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Prognostic nomogram for synchronous metastatic nasopharyngeal carcinoma: a retrospective multicentre study

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Abstract

Background Patients with synchronous metastatic nasopharyngeal carcinoma (smNPC) exhibit significant heterogeneity, and clinical prognostic models suitable for this cohort remain limited. We aimed to develop a prognostic prediction tool to facilitate personalised prognostic assessments and inform treatment decisions for these patients.

Methods This retrospective multicentre study enrolled 556 patients with smNPC. The training cohort comprised 386 patients from Guangxi Medical University Cancer Hospital, while the external validation cohort comprised 170 patients from Wuzhou Red Cross Hospital and Xiangtan Central Hospital. We applied the Cox proportional hazards model to determine factors associated with overall survival (OS). A nomogram prognostic model was developed to predict OS based on the identified prognostic factors. The model's predictive performance was evaluated for discrimination and calibration, and patients were stratified based on their calculated prognostic risk scores. Kaplan–Meier survival curves were employed to assess prognostic differences across the stratified groups.

Results Multivariate analysis identified that M classification, primary tumour radiotherapy, and immunotherapy were significantly associated with OS. A prognostic nomogram integrating these variables exhibited good discrimination (C-index: 0.743) and calibration, which was validated in an external validation cohort. Patients stratified by the model-derived risk scores into high- and low-risk groups showed a significant difference in survival disparity.

Conclusions We established a nomogram prognostic model that effectively facilitated individualised prognostic prediction and risk stratification in patients with smNPC, thereby assisting clinicians in treatment decision-making.

Keywords Synchronous metastasis nasopharyngeal carcinoma, Nomogram, Multimodality treatment, Multicentre study

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Background

Nasopharyngeal carcinoma (NPC) exhibited a higher prevalence in China and Southeast Asia compared to Western countries, where it is relatively rare. Compared with other head and neck cancers, NPC is associated with a higher rate of distant metastasis [1]. Current research indicates that 4–10% of patients present with synchronous metastatic nasopharyngeal carcinoma (i.e., distant metastases at the time of initial diagnosis; smNPC), with the most frequent metastatic sites being the bones, lungs, and liver [2]. The occurrence of distant metastasis significantly worsens the prognosis, with median survival times ranging from 12 to 30 months, despite the application of multidisciplinary comprehensive treatment strategies [3, 4].

SmNPC demonstrates considerable heterogeneity. This variability primarily stems from significant differences in metastatic sites and tumour burden (i.e., the number of metastatic lesions), which directly influence treatment response and survival outcomes [5]. This variability often makes it challenging for clinicians to predict patient survival accurately and select the most appropriate treatment strategy. Thus, an urgent clinical need exists to develop more precise survival prognostic tools for patients with smNPC and to facilitate personalised patient assessment. The tumour-node-metastasis (TNM) staging system is the most widely used prognostic tool. However, the eighth edition of the TNM staging system, released in 2017, uniformly categorises metastatic NPC as stage IVb without further stratification [6]. This lack of detailed differentiation limits the clinicians' ability to perform personalised risk stratification for a heterogeneous population of patients with metastatic NPC and hinders the provision of precise treatment recommendations tailored to individual needs.

Using a multicentre cohort of patients with metastatic NPC, we developed a three-category metastasis (M) classification system that effectively stratified metastatic NPC risk, with M1a defined as ≤5 metastatic lesions, M1b as >5 metastatic lesions without liver metastases, and M1c as >5 metastatic lesions with liver metastases [7]. Although this system is simple to implement, it does not incorporate additional clinical characteristics or treatment-related factors, which limits the accuracy of its predictive capabilities. Therefore, this study aimed to develop a more comprehensive prognostic prediction tool, building on previous research, to assist clinicians in making individualised prognostic assessments and treatment decisions for patients with smNPC.

Methods

Study setting

This multicentre study was approved by the Institutional Review Boards of Guangxi Medical University Cancer Hospital (GXMUCH), Xiangtan Central Hospital (XTCH), and Wuzhou Red Cross Hospital (WZRCH). Written informed consent was deemed unnecessary due to the study's retrospective design.

Study population

This retrospective, multicentre study enrolled 556 patients with smNPC across three medical centres. The training cohort consisted of 386 patients with smNPC diagnosed at GXMUCH from 9 January 2010 to 21 December 2022. The external validation cohort encompassed 122 and 48 patients with smNPC diagnosed and treated at WZRCH and XTCH, respectively, from 8 June 2014 to 25 June 2022. The criteria for inclusion were: (1) histopathologically confirmed NPC; (2) presence of distant metastasis at initial diagnosis, verified by biopsy of metastatic lesions or imaging modalities including computed tomography (CT), chest radiography, abdominal ultrasound, CT, magnetic resonance imaging (MRI), bone scan, or positron emission tomography/CT (PET/CT). The exclusion criteria encompassed: (1) combined with other malignancies; (2) combined with uncontrollable cardiac, pulmonary, renal, or hepatic dysfunction; (3) refusal to undergo antineoplastic therapy; and (4) absence of complete imaging, clinical, and follow-up data. Figure 1 depicts the patient selection process.

Data collection and definition

The following data were collected: (a) patient demographics, including sex, age at the initial diagnosis of NPC, and Epstein–Barr virus (EBV) DNA count before metastasis treatment. (b) Tumour characteristics, such as pathological type and T/N/M stage. All patients underwent restaging of the primary T and N classifications at the three centres by radiation oncologists specialising in head and neck cancers, using the eighth edition of the AJCC Cancer Staging Manual. Patients were classified as M1a, M1b, or M1c according to the M classification previously described in our study [7]. (c) Treatment characteristics, including chemotherapy, immunotherapy, targeted therapy, radiotherapy for primary sites, and local treatments for metastatic sites. The definition of metastasis has been previously outlined [7]. Briefly, suspicious lesions identified by conventional workup or PET/CT were considered metastatic only when confirmed by additional examinations such as CT, MRI, or biopsy.

Treatment and endpoint

With respect to salvage therapy for smNPC, clinicians adopt diverse approaches, considering tumour characteristics, patient performance status, the clinical experience of the physician, as well as the patient's personal preferences and financial circumstances. All patients in this study received at least one form of anti-tumour therapy,

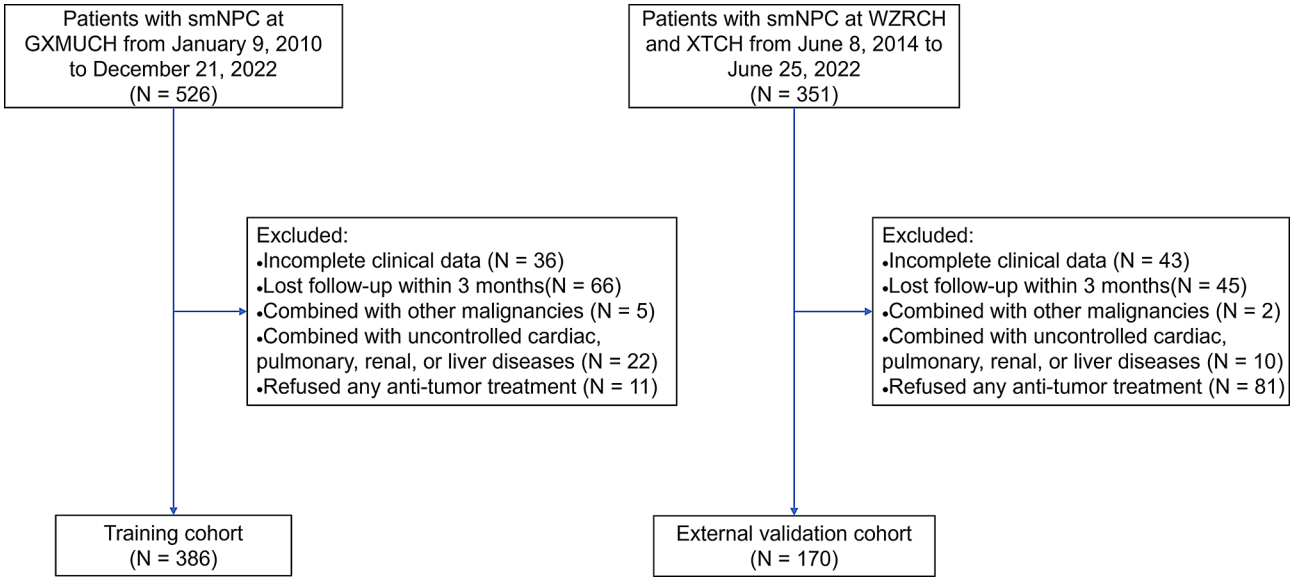

Fig. 1 Flowchart illustrates patients' selection. GXMUCH, Guangxi Medical University Cancer Hospital; WZRCH, Wuzhou Red Cross Hospital; XTCH, Xiangtan Central Hospital

comprising chemotherapy, immunotherapy, targeted therapy, and radiotherapy for primary sites, in conjunction with local treatments for metastatic sites. The local treatment approaches encompassed surgery, radiotherapy, and additional interventional procedures. Comprehensive treatment details were delineated in prior studies [7, 8]. The primary endpoint was overall survival (OS), defined as the time from smNPC diagnosis to either the last known survival date or death from any cause.

Statistical analysis

All statistical analyses were performed using R version 4.3.2 (R Core Team 2023, Vienna, Austria), employing the following packages: 'tableone', 'survival', 'survminer', 'tidyverse', 'plyr', 'timeROC', 'rms', 'ggplot2', and 'rpart'. Continuous variables were analysed using the Student's t-test, while categorical variables were assessed with Pearson's chi-square test and Fisher's exact test. Prognostic factors linked to survival were ascertained utilising the COX proportional hazards model. Variables with a p-value < 0.05 in the univariate Cox regression analysis were selected for inclusion in the multivariate analysis. In the multivariate analysis, factors with a p-value < 0.05 were identified as independent prognostic factors for smNPC and subsequently incorporated into the final nomogram. The hazard ratio for each factor was calculated to assess its impact on the OS. A nomogram prognostic was developed incorporating the independent prognostic factors ascertained from the training cohort, followed by external validation in a distinct cohort. The model's predictive accuracy was assessed based on two key metrics: discrimination and calibration. Discrimination of the model's predictive accuracy was evaluated utilising time-dependent receiver operating characteristic (t-ROC) curves and the concordance index (C-index). Calibration was assessed by contrasting the predicted survival curves against the actual observed survival data, as depicted in calibration plots. Patient risk stratification was performed using recursive partitioning analysis based on the calculated risk scores, categorising patients into low-risk (risk score < 111 points) and high-risk (risk score ≥ 111 points) cohorts. Survival rates were estimated using the Kaplan–Meier method and compared with the log-rank test. The threshold for statistical significance was established at a p-value of < 0.05.

Results

Baseline characteristics and survival outcomes

A total of 556 patients diagnosed with smNPC were enrolled in this study based on established inclusion and exclusion criteria. Table 1 presents a summary of the baseline clinical characteristics for all enrolled patients. The training cohort exhibited a significantly higher proportion of patients with a single metastatic organ compared to the external validation cohort ($p = 0.007$). Furthermore, a larger proportion of patients in the training cohort had five or fewer metastatic lesions than those in the external validation cohort ($p = 0.037$). The remaining clinical characteristics were well balanced between the training and external validation datasets.

In the training dataset, the median duration of follow-up was 20 months (interquartile range [IQR]: 12–31 months), with 260 patients (67.4%) experiencing mortality during this interval. The Kaplan-Meier estimated one-year and three-year survival rates were 78.2% and 29.5%, respectively. In the external validation dataset, the

Table 1 Characteristics of the patients by cohort

Characteristics	Total cohort (*N* = 556)	Training cohort (*N* = 386)	External validation cohort (*N* = 170)	*p*-value
Sex				0.968
Male	447 (80.4%)	311 (80.6%)	136 (80.0%)	
Female	109 (19.6%)	75 (19.4%)	34 (20.0%)	
Age (years)				0.551
Mean (SD)	48.5 (11.8)	48.3 (11.7)	48.9 (12.0)	
Pathology				0.334
WHO type I/II	65 (11.7%)	49 (12.7%)	16 (9.4%)	
WHO type III	491 (88.3%)	337 (87.3%)	154 (90.6%)	
Primary T classification				0.904
T1-2	144 (25.9%)	102 (26.4%)	42 (24.7%)	
T3-4	405 (72.8%)	279 (72.3%)	126 (74.1%)	
Tx	7 (1.3%)	5 (1.3%)	2 (1.2%)	
Primary N classification				0.599
N0-2	253 (45.5%)	179 (46.4%)	74 (43.5%)	
N3	299 (53.8%)	205 (53.1%)	94 (55.3%)	
Nx	4 (0.7%)	2 (0.5%)	2 (1.2%)	
M classification				0.088
M1a	261 (46.9%)	193 (50.0%)	68 (40.0%)	
M1b	161 (29.0%)	104 (26.9%)	57 (33.5%)	
M1c	134 (24.1%)	89 (23.1%)	45 (26.5%)	
Lung metastasis				0.089
No	386 (69.4%)	277 (71.8%)	109 (64.1%)	
Yes	170 (30.6%)	109 (28.2%)	61 (35.9%)	
Liver metastasis				0.267
No	367 (66.0%)	261 (67.6%)	106 (62.4%)	
Yes	189 (34.0%)	125 (32.4%)	64 (37.6%)	
Bone metastasis				0.660
No	179 (32.2%)	127 (32.9%)	52 (30.6%)	
Yes	377 (67.8%)	259 (67.1%)	118 (69.4%)	
Other organ metastasis				0.294
No	401 (72.1%)	284 (73.6%)	117 (68.8%)	
Yes	155 (27.9%)	102 (26.4%)	53 (31.2%)	
Number of metastatic organs				**0.007**
1	346 (62.2%)	255 (66.1%)	91 (53.5%)	
≥2	210 (37.8%)	131 (33.9%)	79 (46.5%)	
Number of metastatic lesions				**0.037**
≤5	261 (46.9%)	193 (50.0%)	68 (40.0%)	
>5	295 (53.1%)	193 (50.0%)	102 (60.0%)	
EBV-DNA (copies/mL)				0.707
≤33,000	490 (88.1%)	342 (88.6%)	148 (87.1%)	
>33,000	66 (11.9%)	44 (11.4%)	22 (12.9%)	
Primary site radiotherapy				0.217
No	248 (44.6%)	165 (42.7%)	83 (48.8%)	
Yes	308 (55.4%)	221 (57.3%)	87 (51.2%)	
Chemotherapy				0.164
No	4 (0.7%)	1 (0.3%)	3 (1.8%)	
Yes	552 (99.3%)	385 (99.7%)	167 (98.2%)	
Immunotherapy				0.584
No	473 (85.1%)	331 (85.8%)	142 (83.5%)	
Yes	83 (14.9%)	55 (14.2%)	28 (16.5%)	
Targeted therapy				0.287
No	473 (85.1%)	333 (86.3%)	140 (82.4%)	

Table 1 (continued)

Characteristics	Total cohort (*N* = 556)	Training cohort (*N* = 386)	External validation cohort (*N* = 170)	*p*-value
Yes	83 (14.9%)	53 (13.7%)	30 (17.6%)	
Local treatment of metastatic lesion(s)				0.205
No	424 (76.3%)	288 (74.6%)	136 (80.0%)	
Yes	132 (23.7%)	98 (25.4%)	34 (20.0%)	

SmNPC, Synchronous metastasis nasopharyngeal carcinoma; EBV, Epstein–Barr virus

median follow-up was 19 months (IQR: 12–27 months), with 114 patients (67.1%) experiencing mortality. The one-year and three-year survival rates were 79.3% and 25.8%, respectively.

Screening prognostic factors for OS in the training cohort

Univariate Cox regression analyses in the training cohort identified several factors significantly associated with OS in patients with smNPC, including age ($p = 0.001$), M classification ($p < 0.001$), Epstein–Barr virus DNA level ($p = 0.014$), and receipt of primary site radiotherapy ($p < 0.001$), immunotherapy ($p < 0.001$), targeted therapy ($p = 0.028$), and local treatment for metastatic lesions ($p = 0.002$). When these significant factors ($p < 0.05$) were included in the multivariate Cox regression model, three variables that were independently associated with OS were identified: M classification ($p < 0.001$), primary site radiotherapy ($p = 0.005$), and immunotherapy ($p < 0.001$) (Table 2).

Establishment and validation of the nomogram prognostic model

In the training cohort, the nomogram prognostic model for OS was developed using independent prognostic factors derived from multivariate Cox analysis. (Fig. 2). The nomogram model's 1- and 3-year t-ROC curves were 0.831 (95% confidence interval [CI], 0.781–0.881) and 0.730 (95% CI, 0.665–0.796), respectively, with a C-index of 0.743 (95% CI, 0.714–0.772; Fig. 3A). The calibration plot confirmed the nomogram's accurate prediction of 1- and 3-year OS for smNPC patients (Fig. 3C).

In the external validation cohort, the developed nomogram model demonstrated strong discrimination and calibration. The AUCs for the 1- and 3-year t-ROC curves of the nomogram model were 0.799 (95% CI: 0.717–0.882) and 0.766 (95% CI: 0.667–0.866), respectively, whereas the C-index was 0.737 (95% CI: 0.692–0.782) (Fig. 3B). The calibration curve further confirmed that the nomogram model retained excellent predictive accuracy in the validation cohort (Fig. 3D).

Prognostic stratification using the nomogram model and subgroup analysis

Recursive partitioning analysis based on nomogram-driven risk scores facilitated risk stratification in smNPC patients. Based on the calculated risk scores, the patients were categorised into two groups: low-risk (risk score < 111 points) and high-risk (risk score ≥ 111 points).

In the training cohort, the low-risk group had a significantly longer median survival time than the high-risk group (35 vs. 15 months, $p < 0.001$; Fig. 4A). In the validation cohort, low-risk patients demonstrated significantly longer median survival than high-risk patients (34 vs. 17 months, $p < 0.001$; Fig. 4B).

Subgroup analysis identified patients likely to benefit from local treatment of metastatic lesions. In the training cohort, the addition of local therapy for metastatic lesions significantly improved prognosis in the low-risk group ($p < 0.05$; Fig. 5A). However, in the high-risk group, local therapy did not provide a significant survival benefit ($p > 0.05$; Fig. 5B). In the external validation cohort, neither the high-risk group nor the low-risk group derived any survival benefit from the local treatment of metastatic lesions ($p > 0.05$ for both groups; Fig. 5C-D).

Discussion

The prognosis of patients with smNPC varies significantly, and accurately predicting survival outcomes remains an urgent clinical need. To address this, we developed and validated a nomogram that predicts survival in patients with smNPC. The construction of a prognostic model typically involves incorporating independent protective and/or risk factors. Broadly speaking, effective treatment methods can be considered protective factors. Therefore, we believe that treatment modalities are crucial patient characteristics that should be included in nomograms for prognostic prediction. Our prognostic model incorporates three key predictive factors: M classification, receipt of immunotherapy, and receipt of primary site radiotherapy. Utilising the advantages of the nomogram, the model allows for the calculation of individual patient risk scores based on their specific characteristics, which in turn enables the prediction of their 1- and 3-year survival rates. The model's predictive performance was validated using both internal and external cohorts. It exhibited robust discrimination and calibration across both training and validation cohorts, demonstrating a potential for clinical application for broader patient populations. Additionally, based on the risk scores derived from the nomogram, we established

Table 2 Univariate and multivariate Cox regression analysis of overall survival in training cohort

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Age	1.02 (1.00–1.03)	**0.001**	1.01 (0.99–1.02)	0.087
Sex				
Male	Reference			
Female	1.02 (0.75–1.38)	0.917		
Primary T classification				
T1-2	Reference			
T3-4	0.84 (0.64–1.11)	0.220		
Tx	2.15 (0.86–5.35)	0.100		
Primary N classification				
N0-2	Reference			
N3	1.18 (0.93–1.52)	0.179		
Nx	2.54 (0.62–10.32)	0.193		
M classification				
M1a	Reference		Reference	
M1b	2.35 (1.75–3.17)	**< 0.001**	2.22 (1.64–3.02)	**< 0.001**
M1c	4.65 (3.43–6.29)	**< 0.001**	4.33 (3.18–5.91)	**< 0.001**
Pathology				
WHO type I/II	Reference			
WHO type III	0.77 (0.55–1.08)	0.135		
EBV-DNA (copies/mL)				
≤33,000	Reference		Reference	
>33,000	1.64 (1.10–2.43)	**0.014**	1.10 (0.73–1.65)	0.659
Primary site radiotherapy				
No	Reference		Reference	
Yes	0.52 (0.41–0.67)	**< 0.001**	0.66 (0.50–0.87)	**0.003**
Immunotherapy				
No	Reference		Reference	
Yes	0.35 (0.20–0.60)	**< 0.001**	0.40 (0.23–0.69)	**0.001**
Targeted therapy				
No	Reference		Reference	
Yes	0.65 (0.45–0.95)	**0.028**	0.80 (0.54–1.19)	0.276
Local treatment of metastatic lesion(s)				
No	Reference		Reference	
Yes	0.62 (0.46–0.84)	**0.002**	0.91 (0.65–1.26)	0.556

a risk stratification system in which patients with a risk score < 111 points were classified as low-risk, whereas those with a risk score ≥ 111 points were classified as high-risk. A significant difference in median survival time was observed between these two groups, with patients in the low-risk group showing markedly better survival outcomes than those in the high-risk group. Our model can provide more direct guidance for clinical decision-making. For instance, patients with M1a disease who receive immunotherapy and/or primary site radiotherapy are classified into the low-risk group (indicating better prognosis), whereas those with M1a disease who do not receive these treatments are classified into the high-risk group (indicating poorer prognosis). Such a straightforward, robust, and practical tool holds significant value in informing personalised treatment decisions for these patients, given the limited availability of reliable prognostic models for smNPC.

Currently, the prognostic models for patients with smNPC remain relatively limited. Chen et al. [9] developed a prognostic scoring model for bone metastatic NPC, based on six risk factors: age > 46 years, N stage > 0, anaemia, bone metastasis interval ≤ 12 months, no radiotherapy to the primary site, and no radiotherapy to the first metastatic site. Although this model provided useful insights, it used the seventh edition of the TNM staging system, which is no longer in use. Consequently, this model cannot be directly applied to contemporary clinical practice. Similarly, Li et al. [10] established a nomogram prognostic model for synchronous metastatic NPC using clinical data from 152 patients. This model is intended for patients with smNPC who receive primary-site radiotherapy after first-line chemotherapy. However, a small sample size and lack of external cohort validation limit the reliability and broader applicability of this model. In contrast, our study used data from a large sample of patients with smNPC. By constructing a prognostic model with a larger patient cohort and validating it with an external cohort, our model addresses some of the limitations of the models from the aforementioned studies and offers a more robust tool for clinical application.

Immunotherapy was a key prognostic factor in the model developed in this study. With the advent of immunotherapy, metastatic nasopharyngeal carcinoma has entered a new therapeutic era. A series of multicentre randomised controlled trials have established the role of immunotherapy as a first-line treatment for metastatic NPC. For instance, the CAPTAIN-1st study [11] compared first-line gemcitabine plus cisplatin (GP) chemotherapy with a combination of carrelizumab and GP chemotherapy in patients with recurrent or metastatic NPC. The results demonstrated that the median progression-free survival (PFS) in the carrelizumab plus chemotherapy group was extended by approximately 3 months compared with that in the chemotherapy-alone group ($p = 0.0002$). Similarly, the JUPITER-02 study [12] found that the combination of toripalimab and GP chemotherapy increased the median PFS by 3.7 months and reduced

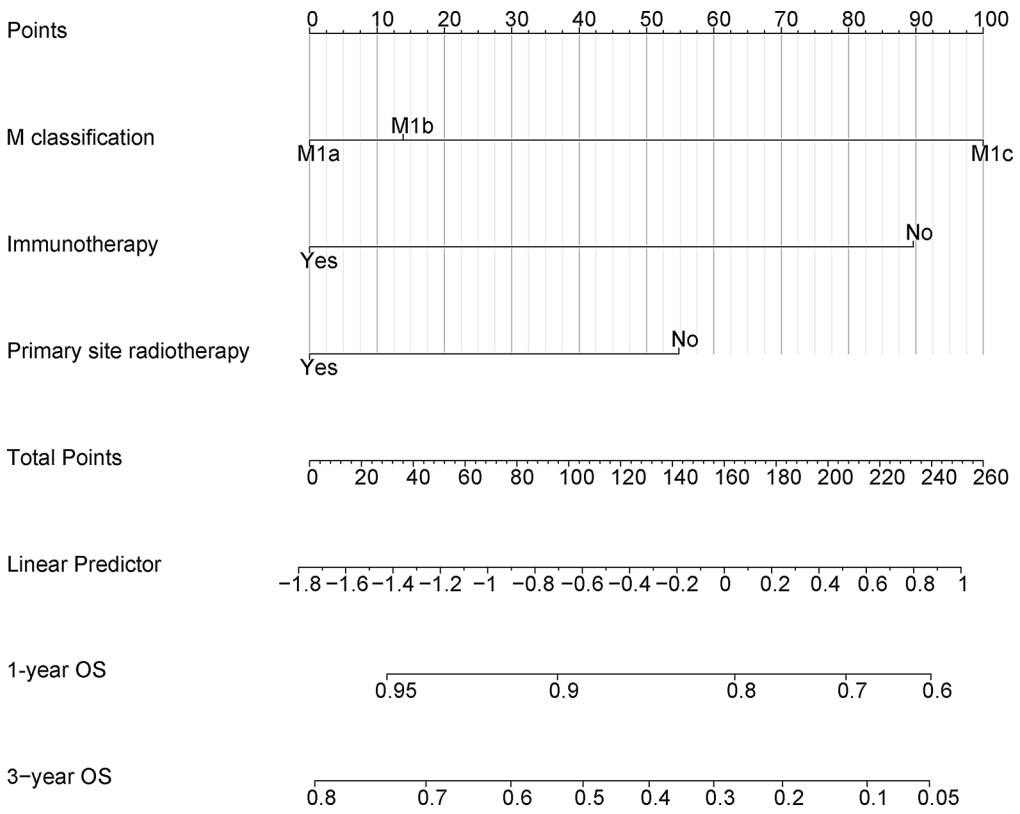

Fig. 2 Prognostic nomogram of survival probabilities at 1-year and 3-year in patients with smNPC

the risk of death or disease progression by 48% in three years. These findings underscore the positive effect of immunotherapy on patient outcomes in metastatic NPC, a conclusion supported by our study.

Additionally, the inclusion of primary lesion radiotherapy as a prognostic factor in our model highlights the importance of controlling primary tumours in the management of smNPC. Recent evidence has increasingly emphasised the importance of primary lesion radiotherapy in improving patient outcomes. For example, Hu et al. [13] analysed data from the Surveillance, Epidemiology, and End Results database and found that patients who received primary lesion radiotherapy had a 50% reduction in the risk of death compared with those who received systemic chemotherapy alone. Similarly, Rusthoven et al. [14] evaluated data from the National Cancer Database on 718 newly diagnosed patients with metastatic NPC and confirmed that combining systemic chemotherapy with primary lesion radiotherapy significantly improved the 5-year OS (28% vs. 10%). Additionally, findings from a multicentre, randomised phase III trial [4] showed that radical radiotherapy for nasopharyngeal and cervical lymph node involvement significantly enhanced survival outcomes in smNPC who were responsive to induction chemotherapy. The survival benefit associated with primary lesion control arises from two main factors: first, the reduction in the risk of nasopharyngeal haemorrhage due to uncontrolled primary tumours, and second, the reduction in tumour cell dissemination. Studies have shown that the number of circulating tumour cells (CTCs) is correlated with tumour burden [15]. Primary lesion radiotherapy reduces both CTC levels and tumour burden, which in turn lowers the likelihood of tumour cell dissemination [16–18]. This evidence underscores the critical role of primary lesion control in improving the prognosis of patients with smNPC.

Local therapy for metastatic lesions is a contentious but essential part of metastatic NPC management [19–25]. Our study found that the local treatment of metastases was not an independent prognostic factor for survival in patients with smNPC. Furthermore, a subsequent subgroup analysis revealed that in the training cohort, patients in the low-risk group appeared to benefit from local treatment of metastases, whereas those in the high-risk group did not. In contrast, neither the high- nor the low-risk groups in the external validation cohort showed any survival advantage from the local treatment of metastases. These findings suggest that when developing treatment strategies for patients with smNPC, priority should be given to managing the primary lesion as opposed to focusing on metastatic lesions. Additionally, although some patients may benefit from the local treatment of metastases, our model was unable to accurately identify

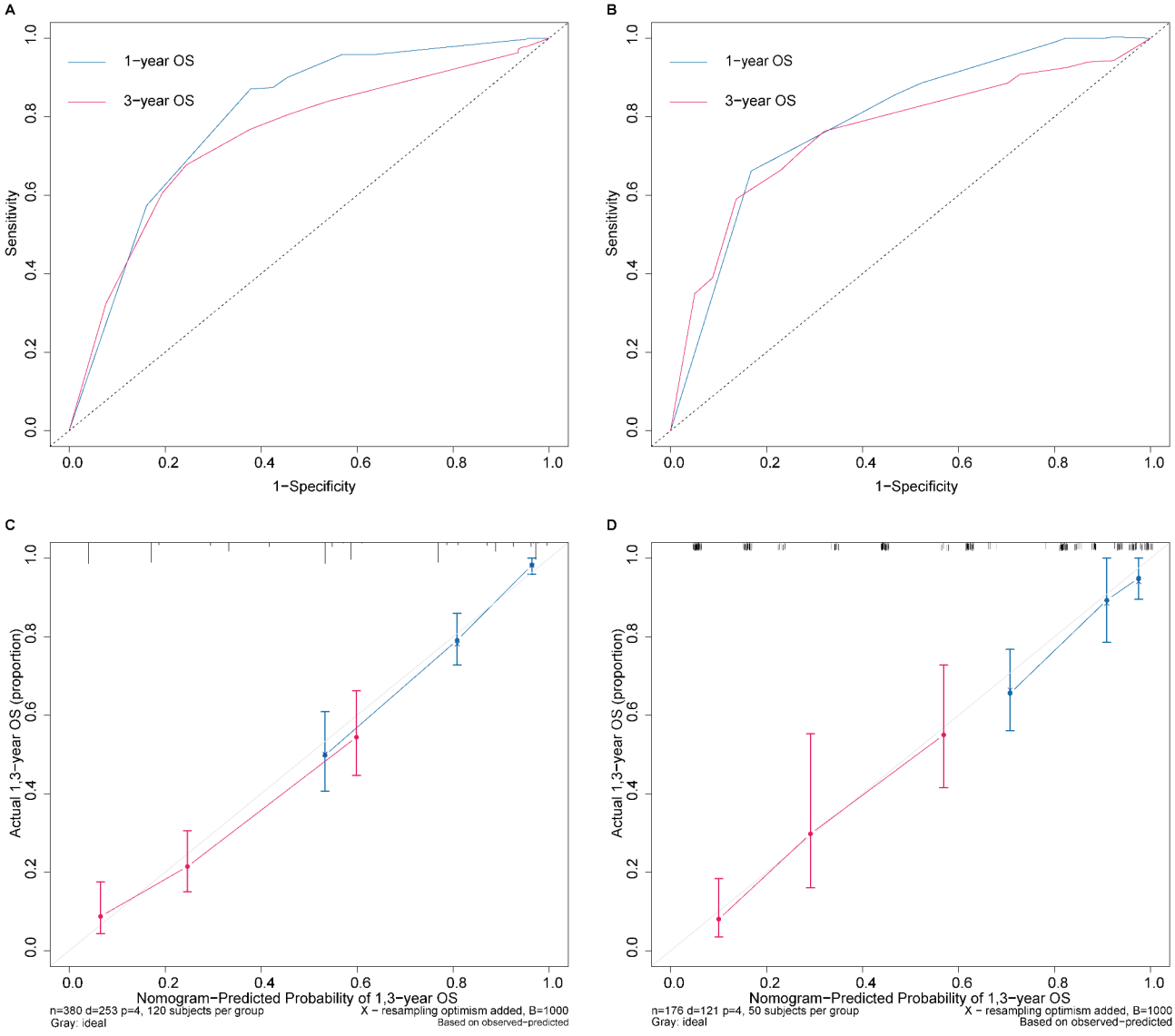

Fig. 3 Time-dependent ROC of the nomogram model at 1-, and 3-year in the training cohort (**A**) and validation cohort (**B**); The calibration curve of the nomogram for predicting OS at 1 and 3 years in the training cohort (**C**) and validation cohort (**D**)

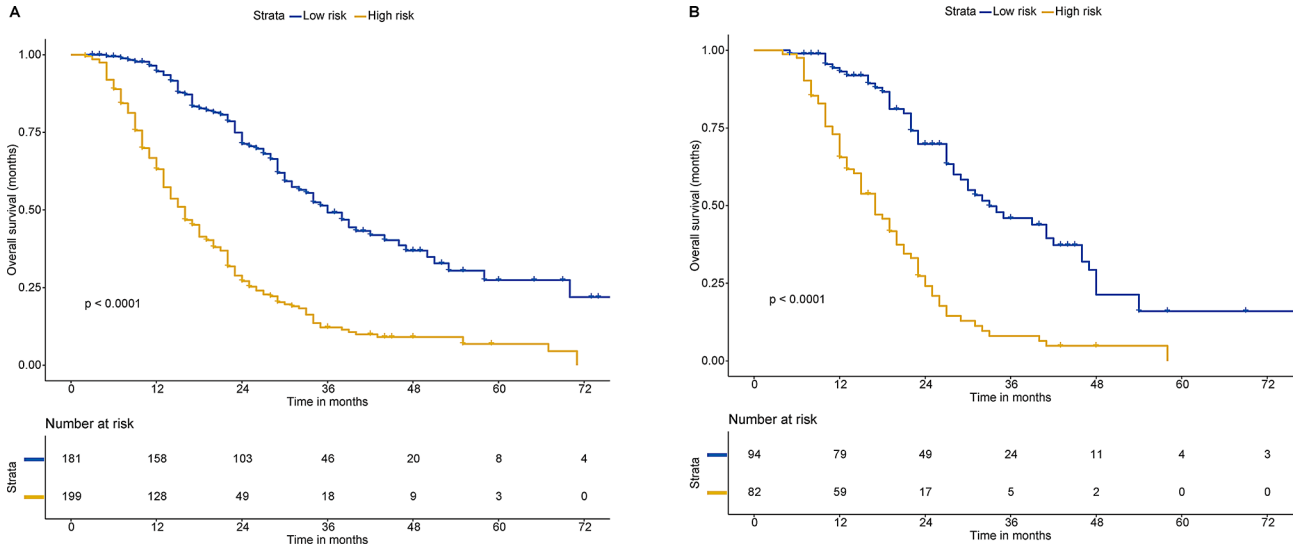

Fig. 4 KM curves for low- and high-risk group patients in the training cohort and external validation cohort

potential responders. Therefore, further model optimisation is required to better predict which patients will benefit from this approach.

Machine learning algorithms are increasingly utilised in the medical field, with LASSO Cox regression and forward selection bootstrapping demonstrating their superiority in constructing prognostic models for nasopharyngeal carcinoma [26–28]. However, in our study, we opted for the traditional Cox multivariate analysis, particularly due to its advantages regarding model interpretability and the handling of correlated predictors. Unlike LASSO, which selects variables based on penalty coefficients, the traditional Cox regression retains all variables within the model, thereby enabling a more direct assessment of the relationship between each predictor and the outcome. This method offers a clearer understanding of the impact of each variable on survival without the need to adjust hyperparameters, as required by LASSO. Moreover, while bootstrapping and forward selection are beneficial for evaluating model stability and reducing overfitting, the traditional Cox model provides a more straightforward interpretation of hazard ratios and their clinical significance, which is crucial for the clinical application of prognostic models.

This investigation has some limitations. First, as this was a retrospective analysis, it is susceptible to selection bias; thus, further prospective studies are required to validate these findings. Additionally, although the study incorporated data from multiple centres, most cases were from NPC-endemic regions. Therefore, the model developed in this study requires further validation in patient cohorts from non-NPC-endemic areas.

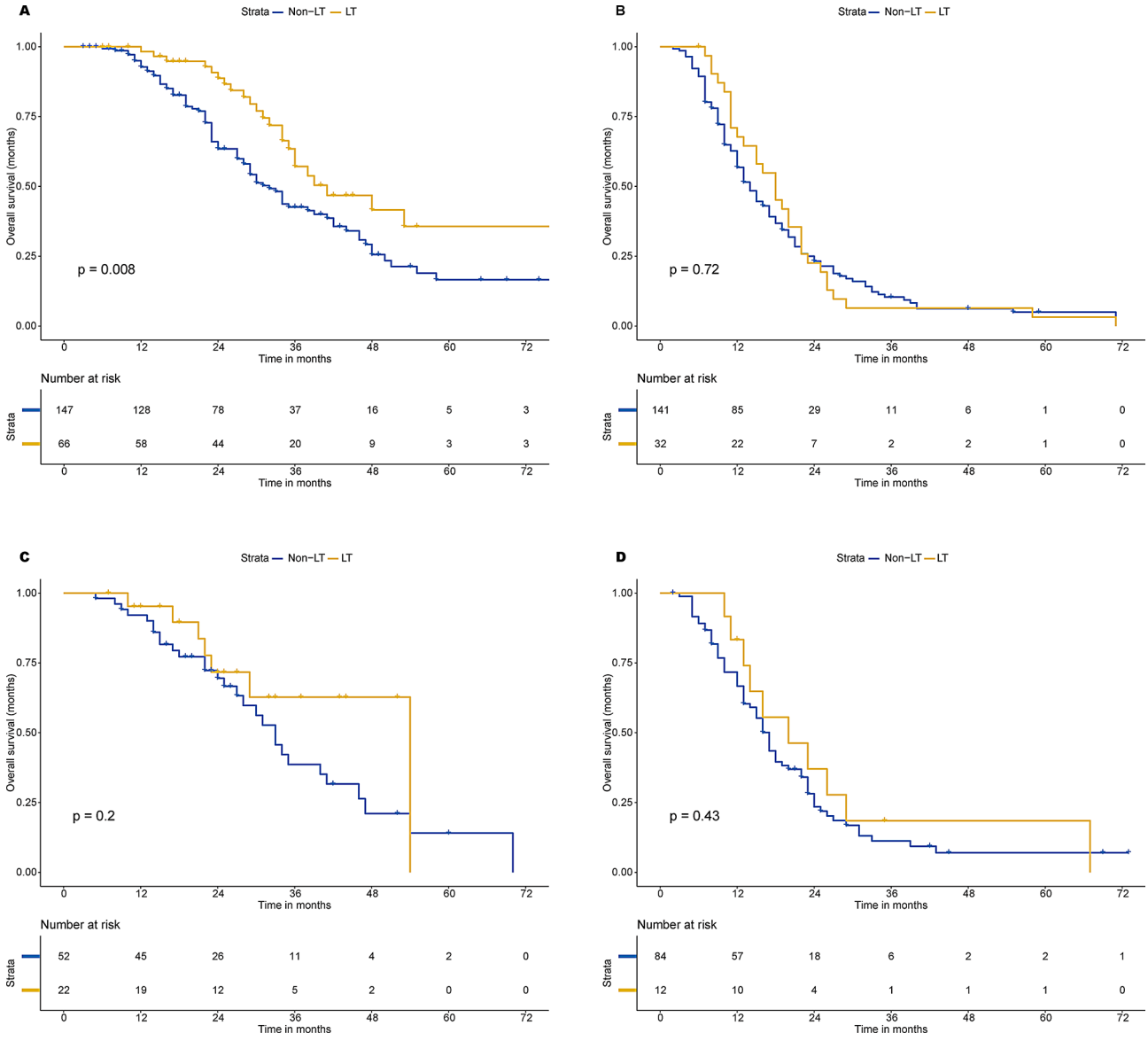

Fig. 5 Comparison of overall survival between patients with and without LT in the low-risk group of the training cohort (**A**) and validation cohort (**C**); Comparison of overall survival between patients with and without LT in the high-risk group of the training cohort (**B**) and validation cohort (**D**). LT, local treatment for metastatic lesion

In conclusion, our nomogram-based prognostic model showed robust performance in personalised survival prediction and risk stratification for smNPC patients. This model has proven valuable in guiding personalised treatment decisions in clinical practice.

Abbreviations

AUC	Area under the curve
CI	Confidence interval
CT	Computed tomography
CTC	Circulating tumour cell
GXMUCH	Guangxi Medical University Cancer Hospital
IQR	Interquartile range
NPC	Nasopharyngeal carcinoma
GP	Gemcitabine plus cisplatin
OS	Overall survival
PFS	Progression-free survival
smNPC	Synchronous metastatic nasopharyngeal carcinoma
t-ROC	Time-dependent receiver operating characteristic
TNM	Tumour-node-metastasis
WZRCH	Wuzhou Red Cross Hospital
XTCH	Xiangtan Central Hospital

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Author contributions
Xiao-Yi Zeng, Ye Li, Jie Ma, Yang Liu and Xiao-Dong Zhu were the principal investigators of this study and conceived the research design. Xiao-Yi Zeng, Ye Li, Jie Ma, Zhi-Chao Zuo, Meng-Jie Jiang, Zhong-Guo Liang and Kai-Hua Chen contributed to data collection. Xiao-Yi Zeng, Ye Li and Jie Ma analyzed the data and prepared the figures. The manuscript was primarily drafted by Xiao-Yi Zeng. Zhu XD, Yang Liu, Qu S, Li L, critically reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This multicentre study was approved by the Institutional Review Boards of Guangxi Medical University Cancer Hospital (GXMUCH), Xiangtan Central Hospital (XTCH), and Wuzhou Red Cross Hospital (WZRCH). Written informed consent was deemed unnecessary due to the study's retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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