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A novel prognostic nomogram based on imaging and molecular parameters for newly diagnosed extranodal natural killer/T-cell lymphoma patients

Running Title: SEC nomogram predicts prognosis of ENKTL

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Contributions
JR and XZ conceived and designed the study. DH, QL, FL, and SL collected and analyzed the data. DH, JR, JX and BL were involved in drafting the manuscript. LL, NM, YD, YZ, SZ, ST, WH, LR, and LG reviewed the manuscript. XZ, JR, and DH had full access to all the data in the study. All authors revised the manuscript and approved the final manuscript as submitted.

Data sharing statement

All data have been included in this article and supporting information

Declaration of interests
All authors declare no competing interests.

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Extranodal natural killer/T-cell lymphoma (ENKTL) is a highly aggressive non-Hodgkin lymphoma strongly associated with Epstein-Barr virus (EBV) infection and is characterized by a high relapse rate.[1] Recently, the 5-year overall survival (OS) of the limited-stage ENKTL has increased to 72% to 74% owing to the introduction of a novel strategy of concurrent chemoradiotherapy.[2] However, the 5-year OS in advanced-stage disease remains around 15–25%.[3] Thus, risk-adapted therapy plays a pivotal role in improving the survival of newly diagnosed patients.[4] Therefore, a better risk classification model could assist in precisely stratifying patients with ENKTL into risk groups and formulating appropriate individualized treatments to improve patient prognosis.

Several risk scoring systems for newly diagnosed ENKTL patients are currently available in clinical practice, including the International Prognostic Index (IPI), the Korean Prognostic Index (KPI), the prognostic index for natural killer lymphoma with or without EBV-DNA (PINK/PINK-E), and the nomogram-revised risk index (NRI).[5-8] Among these systems, the PINK-E is the only scoring system that includes the data from EBV-DNA and is widely used in clinical practice. Several studies have demonstrated the good prognostic value of EBV-DNA and maximum standardized uptake value (SUVmax) in patients with ENKTL.[9-12] However, no risk classification model has used the SUVmax in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and the quantitative value of EBV-DNA. Our previous work has integrated circulating tumor DNA (ctDNA) into the PINK-E to construct the PINK-EC model, which could overcome the poor discrimination efficiency of PINK-E for patients with the low-risk and intermediate-risk groups.[13] However, compared with the classic PINK-E system, our new PINK-EC model showed only slight improvement in terms of Harrell's C-index for OS, which might not satisfy personalized clinical demand. Therefore, a more accurate and precise risk classification model is urgently needed. Here, we developed a nomogram model (we named it SEC, inspired by the initials of "SUVmax", "EBV-DNA" and "ctDNA"), that included the semiquantitative radiomic parameter SUVmax and quantitative molecular parameters such as EBV-DNA and ctDNA to accurately stratify newly diagnosed ENKTL patients for optimal personalized treatment and management.

In this study, 91 patients newly diagnosed with ENKTL were enrolled at Xinqiao Hospital between February 2017 and November 2023 (ClinicalTrials identifier: ChiCTR1800014813). The data collected at diagnosis as previously described,[13,14] included age, gender, B-symptoms, Eastern Cooperative Oncology Group performance status (ECOG PS), primary site, regional lymph node involvement, distant lymph node involvement, numbers of extranodal sites, serum lactate dehydrogenase (LDH), whole blood EBV-DNA copy number, ^{18}FDG PET/CT SUVmax value, ctDNA concentration. In this study, we extended the follow-up time to the date of this analysis. The methodology of ctDNA measurements was as previously reported[13]. This study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT-20,180,005).

Based on the conventional cutoff value, continuous variables such as age and LDH

were divided into two categories. The ideal cutoff values for SUVmax, ctDNA, and EBV-DNA for survival prediction were determined by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Progression-free survival (PFS) was calculated from diagnosis to disease progression, death from any cause, or the date of last follow-up. OS was measured from the date of diagnosis to the date of death due to any cause or the date of the last follow-up. Survival time was estimated using Kaplan-Meier survival curves and compared by log-rank tests. Univariate and multivariate analyses and calculations of hazard ratio (HR) with 95% confidence interval (95% CI) were performed using the Cox regression model. A nomogram was generated based on the independent predictors of survival outcomes determined by univariate and multivariate analyses. A calibration curve (1000 bootstrap resamples) was constructed to assess the consistency between the predicted and observed survival. The discriminatory ability of the model was evaluated by Harrell's C-index. A time-dependent ROC curve was used for the comparison of risk stratification for these prognostic models. All the statistical analyses were performed with IBM SPSS statistical software (version 25.0; IBM Inc., NY, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P<0.05$ was considered statistically significant.

The baseline characteristics of the whole cohort were listed in Online Supplementary Table S1. The optimal cutoff values determined by the ROC analysis for SUVmax, EBV-DNA, and ctDNA were 9.950, 1.4×10^4 copies/mL, and 4.026 log hGE/mL, respectively (Figure 1).

According to the univariate and multivariate Cox regression analyses, the outcomes showed that only the SUVmax, EBV-DNA, and ctDNA concentration were independent prognostic factors for OS (Figure 2A). We did not include LDH in the nomogram construction considering the inconsistent identification of LDH >245 U/L as a risk factor in univariate and multivariate Cox regression analyses. We created a prognostic nomogram SEC to predict the 3- and 5-year OS of ENKTL patients based on the SUVmax, ctDNA, and EBV-DNA level (Figure 2B).

To clarify the predictive ability of the SEC score, calibration plots were generated, and the results demonstrated satisfactory consistency between the nomogram prediction for OS and the actual observation (Figure 3A-B). Harrell's C-index of SEC for PFS and OS prediction was 0.771 (95% CI, 0.710–0.831) and 0.817 (95% CI, 0.768–0.866), respectively, which were better than those of the IPI, KPI, PINK, PINK-E and PINK-EC (Online Supplementary Table S2). These results suggest that the SEC is a more accurate and powerful tool for the prediction of PFS and OS in patients with ENKTL.

To visually display the stratification power of the SEC in ENKTL patients, Kaplan-Meier analysis was performed to evaluate survival outcomes. According to the nomogram, the largest contributing component was less than twice the size of the smallest, and thus, we assigned equal weights, namely 1 point for each risk factor. Patients were stratified into three risk groups based on the SEC score: low risk (0), intermediate risk (1–2), and high risk (3). The 3-year PFS rates of patients in the low-, intermediate- and high-risk groups were 100% (95% CI, NA), 52.6% (95% CI, 39.4–

70.3), and 4.2% (95% CI, 0.6–28.6), respectively, and the 3-year OS rates of patients in the three groups were 100% (95% CI, NA), 62.2% (95% CI, 48.6–79.6), and 4.5% (95% CI, 0.7–30.4), respectively. Furthermore, a pairwise comparison analysis showed that the SEC could discriminate the intermediate-risk group from the low-risk group (PFS: HR = NA; P = 0.003; OS: HR = NA, P = 0.015) and the high-risk group (PFS: HR = 3.424, 95% CI, 1.718–6.824; P < 0.001; OS: HR = 4.965; 95% CI, 2.287–10.777; P < 0.001) (Figure 3C-D).

To further evaluate the risk stratification power of the SEC with current prognostic scoring systems in ENKTL patients, the IPI, KPI, PINK, PINK-E, and PINK-EC also divided patients into three risk groups (Online Supplementary Table S3). Next, time-dependent ROC curves were plotted, and the corresponding AUC was calculated to compare the predictive accuracy of SEC with that of the IPI, KPI, PINK, PINK-E, and PINK-EC. The AUCs of PFS and OS for SEC were greater and more stable than those of the other five prognostic models (Figure 3E-F).

The nomogram SEC was the first to use three semiquantitative or quantitative parameters with specific numerical cutoff values and could distinguish low-, intermediate-, and high-risk stratification well. The good survival of low-risk patients classified by the SCE model proved that they benefited significantly from the available therapies. The prognosis of high-risk patients distinguished by the SEC model was extremely poor, with 3-year PFS and OS values of only 4.2% and 4.5%, respectively, which indicated that we need to develop more effective treatment options. Compared with IPI, KPI, PINK/PINK-E, or PINK-EC, the nomogram SEC had better prognostic prediction, risk stratification, and clinical use. Moreover, we are conducting further validation of the model in a multicenter trial for the rare morbidity of ENKTL.

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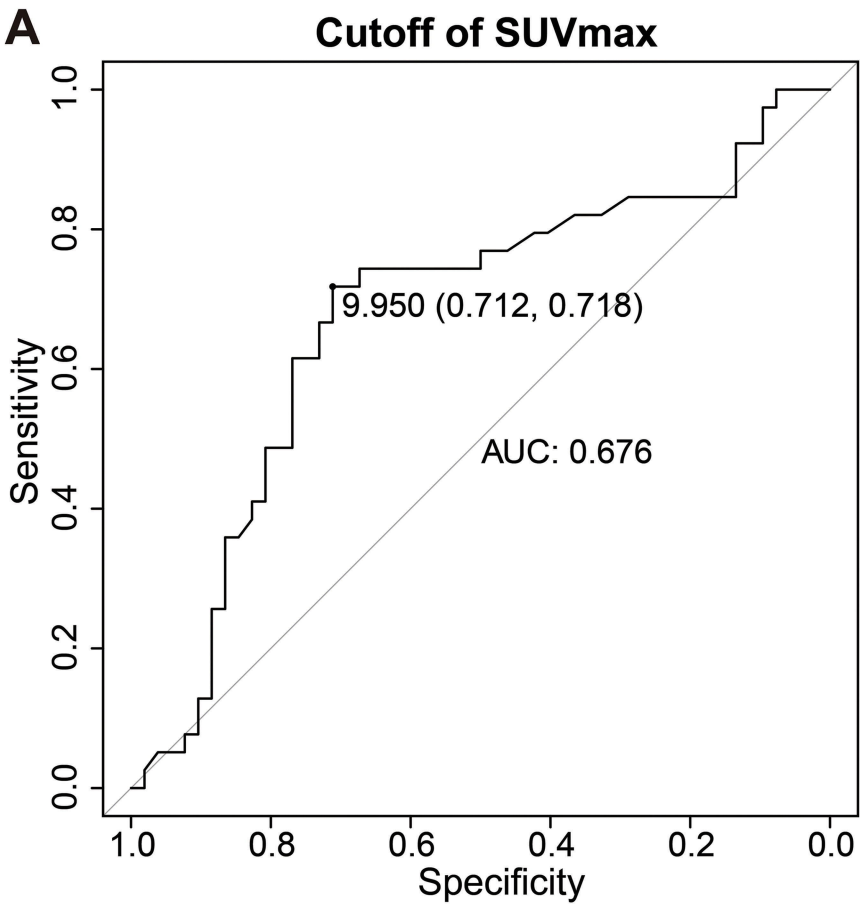
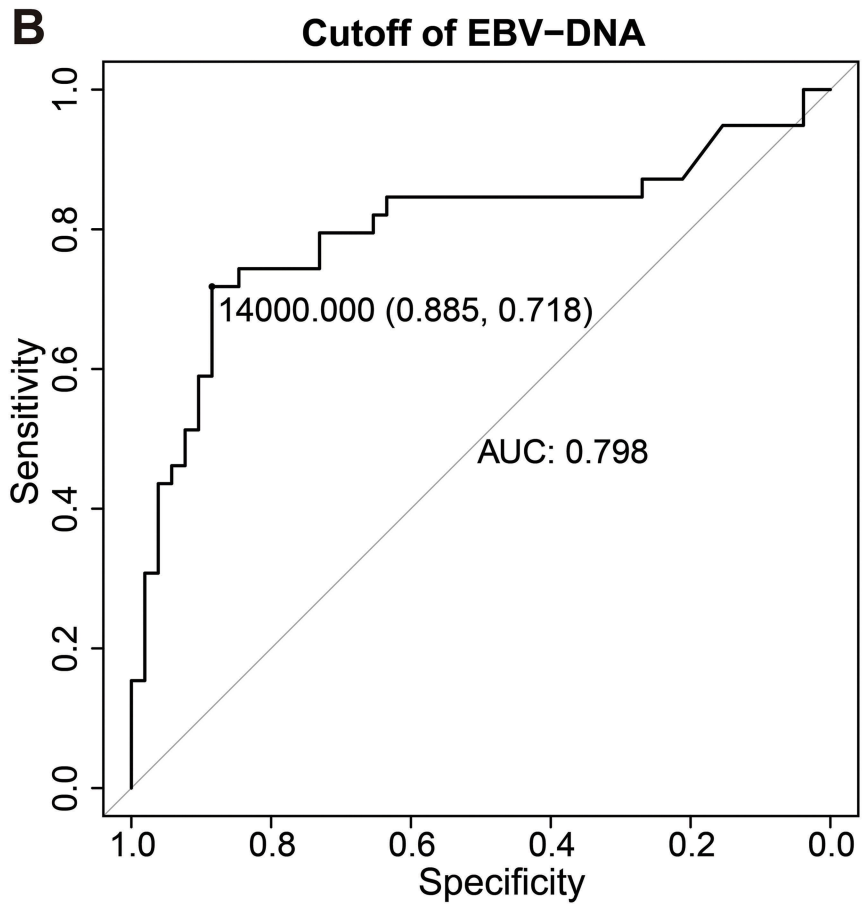
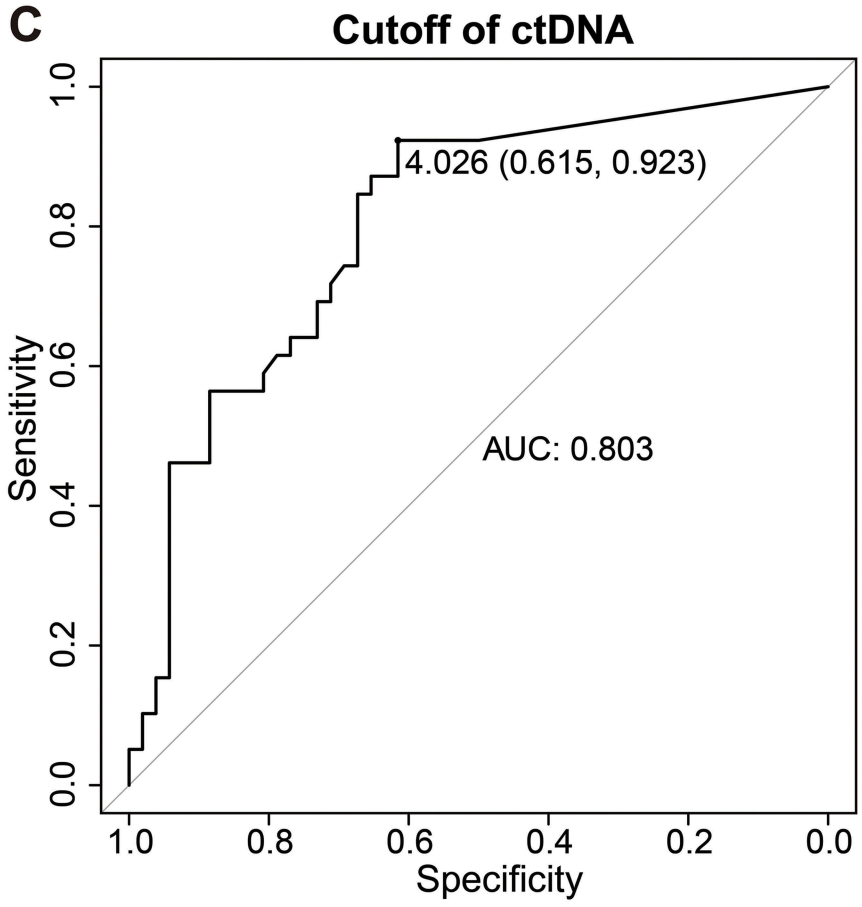
Figure 1. The cutoff values of prognostic parameters for OS. (A) standardized uptake value (SUVmax); (B) Epstein-Barr virus (EBV)-DNA; (C) circulating tumor DNA (ctDNA). OS: overall survival; AUC: area under the curve.

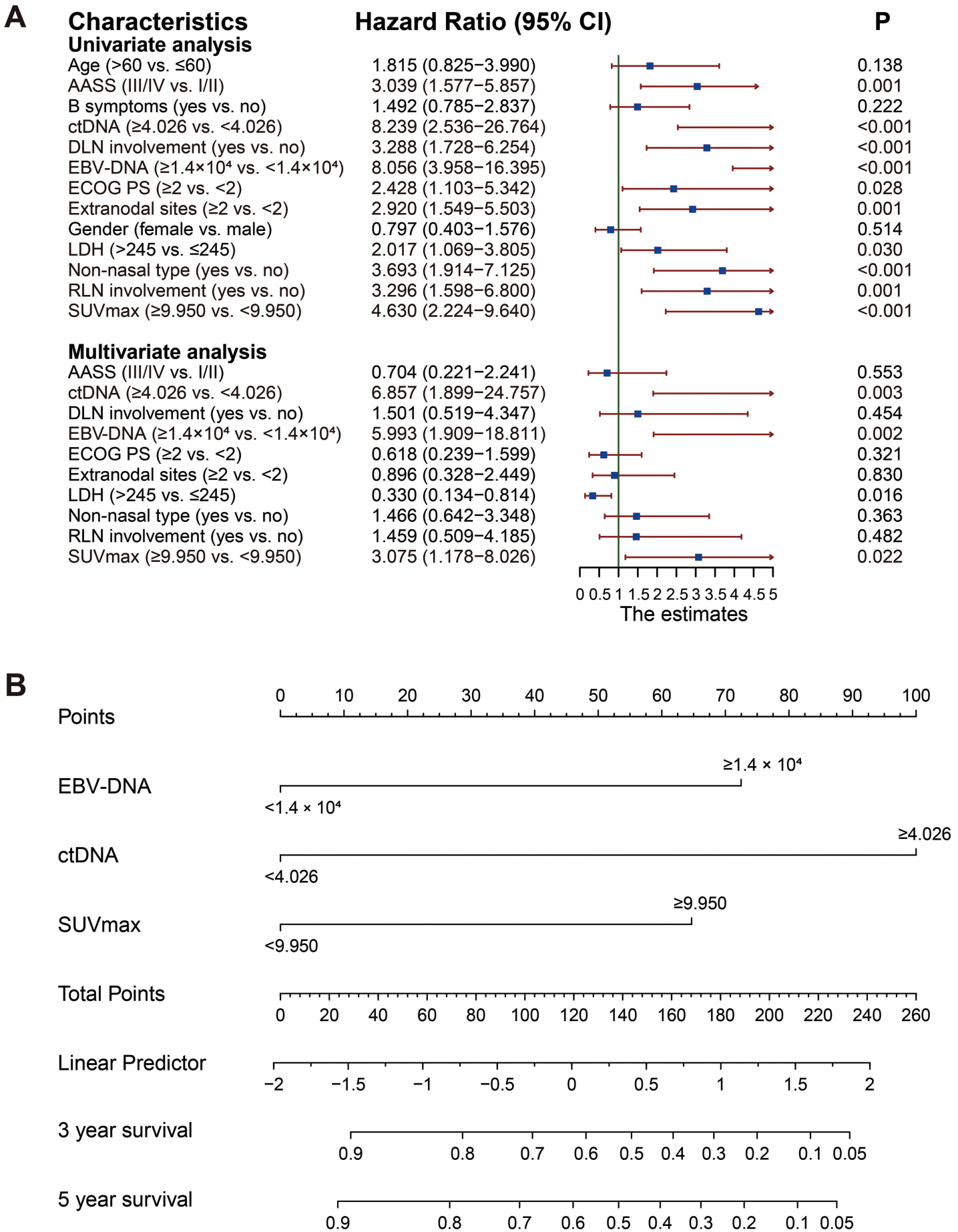
Figure 2. Nomogram constructed by SUVmax, EBV-DNA and ctDNA for newly-diagnosed ENKTL patients. (A) Univariate and multivariate Cox analysis reveals SUVmax, EBV-DNA and ctDNA are independent prognosis factors for overall survival (OS) in ENKTL patients. (B) Nomogram SEC for newly-diagnosed ENKTL patients. SUVmax: standardized uptake value; EBV: Epstein–Barr virus; ctDNA: circulating tumor DNA; ENKTL: extranodal natural killer/T-cell lymphoma; AASS: Ann Arbor staging system; DLN: distant lymph node; ECOG PS: eastern cooperative oncology group performance status; LDH: lactate dehydrogenase; RLN: regional lymph node.

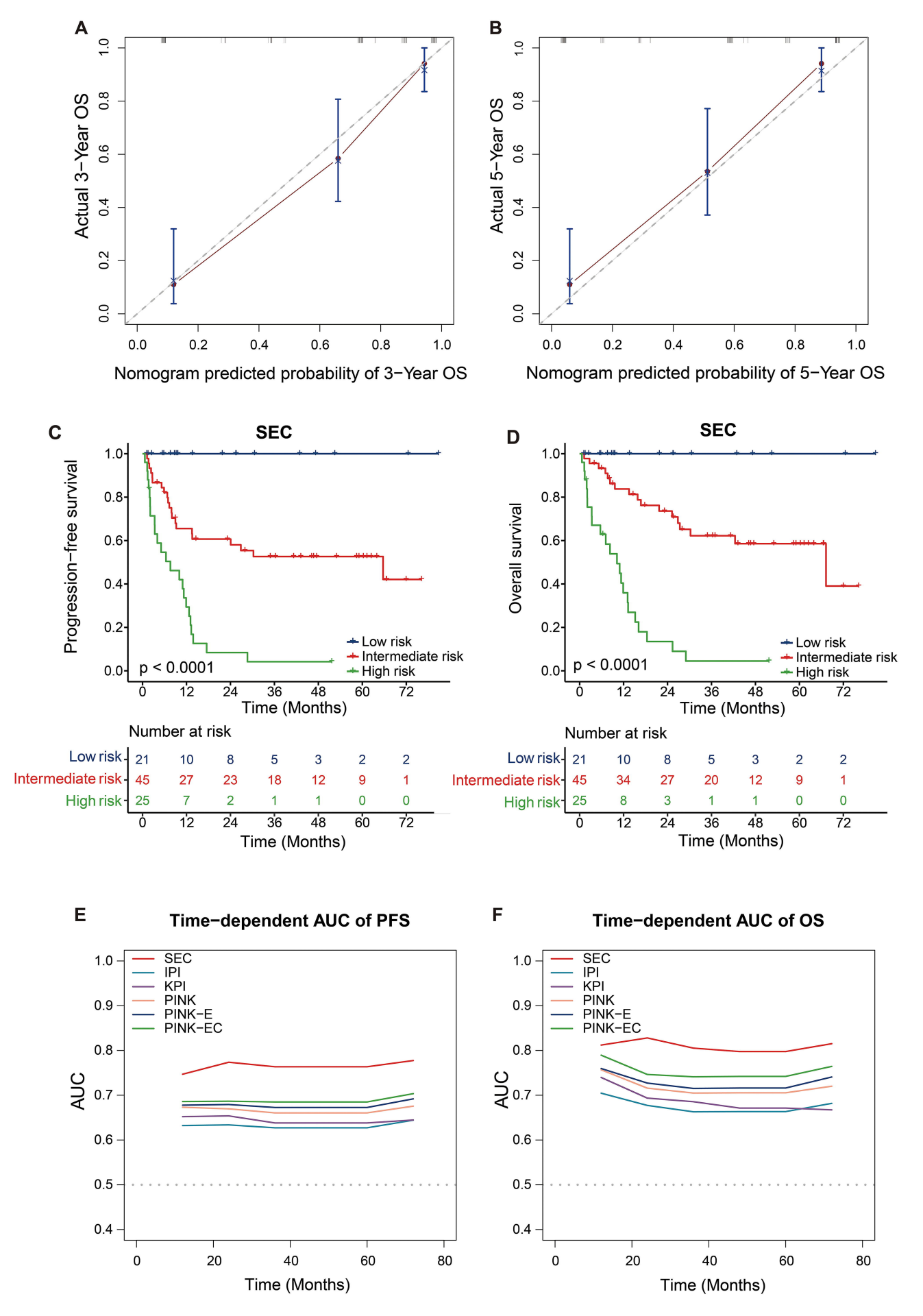
Figure 3. Risk stratification ability and evaluation of nomogram SEC. Calibration curves for the prediction of 3-year (A) and 5-year (B) overall survival (OS). Kaplan-Meier survival analysis shows the differences of progression-free survival (PFS) (C) and OS (D) among the three risk stratifications of SEC. Time-dependent area under the curve (AUC) comparison for different models of PFS (E) and OS (F).


A
Cutoff of SUVmax
9.950 (0.712, 0.718)
AUC: 0.676
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0


B
Cutoff of EBV−DNA
14000.000 (0.885, 0.718)
AUC: 0.798
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0


C
Cutoff of ctDNA
4.026 (0.615, 0.923)
AUC: 0.803
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0.0


A
Characteristics
Hazard Ratio (95% CI)
P
Univariate analysis
Age (>60 vs. ≤60) 1.815 (0.825−3.990) 0.138
AASS (III/IV vs. I/II) 3.039 (1.577−5.857) 0.001
B symptoms (yes vs. no) 1.492 (0.785−2.837) 0.222
ctDNA (≥4.026 vs. <4.026) 8.239 (2.536−26.764) <0.001
DLN involvement (yes vs. no) 3.288 (1.728−6.254) <0.001
EBV-DNA (≥1.4×10⁴ vs. <1.4×10⁴) 8.056 (3.958−16.395) <0.001
ECOG PS (≥2 vs. <2) 2.428 (1.103−5.342) 0.028
Extranodal sites (≥2 vs. <2) 2.920 (1.549−5.503) 0.001
Gender (female vs. male) 0.797 (0.403−1.576) 0.514
LDH (>245 vs. ≤245) 2.017 (1.069−3.805) 0.030
Non-nasal type (yes vs. no) 3.693 (1.914−7.125) <0.001
RLN involvement (yes vs. no) 3.296 (1.598−6.800) 0.001
SUVmax (≥9.950 vs. <9.950) 4.630 (2.224−9.640) <0.001
Multivariate analysis
AASS (III/IV vs. I/II) 0.704 (0.221−2.241) 0.553
ctDNA (≥4.026 vs. <4.026) 6.857 (1.899−24.757) 0.003
DLN involvement (yes vs. no) 1.501 (0.519−4.347) 0.454
EBV-DNA (≥1.4×10⁴ vs. <1.4×10⁴) 5.993 (1.909−18.811) 0.002
ECOG PS (≥2 vs. <2) 0.618 (0.239−1.599) 0.321
Extranodal sites (≥2 vs. <2) 0.896 (0.328−2.449) 0.830
LDH (>245 vs. ≤245) 0.330 (0.134−0.814) 0.016
Non-nasal type (yes vs. no) 1.466 (0.642−3.348) 0.363
RLN involvement (yes vs. no) 1.459 (0.509−4.185) 0.482
SUVmax (≥9.950 vs. <9.950) 3.075 (1.178−8.026) 0.022
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5
The estimates
B
Points
0 10 20 30 40 50 60 70 80 90 100
EBV-DNA
≥1.4 × 10⁴
<1.4 × 10⁴
ctDNA
≥4.026
<4.026
SUVmax
≥9.950
<9.950
Total Points
0 20 40 60 80 100 120 140 160 180 200 220 240 260
Linear Predictor
−2 −1.5 −1 −0.5 0 0.5 1 1.5 2
3 year survival
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05
5 year survival
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.05


A
Actual 3−Year OS
Nomogram predicted probability of 3−Year OS
B
Actual 5−Year OS
Nomogram predicted probability of 5−Year OS
C
SEC
Progression−free survival
p < 0.0001
Low risk
Intermediate risk
High risk
Time (Months)
Number at risk
Low risk 21 10 8 5 3 2 2
Intermediate risk 45 27 23 18 12 9 1
High risk 25 7 2 1 1 0 0
D
SEC
Overall survival
p < 0.0001
Low risk
Intermediate risk
High risk
Time (Months)
Number at risk
Low risk 21 10 8 5 3 2 2
Intermediate risk 45 34 27 20 12 9 1
High risk 25 8 3 1 1 0 0
E
Time−dependent AUC of PFS
AUC
SEC
IPI
KPI
PINK
PINK−E
PINK−EC
Time (Months)
F
Time−dependent AUC of OS
AUC
SEC
IPI
KPI
PINK
PINK−E
PINK−EC
Time (Months)

Supplementary Table S1. Baseline characteristics of 91 newly diagnosed ENKTL patients.

Characteristics	No. (n = 91)	Percentage (%)
Age		
≤60	73	80.2
>60	18	19.8
Gender		
Female	30	33.0
Male	61	67.0
AASS		
I–II	50	54.9
III–IV	41	45.1
ECOG PS		
<2	81	89.0
≥2	10	11.0
B symptoms		
No	52	57.1
Yes	39	42.9
Regional lymph node involvement		
No	37	40.7
Yes	54	59.3
Distant lymph node involvement		
No	60	65.9
Yes	31	34.1
Numbers of extranodal sites		
<2	64	70.3
≥2	27	29.7
LDH		
≤245 U/L	50	54.9
>245 U/L	41	45.1
EBV-DNA		
Negative	16	17.6
Positive	75	82.4
Non-nasal type		
No	68	74.7
Yes	23	25.3
Chemotherapy		
Pegaspargase-based	69	75.8
L-asparaginase-based	13	14.3
Other	9	9.9
HSCT		
Allo-HSCT	2	2.2
Auto-HSCT	11	12.1

No	78	85.7
Treatment		
CT alone	54	59.3
CRT	37	40.7
IPI		
Low (0–1)	53	58.2
Intermediate Low (2)	11	12.1
Intermediate High (3)	20	22.0
High (≥4)	7	7.7
KPI		
Group 1 (0)	18	19.8
Group 2 (1)	19	20.9
Group 3 (2)	21	23.1
Group 4 (≥3)	33	36.2
PINK		
Low risk (0)	39	42.8
Intermediate risk (1)	17	18.7
High risk (≥2)	35	38.5
PINK-E		
Low risk (0–1)	41	45.0
Intermediate risk (2)	17	18.7
High risk (≥3)	33	36.3

AASS: Ann Arbor staging system; ECOG PS: eastern cooperative oncology group performance status; LDH: lactate dehydrogenase; EBV: Epstein–Barr virus; CT: chemotherapy; CRT: chemoradiotherapy; HSCT: hematopoietic stem cell transplantation; IPI: International prognostic index; KPI: Korean Prognostic Index; PINK: prognostic index of natural killer lymphoma; PINK-E: PINK combined with EBV-DNA.

Supplementary Table S2 Harrell's C-index for different models for predicting survival.

	Model	C-index	95% CI
PFS	SEC	0.771	0.710–0.831
	IPI	0.645	0.559–0.732
	KPI	0.662	0.579–0.745
	PINK	0.657	0.572–0.743
	PINK-E	0.653	0.564–0.743
	PINK-EC	0.676	0.591–0.761
OS	SEC	0.817	0.768–0.866
	IPI	0.690	0.610–0.771
	KPI	0.708	0.627–0.788
	PINK	0.719	0.641–0.797
	PINK-E	0.728	0.653–0.802
	PINK-EC	0.759	0.687–0.832

PFS: progression-free survival; OS: overall survival; CI: confidence interval; IPI: International prognostic index; KPI: Korean Prognostic Index; PINK: prognostic index of natural killer lymphoma; PINK-E: PINK combined with Epstein–Barr virus (EBV)-DNA; PINK-EC: PINK-E combined with circulating tumor DNA (ctDNA); SEC: the initials of "standardized uptake value (SUVmax)", "EBV-DNA" and "ctDNA".

Supplementary Table S3. The variables and definitions of the different models.

Model and definition (total point)	Variable	Score
SEC		
Low (0)	SUVmax (≥9.950 vs. <9.950)	1
Intermediate (1–2)	ctDNA (≥4.026 log hGE/mL vs. < 4.026 log hGE/mL)	1
High (3)	EBV-DNA (≥1.4×10^4 copies/mL vs. <1.4×10^4 copies/mL)	1
IPI		
Low (0–1)	Age (>60 years vs. ≤60 years)	1
Intermediate (2–3)	Ann Arbor stage (III–IV vs. I–II)	1
High (4–5)	ECOG score (≥2 vs. 0–1)	1
	Elevated LDH (yes vs. no)	1
	Extranodal sites (2 vs. 0–1)	1
KPI		
Low (0)	Ann Arbor stage (III–IV vs. I–II)	1
Intermediate (1–2)	Elevated LDH (yes vs. no)	1
High (3–4)	B symptoms (yes vs. no)	1
	Regional lymph node (yes vs. no)	1
PINK		
Low (0)	Age (>60 years vs. ≤60 years)	1
Intermediate (1)	Ann Arbor stage (III–IV vs. I–II)	1
High (2–4)	Distant lymph node (yes vs. no)	1
	Non-nasal disease (yes vs. no)	1
PINK-E		
Low (0–1)	Age (>60 years vs. ≤60 years)	1
Intermediate (2)	Ann Arbor stage (III–IV vs. I–II)	1
High (3–5)	Distant lymph node (yes vs. no)	1
	Non-nasal disease (yes vs. no)	1
	EBV-DNA (yes vs. no)	1
PINK-EC		
Low (0–1)	Age (>60 years vs. ≤60 years)	1
Intermediate (2–3)	Ann Arbor stage (III–IV vs. I–II)	1
High (4–6)	Distant lymph node (yes vs. no)	1
	Non-nasal disease (yes vs. no)	1
	EBV-DNA (yes vs. no)	1
	ctDNA (>4.83 log hGE/mL vs. 0-4.83 log hGE/mL)	1

SUVmax: standardized uptake value; EBV: Epstein–Barr virus; ctDNA: circulating tumor DNA; IPI: International prognostic index; KPI: Korean Prognostic Index; PINK: prognostic index of natural killer lymphoma; PINK-E: PINK combined with EBV-DNA; PINK-EC: PINK-E combined with ctDNA; SEC: the initials of "SUVmax", "EBV-DNA" and "ctDNA"; ECOG: eastern cooperative oncology group; LDH: lactate

dehydrogenase.