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ORIGINAL RESEARCH

A Nomogram Based on Tumor Response to Induction Chemotherapy and Plasma Epstein–Barr Virus DNA Level after Induction Chemotherapy to Explore Individualized Treatment of Patients with Locally Advanced Nasopharyngeal Carcinoma

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Purpose: To explore the influence of Epstein–Barr virus (EBV) DNA levels before and after induction chemotherapy (IC), tumor response to IC, and baseline factors on overall survival (OS) in patients with locally advanced nasopharyngeal carcinoma (LA-NPC). A nomogram was subsequently constructed to explore the individualized optimal cumulative cisplatin dose (CCD) in concurrent chemoradiotherapy (CCRT).

Methods: A total of 581 LA-NPC patients were included, randomly divided into training and validation cohorts in a 7:3 ratio. In the training cohort, a nomogram was subsequently established based on multivariate Cox regression analysis and then validated. Subsequently, patients were classified into different risk groups based on the nomogram, and the impact of different levels of CCD on survival outcomes was evaluated.

Results: EBV DNA levels after IC, tumor response to IC, age, and LDH were independent prognostic factors of OS. Schoenfeld residual analysis indicated overall satisfaction of the proportional hazards assumption for the Cox regression model. The C-index of the nomogram was 0.758 (95% CI: 0.695–0.821) for the training cohort and 0.701 (95% CI: 0.589–0.813) for the validation cohort. Calibration curves demonstrated good correlation between the nomogram and actual survival outcomes. DCA confirmed the clinical utility enhancement of the nomogram over the TNM staging system. For OS, patients in the medium/high-risk group with a CCD > 200 mg/m² had better outcomes than those with CCD ≤ 200 mg/m², although the difference was not statistically significant ($p = 0.097$). No significant difference was observed in local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) across various levels of CCD in different risk subgroups ($p > 0.05$).

Conclusion: The nomogram based on EBV DNA levels after IC, tumor response, LDH, and age effectively predicts OS in LA-NPC patients, aids in risk stratification, and may guide treatment decisions.

Keywords: nasopharyngeal carcinoma, Epstein–Barr virus DNA, tumor response, nomogram, cumulative cisplatin dose

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant head and neck tumor originating from the nasopharyngeal epithelia that is highly prevalent in East Asia and Southeast Asia, especially in southern China.[1,2] According to the World Health Organization (WHO) classification, the pathological types of NPC include Keratinizing Nasopharyngeal Carcinoma (K-NPC), Squamous Cell Carcinoma (SCC), and Non-Keratinizing Nasopharyngeal Carcinoma (NK-NPC).[3] In high-incidence regions such as

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southern China, NK-NPC is the predominant type, primarily associated with Epstein-Barr virus (EBV) infection[4,5] Similar to most other malignant tumors, the etiology of NPC is complex and multifactorial, involving environmental factors, EBV infection, genetic susceptibility, and other aspects.[1] Recently, a researcher has proposed conceptualizing NPC as a "unified ecological and evolutionary disease" in a multidimensional spatiotemporal framework, where the cancer tissue itself forms a complex spatial structure ecosystem composed of various cell types and essential stromal resources.[6] Within this system, the interaction between cancer cells and the tumor microenvironment, genetic variations in cancer cells, and adaptation to environmental pressures are key factors driving cancer progression. Through this perspective, researchers are able to gain a more comprehensive understanding of the complexity of cancer and its therapeutic responses, providing new insights for future treatment strategies.

Despite advancements in medical technology that have improved early detection and treatment, approximately 70% of newly diagnosed cases are classified as locally advanced nasopharyngeal carcinoma (LA-NPC), defined as stages III or IVa.[7] Due to the deep anatomical location of LA-NPC and its sensitivity to radiation and chemotherapy, the National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent chemoradiotherapy (CCRT) combined with induction chemotherapy (IC) or adjuvant chemotherapy (AC) as the standard treatment for LA-NPC.[8] Significant progress has been made in the local control of LA-NPC. However, despite standard treatment, a subset of patients still experience recurrence, metastasis, or death.[9] Therefore, it is essential to identify patients with different risk levels and optimize individualized treatment plans. For instance, assessing the balance between the efficacy and toxicities of cumulative cisplatin dose (CCD) in patients with LA-NPC receiving IC and CCRT is crucial.

Currently, clinicians primarily rely on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system to develop treatment plans for patients with NPC. However, this staging system only reflects the basic anatomical characteristics of the tumor and does not take into account the individualized biological information of the patient.

Many studies had combined baseline clinical factors and serological markers to construct nomogram for prognostic prediction in patients with LA-NPC, aiming to identify patients with different prognostic risks.[10–12] However, most of the prognostic factors currently under investigation are primarily based on baseline levels. The majority of NPC are "inflammatory tumors" induced by EBV infection, with more than 95% of patients exhibiting detectable EBV DNA in plasma.[1] Several studies have confirmed that the pre-treatment plasma EBV DNA levels, measured by quantitative PCR, are closely associated with the occurrence and progression of NPC, and can serve as a reliable marker for the detection, monitoring, and prognostic prediction of NPC.[13,14] Currently, the optimal timing for measuring EBV DNA levels has not yet been established, and there is still some controversy regarding this issue. Some scholars believe that the EBV DNA levels after IC is an important prognostic factor for clinical outcomes in NPC patients.[15,16] Moreover, studies have shown that tumor response to IC is correlated with patient prognosis.[17,18] Patients who show stable disease (SD) / progressive disease (PD) after IC, categorized as non-responders, exhibit significantly lower sensitivity to IC compared to those who achieve complete response (CR) / partial response (PR), categorized as responders. Luo found that patients with LA-NPC who respond well to IC have better long-term prognosis.[19] Recently, serum inflammatory markers have been recognized as being associated with the prognosis of NPC.[20] Elevated levels of lactate dehydrogenase (LDH) has been confirmed as risk factors for tumor progression and are widely utilized in prognostic evaluations.[21] After IC, assessing EBV DNA levels and evaluating tumor response to IC can help determine whether these markers provide additional information compared to baseline prognostic indicators, thus offering a basis for the adjustment of subsequent treatment in patients with LA-NPC. This research direction is of significant clinical importance.

Therefore, this study explores the combined prognostic role of EBV DNA levels before and after IC, tumor response to IC, serological, and inflammatory baseline factors in predicting the prognosis of LA-NPC. We also intend to construct a nomogram to stratify patients into different risk groups and further assess whether different risk groups have varying benefits from different CCD during subsequent CCRT. This study aims to predict the prognosis of patients by evaluating both their baseline characteristics and tumor response to IC, thereby providing a basis for the development and timely adjustment of individualized treatment plans. This approach is intended to achieve the goal of enhancing efficacy while reducing toxicity in the treatment of patients with LA-NPC.

Materials and Methods

Patients

A total of 581 patients with LA-NPC who underwent treatment at Guangxi Medical University Cancer Hospital between January 2017 and December 2019 were included in our study. Inclusion criteria were as follows: (1) Pathologically confirmed diagnosis of NPC; (2) Retrospective staging according to the 8th edition of the AJCC staging system, classified as stage III to IVa; (3) receiving IC plus CCRT; (4) available magnetic resonance imaging (MRI) information before treatment and after IC; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2; (6) Complete clinical data available. Exclusion criteria were as follows: (1) any severe comorbidity; (2) suffering from prior/concurrent second primary malignant tumors. This study was retrospective in nature, and all patient data were anonymized, thereby exempting the need for informed consent.

Treatment Methods

All patients received CCRT with induction chemotherapy. Induction chemotherapy regimens included TP (docetaxel 75 mg/m^2, day 1; cisplatin 75 mg/m2, day 1), PF (cisplatin 80 mg/m^2, days 1–3; fluorouracil 750 mg/m^2 continuous intravenous infusion over 120 hours), GP (gemcitabine 1000 mg/m^2, day 1, day 8; cisplatin 80 mg/m^2, days 1) and TPF (docetaxel 60 mg/m^2, day 1; cisplatin 60 mg/m^2, day 1; fluorouracil 600 mg/m^2 continuous intravenous infusion over 120 hours), administered every 3 weeks for 2–3 cycles for induction therapy. The RT method was Intensity-Modulated Radiation Therapy (IMRT). Delineation of the target area and organs at risk followed the guidelines of International Commission on Radiation Units and Measurements Reports (ICRU) 50 and 62. Prescription doses for target areas were as follows: GTVnx received 69.0–75.2 Gy (30–33 fractions), GTVnd or CTVnd received 60.0–73.92 Gy (30–33 fractions), CTV1 received 60.0–64.0 Gy (30–32 fractions), and CTV2 received 54–57.6 Gy (30–32 fractions). Concurrent cisplatin-based chemotherapy (80–100 mg/m^2 every three weeks) was administered during radiotherapy.

Quantification of Plasma EBV DNA Levels and Tumor Response Assessment

Plasma EBV DNA levels were measured before treatment and after the completion of IC. The extracted plasma EBV DNA was analyzed using real-time quantitative PCR. Each patient underwent a nasopharyngeal and neck MRI before and after IC, according to the Response Evaluation Criteria in Solid Tumors criteria 1.1 (RECIST 1.1), The overall biological responses to IC included CR, PR, SD, and PD. Tumor responses in the present study were divided into two levels: "responders" (CR/PR) and "non-responders" (SD/PD).

Data Collection and Follow-up

Baseline data collected included clinical information, serum parameters, and tumor response to IC of all patients, such as gender, age, AJCC 8th edition staging (including T stage, N stage, and clinical stage), tumor response to IC, EBV DNA levels before and after IC, albumin (ALB), alkaline phosphatase (ALP), LDH, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio(LMR), Systemic Inflammatory Response Index (SIRI), Systemic Immune-Inflammation Index (SII), pathological classification (WHO fifth edition), and treatment modalities.

Our primary endpoint was overall survival (OS) (defined as the period from the first day of first therapy to the date of death from any cause), The secondary endpoints were distant metastasis-free survival (DMFS) (defined as the period from the first therapy to the date of distant metastasis), locoregional relapse-free survival (LRFS) (defined as the period from the first day of initial therapy to the date of locoregional relapse), and progression-free survival (PFS) (defined as the period from the start of treatment to the date of disease progression or death from any cause). Follow-up was conducted through various means, including phone calls, outpatient visits, and hospital reexaminations. Within the first 2 years after treatment, follow-up occurred every 3 months; from the 3rd to the 4th year, follow-up was conducted every 6 months, and thereafter, annually. The routine follow-up examinations included symptoms inquiries, physical examinations, nasopharyngoscopy, MRI of the nasopharynx and neck, and testing for EBV DNA. Other systemic examinations such as whole-body CT, 18F-fluorodeoxyglucose positron-emission tomography (PET)-CT, and bone scan were performed when clinically indicated. A pathologic biopsy was performed when clinically necessary to verify locoregional or

distant lesion progression. The follow-up period was measured from the initial day of treatment to the day of death or the last clinical follow-up.

Statistical Analysis

The median age was used as the cutoff value for age. The cut-off values for continuous laboratory variables and risk group stratification were determined using the X-tile program. X-tile uses the Log rank test to assess the differences between various cut-off values in survival data and selects the optimal cutoff point based on the minimum p-value. Patients were randomly assigned to training and validation cohorts in a 7:3 ratio. Baseline characteristics were analyzed for differences using the chi-square test. In the training cohort, univariate and multivariate Cox regression were used to identify independent prognostic factors for survival, with multicategorical unordered variables set as dummy variables. Variance inflation factor (VIF) was calculated to assess multicollinearity in the multivariate Cox regression model. The proportional hazards assumption in the multivariate Cox regression analysis based on independent prognostic factors was assessed using the Schoenfeld residual test. Kaplan-Meier method was performed for survival analysis, and survival rates were compared using the Log rank test.

To maximize the predictive value of the model, we developed a nomogram in the training cohort and tested it in the validation cohort. The concordance index (C-index) of the nomogram was calculated in both training and validation cohorts and compared with the TNM stage to assess model discrimination. Calibration curves were plotted to test the accuracy of the model, and decision curve analysis (DCA) was performed to evaluate whether the nomogram improved the clinical utility of the TNM stage. Patients were classified into low-risk, intermediate-risk, and high-risk subgroups using the cut-off value of the nomogram-defined score. Further analysis was conducted to determine the optimal CCD for patients with different risk levels.

Statistical analysis was carried out with the open source statistical environment R (version 4.3.0, available at www.r-project.org), SPSS 25.0 (IBM Corporation, Armonk, NY), and X-tile program 3.6.1 (Chicago, Rim Lab). $p < 0.05$ were considered statistically significant for differences.

Results

Patient Characteristics

According to the inclusion criteria, we included 581 cases in this study. For the entire cohort, the median age was 44 (range 16-72) years, with 142 (24.4%) females and 439 (75.6%) males. Based on RECIST 1.1 criteria, 5 (0.86%) patients had CR, 348 (59.9%) patients had PR, 226 (45.8%) patients had SD, and 2 (0.3%) patients had PD after IC. The median follow-up time for the entire cohort was 53 months (range: 3–97 months). At the last follow up, 119 patients (20.5%) died, 48 patients (8.3%) experienced local recurrence, 149 patients (25.6%) developed distant metastasis, and 181 patients (31.2%) experienced disease progression. The 3-year, 5-year, and 7-year overall survival rates (%) were 86.5%, 76.0%, and 67.5%, respectively. Patients were randomly allocated to training cohort (n = 407) and validation cohort (n = 174), with baseline characteristics presented in Table 1. There were no statistically significant differences in baseline characteristics between the training and validation cohorts ($p > 0.05$).

Table 1 Baseline Characteristics of Patients With LA-NPC in Total Cohort, Training Cohort and Validation Cohort

Clinical Factors	Total Cohort (N = 581)	Training Cohort (N = 407)	Validation Cohort (N = 174)	*p*
Age(years)				
≤44	300 (51.6%)	209 (51.4%)	91 (52.3%)	0.834
>44	281 (48.4%)	198 (48.6%)	83 (47.7%)	
Gender				
Male	439 (75.6%)	310 (76.2%)	129 (74.1%)	0.602
Female	142 (24.4%)	97 (23.8%)	45 (25.9%)	

(*Continued*)

Table 1 (Continued).

Clinical Factors	Total Cohort (N = 581)	Training Cohort (N = 407)	Validation Cohort (N = 174)	*p*
Pathology				
K-NPC or basaloid SCC	63 (10.8%)	43 (10.6%)	20 (11.5%)	0.741
NK-NPC	518 (89.2%)	364 (89.4%)	154 (88.5%)	
T stage				
T1-2	165 (28.4%)	106 (26.0%)	59 (33.9%)	0.054
T3-4	416 (71.6%)	301 (74.0%)	115 (66.1%)	
N stage				
N0-1	144 (24.8%)	105 (25.8%)	39 (22.4%)	0.387
N2-3	437 (75.2%)	302 (74.2%)	135 (77.6%)	
Clinical stage				
C3	205 (35.3%)	138 (33.9%)	67 (38.5%)	0.288
C4	376 (64.7%)	269 (66.1%)	107 (61.5%)	
IC regimen				
GP	80 (13.8%)	52 (12.8%)	28 (16.1%)	0.768
PF	16 (2.8%)	11 (2.7%)	5 (2.9%)	
TP	14 (2.4%)	10 (2.5%)	4 (2.3%)	
TPF	471 (81.1%)	334 (82.1%)	137 (78.7%)	
IC cycle				
2	55(9.5%)	37 (9.1%)	18 (10.3%)	0.636
3	526 (90.5%)	370 (90.9%)	156 (89.7%)	
CCD (mg/m^2)				
≤200	391 (67.3%)	275 (67.6%)	116 (66.7%)	0.832
>200	190 (32.7%)	132 (32.4%)	58 (33.3%)	
IC response				
CR/PR	352 (60.6%)	250 (61.4%)	102 (58.6%)	0.526
SD/PD	229 (39.4%)	157 (38.6%)	72 (41.4%)	
EBV DNA before IC (copies/mL)				
≤9960	522 (89.8%)	365 (89.6%)	157 (90.2%)	0.841
>9960	59 (10.2%)	42 (10.3%)	17 (9.8%)	
EBV DNA after IC (copies/mL)				
≤5660	500 (86.1%)	351 (86.2%)	149 (85.6%)	0.846
>5660	81 (13.9%)	56 (13.8%)	25 (14.4%)	
ALB (g/L)				
≤38.8	208 (35.8%)	150 (36.9%)	58 (33.3%)	0.417
>38.8	373 (64.2%)	257 (63.1%))	116 (66.7%)	
ALP(U/L)				
≤69	269 (46.3%)	182 (44.7%)	87 (50.0%)	0.242
>69	312 (53.7%)	225 (55.3%)	87 (50.0%)	
LDH(U/L)				
≤249	521 (89.7%)	366 (89.9%)	155 (89.1%)	0.759
>249	60 (10.3%)	41 (10.1%)	19 (10.9%)	
NLR				
≤4	509 (87.6%)	355 (87.2%)	154 (88.5%)	0.667
>4	72 (12.4%)	52 (12.8%)	20 (11.5%)	
PLR				
≤238.4	501 (86.2%)	352 (86.5%)	149 (85.6%)	0.784
>238.4	80 (13.8%)	55 (13.5%)	25 (14.4%)	

(*Continued*)

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Table 1 (Continued).

Clinical Factors	Total Cohort (N = 581)	Training Cohort (N = 407)	Validation Cohort (N = 174)	*p*
LMR				
≤2.3	76 (13.1%)	59 (14.5%)	17 (9.8%)	0.122
>2.3	505 (86.9%)	348 (85.5%)	157 (90.2%)	
SII				
≤547.2	223 (38.4%)	150 (36.9%)	73 (42.0%)	0.247
>547.2	358 (61.6%)	257 (63.1%))	101 (58.0%)	
SIRI				
≤1.9	460 (79.2%)	319 (78.4%)	141 (81.0%)	0.470
>1.9	121 (20.8%)	88 (21.6%)	33 (19.0%)	
Dead				
Yes	119 (20.5%)	91 (22.4%)	28 (16.1%)	0.086
No	462 (79.5%)	316 (77.6%)	146 (83.9%)	
Recurrence				
Yes	48 (8.3%)	36 (8.8%)	12 (6.9%)	0.435
No	533 (91.7%)	371 (91.2%)	162 (93.1%)	
Metastasis				
Yes	149 (25.6%)	109 (26.8%)	40 (23.0%)	0.338
No	432 (74.4%)	298 (73.2%)	134 (77.0%)	
Progress				
Yes	181 (31.2%)	133 (32.7%)	48 (27.6%)	0.225
No	400 (68.8%)	274 (67.3%)	126 (72.5%)	

Note: *$p < 0.05$.

Abbreviations: LA-NPC, Locally Advanced Nasopharyngeal Carcinoma; K-NPC, Keratinizing Nasopharyngeal Carcinoma; SCC, Squamous Cell Carcinoma; NK-NPC, Non-Keratinizing Nasopharyngeal Carcinoma; IC, Induction Chemotherapy; GP, Gemcitabine and Cisplatin; PF, Cisplatin and 5-Fluorouracil; TP, Taxane and Cisplatin; TPF, Taxane, Cisplatin, and 5-Fluorouracil; CCD, Cumulative Chemotherapy Dose; CR/PR, Complete Response/Partial Response; SD/PD, Stable Disease/Progressive Disease; EBV, Epstein-Barr Virus; ALB, Albumin; ALP, Alkaline Phosphatase; LDH, Lactate Dehydrogenase; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index. Categorical variables are expressed as counts and percentages and analyzed using the chi-square test.

Establishment and Validation of the Nomogram

The CCD in CCRT was divided into two groups: CCD ≤ 200 mg/m² and CCD > 200 mg/m², the cut-off values for NLR (4), LMR (2.3), PLR (192.4), SII (547.2), SIRI (1.7), ALB (38.8 g/L), ALP (69.0 U/L), LDH (251 U/L), EBV DNA levels before IC (9360 copies/mL), and EBV DNA levels after IC (5660 copies/mL) were calculated by X-tile software. In the training cohort, we analyzed the prognostic factors for OS. Univariate Cox regression analysis indicated that EBV DNA levels before IC, EBV DNA levels after IC, IC regimen, tumor response to IC, age, CCD, LMR, SIRI, ALB, LDH, and clinical stage were significant prognostic factors for patients ($p < 0.05$).The factors with statistical significance in the univariate analysis were then incorporated into the multivariate Cox regression model, revealing that EBV levels DNA after IC, tumor response to IC, age, and LDH were independent prognostic factors ($p < 0.05$), as shown in Table 2. Although clinical stage was not independent prognostic factors in the Cox regression analysis of this study, their importance is widely recognized.[22] Therefore, we constructed the nomogram for OS by combining the independent prognostic factors with clinical stage (Figure 1).

Collinearity analysis showed that VIF for each independent prognostic factor was close to 1, indicating no significant multicollinearity. The Schoenfeld residual plot (Figure 2) indicated that the multivariate Cox regression analysis based on independent prognostic factors satisfied the proportional hazards assumption overall ($p = 0.851$). There were no time-dependent trends observed for each covariate in the model, all of which met the proportional hazards assumption ($p > 0.05$). Similarly, we constructed a clinical staging model, which is currently the most widely used method for making

Table 2 Univariate and Multivariable Cox Analysis of the Risk Fators for OS in the Training Cohort

Characteristic	Univariate Cox Regression analysis HR (95% CI)	*p*	Multivariate Cox Regression Analysis HR (95% CI)	*p*
Age(years)		<0.001*		<0.001*
≤44	Reference		Reference	
>44	2.519(1.620~3.917)		3.042(1.879~4.923)	
Gender		0.143		–
Male	Reference		–	
Female	0.674(0.398~1.142)		–	
Pathology		0.276		–
K-NPC/basaloid SCC	Reference		–	
NK-NPC	0.651(0.301~1.409)		–	
T stage		0.169		–
T1-2	Reference		–	
T3-4	1.426(0.860~2.365)		–	
N stage		0.232		–
N0-1	Reference		–	
N2-3	1.361(0.821~2.259)		–	
Clinical stage		0.011*		0.283
C3	Reference		Reference	
C4	1.891(1.161~3.080)		1.330(0.790~2.239)	
IC regimen		0.130		–
GP	0.293(0.095~0.903)		–	
PF	2.105(0.868~5.109)		–	
TP	1.138(0.370~3.505)		–	
TPF	Reference		–	
IC cycle		0.231		–
2	Reference		–	
3	0.689(0.375~1.268)		–	
CCD (mg/m^2)		0.007*		0.051
≤200	Reference		Reference	
>200	0.491(0.293~0.823)		0.590(0.347~1.002)	
IC response		0.003*		0.006*
CR/PR	Reference		Reference	
SD/PD	1.874(1.241~2.829)		1.820(1.187~2.790)	
EBV DNA before IC (copies/mL)		<0.001*		0.575
≤9960	Reference		Reference	
>9960	3.131(1.934~5.069)		1.192(0.645~2.204)	
EBV DNA after IC (copies/mL)		<0.001*		0.004*
≤5660	Reference		Reference	
>5660	3.109(2.009~4.811)		2.188(1.290~3.710)	
ALB (g/L)		0.253		–
≤38.8	Reference		–	
>38.8	0.776(0.502~1.199)		–	
ALP(U/L)		0.010*		0.189
≤69	Reference		Reference	
>69	0.010(1.152~2.786)		1.385(0.852~2.250)	
LDH(U/L)		<0.001*		<0.001*
≤249	Reference		Reference	
>249	3.101(1.903~5.056)		3.015(1.761~5.162)	

(*Continued*)

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Table 2 (Continued).

Characteristic	Univariate Cox Regression analysis HR (95% CI)	*p*	Multivariate Cox Regression Analysis HR (95% CI)	*p*
NLR		0.071		–
≤4	Reference		–	
>4	1.624(0.959~2.752)		–	
PLR		0.464		–
≤238.4	Reference		–	
>238.4	0.790(0.420~1.485)		–	
LMR		0.003*		0.455
≤2.3	Reference		Reference	
>2.3	0.474(0.290~0.773)		0.761(0.371~1.561)	
SII		0.171		–
≤547.2	Reference		–	
>547.2	1.369(0.873~2.147)		–	
SIRI		0.002*		0.237
≤1.9	Reference		Reference	
>1.9	1.983(1.274~3.086)		1.512(0.762~3.001)	

Note: *$p < 0.05$.

Abreviations: HR, Hazard Ratio; CI, Confidence Interval; K-NPC, Keratinizing Nasopharyngeal Carcinoma; SCC, Squamous Cell Carcinoma; NK-NPC, Non-Keratinizing Nasopharyngeal Carcinoma; T, Tumor Stage; N, Node Stage; IC, Induction Chemotherapy; GP, Gemcitabine and Cisplatin; PF, Cisplatin and 5-Fluorouracil; TP, Taxane and Cisplatin; TPF, Taxane, Cisplatin, and 5-Fluorouracil; CCD, Cumulative Chemotherapy Dose; CR/PR, Complete Response/Partial Response; SD/PD, Stable Disease/Progressive Disease; EBV, Epstein-Barr Virus; ALB, Albumin; ALP, Alkaline Phosphatase; LDH, Lactate Dehydrogenase; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index. Performed univariate and multivariate analyses using cox analysis.

treatment decisions for NPC. The C-index of the nomogram in the training cohort and validation cohort were 0.758 (95% CI: 0.695–0.821) and 0.701 (95% CI: 0.589–0.813), respectively, which were higher than the C-index of the clinical staging model in the training cohort (0.572, 95% CI: 0.519–0.625) and validation cohort (0.602, 95% CI: 0.529–0.721).

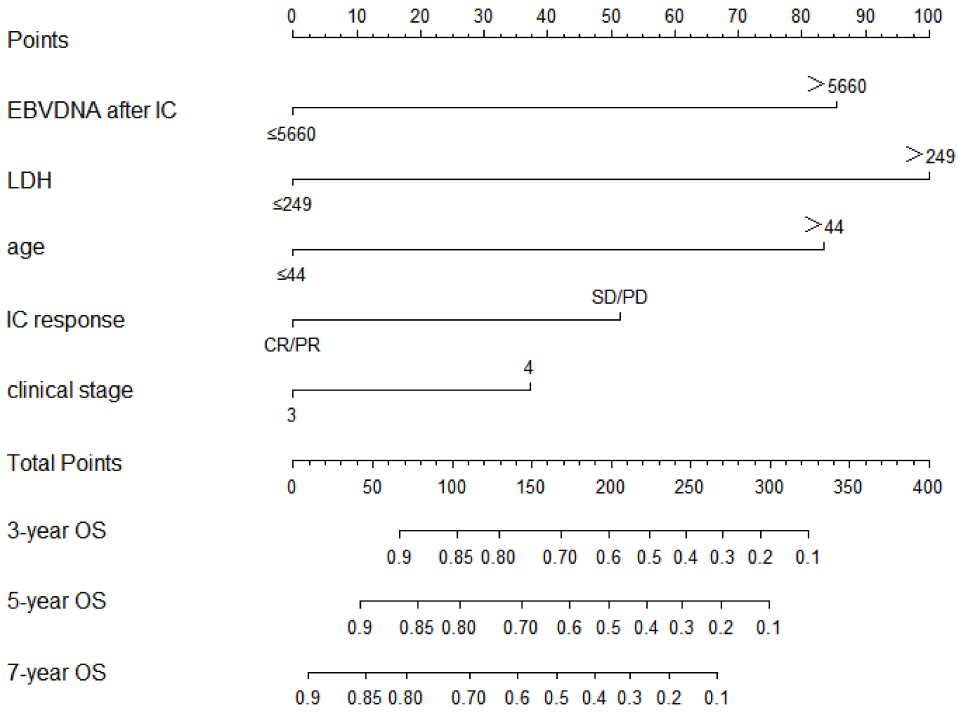

Figure 1 Nomogram for predicting OS in LA-NPC based on EBV DNA after IC and IC response.

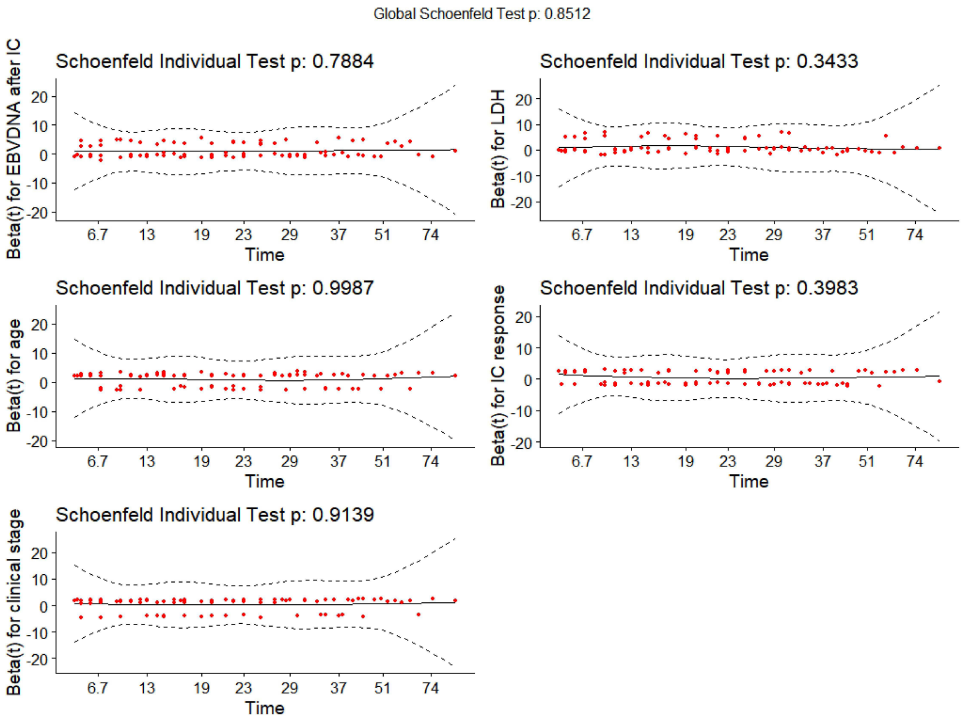

Figure 2 Schoenfeld residuals plot. The regression coefficients of each independent prognostic factors in the multivariate Cox regression model fitted by the nomogram remain stable over time, hovering near the 0 line and exhibiting basic symmetry. The multivariate Cox model and all covariates satisfy the proportional hazards assumption ($p \geq 0.05$).

The calibration curve analysis showed that the nomogram demonstrated strong predictive ability in both the training and validation cohorts, with the curve closely approximating the reference line, indicating a high degree of calibration (Figure 3A and B). DCA showed that the clinical utility of the nomogram in both the training and validation cohorts was higher than that of the clinical staging model (Figure 3C and D).

Risk Stratification and Survival Analysis

We further calculated each patient's risk score based on the nomogram, the X-tile software were used to select the optimal cut-off value of 104 and 183.4 points. Based on these values, patients were classified into low-risk (≤ 83.4), intermediate-risk (83.4 < score ≤183.4), and high-risk (> 183.4) groups. The Kaplan-Meier method was used to plot survival curves, and the results showed statistically significant differences in The 5-year OS rate were 91.2%, 72.6%, and 42.7% (HR = 3.307, 95% CI = 2.506–4.364, $p < 0.001$, Figure 4A), LRFS were 96.6%, 86.0%, and 82.2% (HR = 2.289, 95% CI = 1.487–3.523, $p < 0.001$, Figure 4B), DMFS were 85.9%, 70.3%, and 36.9% (HR = 2.487, 95% CI = 1.947–3.177, $p < 0.001$, Figure 4C), and PFS were 84.6%, 61.7%, and 30.9% (HR = 2.514, 95% CI = 2.012–3.140, $p < 0.001$, Figure 4D) among patients in the low-, intermediate-, and high-risk groups across the entire cohort ($p < 0.05$).

CCRT and Subgroup Survival Analysis

In this study, 227 patients were categorized as low-risk, 293 as intermediate-risk, and only 61 as high-risk. Due to the limited number of high-risk patients, subgroup survival analysis was conducted using two categories: low-risk (227, 39.1%) and combined intermediate- and high-risk as medium/high-risk (354, 60.9%). In the low-risk group, the 5-year OS rate was 92.9% for the CCD ≤ 200 mg/m² group and 89.1% for the CCD > 200 mg/m² group, with no statistically significant difference (HR = 1.235, 95% CI = 0.415–3.680, $p = 0.704$, Figure 5A). In the medium/high-risk group, the OS rate was 63.5% for the CCD ≤ 200 mg/m² group and 76.2% for the CCD > 200 mg/m² group (HR = 0.675, 95% CI = 0.422–1.079, $p = 0.097$, Figure 5B). It can be observed that higher chemotherapy cumulative doses (CCD > 200 mg/m²) did not show a significant difference in the low-risk

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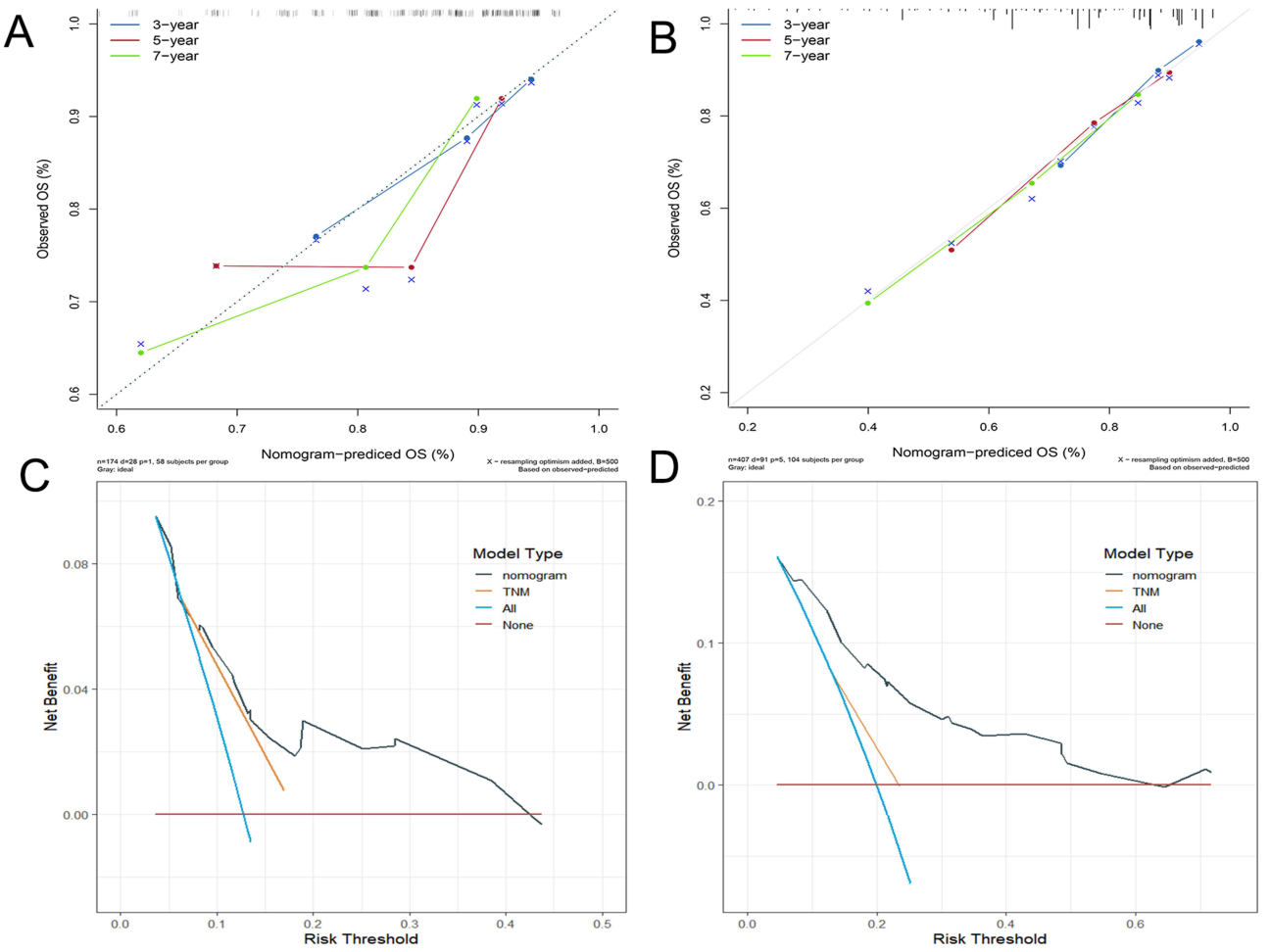

Figure 3 Validation of the nomogram. Calibration curves for the 3, 5, and 7-year OS in the training (**A**) and validation cohorts (**B**) closely align with the standard curve, indicating good model accuracy. (**C** and **D**) depict decision curve analysis (DCA) for the training and validation cohorts, demonstrating that the nomogram provides more net benefit compared to the clinical staging alone in both cohorts.

patients, whereas in the medium/high-risk patients, there was some improvement in survival rates, although this improvement was not statistically significant ($p < 0.05$). Additionally, in patients with LA-NPC in the low-risk and medium/high-risk groups, the LRFS under different CCD doses (Figure 5C and D), DMFS (Figure 5E and F), and PFS (Figure 5G and H) were also not statistically significant ($p \geq 0.05$).

Discussion

This study was the first to combine EBV DNA levels before and after IC, tumor response to IC, serological, and inflammatory baseline factors to jointly explore the OS and subsequent treatment of LA-NPC. We found that EBV DNA levels after IC, tumor response to IC, LDH, and age are independent prognostic factors. The nomogram developed, incorporating clinical staging, successfully stratified patients with locally advanced NPC into low-, intermediate-, and high-risk groups, demonstrating superior performance over clinical staging. In low-risk patients, the OS for the CCD > 200 mg/m² and CCD ≤ 200 mg/m² groups did not show a significant difference. In i medium/high-risk patients, CCD > 200 mg/m² seemed to provide potential benefits for OS, although this was not statistically significant. Therefore, for medium/high-risk patients, the selection of a higher CCD should be carefully considered in terms of OS benefit and potential toxicities. Although this study had made progress in risk stratification, the optimal subsequent treatment strategies for different risk groups still require further exploration.

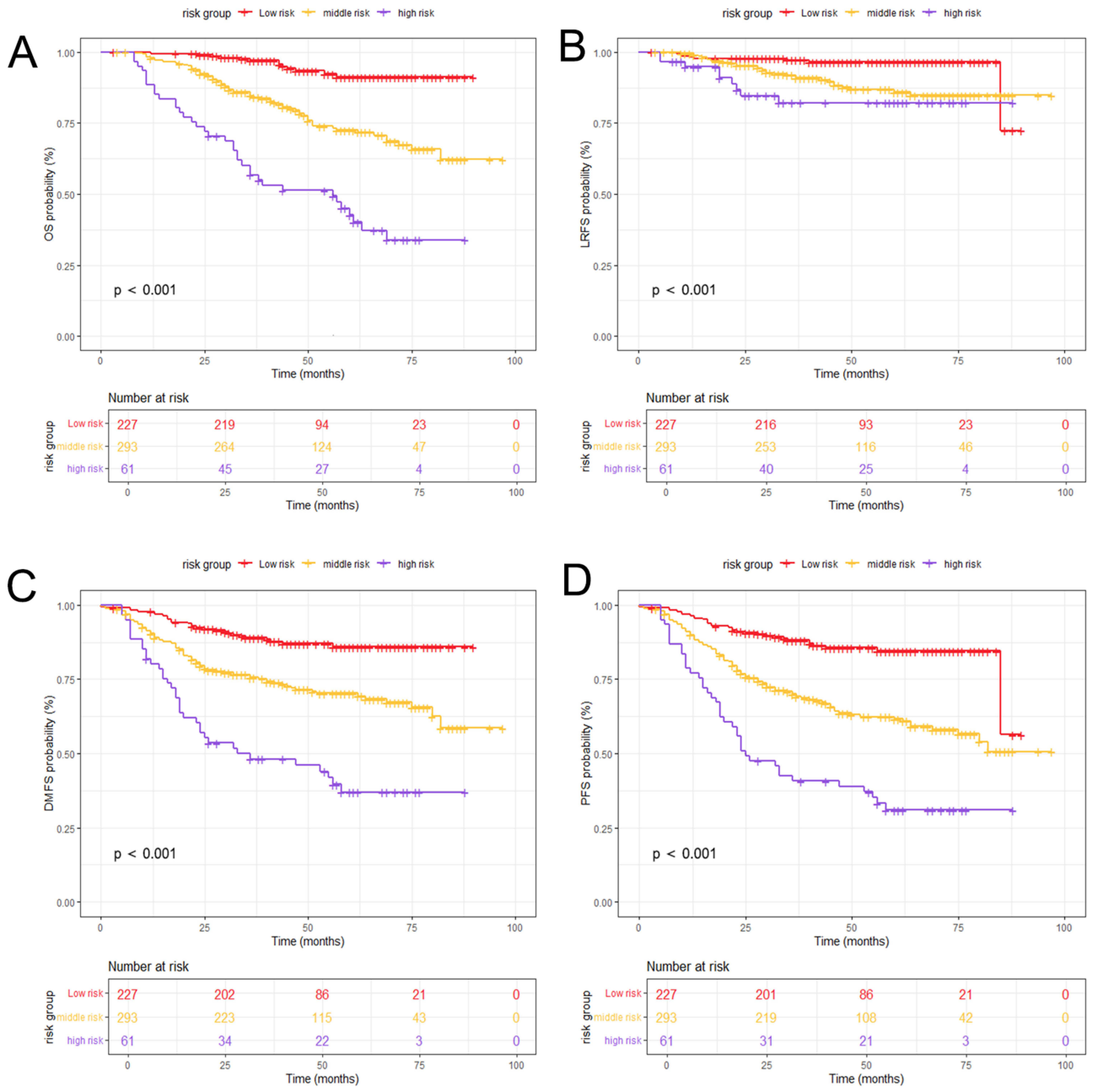

Figure 4 Kaplan-Meier analysis for OS (**A**), LRFS (**B**), DMFS (**C**), and PFS (**D**) among the high-, intermediate-, and low-risk groups as defined by the nomogram. respectively.

The development of modern treatment modalities (eg, IMRT, tomotherapy, targeted therapy, and immunotherapy) has made personalized treatment for LA-NPC increasingly important. As is well known, the implementation of these intensified treatments is often associated with a higher incidence of treatment-related adverse events and economic burden. Therefore, it is important to select the appropriate candidates who will benefit from additional treatment. To achieve this goal, the selection of clinical prognostic factors has become key to personalized treatment. By identifying and analyzing these factors, we can more accurately predict patients' treatment responses and outcomes, thereby aiding in the development of personalized treatment plans that maximize therapeutic efficacy while minimizing unnecessary burdens.

Plasma EBV DNA detection using real-time quantitative PCR technology is currently the most widely used biomarker for NPC in clinical practice.[13] Previous studies have primarily focused on the correlation between pre-

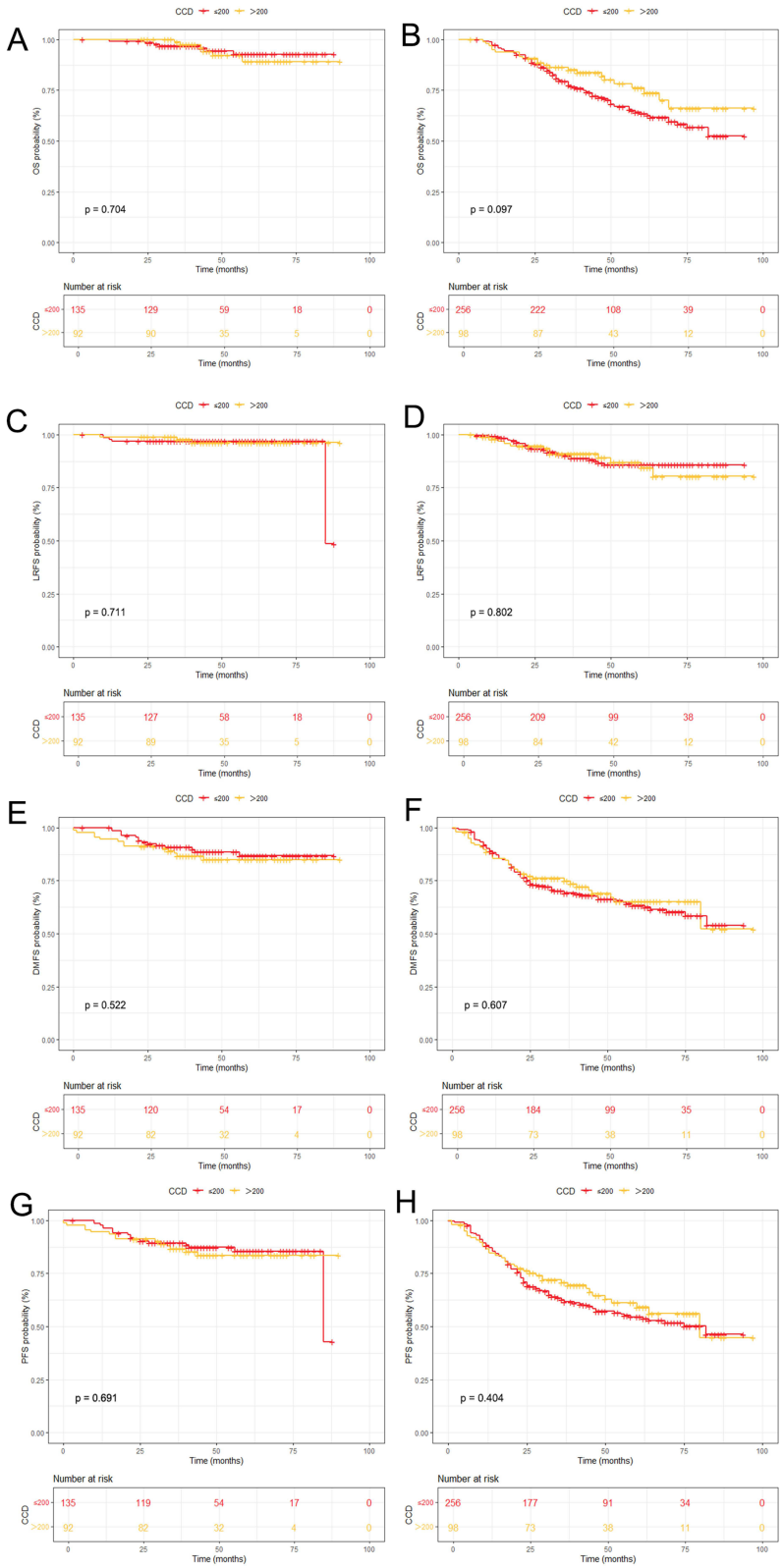

Figure 5 Kaplan-Meier curves for OS (**A** and **B**), LRFS (**C** and **D**), DMFS (**E** and **F**), and PFS (**G** and **H**) between the low-risk group and the medium/high-risk group, stratified by CCD ≤ 200 and CCD > 200 mg/m², as defined by the nomogram.

treatment plasma EBV DNA levels and tumor response, tumor burden, and prognosis;[14] It has been demonstrated that the staging system incorporating EBV DNA provides improved outcome prediction, enhanced risk stratification, and better risk consistency compared to the 8th edition of the TNM staging system.[23] In recent years, the dynamic changes in EBV DNA have gained increasing attention. A study based on longitudinal monitoring of EBV-DNA levels for prognostic risk stratification in LA-NPC has demonstrated that post-induction chemotherapy EBV DNA levels have high prognostic accuracy,[24] our findings are consistent with previous studies. In this study, using a threshold of EBV DNA > 5660 copies/mL after IC, it was found to be an independent risk factor for OS ($p < 0.05$). However, the EBV DNA levels before IC was not confirmed as an independent prognostic factor. This may be due to an interaction effect between the EBV DNA levels before and after IC, and EBV DNA levels after IC had a stronger predictive ability for prognosis.[16]

Previous studies have shown that the tumor response to IC can not only assess chemotherapy sensitivity, but also guide chemotherapy selection based on risk adaptation before CCRT, and assess prognosis.[19,25] Due to its ease of measurement and practicality, the RECIST 1.1 criteria have been widely accepted as the standard method for assessing treatment response in solid tumors.[26] Tumor regression during and after radiotherapy has also been shown to predict clinical outcomes,[27,28] nevertheless, early assessment following induction chemotherapy can assist clinicians in making more personalized treatment decisions. In this study, 60.6% of patients were classified as "responders" (CR/PR), indicating a reduction in tumor burden and an increased sensitivity of tumor cells to treatment. Patients who achieved CR/PR during IC had better prognoses compared to those with SD/PD, consistent with our findings.[25,29] The phenomenon of patients who show non-responders after IC may be caused by a variety of factors at the macro level, including tumor heterogeneity,[30] changes in the tumor microenvironment,[31] and others. Additionally, at the molecular level, it may be related to mechanisms such as drug efflux,[32,33] enhancement of DNA repair[31] cancer stem cell (CSC), pathways,[34] and exosomes,[35] etc.

We also assessed the prognostic value of baseline clinical factors. We found that LDH level > 249 U/L was associated with shorter OS. LDH is an enzyme involved in the glycolytic pathway. Due to the unique metabolic characteristics of tumors, abnormal enzyme synthesis occurs, and the increased release of LDH under hypoxic conditions in malignant tumors can contribute to resistance to radiotherapy and chemotherapy in NPC, thereby reducing OS and PFS.[21,36,37] Most studies have shown that age influences disease-specific survival,[38–40] local control,[41] and distant metastasis.[42] In this study, age > 44 years was identified as one of the independent risk factors. Older patients are more likely to develop comorbidities and exhibit poorer performance status, which may result in reduced tolerance to treatment (radiotherapy and/or chemotherapy), leading to a higher incidence of non-cancer-related deaths. Inflammation and immune responses are implicated in the initiation, promotion, and metastasis of tumors.[43] While indicators such as NLR, PLR, and SII have been shown to be associated with the prognosis of nasopharyngeal carcinoma,[20,44,45] they were not identified as independent prognostic factors in this study, which may be attributed to variations in tumor staging and threshold selection across different studies, as well as the inclusion of additional prognostic factors with stronger predictive value. Clinical staging was not identified as an independent prognostic factor, likely due to the homogeneity of staging in our cohort of locally advanced patients, which results in smaller prognostic differences.

Nomograms have been widely utilized in cancer prognostic decision-making in recent years, yet most studies primarily focus on baseline characteristics of cancer patients.[10–12,46] The integration of EBV DNA holds significant prognostic value in nomograms for LA-NPC research, compared with other EBV DNA-based nomograms,[11,47,48] our model demonstrates more comprehensive variable selection. Our study found that the EBV DNA level after IC had greater prognostic predictive value compared to the baseline level, and that early tumor response to IC also played a significant role in predicting the prognosis of LA-NPC patients. This post-induction chemotherapy assessment is crucial for both treatment and prognosis in LA-NPC patients, as it complements baseline characteristics in predicting prognosis and aids clinicians in adjusting treatment strategies during CCRT. In this study, a nomogram was developed to stratify patients with LA-NPC into low-, intermediate-, and high-risk groups, with significant differences observed in OS, PFS, LRFS, and DMFS ($p < 0.05$). The nomogram demonstrated good discrimination, with C-index values of 0.758 (95% CI: 0.695–0.821) in the training cohort and 0.701 (95% CI: 0.589–0.813) in the validation cohort. The proposed nomogram demonstrated superior C-index performance compared to existing EBV DNA-based prognostic models (C-index 0.758 vs peripheral blood cell-plasma EBV DNA loads nomogram C-index 0.610, SII-EBV DNA nomogram C-index 0.657, and C-reactive protein/albumin ratio-EBV DNA nomogram C-index 0.693).[11,47,48]

In our study, 32.7% of patients received CCD > 200 mg/m² during CCRT. In the low-risk group, CCD ≤ 200 mg/m² was sufficiently effective for patients with LA-NPC. In the medium/high-risk groups, OS was improved with CCD > 200 mg/m² compared to CCD ≤ 200 mg/m², but the difference was not statistically significant. We hypothesize that patients classified as medium or high risk based on this nomogram may potentially benefit from higher CCD, as the combination of radiotherapy and chemotherapy may enhance each other through multiple mechanisms.[49,50] To confirm this hypothesis, longer follow-up or more rigorous clinical trials are needed. Based on our current findings, we suggest that clinicians carefully weigh the survival benefits and potential toxicities of CCD during CCRT, following an assessment of baseline and post-induction chemotherapy conditions. Additionally, while some studies have suggested that CCD ≤ 200 mg/m² may be sufficient, they did not perform subgroup analyses based on risk groups. Therefore, further research is needed to confirm our hypothesis.[51] Another study has indicated that LA-NPC can be de-escalated, with induction chemotherapy followed by radiotherapy alone providing similar benefits to CCRT. However, the study only compared 3-year prognostic follow-up data. Further survival comparisons with extended follow-up are needed.[52] A recent study that integrated longitudinal Epstein–Barr virus DNA combined with multipoint tumor response for prognostic evaluation enabled the personalized identification of patients likely to benefit from AC. Different from this, our study focused on the intensity of CCD during CCRT, while incorporating additional predictive biomarkers.[24] Currently, targeted therapy and immunotherapy have demonstrated significant therapeutic advantages in NPC,[53–55] a big-data, intelligence platform-based analysis has indicated that Cetuximab and Nimotuzumab are promising and effective strategies for patients with LA-NPC undergoing IMRT.[56] Compared to low-risk patients, whether high-risk patients can benefit from additional immunotherapy or targeted therapy, or optimize low-toxicity chemotherapy regimens, reduce CCD doses, or consider alternative treatments, warrants further investigation and the initiation of relevant clinical trials.

The study has several limitations. First, it is a single-center retrospective study, inevitably prone to patient selection bias. Second, the sample size of high-risk patients is relatively small, and combining intermediate- and high-risk groups to assess the efficacy of different CCD may limit the statistical power to detect significant differences between treatment groups. Third, this study did not specifically assess the impact of emerging therapies (eg, immunotherapy) on patient prognosis, nor did it compare the toxicities of CCRT in different CCD groups. Fourth, quality of life (QoL) should be considered a key outcome in future studies. We look forward to further exploration in subsequent studies, particularly relevant prospective clinical trials.

Conclusion

This study investigated the EBV DNA levels after IC, tumor response to IC, LDH, and age as independent prognostic factors for patients with LA-NPC treated with IC + CCRT. A nomogram incorporating the clinical staging system was successfully constructed, which stratified patients with LA-NPC into low-, intermediate-, and high-risk groups. However, no significant improvement in prognosis was observed in patients with CCD ≤ 200 mg/m² versus CCD > 200 mg/m² across different risk groups. The efficacy of higher doses of cisplatin in CCRT for patients in the medium/high-risk groups remains to be validated. Balancing toxicity and efficacy, exploring the potential role of immunotherapy, and considering de-escalation treatment strategies are areas that warrant further investigation to optimize treatment outcomes in LA-NPC patients.

Abbreviations

NPC, Nasopharyngeal carcinoma; LA-NPC, Locally Advanced Nasopharyngeal Carcinoma; NCCN, the National Comprehensive Cancer Network; K-NPC, Keratinizing Nasopharyngeal Carcinoma; SCC, Squamous Cell Carcinoma; NK-NPC, Non-Keratinizing Nasopharyngeal Carcinoma; IC, Induction Chemotherapy; AC, adjuvant chemotherapy; AJCC, the American Joint Committee on Cancer; CCD, Cumulative Chemotherapy Dose; CCRT, concurrent chemoradiotherapy; C-index, concordance index; DCA, decision curve analysis; CR/PR, Complete Response/Partial Response; SD/PD, Stable Disease/Progressive Disease; EBV, Epstein-Barr Virus; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IMRT, Intensity-Modulated Radiation Therapy; ALB, Albumin; ALP, Alkaline Phosphatase; LDH, Lactate Dehydrogenase; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-Inflammation Index;

SIRI, Systemic Inflammation Response Index; OS, overall survival; LRFS, local relapse-free survival; DMFS, distant metastasis-free survival; PFS, progression-free survival; PET, positron-emission tomography; VIF, Variance inflation factor; CSC, cancer stem cell; QoL, quality of life.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Ethics Approval

This study involved anonymized patient data and, due to its retrospective nature, was exempt from the requirement for informed consent. This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital (KY2024855), in compliance with the Declaration of Helsinki.

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Disclosure

The authors declare no competing interests in this work.

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