

High C-Reactive Protein to Albumin Ratio Predicts Inferior Clinical Outcomes in Extranodal Natural Killer T-Cell Lymphoma

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Abstract

Objective: The prognostic value of C-reactive protein to albumin ratio (CAR) has been identified in several cancers but not in extranodal natural killer T-cell lymphoma (ENKTL) as yet. We aimed to evaluate the prognostic value of CAR in ENKTL.

Methods: A retrospective study with 246 patients with ENKTL was performed to determine the prognostic value of pre-treatment CAR and examine the prognostic performance of CAR incorporating with International Prognostic Index (IPI) or natural killer/T-cell lymphoma prognostic index (NKPI) by nomogram.

Results: The Cox regression analyses showed that high CAR (>0.3) independently predicted unfavorable progression-free survival (PFS, $P = .011$) and overall survival (OS, $P = .012$). In the stratification analysis, the CAR was able to separate patients into different prognoses regarding both OS and PFS in Ann Arbor stage I+II as well as III+IV, IPI score 0 to 1, and NKPI score 1 to 2 subgroups (all $P < .05$). Additionally, the predictive accuracy of the IPI-based nomogram incorporating CAR, albumin to globulin ratio (AGR), and IPI for OS and PFS appeared to be lower than the NKPI-based nomogram incorporating CAR, age, AGR, extranodal site, and NKPI.

Conclusion: Pretreatment CAR is a simple and easily accessible parameter for independently predicting OS and PFS in patients with ENKTL.

Keywords

extranodal natural killer T-cell lymphoma (ENKTL), C-reactive protein to albumin ratio (CAR), prognosis, nutrition, inflammation

Introduction

Extranodal natural killer T-cell lymphoma (ENKTL) is a globally rare entity of non-Hodgkin lymphoma (NHL) with high aggressiveness,¹ accounting for less than 1% of NHL in the Western population and 7% to 10% of NHL in Asian and Latin American population.² Generally, ENKTL is a heterogeneous disease with poor prognosis, and most large cohort studies demonstrate a 5-year overall survival (OS) rate less than 50%.¹ Although upfront use of radiotherapy incorporating nonanthracycline-based chemotherapy regimens (eg, etoposide, methotrexate, ifosfamide, platinum, and L-asparaginase) has achieved improved outcome in recent decades, optimal treatment strategy and prognosis of ENKTL remain inadequately defined.³ Considering the unsatisfactory prognosis in a substantial proportion of patients, prognostic stratification according to individual risk is very important and instrumental in facilitating decision-making and treatment modification for physicians.

Several prognostic factors for ENKTL have been widely adopted in recent years, such as age at diagnosis, regional lymph node involvement, Ann Arbor stage, performance

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status, serum lactate dehydrogenase (LDH), paranasal extension, B symptoms, number of extranodal sites, Epstein-Barr virus (EBV) DNA status, and primary tumor invasion. By incorporating these factors, several useful prognostic scoring systems, including the International Prognostic Index (IPI), natural killer/T-cell lymphoma prognostic index (NKPI), and a prognostic nomogram from a Chinese multicenter study, have been proposed.^{1,4-6} More recently, the prognostic index of natural killer lymphoma including age, Ann Arbor stage, distant lymph node involvement, non-nasal type, and EBV DNA status, was developed to predict the prognosis of natural killer cell lymphoma after non-anthracycline-based treatment.³ However, the predictive value of these models remains incomplete and kind of controversial. The predictive accuracy of these systems is limited possibly due to the collection of small patient series over long periods, discrepant definitions of some prognostic factors, inconsistent detection methods for some indicators, and heterogeneous therapeutic regimens.¹ With this regard, some researchers have found that the predictive value of these models may be further improved by other laboratory parameters (fasting blood glucose, C-reactive protein [CRP], platelet count, albumin, soluble interleukin 2 receptor, and absolute lymphocyte count).^{2,7-12}

Growing evidence has shown that systemic nutritional status and inflammation status are critical in determining the clinical course and outcome of patients with cancer. C-reactive protein secreted by hepatocytes is usually induced by pro-inflammatory cytokines in an inflammatory microenvironment. Elevated CRP has been associated with poor prognosis in various types of cancer,^{13,14} including ENKTL.^{7,8} Serum albumin level not only reflects the nutritional status but also serves as indirect indicators of inflammatory activity. Previous studies have shown that hypoalbuminemia may be utilized as an effective indicator of upregulated cancer-related inflammatory response, which is likely associated with the cytokine-induced suppression of albumin synthesis and increased degradation of albumin.^{15,16} Using serum albumin level as a surrogate marker of nutritional status, more and more studies have found that decreased albumin level is a valuable predictor of poor survival outcome in various malignancies.^{17,18} Accordingly, the prognostic score index Glasgow Prognostic Score (GPS), developed by the serum concentration of CRP and albumin, has shown prognostic value in various cancer types including ENKTL,⁷ and their performance seems to be better than the cellular components of systemic inflammation represented by neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR).^{19,20} Nevertheless, the CRP to albumin ratio (CAR), a novel prognostic marker which is believed to reflect nutritional as well as inflammation status of patients, has drew much attention recently. The CAR was found to be a more accurate independent prognostic indicator than other indicators such as GPS, NLR, and PLR in predicting prognosis of various types of cancer.²¹⁻²³ However, to the best of our knowledge, the prognostic value of CAR in ENKTL has never been investigated. Therefore, we

performed the retrospective analysis with a comparatively large sample size to evaluate the prognostic significance of CAR in patients with ENKTL, and we also developed an easily applicable prognostic nomogram based on NKPI with readily accessible parameters for the estimation of clinical outcome in ENKTL.

Materials and Methods

Patients and Study Design

In the present retrospective cohort study, we conducted a secondary analysis of a Chinese ENKTL study concerning the prognostic value of laboratory parameters. The design and patient eligibility criteria have been previously reported.¹⁶ In brief, eligible patients had pathologically confirmed previously untreated ENKTL diagnosed in accordance with the World Health Organization classification of lymphomas and were included with complete pretreatment laboratory data of interest and complete follow-up data including the OS and progression-free survival (PFS). The patient-level data set was de-identified by data providers and made available for the public through the *PeerJ* journal. No institutional review board approval was needed to access data according to the publication policy.

Data Collection

Before treatment, the following baseline clinical data were collected: patient demographics, physical examination, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor site, B symptoms, treatment modalities and chemotherapeutic regimen, white blood cell (WBC) count, serum LDH, baseline serum CRP levels, baseline albumin levels, and Ann Arbor stage. All patients received computed tomography of the chest, abdomen, and pelvis; computed tomography and/or magnetic resonance imaging of the head and neck; and a bone marrow examination. The IPI was calculated based on the variables including age, ECOG PS, Ann Arbor stage, LDH level, and number of extranodal sites. Also, the NKPI was calculated based on the involvement of regional lymph nodes, B symptoms, and LDH level. Extranodal natural killer T-cell lymphoma was categorized as 2 subtypes: upper aerodigestive tract (UAT, including the nasal cavity, Waldeyer's ring, hypopharynx, larynx, and oral cavity) and extra-upper aerodigestive tract (EUAT, any site other than an UAT site).

Calculation of CAR and AGR

The CAR was defined as the baseline serum CRP level (mg/L) divided by the serum albumin (g/L) level at admission. The optimal cutoff level for CAR to predict prognosis of ENKTL was determined using the X-tile software (version: 3.6.1, Copyright Yale University 2003-2005), and this value was therefore used in the further analyses. The albumin to

globulin ratio (AGR) was calculated as the baseline serum albumin (g/L) level divided by the serum globulin (g/L) level. The cutoff value for AGR was set as 1.3 as done previously.^{9,16}

Treatment

The treatment modality of the included patients primarily consisted of chemotherapy alone or radiotherapy with or without chemotherapy. Patients in early stage of the disease received induction chemotherapy followed by involved-field radiotherapy (IFRT), and patients with advanced disease primarily received chemotherapy and IFRT could be delivered as consolidation with palliative or salvage therapy according to the physician's clinical judgment. As previously described,¹⁶ chemotherapy regimens varied over the study period, but they could be categorized as an asparaginase (ASP)-based or anthracycline-based regimen. Involved-field radiotherapy was given with a median dose of 54.6 Gy (range, 18.0-74.0 Gy) in daily fractions of 2.0 to 2.5 Gy (5 days a week).

Statistical Analysis

The cutoff value for WBC was set as the upper limit of normal value to group the patients. The baseline clinicopathologic features in high- and low-CAR groups were compared by Pearson chi-square test (Fisher exact test). Overall survival was measured from the date of diagnosis to the date of death due to any cause or the date of the most recent follow-up. Progression-free survival was measured from the date of diagnosis to the date of disease progression, relapse, death due to any cause, or the most recent follow-up. Survival data were calculated using the Kaplan-Meier method. Survival comparisons were performed using the log-rank test. The survival curves were plotted using the R-based *survminer* package. Significant prognostic variables in univariate analysis were selected for multivariate Cox regression model analysis to determine independent prognostic factors using the forward stepwise method. Considering some variables overlapped with the components of IPI and NKPI, these 2 prognostic indexes were not included in the Cox regression analyses. Hazard ratio (HR) and 95% confidence intervals (95% CIs) were calculated, and a 2-side $P < .05$ was considered statistically significant. All the statistical analyses were performed using SPSS 17.0 statistics software (IBM, Chicago, Illinois). Furthermore, aided by the R-based *rms* package, the nomogram was constructed with the independent prognostic factors incorporating the IPI or NKPI based on the Cox model. Points were assigned based on the weights for the relative importance of each variable in the model. The total score (scaled to range from 0 to 100) for each patient was calculated as a weighted sum based on the contribution from the individual risk factors. The performance of the nomogram was measured by Harrell's concordance index (C-index), and the concordance of

Table 1. Pretreatment Characteristics, Clinical Features, and CAR in Patients With ENKTL.

Features	Group	CAR		P Value
		≤ 0.3 n = 160	> 0.3 n = 86	
Gender (%)	Female	58 (36.2)	18 (20.9)	.02
	Male	102 (63.7)	68 (79.1)	
Age, years (%)	≤60	145 (90.6)	69 (80.2)	.035
	>60	15 (9.4)	17 (19.8)	
BMI, kg/m ² (%)	18.5 to <25	123 (76.9)	54 (62.8)	.015
	<18.5	17 (10.6)	21 (24.4)	
	≥25	20 (12.5)	11 (12.8)	
ECOG score (%)	0-1	145 (90.6)	61 (70.9)	<.001
	≥2	15 (9.4)	25 (29.1)	
Primary site (%)	UAT	142 (88.8)	73 (84.9)	.503
	EUAT	18 (11.2)	13 (15.1)	
Ann Arbor stage (%)	I + II	138 (86.2)	62 (72.1)	.011
	III + IV	22 (13.8)	24 (27.9)	
B symptoms (%)	No	96 (60.0)	20 (23.3)	<.001
	Yes	64 (40.0)	66 (76.7)	
LDH (%)	Normal	129 (80.6)	48 (55.8)	<.001
	Elevated	31 (19.4)	38 (44.2)	
Regional nodes (%)	Negative	107 (66.9)	43 (50.0)	.014
	Positive	53 (33.1)	43 (50.0)	
Extranodal sites (%)	0-1	147 (91.9)	67 (77.9)	.004
	≥2	13 (8.1)	19 (22.1)	
IPI score (%)	0-1	139 (86.9)	53 (61.6)	<.001
	2-3	17 (10.6)	23 (26.7)	
	4-5	4 (2.5)	10 (11.6)	
NKPI score (%)	0	63 (39.4)	7 (8.1)	<.001
	1-2	77 (48.1)	50 (58.1)	
	3-4	20 (12.5)	29 (33.7)	
	≥5	10 (6.2)	14 (16.2)	
AGR (%)	≥1.3	118 (73.8)	36 (41.9)	<.001
	<1.3	42 (26.2)	50 (58.1)	
Treatment (%)	Chemo alone	38 (23.8)	45 (52.3)	<.001
	RT + chemo	122 (76.2)	41 (47.7)	
Chemotherapy (%)	ASP-based	65 (42.2)	40 (48.2)	.455
	A-based	89 (57.8)	43 (51.8)	
Chemo-cycles (%)	<4	64 (40.8)	38 (44.2)	.703
	≥4	93 (59.2)	48 (55.8)	

Abbreviations: A-based, anthracycline based; AGR, albumin to globulin ratio; ASP-based, asparaginase based; CAR, C-reactive protein to albumin ratio; Chemo, chemotherapy; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ENKTL, extranodal natural killer T-cell lymphoma; EUAT, extra-upper aerodigestive tract; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NKPI, natural killer/T-cell lymphoma prognostic index; RT, radiotherapy; UAT, upper aerodigestive tract.

nomogram-predicted versus observed Kaplan-Meier estimates of actual survival probability was also assessed by calibration plot with bootstrap resampling (1000 resamples) method. All the analyses related to nomogram were performed in R, version 3.6.0 (<http://www.r-project.org/>).

Results

Patient Characteristics

Totally, 246 patients fulfilled the inclusion criteria and were enrolled for the study. The baseline characteristics of included

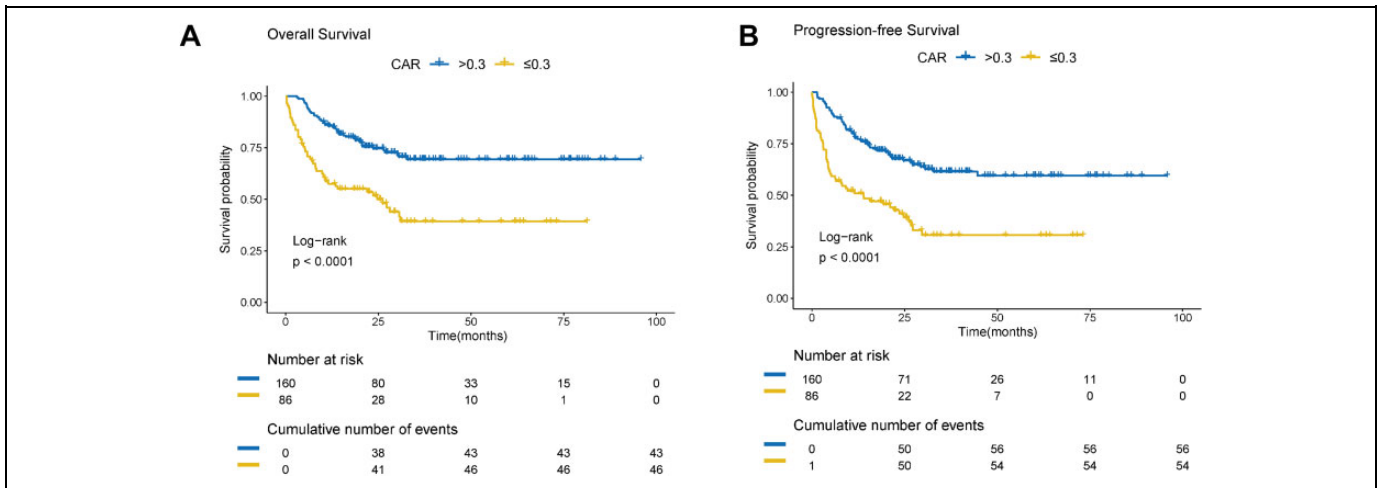


Figure 1. Prognostic impact of pretreatment C-reactive protein to albumin ratio (CAR) in patients with extranodal natural killer T-cell lymphoma (ENKTL). A, Overall survival. B, Progression-free survival.

patients are presented in Table 1. In the study, men predominated (men to women ratio, 2.24:1), and the median age was 42 years (range, 12-79); only 13% of the patients were aged more than 60 years. As for the BMI of the 246 patients, 38 (15.4%) patients were underweight (BMI < 18.5 kg/m²), 31 (12.6%) patients were overweight or obese, and 177 (72%) patients were normal weight. Most of the patients (206, 83.7%) displayed a favorable performance status (ECOG PS 0-1), and the primary site of tumor was UAT (215, 87.4%). Elevated LDH levels were observed in 69 (28%) patients. Regional lymph nodes were involved in 96 (39%) patients, and B symptoms were present in 130 (52.8%) patients. According to the Ann Arbor staging system, 46 (18.7%) patients had stage III-IV disease, and 200 (81.3%) patients were diagnosed with stage I-II disease. Thirty-two (13%) patients were submitted with 2 or more extranodal sites of tumor, and 154 (62.6%) patients had a high AGR (≥ 1.3). The majority of patients were scored as low-risk disease according to the IPI (0-1, 78%), and 16.3% of patients were scored as moderate-risk disease. However, 28.5% of patients had no risk factor according to the NKPI score system, and 51.6% of patients presented 1 to 2 risk factors. As for the treatment modality, 83 (33.7%) patients received chemotherapy alone and 163 (66.3%) patients received radiotherapy with or without chemotherapy. Of the patients receiving chemotherapy, ASP-based regimen was given to 105 (42.7%) patients, and anthracycline-based regimen was given to 132 (53.7%) patients.

Determination of Optimal Cutoff Value of CAR and Associations With Clinicopathologic Variables

The optimal cutoff value of CAR was estimated by X-tile software (version 3.6.1). The results suggested that a cutoff value of 0.3 for CAR had the most significant predictive value for OS. Therefore, the patients were divided into high CAR group (CAR > 0.3) and low CAR group (CAR \leq 0.3), and the high

group had a poorer OS (log-rank test, $P < .0001$; Figure 1A). Similarly, patients with a high CAR had a significantly shorter PFS than those with low CAR (log-rank test, $P < .0001$; Figure 1B).

The baseline characteristics differed significantly between patients with low or high CAR. Patients with high CAR was more frequent to be observed in male ($P = .02$) and tended to have lower BMI (<18.5 kg/m², $P = .015$). Patients in the high CAR group presented with significantly more adverse clinical features, including an older age (>60, $P = .035$), advanced disease (stage III-IV, $P = .011$), high ECOG PS score ($P < .001$), elevated LDH ($P < .001$), B symptoms ($P < .001$), involvement of regional lymph nodes ($P = .014$), more extranodal sites of tumor ($P = .004$), lower AGR ($P < .001$), and higher IPI score ($P < .001$) and NKPI score ($P < .001$). Additionally, more patients with a high CAR needed to receive radiotherapy \pm chemotherapy treatment (Table 1).

Survival Analysis

After a median follow-up duration of 22.5 months, an estimated 5-year OS and PFS rate in 246 patients were 59% and 49%, respectively. As shown in Table 2, univariate Cox proportional analysis revealed that age at diagnosis ($P = .003$), ECOG PS score ($P < .0001$), Ann Arbor stage ($P < .0001$), presence of B symptoms ($P = .008$), involvement of regional lymph node ($P = .0002$), extranodal sites ($P < .0001$), LDH level ($P < .0001$), AGR ($P = .002$), CAR ($P < .0001$), treatment ($P < .0001$), and chemotherapy regimen ($P = .001$) were significantly correlated with OS in patients with ENKTL. In the multivariable analysis by applying the forward stepwise Cox regression, age at diagnosis ($P < .0001$), involvement of regional lymph node ($P = .032$), extranodal sites ($P = .014$), CAR ($P = .012$), treatment ($P < .0001$), and chemotherapy regimen ($P < .0001$) were identified as independent predictors of OS (Table 2).

Table 2. Univariate and Multivariate Cox Proportional Hazards Regression of Prognostic Factors on Overall Survival in Patients With ENKTL.

Variables	Univariate			Multivariate		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age, years (>60 vs ≤60)	2.165	1.289-3.634	.003	3.424	1.946-6.024	<.0001
Gender (male vs female)	1.187	0.748-1.885	.467			
ECOG score (≥2 vs 0-1)	3.293	2.093-5.183	<.0001			
Primary site (EUADT vs UADT)	1.688	0.982-2.901	.058			
Ann Arbor stage (III + IV vs I + II)	3.058	1.955-4.782	<.0001			
B symptoms (yes vs no)	1.789	1.160-2.759	.008			
Regional nodes (positive vs negative)	2.177	1.435-3.303	.0002	1.612	1.041-2.496	.032
BMI, kg/m ²						
Normal, 18.5 to <25	Ref					
<18.5	0.827	0.448-1.526	.543			
Overweight, ≥25	0.527	0.242-1.147	.106			
Extranodal sites (≥2 vs 0-1)	3.848	2.373-6.239	<.0001	1.936	1.145-3.274	.014
LDH (elevated vs normal)	2.574	1.694-3.918	<.0001			
AGR (<1.3 vs ≥1.3)	1.95	1.282-2.966	.002			
WBC (>10 vs ≤10, 10 ⁹ /L)	0.764	0.334-1.751	.525			
CAR (>0.3 vs ≤0.3)	2.755	1.816-4.181	<.0001	1.781	1.138-2.786	.012
Treatment (RT + chemo vs chemo alone)	0.2	0.130-0.307	<.0001	0.264	0.164-0.422	<.0001
Chemotherapy (A-based vs ≤ASP-based)	2.254	1.385-3.669	.001	3.032	1.824-5.042	<.0001
Chemo-cycles (≥4 vs <4)	0.665	0.439-1.008	.054			

Abbreviations: A-based, anthracycline based; AGR, albumin to globulin ratio; ASP-based, asparaginase based; BMI, body mass index; CAR, C-reactive protein to albumin ratio; Chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ENKTL, extranodal natural killer T-cell lymphoma; EUAT, extra-upper aerodigestive tract; LDH, lactate dehydrogenase; RT, radiotherapy; UAT, upper aerodigestive tract; WBC, white blood cell.

Table 3. Univariate and Multivariate Cox Proportional Hazards Regression of Prognostic Factors on Progression-Free Survival in Patients With ENKTL.

Variables	Univariate			Multivariate		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Age, years (>60 vs ≤60)	1.655	0.998-2.745	.051			
Gender (male vs female)	1.237	0.813-1.882	.321			
ECOG score (≥2 vs 0-1)	3.492	2.310-5.278	<.0001			
Primary site (EUAT vs UAT)	2.198	1.363-3.545	.001			
Ann Arbor stage (III/IV vs I/II)	3.478	2.324-5.231	<.0001			
B symptoms (yes vs no)	1.911	1.293-2.825	.001			
Regional nodes (positive vs negative)	2.056	1.413-2.992	<.001			
BMI, kg/m ²						
Normal, 18.5 to <25	Ref					
<18.5	0.894	0.523-1.528	.682			
Overweight, ≥25	0.665	0.354-1.247	.204			
Extranodal sites (≥2 vs 0-1)	4.699	2.997-7.366	<.0001	2.926	1.762-4.860	<.0001
LDH (elevated vs normal)	2.170	1.478-3.185	<.0001			
AGR (<1.3 vs ≥1.3)	2.054	1.408-2.997	<.001	2.090	1.400-3.128	.0003
WBC (>10 vs ≤10, 10 ⁹ /L)	0.849	0.413-1.744	.656			
CAR (>0.3 vs ≤0.3)	2.603	1.789-3.790	<.0001	1.697	1.127-2.555	.011
Treatment (RT chemo vs chemo alone)	0.233	0.159-0.341	<.0001	0.367	0.241-0.561	<.0001
Chemotherapy (A-based vs ≤ASP-based)	2.364	1.533-3.645	<.0001	2.982	1.921-4.629	<.0001
Chemo-cycles (≥4 vs <4)	0.862	0.591-1.257	.440			

Abbreviations: A-based, anthracycline based; AGR, albumin to globulin ratio; ASP-based, asparaginase based; BMI, body mass index; CAR, C-reactive protein to albumin ratio; Chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ENKTL, extranodal natural killer T-cell lymphoma; EUAT, extra-upper aerodigestive tract; LDH, lactate dehydrogenase; RT, radiotherapy; UAT, upper aerodigestive tract; WBC, white blood cell.

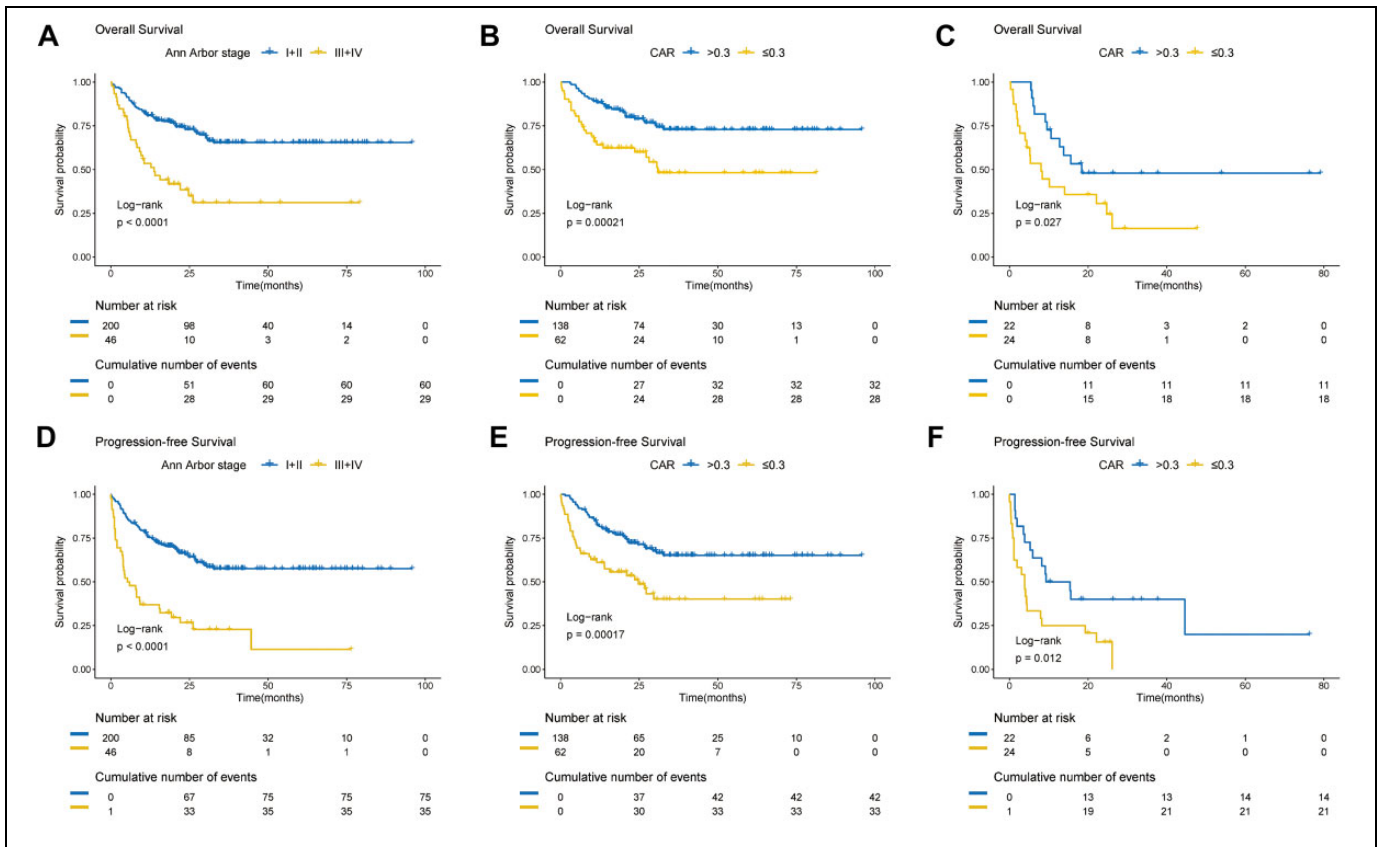


Figure 2. Prognostic impact of pretreatment C-reactive protein to albumin ratio (CAR) in patients with extranodal natural killer T-cell lymphoma (ENKTL) having different Ann Arbor stage. A and D, Prognostic impact of Ann Arbor stage on overall survival (A) and progression-free survival (D). B and E, Prognostic impact of pretreatment CAR on overall survival (B) and progression-free survival (E) in patients with ENKTL having Ann Arbor stage I+II. C and F, Prognostic impact of pretreatment CAR on overall survival (C) and progression-free survival (F) in patients with ENKTL having Ann Arbor stage III+IV.

In terms of PFS (Table 3), univariable analysis indicated that ECOG PS score ($P < .0001$), primary site of tumor ($P = .001$), Ann Arbor stage ($P < .0001$), presence of B symptoms ($P = .001$), involvement of regional lymph node ($P < .001$), extranodal sites ($P < .0001$), LDH level ($P < .0001$), AGR ($P < .001$), CAR ($P < .0001$), treatment ($P < .0001$), and chemotherapy regimen ($P < .0001$) were significantly correlated with PFS in patients with ENKTL. The multivariable analysis also suggested that extranodal sites ($P < .0001$), AGR ($P = .0003$), CAR ($P = .011$), treatment ($P < .0001$), and chemotherapy regimen ($P < .0001$) could independently predict PFS in patients with ENKTL.

Prognostic Impact of CAR in Subgroup Analysis

To further investigate the prognostic value of CAR, the subgroup analysis was performed in several important prognostic indexes including Ann Arbor stage, IPI, and NKPI. As shown in Figure 2, the Ann Arbor stage was significantly associated with both OS and PFS (log-rank test, both $P < .0001$). The subgroup analysis revealed that high CAR (>0.3) significantly worsen the OS either in I-II stage ($P = .00021$) or III-IV stage ($P = .027$) as well as PFS in different stages (I-II, $P = .00017$,

III-IV, $P = .0017$). Similarly, the IPI score was also revealed as a predictor of OS as well as PFS in patients with ENKTL (both $P < .0001$). As shown in Figure 3, regardless of whether it was for PFS or OS, the predictive capacity of CAR was much higher in patients with IPI score 0 to 1, further separating patients into 2 entities (OS, $P = .0015$; PFS, $P = .00066$). Although with similar trend, CAR failed to distinguish prognostic subsets among patients in the IPI score 2 to 3 group regarding OS or PFS. The subgroup analysis for IPI score 4 to 5 was not performed due to insufficient samples. Likewise, as shown in Figure 4, NKPI stratified patients into 3 groups with significantly different prognoses for OS and PFS (both $P < .0001$). The CAR further differentiated patients with different prognoses in the NKPI score 1 to 2 group regarding OS ($P = .0055$) and PFS ($P = .00061$) but failed in NKPI score 0 or 3 to 4 group.

Comparison of the Predictive Accuracy for OS Between the Nomograms

In view of the importance of IPI and NKPI in ENKTL, the nomogram to predict 5-year OS or PFS was developed using the independent predictors in the multivariable analysis (age at

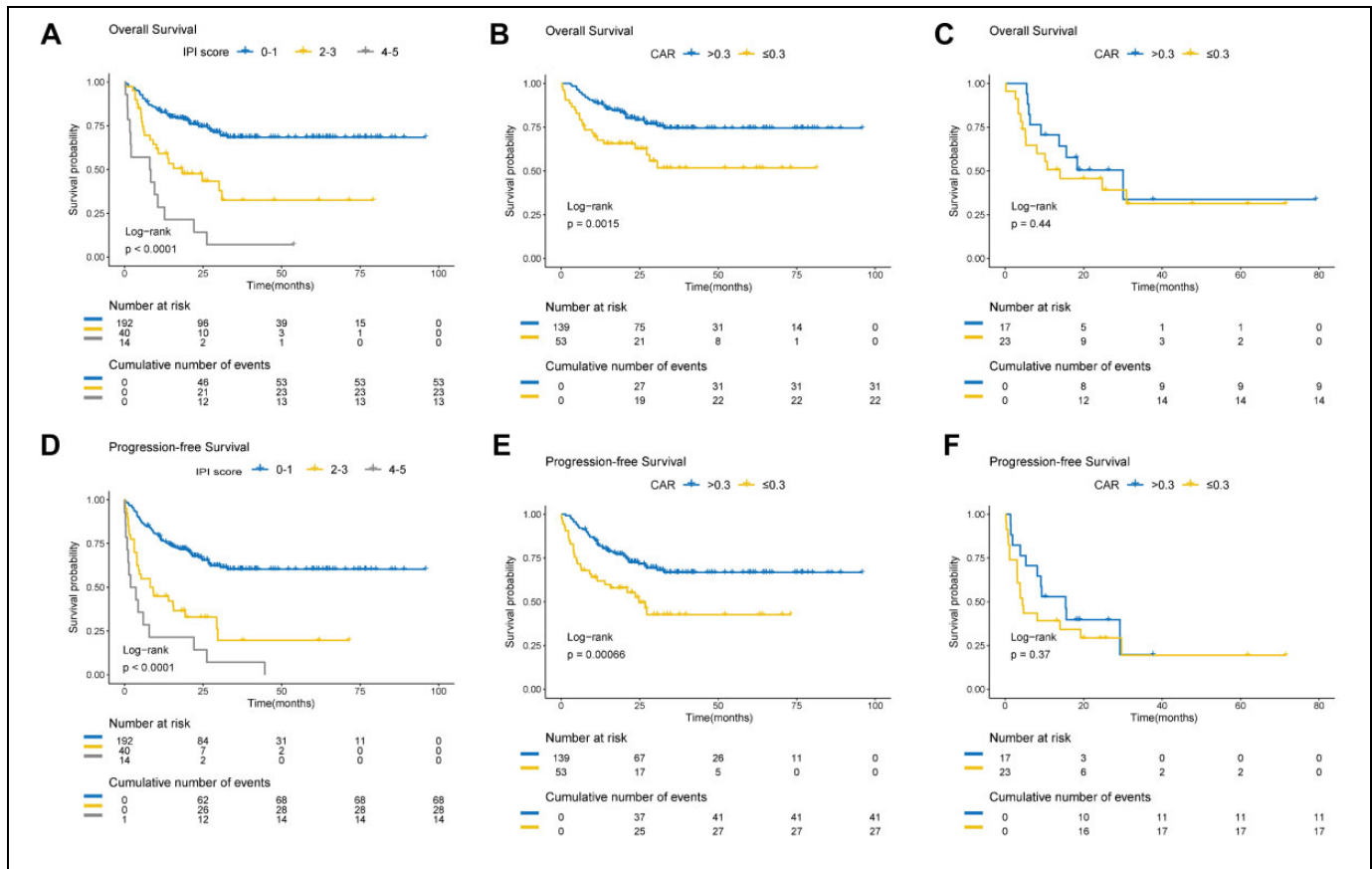


Figure 3. Prognostic impact of pretreatment C-reactive protein to albumin ratio (CAR) in patients with extranodal natural killer T-cell lymphoma (ENKTL) having different International Prognostic Index (IPI) score. A and D, Prognostic impact of IPI score on overall survival (A) and progression-free survival (D). B and E, Prognostic impact of pretreatment CAR on overall survival (B) and progression-free survival (E) in patients with ENKTL with IPI score 0-1. C and F, Prognostic impact of pretreatment CAR on overall survival (C) and progression-free survival (F) in patients with ENKTL having an IPI score 2 of 3.

diagnosis, extranodal sites, CAR, and AGR) incorporating IPI or NKPI. We first included the age at diagnosis, extranodal sites, CAR, AGR, and NKPI to construct the nomogram (Figure 5). The predictive accuracy of the nomogram for OS and PFS as measured by the concordance index (C-index) was 0.710 and 0.700, respectively, which was higher than that with NKPI alone (C-index for OS: 0.676, PFS: 0.669). Additionally, we also developed a nomogram with the IPI. In consideration of the selected independent predictors (age at diagnosis and extranodal sites) partially overlapped with the components of IPI, we include CAR, AGR, and IPI to construct the nomogram (data not shown). As a result, the predictive accuracy of the IPI-based nomogram for OS and PFS as measured by the concordance index (C-index) was 0.690 and 0.689, which was lower than the NKPI-based nomogram. As shown in Figure 5, the calibration plots for the probability of OS and PFS also showed good concordance between the actual observed outcome and the NKPI-based nomogram prediction. In light of the difference of chemotherapy regimens, we examined the predictive capability of NKPI-based nomogram in patients receiving ASP-based and anthracycline-based chemotherapy. As a result,

the predictive accuracy of the NKPI-based nomogram for OS as measured by the concordance index (C-index) was 0.726 in patients receiving ASP-based chemotherapy, which tends to be higher than that in patients receiving anthracycline-based chemotherapy with a C-index of 0.709. However, the C-index of NKPI-based nomogram for PFS was 0.706 in patients receiving ASP-based chemotherapy, which tends to be lower than that in patients receiving anthracycline-based chemotherapy with a C-index of 0.717.

Discussion

To improve risk-based stratification for therapy, we attempted to verify the prognostic value of laboratory biomarker CAR in patients with ENKTL. In the last decades, 2 prognostic scoring systems, IPI and NKPI, were widely accepted for the prognostication of ENKTL. However, the predictive capability of the 2 systems were subjected to inherent defects. Although the IPI has prognostic value in many subtypes of NHL, its prognostic value remains controversial in ENKTL because it may underestimate the risk in some of the patients with ENKTL. The prognostic value of NKPI has been well validated in many

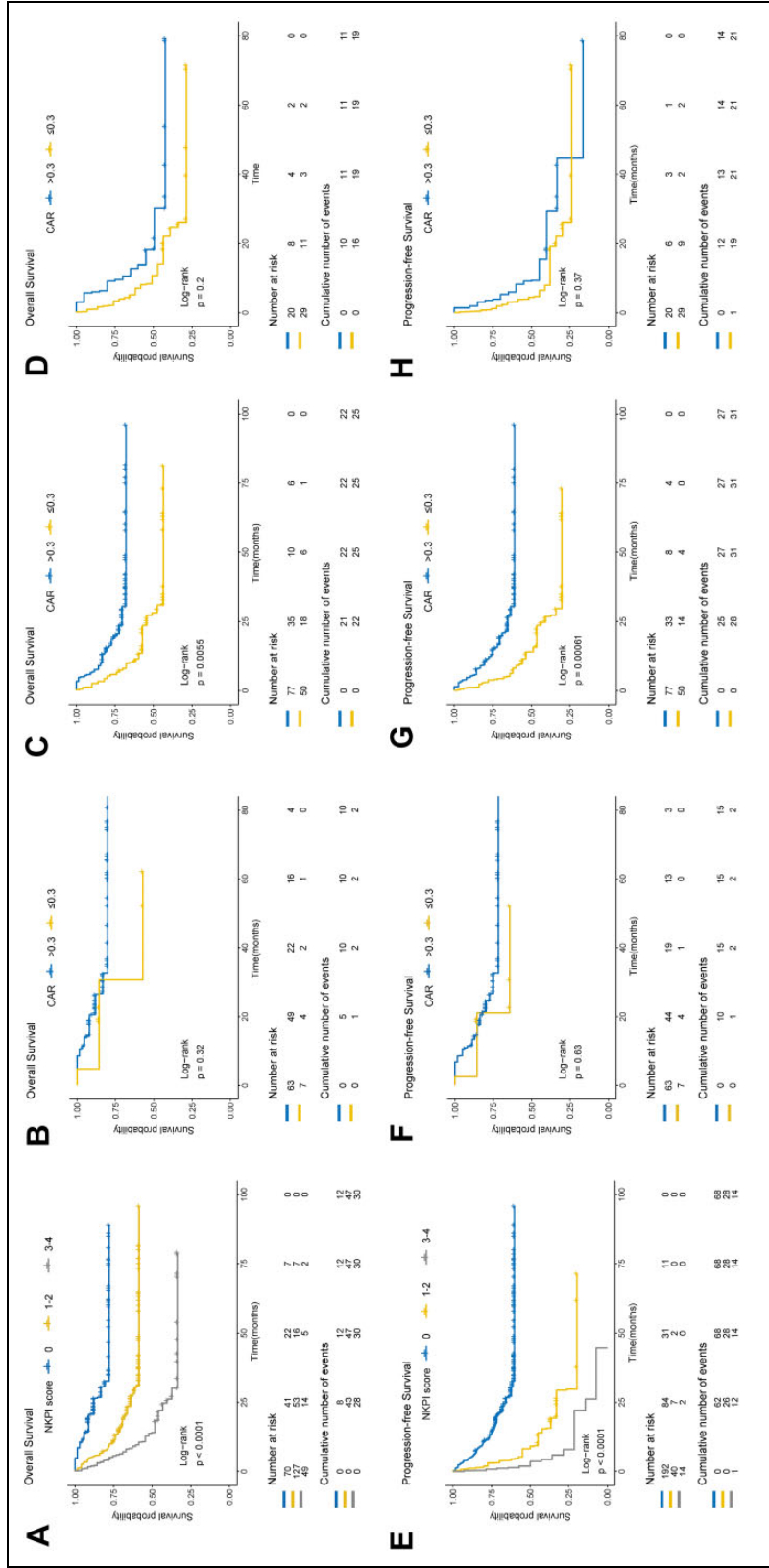


Figure 4. Prognostic impact of pretreatment C-reactive protein to albumin ratio (CAR) in patients with extranodal natural killer T-cell lymphoma (ENKTL) with different natural killer/T-cell lymphoma prognostic index (NKPI) score. A and E, Prognostic impact of NKPI score on overall survival (A) and progression-free survival (E). B and F, Prognostic impact of pretreatment CAR on overall survival (B) and progression-free survival (F) in patients with ENKTL with NKPI score 0. C and G, Prognostic impact of pretreatment CAR on overall survival (C) and progression-free survival (G) in patients with ENKTL with NKPI score 1-2. D and H, Prognostic impact of pretreatment CAR on overall survival (D) and progression-free survival (H) in patients with ENKTL with NKPI score 3 to 4.

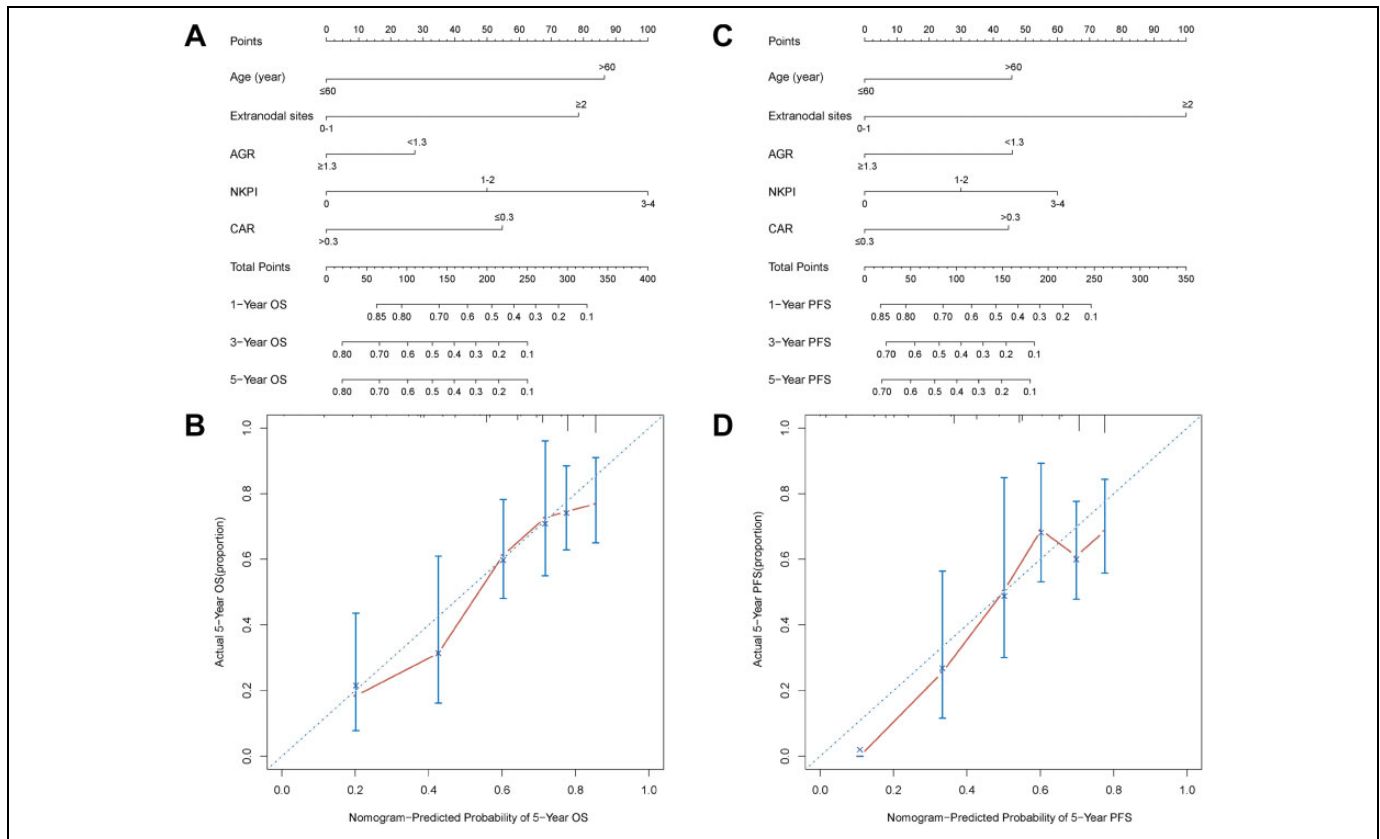


Figure 5. Nomogram for predicting overall survival (OS) and progression-free survival (PFS) in patients with extranodal natural killer T-cell lymphoma (ENKTL). A and C, To use the nomogram, the value attributed to an individual patient is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is then drawn downward to the survival axis to determine the 1-, 3-, 5-year OS (A) and 1-, 3-, and 5-year PFS (C) likelihood. B and D, Internal validation of the nomogram to predict 5-year OS and PFS likelihoods in patients with ENKTL. The nomogram-predicted probability of OS or PFS is plotted on the x-axis; the actual OS or PFS is plotted on the y-axis. AGR indicates albumin to globulin ratio; CAR, C-reactive protein to albumin ratio; ENKTL, extranodal natural killer T-cell lymphoma; NKPI, natural killer/T-cell lymphoma prognostic index.

previous studies; however, its value is also questioned recently because NKPI is derived from a cohort of patients with ENKTL mainly receiving anthracycline-based chemotherapy, and the NKPI might be further improved by other laboratory data. Hence, we enrolled 246 patients with ENKTL to confirm the prognostic value of CAR and examine the collaboration performance of CAR with NKPI or IPI. In the present study, we determined a cutoff value of 0.3 for CAR and demonstrated a significantly inferior clinical outcome in patients with ENKTL having high CAR (>0.3). Additionally, CAR in combination with NKPI was more powerful to predict the prognosis of ENKTL than NKPI alone or that in combination with IPI by applying a nomogram.

The impact of inflammation and nutrition status on the clinical outcome of various types of cancer has been generally proven. Typically, CRP and albumin are useful surrogate markers for inflammation and nutrition, respectively. In ENKTL, pretreatment serum CRP level was found to represent an independent predictor of clinical outcome, and the prognostic value of a prognostic model incorporating CRP level, age at diagnosis, hypoalbuminemia, and LDH level was demonstrated to be

superior to both IPI and NKPI.⁸ Glasgow Prognostic Score, a cumulative prognostic score based on CRP and albumin levels, was found superior to IPI and NKPI in discriminating patients with ENKTL having different outcomes in low-risk groups.⁷ However, these prognostic score models were potential to cause underestimation (a lower CRP level) or overestimation (a lower albumin level) of the prognostic evaluation in patients due to the qualitative nature of the scores. Recently, CAR, a novel prognostic index incorporating inflammation and nutrition status, was reported to predict survival in many types of cancer. Kinoshita et al first demonstrated a higher prognostic ability of CAR in hepatocellular carcinoma compared to other established inflammation-based prognostic scores including GPS and NLR.²⁴ Since then, Tsujino et al revealed that the CAR was superior to other inflammation-based prognostic scores, including NLR, PLR, GPS, and modified GPS (mGPS) to predict survival in renal cell carcinoma.²⁵ Liu et al reported a superior ability of CAR in predicting prognosis in gastric cancer with curative resection compared to NLR, PLR, GPS, mGPS, high-sensitivity mGPS, and systemic immune-inflammation index.²⁶ Xu et al also demonstrated a higher

predictive accuracy of CAR for esophageal squamous cell carcinoma compared to the NLR and PLR, but not mGPS.²⁷ Such findings supporting a remarkable prognostic value of CAR were repeatedly validated in many malignancies such as oral squamous cell carcinoma,²⁸ advanced pancreatic cancer,²² non-small cell lung cancer,²⁹ cervical cancer,³⁰ and bladder cancer.³¹ Collectively, most previous reports support that the prognostic ability of the CAR could be comparable even superior to that of other conventional inflammation-based prognostic scores including GPS, NLR, and NLR. However, the prognostic value of CAR in ENKTL has never been investigated as yet.

As a rare disease with poor prognosis, no standard treatment based on randomized control trials has been established yet for ENKTL, and the current practices were mainly driven from population-level data. Therefore, the search for effective predictive indicators could help clinicians find the most appropriate approach for patients and avoid overtreatment. In the present study, we divided patients into 2 groups using a cutoff value of 0.3 for CAR. Our data demonstrated a notable difference in clinical behaviors and survival outcome between the higher and lower CAR groups. Patients with ENKTL having low CAR were more likely to experience a inferior clinical outcome and significant adverse clinical events, including older age, underweight, inferior performance status, advanced cancer stage, elevated LDH, B symptoms, multiple extranodal involvement, regional node invasion, lower AGR, and higher IPI and NKPI scores. Additionally, more male patients were found to have a high CAR. Furthermore, after controlling these confounding variables, high CAR remained an independent predictor of poor OS and PFS. However, inconsistent with the present study, although high CAR was shown to be associated with a poor survival in limited-stage UAT NK/T-cell lymphoma, Song et al failed to be demonstrated as an independent predictor³² of which the inconsistency may be attributed to the different subtype of ENKTL. Another possible explanation for this inconsistency was that their study with a small sample size ($n = 100$) may be underpowered to examine the prognostic value of CAR in ENKTL. Moreover, in keeping with previous findings in ENKTL,^{9,16} the AGR, a frequently reported prognostic index which reflected the nature of both immunity and inflammation in diffuse large B-cell lymphoma,^{33,34} also maintained its independent prognostic value in ENKTL.

In this study, we also tried to apply pretreatment CAR to improve prognosis prediction of patients with ENKTL. After confirming the independent predictive value, we explored the prognostic role of CAR in different subgroups underlying several important prognostic systems for ENKTL including Ann Arbor stage, IPI, and NKPI. Ann Arbor stage was proved to be an independent prognostic factor for patients with ENKTL in most studies. In this study, lower stage was significantly associated with improved survival, although the stage was not shown as an independent predictor of survival. However, CAR, a simple and easily accessible laboratory parameter, was found to effectively separate patients either in the I + II or III + IV stages based on survival outcome (Figure 2). Despite the role of IPI, the prognosis of ENKTL remained controversial, and it

was a commonly used tool for risk stratification in non-Hodgkin lymphoma in clinical practice.¹² The newly proposed NKPI for ENKTL was reported to have better prognostic capability than the IPI.⁵ Consistent with previous studies, OS and PFS of patients in this study varied significantly by IPI and NKPI scores, and patients with lower scores generally had better prognosis. However, the predictive ability of these 2 prognostic systems were usually limited by the derived factors such as unbalanced distribution of different risk groups and differentiated chemotherapy regimens.¹ In addition, the factors included in these 2 prognostic systems were primarily related to tumor burden and patient characteristics, while the information on inflammation and nutrition status of patients was devoid. In accordance with the previous study,² our results revealed that the IPI placed most of patients (78%) in the low-risk group. However, the CAR was able to separate patients in the low-risk category of IPI based on survival outcome (Figure 3). Moreover, the CAR could also effectively separate patients in the intermediate-risk category of NKPI based on survival outcome, and a trend to separate patients in the high-risk category was observed. Collectively, these findings suggest that CAR may be a powerful prognostic indicator for ENKTL, and the prognostic performance of IPI and NKPI may be further improved by combining the CAR. Therefore, we developed nomograms to examine the prognostic capability of CAR incorporating IPI or NKPI in ENKTL. Our nomograms utilized independent predictors such as, age, extranodal site, AGR, CAR, and the 2 commonly used prognostic systems IPI and NKPI, which resulted in 2 prognostic nomograms: the IPI-based nomogram and NKPI-based nomogram. As the IPI had already comprised age and extranodal site, the IPI-based nomogram was constructed with AGR, CAR, and IPI. Another, the NKPI-based nomogram was constructed with age, extranodal site, AGR, CAR, and NKPI. Our results indicated that the NKPI-based nomogram had a favorable level of predictive accuracy with a C-index of 0.71 for OS and 0.70 for PFS compared to the IPI-based nomogram with a C-index of 0.69 for OS and 0.689 for PFS, which was supported by a calibration curve. Likewise, the NKPI-based nomogram appeared to have a better discrimination ability than the NKPI alone (C-index: 0.676 for OS and 0.669 for PFS). These findings suggested that the NKPI-based nomogram may be more powerful and suitable for predicting the prognosis of NKPI-based nomogram than the previous commonly used prognostic systems. With the consideration of potential influence of different chemotherapy regimens, our results indicated the predictive performance of NKPI-based nomogram in predicting OS tended to be favorable (C-index: 0.726) in patients receiving ASP-based chemotherapy compared to those receiving anthracycline-based chemotherapy (C-index: 0.709); however, the predictive performance of NKPI-based nomogram in predicting PFS in patients receiving ASP-based chemotherapy (C-index: 0.706) seemed to be nonsuperior to those receiving anthracycline-based chemotherapy (C-index: 0.717). Nevertheless, the applicability of the NKPI-based nomogram should be further validated due to the limited sample size in the subgroups.

Several limitations should be acknowledged. The main limitations were the retrospective design of this study and a small sample size from a single center, particularly the subgroup with different chemotherapy regimens. Therefore, prospective studies with a large number of samples are needed to confirm the prognostic value of CAR and NKPI-based nomogram proposed. Moreover, an external validation may improve our confidence to draw robust conclusions. Then, heterogeneity in treatment strategy and study population may have interfered with the interpretation of the results in this study. Additionally, stem cell transplant is an important approach for the treatment of ENKTL; however, the lack of relevant information in the study may possibly affect the results. Some important prognostic biomarkers reported in recent years, such as circulating EBV DNA and Ki-67 score, were not included as variables to construct the nomogram because these markers are not widely employed in the early-phase diagnosis and treatment. Nevertheless, some strengths of the current study are deserved to be highlighted as well. First, the predictive capability of the presently used prognostic systems and Ann Arbor stage is limited in predicting prognosis of patients with ENKTL. Although the NKPI was newly proposed for the prognostication of ENKTL, it might be powerless when subjected to individuals with nonanthracycline chemotherapy, which is likely to be improved by informative laboratory biomarkers as indicated by the present study. Second, CAR and AGR are both clinically feasible as reported by most studies concerning various types of cancer, and the measurement of CAR and AGR is noninvasive, easy to acquire, and affordable for the patients in clinical practice.

In conclusion, our study demonstrated that CAR was a powerful and independent predictor of survival outcomes in patients with ENKTL. The nomogram model incorporating CAR and NKPI may improve the prognosis prediction of patients with ENKTL. However, further studies are needed to focus on validating these findings, both externally and in a prospective manner.

Authors' Note

Quan-shu Di, Tao Xu, and Ying Song contributed equally to this work. Q. Di, G. Wan, and X. Cai contributed to conception and design. G. Wan and X. Cai contributed to administrative support. T. Xu and Y. Song contributed to provision of study materials or patients. J. Tang, W. Zhang, and C. Li contributed to collection and assembly of data. Q. Di, Z. Zuo, F. Cao, and X. Yu contributed to data analysis and interpretation. All authors contributed to manuscript writing and final approval of manuscript.

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