Research Square

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Selection and validation of intensity-modulated radiotherapy (IMRT) alone beneficiaries among elderly patients with stage T1-2N1M0 nasopharyngeal carcinoma and ACE-27 scores < 2: a multi-center study

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Abstract

Background

Elderly patients are underrepresented in clinical trials supporting concurrent chemoradiotherapy (CCRT) as the standard treatment for patients with stage T1-2N1M0 nasopharyngeal carcinoma (NPC). This study aimed to develop and validate a prognostic nomogram in elderly patients (≥ 60 years) with stage T1-2N1M0 NPC to distinguish low-risk subgroup for whom intensity-modulated radiotherapy (IMRT) alone is sufficient.

Methods

This multi-center study retrospectively analyzed 615 elderly patients with stage T1-2N1M0 NPC and Adult Comorbidity Evaluation-27 (ACE-27) scores < 2, including 297 and 318 patients in the training and validation cohorts, respectively. A nomogram for cancer-specific survival (CSS) was developed using multivariable Cox regression and validated using concordance indices (C-index), calibration curves, and decision curve analysis (DCA). Survival outcomes were compared using log-rank tests.

Results

Four independent predictors for CSS were identified to construct the nomograms: age, Epstein-Barr virus DNA (EBV-DNA), and extracapsular spread (ECS) of retropharyngeal and cervical lymph nodes. Nomogram A incorporated all four predictors. Nomograms B, C, and D were constructed based on T stage, EBV-DNA, and their combination, respectively. In the training cohort, the C-index of Nomogram A was 0.768, which was statistically higher than those of Nomogram B (0.530), Nomogram C (0.635), and Nomogram D (0.641). Calibration curves and DCA demonstrated good calibration and clinical utility for Nomogram A. Risk stratification using Nomogram A showed that in the low-risk group, IMRT alone achieved comparable 5-year CSS to chemoradiotherapy (CRT). These findings were confirmed in the validation cohort.

Conclusions

A nomogram integrating lymph node ECS, age, and EBV-DNA was developed to effectively identify optimal candidates among elderly patients with stage T1-2N1M0 NPC and ACE-27 scores < 2 for treatment with IMRT alone.

Clinical trial number

Not applicable.

Introduction

Nasopharyngeal carcinoma (NPC) exhibits a distinct geographical distribution pattern, with approximately 70% of global cases concentrated in East and Southeast Asia [1]. In recent years, with the widespread application of intensity-modulated radiotherapy (IMRT), the 5-year overall survival (OS) rate for stage II NPC has exceeded 90%, thus the benefit of chemotherapy for stage II NPC remains controversial. Perhaps the addition of chemotherapy may lead to minimal survival benefits but increased toxicities for the low-risk patients with stage II NPC. Current guidelines recommend stratified treatment for stage II NPC by incorporating tumor size and pretreatment Epstein–Barr virus (EBV) DNA level as risk stratification factors [2]. In particular, platinum-based chemotherapy combined with IMRT is recommended as the standard treatment for the N1 subgroup with adverse features including lymph nodes ≥ 3 cm, lymph node extracapsular spread (ECS), and EBV-DNA ≥ 4000 copies/mL, whereas radiotherapy alone is proposed for the others.

With the intensification of aging worldwide, the proportion of the elderly (≥ 60 years) NPC patients is rising, thus the treatment of this specific population has become a major health burden [3]. Nevertheless, the elderly patients are frequently excluded from the main phase II/III clinical trials in NPC, which mainly include the adults aged 18–60 years, leading to a notable gap in evidence regarding the optimal strategy for this population [4]. Moreover, due to diminished organ function, reduced treatment tolerance and higher comorbidity burdens (e.g., Adult Comorbidity Evaluation-27 (ACE-27) scores ≥ 2), the elderly patients may present with a higher incidence of treatment-related toxicities that potentially offset underlying survival benefits [5, 6]. Hence, applying the current treatment guidelines tailored for younger adults directly to the elderly is not appropriate.

Accumulating evidence suggests that MRI-derived lymph node radiomic features (e.g., ECS, cervical nodal necrosis (CNN), maximal axial diameter (MAD)), which potentially reflect essential prognosis-associated biological properties of NPC cells, were significantly associated with the prognosis of NPC patients [7–9]. Several previous studies have effectively developed predictive models for identifying the low-risk subgroup among stage II NPC patients for whom the addition of chemotherapy to IMRT could be omitted without compromising disease control [10–12]. However, there is currently a lack of studies developing a risk prediction model integrating MRI-detected lymph node radiomics features with clinical characteristics to help guiding individualized stratified treatment for the elderly patients with stage II NPC.

Therefore, we conducted this multicenter retrospective analysis to develop and validate a predictive model integrating pretreatment MRI nodal features and EBV-DNA levels to precisely identify the low-risk group in elderly patients with stage T1-2N1M0 NPC and ACE-27 < 2 who would benefit from IMRT alone, consequently, guiding personalized treatment strategies for this specific population according to risk stratification.

Materials and methods

Data Extraction and Study Population

The study flowchart is illustrated in Fig. 1. Patients diagnosed with NPC between January 2010 and December 2022 were identified from Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University and Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China. This retrospective study was approved by the Institutional Ethics Committees of the Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University (2024-ZN021) and Sun Yat-sen University Cancer Center (B2023-344-Y01), with the requirement for informed written consent waived. Patients were included if they met the following criteria: (a) initial diagnosis of non-metastatic, pathologically confirmed NPC; (b) classified as stage II with nodal stage N1(stage T1-2N1M0) according to the 8th American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system; (c) received curative-intensity IMRT (with or without platinum-based chemotherapy); (d) pre-treatment magnetic resonance imaging (MRI) of the head and neck was performed; (e) with age ≥ 60 years and ACE-27 scores <2. Patients were excluded if: (a) medical information or treatment plan data were incomplete; (b) received any prior chemotherapy or EGFR-targeted therapy for NPC before enrollment; (c) ACE-27 scores ≥ 2, indicating moderate to severe comorbidities. Consequently, a total of 615 elderly patients with Stage T1-2N1M0 NPC and ACE-27 scores < 2 were enrolled in this multicenter retrospective study, with the training cohort (Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University) and external validation cohort (Sun Yat-sen University Cancer Center) consisting of 297 and 318 patients, respectively. Clinical data such as demographics, diagnostic and treatment information, smoking status, and pre-treatment hematological and biochemical parameters were collected from the two centers.

Treatments

As previously reported in the IMRT guidelines, all patients in this study received IMRT [5]. The treatment modalities included radiotherapy alone (RT), concurrent chemoradiotherapy (CCRT), induction chemotherapy followed by concurrent chemoradiotherapy (IC+CCRT), and other regimens (e.g., adjuvant chemotherapy).

Chemotherapy

Induction chemotherapy (IC) consisted of either the TPF regimen-docetaxel (60 mg/m² on day 1), cisplatin (60 mg/m² on day 1), and 5-fluorouracil (600 mg/m² via 120-hour continuous infusion) or the GP regimen-gemcitabine (1000 mg/m² on days 1 and 8) plus cisplatin (70 mg/m² on day 1). Adjuvant chemotherapy (AC) involved the PF regimen: cisplatin (80 mg/m²) and 5-fluorouracil (750 mg/m² administered as a 96-hour continuous infusion). Concurrent chemoradiotherapy (CCRT) involved

cisplatin administered at a dose of 80 mg/m² via intravenous infusion, repeated every 3 weeks for a total of 2–3 cycles concurrently with IMRT.

Radiotherapy

Radiation doses were prescribed as follows: primary nasopharyngeal tumors received 68–70 Gy, while metastatic cervical lymph nodes were irradiated with 60–70 Gy. Elective irradiation of regions at risk for subclinical spread, including bilateral cervical lymphatics and areas of potential local infiltration, was delivered at dose ≥ 54 Gy.

MRI Evaluation

All enrolled patients underwent MRI of the head and neck region. Detailed scanning parameters are provided in the supplementary materials. Three radiologists independently assessed the MRI imaging features, and any disagreements were resolved through consensus. The diagnostic criteria for lymph node necrosis (CNN) on MRI were as follows: focal hyperintensity on T2-weighted imaging (T2WI) or focal hypointensity on T1-weighted imaging (T1WI), with or without contrast enhancement. The imaging criteria for ECSCLN and ECSRLN included infiltration into the surrounding fat plane, spiculated margin, and involvement of adjacent muscles, nerves, or the parotid gland. Positive lymph nodes were defined according to the criteria outlined in previous studies [13]. The maximum axial diameter of lymph nodes was measured on the largest cross-sectional image.

Endpoints

The primary endpoint of this study was cancer-specific survival (CSS), defined as the time from diagnosis or treatment initiation to death due to the cancer. The secondary endpoints included: distant metastasis-free survival (DMFS), defined as the time to the first occurrence of distant metastasis; locoregional recurrence-free survival (LRFS), defined as the time to the first recurrence at the primary tumor site or in the regional lymph nodes; and progression-free survival (PFS), defined as the time to the first radiological or clinical disease progression or death from any cause.

Follow-Up

Patients were monitored every three months during the first two years, every six months from years 3 to 5, and annually thereafter. Each follow-up included a physical examination, nasopharyngoscopy, head and neck MRI, chest radiography or CT, abdominal ultrasonography or CT, and plasma EBV-DNA quantification. Suspected recurrence or metastasis was confirmed via fine-needle aspiration or biopsy. For inaccessible lesions, clinical diagnosis required concordant findings from at least two imaging modalities (e.g., MRI, CT, chest radiography, abdominal ultrasonography, bone scintigraphy, or [^{18}F] FDG

PET/CT) indicating relapse. Equivocal imaging results prompted close surveillance until subsequent assessments clarified the disease status.

Statistical Analysis

Categorical variables were compared by the chi-square test. All the continuous variables were converted into binary based on the optimal cut-off point determined using receiver operating characteristic (ROC) curve analyses. Variables were selected for inclusion in the multivariable Cox regression model based on prior clinical knowledge and biological plausibility regarding their prognostic relevance in nasopharyngeal carcinoma. In the multivariable analysis, variables with a P-value < 0.05 were incorporated into the nomogram model for predicting 2-, 3-, and 5-year CSS. Hazard ratios (HR) and 95% confidence intervals (CI) for these prognostic factors were presented in a table. Calibration and discriminative ability of the nomogram were assessed using calibration curves and the concordance index (C-index), respectively. Internal validation was conducted with 500 bootstrap resamples to obtain stable calibration error distributions and confidence interval estimates. The calibration curves of the models were evaluated using the calibration slope, Hosmer-Lemeshow (H-L) test with its P-value, and Brier Score to assess their performance [14]. Decision curve analysis (DCA) was performed to evaluate the clinical utility of the nomograms by quantifying the net benefit (NB) across a range of threshold probabilities. Patients were stratified into low-risk and high-risk groups based on the total score calculated from the established nomogram. Time-to-event data for the low-risk and high-risk groups were analyzed using Kaplan-Meier curves, and differences between groups were compared with the log-rank test. All statistical analyses were performed using SPSS 27.0 and R 4.2.1 software. A two-sided P-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

There were 297 and 318 eligible patients retrospectively enrolled from Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University (the training cohort) and Sun Yat-sen University Cancer Center (external validation cohort), respectively. Baseline characteristics are summarized in Table 1. The baseline characteristics were well-balanced between radiotherapy (RT) group and chemoradiotherapy (CRT) group in the two cohorts.

Table 1
Patients' demographic and clinical characteristics of the two cohorts.

Characteristics	Training cohort (n = 297)			Validation cohort (n = 318)		
	RT	CRT	P-value	RT	CRT	P-value
Total	98	199		122	196	
Age, years						
< 65	48 (49.0%)	120 (60.3%)	0.06	82 (67.2%)	143 (73.0%))	0.27
≥ 65	50 (51.0%)	79 (39.7%)		40 (32.8%)	53 (27.0%)	
Sex						
Female	32 (32.7%)	58 (29.1%)	0.54	43 (35.2%)	51 (26.0%)	0.08
Male	66 (67.3%)	141 (70.9%)		79 (64.8%)	145 (74.0%)	
T stage[a]						
T1	17 (17.3%)	30 (15.1%)	0.61	26 (21.3%)	37 (18.9%)	0.60
T2	81 (82.7%)	169 (84.9%)		96 (78.7%)	159 (81.1%)	
EBV-DNA, copies/ml						
< 4000	36 (36.7%)	61 (30.7%)	0.29	23 (18.9%)	38 (19.4%)	0.91
≥ 4000	62 (63.3%)	138 (69.3%)		99 (81.1%)	158 (80.6%)	
CNNCLN						
No	84 (85.7%)	162 (81.4%)	0.36	103 (84.4%)	165 (84.2%)	0.95
Yes	14 (14.3%)	37 (18.6%)		19 (15.6%)	31 (15.8%)	
CNNRLN						
No	90 (91.8%)	192 (96.5%)	0.10*	116 (95.1%)	187 (95.4%)	0.89

[a] Using the 8th edition of the UICC/AJCC TNM staging system.

* Fisher's Exact Test.

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; EBV-DNA, Epstein-Barr virus DNA; CNN, cervical nodal necrosis; CLN, cervical lymph node; RLN, retropharyngeal lymph node; ECS, extracapsular spread; MAD, maximal axial diameter; ACE-27, Adult Comorbidity Evaluation-27.

Characteristics	Training cohort (n = 297)			Validation cohort (n = 318)		
	RT	CRT	P-value	RT	CRT	P-value
Yes	8 (8.2%)	7 (3.5%)		6 (4.9%)	9 (4.6%)	
ECSCLN						
No	80 (81.6%)	157 (78.9%)	0.58	97 (79.5%)	171 (87.2%)	0.07
Yes	18 (18.4%)	42 (21.1%)		25 (20.5%)	25 (12.8%)	
ECSRLN						
No	88 (89.8%)	175 (87.9%)	0.64	110 (90.2%)	173 (88.3%)	0.60
Yes	10 (10.2%)	24 (12.1%)		12 (9.8%)	23 (11.7%)	
MADCLN(mm)						
< 14	46 (46.9%)	103 (51.8%)	0.46	32 (26.2%)	72 (36.7%)	0.06
≥ 14	52 (53.1%)	96 (48.2%)		90 (73.8%)	124 (63.3%)	
MADRLN(mm)						
< 7	52 (53.1%)	105 (52.8%)	0.96	66 (54.1%)	94 (48.0%)	0.29
≥ 7	46 (46.9%)	94 (47.2%)		56 (45.9%)	102 (52.0%)	
Smoking						
No	61 (62.2%)	118 (59.3%)	0.63	80 (65.6%)	121 (61.7%)	0.49
Yes	37 (37.8%)	81 (40.7%)		42 (34.4%)	75 (38.3%)	
BMI						
< 21	52 (53.1%)	111 (55.8%)	0.66	93 (76.2%)	152 (77.6%)	0.79
≥ 21	46 (46.9%)	88 (44.2%)		29 (23.8%)	44 (22.4%)	
ACE-27 score						

[a] Using the 8th edition of the UICC/AJCC TNM staging system.

* Fisher's Exact Test.

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; EBV-DNA, Epstein-Barr virus DNA; CNN, cervical nodal necrosis; CLN, cervical lymph node; RLN, retropharyngeal lymph node; ECS, extracapsular spread; MAD, maximal axial diameter; ACE-27, Adult Comorbidity Evaluation-27.

Characteristics	Training cohort (n = 297)			Validation cohort (n = 318)		
	RT	CRT	P-value	RT	CRT	P-value
0	70 (71.4%)	148 (74.4%)	0.59	93 (76.2%)	140 (71.4%)	0.35
1	28 (28.6%)	51 (25.6%)		29 (23.8%)	56 (28.6%)	
[a] Using the 8th edition of the UICC/AJCC TNM staging system.						
* Fisher's Exact Test.						
Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; EBV-DNA, Epstein-Barr virus DNA; CNN, cervical nodal necrosis; CLN, cervical lymph node; RLN, retropharyngeal lymph node; ECS, extracapsular spread; MAD, maximal axial diameter; ACE-27, Adult Comorbidity Evaluation-27.						

Survival Outcomes

With a median follow-up of 55.7 months (IQR: 38.7–91.1 months) in the training cohort and 55.7 months (IQR: 38.7–77.4 months) in the validation cohort, cancer-specific mortality rates were 12.1% (n = 36) and 11.3% (n = 36), respectively. Survival rates across cohorts are detailed below (Table S1). We explored the prognostic value of each demographic and clinical characteristic, laboratory indicator, and MRI feature in the training cohort. Then, 13 variables were selected from the training cohort for multivariate analysis (Table 2). In the stepwise multivariate analysis, age (HR: 3.57, 95% CI: 1.63–7.80, P = 0.001), EBV-DNA (HR: 3.31, 95% CI: 1.57–6.98, P = 0.002), ECSCLN (HR: 3.42, 95% CI: 1.56–7.49, P = 0.002), and ECSRLN (HR: 2.81, 95% CI: 1.05–7.54, P = 0.040) were independent significant prognostic factors for CSS (Table 2).

Table 2
Factors selected into the combined model*

Variables	Categories	Multivariable Analysis		Selected into the model	
		HR (95% CI)	P value	HR (95% CI)	P value
Age, years	< 65	Reference		Reference	
	≥ 65	3.57(1.63,7.80)	0.001	2.97(1.43,6.13)	0.003
Gender	Female	Reference			
	Male	2.20(0.77,6.34)	0.143	No	
T stage[a]	T1	Reference			
	T2	1.29(0.46,3.62)	0.628	No	
EBV-DNA, copies/ml	< 4000	Reference		Reference	
	≥ 4000	3.31(1.57,6.98)	0.002	3.39(1.66,6.92)	0.001
CNNCLN	No	Reference			
	Yes	1.02(0.41,2.56)	0.960	No	
CNNRLN	No	Reference			
	Yes	0.61(0.07,5.40)	0.653	No	
ECSCLN	No	Reference		Reference	
	Yes	3.42(1.56,7.49)	0.002	3.26(1.66,6.39)	0.001
ECSRLN	No	Reference		Reference	
	Yes	2.81(1.05,7.54)	0.040	2.19(0.94,5.11)	0.070
MADCLN(mm)	< 14	Reference			
	≥ 14	0.98(0.43,2.23)	0.968	No	
MADRLN(mm)	< 7	Reference			
	≥ 7	0.68(0.32,1.43)	0.309	No	

*Multivariate analyses were performed using a Cox proportional hazards model with all variables treated as categorical variables.

[a] Using the 8th edition of the UICC/AJCC TNM staging system.

Abbreviations: HR, hazard ratio; CI, confidence interval; EBV-DNA, Epstein-Barr virus DNA; MAD, maximal axial diameter; CLN, cervical lymph node; RLN, retropharyngeal lymph node; ECS, extracapsular spread; CNN, cervical nodal necrosis; ACE-27, Adult Comorbidity Evaluation-27.

Variables	Categories	Multivariable Analysis		Selected into the model	
		HR (95% CI)	P value	HR (95% CI)	P value
Smoking	No	Reference			
	Yes	1.05(0.46,2.38)	0.911	No	
BMI	< 21	Reference			
	≥ 21	0.98(0.48,2.00)	0.955	No	
ACE-27	0	Reference			
	1	1.25(0.56,2.80)	0.584	No	

*Multivariate analyses were performed using a Cox proportional hazards model with all variables treated as categorical variables.

[a] Using the 8th edition of the UICC/AJCC TNM staging system.

Abbreviations: HR, hazard ratio; CI, confidence interval; EBV-DNA, Epstein-Barr virus DNA; MAD, maximal axial diameter; CLN, cervical lymph node; RLN, retropharyngeal lymph node; ECS, extracapsular spread; CNN, cervical nodal necrosis; ACE-27, Adult Comorbidity Evaluation-27.

Nomogram development and its predictive accuracy

In the development and comparison of predictive models for CSS in elderly patients with stage T1-2N1M0 NPC, four distinct nomograms were constructed based on varying predictor combinations: Nomogram A integrated ECSCLN, ECSRLN, EBV-DNA, and age; Nomogram B utilized T stage alone; Nomogram C relied solely on EBV-DNA; and Nomogram D combined T stage and EBV-DNA. In the training cohort, Nomogram A demonstrated a significantly higher C-index (0.768, 95% CI: 0.691–0.838) compared with Nomogram B (0.530, 95% CI: 0.493–0.578, P < 0.001), Nomogram C (0.635, 95% CI: 0.546–0.728, P = 0.028), and Nomogram D (0.641, 95% CI: 0.552–0.740, P = 0.042) (Table 3). This superiority was consistently replicated in the validation cohort, where the C-index of Nomogram A (0.878, 95% CI: 0.803–0.934) substantially exceeded those of the other Nomograms (all P < 0.01) (Table 3).

Table 3
The C-indexes of nomograms for the prediction of CSS in the training cohort and validation cohort*.

Models	Training cohort		Validation cohort	
	C-index (95% CI)	P	C-index (95% CI)	P
Nomogram A	0.768(0.691,0.838)	Reference	0.878(0.803,0.934)	Reference
Nomogram B	0.530(0.493,0.578)	< 0.001	0.518(0.463,0.584)	< 0.001
Nomogram C	0.635(0.546,0.728)	0.028	0.698(0.608,0.779)	0.002
Nomogram D	0.641(0.552,0.740)	0.042	0.711(0.618,0.800)	0.004

*Model discrimination was assessed using the Concordance Index (C-index), calculated from the Dxy statistic of the Cox proportional hazards models. Bootstrap resampling (n = 1000) was employed to estimate 95% confidence intervals.

Nomogram A: including ECSCLN, ECSRLN, age, and pretreatment EBV-DNA; Nomogram B: only including T stage; Nomogram C: only including pretreatment EBV-DNA;Nomogram D: including T stage and pretreatment EBV-DNA.

To identify the optimal model for clinical use, we compared the calibration performance of four nomograms (A-D). In the training cohort, Nomogram A demonstrated excellent calibration metrics across all timepoints, with slopes near the ideal value of 1 (2-year: 1.195, 3-year: 0.984, 5-year: 1.283) and low Brier scores (2-year: 0.033, 3-year: 0.054, 5-year: 0.078), indicating accurate predictions (Fig. 2B, Fig. 2D, and Fig. 2F). In contrast, Nomogram B showed significant miscalibration at the 2-year timepoint (slope: 5.226, H-L P-value: < 0.001, Figure S1A). Nomogram C exhibited substantial miscalibration with slopes markedly below 1 at 2 and 3 years (2-year: 0.198, H-L P-value: < 0.001; 3-year: 0.222, H-L P-value: 0.014, Figure S2A, and Figure S2C). In Nomogram D, the slopes deviated substantially from 1 at 2 and 3 years (2-year: 0.436, 3-year: 0.475, Figure S3A and Figure S3C), reflecting poorer reliability.

In the validation cohort, Nomogram A maintained robust performance, with calibration slopes remaining close to 1 (2-year: 1.244, 3-year: 1.359, 5-year: 1.477), nonsignificant H-L test P-values at 2 and 3 years (2-year: 0.528, 3-year: 0.189), and consistently low Brier scores (2-year:0.028, 3-year:0.040, 5-year:0.076) (Fig. 2C, Fig. 2E and Fig. 2G). Nomogram B demonstrated significant miscalibration across all timepoints, as evidenced by calibration slopes substantially deviating from the ideal value of 1 (2-year: -1.353, 3-year: 0.497, 5-year: -0.076) along with highly significant H-L test P-values at both 2 and 3 years (2-year: < 0.001, 3-year: < 0.001) (Figure S1B, Figure S1D, and Figure S1F). Nomogram C showed significant miscalibration at 2 and 3 years, with elevated slopes (1.595 and 1.347, respectively) and highly significant H-L test P-values (< 0.001 at both timepoints) (Figure S2B and Figure S2D). Nomogram D showed instability, with a notably high slope at 2 years (1.656) and significant miscalibration at 5 years (P = 0.013) (Figure S3B, Figure S3D, and Figure S3F).

Decision curve analysis (DCA) was performed to evaluate the clinical utility of the nomograms. In the training cohort, the DCA demonstrated that Nomogram A yielded a higher net benefit than the other

nomograms (B, C, and D) across a wide range of threshold probabilities for predicting 2-, 3-, and 5-year CSS (Fig. 3A, Fig. 3C, and Fig. 3E). Similarly, in the validation cohort, Nomogram A maintained a superior net benefit compared to other nomograms (B, C, and D). The results were shown in Fig. 3B, Fig. 3D, and Fig. 3F.

Risk Stratification

We employed Nomogram A constructed from the multimodal model for risk stratification due to its superior accuracy in predicting disease progression compared to other models. The optimal cut-off value for risk stratification was determined as the median total score of the training cohort (89 points), which provided a straightforward and commonly used method for dichotomizing patients into risk groups. Using this cut-off value, all patients were categorized into low-risk group (total score < 89 points) and high-risk group (total score ≥ 89 points). Survival curves for CSS, LRFS, DMFS, and PFS across these risk groups are presented in Fig. 4. In the training cohort, patients in the high-risk group showed significantly inferior 5-year survival rates compared to those in the low-risk group (CSS: 63.80% vs. 91.40%, P < 0.001, Fig. 4A; LRFS: 90.39% vs. 98.94%, P = 0.005, Fig. 4B; DMFS: 83.28% vs. 100.00%, P < 0.001, Fig. 4C; and PFS: 76.68% vs. 97.94%, P < 0.001, Fig. 4D).

The robust risk stratification was consistently validated in the external validation cohort. The survival outcomes between the risk groups remained highly statistically significant, with the high-risk group demonstrating markedly inferior 5-year survival rates compared to the low-risk group across all endpoints, including CSS (80.91% vs. 99.35%, P < 0.001, Figure S4A), LRFS (86.70% vs. 99.19%, P < 0.001, Figure S4B), DMFS (70.97% vs. 98.55%, P < 0.001, Figure S4C), and PFS (81.43% vs. 100.00%, P < 0.001, Figure S4D).

Association Between Treatment Modalities and Survival Outcomes Across Risk Strata

In the training cohort, there were 98, 134, 36, and 29 patients receiving RT alone, CCRT, IC+CCRT, and other chemoradiotherapy regimens, respectively. In the validation cohort, there were 122, 132, 35, and 29 patients receiving RT alone, CCRT, IC+CCRT, and other chemoradiotherapy regimens, respectively. We further evaluated the impact of various treatment strategies, including RT alone, CCRT, IC+CCRT, and other regimens, on survival outcomes in different risk groups. In the training cohort, significant differences in 5-year survival outcomes were observed among treatment strategies for high-risk patients in terms of CSS, LRFS, and PFS (all P < 0.05; Fig. 5 and Figure S5). Specifically, patients receiving RT alone showed significantly poorer outcomes in these endpoints compared to those receiving CCRT. Although a difference in DMFS was observed, it was not statistically significant (P = 0.393, Fig. 5D). In contrast, no significant differences were detected among any treatment modalities for low-risk patients (all P > 0.05; Fig. 5 and Figure S5). In the validation cohort, these findings were confirmed and strengthened. Among high-risk patients, significant differences were observed not only for CSS, LRFS, and PFS, but also for DMFS (all P < 0.05; Fig. 5 and Figure S6). Consistently, the RT alone group

demonstrated substantially inferior survival across all endpoints compared to the CCRT group. Conversely, no significant survival differences were observed among treatment modalities for low-risk patients (all P > 0.05; Fig. 5 and Figure S6).

Discussion

To the best of our knowledge, this is the first multi-center study to develop and validate a comprehensive nomogram integrating MRI-detected lymph node ECS and pretreatment EBV-DNA level for CSS among a specific population of elderly patients with stage T1-2N1M0 NPC and ACE-27 < 2. CCRT has been recommended as the standard treatment for stage II NPC patients based on clinical trials conducted during the two-dimensional radiotherapy period [15, 16]. However, the precise dose distribution of IMRT optimizes tumor locoregional control, potentially diminishing the survival benefit of chemotherapy. Therefore, the role of chemoradiotherapy in stage II NPC remains contentious in the IMRT era. Individualized stratified treatment is proposed for the stage II NPC patients in the current guidelines, which recommend radiotherapy alone for the N1 subgroup without adverse features including lymph nodes ≥ 3 cm, nodal ECS, and EBV-DNA ≥ 4000 copies/ml. However, elderly patients are routinely excluded from clinical trials due to patient scarcity, inadequate organ reserve, and reduced treatment tolerance, leading to a scarcity of evidence for this specific population. Thus, the direct applicability of the existing guidelines to the elderly population seems questionable. It's essential to establish a risk prediction model to identify the low-risk subgroup among elderly patients with T1-2N1 NPC who would benefit from IMRT alone.

Clinical TNM staging, primarily reliant on anatomical parameters based on MRI, inadequately incorporates radiomic nodal features and tumor biomarkers such as EBV-DNA, consequently limiting its application in risk stratification, particularly within the specific subgroup with stage T1-2N1 NPC. Several recent studies have effectively integrated radiomic features and molecular biomarkers to develop predictive models for refined risk stratification [8, 11, 17]. For example, we previously developed a nomogram combining MRI-derived nodal characteristics and EBV-DNA for PFS of stage II NPC patients aged < 60 years, then effectively identified the low-risk patients who would be optimal candidates for RT alone [11]. Wu et al. identified a low-risk subgroup with EBV-DNA ≤ 4000 copies/mL and stage T1-2 from a cohort of 1,714 NPC patients aged ≥ 60 years by developing a risk-stratification model based on recursive partitioning analysis (RPA), and showed that the low-risk subgroup achieved no significant survival benefits from chemoradiotherapy [17]. However, there is still a lack of combined predictive models integrating MRI-derived radiomic features and molecular biomarkers specific for the risk stratification of elderly patients with stage T1-2N1M0 NPC.

In real-world settings, clinicians may prone to consider radiotherapy alone for the treatment of elderly NPC patients with moderate and severe comorbidities (ACE-27 ≥ 2), which probably increase the potential selection bias and interfere with the accuracy of efficacy evaluation between chemoradiotherapy and radiotherapy alone among the elderly NPC patients. In addition, the elderly NPC patients with ACE-27 ≥ 2 may experience a higher incidence of non-cancer-related death events (e.g.,

cardiovascular diseases) and treatment-related toxicities that potentially offset underlying survival benefits [18]. Therefore, we enrolled the elderly patients with mild comorbidity (ACE-27 < 2) and defined cancer-specific survival (CSS) as the primary endpoint, thereby more accurately reflecting the risk of cancer-specific death and enhancing the clinical application of our findings.

In our present study, age, EBV-DNA, and ECS of RLN and CLN were identified as independent prognostic factors for CSS in elderly, stage T1-2N1M0 NPC patients with ACE-27 < 2. Our result showed that the presence of lymph node ECS predicted a poor prognosis in this specific population, partially consistent with the findings from a meta-analysis based on 9 studies with 7532 NPC patients reported by Tsai et al., which showed that radiologic extranodal extension (rENE) was associated with worse OS and DMFS [19]. The potential explanation may be that after tumor cells break through the lymph node capsule, they invade the surrounding tissues, remodel the tumor microenvironment, evade immune surveillance, and establish new dissemination routes, so as to obtain stronger distant metastatic potential [20]. A recent study has confirmed that YAP signaling activated metastasis-associated fibroblasts (MAFs) promote ECS related extracellular matrix remodeling by highly expressing COL1A1, FN1, Tenascin C and MMP-2 in oral squamous cell carcinoma [21]. ECS was also demonstrated to be associated with the overexpression of matrix metalloproteinases (MMPs) and epidermal growth factor receptor (EGFR), which promote progression and distant metastasis of NPC [22].

Furthermore, we also revealed that the pretreatment EBV-DNA level was a robust prognostic biomarker for this population, which was consistent with the findings from previous studies [23, 24]. For example, in exploratory analyses of the KEYNOTE-122 trial, higher baseline plasma EBV DNA levels were associated with worse PFS and OS in both the pembrolizumab group and the standard-chemotherapy group [23]. This suggests that EBV DNA can be used as a prognostic marker independent of treatment modality.

We further developed and validated a combined model based on age, EBV-DNA and ECS specific for elderly patients with stage T1-2N1M0 NPC and mild comorbidity (ACE-27 < 2), with superior predictive accuracy and discriminative ability to the current TNM staging system. Based on the combined model, we successfully stratified this population into low-risk and high-risk groups. More importantly, it effectively differentiated the subgroup that could benefit from IMRT alone. Our results revealed that there was no significant difference in CSS between RT alone and CRT in the low-risk group, whereas a significant survival benefit from CRT was observed in the high-risk group. These findings were partially consistent with the results of several previous studies [10, 25–27]. For example, we previously accurately identified a low-risk group within patients with stage II NPC (< 60 years) who would benefit from IMRT alone through a deep learning-based prognostic and predictive model [10]. Ding et al. also identified rENE as a key factor for predicting OS in their nomogram model, with the C-index of 0.75 and 0.76 in the training cohort and validation cohort, respectively, which was better than that of the 8th edition of TNM staging system [25]. Hu et al. found that rENE (+) was an independent prognostic factor for DMFS and OS in the patients with T1-2N1 NPC, and the addition of chemotherapy to radiotherapy did not affect DMFS and OS in the rENE (-) subgroup [26]. In brief, the integrated clinical-radiomic model we have established

provides an effective and practical tool for personalized treatment decision-making for this specific population, among which RT alone may be sufficient without diminished disease control or increased toxicities for the low-risk subgroup, aligning with the "less is more" philosophy of treatment de-escalation [28, 29].

However, several limitations may be considered. Firstly, although the distribution of baseline characteristics between the CRT group and RT group was well-balanced and external validation was performed, as a retrospective study, the present study may be susceptible to selection bias, thus we recommend that prospective studies be conducted to further validate our conclusions. Secondly, the assessment of MRI-based nodal ECS was confirmed by radiologist consensus, whereas it remained inherently subjective. Thus, artificial intelligence (AI) and deep learning algorithms may be employed to improve the standardization and repeatability of the assessment in future studies. Thirdly, despite variations in EBV DNA quantification and absence of the globally standardized methods of plasma EBV DNA detection, the EBV DNA data were binarized in this study to avoid further bias by reducing data variance to ensure model generality. Fourthly, the molecular mechanisms of ECS, especially the interaction between EBV-related factors and ECE, need to be further explored Finally, external validation was confined to a single institution. Thus, large-scale, multicenter prospective studies are warranted to further validate our findings.

In conclusion, a combined nomogram integrating lymph node ECS, age, and EBV-DNA provides a robust prediction of CSS for the elderly patients with stage T1-2N1M0 NPC and ACE-27 < 2, thereby effectively identifying optimal candidates for IMRT alone, consequently guiding decision-making regarding individualized treatment de-escalation.

Declarations

Abbreviations

ACE-27, Adult Comorbidity Evaluation-27; C-index, concordance index; CRT, chemoradiotherapy; CSS, cancer-specific survival; DCA, decision curve analysis; EBV-DNA, Epstein-Barr Virus DNA; ECS, extracapsular spread; IMRT, intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; RT, radiotherapy.

Conflict of interest statement

The authors declare no conflicts of interest.

Ethics Statement

This retrospective study was approved by the Institutional Ethics Committee of the Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital of Guangzhou Medical University, and the Institutional Ethics Committee of Sun Yat-sen University Cancer Center. The requirement for informed written consent was waived by the ethics committees due to the retrospective nature of the study.

Supplementary Figure S1.

Calibration curves of Nomogram B for 2-, 3-, and 5-year CSS.

Supplementary Figure S2.

Calibration curves of Nomogram C for 2-, 3-, and 5-year CSS.

Supplementary Figure S3.

Calibration curves of Nomogram D for 2-, 3-, and 5-year CSS.

Supplementary Figure S4.

Kaplan-Meier curves of risk groups stratified by Nomogram A (validation cohort).

Supplementary Figure S5.

Treatment modality comparison in the training cohort.

Supplementary Figure S6.

Treatment modality comparison in the validation cohort.

Supplementary Doc.S1.

File containing legends for all supplementary figures.

Supplementary Doc.S2.

MR Detailed scanning parameters.

Supplementary Table S1.

Survival rates across cohorts.

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Author Contribution

YB Zhang: Conceptualization, Methodology, Writing-Original Draft, Software. HW Yu: Investigation, Formal analysis, Data Curation. HX Mo: Resources, Validation. HT Cai: Data Curation, Methodology, Software. LJ Zhang: Visualization. Q Yang: Resources, Supervision. XD Lin: Project Administration. YH Tian: Writing - Review & Editing. XL Chen: Supervision, Project Administration, Methodology. YF Wen: Supervision, Project Administration, Funding Acquisition, Writing-Review & Editing.

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Figures

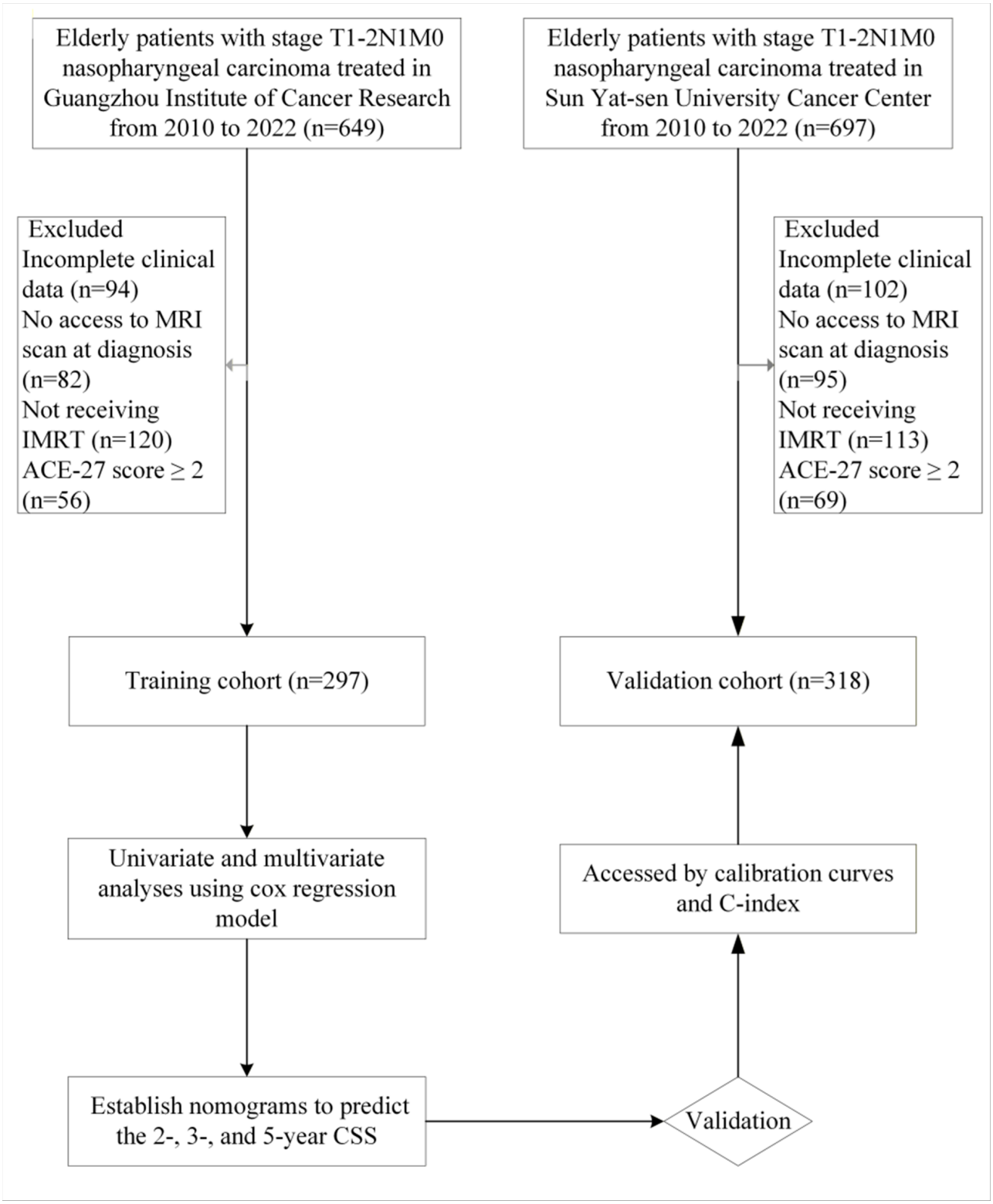


Figure 1

Flowchart showing the study design and patient selection process.

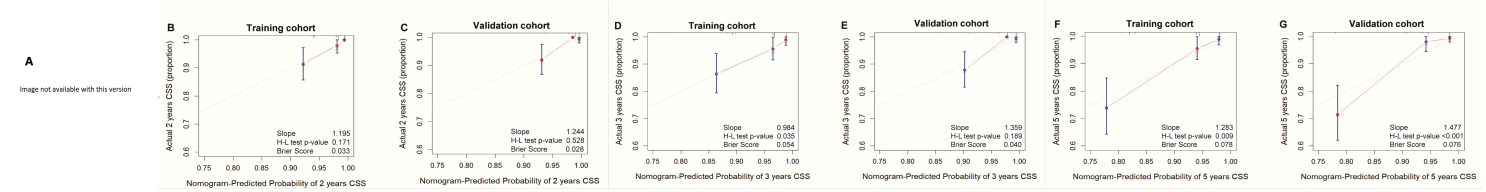


Figure 2

Nomogram A (A) and its calibration curves for predicting the 2-year, 3-year, 5-year CSS in the training cohort (B, D, F) and validation cohort (C, E, G). Abbreviations: EBV-DNA, Epstein-Barr virus DNA; ECS, extracapsular spread; CLN, cervical lymph node; RLN, retropharyngeal lymph node; CSS, cancer-specific survival; H-L, Hosmer-Lemeshow.

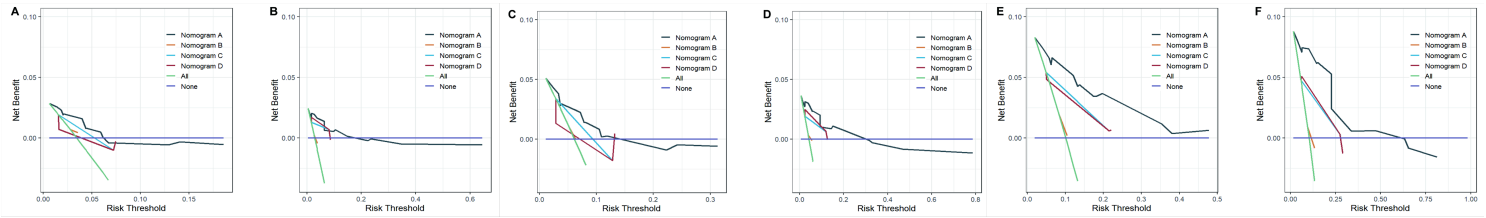


Figure 3

Decision curves analyses of the Nomogram A, B, C, and D predicting the 2-year, 3-year, and 5-year CSS in the training cohort (A, C, E) and validation cohort (B, D, F). Nomogram A: including ECSCLN, ECSRLN, age, and pretreatment EBV-DNA; Nomogram B: only including T stage; Nomogram C: only including pretreatment EBV-DNA; Nomogram D: including T stage and pretreatment EBV-DNA. Abbreviations: EBV-DNA, Epstein-Barr virus DNA; ECS, extracapsular spread; CLN, cervical lymph node; RLN, retropharyngeal lymph node; CSS, cancer-specific survival.curves analyses of the Nomogram A, B, C, and D predicting the 2-year, 3-year, and 5-year CSS in the training cohort (A, C, E) and validation cohort (B, D, F). Nomogram A: including ECSCLN, ECSRLN, age, and pretreatment EBV-DNA; Nomogram B: only including T stage; Nomogram C: only including pretreatment EBV-DNA; Nomogram D: including T stage and pretreatment EBV-DNA. Abbreviations: EBV-DNA, Epstein-Barr virus DNA; ECS, extracapsular spread; CLN, cervical lymph node; RLN, retropharyngeal lymph node; CSS, cancer-specific survival.

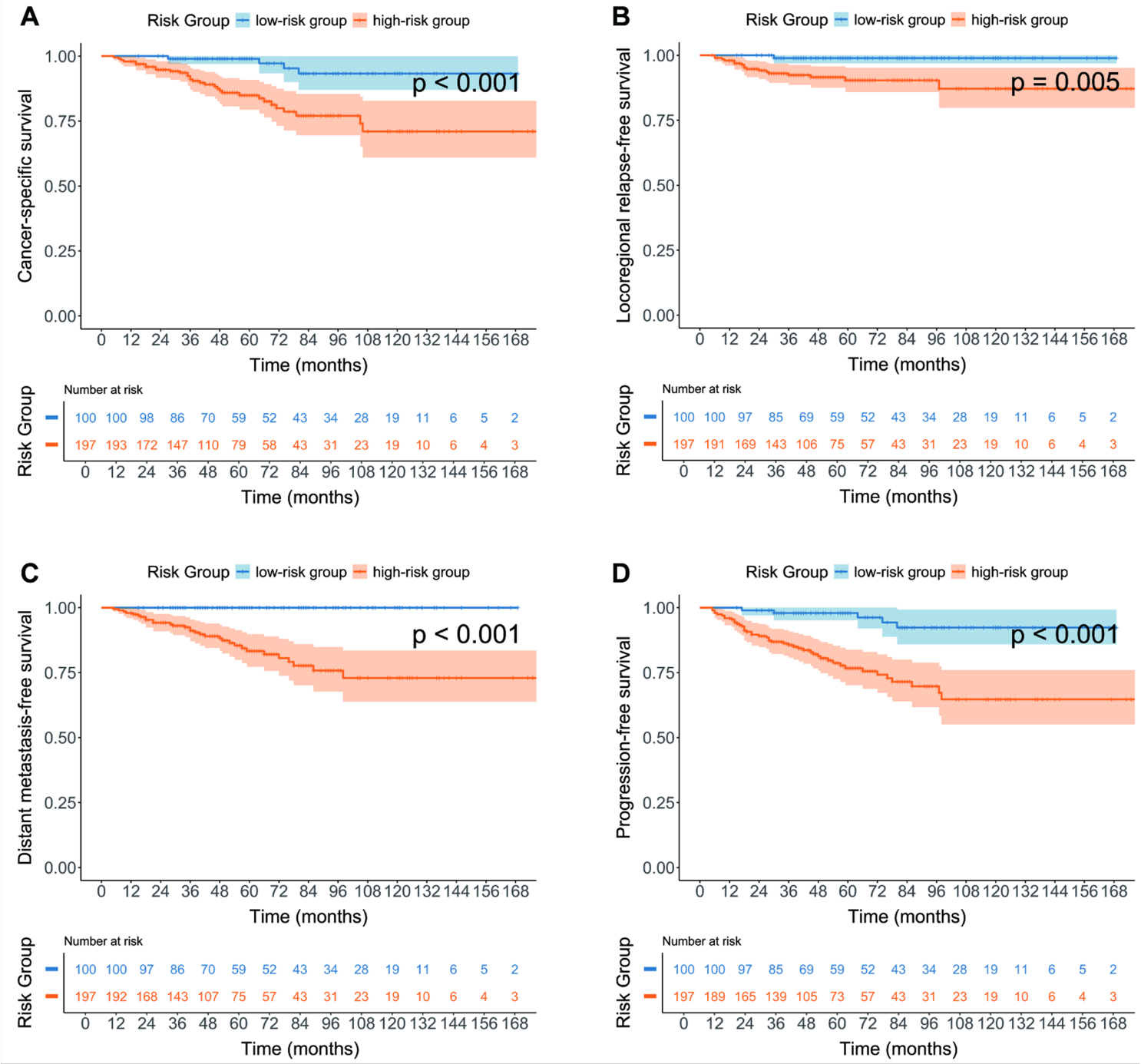


Figure 4

Kaplan-Meier curves of low- and high-risk groups stratified by Nomogram A in the training cohort for CSS (A), LRFS (B), DMFS (C) and PFS (D). Abbreviations: CSS, Cancer-specific Survival; LRFS, Locoregional recurrence-free survival; DMFS, Distant metastasis-free survival; PFS, progression-free survival.

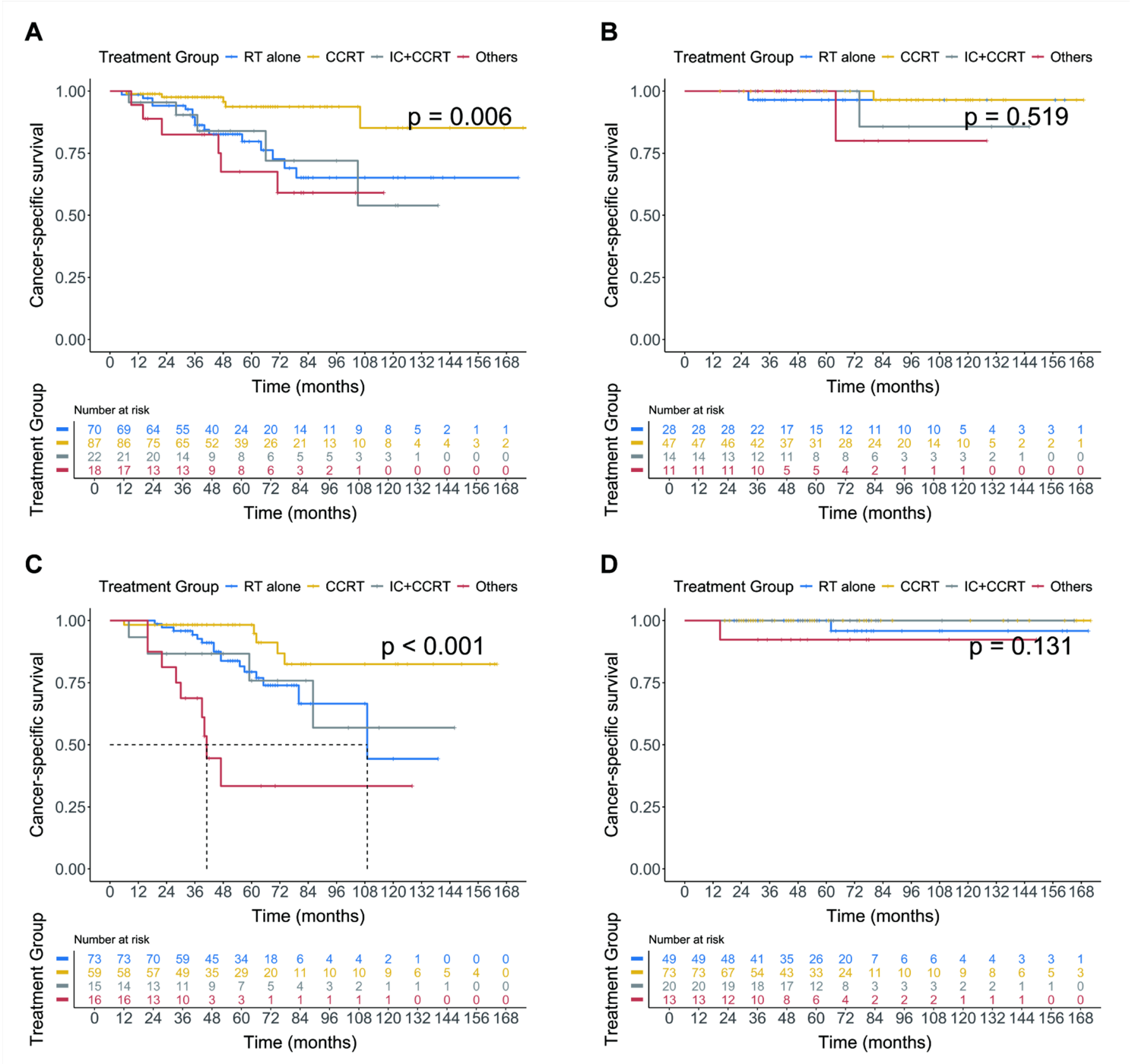


Figure 5

Results of the comparison between patients receiving RT alone and those receiving other treatment modalities with regard to CSS in the high-risk (A) and low-risk (B) groups of the training cohort, and the high-risk (C) and low-risk (D) groups of the validation cohort. Abbreviations: RT, radiotherapy; CSS, Cancer-specific Survival.

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