Journal of Inflammation Research

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ORIGINAL RESEARCH

A Nomogram Based on Platelet Distribution Width-to-Lymphocyte Ratio to Predict Overall Survival in Patients with Locoregionally Advanced Nasopharyngeal Carcinoma

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Purpose: To evaluate the prognostic significance of platelet distribution width-to-lymphocyte ratio (PDWLR) in patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC). Moreover, a nomogram based on PDWLR was built and validated to predict the overall survival (OS) of this population.

Patients and Methods: All LA-NPC patients who were diagnosed and treated between January 2015 and December 2017 at Guangxi Medical University Cancer Hospital were included. Cox regression analyses were performed to assess PDWLR and clinical features that might affect OS to screen for independent predictors. The independent predictors and important clinical variables were used to build and validate a nomogram for predicting OS. Then, the capability of the model was estimated by discrimination, calibration and clinical usefulness. Risk stratification was conducted using the nomogram-calculated risk score, and the comparison of survival in the high-risk group and the low-risk group was through Kaplan–Meier method.

Results: This study included 746 LA-NPC patients. Multivariate Cox analysis suggested that age (hazard ratio [HR]: 1.81, 95% confidence interval [CI]: 1.18–2.78, P = 0.007), gender (HR: 2.03, 95% CI: 1.12–3.68, P = 0.019), pre-treatment plasma Epstein–Barr virus (EBV) DNA (HR: 1.55, 95% CI: 1.01–2.39, P = 0.047), PDWLR (HR: 2.61, 95% CI: 1.67–4.09, P < 0.001) were independent predictors of OS. Compared to the 8th edition TNM staging system, the nomogram based on the above four factors and important clinical variables (T stage and N stage) demonstrated better predictive performance. Moreover, the model had the ability to identify individuals at high risk.

Conclusion: PDWLR was a promising negative predictor for patients with LA-NPC. The nomogram based on PDWLR demonstrated better predictive performance than the current staging system.

Keywords: nomogram, platelet distribution width-to-lymphocyte ratio, inflammatory biomarker, locoregionally advanced nasopharyngeal carcinoma, overall survival

Introduction

Nasopharyngeal carcinoma (NPC) originates from nasopharyngeal mucosal epithelium, and its geographical distribution is extremely uneven.[1] According to Global Cancer Statistics and Cancer statistics in China, it was estimated that there were 120,416 new cases of NPC worldwide and 64,165 new cases in China, representing half of all new cases worldwide in 2022.[2,3] The non-keratinizing subtype is the most primary pathology subtype in endemic areas and has a strong correlation with infection of Epstein–Barr virus (EBV).[4] Owing to the insidious, non-specific early symptoms and the complex anatomy of the

Received: 11 March 2024
Accepted: 18 June 2024
Published: 3 July 2024

nasopharynx, there are over 70% of the patients diagnosed in locally advanced stage.[1] Currently, concurrent chemoradiotherapy (CCRT) is the core regimen for locally advanced nasopharyngeal carcinoma (LA-NPC), but there are still some patients who fail treatment due to loco-regional recurrence and distant metastasis.[5,6] For such patients, the choice of CCRT alone, induction chemotherapy (IC) after CCRT or CCRT after adjuvant chemotherapy (AC) is still controversial.[7–12] Thus, identifying patients who may benefit from additional chemotherapy is important and challenging.

Presently, the 8th edition tumor-node-metastasis (TNM) staging system is the primary basis for treatment options and prognostic prediction for patients with NPC.[13,14] Although LA-NPC patients are in the same TNM stage, they may possess different clinical outcomes as individual differences and tumor heterogeneity, suggesting that relying on the anatomy-based staging system alone for clinical decision making is not sufficient. It is important and urgent to discover a new biomarker with higher specificity and sensitivity and incorporate it into the system for better prediction of survival, identification of patients with poor prognosis at high-risk and individualized treatment to enhance survival.

EBV DNA is currently the most widely used hematological marker in NPC, which can be used for screening, predicting prognosis and monitoring early recurrence of nasopharyngeal carcinoma patients.[15–17] Multiple studies have shown that the incorporation of pretreatment plasma EBV DNA in the TNM staging system improves the prognosis of patients with NPC.[18,19]

It is widely acknowledged that the inflammatory and immune status of the host lead to tumor genesis, progression and metastasis.[20–22] Lymphocytes are involved in the anti-tumor immune process and are also an essential constituent of the immune response. It has been demonstrated that the lymphocyte infiltration in tumor lesions is related to better outcome in many malignancies.[23–25] Meanwhile, increasing evidence shows that the tumor microenvironment, inflammation, angiogenesis and cancer progression are associated with platelet activation.[26–28] Platelet distribution width (PDW) represents a direct reflection of the variability in platelet size, which is a more comprehensive indicator of platelet activity than platelet count.[29,30] Preceding studies have demonstrated that high level of PDW is relevant to a worse prognosis in various cancers.[31] Xie et al suggested that PDW is an available prognostic biomarker for NPC patients.[32] Therefore, we are interested in investigating platelet distribution width-to-lymphocyte ratio (PDWLR), a novel biomarker of inflammation that combines lymphocytes and PDW. Recently, PDWLR has been proven to be a negative predictor of liver cancer, but its prognostic value is inconclusive in NPC.[33]

Therefore, the purpose of the study was to determine whether PDWLR affected the prognosis of LA-NPC patients. Moreover, a nomogram based on PDWLR was built and validated to predict overall survival (OS) in LA-NPC.

Materials and Methods

Participants and Data Collection

A retrospective study of 746 patients with LA-NPC newly diagnosed and treated between January 2015 and December 2017 at Guangxi Medical University Cancer Hospital was conducted. Patients were included if they met these criteria: (a) histopathology confirmed NPC; (b) aged between 18 and 65 years at diagnosis; (c) had complete medical records and follow-up data; (d) with stage III or IVA (the 8th edition TNM staging system); (e) underwent CCRT ± IC/AC. Patients were excluded if they met these criteria: (a) had other malignancies at diagnosis; (b) received other anti-tumor therapy previously; (c) preexistent anticoagulation and/or antiplatelet therapy regularly; (d) with thrombotic diseases, acute infections, hematologic disorders or autoimmune diseases. The study was certified by the Medical Ethics Committee of Guangxi Medical University Cancer Hospital (IRB approval number: LW2024030), which adhered to the Declaration of Helsinki. No further written informed consent was required due to the nature of the retrospective study. All patient data were anonymized.

The following variables were collected: baseline clinical characteristics: age, gender, T stage, N stage and TNM stage; treatment; laboratory indexes: the peripheral blood was collected within 2 weeks before treatment to measure plasma EBV DNA and PDWLR. Plasma EBV DNA levels were determined by amplifying the Bam HI-W region of its genome using real-time quantitative polymerase-chain reaction (RT-qPCR) technology. The formula for calculating PDWLR was as follows: PDW (fl.) / lymphocyte count (10^9/L).

Treatment and Follow-Up

For LA-NPC patients, the National Comprehensive Cancer Network (NCCN) guidelines recommend CCRT ± IC/AC. All patients underwent intensity-modulated radiotherapy (IMRT) 5 days a week, 1 fraction daily for a total of 30–33 fractions. In detail, the total prescribed doses were about 70–74 Gy to the primary tumor volumes, 60–70 Gy to the volumes of the involved cervical lymph nodes, 60–62 Gy to high-risk clinical target volumes and 50–56 Gy to low-risk clinical target volumes. Concurrent chemotherapy (2–3 cycles) was performed with cisplatin single-agent (cisplatin 100 mg/m^2/d day 1). Induction chemotherapy (2–3 cycles) or adjuvant chemotherapy (1–4 cycles) regimens including GP regimen (gemcitabine 1000 mg/m^2/d on days 1 and 8; cisplatin 80 mg/m^2/d day 1), TPF (docetaxel 60 mg/m^2/d day 1; cisplatin 60 mg/m^2/d day 1; 5-fluorouracil 600 mg/m^2/d on days 1–5), PF (cisplatin 80 mg/m^2/d day 1; 5-fluorouracil 600 mg/m^2/d on days 1–5), and TP (docetaxel 75 mg/m^2/d, day 1; cisplatin 75 mg/m2/d, day 1). Carboplatin, nedaplatin or loplatin were used in patients who could not tolerate cisplatin. The number of chemotherapy cycles depended on patients' tolerance. All of the chemotherapy regimens were performed in 21-day cycles. After treatment, patients underwent regular reviews at specific intervals: every 3 months for the first 2 years, semi-annually for the third to fifth years, and annually after 5 years. The reviews comprised physical and hematology examinations, nasopharyngeal endoscopy, head and neck magnetic resonance imaging (MRI), chest and abdominal computed tomography (CT), and whole-body bone scan or positron emission tomography and CT (PET-CT) if necessary. Overall survival (OS) was the study's primary endpoint and defined as the period between diagnosis and last follow-up or death.

Statistical Analysis

According to the ratio of 1:1, the study population was randomly assigned to the training cohort and the validation cohort (caret in R, version 6.0–94). The cut-off value of pre-treatment plasma EBV DNA was 5000 copies/mL, which was set by the detectable threshold in the hospital laboratory. Mann–Whitney *U*-tests were employed for continuous variables and chi-square tests were used for categorical variables to compare the clinical characteristics of patients between the two cohorts. As per the cut-off values determined by survival receiver operating characteristic (survival-ROC) curve analysis in the training cohort, continuous variables were subdivided into binary variables (survivalROC in R, version 1.0.3.1). The multivariate Cox analysis was performed on statistically significant variables ($P < 0.05$) in univariate Cox analysis and clinically important variables to determine independent prognostic factors. These factors were then combined with clinically important variables to create a nomogram for predicting the LA-NPC patients' OS (rms in R, version 6.7–1). To assess the discriminatory ability of the nomogram and the 8th edition TNM staging, Harrell's consistency index (C index) and receiver operating characteristic (ROC) curves were used. The calibration curves, measured by bootstrap verification with 1000 resamples, were plotted to estimate the goodness-of-fit between observed and predicted survival rates of the nomogram. Decision curve analysis (DCA) was employed to evaluate the clinical efficacy of the predictive model (ggDCA in R, version 1.1). The total risk score was calculated by summing the score derived from the degree of contribution of each factor in the nomogram. Through the cut-off value of the risk score determined by survival-ROC curve, the patients were categorized into high-risk and low-risk groups, and the survival differences between two groups were assessed by the Log rank test of the Kaplan–Meier survival curves. The R software version 4.3.2 was used for statistical analyses, and the two-tailed P values <0.05 were considered statistically significant in all tests.

Results

Patient Characteristics

The study involved 746 patients who were randomly assigned to the training cohort of 374 and the validation cohort of 372 in a 1:1 ratio. Table 1 showed the clinical characteristics of the study population. No statistically significant differences were observed between the two cohorts ($p = 0.332–0.832$). In the total study population, the median age was 45 years (interquartile range [IQR]: 37–53 years), 558 (74.8%) were male and the median PDWLR was 8.70 (IQR: 6.97–10.61). At a median follow-up of 78.3 months (95% confidence interval [CI]: 77.5–79.9), 186 (24.93%) patients died. The 3-year OS rate was 86.4% (95% CI: 84.0%–88.9%) and 5-year OS rate was 77.3% (95% CI: 74.4%–80.4%).

Table 1 Clinical Characteristics of the Study Population

Characteristics	Total (n=746)	Training Cohort (n=374)	Validation Cohort (n=372)	p
Age (median [IQR])	45 [37, 53]	46 [37, 53]	45 [37, 52]	0.757
Gender (%)				
Female	188 (25.20)	88 (23.53)	100 (26.88)	0.332
Male	558 (74.80)	286 (76.47)	272 (73.12)	
EBV DNA (%)				
<5000	365 (48.93)	181 (48.40)	184 (49.46)	0.827
≥5000	381 (51.07)	193 (51.60)	188 (50.54)	
T stage (%)				
T1	27 (3.62)	11 (2.94)	16 (4.30)	0.346
T2	194 (26.01)	107 (28.61)	87 (23.39)	
T3	321 (43.03)	156 (41.71)	165 (44.35)	
T4	204 (27.35)	100 (26.74)	104 (27.96)	
N stage (%)				
N0	18 (2.41)	10 (2.67)	8 (2.15)	0.757
N1	232 (31.10)	111 (29.68)	121 (32.53)	
N2	310 (41.55)	155 (41.44)	155 (41.67)	
N3	186 (24.93)	98 (26.20)	88 (23.66)	
TNM stage (%)				
Stage III	388 (52.01)	191 (51.07)	197 (52.96)	0.658
Stage IVA	358 (47.99)	183 (48.93)	175 (47.04)	
Treatment (%)				
CCRT	323 (43.30)	160 (42.78)	163 (43.82)	0.832
CCRT+IC/AC	423 (56.70)	214 (57.22)	209 (56.18)	
PDWLR (median [IQR])	8.70 [6.97, 10.61]	8.70 [6.95, 10.59]	8.72 [6.70, 10.76]	0.534

Abbreviations: IQR, interquartile range; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; PDWLR, platelet distribution width-to-lymphocyte ratio.

Univariate and Multivariate Cox Analyses for Detecting the Factors Affected OS in the Training Cohort

The optimum cut-off values of age and PDWLR were determined by the survival-ROC curves to be 52 years and 11.68, respectively (Supplementary Figure 1). Factors that may affect OS in LA-NPC patients were included in univariate and multivariate Cox analyses (Table 2). The results showed significant independent risk factors for OS were as follows: age (hazard ratio [HR]: 1.81, 95% CI: 1.18–2.78, P = 0.007), gender (HR: 2.03, 95% CI: 1.12–3.68, P = 0.019), EBV DNA (HR: 1.55, 95% CI: 1.01–2.39, P = 0.047), PDWLR (HR: 2.61, 95% CI: 1.67–4.09, P < 0.001).

Construction, Validation and Risk Stratification of the Nomogram

A nomogram based on independent risk factors identified by multivariate analysis, including age, gender, EBV DNA, PDWLR, and important clinical variables such as T stage, N stage, to forecast OS of patients with LA-NPC was constructed (Figure 1). The above factors were assigned a score on a scale of 0 to 100 separately according to their contribution to OS, and the scores of all covariates were added to obtain the total risk score, which corresponded to the predicted probability of OS at 3 years and 5 years (Table S1). The nomogram had a higher C-index than the 8th staging system in the training and validation cohorts (training cohort: 0.706, 95% CI: 0.655–0.757 versus 0.627, 95% CI: 0.580–0.674, P < 0.001; validation cohort: 0.685, 95% CI: 0.634–0.736 versus 0.614, 95% CI: 0.567–0.661, P < 0.001) (Table 3). Similarly, the ROC curves demonstrated that the nomogram outperformed the current TNM staging, as evidenced by a larger area under the curve (AUC) (Figure 2). Overall, the nomogram showed a more satisfactory discrimination. The calibration curves indicated the predicted probabilities of 3-year and 5-year OS were generally consistent with the actual probabilities, suggesting that the model had accurate predictive ability (Figure 3). Furthermore,

Table 2 Univariable and Multivariable Cox Regression Analyses in the Training Cohort

Characteristics	Univariable Cox Analysis		Multivariable Cox Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age				
≤52	Reference		Reference	
>52	1.99 (1.31–3.02)	0.001	1.81 (1.18, 2.78)	0.007
Gender				
Female	Reference		Reference	
Male	2.02 (1.12–3.64)	0.019	2.03 (1.12, 3.68)	0.019
EBV DNA				
<5000	Reference		Reference	
≥5000	1.68 (1.10–2.56)	0.015	1.55 (1.01, 2.39)	0.047
T stage				
T1	Reference		Reference	
T2	1.35 (0.32–5.67)	0.686	1.17 (0.27, 5.04)	0.829
T3	1.10 (0.26–4.61)	0.895	1.18 (0.27, 5.08)	0.823
T4	2.39 (0.57–9.93)	0.232	2.43 (0.55, 10.68)	0.240
N stage				
N0	Reference		Reference	
N1	2.43 (0.33–17.95)	0.385	2.22 (0.30, 16.59)	0.437
N2	2.45 (0.34–17.88)	0.377	2.69 (0.36, 20.26)	0.338
N3	3.90 (0.53–28.50)	0.180	4.39 (0.57, 33.51)	0.154
Treatment				
CCRT	Reference		Reference	
CCRT+IC/AC	1.23 (0.81–1.87)	0.335	0.81 (0.51, 1.28)	0.357
PDWLR				
≤11.68	Reference		Reference	
>11.68	2.93 (1.89–4.54)	<0.001	2.61 (1.67, 4.09)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; PDWLR, platelet distribution width-to-lymphocyte ratio.

the decision curve analyses (DCA) underscored a higher net clinical benefit of PDWLR-based nomogram to predict OS (Figure 4). Risk stratification was established by categorizing training and validation cohorts into low-risk and high-risk groups based on the cut-off value (169) of the total risk score of the model via the survival-ROC curve in the training cohort (Supplementary Figure 1). The Kaplan–Meier curves exhibited the prognosis of the high-risk group was worse than that of the low-risk group ($P < 0.0001$), demonstrating the model had the ability to identify high-risk individuals (Figure 5).

Discussion

For all we know, this study is the first to investigate the prognostic significance of PDWLR in patients with LA-NPC. Additionally, we have developed and validated a nomogram that combines PDWLR with clinically relevant variables to predict OS in patients with LA-NPC. Our model demonstrated superior predictive power and greater clinical utility compared to the 8th edition TNM staging.

The NCCN recommend CCRT with or without AC/IC for patients with LA-NPC. Nevertheless, not all LA-NPC patients receiving CCRT can benefit from additional chemotherapy due to tumor heterogeneity.[7,11] Therefore, early identification of those high-risk patients with poor survival is particularly important to guide individualized treatment.

The study confirms previous findings that older age, male, and detectable pre-treatment EBV DNA are associated with a poor prognosis.[34–36] Furthermore, it reveals that PDWLR is an independent prognostic predictor in LA-NPC,

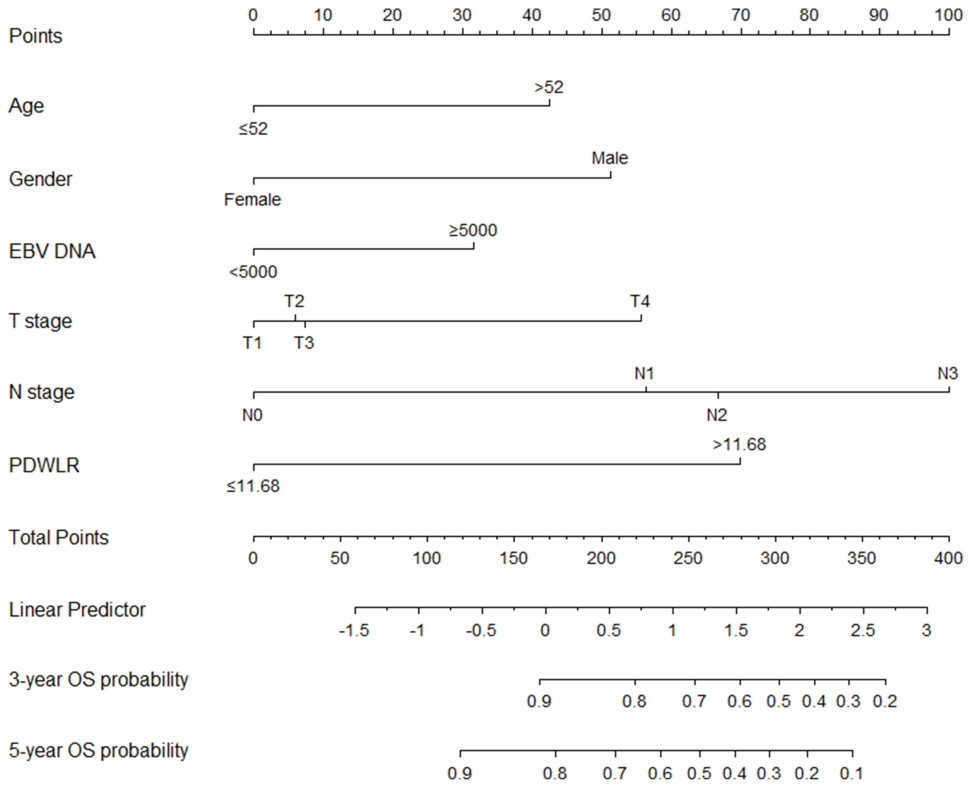

Figure 1 Nomogram predicting 3-year and 5-year OS in LA-NPC patients.
Notes: Scores were assigned to each covariate based on its contribution to the outcome event. The sum of the scores for all variables corresponds to the predicted probability of 3-year and 5-year OS for the patient.
Abbreviations: OS, overall survival; LA-NPC, locoregionally advanced nasopharyngeal carcinoma.

indicating that high PDW and low lymphocytes are related to a worse prognosis. Although the mechanism linking PDWLR and poor cancer prognosis is currently unknown, there are possible explanations that can be proposed.

Inflammatory markers and metabolites of tumor cells, which make up the immune microenvironment of the tumor in the peripheral blood, correlate with the prognosis of cancer patients.[37–39] Evidence is accumulating that platelets are responsible for tumor initiation and progression. Platelet activation can protect circulating tumor cells (CTCs) from immune cell-induced cell death by creating a physical barrier and interfering with cancer cell recognition.[40–42] Additionally, they can also promote cancer cell growth and induce epithelial–mesenchymal transition (EMT), enhancing cancer cell migration and invasion.[43,44] Among various malignant tumors, elevated platelets have a strong correlation with low survival rates.[45–47] However, it is important to note that platelet count can be influenced by both apoptosis and production. Therefore, a normal platelet count may not necessarily indicate the absence of a pro-inflammatory cancer phenotype, as compensatory mechanisms can mask its presence. Platelets are generally small in size. However, when they are activated, they undergo qualitative changes. Apoptotic platelets are replaced by immature platelets with high

Table 3 Comparison of the C-Index in the Nomogram and the TNM Staging System

Variables	Training Cohort		Validation Cohort	
	C-Index (95% CI)	P	C-Index (95% CI)	P
TNM stage	0.627 (0.580–0.674)	Reference	0.614 (0.567–0.661)	Reference
Nomogram	0.706 (0.655–0.757)	<0.001	0.685 (0.634–0.736)	<0.001

Abbreviation: CI, confidence interval.

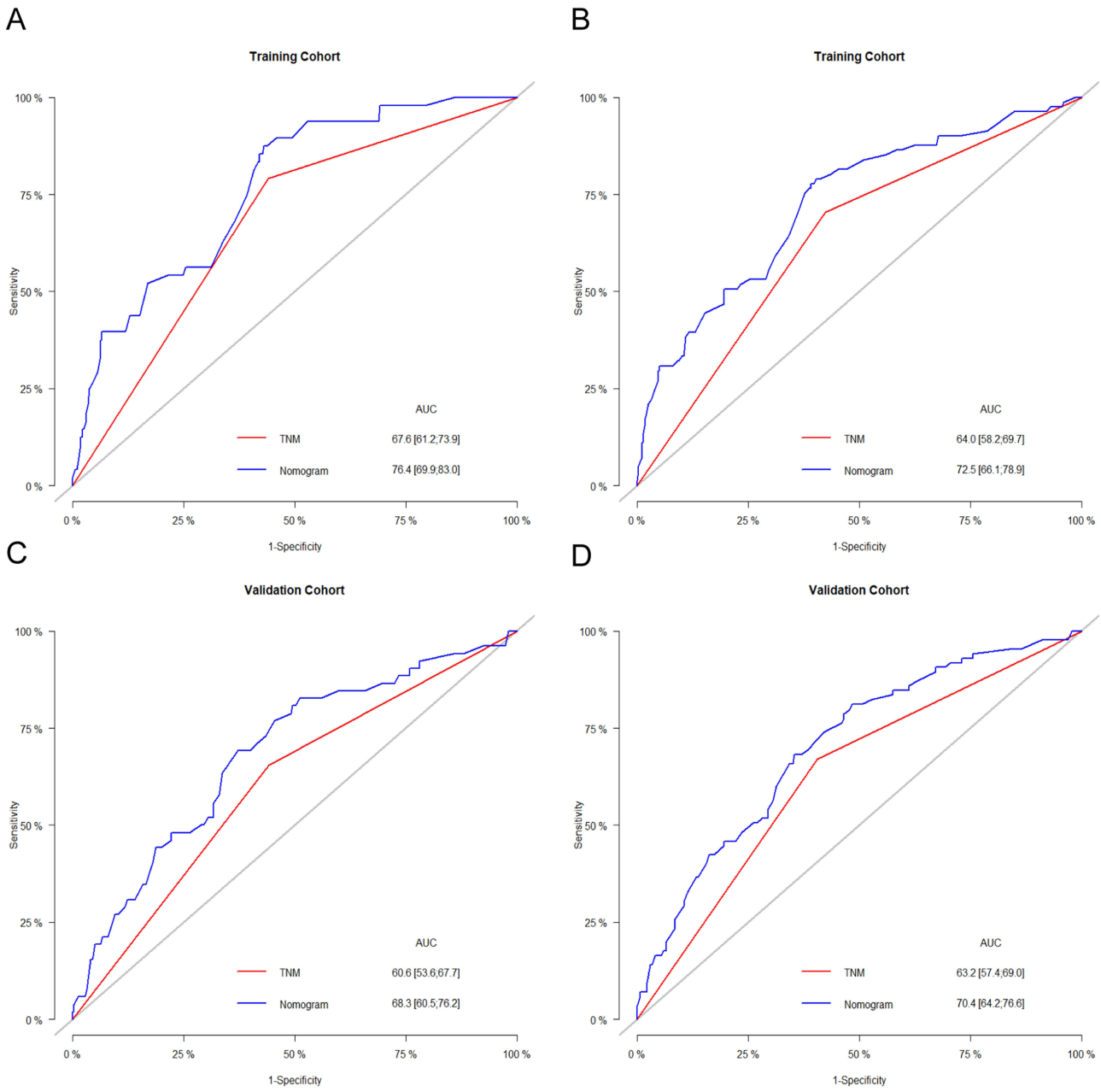

Figure 2 ROC curves comparing the nomogram and TNM staging system for predicting OS.
Notes: ROC curves to predict the 3-year and 5-year OS in the training cohort (**A** and **B**) and validation cohort (**C** and **D**). The closer the area under the curve (AUC) of ROC curve was to 1, the better the ability to predict OS.
Abbreviations: ROC, receiver operating characteristic; OS, overall survival.

enzymatic activity, and gradually, large platelets become more predominant. Therefore, platelet size and heterogeneity can be more indicative of platelet activity.[48]

PDW is an indicator of platelet distribution size heterogeneity and a symbol of platelet anisocytosis that increases with platelet activation. It is a more accurate reflection of platelet activity than platelet count.[30] Xie et al has found that a high PDW is closely referable to a poorer prognosis in patients with NPC.[32] Moreover, lymphocytes are a vital element of the body's immune response and immune surveillance, and they play a critical role in identifying and eliminating tumor cells.[49,50] Lymphocyte-mediated and released lymphokines can also impede tumor growth and activate other anti-tumor immune processes.[51] Based on these findings, high PDWLR levels, characterized by high PDW and low

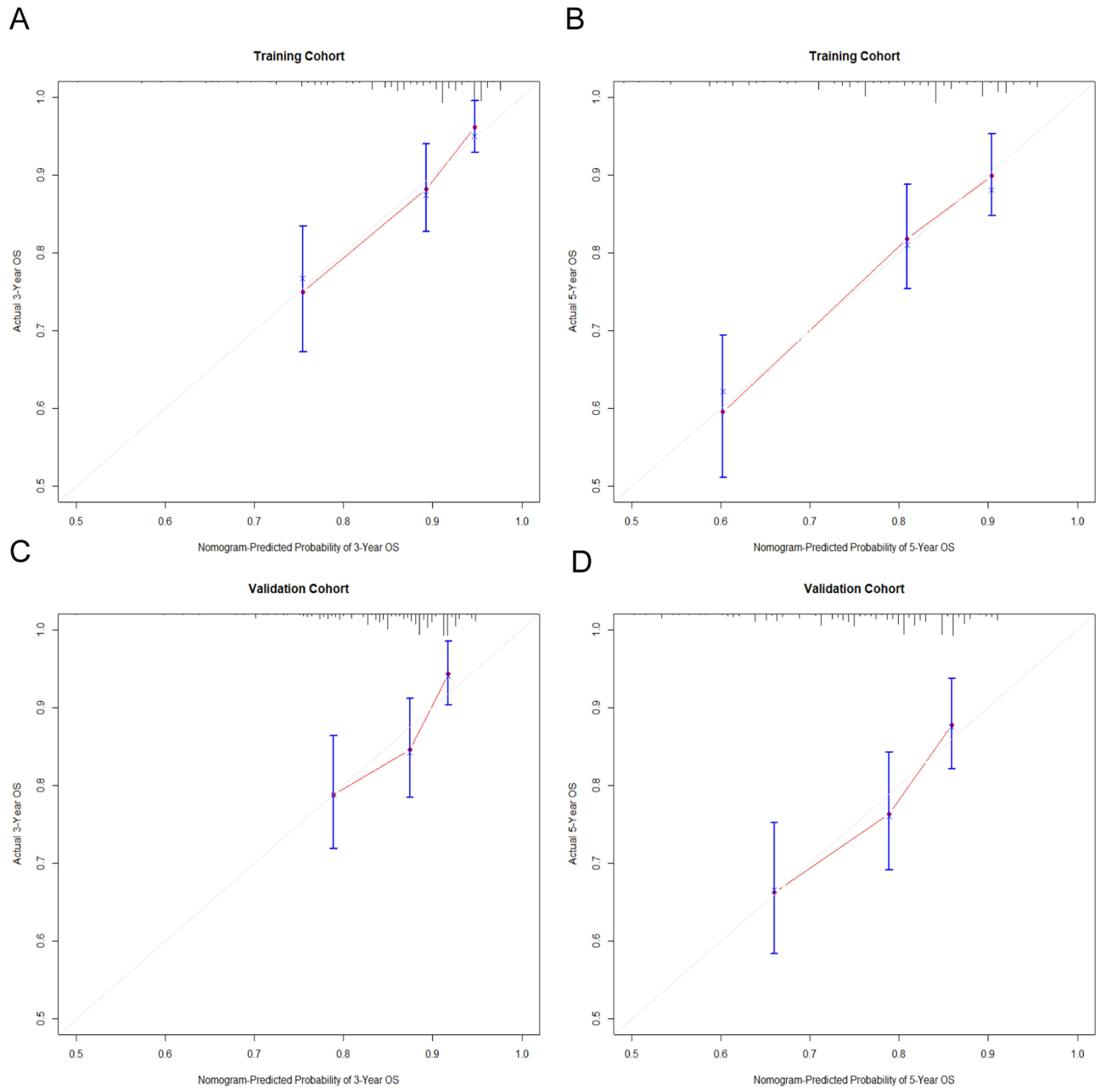

Figure 3 Calibration curves for the nomogram of OS.
Notes: Calibration curves to predict the 3-year and 5-year OS of the nomogram in the training cohort (**A** and **B**) and validation cohort (**C** and **D**). The graph displayed the predicted and observed overall survival (OS) represented by the horizontal and vertical coordinates, respectively. The diagonal line indicated when the predicted probability equalled the actual probability. The predicted probability matched the actual probability more closely when the nomogram curve was closer to the diagonal line.
Abbreviation: OS, overall survival.

lymphocyte counts may indicate tumor progression and poor immune response, and more accurately predict prognosis in NPC. Therefore, patients with high PDWLR require a more aggressive treatment regimen.

Statistical prediction models have been widely applied in many kinds of tumors due to their objectivity, simplicity and ability to provide reliable information about prognosis for each patient. One prediction tool commonly used is the nomogram. It created a simple graphical representation of the prediction model based on statistical principles to generate numerical probabilities of clinical events. The nomogram has been shown to have more accurate prognostic predictive power compared to the clinical TNM system.[52,53] Therefore, we have developed a model that combines age, gender,

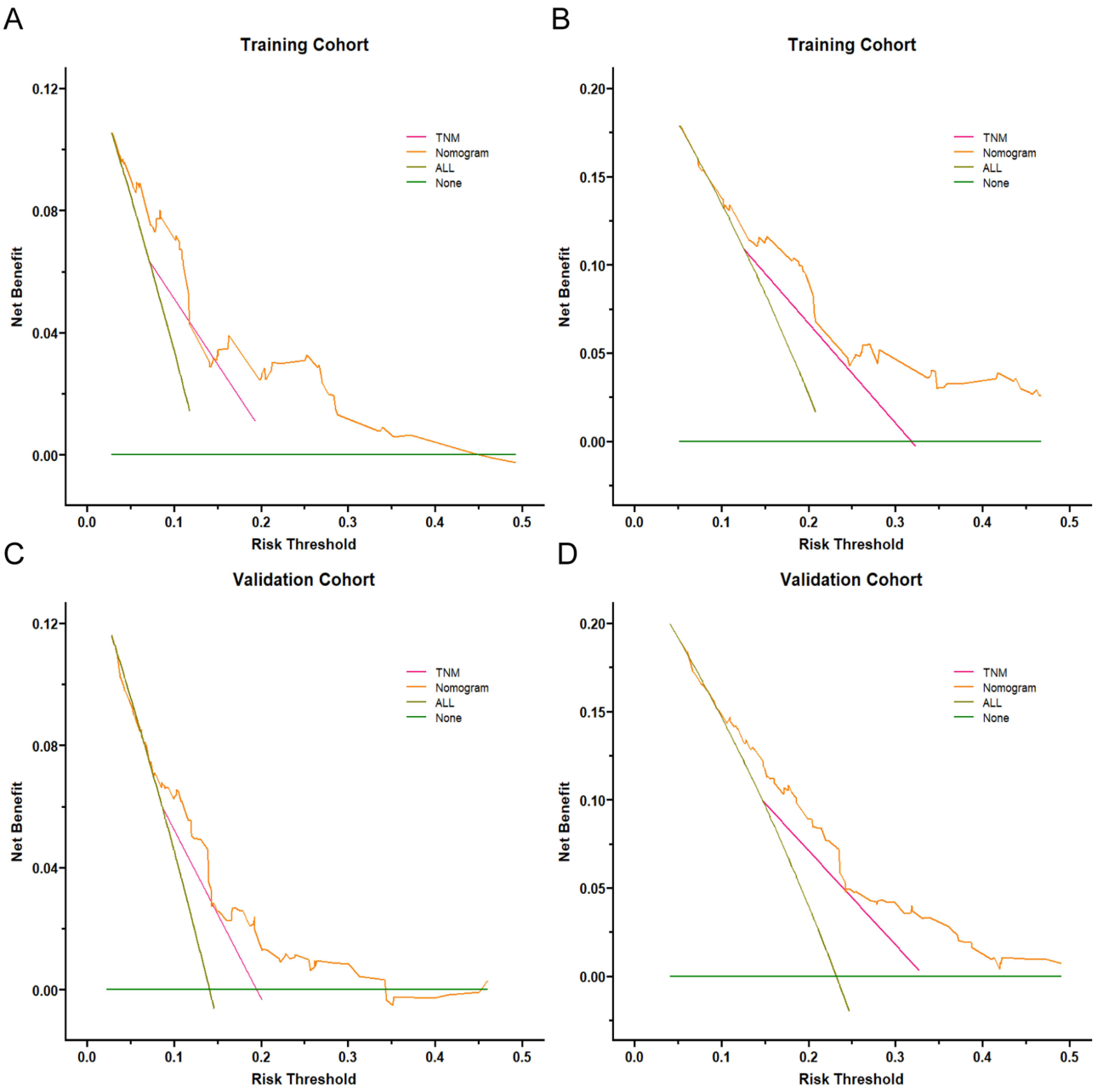

Figure 4 Decision curves comparing the nomogram and TNM staging system for predicting OS.
Notes: Decision curves to predicted the 3-year and 5-year OS of the nomogram in the training cohort (**A** and **B**) and validation cohort (**C** and **D**). The x-axis was the threshold probability. y-axis was the net benefit, which was weighted according to the proportion of true-positive results minus the proportion of false-positive results, and the ratio of the threshold probabilities. A higher net benefit reflected better clinical utility with the same probability.
Abbreviation: OS, overall survival.

EBV DNA, T stage, N stage and PDWLR to more accurately predict OS in LA-NPC, while allowing for risk stratification and individualized treatment plans.

However, this study has limitations that cannot be ignored. First, as it was studied in an NPC endemic area, the findings may not be generalizable to non-endemic areas. Second, it was a single-center study with a small number of cases that was only internally validated and needed to be followed by a multicenter, larger, prospective study for external validation. Third, this study was retrospective, which was inevitably subject to selection bias. Fourth, plasma EBV DNA testing was not standardized. Fifth, the study put emphasis on the initial radical treatment of LA-NPC patients without considering the effect of subsequent salvage therapy on OS.

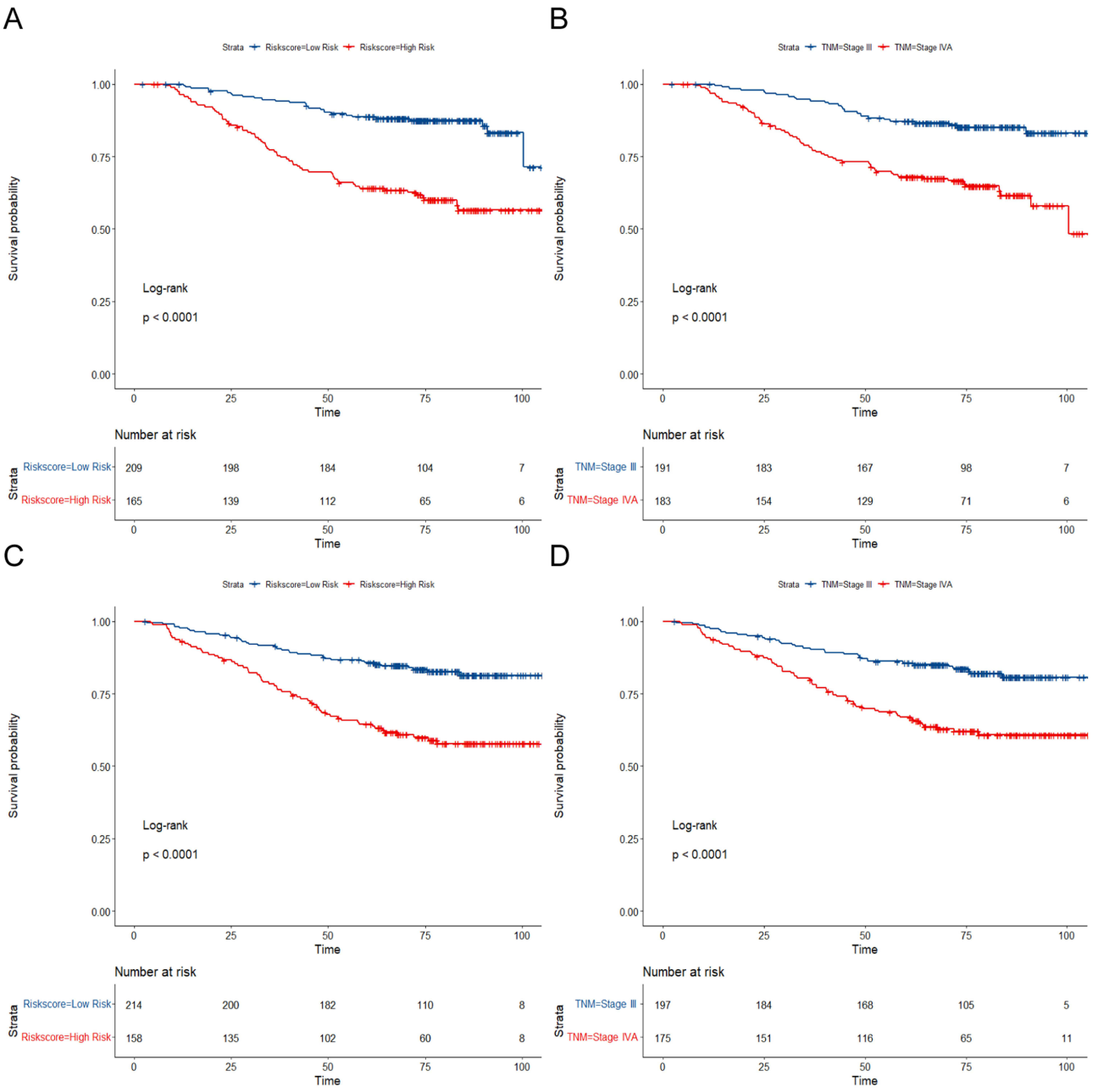

Figure 5 Kaplan–Meier curves demonstrating OS in patients of LA-NPC.
Notes: Kaplan–Meier survival curves for OS of the training cohort (**A** and **B**) and validation cohort (**C** and **D**) in different models. The nomogram was divided into a high-risk group and a low-risk group comparison (**A** and **C**); the 8th edition staging system was divided into stage III and stage IVA comparisons (**B** and **D**).
Abbreviations: OS, overall survival; LA-NPC, locoregionally advanced nasopharyngeal carcinoma.

Conclusion

The study confirmed that PDWLR was an independent predictor of OS in LA-NPC and a promising prognostic indicator due to its affordability and simplicity in clinical practice. The Cox regression analysis identified age, gender, pre-treatment EBV DNA, and PDWLR as independent predictors of OS in LA-NPC. A nomogram was utilized to predict the OS of LA-NPC patients based on the above factors and clinical variables, including T stage and N stage. Compared to the 8th edition TNM staging system, the nomogram exhibited superior predictive performance and risk stratification. This provides physicians with valuable information to identify patients at high-risk and select more aggressive treatment.

Funding

This study was supported by the Key Research and Development Program Project of Guangxi Zhuang Autonomous Region (grant number GuikeAB23026020), Joint Project on Regional High-Incidence Diseases Research of Guangxi Natural Science Foundation (2023GXNSFBA026012), the Independent Project of Key Laboratory of Early Prevention & Treatment for Regional High-Incidence-Tumor (grant number GKE-ZZ202306 and GKE-ZZ202230).

Disclosure

All authors declare no conflicts of interest in this work.

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