 patients newly diagnosed with nasal ENKTL, who received chemotherapy, radiotherapy or both at the Sun Yat-sen University Cancer Center from January 2003 to 2014. The inclusion criteria in this study were as follows: (1) pathologically confirmed diagnosis of NK/T cell lymphoma according to the WHO classification, (2) NK/T cell are positive in the detection of CD3, CD56, and cytotoxic molecules by immunohistochemical, Epstein–Barr virus (EBV) by in situ hybridization, (3) no previous or concomitant malignant tumor and no previous anti-cancer treatments, (4) available serum samples

obtained prior to the initial treatment and stored at -80°C , and (5) adequate clinical information and follow-up data. Patients were excluded if found any clinical evidence to support chronic active inflammatory, such as rheumatoid arthritis and pancreatitis. Patients with other subtypes of NHL, including unspecified peripheral T cell lymphoma or blastic NK-cell lymphoma/leukemia, were not included.

All patients were staged by using the standard Ann Arbor staging system. The International Prognostic Index (IPI; age, PS, stage, LDH level, extranodal sites) and NK/T cell lymphoma Prognostic Index (KPI; stage, LDH level, B symptoms, regional lymph nodes) [2] were calculated on the basis of patient demographics, physical examination, Eastern Cooperative Oncology Group performance status (ECOG PS), B symptoms, the value of lactate dehydrogenase (LDH) from serum biochemistry, magnetic resonance imaging (MRI) of the head and neck and computed tomography (CT) scan of the chest, abdomen and pelvis, positron emission tomography–computed tomography (PET-CT) of the whole body, bone marrow aspiration, and trephine biopsy. Complete blood counts and serum Epstein–Barr virus-DNA (EBV-DNA) copy number were routinely examined.

Treatment

Patients received treatment strategies as follows: (1) patients with early-stage ENKTL received chemotherapy followed by involved-field radiotherapy (IFRT) and (2) patients with advanced stage ENKTL received chemotherapy alone. The chemotherapy regimens were as follows: (1) EPOCH (etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone); (2) GELOX (gemcitabine, oxaliplatin, L-asparaginase) [16]; and (3) CHOP-L (CHOP plus L-asparaginase). Patients were given at least two cycles. A maximum of six initial chemotherapy cycles were utilized. Involved-field radiotherapy median total dose was 56 Gy with a range of 45–60 Gy, which was given as daily 2 Gy with 5 fractions each week. The treatment response was assessed in accordance with standard response criteria for non-Hodgkin lymphoma [17]. After the whole treatment was completed, patients were followed-up and evaluated by their oncologist in the outpatient department.

ELISA

Sandwich enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, CA, USA) were used to measure serum IL-15 levels. All venous blood samples were obtained from patients at diagnosis and twelve healthy subjects. The blood samples were centrifuged, and serum was collected and stored at -80°C until further assay. Serum samples were

routinely analyzed by ELISA according to the manufacturer’s protocol. Briefly, standards and samples were added to a microplate, which have been precoated with a mouse monoclonal antibody specific to IL-15. After removal of any unbound antibody or enzyme reagent by washing, a substrate solution was added to the wells; color development was terminated by Stop Solution; and the resulting absorbance was read at 450 nm using a spectrophotometer (Tecan, Mannedorf, Switzerland). IL-15 concentrations were interpolated from a standard curve, which was generated using the recombinant IL-15 protein. All samples were analyzed in triplicate, and the results were averaged.

Statistical analysis

Serum IL-15 concentration was presented as median (min, max), while categorical data are expressed as *n* (%). Differences between the two groups were tested using Mann–Whitney *U* test or Chi-square test. The receiver operating characteristics (ROC) curve analysis was used to determine

the cutoff concentration for serum IL-15 in the prediction of survival. The Kaplan–Meier method and log-rank test were applied for univariate analyses of the impacts of several pretreatment characteristics on survival, including IL-15. Variables which were significant at *P* < 0.05 in univariate analysis were entered into multivariate analysis. Multivariate analysis was used to assess the prognostic impact of selected variables, according to the Cox regression model.

Results

Patient characteristics

In total, 112 patients (73 male, 39 female; median age 44 years) met the inclusion criteria. The clinical characteristics of the 112 patients are listed in Table 1. Most patients (101 cases, 90.2 %) displayed a favorable performance status (ECOG PS 0–1). Forty-six patients (41.1 %)

Table 1 Correlation of serum IL-15 level with clinicopathological features in ENKTL patients

Characteristics	Median concentration [pg/mL (range)]	<i>P</i> value	Low IL-15 group [n (%)]	High IL-15 group [n (%)]	<i>P</i> value
No. of cases			64 (57.1)	48 (42.9)	
Age		0.923	43 (19–76)	46 (15–72)	0.807
≤60	3.71 (1.19–13.45)		51 (79.7)	40 (83.3)	
>60	4.24 (1.89–8.84)		13 (20.3)	8 (16.7)	
Gender (male)	3.87 (1.34–8.84)	0.122	41 (64.1)	32 (66.7)	0.843
ECOG PS		0.001			0.201
0–1	3.63 (1.19–13.45)		60 (93.8)	41 (85.4)	
≥2	5.65 (2.33–8.56)		4 (6.2)	7 (14.6)	
B symptoms (yes)	4.60 (1.43–13.45)	0.019	20 (31.3)	26 (54.2)	0.02
LDH >245 U/l	5.08 (2.21–13.45)	0.002	15 (23.4)	19 (39.6)	0.216
EBV-DNA ^a		0.001	3,080 (0–20,000,000)	12,400 (0–50,000,000)	<0.001
<6,150	3.30 (1.19–13.45)		45 (70.3)	15 (31.3)	
≥6,150	4.93 (1.34–8.84)		19 (29.7)	33 (68.7)	
Regional LN involvement	4.35 (1.19–8.84)	0.002	24 (37.5)	34 (70.8)	<0.001
Ann Arbor stage		0.104			0.248
I/II	3.74 (1.19–13.45)		53 (82.8)	35 (72.9)	
III/IV	5.35 (1.43–8.84)		11 (17.2)	13 (27.1)	
IPI score		0.013			0.067
0–1	3.64 (1.19–13.45)		54 (84.4)	33 (68.8)	
2–5	5.47 (1.43–8.84)		10 (15.6)	15 (31.2)	
KPI score		0.001			0.013
0–1	3.40 (1.19–7.26)		42 (65.6)	20 (41.7)	
2–4	4.62 (1.43–13.45)		22 (34.4)	28 (58.3)	
CR after CT	2.85 (1.19–5.97)	0.001	28 (43.8)	14 (29.2)	0.167

^a The median value of EBV-DNA copy number for all patients was 6,150 copies/mL
 ECOG PS Eastern Cooperative Oncology Group performance status, LN lymph node, LDH lactate dehydrogenase, EBV-DNA, Epstein–Barr virus-DNA, IPI International Prognostic Index, KPI Korean Prognostic Index, CT chemotherapy, CR complete remission

presented with B symptoms. Elevated LDH levels were observed for 34 cases (30.4 %). Fifty-eight patients (51.8 %) displayed regional lymph node involvement. Most patients (88 cases, 78.6 %) had localized disease (Stage I/II). According to the IPI, a majority of the patients (87 cases, 77.7 %) were classified as low/low–intermediate risk (IPI = 0–1), and 25 patients (22.3 %) were categorized as intermediate–high/high risk (IPI = 2–5). The number of patients with KPI = 0–1 (62 cases, 55.4 %) was significantly higher than those with KPI = 2–4 (50 cases, 44.6 %).

Baseline serum IL-15 levels

The mean concentration of serum IL-15 for all patients was 4.1 pg/mL with a median of 3.76 pg/mL (range 1.19–13.45 pg/mL). Serum IL-15 was detected in ten healthy volunteers, and the median concentration was 0.67 pg/mL (range 0–1.12 pg/mL), which was significantly lower than that of ENKTL patients ($P < 0.001$). To identify an optimal cutoff point for survival outcomes, the ROC curve analysis was selected. The most discriminative cutoff concentration of serum IL-15 was 3.94 pg/mL with an area under the curve (AUC) value of 0.776 [95 % confidence interval (CI) 0.679–0.872, $P < 0.001$] (Fig. 1). Based on the ROC analysis result, we used the IL-15 level >3.94 mg/L as the cutoff value in the present study. Based on this cutoff value, 67 patients (57.1 %) were categorized into the low-CRP group (≤ 3.94 mg/L), and 48 patients (42.9 %) were categorized into the high-CRP group (>3.94 mg/L). The baseline clinical features of the patients in the low-CRP group were compared with those in the high-CRP group (Table 1). The high-CRP group was characterized by a higher proportion of patients with more frequent B symptoms, elevated serum EBV-DNA levels, more common Regional LN involvement and elevated KPI scores. As shown in Table 1, the serum IL-15 level was significantly higher in patients with elevated LDH levels, poor PS, no complete response (CR) after chemotherapy, etc. However, there was no significant correlation between serum IL-15 level and gender, age, Ann Arbor stage.

Treatment modalities and response

The primary treatment modalities were as follows: (a) 88 cases (78.6 %) received chemotherapy followed by radiotherapy (RT); and (b) 24 cases (21.4 %) received chemotherapy alone; the treatment details and responses are listed in Table 2. No significant difference was found in the treatment modalities as well as chemotherapy regimens between the patients with IL-15 levels ≤ 3.94 mg/L and patients displaying IL-15 levels >3.94 mg/L ($P = 0.248$).

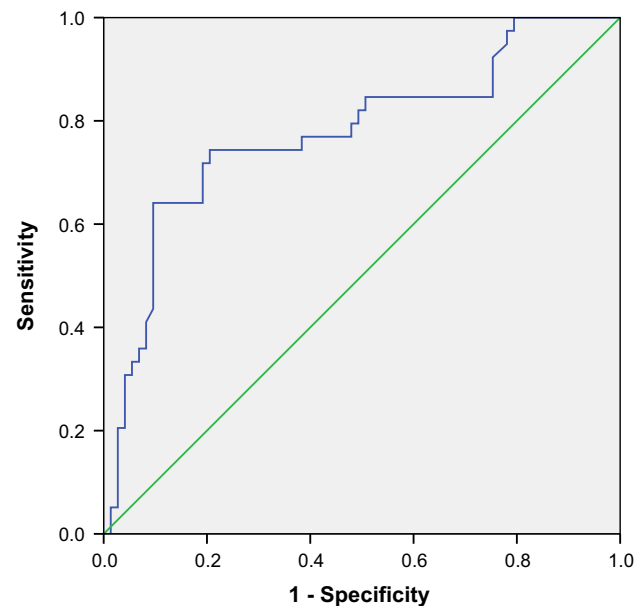


Fig. 1 ROC curve analysis for the optimal cutoff point of serum IL-9. The most discriminative cutoff concentration of serum IL-15 was 3.94 pg/mL with an AUC value of 0.776. The sensitivity and specificity were 74.4 and 72.6 %, respectively

Table 2 Primary treatment and response in patients with extranodal natural killer (NK)/T cell lymphoma

Treatment	Low IL-15 group [n (%)]	High IL-15 group [n (%)]	<i>P</i> value
Treatment modalities			0.248
CT followed by RT	53 (82.8)	35 (72.9)	
CT alone	11 (17.2)	13 (27.1)	
Chemotherapy regimens			0.157
GELOX	27 (42.2)	14 (29.2)	
EPOCH	33 (51.6)	29 (60.4)	
CHOP-L	4 (6.2)	5 (10.4)	
Complete remission	50 (78.1)	23 (47.9)	0.001

CT chemotherapy, RT radiotherapy, GELOX gemcitabine + oxaliplatin + L-asparaginase, EPOCH etoposide + doxorubicin + vincristine + cyclophosphamide + prednisone, CHOP-L cyclophosphamide + doxorubicin + vincristine + prednisone + L-asparaginase

After the initial treatment, 73 of the 112 treated patients (65.2 %) achieved a CR. The rate of CR to initial treatment was significantly higher in the low IL-15 group than in the high IL-15 group (78.1 vs. 47.9 %, respectively, $P = 0.001$).

Survival and prognostic factors

Within a median follow-up time of 31 months (5–152), the 5-year PFS and OS rates for all 112 patients were 51.7 (95 % CI 40.9–62.5 %) and 60.6 % (95 % CI 50.4–70.8 %), respectively. Patients in low IL-15 group had significantly better PFS (5-year PFS 77.5 vs. 14.1 %, $P < 0.001$; Fig. 2a) and OS (5-year OS 80.6 vs. 36.6 %, $P < 0.001$; Fig. 2b). In the patients received chemotherapy alone ($n = 2,421.4$ %), elevated serum IL-15 levels were associated with shorter PFS and OS ($P = 0.035$ and

$P = 0.028$, respectively) and also related to inferior PFS and OS ($P < 0.001$ and $P < 0.001$, respectively) in the patients received chemotherapy followed by radiotherapy ($n = 8,878.6$ %). Significant survival differences were found between the patients who gained CR after chemotherapy and those without CR ($P < 0.001$ and $P < 0.001$, respectively, Fig. 3a, b).

Table 3 displays the results of the univariate and multivariate analysis of the potential predictors of PFS and OS. Multivariate analysis using the forward conditional Cox regression model identified IL-15 levels >3.94 mg/L

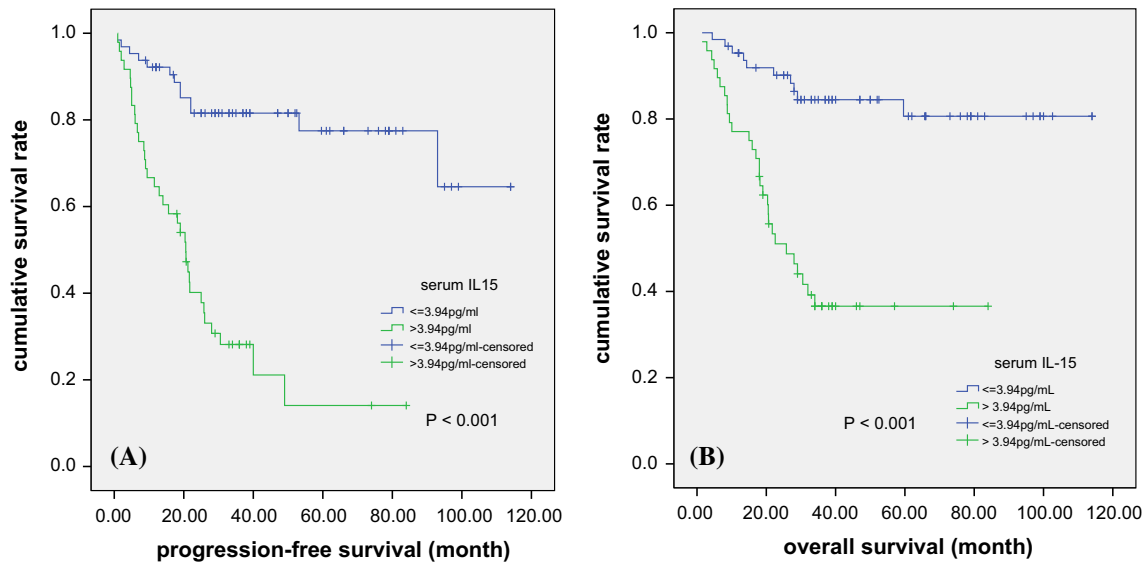


Fig. 2 Survival outcome of patients based on the serum IL-15 level. **a** Progression-free survival (PFS) of patients according to serum IL-15 level (≤ 3.94 vs. >3.94 mg/L). **b** Overall survival (OS) of patients according to baseline IL-15 level (≤ 3.94 vs. >3.94 mg/L)

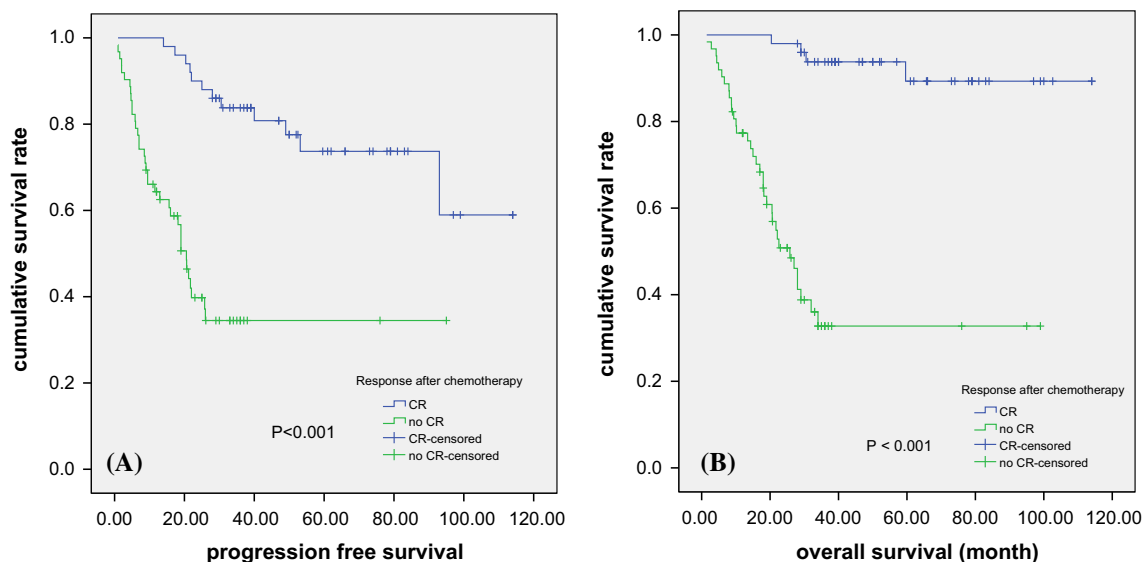


Fig. 3 Survival outcome of patients based on response after chemotherapy (CT). **a** Progression-free survival (PFS) of patients according to response after CT (CR vs. no CR). **b** Overall survival (OS) of patients according to response after CT (CR vs. no CR)

Table 3 Univariate and multivariate analysis of factors associated with progression-free survival and overall survival of all patients

Clinical characteristics	Progression-free survival			Overall survival		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	<i>P</i> value	RR (95 % CI)	<i>P</i> value	<i>P</i> value	RR (95 % CI)	<i>P</i> value
Age >60 (years)	0.988			0.207		
Gender (male)	0.773			0.214		
ECOG PS ≥ 2	0.150			0.186		
B symptoms	0.002	1.965 (1.079–3.580)	0.027	0.015		
Elevated serum LDH	0.004			0.002		
EBV-DNA	0.001			0.001	2.141 (1.043–4.395)	0.038
Regional LN involvement	0.002			0.014		
Serum IL-15 >3.94 pg/mL	<0.001	4.138 (2.043–8.383)	<0.001	<0.001	2.943 (1.305–6.639)	0.009
Stage III/IV	<0.001			<0.001	2.608 (1.009–6.742)	0.048
IPI score ≥ 2	<0.001			<0.001		
KPI score ≥ 2	<0.001			<0.001		
Response after CT (no CR vs. CR)	<0.001	3.101 (1.939–4.957)	<0.001	<0.001	3.101 (1.939–4.957)	<0.001

PFS progression-free survival, *OS* overall survival, *RR* relative risk, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EUNKTL* extraperitoneal aerodigestive tract NK/T cell lymphoma, *LDH* lactate dehydrogenase, *IPI* International Prognostic Index, *KPI* Korean Prognostic Index

Table 4 Distribution of patients inside risk groups and OS by IPI and KPI

Prognostic model	No. of patients (%)	5-year OS (%)	<i>P</i> value
IPI score			
0–1	87 (77.7)	70.2	<0.0001
2–3	18 (16.1)	10.4	
4–5	7 (6.2)	0	
KPI score			
0–1	62 (55.4)	75.1	<0.0001
2–4	50 (44.6)	39.2	

OS overall survival, *IPI* International Prognostic Index, *KPI* Korean Prognostic Index

(RR = 4.138, 95 % CI 2.043–8.383, $P < 0.001$), B symptoms (RR = 1.965, 95 % CI 1.079–3.580, $P = 0.027$), and no CR after chemotherapy (RR = 3.101, 95 % CI 1.939–4.957, $P < 0.001$) as three adverse factors for PFS. In the multivariate analysis for OS, IL-15 levels >3.94 mg/L (RR = 2.943, 95 % CI 1.305–6.639, $P = 0.009$), stage III/IV (RR = 2.608, 95 % CI 1.009–6.742, $P = 0.048$), no CR after chemotherapy (RR = 2.515, 95 % CI 1.454–4.348, $P = 0.001$), and serum EBV-DNA (RR = 2.141, 95 % CI 1.043–4.395, $P = 0.038$) were found to be significant independent predictors of OS.

The distribution of patients inside risk groups based on IPI score and KPI score is presented in Table 4. In the IPI score, more than 70 % of all cases were in the low-risk category (with no or one adverse factor), but

this prognostic model failed to differentiate patients with different outcomes in the low-risk group. The KPI model balanced distribution of patients into different risk groups better than IPI model (score 0–1: 62 cases, 55.4 %; score 2–4: 50 cases, 44.6 %). However, the KPI model also had no discriminating power in patients with no or one adverse factors (5-year OS 70.6 vs. 63.3 %, $P = 0.425$).

For patients in the low-risk category according to IPI, serum IL-15 level at diagnosis could distinguish those with good outcomes from those with poor outcomes. Serum IL-15 level can divide the patients in IPI score of 0–1 group ($n = 87$, 77.7 %) into two subgroups with significant differences in PFS and OS ($P < 0.001$ and $P < 0.001$, respectively, Fig. 4a, b). Similarly, in patients with KPI score of 0–1 ($n = 62$, 55.4 %), serum IL-15 level at diagnosis also helped to differentiate patients with different prognoses ($P < 0.001$ and $P < 0.001$, respectively, Fig. 4c, d).

Discussion

Previous studies have confirmed the role of IL-15 in various hematological malignancies, including adult T cell leukemia, acute lymphoblastic leukemia, and NK/T cell lymphoma [14, 18, 19]. A clinical study in adult ALL indicated that higher IL-15 expression was significant associated with shorter survival. However, the prognostic role of IL-15 in ENKTL remains unclear. In this study, we

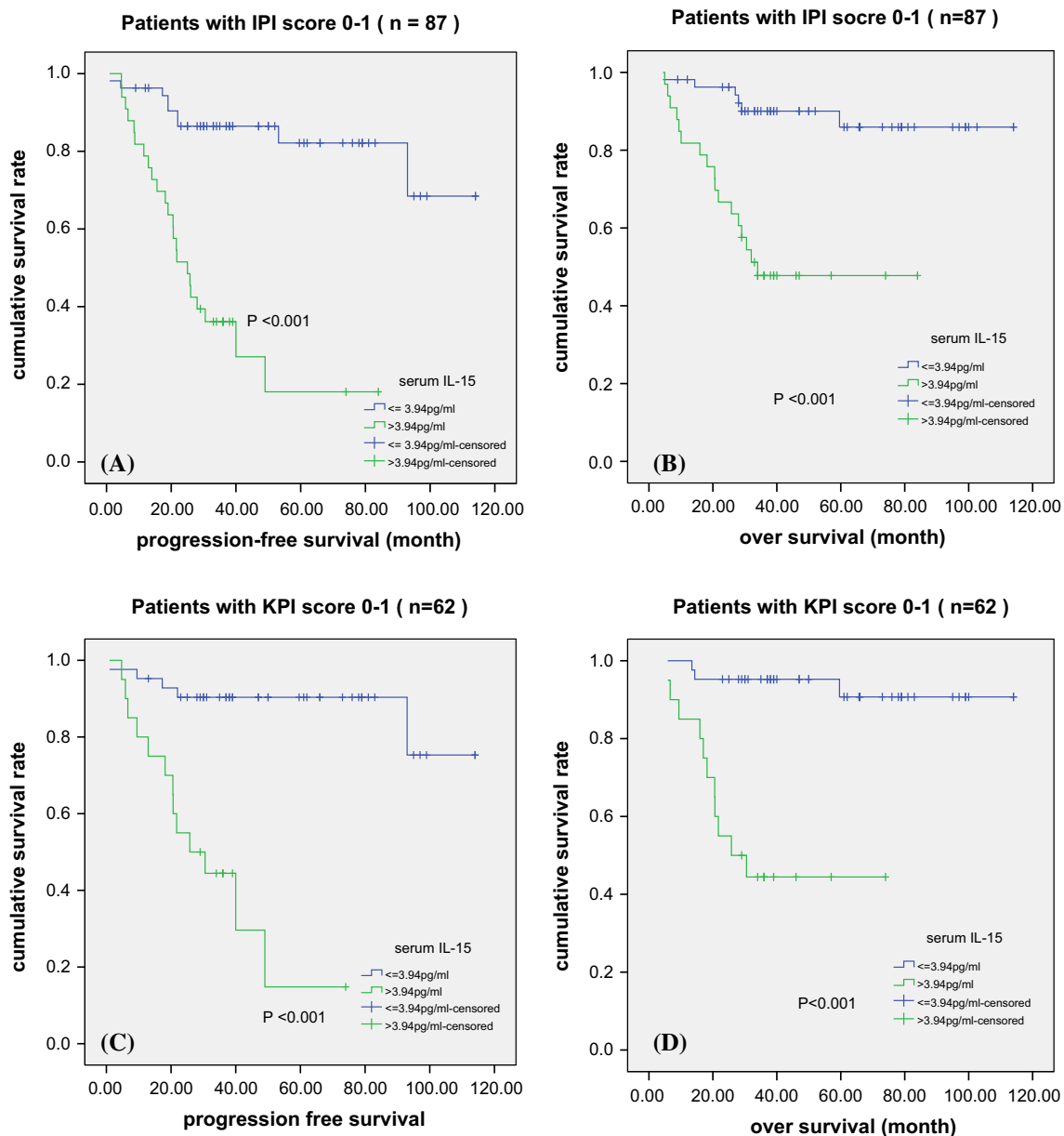


Fig. 4 Progression-free survival (PFS) and Overall survival (OS) according to serum IL-15 level (≤ 3.94 vs. > 3.94 mg/L) at diagnosis in patients with extranodal natural killer T cell lymphoma, nasal type (ENKTL). Kaplan–Meier plots of PFS (a) and OS (b) for subgroups

with low International Prognostic Index (IPI) score of 0–1; Kaplan–Meier plots of PFS (c) and OS (d) for subgroups with low Korean Prognostic Index (KPI) score of 0–1

found that the serum concentration of IL-15 in ENKTL patients was much higher than in normal healthy people. In ENKTL patients, the levels of serum IL-15 significantly correlated with clinicopathological features, such as elevated LDH levels, poor PS, and no complete response (CR) after chemotherapy. Furthermore, elevated serum concentration of IL-15 was related to poor responses to chemotherapy or chemoradiotherapy. According to the Cox regression model that included the serum levels of IL-15, responses after chemotherapy, stage III/IV, serum EBV-

DNA, B symptoms, and so on, it was concluded that serum IL-15 and responses after chemotherapy were independent prognostic factors for both PFS and OS.

In the present study, we measured serum IL-15 levels in healthy volunteers and patients with ENKTL. We found that IL-15 was fairly low in the healthy controls (median concentration 0.67 pg/mL), but it showed a relative higher level in patients with ENKTL, with a median value of 3.76 pg/mL. The results of the current study are consistent with the recent study of Chow et al. [14] in which serum

IL-15 levels were first reported as a specific tumor biomarker for ENKTL patients. IL-15 is a pleiotropic cytokine that influences proliferation, differentiation, resistance to apoptosis [20], and cellular localization of T [21] and B lymphocytes [7], neutrophils [22], and natural killer (NK) cells [23]. Thus, it is easy to explain the correlation between IL-15 and B symptoms, elevated serum LDH and response to treatment. However, it remains unclear why IL-15 levels were also associated with EBV-DNA.

According to the ROC curve analyses, 3.94 pg/mL was an optimal cutoff value for distinguishing between poor outcomes and good outcomes. Patients with low IL-15 levels (≤ 3.49 pg/mL) tended to have higher CR rates (78.1 %) than those with high IL-15 levels (> 3.49 pg/mL) (47.9 %) ($P = 0.001$). Specifically, 5-year PFS and OS rate in the low IL-15 level group were clearly longer than those in the high IL-15 level group (PFS 77.5 vs. 14.1 %, $P < 0.001$; OS 80.6 vs. 36.6 %, $P < 0.001$). Multivariate analysis also indicated that IL-15 was an independent prognostic factor for PFS and OS. All these data confirmed that serum IL-15 was closely correlated with treatment response and prognosis in ENKTL, implying a significant role for IL-15 in the pathogenesis and development of this disease. Nevertheless, IL-15 can lead to either a favorable or unfavorable clinical prognosis depending on the tumor. Yajima et al. [24] examined the effects of in vivo over-expression of IL-15 on protection against two types of murine B16 melanoma lines, B16.44, and B16F10 cells in IL-15 transgenic (Tg) mice and found that tumor growth was severely retarded in IL-15 Tg mice after subcutaneous (s.c.) inoculation with B16.44 or B16F10 cells. The inconsistent roles of IL-15 in tumors may be partly attributed to different immune effects or single nucleotide polymorphisms.

Although ENKTL is a distinctive entity with poor prognosis, approximately 70 % of the patients in our study were categorized as low risk based on IPI score. Accordingly, patients with adverse and good clinical outcomes were found in the group with IPI score < 2 . The prognostic value of IPI and KPI model was evaluated in the present study. These two models were highly prognostic in the univariate analysis. The KPI model balanced distribution of patients into different risk groups. However, patients were allocated disproportionately within the IPI prognostic model. Moreover, all these three models failed to identify patients with poor prognosis in the low-risk category (with no or one adverse factor). When adding serum IL-15 at diagnosis to the two models, the low-risk patients were separated on the basis of different survival outcomes with sufficient statistical power.

A possible role for IL-15 in malignant disorders of the immune system was first suggested by its identification in an adult T cell leukemia-lymphoma cell line and the fact

that IL-15 transgenic mice develop an NK/T large granular lymphocyte leukemia—like disease [25]. The mechanisms underlying the relationship between elevated serum IL-15 levels and poor prognosis are not clear; however, several potential explanations have been proposed. Functionally, IL-15 supports cell expansion and maintenance by (1) inducing strong proliferative signals via JAK/STAT and Ras/MAPK signaling pathways and (2) preventing cell death by increasing antiapoptotic proteins Bcl-2 and Bcl-X1, as well as decreasing proapoptotic proteins Bim and Puma through activation of the PI3 K pathway [26–31]. Indeed, Chow et al. [14] found that IL-15 can also maintain the survival of NK-92 cells by preserving AKT phosphorylation. Recent studies show that IL-15 enhances cellular proliferation and upregulates CNS homing molecules in pre-B acute lymphoblastic leukemia by inducing STAT5, ERK 1/2, and to a lesser extent PI3K and NF- κ B phosphorylation [25]. Further studies, however, are needed to elucidate the cellular mechanisms of IL-15-mediated signaling in NK/T cell lymphoma.

In conclusion, this is the first study that confirms the close relationship of IL-15 with several clinical features of ENKTL, including B symptoms, Regional LN involvement, etc. Serum IL-15, which can be easily measured in clinical practice, may be a significant independent prognostic factor for this disease. These results suggest a role for IL-15 in the pathogenesis of ENKTL and offer new insight into potential therapeutic strategies. Future prospective studies are warranted to confirm our findings.

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Conflict of interest None.

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