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ORIGINAL ARTICLE

Prognostic nomogram for overall survival in previously untreated patients with extranodal NK/T-cell lymphoma, nasal-type: a multicenter study

Y Yang[1,11], Y-J Zhang[2,11], Y Zhu[3], J-Z Cao[4], Z-Y Yuan[5], L-M Xu[5], J-X Wu[6], W Wang[6], T Wu[7], B Lu[7], S-Y Zhu[8], L-T Qian[9], F-Q Zhang[10], X-R Hou[10], Q-F Liu[1] and Y-X Li[1]

The aim of this study was to develop a widely accepted prognostic nomogram for extranodal NK/T-cell lymphoma, nasal-type (NKTCL). The clinical data from 1383 patients with NKTCL treated at 10 participating institutions between 2000 and 2011 were reviewed. A nomogram was developed that predicted overall survival (OS) based on the Cox proportional hazards model. To contrast the utility of the nomogram against the widely used Ann Arbor staging system, the International Prognostic Index (IPI) and the Korean Prognostic Index (KPI), we used the concordance index (C-index) and a calibration curve to determine its predictive and discriminatory capacity. The 5-year OS rate was 60.3% for the entire group. The nomogram included five important variables based on a multivariate analysis of the primary cohort: stage; age; Eastern Cooperative Oncology Group performance status; lactate dehydrogenase; and primary tumor invasion. The calibration curve showed that the nomogram was able to predict 5-year OS accurately. The C-index of the nomogram for OS prediction was 0.72 for both cohorts, which was superior to the predictive power (range, 0.56–0.64) of the Ann Arbor stage, IPI and KPI in the primary and validation cohorts. The proposed nomogram provides an individualized risk estimate of OS in patients with NKTCL.

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INTRODUCTION

Extranodal NK/T-cell lymphoma, nasal-type (NKTCL) is a rare disease globally;[1–5] however, it is the most common subtype of peripheral T-cell lymphomas in China.[6,7] This entity has an aggressive, remarkably variable clinical course: some patients have a long survival duration in the context of indolent disease, whereas other patients have a rapidly progressive course and die within 2–3 years.[3–15] The treatment outcomes of NKTCL are generally poor, and vary widely between the published series.[1–5,7–15] The 5-year overall survival (OS) rates in large cohort studies range from 30–86%, with most studies demonstrating rates of $< 50\%$.[1–5,7–12] The prognosis and optimal therapy of NKTCL remain inadequately defined. The Ann Arbor staging system, which was originally used in Hodgkin lymphomas, is useful to assess prognosis, and has also been widely adopted for non-Hodgkin's lymphomas. Patients are given one of four stages (I–IV), each with a distinct prognosis; however, the predictive accuracy of this system has been shown to be limited for NKTCL.[3,8] Although previous studies have identified important prognostic factors for NKTCL,[1–5,7–15] only a few studies have attempted to develop prognostic scoring systems that predict outcomes.[8,13–16] None has gained widespread acceptance, possibly because they were typically raised from small patient series that are collected over long periods, selected with inconsistent definitions of only certain prognostic factors, and included heterogeneous treatments.[1–3,8,13–15]

The visual format of nomograms means that they can provide a statistical predictive model that is readily understood by patients and their physicians. In accordance with this, it has been demonstrated in studies of several malignancies that nomograms permit improved predictive accuracy for clinical outcomes when compared with the use of pre-defined risk stratifications.[17–19] The main aims of this study were to identify prognostic factors for OS, to develop an easily applicable prognostic nomogram for the estimation of outcomes and to validate its predictive capacity in an independent cohort. To our knowledge, this is the first study to develop a NKTCL-specific nomogram based on a large cohort of patients. This study also evaluated whether this model can provide more accurate predictions of survival compared with currently available staging or prognostic scoring systems.

[1]Department of Radiation Oncology, Cancer Hospital and Institute, Peking Union Medical College (PUMC) and Chinese Academy of Medical Sciences (CAMS), Beijing, People's Republic of China; [2]Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China; [3]Zhejiang Cancer Hospital, Hangzhou, Zhejiang, People's Republic of China; [4]Shanxi Cancer Hospital, Taiyuan, Shanxi, People's Republic of China; [5]Cancer Hospital, Tianjin Medical University, Tianjin, People's Republic of China; [6]Fujian Provincial Cancer Hospital, Fuzhou, Fujian, People's Republic of China; [7]Guizhou Cancer Hospital, Guiyang, Guizhou, People's Republic of China; [8]Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, Hunan, People's Republic of China; [9]The Affiliated Provincial Hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China and [10]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, People's Republic of China. Correspondence: Professor Y-X Li, Department of Radiation Oncology, Cancer Hospital and Institute, Peking Union Medical College (PUMC) and Chinese Academy of Medical Sciences (CAMS), Panjiayuannanli, Chao District, Beijing 100021, People's Republic of China.
E-mail: yexiong12@163.com
[11]These authors contributed equally to this work.
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PATIENTS AND METHODS

Patients and study design

A cohort of 1383 patients with previously untreated NKTCL was recruited from 10 Chinese institutions between 2000 and 2011. All patients were diagnosed according to typical histological and immunophenotypic features of NKTCL, based on the World Health Organization classification.[20] Accordingly, tumor cells were negative for B-cell antigens (CD20 and CD79a), but positive either for CD3ε and CD56, or for CD3ε, cytotoxic molecules (granzyme-B, T-cell intracellular antigen-1 and perforin) and Epstein–Barr virus if cells were CD56-negative. Patients who did not have complete clinical information or immunohistochemistry, or who were lost to follow-up immediately after treatment, were excluded from this study. The primary cohort comprised 708 patients from North China, and the validation cohort consisted of an independent series of 675 patients from South China. This project was approved by our institutional review board.

Evaluation, definition and treatment

Pretreatment evaluations included a history and physical examination; endoscopy of the upper aerodigestive tract; routine biochemistry and lactate dehydrogenase (LDH); computed tomography scans of the chest, abdomen and pelvis, computed tomography and/or magnetic resonance imaging of the head and neck; and bone marrow examination. All patients were staged according to the Ann Arbor staging system, and were stratified according to the original International Prognostic Index (IPI) and Korean Prognostic Index (KPI).[8,16]

The primary site was defined according to the anatomical site of origin, including the nasal cavity, nasopharynx, paranasal sinus, tonsil, tongue base, oropharynx, hypopharynx, larynx, hard and soft palate, oral cavity, skin and soft tissue, gastrointestinal tract, testis and other extranodal sites. Primary tumor invasion (PTI) was defined as the presence of primary disease that extended into neighboring structures or organs, or the involvement of multiple, contiguous primary sites, regardless of either the stage or primary site.[7,9,11,21,22]

The majority of patients with stage I and II disease (86.6%) received combined modality treatment ($n=850$, 66.8%) or radiotherapy alone ($n=253$, 19.9%); only 13.4% received chemotherapy alone ($n=170$). Patients with stage III and IV disease received initial chemotherapy either with irradiation to the primary tumor ($n=40$, 36.4%) or without ($n=66$, 60.0%), or palliative radiotherapy ($n=4$, 3.6%). Radical radiotherapy was given with 6-MV or 8-MV linear accelerator. The median dose was 50 Gy with a range of 36–74 Gy, at a dose per fraction of 1.8–2 Gy. Of 1126 patients receiving chemotherapy, 767 (68.1%) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like regimens, 208 (18.5%) with asparaginase and/or gemcitabine contained regimens, and 151 (13.4%) with other dose-density regimens.

Construction and validation of the nomogram

In the design of the nomogram, we identified clinical features that have previously been demonstrated to be associated with survival, and incorporated these as prognostic features.[1–16,21–30] These factors included sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), Ann Arbor stage, PTI, B symptoms, LDH, regional lymph node involvement and primary disease site. For each factor, we used the multivariate Cox proportional hazards model to give the predicted 5-year OS. Nomogram validation comprised several stages. First internal validation was undertaken, with a concordance index (C-index) being estimated by analyzing the area under the curve of the receiver operating characteristic curve. Next, we constructed a calibration plot to determine whether the predicted and observed probabilities for survival were in concordance. Bootstrap resampling (1000 resamples) was used for this plot. Finally, we performed external validation, in which the nomogram was used to assess each patient in the validation cohort, and Cox regression analysis was performed using each patient's total score as an independent factor. The regression analysis was then used to derive the C-index and the calibration curve.

Statistical analyses

The primary end point was OS as calculated from the start of initial treatment until the time of death of any cause, or until the last follow-up. Survival curves were estimated with the Kaplan–Meier method and compared with a log-rank test stratified according to the prognostic factors. The nomogram was constructed based on the Cox model parameter estimates in the primary cohort. The selection of the final model was performed using a backward step down-selection process.

Table 1. Clinical characteristics of patients with extranodal NK/T-cell lymphoma, nasal-type

Characteristic	*All patients* No. (%)	*Primary cohort* No. (%)	*Validation cohort* No. (%)	P-*value*
Total	1383	708	675	
Sex				*0.405*
Male	971 (70.2)	490 (69.2)	481 (71.3)	
Female	412 (29.8)	218 (30.8)	194 (28.7)	
Age (years)				*0.001*
$\leqslant 60$	1189 (86.0)	630 (89.0)	559 (82.8)	
>60	194 (14.0)	78 (11.0)	116 (17.2)	
Primary site				*0.042*
UADT	1355 (98.0)	699 (98.7)	656 (97.2)	
Extra-UADT	28 (2.0)	9 (1.3)	19 (2.8)	
Ann Arbor stage				*< 0.001*
I	947 (68.5)	465 (65.7)	482 (71.4)	
II	326 (23.5)	186 (26.2)	125 (20.7)	
III	30 (2.2)	24 (3.4)	6 (0.9)	
IV	80 (5.8)	33 (4.7)	47 (7.0)	
Primary tumor invasion				*0.008*
Yes	751 (54.3)	360 (50.8)	391 (57.9)	
No	632 (45.7)	348 (49.2)	284 (42.1)	
B symptoms				*0.967*
Yes	557 (41.7)	295 (41.7)	282 (41.8)	
No	806 (58.3)	413 (58.3)	393 (58.2)	
Regional lymph node				*0.444*
Yes	417 (30.2)	220 (31.1)	197 (29.2)	
No	966 (69.8)	488 (68.9)	478 (70.8)	
Elevated LDH				*< 0.001*
Yes	472 (34.1)	279 (39.4)	193 (28.6)	
No	911 (65.9)	429 (60.6)	482 (71.4)	
ECOG score				*0.008*
0–1	1283 (92.8)	644 (91.0)	639 (94.7)	
$\geqslant 2$	100 (7.2)	64 (9.0)	36 (5.3)	
IPI				*0.548*
0–1	1216 (87.9)	615 (87.5)	601 (89.0)	
2	122 (8.8)	70 (9.5)	52 (7.7)	
3	34 (2.5)	17 (2.3)	17 (2.5)	
4–5	11 (0.8)	6 (0.7)	5 (0.8)	
KPI				*0.036*
Group 1	465 (33.6)	218 (30.8)	247 (36.6)	
Group 2	445 (32.2)	224 (31.6)	221 (32.7)	
Group 3	315 (22.8)	179 (25.3)	136 (20.2)	
Group 4	158 (11.4)	87 (12.3)	71 (10.5)	
Treatment				*< 0.001*
CT alone	236 (17.1)	99 (14.0)	137 (20.3)	
RT alone	257 (18.6)	180 (25.4)	77 (11.4)	
CMT	890 (64.4)	429 (60.6)	461 (68.3)	

Abbreviations: CMT, combined modality treatment; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; KPI, Korean Prognostic Index; LDH, lactate dehydrogenase; RT, radiotherapy; UADT, upper aerodigestive tract.

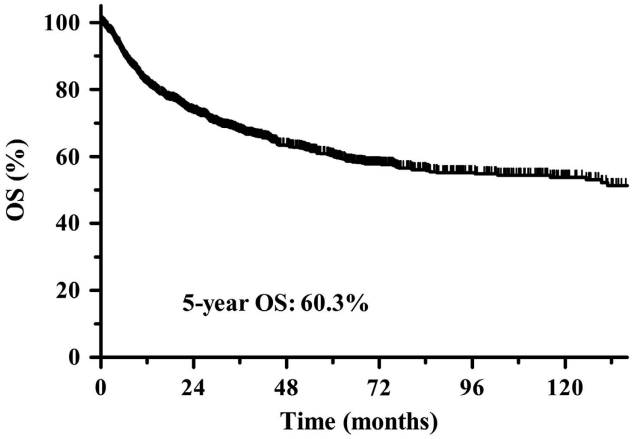

Figure 1. Kaplan–Meier overall survival (OS) curve for all 1383 patients included in the analyses.

Nomogram construction and validation were performed with Iasonos' guide.[31] Statistical analyses were performed using IBM SPSS Statistics, Version 20.0 and the *Hmisc, rms, survival ROC* package in R, version 3.0.2 (http://www.r-project.org/).

RESULTS

Clinical features and survival

The baseline characteristics of NKTCL patients in the study are listed in Table 1. There were more men than women (ratio, 2.36:1). The median age was 43 years (range, 7–87 years); only 14.0% of the patients were aged >60 years. Most patients (>90%), presented with early-stage disease, had good performance status (ECOG score, 0–1), and their primary disease was primarily located in the upper aerodigestive tract. Regional lymph nodes were involved in 30.2% of patients, and elevated LDH was present in 34.1% of patients. PTI was present in 54.3% of patients. The majority of patients were scored as low-risk according to the IPI (0–1, 87.9%) or low to low-intermediate risk groups using the KPI (groups 1–2, 65.8%). Similar clinical characteristics were observed in both cohorts (Table 1).

The median follow-up time was 46 months for surviving patients. The 5-year OS rate for the entire group was 60.3% (Figure 1), with 63.8% for the primary cohort and 56.5% for the validation cohort.

Nomogram development and internal validation

In the univariate analysis, the prognostic factors that predicted poor OS in the primary cohort were as follows: age >60 years; ECOG score ⩾2; elevated LDH; primary site outside the aerodigestive tract (extra-upper aerodigestive tract); regional lymph node involvement; stage II and III–IV disease; and the presence of PTI (Table 2). Multivariate analyses demonstrated that the Ann Arbor stage, ECOG score, LDH and PTI were independent risk factors for OS (Table 3).

A nomogram to predict 5-year OS was developed using the results from the multivariate analysis (Figure 2). As ECOG score, LDH, stage and PTI were independent risk factors that predicted survival in the multivariate analysis, these variables were included in the nomogram. In addition, considering the high associated hazard ratio (1.35), age was also incorporated into the model. The predictive accuracy for 5-year OS as measured by the C-index was 0.72 in the internal validation (Figure 3a). The calibration plot for the probability of 5-year OS showed a good correlation between the actual observed outcome and the prediction by the nomogram (Figure 3b).

Table 2. Overall survival in univariate analysis for patients with extranodal NK/T-cell lymphoma, nasal-type

Characteristic	*Primary cohort*		*Validation cohort*	
	5-year OS (%)	P-*value*	*5-year OS (%)*	P-*value*
Sex		*0.477*		*0.172*
Male	62.4		54.3	
Female	67.1		61.6	
Age (years)		*0.050*		*<0.001*
⩽60	64.6		59.2	
>60	57.2		42.7	
Primary site		*0.008*		*0.422*
UADT	64.2		56.5	
Extra-UADT	24.7		54.6	
Ann Arbor stage		*<0.001*		*<0.001*
I	72.5		62.3	
II	52.5		49.4	
III–IV	27.2		14.4	
Primary tumor invasion		*<0.001*		*<0.001*
Yes	54.1		46.5	
No	73.5		70.5	
B symptoms		*0.469*		*0.004*
Yes	61.7		48.8	
No	65.1		61.0	
Regional lymph node		*<0.001*		*<0.001*
Yes	49.4		45.2	
No	70.2		60.3	
Elevated LDH		*<0.001*		*<0.001*
Yes	55.2		40.8	
No	69.6		63.0	
ECOG score		*<0.001*		*<0.001*
0–1	66.0		59.2	
⩾2	40.6		10.1	
IPI		*<0.001*		*<0.001*
0–1	67.0		60.4	
2	46.3		33.4	
3	32.6		0	
4–5	0		0	
KPI		*<0.001*		*<0.001*
Group 1	73.4		69.6	
Group 2	69.4		53.6	
Group 3	56.9		50.9	
Group 4	38.5		26.9	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; KPI, Korean Prognostic Index; LDH, lactate dehydrogenase; UADT, upper aerodigestive tract.

External validation of nomogram for OS

The nomogram was externally validated by the calibration plot in Figure 4, and by computing the bootstrap C statistic in an independent validation cohort of 675 patients. The C-index of the nomogram for the prediction of the 5-year OS was 0.72 in the external validation step (Figure 4a), which demonstrated that it is

a model with a good level of discriminative ability. The calibration curve suggests that the nomogram was well calibrated; the 5-year OS showed an optimal agreement between the actual observation and the nomogram prediction (Figure 4b).

Comparison of the predictive accuracy for OS between the nomogram and current staging or prognostic scoring systems

As shown in Figure 5, the Ann Arbor stage, IPI and KPI showed good levels of prognostic stratification between low-risk and high-risk patients in both cohorts. However, the Ann Arbor stage was unsatisfactory for the stratification of patients with stage III or IV disease (Figures 5a and b). Patients with stage III and IV disease had an extremely poor prognosis, with a chance of surviving up to 5 years from treatment of $< 30\%$. In addition, the IPI was not satisfactory for discriminating between intermediate-high risk and high-risk patient groups in both cohorts (Figures 5c and d). Furthermore, the KPI was unsatisfactory for stratifying between group 1 and group 2 patients in the primary cohort or between group 2 and group 3 patients in the validation cohort (Figures 5e and f).

When compared with the Ann Arbor stage, IPI and KPI, the nomogram displayed better levels of accuracy for predicting survival in both cohorts. The C-index of the nomogram in the primary cohort (0.72) was higher than the Ann Arbor stage (0.64), IPI (0.56) and KPI (0.63). Similarly, in the validation cohort, the C-indices of the Ann Arbor stage (0.60), IPI (0.58) and KPI (0.63) were lower than that of the nomogram (0.72). These results suggest that the nomogram was a more accurate and useful tool for the prediction of OS in patients with NKTCL.

Table 3. Multivariate analysis of 708 patients in the primary cohort

	Overall survival		
Variable	*HR*	*95% CI*	P-*value*
Ann Arbor stage			
I			
II	1.86	1.40–2.46	< 0.001
III–IV	3.60	2.46–5.26	< 0.001
Primary tumor invasion (yes vs no)	1.78	1.37–2.32	< 0.001
Age (>60 vs $\leqslant 60$)	1.35	0.93–1.98	0.116
Elevated LDH (yes vs no)	1.33	1.03–1.72	0.030
ECOG score ($\geqslant 2$ vs 0–1)	1.84	1.28–2.64	0.001

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase.

DISCUSSION

The rarity of the NKTCL as a clinical entity means that any attempts to create predictive models to give an indication of prognosis will be extremely challenging. It is therefore perhaps unsurprising that efforts to date have given variable results.[8,13–15,25] We developed a nomogram specific to previously untreated patients with NKTCL presenting at 10 Chinese institutions. The nomogram aimed to estimate the probability of 5-year OS based on a multivariate Cox proportional hazards model that included five clinical variables measured at presentation. Based on a large patient population, the nomogram has been validated as a reliable tool to predict survival in these patients, independent of treatment, and has been shown to be superior to Ann Arbor staging, IPI or KPI. Furthermore, the clinical variables that we have incorporated into the nomogram will be documented by any physician caring for patients with NKTCL, enhancing its practical utility.

Extranodal NKTCL is a heterogeneous disease, and several clinical features have emerged as important prognostic factors over the last 10 years.[4–15,21–30] Our nomogram utilizes clinically significant variables that have been previously associated with outcomes for NKTCL,[1–4,7–12] as well as other variables that we believed to be potentially relevant based on our experience and that of other clinicians.[7,11,26–30] The final nomogram model consisted of five variables from routine clinical practice: Ann Arbor stage, ECOG performance status, age, LDH and PTI. The most significant factor with regard to prognostic relevance to OS in the multivariate analysis was the Ann Arbor stage (I, II vs III/IV). In contrast to current staging or prognostic scoring systems, the NKTCL-specific nomogram included PTI as a novel independent predictive factor for OS. It should be emphasized that patients with NKTCL may present with local invasion of the primary tumor, which extends into adjacent anatomic structures or organs; for example, 20–60% of patients have paranasal extension or local tumor invasion (defined as T3 or T4 according to the TNM classification).[7,8,12,25–27] Therefore, the evaluation of the extent of primary tumor and its local invasion is important to assess the prognosis of this particular extranodal lymphoma. Many studies, including those from our group, have reported a prognostic effect of extensive primary disease on outcome in NKTCL.[7–9,12,21–23,27–30] The presence of paranasal extension or local tumor invasion has been demonstrated to be associated with poor outcomes for NKTCL.[7–9,12,21–23,27–30] Similarly, other studies have also reported that bulky disease is significantly associated with shorter survival durations for other lymphomas, such as Hodgkin lymphoma and diffuse large B-cell lymphoma.[32,33] Based on these findings, PTI

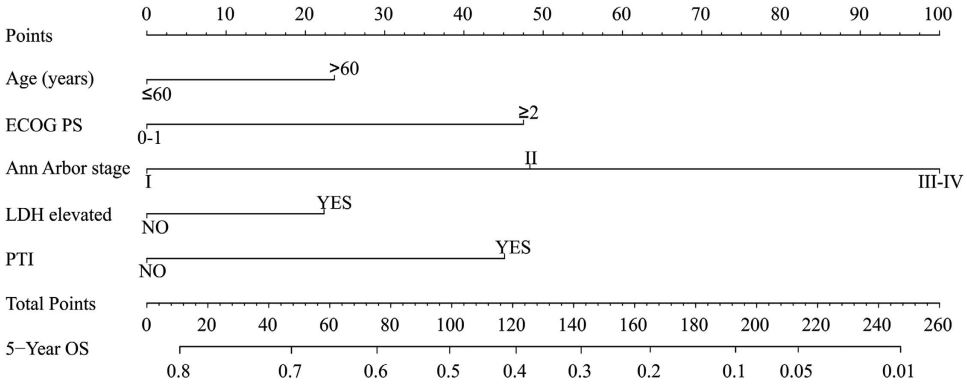

Figure 2. Nomogram for patients with extranodal NK/T-cell lymphoma, nasal-type. To use the nomogram, the value attributed to an individual patient is located on each variable axis, and a line is drawn upwards to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and a line is then drawn downwards to the survival axis to determine the 5-year OS likelihood. ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, pretreatment level of serum lactate dehydrogenase; PTI, primary tumor invasion; OS, overall survival.

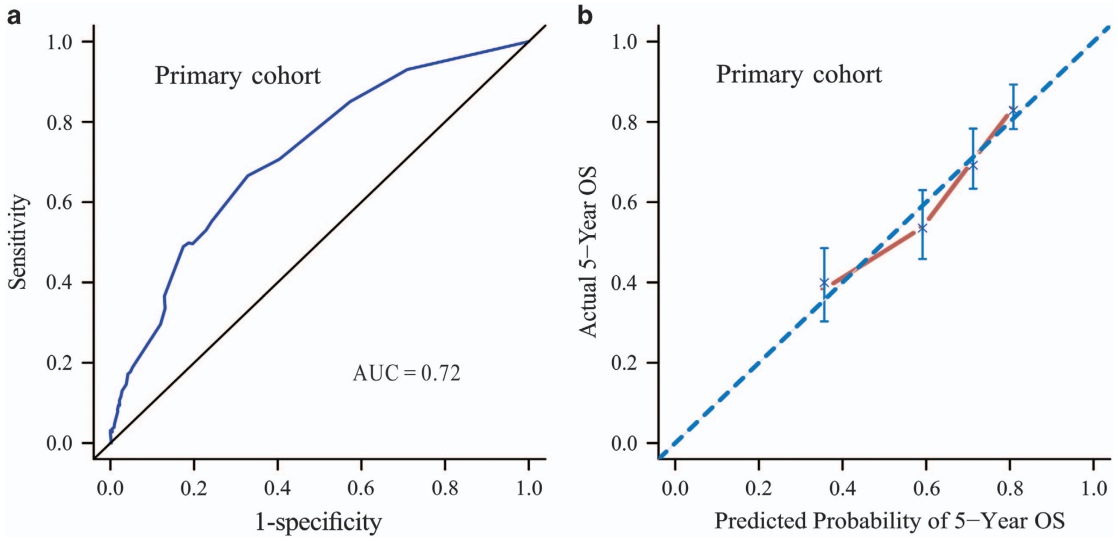

Figure 3. Internal validation of the nomogram to predict overall survival (OS) likelihoods in patients with extranodal NK/T-cell lymphoma, nasal-type in the primary cohort. Discrimination: the area under the receiver operating characteristic (ROC) curve (AUC) was 0.72 (**a**). Calibration: the calibration curve for the prediction of 5-year OS (**b**); the nomogram-predicted probability of OS is plotted on the *x* axis; the actual OS is plotted on the *y* axis.

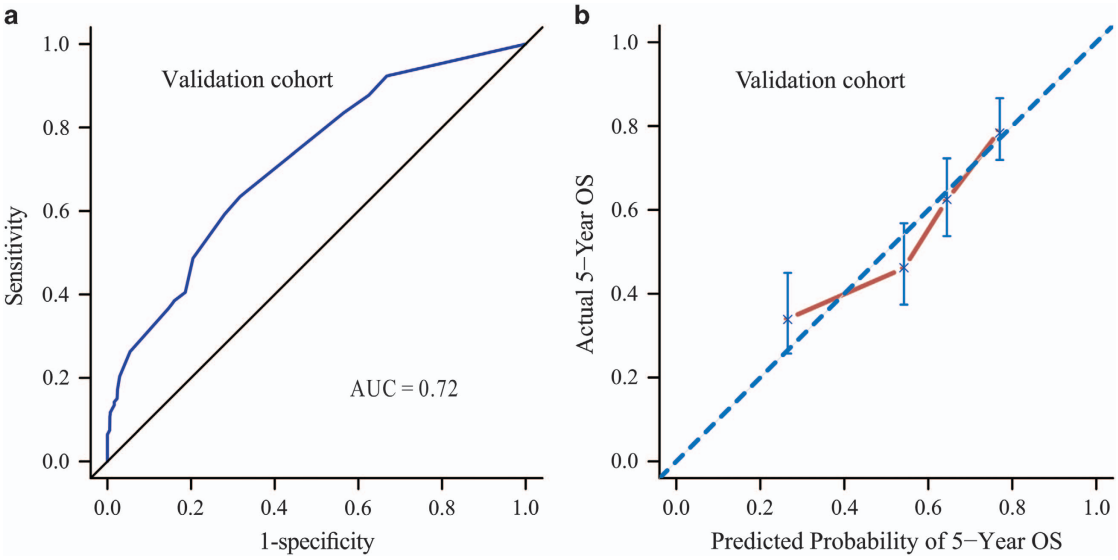

Figure 4. External validation of the nomogram to predict overall survival (OS) likelihoods in patients with extranodal NK/T-cell lymphoma, nasal-type in the validation cohort. Discrimination: the area under the receiver operating characteristic (ROC) curve (AUC) was 0.72 (**a**). Calibration: the calibration curve for the prediction of 5-year OS (**b**); the nomogram-predicted probability of OS is plotted on the *x* axis; the actual OS is plotted on the *y* axis.

may be viewed as a new marker of tumor load for NKTCL, and its incorporation into our nomogram can contribute to improvements in risk stratification and better informed treatment decisions. As our aim was to generate a predictive tool for use at initial presentation and diagnosis, we chose not to include the potential impact of different treatment modalities in the prognostic analysis. Further studies should aim to stratify patients into different risk categories and establish a risk-adapted therapy for early-stage NKTCL.

The effects of several separate clinical variables are integrated by a nomogram to give an individualized risk assessment for each patient. The benefits of this methodology, compared with standard staging systems or prognostic scores, are clear from studies in several clinical settings.[17–19] Similar to these studies, our analysis of the newly developed nomogram for the prediction of OS in patients with NKTCL indicated that it had a favorable level of predictive accuracy compared with the Ann Arbor staging system, IPI and KPI. The C-index for the nomogram was 0.72 in both the primary and validation cohorts, whereas the C-indices of the Ann Arbor stage, IPI and KPI were all $\leqslant$0.64 (range, 0.56–0.64). Consistent with previous studies,[2,7,12,29] patients with NKTCL in this series were predominantly young males with early-stage disease and good performance status, which placed the majority of patients in the low-risk groups (0–1) according to the IPI or KPI. Only a small proportion ($<$15%) of patients with NKTCL were categorized as high-risk by the IPI or KPI. The Ann Arbor stage, IPI and KPI assign patients to four risk groups with different predicted survivals, but are not sufficient to segregate patients into risk groups for NKTCL and cannot consistently predict prognosis.[12,15,24] The Kaplan–Meier curves for OS in this series

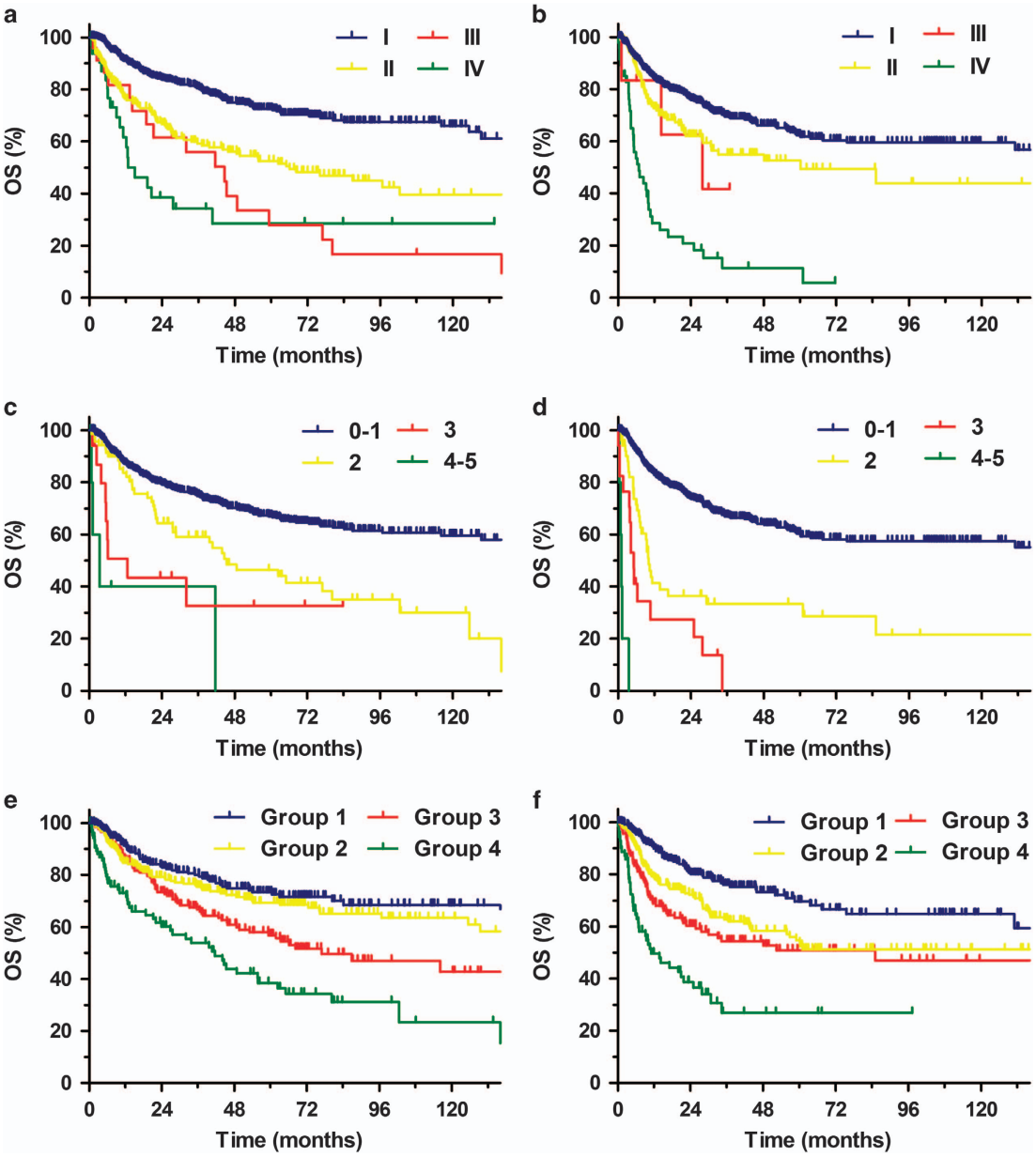

Figure 5. Kaplan–Meier survival curves of the primary cohort according to the Ann Arbor stage (**a**), International Prognostic Index (**c**) and Korean Prognostic Index (**e**); and the validation cohort according to the Ann Arbor stage (**b**), International Prognostic Index (**d**) and Korean Prognostic Index (**f**).

showed a convergence between Ann Arbor stage III and IV disease, intermediate-high and high-risk categories according to the IPI, and group 1 and group 2 or group 3 risk categories according to the KPI.

Although the nomogram model demonstrated good levels of accuracy for the prediction of OS, there are some limitations to our model. First, the prognostic factors we used were restricted to common clinical features; some potential biomarkers, such as Ki-67 scores, cyclooxygenase-2 and circulating Epstein–Barr virus-DNA were not included as variables in the nomogram.[34–37] However, the results of immunohistochemical staining are often inconsistent, assays for many biological or molecular markers are not widely available, and it may be difficult to standardize such results across clinical practice.[34–38] Second, because the current study was principally performed from within the endemic area (China), it remains unclear whether this nomogram can be applied to patients from other geographical regions or non-endemic areas, such as Western countries. As more effective diagnostic and therapeutic strategies emerge for this challenging condition,[10,39–42] these too will require reassessment in the context of the prognostic tool we have developed. The refinement of the nomogram, with the identification of additional clinical, pathological or molecular predictors, will permit the optimization of this model.[36–38]

In conclusion, we have developed and externally validated a nomogram that can predict 5-year OS for NKTCL with a high degree of accuracy based on a large cohort of affected patients from within the endemic area. The proposed nomogram shows a better level of discrimination than the Ann Arbor stage, IPI and KPI, and also provides an individual estimation of risk for patients with NKTCL. Additional studies are required to determine whether this nomogram can be applied to other patient groups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YXL designed the research; YXL, YY and QFL collected and analyzed the data; YJZ, YY and YXL wrote the paper; all authors provided study materials or patients and approved the paper.

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