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The Novel Prognostic Index Model of Combining Circulating Tumor DNA and PINK-E Predicts the Clinical Outcomes for Newly Diagnosed Extranodal NK/T-cell Lymphoma

Dezhi Huang[1,2,*], Qiong Li[1,2,*], Xinlei Li[1,2], Naya Ma[1,2], Yishuo Duan[1,2], Lidan Zhu[1,2], Jiali Li[1,2], Qin Wen[1,2], Lei Gao[1,2], Cheng Yang[1,2], Lingyi Rao[1,2], Li Gao[1,2], Xi Zhang[1,2], Jun Rao[1,2]

Correspondence: Jun Rao (raojun1129@126.com); Xi Zhang (zhangxxi@sina.com); Li Gao (gaotiantiantiger@163.com).

ABSTRACT

Extranodal NK/T-cell lymphoma (ENKTL) is a highly aggressive and heterogeneous disease with poor clinical outcome. Our previous work had demonstrated that circulating tumor DNA (ctDNA) analyses were feasible in ENKTL, and dynamic tracing of ctDNA could be used to monitor the disease status. However, the prognostic value of ctDNA in ENKTL has not been fully investigated. Patients with newly diagnosed ENKTL from February 2017 to December 2021 (n = 70) were enrolled. The pretreatment ctDNA concentration (hGE/mL) was measured. The prognostic value of ctDNA, international prognostic index (IPI), Korean prognostic index (KPI), PINK-E, and the combination of PINK-E and ctDNA (PINK-EC) were investigated in our cohort. The IPI and PINK-E risk categories had a significant difference in progression-free survival (PFS) and overall survival (OS) between the low-risk and intermediate-risk groups. The KPI risk category had a difference in PFS and OS between the intermediate-risk and high-risk groups. Furthermore, integrating ctDNA into the PINK-E model could overcome the shortcomings of other prognostic models, which could significantly distinguish the different-risk groups. Overall, our results demonstrated that PINK-EC showed a superior prognostic prediction value and stability compared with IPI, KPI, and PINK-E. The integration of molecular features of the tumor into classic risk categories might better characterize a high-risk group where novel treatment approaches are most needed.

INTRODUCTION

Extranodal NK/T-cell lymphoma (ENKTL) is a highly aggressive and heterogeneous disease predominant in Asian and South American populations.[1–4] Substantial heterogeneity in survival exists for newly diagnosed ENKTL, and the reported 5-year overall survival (OS) rates vary from 40% to 90%.[5] For patients with low-risk early-stage disease, radiotherapy alone could achieve a favorable OS, and incorporation of chemotherapy may not provide additional benefit. For high-risk early-stage patients, the combination of radiotherapy and chemotherapy is necessary, and for advanced patients, more effective treatment strategies need to be explored.[6] Risk-adapted therapy plays a pivotal role in improving the survival of newly diagnosed patients. Therefore, the implementation of an optimal risk classification model for ENKTL would provide a significant advancement in the decision-making of therapeutic strategies.

Several risk scoring systems for the newly diagnosed ENKTL are used in current clinical practice, including the international prognostic index (IPI) scoring system, Korean prognostic index (KPI), prognostic index for natural killer cell lymphoma (PINK), and PINK-E combined with Epstein-Barr virus (EBV)-DNA (PINK-E). Although the IPI has been validated in multiple subtypes of lymphoma,[7–12] it remains controversial in ENKTL. Based on the IPI score, over 80% of ENKTL patients were categorized as low risk, which did not show independent prognostic significance in some centers.[13–16] Lee et al[13] proposed categorizing patients based on the KPI and local tumor invasiveness, which had better predictive potential than the IPI scoring system, but which was not predictive in patients with extranasal disease.[14] In addition, nonanthracycline-based chemotherapy was the standard chemotherapy strategy for ENKTL, and IPI and KPI were both developed in patients who were primarily treated with CHOP or CHOP-like regimens, which were found no longer applicable.[15,16] As a result, Kim et al proposed a new prognostic model PINK, including four risk factors (age, stage, non-nasal type, and distant lymph-node involvement), which showed superior predictive ability compared with

[1]Medical Center of Hematology, Xinqiao Hospital, Army Medical University, Chongqing, China
[2]State Key Laboratory of Trauma, Burns and Combined Injury, Army Medical University, Chongqing, China
*DH and QL have contributed equally to this article.
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the IPI and KPI.[17] Furthermore, elevated EBV-DNA in the peripheral blood was significantly associated with inferior survival in the same analysis. Incorporating EBV-DNA into PINK (PINK-E) appears to be much more accurate to predict outcomes.[18] As a result, the NCCN Guidelines also recommend the measurement of EBV-DNA load and the calculation of prognostic index (PINK or PINK-E) as part of the initial workup.[6] However, the PINK and PINK-E models were not as powerful in some cohorts and had been found to fail to distinguish patients proportionately, and some studies showed that they did not discriminate prognosis well among different-risk groups in ENKTL.[17,19,20] Therefore, new prognostic models needed to be explored.[21]

Circulating tumor DNA (ctDNA) comprises the fraction of circulating cell-free DNA (cfDNA) originating from cancer cells.[22] ctDNA in the plasma was increasingly being used as a biomarker to guide clinical decision-making, leading to a better diagnosis, evaluation of the best treatment, and longitudinal disease monitoring, among other clinical uses.[23,24] Pretreatment ctDNA levels and molecular responses were independently prognostic of outcomes in aggressive lymphomas, suggesting ctDNA could improve pretreatment risk stratification.[25] Alig et al[26] demonstrated that pretreatment ctDNA levels predicted a shorter diagnosis-to-treatment interval (DTI) independent of the IPI score. Fu et al. generated models for predicting OS or progression-free survival (PFS) using ctDNA together with the IPI, which had a better accuracy of prognostic prediction.[27] Our previous work demonstrated that the plasma ctDNA was feasible, and we also unveiled the mutation spectrum of ENKTL patients and found that the concentration of ctDNA was positively correlated with tumor stage and tumor burden, but the prognostic significance of ctDNA was not fully elucidated.[28] In this study, we analyzed the specific prognostic significance of ctDNA, and we also developed a novel prognostic index model incorporating ctDNA into PINK-E (PINK-EC) for the estimation of clinical prognosis in ENKTL. This novel model provides important details for guiding personalized therapy.

METHODS

Patients

In this study, 70 patients newly diagnosed with ENKTL were enrolled (ClinicalTrials identifier: ChiCTR1800014813) (Suppl. Figure S1). All consecutive patients who were deemed appropriate for this study during the study period were included without selection. Histological diagnoses were established independently by at least two experienced senior pathologists according to the WHO classification of tumors of hematopoietic and lymphoid tissue criteria.[29] All patients underwent baseline staging using laboratory, radiographic, and bone marrow examinations upon diagnosis. Patients were reviewed routinely by a combination of clinical assessment and CT or fluorodeoxyglucose-PET (FDG-PET) before the administration of chemotherapy. FDG-PET is often used as an interim scan, and the metabolic tumor volume (MTV) is determined from the initial and interim PET images using PET Edge software (MIM Software Inc., Cleveland, OH). After the initial stage assessment, all patients were given 6–8 cycles of first-line chemotherapy regimens with or without radiotherapy according to the latest NCCN guidelines, and patient tolerance and comorbidities.[6,30] Serial ctDNA profiling was conducted during the patient's therapy course. The Eastern Cooperative Oncology Group (ECOG) performance status was also assessed. The stage was evaluated in accordance with the Ann Arbor staging system. Patient characteristics and treatment regimens of each therapy cycle were collected from each patient. All participants provided informed written consent before undergoing any study-related procedures in accordance with the Declaration of Helsinki. This study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT-20,180,005).

Data collection and ctDNA measurement

All data were collected based on the previous work published by our research group.[28] Briefly, peripheral blood samples of all patients were collected using 10 mL EDTA vacutainer tubes and processed within 4 hours at a constant temperature of 4°C before treatment, and plasma samples at baseline, on the interim day, and at final response assessment were collected for ctDNA analysis. cfDNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Valencia, CA) following the manufacturer's instructions. The DNA concentration and quality were estimated using a Qubit fluorometer (Invitrogen). The ctDNA quality was assessed using an Agilent 2100 Bioanalyzer and DNA HS Kit (Agilent Technologies, Palo Alto, CA). NGS libraries were constructed using the SureSelect Library Prep Kit (Agilent Technologies, Palo Alto, CA). Quantification of the library was performed using the Agilent DNA 1000 Kit (Agilent Technologies). Sequencing was performed on the Illumina MiSeq system (Illumina, San Diego, CA) following the manufacturer's protocol. Targeted sequencing gene panels including the coding exons and splice sites of 41 genes (Yuanqi Biopharmaceutical Co., Shanghai, China) that are recurrently mutated in NK/T-cell lymphoma were specifically designed for this study, including the genes *ADAM3A*, *APC*, *ARID1A*, *ARID1B*, *ARID2*, *ASXL3*, *ATM*, *BCOR*, *BCORL1*, *CD28*, *CHD8*, *CREBBP*, *DDX3X*, *DNMT3A*, *EP300*, *EZH2*, *FYN*, *IDH2*, *IL2RG*, *JAK1*, *JAK3*, *KDM6A*, *KMT2A*, *KMT2D*, *MGA*, *NF1*, *NOTCH1*, *PRDM1*, *PTPN1*, *RHOA*, *SETD2*, *SOCS1*, *STAT3*, *STAT5B*, *STAT6*, *TET1*, *TET2*, *TNFRSF14*, *TP53*, *TRAF3*, *and ZAP608*. The concentrations of ctDNA were expressed in haploid genome equivalents per mL (hGE/mL) and were calculated by multiplying the mean ctDNA mutant allele frequency (MAF) by the input concentration of cfDNA in pg/mL as determined by fluorometry and then dividing by 3.3.[31] In this study, we extended the follow-up time to the date of this analysis.

PINK-EC risk classification

According to the patient's clinical characteristics, the IPI (age, ECOG, stage, lactate dehydrogenase [LDH] level, extranodal sites), KPI (stage, LDH level, B symptoms, regional lymph nodes), and PINK-E (age, stage, non-nasal type, distant lymph-node involvement, and EBV-DNA status) were calculated for survival analysis. When integrating the ctDNA concentration into the PINK-E scoring system, we constructed a novel prognostic index model (PINK-EC). Patients were stratified into 3 risk groups by combining the indices of these parameters (low, 0–1; intermediated, 2–3; high, 4–6) (Suppl. Table S1).

Statistical analysis

The appropriate cutoff for ctDNA was determined by receiver operator characteristic (ROC) curves and the area under the curve (AUC). 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. The hazard ratio (HR) and 95% confidence interval (95% CI) were calculated by the Cox proportional hazards model. Discrimination was evaluated by Harrell's concordance index (C-index) and the AUC. The model was validated internally using 1000 bootstrap samples. Calibration was evaluated by a calibration plot, which compares the relationship between the prediction and actual observation for survival time. Time-dependent ROC was used for the comparison of risk stratification for these prognostic models. Statistical analyses were executed by IBM SPSS statistical software (version 25.0, IBM Inc, NY) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Several packages were used in the R environment, including "pROC," "survival," "survminer," "pec," "ggplot2," and "rms." A two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Patient characteristics of the whole cohort are listed in Table 1. The median age was 47 years old (range: 10–71 years). The male-to-female ratio was 2.18:1. Nearly half of the patients had advanced disease (Ann Arbor stages III and IV, n = 33, 47.1%), and 29 patients (41.4%) had B symptoms. Forty patients (57.1%) had lymph-node involvement, and 17 patients (24.3%) presented with the non-nasal type. Notably, 57 patients (81.4%) were diagnosed with EBV positive.

According to the IPI scoring system, 39 of 70 patients (55.7%) were classified as low risk, 11 patients (15.7%) as intermediate-low risk, 16 patients (22.9%) as intermediate-high risk, and 4 patients (5.7%) as high risk. PINK-E categories distinguished patients into low-, intermediate-, and high-risk groups at rates of 44.3%, 20%, and 35.7%, respectively.

Treatment and outcomes

After the initial stage assessment, the treatment strategies included chemotherapy alone (n = 39, 55.7%) and combination chemotherapy with radiotherapy (n = 31, 44.3%). The initial treatment regimens were administered as follows: 52 patients (74.3%) received pegaspargase-based chemotherapy regimens, 7 patients (10%) received L-asparaginase-based chemotherapy regimens, 6 patients (8.57%) received CHOP-like chemotherapy regimens, 4 patients (5.71%) received DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) chemotherapy regimens, and one patient (1.42%) received the IMEP (ifosfamide, methotrexate, etoposide, and prednisolone) chemotherapy regimens (Table 1).

At the first follow-up assessment after treatment, the median follow-up time was 739 days (range, 582–1070 days), and 23 patients (32.9%) had died of tumor progression or relapse or treatment-related toxicity. Thirty-two (45.7%) patients achieved complete remission (CR), and 11 (15.7%) patients achieved partial remission (PR) after initial first-line therapy. There were 20 patients (28.6%) with progression of disease within 2 years (POD24), and the OS of patients with POD24 was poorer than that of patients with non-POD24 ($P < 0.0001$) (Suppl. Figure S2). The 3-year OS rate and the 3-year PFS rate of the 70 patients were 62.6% and 48.7%, respectively.

Comparison of patients' PFS and OS among the three classical models

All patients' risk classifications were calculated based on the IPI, KPI, and PINK-E scoring systems, which were presented in Suppl. Table S1. Regarding the IPI scoring system, the Kaplan-Meier analysis showed that the intermediate-risk group had inferior PFS and OS than the low-risk group (PFS, HR = 2.820, 95% CI = 1.330-5.979, $P = 0.0035$; OS, HR = 3.371, 95% CI = 1.353-8.401, $P = 0.0038$), but there was no difference between the intermediate- and high-risk groups (PFS, HR = 1.369, 95% CI = 0.346-5.412, $P = 0.61$; OS, HR = 1.106, 95% CI = 0.236-5.187, $P = 0.89$) (Suppl. Figure S3A and D). The KPI scoring system could separate the intermediate-risk and high-risk groups well (PFS, HR = 2.714, 95% CI = 1.261-5.842, $P = 0.0054$; OS, HR = 3.232, 95% CI = 1.306-8.001, $P = 0.0054$); however, it could not distinguish the low-risk group from the intermediate-risk group (PFS, HR = 1.258, 95% CI = 0.963-3.682, $P = 0.69$; OS, HR = 1.825, 95% CI = 0.674-6.942, $P = 0.44$) (Suppl. Figure S3B and E). The PINK-E model distributed 31 patients (44.3%) into the low-risk group, the survival of patients with low- and intermediate-risk groups were significantly different (PFS, HR = 4.283, 95% CI = 1.350-13.589, $P = 0.0025$; OS, HR =5.585, 95% CI =1.268-24.599, $P = 0.0059$), but this model failed to discriminate between patients with high risk and those with intermediate risk (PFS, HR = 1.322, 95% CI = 0.612-2.857, $P = 0.49$; OS, HR = 1.789, 95% CI = 0.739-4.332, $P = 0.22$) (Suppl. Figure S3C and F).

Table 1

Baseline Characteristics of 70 Untreated ENKTL Patients

Characteristics	No. (n = 70)	Percentage (%)
Age		
≤60	61	87.1
>60	9	12.9
Sex		
Female	22	31.4
Male	48	68.6
AASS		
I/II	37	52.9
III/IV	33	47.1
ECOG		
<2	63	90
≥2	7	10
Extranodal sites		
<2	48	68.6
≥2	22	31.4
LDH		
>245 U/mL	33	47.1
≤245 U/mL	37	52.9
B symptoms		
No	41	58.6
Yes	29	41.4
Regional lymph node		
No	30	42.9
Yes	40	57.1
Distant lymph node		
No	44	62.9
Yes	26	37.1
Non-nasal type		
No	53	75.7
Yes	17	24.3
EBV-DNA		
Positive	57	81.4
Negative	13	18.6
Treatment		
CT alone	39	55.7
CRT	31	44.3
Chemotherapy		
Pegaspargase-based	52	74.3
L-asparaginase-based	7	10
Other	11	15.7
IPI		
Low (0-1)	39	55.7
Intermediate low (2)	11	15.7
Intermediate high (3)	16	22.9
High (≥4)	4	5.7
KPI		
Group 1 (0)	13	18.6
Group 2 (1)	14	20
Group 3 (2)	19	27.1
Group 4 (≥3)	24	34.3
PINK-E		
Low-risk (0–1)	31	44.3
Intermediate risk (2)	14	20
High risk (≥3)	25	35.7

AASS = Ann Arbor staging system; CRT = chemoradiotherapy; CT = chemotherapy; EBV = epstein-barr virus; ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = International Prognostic Index; KPI = Korean Prognostic Index; LDH = lactate dehydrogenase; PINK-E = prognostic index for natural killer cell lymphoma-EBV.

Novel prognostic model development and internal validation

Of the 70 patients recruited in this study, mutations were detected in the plasma of 53 (75.7%) patients. The optimal cutoff value of ctDNA was estimated by the AUC of the ROC curve and the threshold was 4.83 hGE/mL (Figure 1A). The 3-year OS rates

of patients with low ctDNA concentrations and high ctDNA concentrations were 86.7% and 49.4%, respectively, while the 3-year PFS rates of patients in the two groups were 69.0% and 37.3%, respectively. The Kaplan-Meier analysis showed that patients with high ctDNA concentrations had significantly poorer survival than those with low ctDNA concentrations (PFS, HR = 2.290, 95% CI = 1.033-5.079, P = 0.036; OS, HR = 4.633, 95% CI = 1.376-15.600, P = 0.0065) (Figure 1B and C).

Since ctDNA concentration is a prognostic predictor for OS in patients with ENKTL, we integrated ctDNA into PINK-E (PINK-EC) to build a novel prognostic model. To clarify the predictive ability of the PINK-EC score, the discrimination and calibration were examined. Harrell's C-index of PINK-EC for PFS and OS prediction was 0.691 (95% CI = 0.597-0.786) and 0.779 (95% CI = 0.696-0.863), respectively, which was better than that of IPI, KPI, and PINK-E (Suppl. Table S2). Similarly, our results showed that the AUC of PINK-EC was higher than that of the IPI, KPI, and PINK-E for 1- and 3-year OS (Suppl. Figure S4). For the 1000 bootstrap samples, the calibration plots for 1- and 3-year OS reported good consistency between the prediction and actual observation (Figure 2).

Prognostic performance and predictive accuracy of PINK-EC

To evaluate the prognostic power of PINK-EC in ENKTL patients, Kaplan-Meier analysis was performed to examine the survival outcomes. The 3-year PFS rates of patients with low-, intermediate- and high-risk groups were 84.4%, 48.5%, and 15.7%, respectively, and the 3-year OS rates of patients in the three groups were 92.3%, 70.4%, and 21.8%, respectively. Furthermore, a pairwise comparison analysis showed that PINK-EC could discriminate the intermediate-risk group from the low-risk group (PFS, HR = 3.993, 95% CI = 1.498-10.649, P = 0.019; OS, HR = 6.642, 95% CI = 1.788-24.673, P = 0.039) and the high-risk group (PFS, HR = 2.290, 95% CI = 1.088-4.818, P = 0.019; OS, HR = 3.243, 95% CI = 1.351-7.786, P = 0.0044) (Figure 3).

To further evaluate the risk stratification power of PINK-EC with current prognostic scoring systems in ENKTL patients, time-dependent ROC curves were plotted, and corresponding AUC was calculated to compare the predictive accuracy of PINK-EC with IPI, KPI, and PINK-E. The AUCs of PFS and OS for PINK-EC were greater and more stable than those of the other three prognostic models (Figure 4).

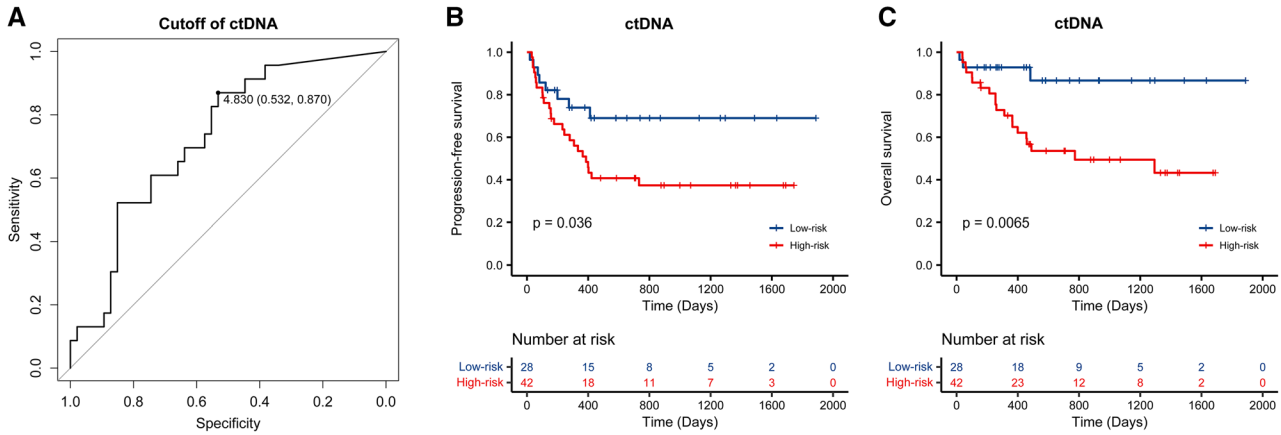

Figure 1. The prediction ability of ctDNA. (A) The cutoff value of ctDNA in ENKTL; (B) Risk stratification and overall survival according to ctDNA; and (C) Risk stratification and progression-free survival according to ctDNA. ctDNA = circulating tumor DNA; ENKTL = extranodal NK/T-cell lymphoma.

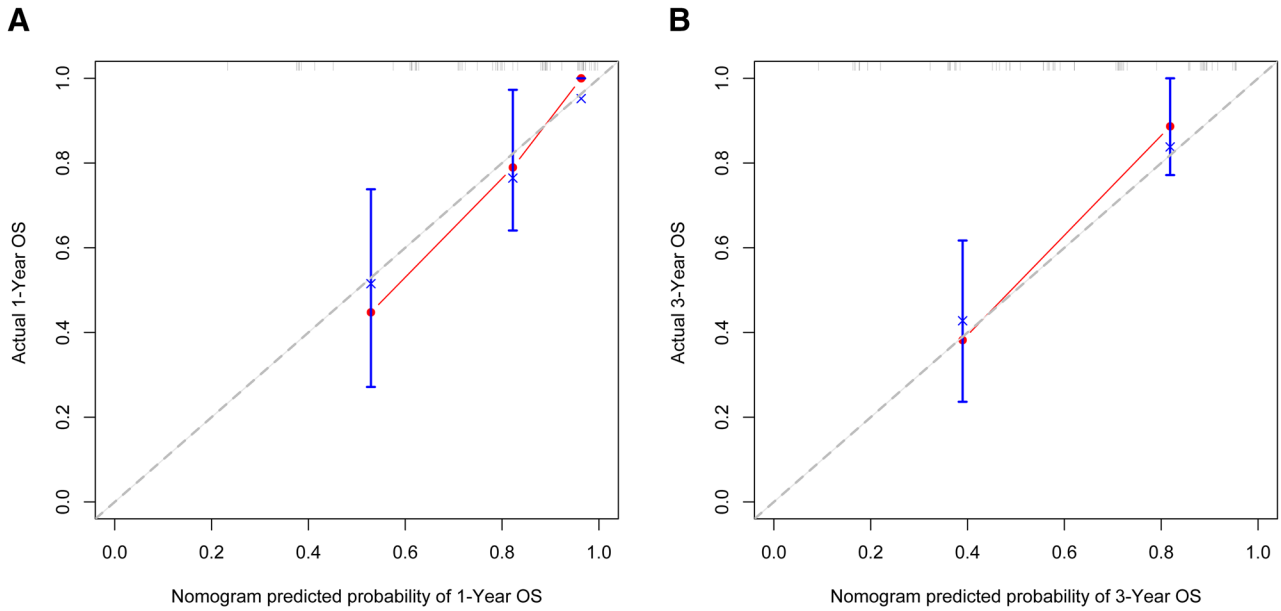

Figure 2. Calibration plot comparing the predicted and actual survival probabilities at 1-year OS (A) and 3-year OS (B). OS = overall survival.

DISCUSSION

In this study, we found that ctDNA concentration was significantly associated with the prognosis of ENKTL patients, which could be used to improve the performance of the frequently used models. Integrating ctDNA into PINK-E had an optimal Harrell's C-index and AUC, and showed better predictive abilities. Taken together, our results demonstrated that the novel prognostic model had superior prognostic value and might be used to guide personalized treatment strategies for patients.

ENKTL is a rare subtype of non-Hodgkin lymphoma with poor outcome, the 5-year OS rates in large cohort studies range from 30% to 86%, and most studies showed that the rates were less than 50%.[4,32] To date, neither an optimal treatment strategy nor a valuable prognostic index has been identified.[5,33] Several prognostic models have been used for ENKTL, including IPI,[34] KPI,[13] PINK, and PINK-E.[15] However, these prognostic models for ENKTL are still controversial. Although the IPI systematically predicted the prognosis for aggressive NHL, it failed to properly predict survival outcomes in a few studies of early-stage ENKTL. Moreover, the KPI was not a significant predictor of survival for nasal-type ENKTL.[35] PINK was applicable in the era of nonanthracycline-based treatment; however, patients could not be assessed individually.[16] Some studies even indicated that PINK was even inferior to IPI or KPI.[36] In our cohort, the IPI could discriminate intermediate- and low-risk groups but failed to separate high-risk from intermediate-risk groups. Contrary to the IPI model, the KPI could distinguish intermediate- and high-risk groups but failed to discriminate intermediate-risk from low-risk groups. The PINK-E model distributed patients into the low-risk group more than the IPI and KPI. It distinguished between low- and intermediate-risk groups well, but could not distinguish between high- and intermediate-risk groups. Therefore, novel prognostic models need to be explored.

ctDNA is released from apoptotic or necrotic tumor cells and is part of cell-free DNA (cfDNA) ranging from 3% to 93%.[37,38] The vital merit of ctDNA is that it confers dynamic detailed information about tumor biology without the necessity for frequent biopsies.[39] The possibility of using ctDNA as a surrogate for treatment response and survival is an attractive concept; this surrogate will arguably reduce study duration and expedite the development of new therapies.[40] Some studies have reported that monitoring ctDNA can reflect treatment response, monitor disease progression, and facilitate prediction of prognosis in some solid cancers.[39,41–43] Recently, some research reported that ctDNA had prognostic value in lymphoma patients.[25,27,44] Our previous work had demonstrated that ctDNA assessment could predict the therapy response and monitor disease status in a noninvasive way in ENKTL.[28] The plasma ctDNA concentration was significantly correlated with the MTV. In the present study, our results further indicated that high ctDNA concentration significantly predicted shorter PFS and OS. As IPI, KPI, and PINK-E could not stratify these patients well, we combined ctDNA with PINK-E to construct a novel prognostic model PINK-EC for ENKTL. Compared with the traditional scoring system, PINK-EC exhibited several significant advantages for prognosis evaluation and clinical application. First, currently available prognostic indices for ENKTL, for example, IPI, KPI, and PINK-E, do not incorporate molecular mutations as one of the prognostic markers.[45] To the best of our knowledge, PINK-EC was the first prognostic model incorporating ctDNA concentration for ENKTL. Second, the PINK-EC score integrated molecular pathology results, providing superior predictive accuracy and stability. Third, PINK-EC divided these patients more evenly into three different-risk groups and differentiated them from each other. Finally, PINK-EC could effectively identify high-risk populations, which could assist clinicians in formulating effective and appropriate treatment modalities in a timely manner. Nevertheless, there are also some limitations for PINK-EC. First, the value of the ctDNA threshold and whether PINK-EC is stable and applicable in other centers remain to be validated. Second, as ENKTL is a rare subtype of NHL with poor prognosis, this study recruited patients from a single center, and it is unknown whether regional variation affects the concentration of ctDNA. Therefore, the prognostic efficiency of PINK-EC needs to be further validated in a large-scale multicenter clinical study in the future. In addition, the other issues that concerned us included sequencing depth, the excluded strategy of germline mutations and clonal hematopoiesis.

Apart from these traditional scoring models, some other biomarkers were also used for ENKTL, for example, 25-hydroxy

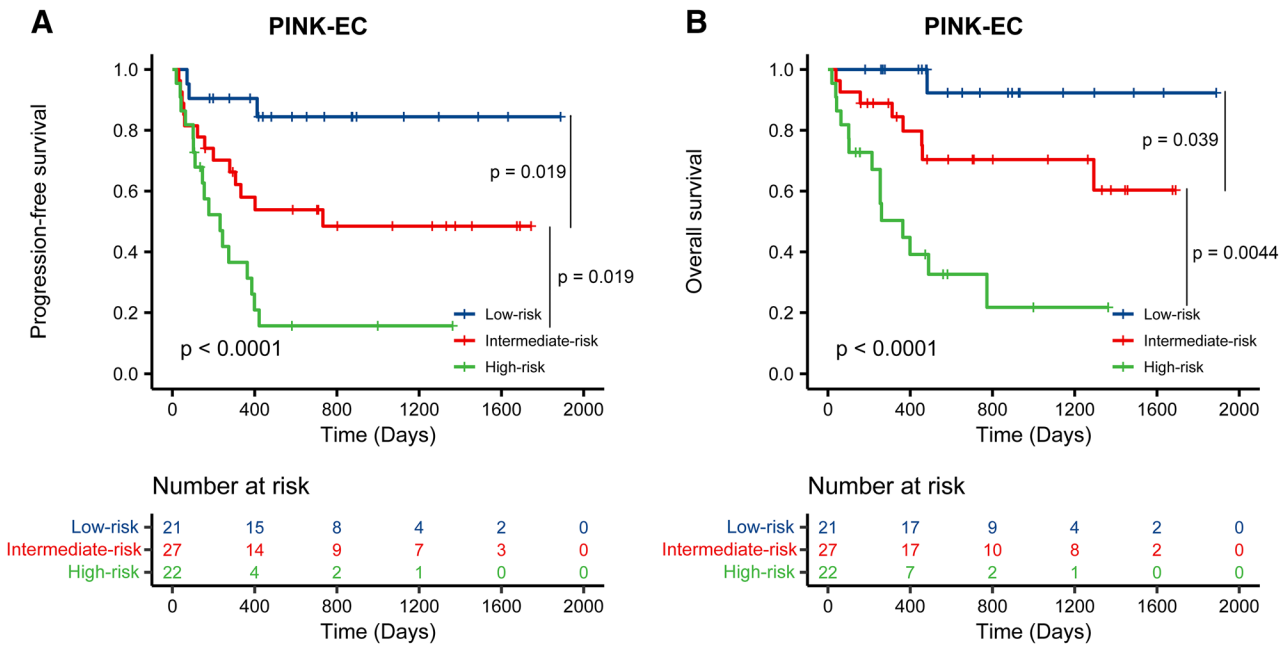

Figure 3. Kaplan-Meier curve shows the different PFS (A) and OS (B) among the three grades based on PINK-EC score. OS = overall survival; PFS = progression-free survival; PINK = PINK-E and ctDNA.

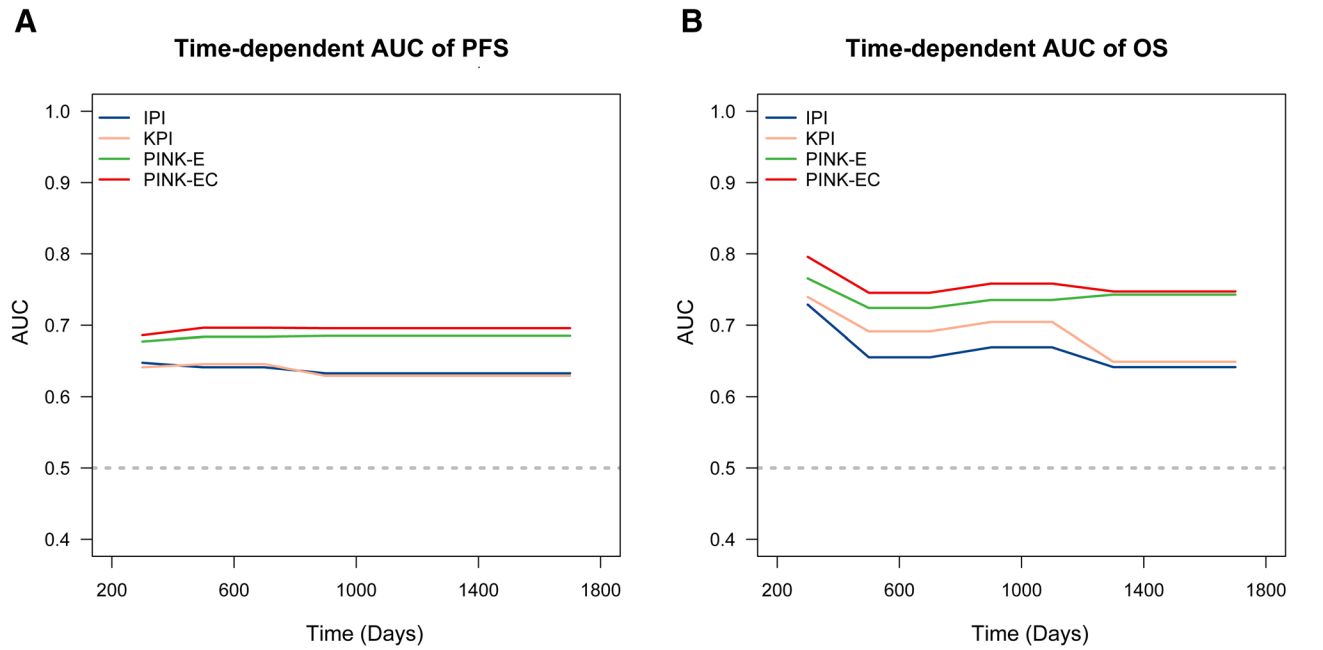

Figure 4. Time-dependent AUC comparison in IPI, KPI PINK-E, and PINK-EC models: (A) PFS and (B) OS. AUC = area under the curve; IPI = international prognostic index; KPI = Korean prognostic index; OS = overall survival; PFS = progression-free survival; PINK = PINK-E and ctDNA.

vitamin D,[46] prognostic nutritional index,[47,48] C-reactive protein to albumin ratio (CAR),[49] and maximum standardized uptake value (SUVmax).[33] ctDNA analysis has increased sensitivity and specificity compared with the analysis of other circulating biomarkers and SUVmax.[28,50,51] Moreover, ctDNA provides a dynamic real-time profiling and identifies these novel mutations in a timely manner on serial monitoring independently, making it the ideal tool for monitoring minimal residual disease (MRD) in ENKTL,[40,52] and could correct tumor heterogeneity and biopsy site bias. Recently, a new model of a 7-SNP-based classifier based on the status of seven single-nucleotide polymorphisms (SNPs) was constructed for ENKTL, which initiated the use of molecular mutations to construct prognostic model for ENKTL.[53] However, the underlying mechanisms of the tumorigenesis and development of ENKTL that are regulated by the seven genes have not been fully clarified, and this model needs prospective study to be validated further.[54]

In summary, our study was the first to prospectively assess the prognostic value of the PINK-EC model in ENKTL patients. We found that the combination model had a superior advantage in identifying the risk classification of patients. However, as a limited number of patients were enrolled in our study, a potential source of selection bias might exist. Thus, a multicenter prospective study is needed to verify the prognostic significance of PINK-EC for the rare morbidity of ENKTL.

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AUTHOR CONTRIBUTIONS

JR conceived and designed the study. QL, DH, and JL collected and analyzed the data. JR, DH, QL, and CY wrote the article. LZ, QW, XL, NM, YD, LG, CY, LR, LG, and XZ reviewed and revised the article.

DATA AVAILABILITY

All data generated and analyzed during this study are included in this article and its supplementary information files.

DISCLOSURES

The authors have no conflicts of interest to disclose.

ETHICS STATEMENT

The study was approved by the China Ethics Committees of Registering Clinical Trials (ChiECRCT-2018005).

SOURCES OF FUNDING

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