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

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 limited-stage ENKTL has increased to 72-74% as the result of the introduction of a novel strategy of concurrent chemoradiotherapy.[2] However, the 5-year OS in advanced-stage disease remains around 15-25%.[3] Since risk-adapted therapy plays a pivotal role in improving the survival of newly diagnosed patients,[4] a better risk classification model could assist in precisely stratifying patients with ENKTL into risk groups and formulating appropriate individualized treatments to improve 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 data regarding 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 SUVmax in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and the quantitative value of EBV-DNA. In previous work, we 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 in 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"), which 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) level, whole blood EBV-DNA copy number, ^{18}FDG PET/CT SUVmax value and ctDNA concentration. In this study, we extended the follow-up time to the date of this analysis. The methodology of ctDNA measurements was reported previously.[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 concentration were divided into two categories. The ideal cutoff values for SUV_{max}, 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 ratios (HR) with 95% confidence intervals (95% CI) were performed using Cox regression models. A nomogram was generated based on the independent predictors of survival outcomes determined by univariate and multivariate analyses. A calibration curve (1,000 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). A two-sided $P<0.05$ was considered statistically significant.

The baseline characteristics of the whole cohort are 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 haploid genome equivalents per milliliter (hGE/mL), respectively (Figure 1).

According to the univariate and multivariate Cox re-

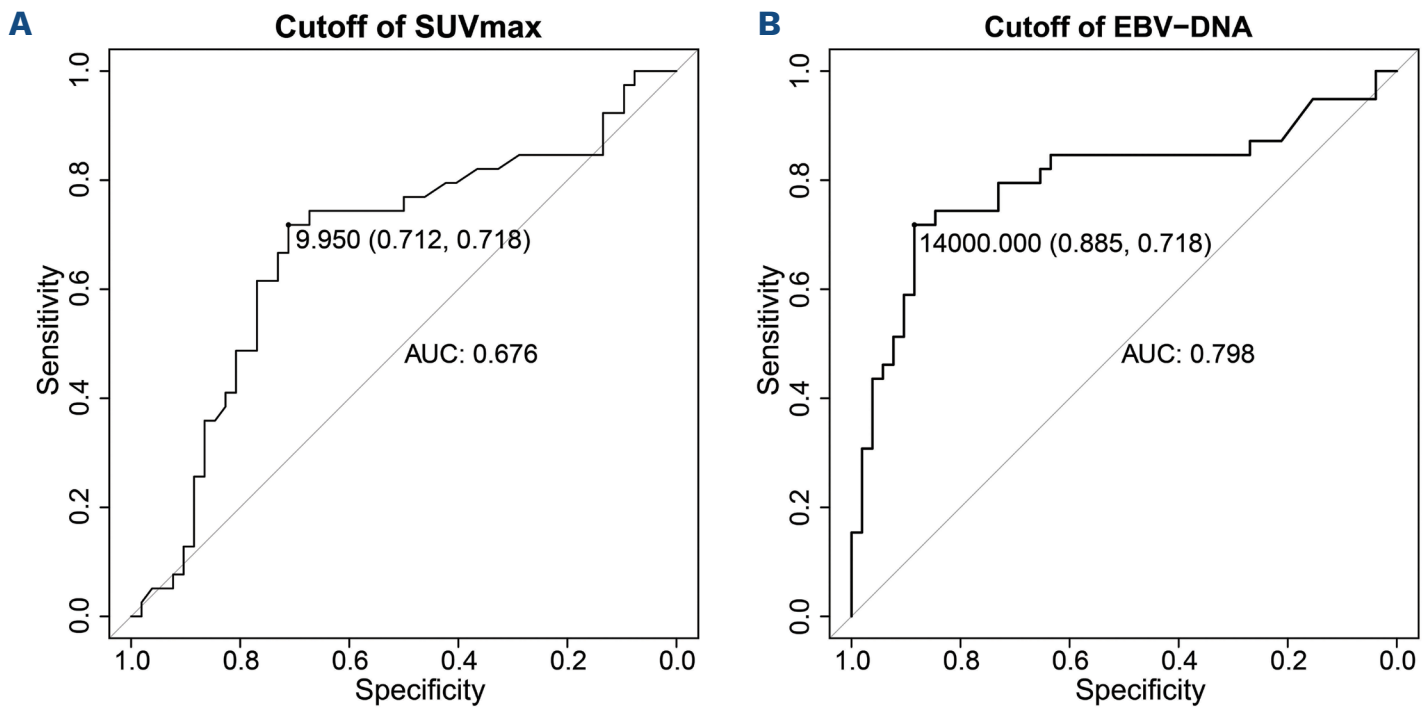

Figure 1. The cutoff values of prognostic parameters for overall survival. (A) standardized uptake value (SUVmax); (B) Epstein-Barr virus (EBV)-DNA; (C) circulating tumor DNA (ctDNA). OS: overall survival; AUC: area under the curve.

gression 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 construction of the nomogram 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 values and the actual observation (Figure 3A, B). Harrell's C-index of the SEC for PFS and OS prediction were 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 (O*nline 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 we, therefore, 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: not applicable [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;

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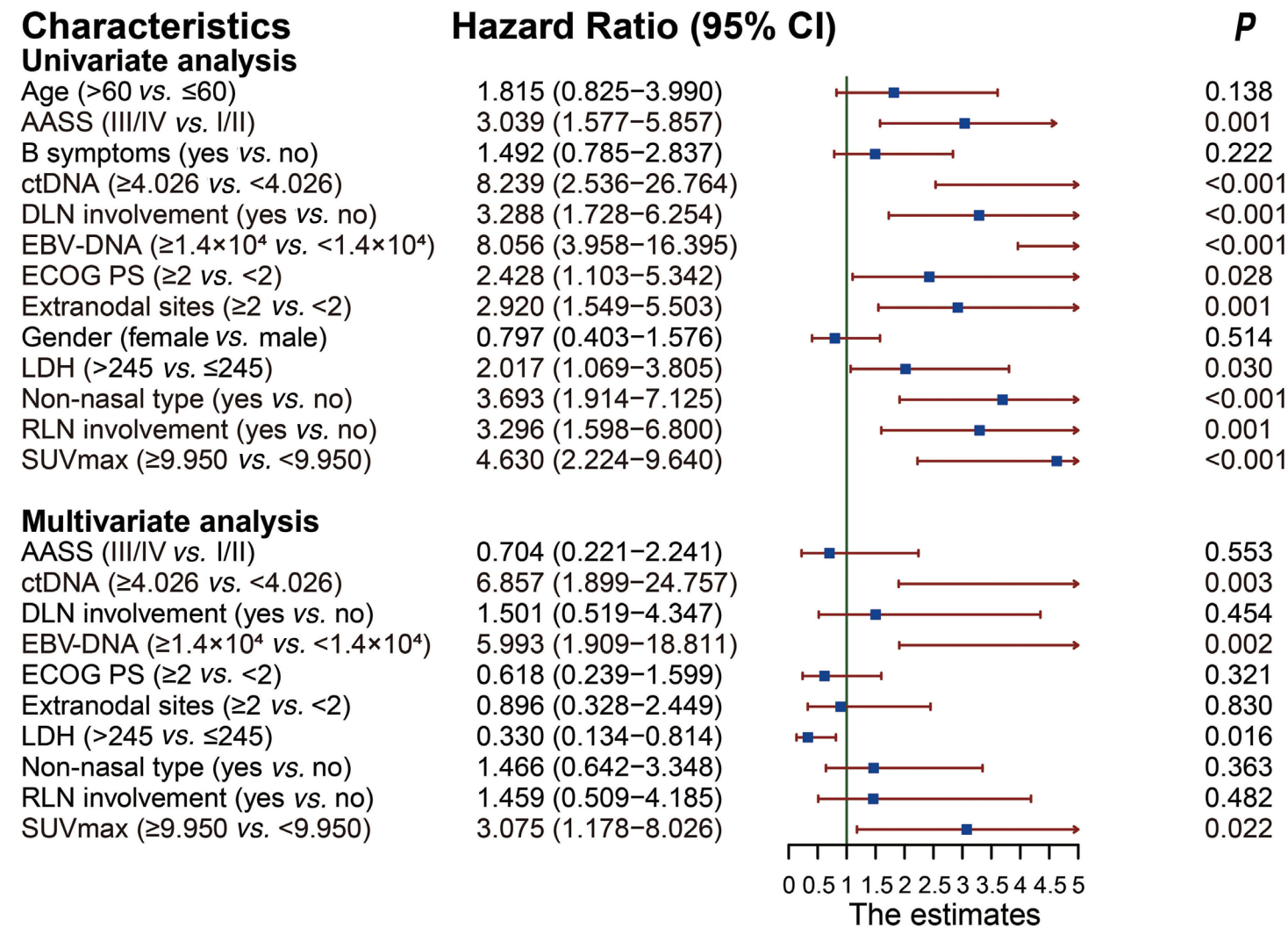

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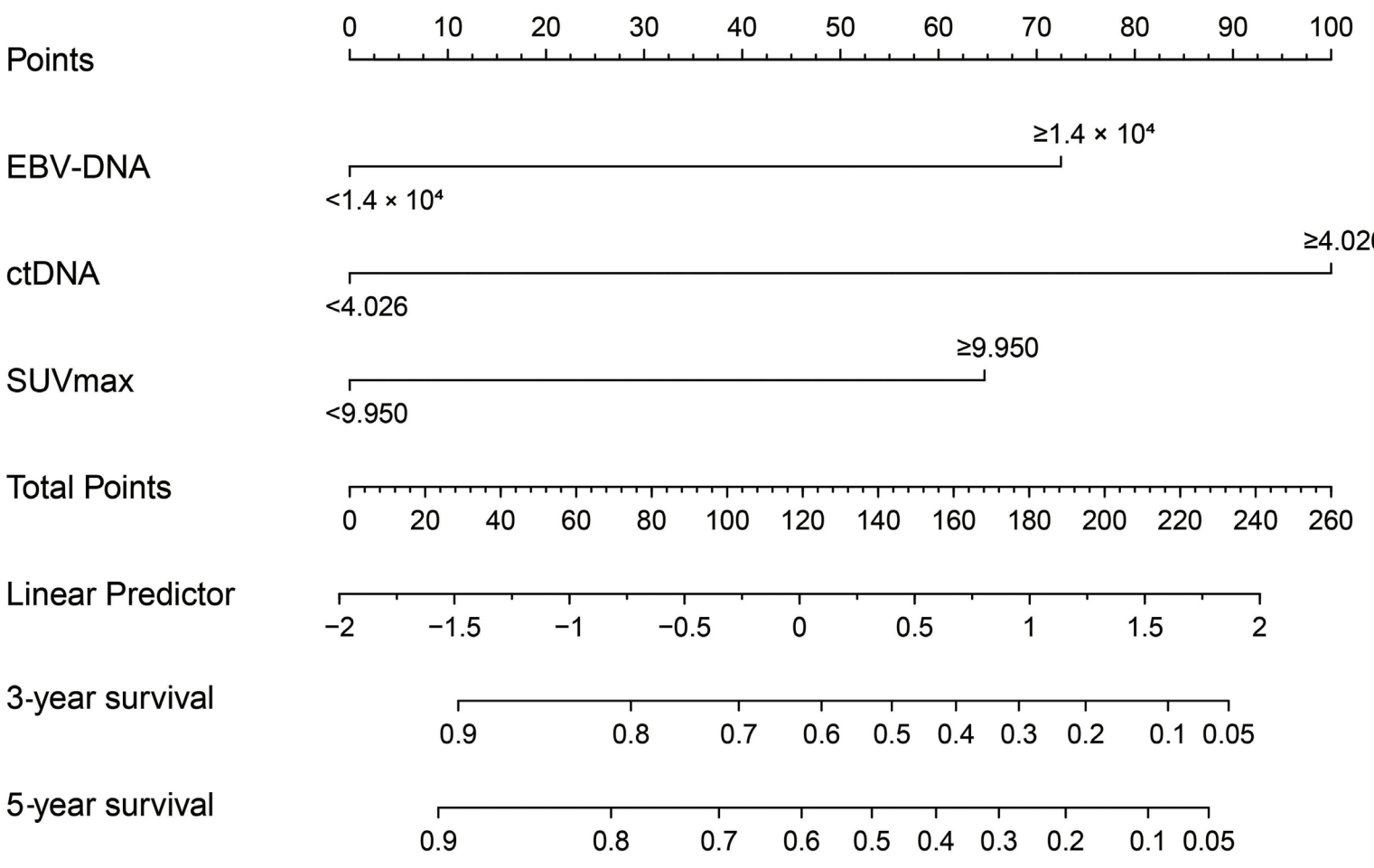

Figure 2. Nomogram constructed from the standardized uptake value, Epstein-Barr virus DNA and circulating tumor DNA for patients with newly-diagnosed extranodal natural killer/T-cell lymphoma. (A) Univariate and multivariate Cox analyses reveal that standardized uptake value, Epstein-Barr virus-DNA and circulating tumor DNA are independent prognostic factors for overall survival in patients with extranodal natural killer/T-cell lymphoma. (B) The SEC nomogram for newly-diagnosed ENKTL patients. 95% CI: 95% confidence interval; AASS: Ann Arbor staging system; ctDNA: circulating tumor DNA; DLN: distant lymph node; EBV: Epstein-Barr virus; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; RLN: regional lymph node; SUVmax: standardized uptake value.

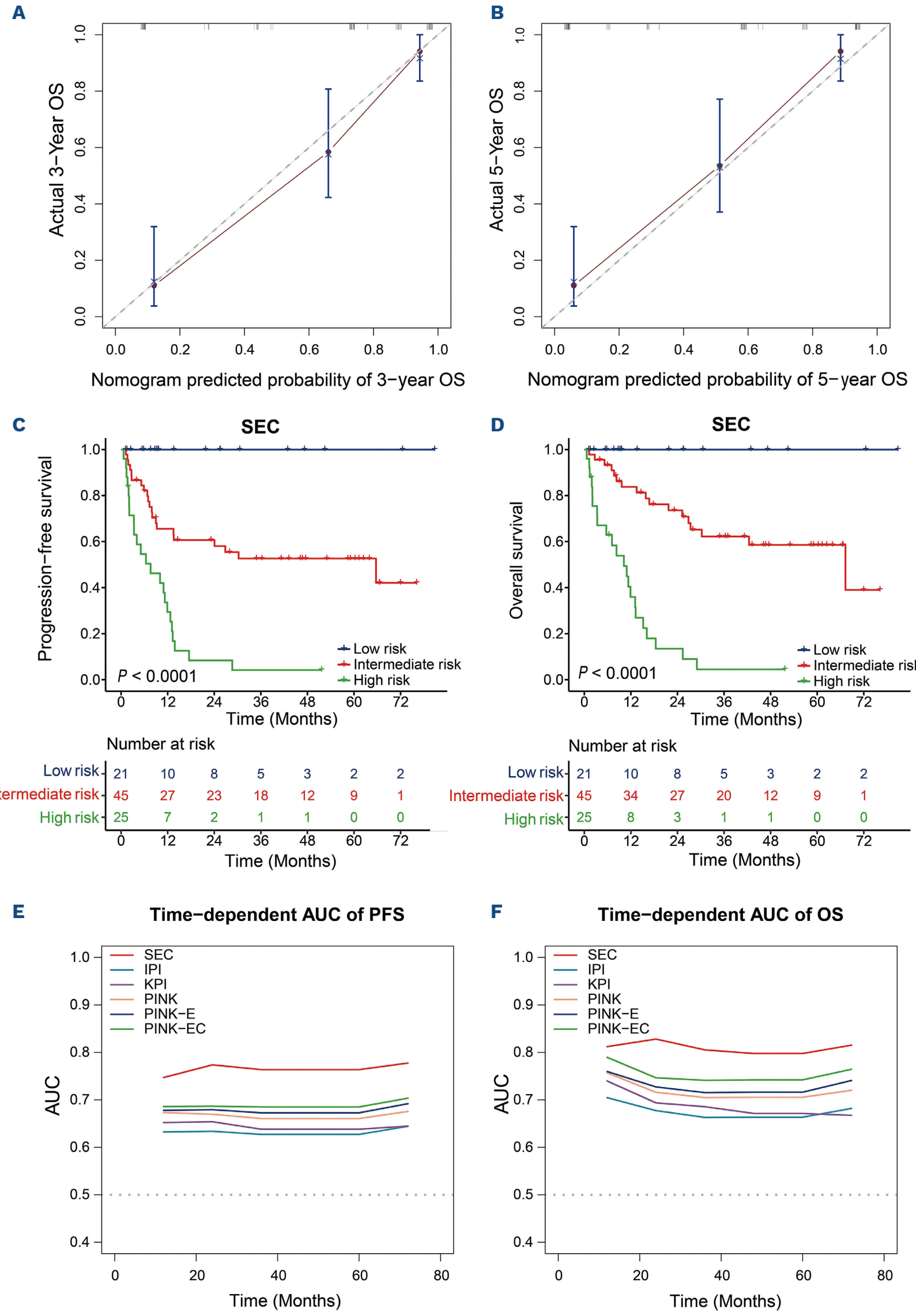

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Figure 3. Risk stratification ability and evaluation of the SEC nomogram. (A, B) Calibration curves for the prediction of 3-year (A) and 5-year (B) overall survival. (C, D) Kaplan-Meier survival analysis shows the differences of progression-free survival (C) and overall survival (D) among the three risk stratifications of SEC. (E, F) Time-dependent area under the curve comparisons for different models of progression-free survival (E) and overall survival (F). OS: overall survival; AUC: area under the curve; PFS: progression-free survival; SEC: the new nomogram; IPI: International Prognostic Index; KPI: Korean Prognostic Index; PINK: prognostic index for natural killer lymphoma; PINK-E: PINK with Epstein-Barr virus-DNA; PINK-EC: PINK-E with circulating tumor DNA.

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 were calculated to compare the predictive accuracy of SEC with those of the IPI, KPI, PINK, PINK-E, and PINK-EC. The AUC of PFS and OS for SEC were greater and more stable than those of the other five prognostic models (Figure 3E, F).

The SEC nomogram is the first to use three semiquantitative or quantitative parameters with specific numerical cutoff values and could distinguish low-, intermediate-, and high-risk groups well. The good survival of low-risk patients classified by the SEC 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 SEC nomogram had better prognostic prediction, risk stratification, and clinical use. We are currently conducting further validation of the model in a multicenter trial for the rare morbidity of ENKTL.

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Disclosures

No conflicts of interest to disclose.

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.

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Data-sharing statement

All data have been included in this article and the online supporting information.

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