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ORIGINAL RESEARCH

Development and Validation of a Neutrophil Percentage-to-Albumin Ratio-Based Nomogram for Predicting Overall Survival in Locally Advanced Nasopharyngeal Carcinoma

Xiaohui Yang[1], Lu Huang[2], Song Qu[1]

[1]Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, People's Republic of China; [2]Affiliated Wu-Ming Hospital of Guangxi Medical University, Nanning, Guangxi, People's Republic of China

Correspondence: Song Qu, Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, 530200, People's Republic of China, Tel +86 13607887386, Email 13607887386@163.com

Purpose: Hematology-based inflammatory-nutritional composite indices are robust prognostic biomarkers for malignancies due to their survival correlation. This study explored the prognostic value of the neutrophil percentage-albumin ratio (NPAR) – a composite marker reflecting systemic inflammation and nutrition – in locally advanced nasopharyngeal carcinoma (LA-NPC), whose predictive role in LA-NPC survival remains underexplored.

Patients and Methods: A retrospective study of 536 LA-NPC patients who received definitive radiotherapy at Guangxi Medical University Cancer Hospital was conducted. Patients were randomized into training (n=321, 60%) and validation (n=215, 40%) cohorts via the `sample()` function in R. NPAR and other continuous variables were dichotomized using optimal cut-offs from the `survminer` package in R. Kaplan-Meier and Log-rank analyses compared survival; least absolute shrinkage and selection operator (LASSO) regression identified key prognostic parameters, with univariate and multivariate Cox regression confirming independent survival factors. A prognostic nomogram was built from these factors, and its predictive efficacy was evaluated via calibration curves (accuracy), Harrell's C-index (discrimination), time-dependent receiver operating characteristic (tROC) curves, and decision curve analysis (DCA; clinical utility).

Results: Multivariate Cox regression for overall survival (OS) in the training cohort identified NPAR, age, TNM stage, pretreatment EBV DNA level, and hypertension as independent prognostic factors for LA-NPC. A nomogram integrating these five variables was constructed. Calibration curves, C-index, tROC curves, and DCA confirmed that the nomogram accurately predicted 3- and 5-year OS probabilities, with high consistency between predicted and observed outcomes. Furthermore, the nomogram outperformed the 8th edition TNM staging system in terms of predictive performance, as evidenced by superior C-index, tROC, and DCA results.

Conclusion: NPAR, an accessible routine blood-based hematological biomarker, is a promising prognostic indicator for LA-NPC. The nomogram integrating NPAR and key clinical parameters enables more accurate personalized treatment stratification, facilitating precision management and yielding translational potential for improved LA-NPC outcomes.

Keywords: NPAR, locally advanced nasopharyngeal carcinoma, prognostic nomogram

Introduction

Nasopharyngeal carcinoma (NPC) is a highly aggressive malignant head and neck tumor originating from the epithelial cells of the nasopharyngeal mucosa. Because the nasopharynx is anatomically concealed and early-stage NPC lacks specific clinical manifestations, most patients present with locally advanced disease at initial diagnosis. Some even develop distant metastasis, which adversely affects treatment outcomes and prognosis. Accumulating clinical evidence indicates that the 5-year overall survival (OS) rate of stage III NPC patients is only 89.2%, while that of stage IV patients drops to 73.7%. This indicates that advanced-stage patients have a significantly poorer prognosis,[1] thereby highlighting

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the core value of early diagnosis and timely intervention in the whole-course management of NPC. Currently, the TNM staging system, developed by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), serves as a core tool for clinically evaluating NPC patients' prognosis and guiding treatment decision-making.[2] Specifically, the traditional 8th edition AJCC TNM staging system stratifies prognostic risks mainly based on anatomical features, including tumor size, lymph node involvement, and distant metastasis. However, this staging system has notable limitations in NPC prognosis prediction. On the one hand, as a classification tool, it cannot account for tumor heterogeneity, leading to significant variations in survival outcomes among patients within the same TNM stage. On the other hand, this system focuses solely on tumor anatomical progression and fails to fully reflect patients' systemic health status. Numerous studies have demonstrated that systemic inflammatory response and nutritional status are key prognostic factors for cancer patients.[3,4] However, the existing TNM staging system does not incorporate these systemic indicators, which limits its clinical efficacy in prognostic assessment. Therefore, identifying reliable biomarkers for predicting metastasis and mortality risks to assist clinical decision-making is an important research direction in the translational medicine of locally advanced nasopharyngeal carcinoma (LA-NPC).

To date, Epstein-Barr virus (EBV) DNA remains the only biomarker with established clinical utility in NPC.[5–7] However, a growing body of evidence indicates that relying solely on this single tumor-associated indicator cannot fully capture the complex array of prognostic factors driving disease progression, and its prognostic predictive efficacy remains inadequate. Therefore, exploring novel and reliable biomarkers, developing a multi-factor-integrated nomogram prediction model, and thus providing a complementary risk stratification tool for the existing prognostic evaluation system have become core research priorities in NPC prognostic research.

In recent years, numerous studies have demonstrated that cancer-related inflammation and nutritional status play pivotal roles in tumorigenesis and progression. Relevant indicators, including the neutrophil-to-lymphocyte ratio (NLR),[7] systemic immune-inflammation index (SIRI),[8] and platelet-to-albumin ratio (PAR),[9] have been extensively investigated for their prognostic value in NPC. As an emerging composite indicator that integrates systemic inflammatory responses and nutritional status, the Neutrophil Percentage to Albumin Ratio (NPAR) has been established to possess distinct prognostic value in multiple solid malignancies.[10–12] However, the role of NPAR in prognostic assessment for patients with LA-NPC remains insufficiently elucidated, and no prognostic models based on this indicator have been developed to date. Based on this research gap, the present study innovatively centers on the NPAR indicator, with the primary aim of systematically evaluating its prognostic significance in LA-NPC via retrospective cohort analysis. This study further seeks to develop, for the first time, an NPAR-based nomogram prognostic model to predict long-term survival outcomes in LA-NPC patients, thereby overcoming the limitations of conventional single staging systems. The core implication of this study lies in its potential to deliver a novel and clinically practical quantitative prognostic assessment tool for clinical practice. This tool is expected to help clinicians more accurately stratify patients' survival risks, formulate personalized treatment strategies, and ultimately enhance patients' overall survival rates and quality of life.

Materials and Methods

Research Population

This retrospective study enrolled patients with LA-NPC who were treated at Guangxi Medical University Cancer Hospital between March 2015 and July 2022. To ensure research standardization and data reliability, included patients had to meet all the following criteria: (1) Histopathologically confirmed as newly diagnosed, non-metastatic, undifferentiated non-keratinizing nasopharyngeal carcinoma via nasopharyngeal biopsy and imaging examinations; (2) Staged as III or IVA according to the 8th edition of the UICC/AJCC staging system; (3) Treated with radical concurrent chemoradiotherapy-(CCRT), with the possibility of receiving neoadjuvant or adjuvant chemotherapy; (4) Completed hematological tests, imaging examinations, and nasopharyngoscopy performed within one week prior to initiation of treatment; (5) With complete hospitalization records and follow-up data. Patients were excluded if they meet any of the following criteria: (1) Presence of distant metastasis at initial diagnosis or concurrent other primary malignancies; (2) Pre-treatment history of hematological disorders, infectious diseases, or nutritional deficiencies; (3) Failure to receive complete radical treatment; (4) Incomplete clinical records or lost to follow-up. The case selection process is detailed in Figure 1. Following rigorous

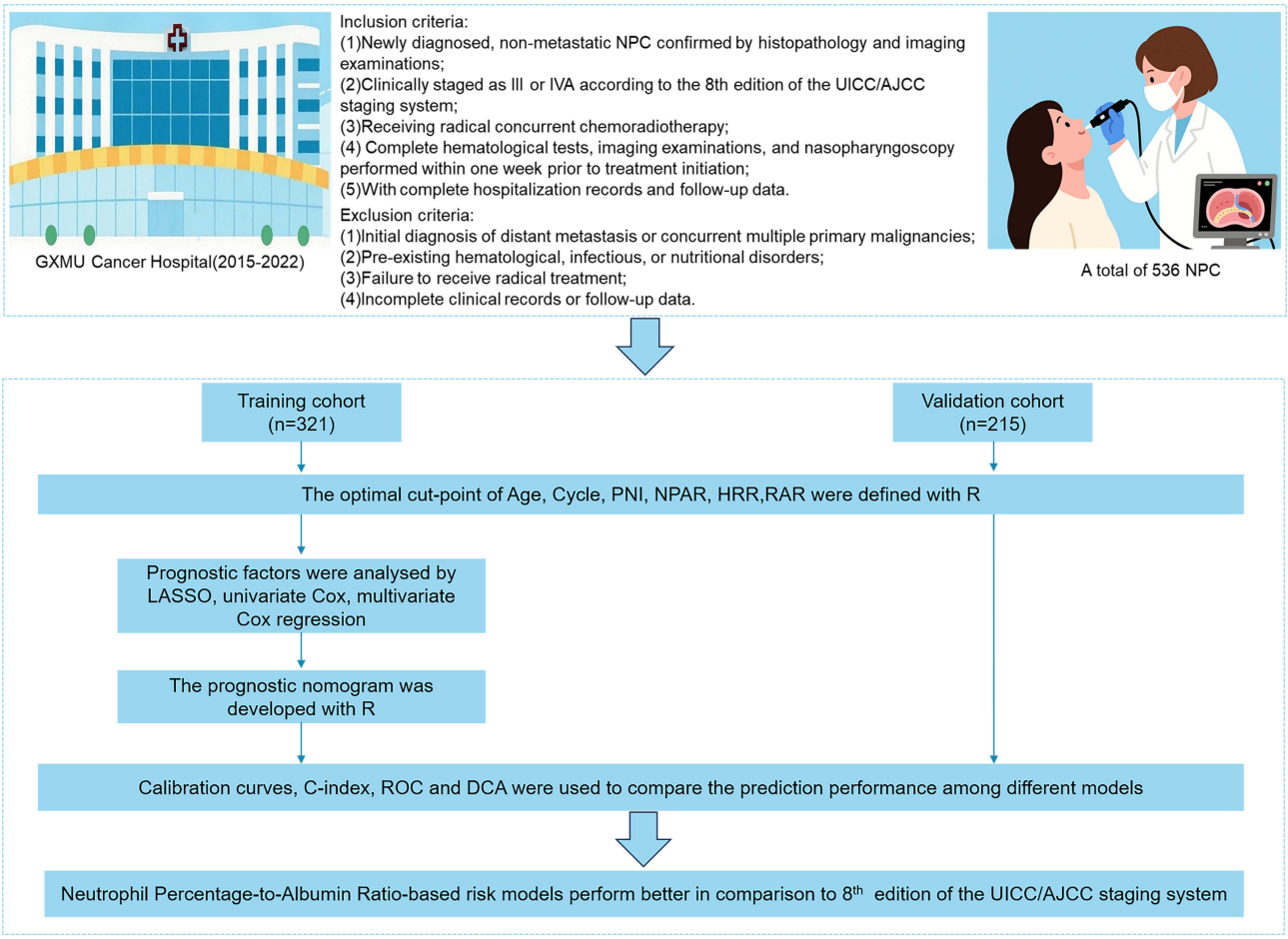

Figure 1 Flow chart of the study design.
Abbreviations: NPC, nasopharyngeal carcinoma; Cycle, total cycles of induction plus concurrent chemotherapy; PNI, prognostic nutritional index; NPAR, neutrophil percentage to albumin ratio; HRR, hemoglobin-to-red blood cell distribution width ratio; RAR, red blood cell distribution width-to-albumin ratio; LASSO, the least absolute shrinkage and selection operator; ROC, receiver operating characteristic; DCA, decision-curve analysis; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer.

screening against inclusion and exclusion criteria, 536 patients were eligible and included in the study. This research adhered to the principles of the Declaration of Helsinki and relevant ethical guidelines, with approval from the Guangxi Medical University Cancer Hospital Ethics Review Committee (No. KY2025985). Informed consent was waived due to its retrospective nature of the study. Data was anonymized to protect the privacy of the participants.

Research Variables

A total of 536 patients with LA-NPC were included in this study. The following clinical data were extracted from their medical records: age, gender, ethnicity, family history of cancer, alcohol use history, smoking history, history of hypertension, history of diabetes, hepatitis B virus (HBV) infection status, T stage, N stage, TNM stage, number of chemotherapy cycles (defined as the total number of cycles of neoadjuvant chemotherapy and concurrent chemotherapy), receipt of adjuvant chemotherapy, and receipt of targeted therapy.

Laboratory indicators were derived from blood samples collected one week prior to the initiation of treatment, including pre-treatment inflammatory biomarkers, nutritional indices, and EBV DNA levels.

The formulas for calculating inflammatory and nutritional indicators are as follows:

PNI (prognostic nutritional index) = Serum Albumin (g/L) + 5 × Total Lymphocyte Count (10^9/L);[13]

NPAR (neutrophil percentage-to-albumin ratio) = Neutrophil Percentage (%) / Serum Albumin (g/dL [or g/L x 10]);[14,15]

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HRR (hemoglobin-red blood cell distribution width ratio) = Hemoglobin (g/dL) / Red Blood Cell Distribution Width (%);[16]

RAR (red blood cell distribution width to albumin ratio) = Red Blood Cell Distribution Width (%) / Serum albumin (g/dL [or g/L x 10]);[17]

Determination of Optimal Cutoff Points

The cut-off values for Age, Cycle (total number of chemotherapy cycles), PNI, NPAR, HRR, and RAR were all determined via the optimal stratification method. We calculated the optimal cut-off values for each continuous variable based on maximum rank statistics, using the `surv_cutpoint() `function in the `survminer` package of R software. This outcome-oriented method enables the selection of critical values with the most significant correlation with OS. The grouping criteria for EBV DNA in this study were as follows: with the cut-off value set at 5000 copies/mL (as established by our laboratory),[18] EBV DNA test results were categorized into two groups: detectable and undetectable Meanwhile, according to pre-treatment EBV DNA level, the study participants were further stratified into high- level and low- level groups, and the grouped data were incorporated into subsequent statistical analyses.

Treatment and Follow-Up

In this study, all patients received radical radiotherapy as the primary treatment. Specific radiation doses were as follows: ≥70Gy for the primary tumor; 60–70Gy for involved cervical lymph nodes; and 54Gy for prophylactic irradiation of cervical lymph nodes. All irradiations were delivered using a 30–33 fractionation schedule. Chemotherapy regimens were as follows: concurrent chemotherapy used platinum-based agents (eg, cisplatin), administered every 3 weeks for a total of 2–3 cycles. Neoadjuvant chemotherapy employed the TPF or GP regimen, given every 3 weeks for 2–3 cycles. Adjuvant chemotherapy adopted the PF regimen or capecitabine-based intermittent chemotherapy, with selection based on the patient's individual performance status and disease stage as assessed by the treating physician.

Following treatment completion, the patient follow-up schedule was as follows: every 3 months for the first 2 years post-treatment; every 6 months from the 3 to 5 years; and annually thereafter. The primary endpoint of this study is OS, defined as the interval from the date of initial diagnosis to the date of patient death or the date of last follow-up.

Research Design and Statistical Analysis

A total of 536 participants were included in this study, with 114 outcome events recorded. In the multivariate analysis, each variable had over 10 events, confirming adequate statistical power for the study.[19] The 536 patients were randomly allocated at a 3:2 ratio via simple random sampling using the `sample()` function in R, with 321 (60%) assigned to the training set and 215 (40%) to the validation set. Continuous variables were presented as median (interquartile range) and categorical variables as frequencies (percentages). Group comparisons were performed using the Pearson's chi-squared test or Fisher's exact test for categorical variables, and the Mann–Whitney *U*-test for continuous variables. Minor missing data were addressed using the `mice` package in R via multiple imputation to maximize sample size retention.[20] The optimal cutoff values for continuous variables were computed using the `survminer` package in R, with survival status as the endpoint, and these variables were then converted to binary variables. Using the `glmnet` package in R, we applied least absolute shrinkage and selection operator (LASSO) Cox regression to the training set. Optimal predictive features were selected via cross-validation, a step that helped prevent overfitting and the omission of highly correlated factors. Subsequently, a univariate Cox proportional hazards regression model was used to systematically evaluate the association between each study variable and patients' overall survival (OS). Variables with a $P < 0.05$ from the univariate analysis were further included in a multivariate Cox regression model. Finally, independent prognostic factors with a $P < 0.05$ were identified. An individualized prognostic nomogram was subsequently constructed based on these factors using the "nomogram ()" function, enabling the visual prediction of patients' 3-year and 5-year OS rates. Model performance was validated using the following methods: Firstly, the `survival` and `timeROC` packages were used to separately calculate the C-index and generate time-dependent receiver operating characteristic (tROC) curves to assess the discriminative ability of the model. Secondly, the `calibrate()` function was used to plot calibration curves for evaluating the calibration performance of the model, and its internal validity was tested via the bootstrap method. Thirdly, the `ggDCA` package

was utilized to perform decision curve analysis (DCA) to compare the net prognostic benefit between this nomogram and the TNM staging system.

Prognostic risk scores for each patient were calculated using the nomogram. The optimal cutoff value was determined using the `survminer` package in R to stratify patients into high-risk and low-risk groups. Survival curves were plotted using the Kaplan-Meier method, with between-group differences compared via the Log rank test. All statistical analyses were performed using the SPSS Statistics (IBM Corp., Armonk, NY, USA; version 27.0) and R software (version 4.5.0; R Core Team, Vienna, Austria). A two-sided p-value<0.05 was considered statistically significant.

A detailed flowchart of patient recruitment, data collection, and analysis is presented in Figure 1.

Results

Baseline Characteristics of the Study Participants

This study enrolled 536 patients with LA-NPC who received radical chemoradiotherapy. Of these, 390 (72.761%) were male and 146 (27.239%) female; the median age was 46 years (range, 17–69 years), median follow-up duration 60.50 months (range, 5–124 months), and 114 patients (21.269%) died during follow-up. Regarding ethnic distribution, the Han ethnicity accounted for 65.112%, with ethnic minorities (Zhuang, Yao, Mulao, etc.) comprising 34.888%. Based on the 8th edition UICC/AJCC TNM staging system, 138 cases (25.746%) were staged T1–T2, 398 (74.254%) T3–T4, 149 (27.799%) N0–N1, and 387 (72.201%) N2–N3. All patients were randomly allocated to a training set (n=321) and a validation set (n=215) at a 3:2 ratio. Detailed clinical baseline characteristics of both groups are presented in Table 1, with no significant differences observed in demographic or clinical features between the two groups (all P>0.05).

Table 1 Baseline Demographics of Patients with LA-NPC, Their Clinical Characteristics, and Inter-Cohort Differences

Characteristics	All Patients (N=536) [cases (%)]	Training Cohort (N=321) [cases (%)]	Validation Cohort (N=215) [cases (%)]	P
Gender				0.853
Male	390 (72.761)	235 (73.209)	155 (72.093)	
Female	146 (27.239)	86 (26.791)	60 (27.907)	
Age				0.802
(Median [IQR])	46 (38–54)	46 (38–54)	47 (38–54)	
Ethnic Minorities				0.310
Han	349 (65.112)	215 (66.978)	134 (62.326)	
Minority	187 (34.888)	106 (33.022)	81 (37.674)	
Family history				1.000
No	487 (90.858)	292 (90.966)	195 (90.698)	
Yes	49 (9.142)	29 (9.034)	20 (9.302)	
Smoking				0.704
No	338 (63.060)	205 (63.863)	133 (61.860)	
Yes	198 (36.940)	116 (36.137)	82 (38.140)	
Alcohol				0.112
No	371 (69.216)	231 (71.963)	140 (65.116)	
Yes	165 (30.784)	90 (28.037)	75 (34.884)	
Hypertension				1.000
No	495 (92.351)	296 (92.212)	199 (92.558)	
Yes	41 (7.649)	25 (7.788)	16 (7.442)	

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients (N=536) [cases (%)]	Training Cohort (N=321) [cases (%)]	Validation Cohort (N=215) [cases (%)]	P
Diabetes				0.844
No	511 (95.336)	307 (95.639)	204 (94.884)	
Yes	25 (4.664)	14 (4.361)	11 (5.116)	
Hepatitis B				0.416
No	462 (86.194)	273 (85.047)	189 (87.907)	
Yes	74 (13.806)	48 (14.953)	26 (12.093)	
T stage				0.150
T1+T2	138 (25.746)	75 (23.364)	63 (29.302)	
T3+T4	398 (74.254)	246 (76.636)	152 (70.698)	
N stage				0.803
N0+N1	149 (27.799)	91 (28.349)	58 (26.977)	
N2+N3	387 (72.201)	230 (71.651)	157 (73.023)	
TNM stage				0.386
III	162 (30.223)	92 (28.660)	70 (32.558)	
IVA	374 (69.776)	229 (71.340)	145 (67.442)	
Cycle (median [IQR])	5 [5,6]	5 [5, 6]	5 [5, 6]	0.920
Adjuvant chemotherapy				0.137
No	485 (90.485)	285 (88.785)	200 (93.023)	
Yes	51 (9.515)	36 (11.215)	15 (6.977)	
Targeted therapy				0.211
No	356 (66.418)	206 (64.174)	150 (69.767)	
Yes	180 (33.582)	115 (35.826)	65 (30.232)	
EBV DNA				0.113
<5000	383 (71.455)	238 (74.143)	145 (67.442)	
≥5000	153 (28.545)	83 (25.857)	70 (32.558)	
PNI (median [IQR])	48.600 [45.400, 51.588]	48.600 [45.275, 51.625]	48.600 [45.600, 51.500]	0.750
NPAR (median [IQR])	15.709 [14.017, 17.519]	15.626 [14.020, 17.508]	15.822 [13.930, 17.537]	0.900
HRR (median [IQR])	1.066 [0.950, 1.168]	1.066 [0.938, 1.165]	1.066 [0.968, 1.172]	0.688
RAR (median [IQR])	3.317 [3.083, 3.625]	3.325 [3.082, 3.628]	3.308 [3.092, 3.625]	0.729

Abbreviations: LA-NPC, locally advanced nasopharyngeal carcinoma; Cycle, total cycles of induction plus concurrent chemotherapy; PNI, prognostic nutritional index; NPAR, neutrophil percentage to albumin ratio; HRR, hemoglobin-to-red blood cell distribution width ratio; RAR, red blood cell distribution width-to-albumin ratio; IQR, interquartile range.

Determination of Optimal Cut-off Values for Key Indicators

In the training set, the optimal cut-off values for age, number of chemotherapy cycles, PNI, NPAR, HRR, and RAR were calculated using the `survminer` package in R as 42, 5, 45.35, 18.821, 1.243, and 4.046, respectively. Patients in both the training and validation sets were stratified into low- and high-level groups based on the optimal cut-off values for each indicator, as follows: Age <42 vs ≥42; Cycles ≤5 vs >5; PNI ≤45.350 vs >45.350; NPAR ≤18.821 vs >18.821; HRR ≤1.243 vs >1.243; RAR ≤4.046 vs >4.046. Kaplan-Meier survival curve analysis revealed significant differences in survival rates between low- and high-level groups for age (Figure 2A: HR=2.620, 95% CI:1.471–4.665, P<0.001) and NPAR in the training set (Figure 2D: HR=1.850, 95% CI:1.027–3.331, P=0.041). By contrast, no statistically significant differences were observed for number of chemotherapy cycles (Figure 2B: HR=0.577, 95% CI:0.309–1.076, P=0.084),

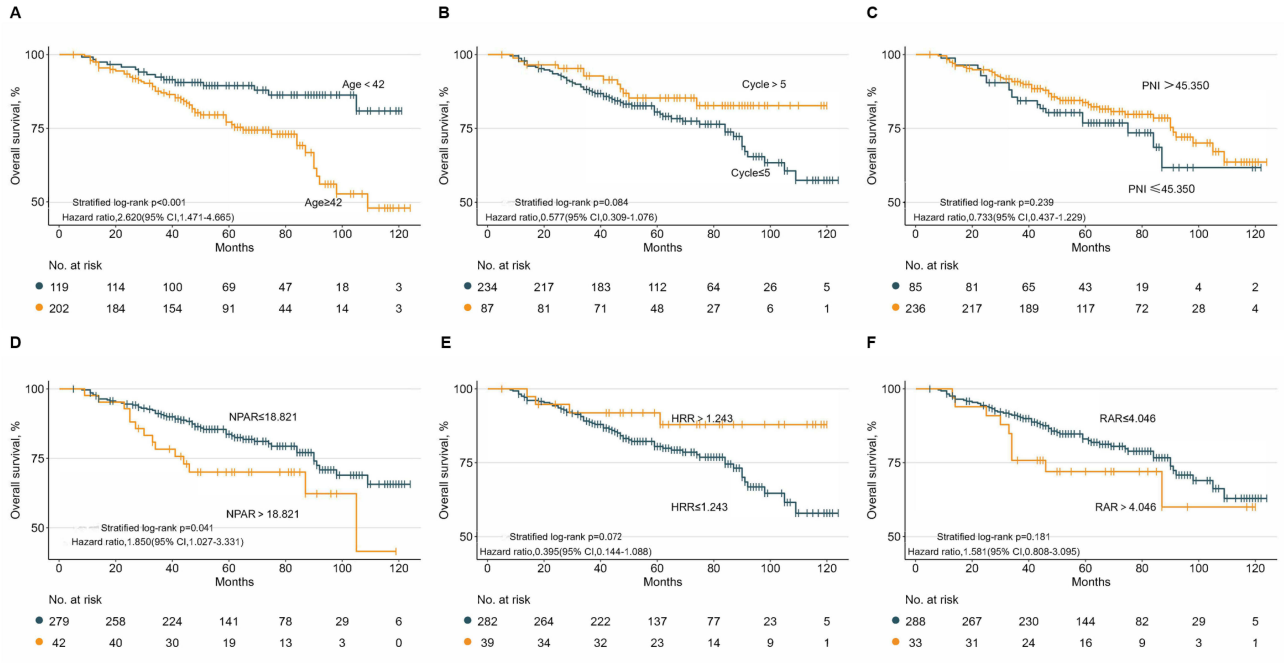

Figure 2 Kaplan-Meier curves for OS in the training cohort, stratified by the cut-off value of each index: (**A**) age, (**B**) Cycle, (**C**) PNI, (**D**) NPAR, (**E**) HRR, and (**F**) RAR.
Abbreviations: OS, overall survival, Cycle, total cycles of induction plus concurrent chemotherapy; PNI, prognostic nutritional index; NPAR, neutrophil percentage to albumin ratio; HRR, hemoglobin-to-red blood cell distribution width ratio; RAR, red blood cell distribution width-to-albumin ratio.

PNI (Figure 2C: HR=0.733, 95% CI:0.437–1.229, P=0.239), HRR (Figure 2E: HR=0.395, 95% CI:0.144–1.088, P=0.072), and RAR (Figure 2F: HR=1.581, 95% CI:0.808–3.095, P=0.181) between the stratified groups.

Identification of Independent Predictors of OS in LA-NPC

Using the LASSO Cox proportional hazards regression model (Figure 3A), 12 potentially prognostic variables associated with OS were identified (Figure 3B). All variables with non-zero regression coefficients from the LASSO Cox model were included in univariate Cox proportional hazards regression analyses (Table 2). Variables with a statistically significant association (P<0.05) from univariate analyses were further incorporated into multivariate Cox proportional

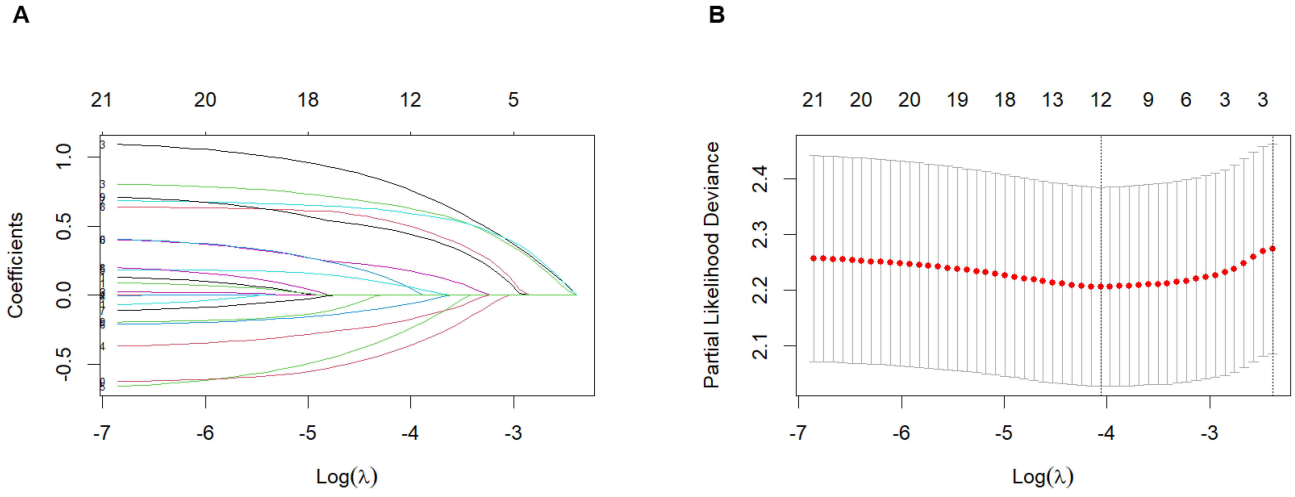

Figure 3 Visualization of LASSO Cox regression for screening clinical characteristics and peripheral blood indices.
Notes: (**A**) LASSO coefficient profiles of 12 risk factors; (**B**) Selection of the optimal tuning parameter (λ) via partial likelihood deviance in LASSO Cox regression analysis.
Abbreviation: LASSO, the least absolute shrinkage and selection operator.

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Table 2 Regression Coefficients of the LASSO Cox Model

Serum Marker	β
Age	0.635
Family history	0.067
Smoking	0.182
Hypertension	0.511
Hepatitis B	0.072
TNM	0.778
Cycle	−0.182
Adjuvant chemotherapy	−0.260
Targeted therapy	−0.069
EBV DNA	0.598
NPAR	0.452
HRR	−0.377

Abbreviations: LASSO, the least absolute shrinkage and selection operator; Cycle, total cycles of induction plus concurrent chemotherapy; EBV DNA, Epstein-Barr virus DNA; NPAR, neutrophil percentage to albumin ratio; HRR, hemoglobin-to-red blood cell distribution width ratio;

hazards regression, which identified five independent prognostic factors for OS in patients with LA-NPC: Age≥42 years (P=0.003), hypertension (P=0.049), stage IVA (P=0.008), EBV DNA≥5000 copies/mL (P=0.004), and NPAR>18.821 (P=0.022) (Table 3). These multivariate Cox regression results were visualized in a forest plot of hazard ratios (Figure 4).

Table 3 Univariate and Multivariate Cox Proportional Hazard Analysis of the Training Cohort

Characteristic	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Female	Reference			
Male	1.019(0.600–1.732)	0.944		
Age				
<42	Reference		Reference	
≥42	2.620(1.471–4.665)	0.001	2.490(1.371–4.524)	0.003
Ethnic Minorities				
Minority	Reference			
Han	0.921(0.563–1.509)	0.745		
Family history				
No	Reference			
Yes	1.676(0.856–3.284)	0.132		

(*Continued*)

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Table 3 (Continued).

Characteristic	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Smoking				
No	Reference			
Yes	1.546(0.953–2.506)	0.077		
Alcohol				
No	Reference			
Yes	1.074(0.631–1.826)	0.793		
Hypertension				
No	Reference		Reference	
Yes	2.598(1.278–5.284)	0.008	2.071(1.003–4.277)	0.049
Diabetes				
No	Reference			
Yes	0.604(0.147–2.471)	0.483		
Hepatitis B				
No	Reference			
Yes	1.169(0.595–2.297)	0.650		
T stage				
T1+T2	Reference			
T3+T4	1.089(0.604–1.965)	0.777		
N stage				
N0+N1	Reference			
N2+N3	1.185(0.691–2.033)	0.537		
TNM stage				
III	Reference		Reference	
IVA	3.734(1.708–8.164)	<0.001	2.900(1.314–6.399)	0.008
Cycle				
≤5	Reference			
>5	0.577(0.309–1.076)	0.084		
Adjuvant chemotherapy				
No	Reference			
Yes	0.451(0.141–1.439)	0.178		
Targeted therapy				
No	Reference			
Yes	0.620(0.348–1.105)	0.105		
EBV DNA				
<5000	Reference		Reference	
≥5000	2.326(1.434–3.775)	<0.001	2.084(1.272–3.414)	0.004
PNI				
≤45.350	Reference			
>45.350	0.733(0.437–1.229)	0.239		
NPAR				
≤18.821	Reference		Reference	
>18.821	1.850(1.027–3.331)	0.041	2.031(1.107–3.728)	0.022

(*Continued*)

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Table 3 (Continued).

Characteristic	Univariate Cox Analysis		Multivariate Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
HRR				
≤1.243	Reference			
>1.243	0.395(0.144–1.088)	0.072		
RAR				
≤4.046	Reference			
>4.046	1.581(0.808–3.095)	0.181		

Abbreviations: Cycle, total cycles of induction plus concurrent chemotherapy; EBV DNA, Epstein-Barr virus DNA; PNI, prognostic nutritional index; NPAR, neutrophil percentage to albumin ratio; HRR, hemoglobin-to-red blood cell distribution width ratio; RAR, red blood cell distribution width-to-albumin ratio.

Development and Validation of a Novel NPAR-Based Prognostic Nomogram

Based on the five independent prognostic factors identified by the aforementioned multivariate Cox proportional hazards regression model, a novel and practical nomogram was developed in this study to visually estimate 3-year and 5-year OS probabilities in patients with LA-NPC (Figure 5). Clinicians can utilize this nomogram to assess the prognostic risk of individual patients prior to formulating treatment plans. The nomogram assigns corresponding scores to each factor based on patient characteristics: for instance, patients aged≥42 years receive a higher score in the "age" dimension, while those with stage IVA disease score higher in the "clinical stage" dimension compared to patients with stage III disease. By

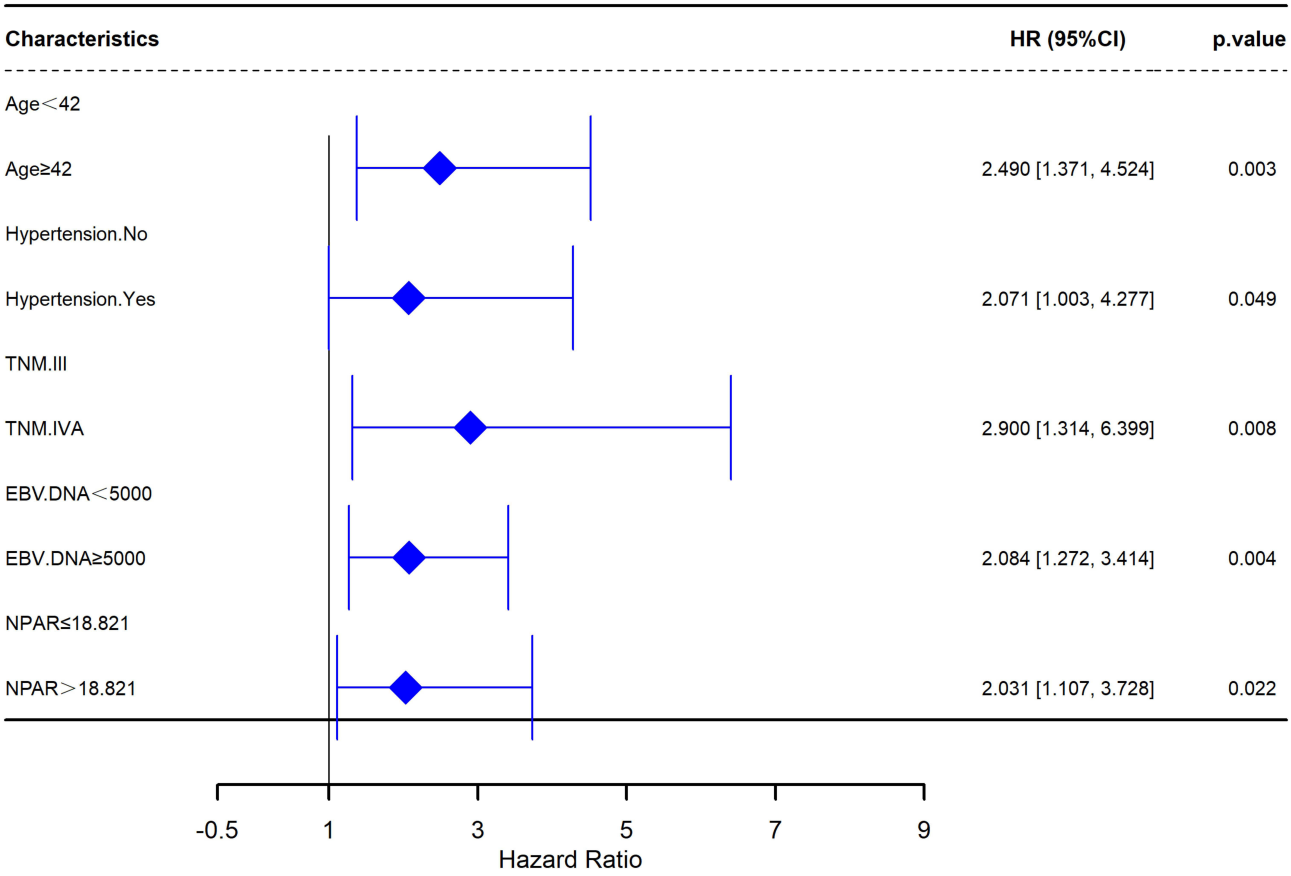

Figure 4 Forest plot of multivariate Cox regression analysis for OS in the training cohort of LA-NPC.
Abbreviations: OS, overall survival; LA-NPC, locally advanced nasopharyngeal carcinoma.

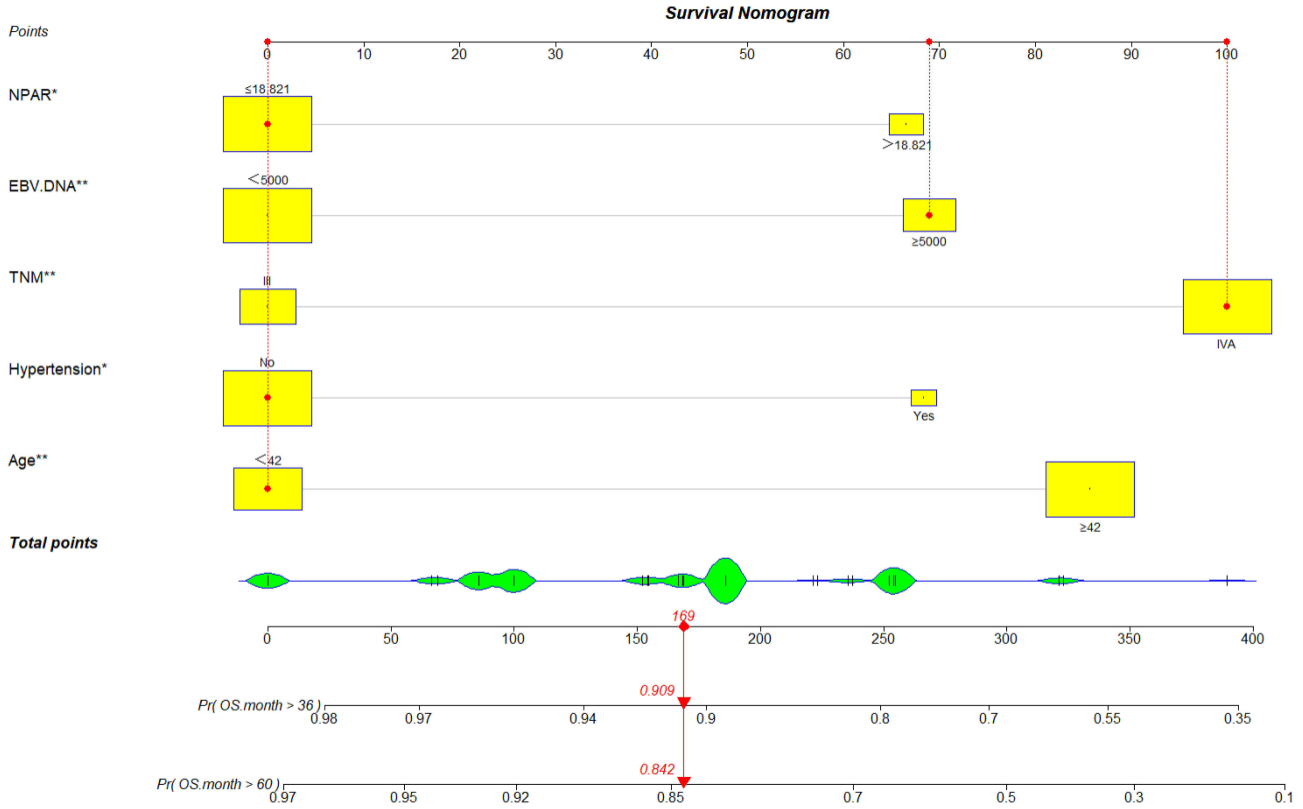

Figure 5 Prognostic nomogram for predicting 36-month and 60-month OS in the training cohort of LA-NPC, incorporating variables including NPAR, EBV DNA, TNM stage, hypertension and age.

Notes: The single asterisk (*) and double asterisks (**) adjacent to variable names (eg, NPAR, EBV DNA) indicate the statistical significance of each variable as an independent prognostic factor (derived from multivariate Cox proportional hazards regression analysis), corresponding to the 0.05 and 0.01 levels, respectively.

Abbreviations: OS, overall survival; LA-NPC, locally advanced nasopharyngeal carcinoma; NPAR, neutrophil percentage to albumin ratio; EBV DNA, Epstein-Barr virus DNA.

summing the scores of all five factors, clinicians can estimate a patient's OS probability. An illustrative case is as follows: a 41-year-old patient with no history of hypertension, clinical stage IVA, EBV DNA≥5000 copies/mL, NPAR≤18.821, with a total score of 169, corresponding to estimated 3-year and 5-year OS probabilities of 90.9% and 84.2%, respectively.

The predictive accuracy and performance of the nomogram were validated using multiple statistical metrics and graphical assessments. For the prognostic nomogram developed in this study—which incorporates NPAR and the other four identified independent prognostic factors—the calibration curves for 3-year and 5-year OS prediction (Figure 6) showed a high degree of alignment with the 45-degree diagonal, indicating strong consistency between the model-predicted risk probabilities and the observed clinical outcomes.

Time-dependent ROC curves were used to evaluate the model's predictive accuracy for OS. A higher area under the curve (AUC) indicates superior predictive performance, facilitating more precise prognostic stratification. In the training set, the nomogram yielded AUCs of 0.663 (95% CI: 0.573–0.754) and 0.704 (95% CI: 0.626–0.782) for 3- and 5-year OS, respectively; corresponding values in the validation set were 0.797 (95% CI: 0.702–0.892) and 0.765 (95% CI: 0.684–0.847), all outperforming those of the conventional TNM staging system (Figure 7). Additionally, the C- indices in the training and validation sets were 0.686 (95% CI: 0.621–0.751) and 0.753 (95% CI: 0.688–0.819), respectively, which were significantly higher than those of the conventional 8th edition TNM staging system (training set: 0.591 [95% CI: 0.545–0.638]; validation set: 0.626 [95% CI: 0.577–0.675]). These findings further confirm that the nomogram exhibits superior predictive accuracy compared with the conventional TNM staging system.

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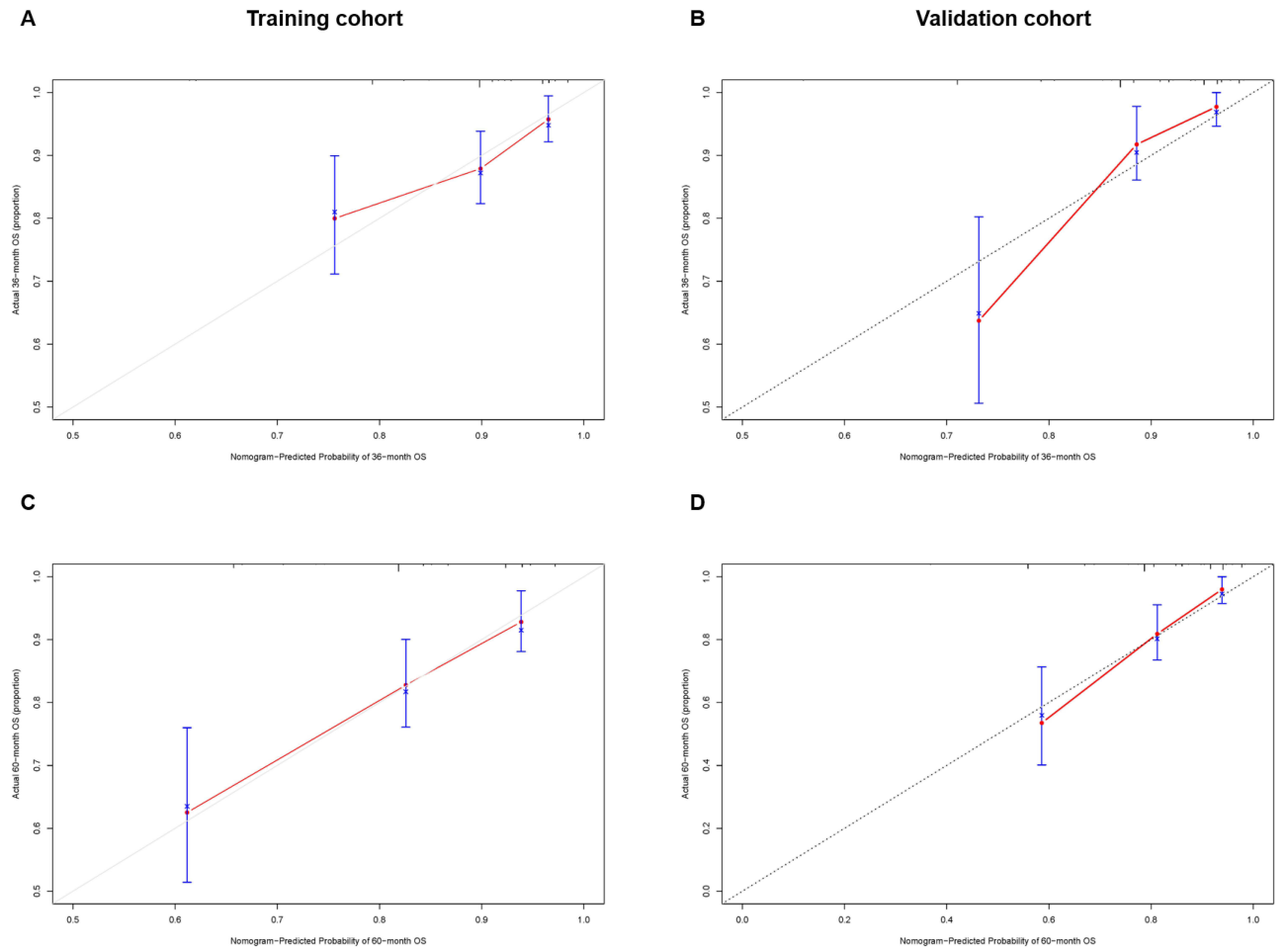

Figure 6 Calibration plots for evaluating 3-year and 5-year OS in patients with LA-NPC.
Notes: (**A, C**) Calibration plots for 3-year and 5-year OS in the training cohort; (**B, D**) Calibration plots for the same endpoints in the validation cohort. The X-axis represents the nomogram-predicted probability of survival, and the Y-axis represents the actual observed survival probability. Bars indicate 95% confidence intervals (derived from Kaplan-Meier analysis), while the diagonal line serves as the ideal reference line (perfect agreement between predicted and observed outcomes).
Abbreviations: OS, overall survival; LA-NPC, locally advanced nasopharyngeal carcinoma.

DCA quantifies the net benefit across a range of threshold probabilities to determine the clinical utility of a nomogram. The results of this study demonstrated that the novel nomogram-based risk model yielded a significantly superior net benefit at all threshold probabilities compared with the clinically established TNM staging system (Figure 8).

Collectively, these findings indicate that the novel nomogram developed in this study is superior to the conventional 8th edition UICC/AJCC TNM staging system in terms of both predictive accuracy for individual survival outcomes and clinical utility.

Prognostic Risk Stratification and Value Based on the Nomogram

To further validate the clinical utility of the nomogram, prognostic risk stratification was performed. In the training cohort, patients were stratified into low-risk (total score ≤ 353.521) and high-risk (total score > 353.521) groups using nomogram-derived total scores, with significant prognostic differences observed between the two groups. The same cutoff value was applied to stratify patients in the validation cohort. Kaplan-Meier survival curves (Figure 9) demonstrated significant separation between the survival curves of the two risk groups in both cohorts, with the high-risk group showing markedly worse survival outcomes than the low-risk group (training cohort: P<0.0001; validation cohort: P=0.00013). Furthermore, within the conventional 8th edition UICC/AJCC TNM staging system, OS rates differed significantly between stage III and IVA patients (training cohort: P=0.00039; validation cohort: P=0.00017). However,

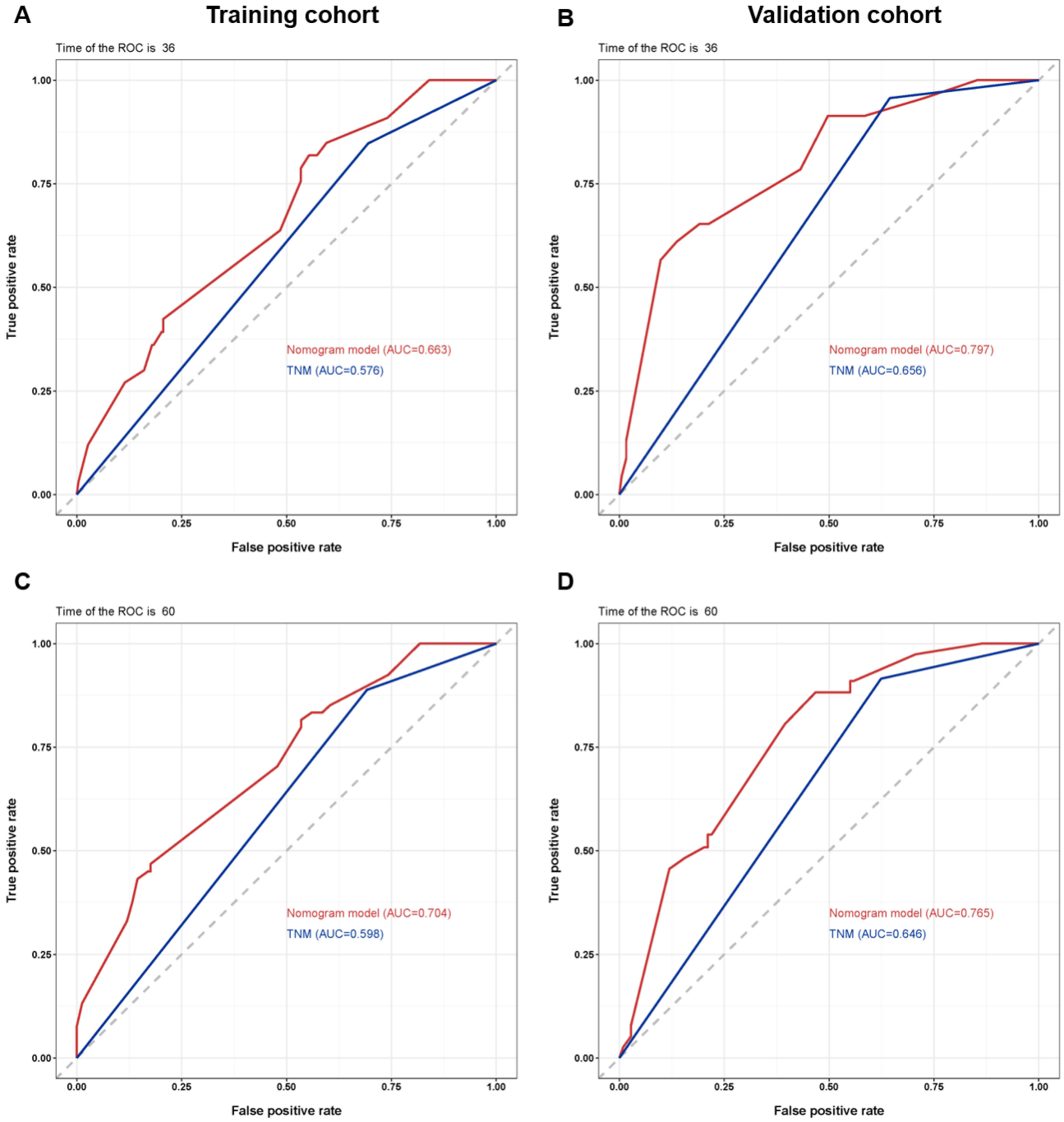

Figure 7 Time-dependent ROC curves for OS prediction.
Notes: (**A**) 3-year ROC curve in the training cohort; (**B**) 3-year ROC curve in the validation cohort; (**C**) 5-year ROC curve in the training cohort; (**D**) 5-year ROC curve in the validation cohort. The red curve represents the nomogram model, and the blue curve represents the TNM staging system. Annotated AUC values indicate that the nomogram model exhibits superior OS predictive performance compared with the TNM staging system across both cohorts and time points.
Abbreviations: ROC, receiver operating characteristic; OS, overall survival; AUC, area under the curve.

the nomogram exhibited superior discriminatory ability for identifying high- and low-risk subgroups compared with the conventional TNM staging system.

Discussion

Nasopharyngeal carcinoma is a malignancy characterized by distinct geographical clustering, with high endemicity primarily in East and Southeast Asia.[21] LA-NPC constitutes approximately 70–80% of newly diagnosed NPC cases in

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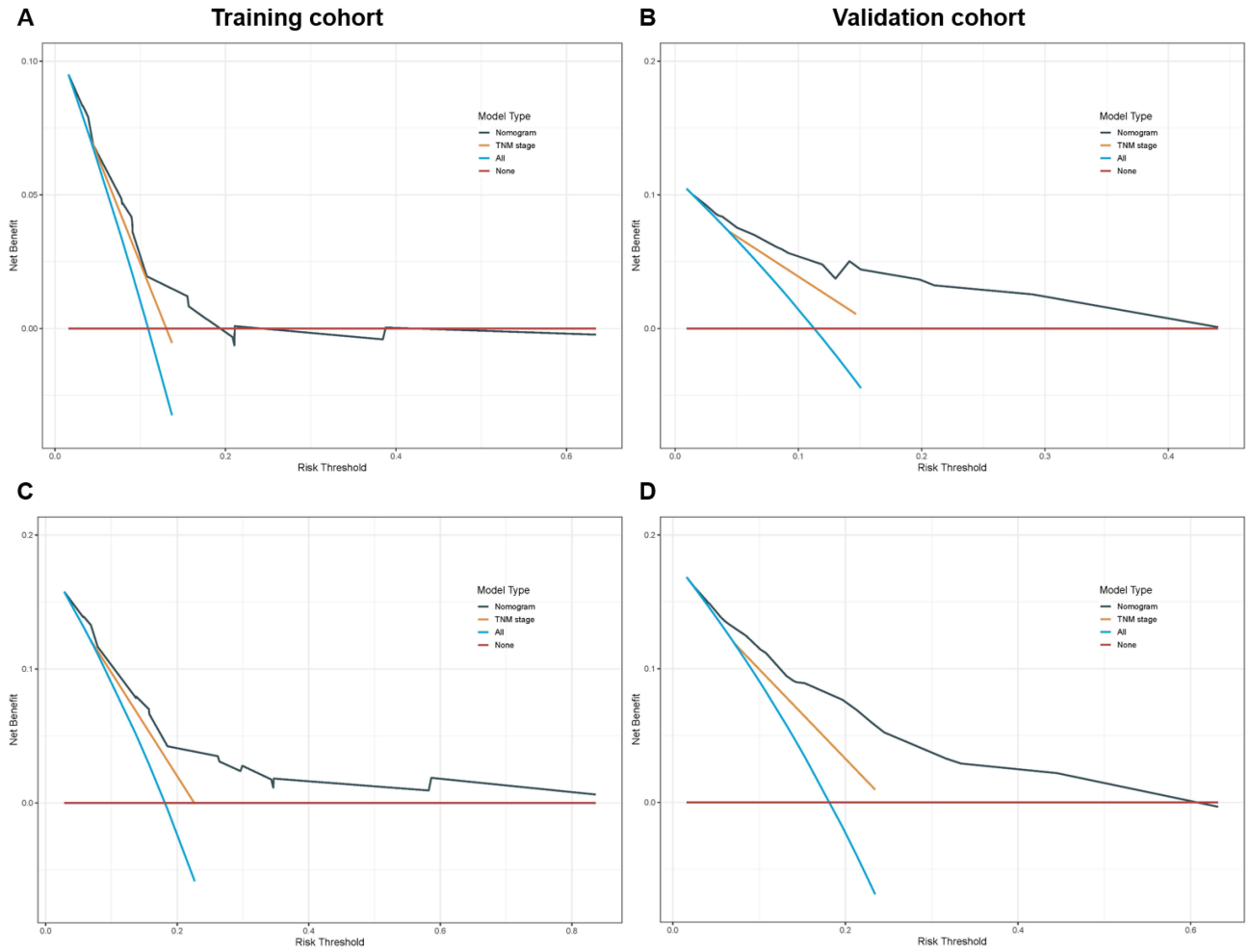

Figure 8 DCA for net benefit comparison between the nomogram model and traditional TNM staging system.
Notes: (**A**) 3-year OS DCA curve in the training cohort; (**B**) 3-year OS DCA curve in the validation cohort; (**C**) 5-year OS DCA curve in the training cohort; (**D**) 5-year OS DCA curve in the validation cohort. The x-axis represents the threshold probability, and the y-axis denotes the net benefit. The curves indicate that the nomogram model achieves a significantly higher net benefit than the traditional TNM staging system for both 3-year and 5-year OS in the training cohort (consistent trends are observed in the validation cohort).
Abbreviation: DCA, decision-curve analysis; OS, overall survival.

endemic regions, representing the most prevalent and clinically complex subtype in clinical practice.[22,23] Enhancing outcomes for LA-NPC patients holds substantial practical significance and important public health implications, as it elevates the overall quality of NPC diagnosis and treatment and mitigates regional disease burden. Definitive chemoradiotherapy serves as the standard therapeutic modality for LA-NPC.[21] With the widespread adoption of intensity-modulated radiotherapy (IMRT) technology and the clinical application of targeted agents, remarkable clinical breakthroughs and enhancements in LA-NPC treatment efficacy have been achieved over the past few decades. Despite these advancements, the clinical management of LA-NPC remains beset by notable challenges. For LA-NPC patients, the primary clinical objective during first-line treatment is to achieve effective tumor control and curative intent. Notably, marked interpatient heterogeneity in survival outcomes persists, even among patients with identical clinical staging. This heterogeneity is driven by variations in tumor biological behavior,[24] tumor microenvironment,[25] and host-related factors.[26] As a result, the clinical imperative for personalized therapy has grown increasingly pressing. For patients with low-risk disease, treatment de-escalation is warranted to reduce late-term toxicities without compromising efficacy; for those with high-risk disease, treatment intensification is warranted to improve survival outcomes while avoiding unnecessary toxicity. The successful implementation of such risk stratification is increasingly dependent on the clinical application of biomarkers.[27] Thus, identifying reliable biomarkers to optimize disease risk stratification and driving

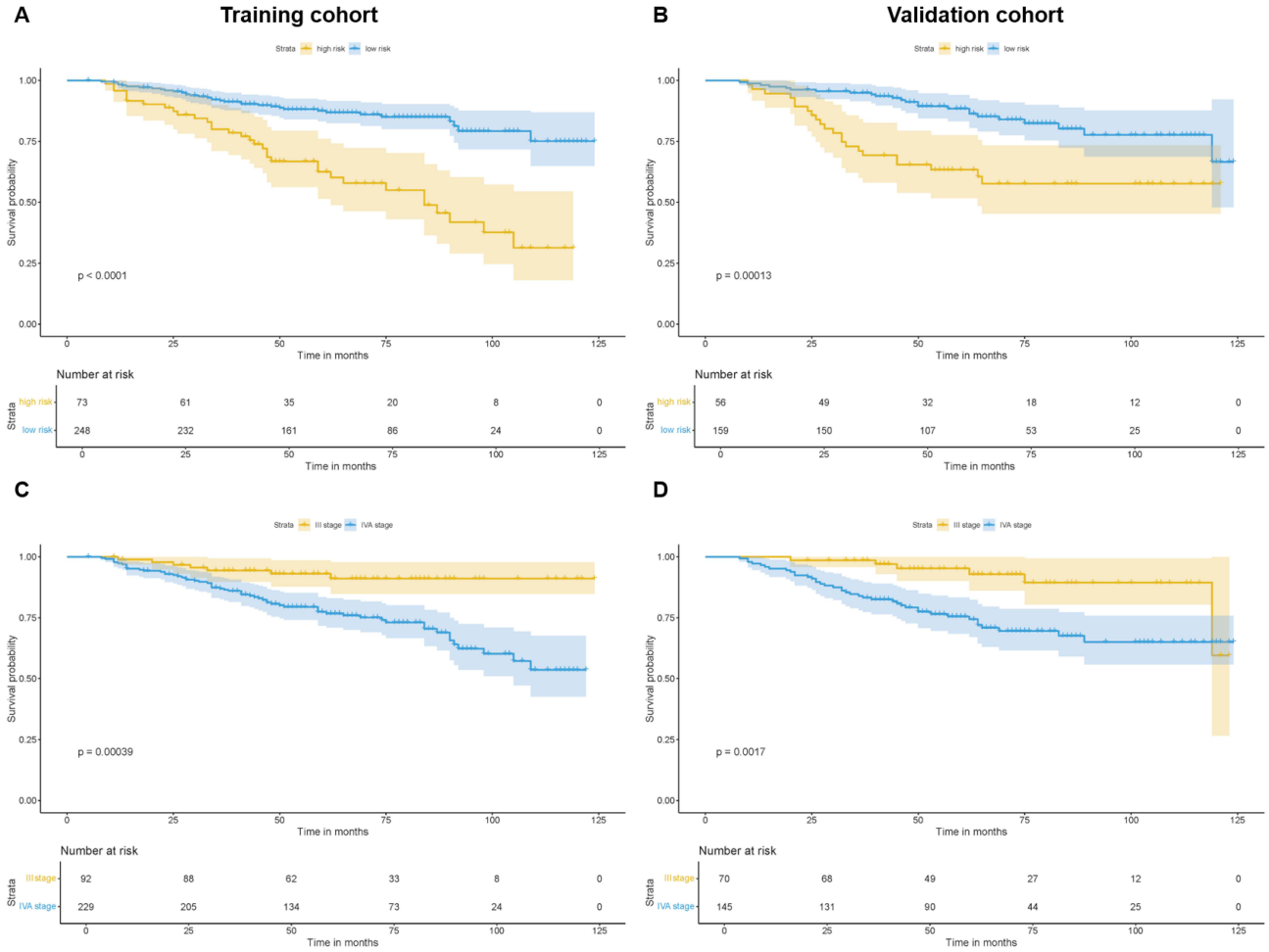

Figure 9 Kaplan-Meier curves for OS in patients with LA-NPC.

Notes: (**A**) Comparison of OS between nomogram-defined high-risk and low-risk groups in the training cohort; (**B**) Comparison of OS between nomogram-defined high-risk and low-risk groups in the validation cohort; (**C**) Comparison of OS between UICC/AJCC 8th edition stage III and IVA groups in the training cohort; (**D**) Comparison of OS between UICC/AJCC 8th edition stage III and IVA groups in the validation cohort. The p-values presented in each panel indicate significant OS differences between the compared groups.

Abbreviations: OS, overall survival; LA-NPC, locally advanced nasopharyngeal carcinoma; UICC, Union for International Cancer Control; AJCC, American Joint Committee on Cancer.

personalized therapy through strategic adjustment of treatment intensity remain key research priorities for oncology researchers and clinicians.

The intricate crosstalk between inflammatory responses, nutritional status, and tumor progression has emerged as a pivotal area of focus in NPC and translational oncology research. Against this backdrop, the present study enrolled 536 patients with LA-NPC to systematically evaluate the prognostic utility of peripheral blood-based composite biomarkers, including PNI, NPAR, PHR, and HRR. Our findings demonstrated that, beyond conventional clinical covariates such as TNM staging, pretreatment EBV DNA level, age, and hypertension status, NPAR emerged as an independent prognostic marker associated with survival outcomes in LA-NPC patients. Building on this critical finding, we further constructed a prognostic nomogram by integrating NPAR with four key clinical parameters to enable personalized survival probability prediction in LA-NPC patients. Subsequent validation confirmed that this nomogram exhibits robust discriminative power and excellent calibration, providing a reliable tool for the clinical prognostic assessment of LA-NPC.

Numerous prior studies have definitively established that inflammatory responses and nutritional status are closely associated with the occurrence, development, and prognosis of NPC.[18,28] Building on this evidence, the present study is the first to apply NPAR to predicting survival outcomes in patients with LA-NPC, filling the research gap in LA-NPC prognostic assessment using this index. Numerous studies have shown that high NPAR levels are strongly linked to poor

prognosis in various cancers, such as oral cancer, bladder cancer, and breast cancer.[10,29,30] Moreover, both neutrophils and albumin possess independently validated prognostic value. They can serve as standalone prognostic indicators or act as core components of different composite scoring systems, and their prognostic value is well-established in both scenarios. However, the specific molecular mechanisms connecting NPAR to LA-NPC prognosis remain incompletely understood to date. Nevertheless, based on the distinct biological functions of neutrophils and albumin, along with their well-documented potential impact on NPC patients' survival outcomes, we can make reasonable inferences and interpretations regarding these association mechanisms.

First, as the core effector cells of acute inflammation, neutrophils play a critical role in mediating inflammatory responses and promoting tumor progression.[31] Neutrophils are the major components of peripheral polymorphonuclear leukocytes (PMNs). They can be recruited by the tumor microenvironment and release bioactive molecules such as matrix metalloproteinase 9 (MMP-9) and neutrophil elastase. These molecules degrade the extracellular matrix, promote tumor angiogenesis, and ultimately accelerate tumor invasion and distant metastasis.[32,33] Studies by Trellakis et al further support this mechanism: they found that PMN counts in patients with head and neck squamous cell carcinoma (HNSCC) were significantly higher than those in healthy volunteers, while there was no significant difference in peripheral blood lymphocyte counts between the two groups.[34] This suggests that elevated PMNs may be a specific manifestation of tumor-associated inflammation. In the field of NPC, numerous prior studies have consistently confirmed that increased pre-treatment neutrophil counts are significantly associated with poor prognosis in NPC patients,[26,35] providing direct clinical evidence for the rationality of neutrophils as a prognostic predictor in LA-NPC.

Second, albumin is synthesized by the liver and serves as a core biomarker reflecting both the body's nutritional status and chronic inflammation levels.[9] Decreased albumin levels are regarded as an important indicator of poor prognosis in various cancers, and NPC is no exception. One study showed that although albumin levels are within the normal range in most NPC patients at diagnosis, pre-treatment albumin < 43 g/L can independently predict poor prognosis.[36] Xiao-Jing Du et al further confirmed through a retrospective analysis of clinical data from 694 LA-NPC patients that low pre-treatment serum albumin levels are directly correlated with poorer survival rates in these patients.[37] The underlying regulatory mechanism may be closely related to inflammatory responses mediated by EBV infection. As a key pathogenic factor in NPC, EBV can stimulate the body to produce inflammatory cytokines such as interleukin (IL)-1, IL-6, vascular endothelial growth factor (VEGF), and tumor necrosis factor-α (TNF-α). On the one hand, these cytokines promote hepatic synthesis of C-reactive protein (CRP); on the other hand, they inhibit albumin synthesis and accelerate its catabolism, ultimately leading to a decrease in serum albumin levels.[9,38,39] Furthermore, a recently published meta-analysis encompassing 10 studies with a total of 7339 NPC patients further consolidated this conclusion from an evidence-based medicine perspective: low pre-treatment serum albumin levels are significantly associated with poorer OS and distant metastasis-free survival (DMFS) in patients.[40]

Notably, serum neutrophil and albumin levels are susceptible to interference from multiple confounding factors such as chronic liver disease and fluctuations in fluid volume. Single indicators exhibit high detection variability and cannot comprehensively reflect the body's inflammatory-nutritional balance state. As a combined index of these two parameters, NPAR not only reduces the detection bias of single indicators and improves assessment sensitivity but also integrates dual information on inflammatory responses and nutritional status to accurately reflect the degree of the body's inflammatory-nutritional imbalance. Essentially, high NPAR levels represent elevated circulating neutrophil counts, decreased albumin concentrations, or the coexistence of both. This imbalanced state is directly associated with adverse survival outcomes in LA-NPC patients, which not only echoes the core role of inflammation and nutrition in NPC progression but also further confirms the scientific validity, stability, and clinical superiority of NPAR as a prognostic predictor for LA-NPC.

In recent years, the association between hypertension and increased cancer risk has attracted widespread attention in clinical and research settings. Multiple prospective studies have confirmed that hypertension may constitute a significant risk factor for cancer development.[41,42] This aligns closely with the findings of the present study, where LA-NPC patients with hypertension exhibited significantly poorer survival outcomes. The underlying mechanisms may be explained as follows: First, hypertension is strongly biologically linked to tumor angiogenesis. Hypertensive patients frequently show elevated plasma VEGF levels. As a key regulator of tumor angiogenesis, VEGF directly drives cancer cell proliferation

and metastasis, ultimately accelerating disease progression.[43] Second, hypertension may indirectly affect LA-NPC prognosis by influencing EBV activity. As noted in studies by Kena Lin et al, hypertensive status may increase levels of inflammatory cytokines or enhance immune activation, thereby elevating the risk of EBV reactivation.[44] A notable observation in this study is that, within both high- and low-NPAR subgroups, LA-NPC patients with hypertension had significantly poorer prognosis than those without hypertension (Figure S1). This finding may be attributable to the biological crosstalk between NPAR and hypertension, as studies by Xinfu Huang et al demonstrated that elevated NPAR levels are significantly associated with increased cardiovascular risk.[45] Thus, the interaction between hypertension and NPAR may exert a synergistic effect, exacerbating the adverse prognostic impact in LA-NPC patients. Third, hypertension may impact treatment outcomes by interfering with anti-tumor therapy: elevated blood pressure can lead to chemotherapy interruptions or dose reductions, directly diminishing treatment efficacy. Furthermore, as a key risk factor for cardiovascular disease, hypertension may trigger complications such as heart failure, sudden cardiac death, and ischemic stroke—events that significantly increase overall mortality in cancer patients.[46] Moreover, hypertension often coexists with factors like high-fat diets, excessive salt intake, obesity, and diabetes; these confounders affect tumor progression through multiple pathways, further exacerbating poor prognosis.[47] Fourth, from the perspective of risk factor accumulation, the interplay of hypertension with the aforementioned metabolic abnormalities and cardiovascular risks creates a "host internal environment" unfavorable to tumor control, which may represent the integrated mechanism underlying its association with poor prognosis. In summary, the findings of this study clearly indicate that concurrent hypertension is a significant prognostic indicator of poor outcomes in LA-NPC patients. Thus, this factor warrants close attention during post-treatment surveillance. For LA-NPC patients with hypertension, rigorous multidisciplinary monitoring and long-term follow-up are warranted, with optimal patient care delivered through integrated oncological and cardiovascular care protocols to improve survival outcomes.[48]

Furthermore, this biomarker can be effectively combined with key clinical variables (including age, clinical stage, pretreatment EBV DNA levels, and hypertension status), thereby allowing seamless incorporation into routine clinical practice. On this basis, clinicians are empowered to precisely stratify LA-NPC patients according to their risk profiles, providing robust evidence to guide the development of personalized treatment regimens and ultimately improving overall clinical outcomes for this patient population.

The conclusions of this study should be interpreted with caution, as it has the following acknowledged limitations: First, this study adopted a retrospective design, making it difficult to fully control for potential confounding variables. This may lead to overestimation or underestimation of the association effect size, thereby compromising the accuracy of the conclusions. Second, the NPAR cutoff value and its prognostic impact were based solely on pretreatment laboratory data from a single time point and corresponding OS outcomes, without fully accounting for the dynamic fluctuations in neutrophil and albumin levels. Since repeated measurements were not performed throughout CCRT and the follow-up period, we failed to capture the dynamic changes in NPAR. Future large-scale prospective studies should focus on the dynamic characteristics of NPAR across the entire disease course to establish an optimal cutoff value with greater clinical utility, which will further enhance the precision of prognostic stratification for LA-NPC patients. Third, the study data were derived from a single center, with only internal validation completed; external validation using independent datasets has not yet been conducted. Subsequent studies should incorporate multicenter, large-scale independent cohorts for external validation to improve the generalizability and clinical utility of this prognostic model. Fourth, as a non-specific inflammatory-nutritional composite index, the molecular mechanism underlying NPAR's association with LA-NPC prognosis remains incompletely elucidated. This study did not conduct an in-depth analysis of the potential interactions between NPAR and other nutritional indicators (eg, BMI, lymphocyte count) or immune-inflammatory factors (eg, CRP, IL-6), missing the opportunity to uncover the underlying mechanisms of its prognostic value. Future research should integrate basic experiments with clinical studies to clarify how NPAR regulates LA-NPC progression at the molecular level. Fifth, the study population was limited to LA-NPC patients, excluding those with early-stage NPC or distant metastasis. This limits the generalizability of the conclusions. Subsequent studies will expand the study population to verify the prognostic value of NPAR across different NPC stages and clarify its clinical applicability boundaries.

Conclusion

In conclusion, this study demonstrates that NPAR—a composite biomarker reflecting systemic inflammatory and nutritional status—holds substantial prognostic value in LA-NPC. This further underscores the necessity of incorporating inflammatory and nutritional status assessments into prognostic stratification and clinical management of LA-NPC. Accordingly, we successfully developed and validated a novel prognostic nomogram by integrating NPAR with key clinical parameters (age, TNM stage, pretreatment EBV DNA level, and hypertension status). Featuring simplicity, excellent discriminative power, good calibration, and strong clinical applicability, this nomogram enables clinicians to accurately predict the survival outcomes of individual LA-NPC patients, thereby providing a robust foundation for optimizing treatment regimens and advancing personalized patient care for this population.

Data Sharing Statement

Data can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Patient Data Confidentiality

This study conforms to the Declaration of Helsinki and has been approved by the Ethics Review Committee of Guangxi Medical University Cancer Hospital (Approval No. KY2025985). The original data used in this study are managed by the Guangxi Medical University Cancer Hospital. The Ethics Review Committee of Guangxi Medical University Cancer Hospital waived the requirement for written informed consent from participants or their legal guardians/next of kin, as this paper reports a retrospective observational study with no identifiable patient information.

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Author Contributions

Xiaohui Yang: Conceptualization, methodology, investigation, resources, visualization, Methodology, and writing - original draft.

Lu Huang: Data curation, formal analysis, Validation, and writing-review and editing.

Song Qu: Supervision, project administration, and funding acquisition.

All authors took part in drafting, revising, or critically reviewing the article; approved the final version for publication; agreed on the journal of submission; and accept responsibility for the accuracy and integrity of the work.

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Disclosure

The authors declare no conflict of interest.

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