Integrating pretreatment ^{18}F-FDG PET-CT parameters, peripheral blood indicators and clinical characteristics in predicting chemotherapy plus immunotherapy outcomes for de novo metastatic nasopharyngeal carcinoma

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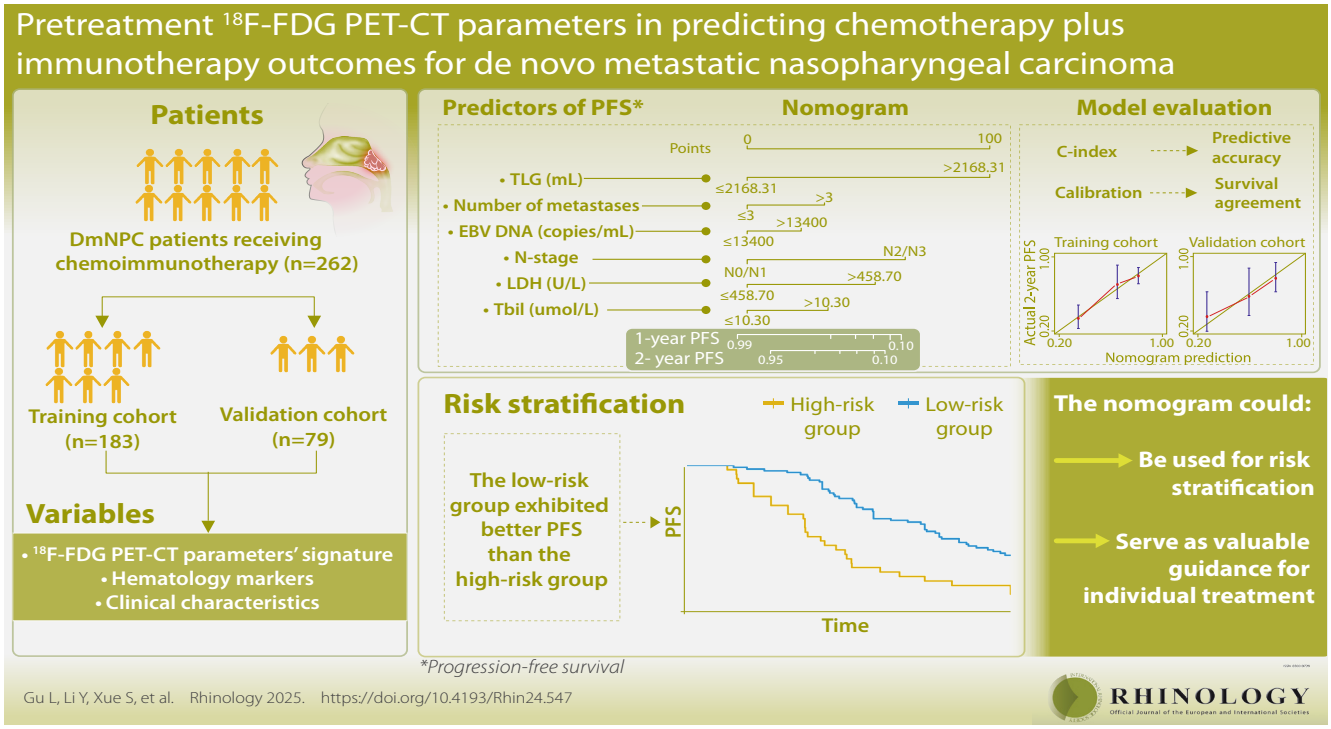

Abstract

Background: To develop a prognostic nomogram based on pretreatment ^{18}F-FDG PET-CT radiomics parameters, peripheral blood indicators and clinical characteristics for risk stratification in patients with de novo metastatic nasopharyngeal carcinoma (dmNPC) receiving immunochemotherapy. **Methodology**: The eligible patients were randomly divided into training (n=183) and validation (n=79) cohorts. Least absolute shrinkage and selection operator regression was used for variable selection. Multivariate Cox regression analysis was performed to identify independent prognostic factors for progression-free survival (PFS). The predictive accuracy and discriminative ability of the nomogram were determined with a concordance index (C-index) and calibration curve. **Results**: Multivariate Cox analysis suggested that total lesion glycolysis, number of metastases, Epstein–Barr virus DNA, N-stage, lactate dehydrogenase, and total bilirubin were independent predictors of PFS and were used to develop a nomogram that could classify patients into low- and high-risk groups. The C-index of the nomogram for predicting disease progression was 0.75, which was significantly higher than the C-indices of the TNM stage and EBV DNA. The patients were then stratified into low- and high-risk groups based on the calculated scores. The median PFS was significantly higher in the low-risk group than in the high-risk group. **Conclusions**: The proposed nomogram with PET-CT parameters, peripheral blood indicators and clinical characteristics resulted in accurate prognostic prediction for patients with dmNPC receiving chemotherapy plus PD-1 inhibitors and could provide risk stratification for these patients.

Key words: nasopharyngeal carcinoma, ^{18}F-FDG PET-CT parameters signature, peripheral blood indicators, PD-1 inhibitors, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy with distinct geographical distribution that is particularly prevalent in east and southeast Asia [1–3]. At the time of initial diagnosis, approximately 4–14.8% of patients exhibit distant metastasis, accounting for the worse prognosis of primary NPC [1,4,5]. Endemic NPCs are associated with Epstein-Barr virus (EBV) infection and are characterised by the presence of substantial immune infiltration of T lymphocytes, and 89-95% of patients have high programmed death ligand-1 (PD-L1) expression, which makes immunotherapy a promising treatment option in this setting [6–8]. Recently, three large multicenter phase 3 trials have consistently reported that adding a PD-1 inhibitor to chemotherapy for metastatic or recurrent NPC demonstrates robust anticancer activity and significantly improves the objective response rate and progression-free survival (PFS) compared to chemotherapy alone. As a result, this combination has become the first-line treatment [7,9,10]. However, not all patients benefit from PD-1 inhibitors, and approximately 50% of patients develop disease progression during the first 2 years. Therefore, there is an urgent need to identify biomarkers of patients who may respond to PD-1 inhibitors [11].

Previous studies have demonstrated that the expression of human leukocyte antigen A and B, presence of tertiary lymphatic structures, tumour infiltrating lymphocyte density, and tumour mutation burden are associated with patient survival outcomes [12–15]. However, these markers fail to consistently predict responses and are yet to be translated into routine clinical practice. ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET-CT) is a sensitive imaging modality that provides anatomic and glycolytic metabolism information from the tumour [11] and is widely used to stage and monitor treatment responses in patients with NPC [16]. Quantitative ^{18}F-FDG PET-CT parameters, including standard uptake values (SUV), metabolic tumour volume (MTV), and total lesion glycolysis (TLG), are potential markers for predicting survival in patients with other malignancies undergoing PD-1 inhibitor therapy [11,17]. However, the role of PET-CT parameters in predicting response and survival in patients with recurrent or metastatic NPC treated with chemotherapy plus anti-PD-1 therapy remains elusive. Hence, we conducted this study to explore the prognostic value of PET-CT parameters in de novo metastatic nasopharyngeal carcinoma (dmNPC) and to develop a model based on ^{18}F-FDG PET-CT parameters, peripheral blood indicators, and clinical characteristics to predict the outcomes of patients with dmNPC treated with chemotherapy plus PD-1 inhibitors. We hypothesised that this model could help clinicians identify patients sensitive to PD-1 inhibitors and facilitate individual treatment decisions.

Materials and methods

Patients

This is a retrospective study to predict the prognosis of dmNPC patients treated with chemotherapy combined with PD-1 inhibitors. From July 2018 to August 2022, 314 patients with biopsy-proven, newly diagnosed dmNPC at the Sun Yat-Sen University Cancer Centre (SYSUCC) were consecutively enrolled in this study. The inclusion criteria were as follows: 1) age ≥18 years; 2) received chemotherapy plus PD-1 antibody as first-line treatment followed by PD-1 inhibitor maintenance therapy and no previous therapy; 3) Eastern Cooperative Oncology Group (ECOG) score of 0–1; 4) no previous or synchronous malignant tumours; 5) satisfactory liver and renal functions (aspartate transaminase and alanine transaminase levels less than 2.5 times the upper normal limit; and creatinine clearance rate at least 60 mL/min); 6) receipt of ^{18}F-FDG PET-CT within 1 week prior to commencing treatment; 7) available radiologic evaluation data; and 8) complete treatment and laboratory data. A flowchart of the study is shown in Figure 1. The included participants were grouped randomly using R into training and validation sets (ratio: 7:3) [18,19]. This study was approved by the Institutional Review Board and Ethics Committee of the SYSUCC (approval number: SL-B2022-264-02).

Pretreatment evaluation and treatment

Pretreatment evaluation included a detailed medical history and complete physical examination, haematologic and biochemical analyses, electrocardiography, nasoendoscopy, and magnetic resonance imaging (MRI) of the head and neck. Whole-body ^{18}F-FDG PET-CT is mandatory for staging distant metastasis. Patients with suspected findings of distant metastases on imaging, need to undergo pathological confirmation. All eligible patients underwent platinum-based chemotherapy plus anti-PD-1 immunotherapy with or without intensity-modulated radiotherapy (IMRT) to the nasopharynx and neck. Patients started IMRT after 6 cycles of chemotherapy plus PD-1inhibitors, and received PD-1 inhibitor every 3 weeks, until unacceptable toxicity developed, the disease progressed, the investigators decision, the patient withdrew informed consent, up to a maximum of 2 years. PD-1 inhibitor immunotherapy was continued during radiotherapy.

Imaging and image analysis

The ^{18}F-FDG PET-CT image acquisition protocol is described in detail in Appendix S1 [3,20]. The volumes of interest (VOIs) in the PET images were automatically contoured using Syngo.via software. As described in previous studies, an SUV of 2.5 was adopted as the threshold for VOI analysis, while benign lesions were excluded [16,21]. All lesions with uptake above the threshold were automatically contoured on PET-CT images. Benign lesions were manually excluded. Following contouring, MTV, SUVmax, and SUVpeak were automatically calculated. Finally, TLG was calculated as the MTV multiplied by the whole-body tumour mean SUV, and the PET-CT-derived number of metastases was

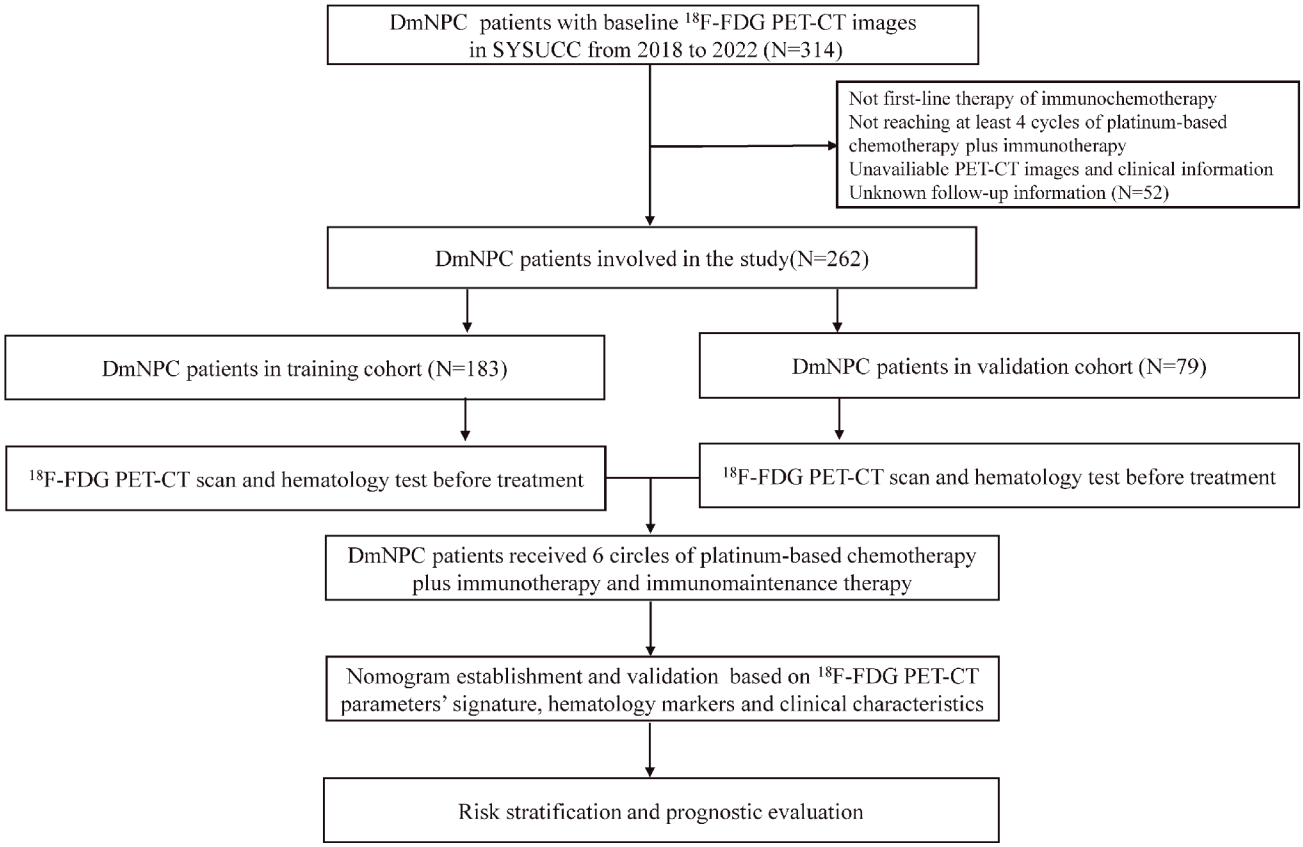

Figure 1. Flow chart of the study.

included in the analyses.

Data assessment

We evaluated 35 potential prognostic indicators for PFS based on PET-CT parameters, clinical characteristics, and baseline peripheral blood factors. PET-CT parameters included SUVmax, SUVpeak, SUVmean, MTV, and TLG. The clinical features of each patient at admission included age, sex, smoking history, histological findings, ECOG performance score, body mass index, TNM stage, liver involvement (liver metastases), and number of metastases (distant metastases). Baseline peripheral blood factors included C-reactive protein (CRP) levels, lactate dehydrogenase (LDH) levels, serum albumin (ALB) levels, serum amyloid A levels, Creatinine, total bilirubin (Tbil), uric acid, white blood cell, haemoglobin, platelets, neutrophil, monocyte, lymphocyte, plasma EBV DNA, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio, nutritional risk index (NRI), prognostic nutritional index (PNI), and systemic immune-inflammation index (SII).

Follow-up and endpoints

Follow-ups were conducted using medical records or phone calls. All patients were followed-up at least every 6 weeks for the first 12 months and every three months thereafter until death. Detailed history, complete physical examination, plasma EBV DNA test, nasopharyngeal endoscopy, MRI of the nasopharynx and neck, chest and abdominal CT, whole-body bone scan, or ^{18}F-FDG PET-CT were routinely performed or when tumour progression was clinically indicated. The primary endpoint was PFS, which was defined as the date of dmNPC diagnosis to the date of disease progression or all-cause death. Secondary endpoints included overall survival (OS), objective response rate (ORR), and disease control rate (DCR). The OS duration was measured from the date of diagnosis of dmNPC to all-cause death or the last follow-up. ORR was defined as complete response (CR) or partial response (PR) with at least one sequential tumour assessment confirmed according to the Response Evaluation Criteria in Solid Tumours v.1.1. Disease control (DC) was defined as radiologically confirmed complete response (CR), partial response (PR), and stable disease (SD).

Statistical analysis

All continuous variables were converted into binary variables based on the optimal cutoff point and receiver operating characteristic curves. Categorical variables are expressed as numbers (percentages). Chi-square test or Fisher's exact test was used to compare categorical data between the primary and validation cohorts. The least absolute shrinkage and selection

Table1. Baseline demographics and disease characteristics.

Variable	Training cohort (N=183) No. (%)	Validation cohort (N=79) No. (%)	P Value
Age, median (IQR), year	44 (36, 53)	45 (36, 53)	0.58
Sex			0.48
Male	146 (79.8)	66 (83.5)	
Female	37 (20.2)	13 (16.5)	
Smoking			0.11
Yes	82 (44.8)	27 (34.2)	
No	101 (55.2)	52 (65.8)	
Histologic findings			0.54
Keratinizing (type I)	1 (0.5)	1 (1.3)	
Nonkeratinizing differentiated (type II)	0 (0.0)	0 (0.0)	
Nonkeratinizing undifferentiated (type III)	182 (99.5)	78 (98.7)	
ECOG			0.18
0	12 (6.6)	2 (2.5)	
1	171 (93.4)	77 (97.5)	
T stage			0.09
T1-2	10 (5.5)	9 (11.4)	
T3-4	173 (94.5)	70 (88.6)	
N stage			0.44
N0-1	30 (16.4)	10 (12.7)	
N2-3	153 (83.6)	69 (87.3)	
Pretreatment EBV DNA, median (IQR), copies/mL	4260 (595, 20300)	6800 (1750, 21000)	0.20
No. of metastases			0.50
≤3	80 (43.7)	31 (39.2)	
>3	103 (56.3)	48 (60.8)	
Liver involvement			0.16
Yes	55 (30.1)	17 (21.5)	
No	128 (69.9)	62 (78.5)	
Lung involvement			0.06
Yes	47 (25.7)	12 (15.2)	
No	136 (74.3)	67 (84.8)	
Bone involvement			0.05
Yes	124 (67.8)	63 (79.7)	
No	59 (32.2)	16 (20.3)	
SUVmax, median (IQR)	15.90 (12.57, 21.20)	16.71 (13.08, 21.19)	0.78
SUVpeak, median (IQR)	11.71 (9.25, 15.35)	12.00 (9.55, 15.33)	0.63
SUVmean, median (IQR)	5.86 (5.07, 7.34)	5.90 (4.74, 7.46)	0.78
MTV , median (IQR), mL	75.48 (45.04, 139.66)	103.08 (46.68, 138.58)	0.22
TLG , median (IQR), mL	412.83 (231.59, 775.48)	524.98 (283.35, 829.44)	0.11
Tumor response			0.46
CR	26 (14.2)	12 (15.2)	
PR	65 (35.5)	21 (26.6)	
SD	23 (12.6)	8 (10.1)	
PD	69 (37.7)	38 (48.1)	
Anti-PD-1 agent			0.59
Camrelizumab	50 (27.3)	26 (32.9)	

Variable	Training cohort (N=183) No. (%)	Validation cohort (N=79) No. (%)	P Value
Tislelizumab	37 (20.2)	14 (17.7)	
Toripalimab	63 (34.5)	25 (31.6)	
Pabolizumab	5 (2.7)	1 (1.3)	
Nivolumab	2 (1.1)	0 (0.0)	
Sintilimab	26 (14.2)	13 (16.5)	

*Tumor stage was based on the American Joint Committee on Cancer, 8th edition. All statistical tests were two-sided. Abbreviations: No., number; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; EBV, Epstein-Barr virus; SUV, standard uptake value; MTV, metabolically tumor volume; TLG, total lesion glycolysis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PD-1, programmed death-1.

operator (LASSO) regression was utilised to select potentially significant factors to prevent overfitting and eliminate collinearity of the candidate variables [22,23]. By adjusting the penalty value (λ), LASSO reduces the coefficients of factors not correlated with PFS in patients with dmNPC to zero. We selected the optimal penalty value (λ) for which the cross-validation error is the smallest. Finally, backward stepwise multivariate Cox regression analyses were conducted to test the independent significance of different characteristics selected using the LASSO method. Based on the significant features of the multivariate model, we utilized 1-year and 2-year PFS as time points for constructing a nomogram. Nomograms are graphical depictions of predictive statistical models for individual patients [24], and have shown superior predictive performance compared to traditional staging systems in forecasting outcomes for cancer patients [25]. As a result, they are increasingly being considered as a potential alternative or even a new standard for guiding treatment decisions in cancer patients. Calibration capacities were evaluated using a calibration plot. The predictive performance of the nomogram was evaluated with the concordance index (C-index). Comparisons between the nomogram, EBV DNA alone, and the current staging systems in the entire population and subgroups of patients treated with locoregional radiotherapy (LRRT) were performed using the C-index. Decision curve analysis (DCA) curves were generated to assess the clinical application. Bootstraps with 1000 re-samples and 10-fold cross-validation were applied to avoid overfitting. Furthermore, we stratified the patients into two categories based on the cutoff value of the total points derived from the established nomogram: low- and high-risk groups. Differences in PFS and OS between the low- and high-risk groups were compared using a log-rank test and depicted through the Kaplan–Meier method. All statistical analyses were conducted employing SPSS (version 25.0; IBM Inc., Armonk, NY, USA) and R version 4.1.3 (R Development Core Team, Vienna, Austria).

Results

Patient characteristics

The median age of the 262 patients included in this study was 44 years (interquartile range (IQR): 38-55), with 212 men (80.9%) and 50 women (19.1%). The most site of metastasis was the bone (187, 71.4%), followed by the liver (72, 27.5%) and lungs (59, 22.5%). A total of 111 patients (42.4%) exhibited more than three metastases at the time of diagnosis. As of the last follow-up date of 31 March 2024, the median follow-up time was 28.00 (IQR: 21.58–37.76) months. The median progression-free survival (mPFS) time of the entire cohort was 22.00 (IQR: 13.12–21.66) months with 1-year and 2-year probabilities of PFS (OS) at 77.1% (90.5%) and 42.7% (67.2%), respectively. The ORR was 47.3% (95% CI: 41.4–53.4%), and the DCR was 59.2% (95% CI: 52.9–65.1%). The study cohort was randomly divided into training (n =183) and validation (n = 79) cohorts at a ratio of 7:3 (18,19). All baseline characteristics were similar between the training and validation cohorts (Table 1).

Prognostic analysis

The initial candidate predictive factors of PFS are listed in Supplementary Table 2. Through LASSO regression, nine non-zero coefficients out of 35 factors in the training cohort were selected by setting an optimal penalty value of 0.06415 (Figure S1). Subsequently, we conducted multivariate Cox regression analyses, which exhibited that TLG (HR: 8.80, 95% CI: 1.70–45.66, p=0.01), number of metastases disease (HR: 1.80, 95% CI: 1.00–3.19, p=0.05), N-stage (HR: 4.62, 95% CI: 1.42–15.00, p=0.01), LDH level (HR: 2.68, 95% CI: 1.22–5.90, p=0.01), and Tbil level (HR: 2.37, 95% CI: 1.39–4.06, p<0.01) were identified as independent significant prognostic factors for PFS of patients with dmNPC who received chemotherapy plus PD-1 inhibitors (Table 2). The data of TLG and number of tumor metastases disease was obtained from PET-CT image analysis. Notably, the pretreatment EBV DNA level was possibly associated with PFS in the LASSO regression analyses, whereas it was not a significant factor in the multivariate analysis. However, considering its potential prognostic value in these patients, the pretreatment EBV DNA level was included in the following model [26].

Model establishment and validation

A nomogram was developed to predict the 1-year and 2-year PFS of patients with dmNPC who received first-line chemothe-

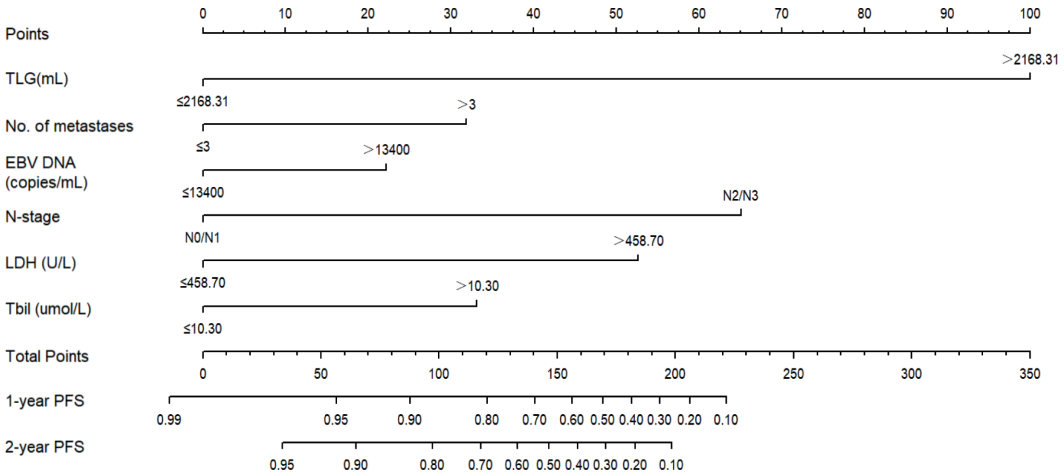

Figure 2. Prognostic nomogram for 1- and 2-year PFS in patients with dmNPC who received chemotherapy plus PD-1 inhibitor. The nomogram model was established based on TLG, number of metastases, EBV DNA level, N-stage, LDH level, Tbil level. Each variable was assigned a score based on its contribution to the outcome event. The total points for each patient were calculated by summing the allocated scores for each factor in the nomogram.

rapy combined with PD-1 inhibitors using the indicators of TLG, number of metastatic diseases, N-stage, LDH level, Tbil level, and plasma EBV DNA level (Figure 2). The calibration plot of the nomogram demonstrated high concordance between the nomogram-based predictions and the observed outcomes in both the training and validation cohorts (Figure 3). Furthermore, the predictive power for 2-year PFS of patients with dmNPC between nomogram, plasma EBV DNA level, and current TNM staging systems were compared. In the training cohort, the C-index for PFS prediction was 0.75 (95% CI, 0.69-0.81) of the nomogram, which was statistically significantly higher than the C-indices of EBV DNA alone and the current staging system. Interestingly, similar statistical results were obtained in the validation cohort (Table S1). DCA used to evaluate the potential clinical application of the nomogram, which demonstrated excellent predictive performance in the training and validation cohorts (Figure S2).

Subgroup analyses in patients treated with LRRT

LRRT or IMRT to the primary and nodal regions is reportedly associated with increased long-term survival in patients with dmNPC in clinical practice [4, 26–28]. Therefore, we tested whether the prognostic discrimination of the nomogram could be applied to patients with dmNPC treated with. Notably, the C-index of the nomogram was 0.71 (95% CI, 0.62–0.80, $p < 0.01$), which was significantly higher than the C-indices of EBV DNA level alone and the TNM staging system (Table S1). Similar results were observed in a subgroup of patients who received LRRT in the validation cohort.

Risk group stratification

Based on the best cut-off values of the total score derived from the nomogram, the study population was stratified low-risk (total score ≤120) versus high-risk (total score >120) groups. Figure S3 shows the Kaplan–Meier survival curves for PFS and OS of the different risk groups; the low-risk group exhibited significantly better survival outcomes than the high-risk group (mPFS, not reached vs. 14.85 months [95%CI: 11.00–21.00], $p < 0.01$). Furthermore, we further observed that the ORR was higher in the low-risk group versus the high-risk group (Figure S4A). In addition, the DCR was better in the low-risk group versus the high-risk group (Figure S4B).

Discussion

Immune checkpoint inhibitors combined with platinum-based chemotherapy have revolutionised the treatment paradigm for patients with dmNPC. However, patient selection and risk stratification remain challenging, and there is an urgent need for better predictive and prognostic biomarkers. To the best of our knowledge, this is the first study to describe the development and validation of a nomogram integrating baseline ^{18}F-FDG PET-CT parameters, peripheral blood indicators, and clinical characteristics for prognostic prediction and individualised treatment guidance of patients with dmNPC receiving chemotherapy plus PD-1 inhibitors in a non-invasive manner. The nomogram, which included TLG, number of metastases, plasma EBV DNA level, N stage, LDH, and Tbil, had better predictive accuracy than those of EBV DNA alone and the current conventional staging system in the training and validation cohorts. Interestingly, we observed similar results in a subgroup of patients who were treated with LRRT. Moreover, the nomogram was powerful in discriminating between high- and low-risk patients, indicating that it could serve as a reliable tool for the future individual management of patients with dmNPC and for selecting patients who are sensi-

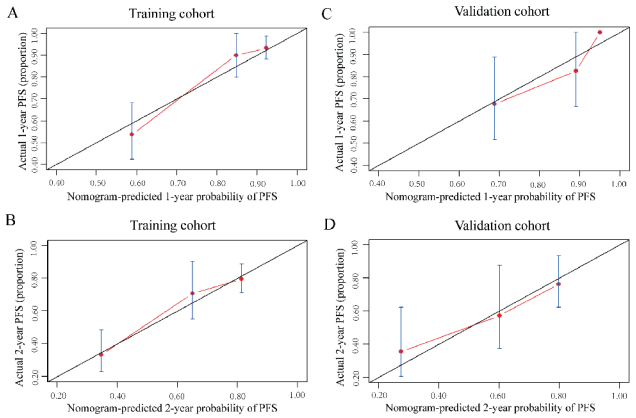

Figure 3. The calibration plots of the established nomogram in predicting the 1-year and 2-year PFS in patients with dmNPC who received chemotherapy plus PD-1 inhibitor in the training cohort (A, B) and validation cohort (C, D).

tive to immunotherapy.

Recent literature indicates that the role of ^{18}F-FDG PET-CT in predicting the treatment response to chemotherapy plus PD-1 inhibitors in cancer is not well-documented [29,30]. Kong et al. found that compared to false-positive progression patients with metastatic melanoma, biopsy-proven progression patients demonstrated a trend toward higher SUVmax values [31]. Wang et al. suggested that SUVmax and SUVmean were significantly associated with a complete pathological response in patients with oesophageal squamous cell carcinoma after neoadjuvant immunochemotherapy, with high sensitivity and specificity. Kim et al. showed that baseline SUVmax, MTV, and TLG were independent prognostic factors for PFS in patients with non-small-cell lung cancer (NSCLC) receiving pembrolizumab and chemotherapy as first-line treatment [30]. Consistent with previous studies, we found that PET-CT parameters, especially TLG, are potential markers for patients with dmNPC receiving first-line platinum-based chemotherapy plus PD-1 inhibitor therapy. TLG is an important composite parameter representing tumour volume and metabolic status [32] and can reflect tumour burden, hypoxia in the tumour microenvironment, T cell activation, molecular heterogeneity, or other undefined factors [11,17].

In addition, many peripheral blood elements, such as EBV DNA, CRP, LDH, ALB level, and MLR, are independent predictors of NPC [14,33–36]. Various nutritional indicators such as NRI and PNI are strongly associated with immunotherapy response, chemotherapy tolerance, and survival outcomes in patients with NPC [37]. However, in this study, we found that LDH and Tbil levels were independent factors in patients with dmNPC who received chemotherapy plus PD-1 inhibitors. LDH, a metabolic enzyme in the glycolytic pathway, facilitates the conversion of pyruvate to lactate, which promotes tumour proliferation and progression [38]. Thus, LDH may be involved in regulating the apoptosis of tumour-infiltrated lymphocytes or altering their functions, as well as supporting the accumulation and differentiation of immunosuppressive lymphocytes [39,40]. In patients with NSCLC who receive PD-1 inhibitor therapy, high LDH levels ware significantly associated with poor PFS and OS [41], which is consistent with our findings. Plasma EBV DNA levels significantly influence the diagnosis, clinical management, development, and prognosis of dmNPC. Li et al. showed that EBV DNA level is an independent factor for recurrence in patients with NPC receiving PD-1 inhibitors [14]. Considering its vital role, we hypothesised that EBV DNA levels should be considered in the nomogram. Notably, in our model, the underlying mechanism of Tbil and immunochemotherapy for NPC remains unclear, and one possible explanation is that Tbil levels are related to chemoradiotherapy tolerance. In our study, the number of distant metastases and N stage were also independent prognostic factors for PFS, which reflected the anatomical structure and aggressiveness of the tumour to a certain extent and were thus included in the nomogram model. In the analyses, the C-indices were 0.75 and 0.74 in the training cohort and validation cohorts, respectively. This indicated considerable discrimination and calibration ability in predicting prognosis of patients with dmNPC treated with first-line chemotherapy plus PD-1 inhibitor therapy. In addition, the current clinical decision-making and prognosis estimation for dmNPC are mainly based on the TNM staging system and plasma EBV DNA. However, comparing the predictive performance of the model, TNM staging system, and EBV DNA levels alone, the model showed superior performance compared with both EBV DNA levels alone and the TNM staging system.

Combined-modality treatment consisting of palliative chemotherapy followed by LRRT has been recognised to provide durable locoregional control and even cure in patients presenting with dmNPC, and LRRT is recommended by both the NCCN [42] and CSCO [43] guidelines for patients with dmNPC who achieve CR/PR after three cycles of chemotherapy. However, the efficacy of LRRT in this era of immunotherapy remains unclear. A recent retrospective study showed that immunochemotherapy plus subsequent LRRT prolonged the survival of patients with dmNPC, with manageable toxicities [44]. Thus, we further analysed the performance of the nomogram in patients treated with LRRT separately. In the training and validation cohorts, the C-indices of the nomogram in predicting PFS for patients receiving chemotherapy plus PD-1 antibodies were 0.71 and 0.77, respectively, which were statistically significantly higher than the values of current TNM staging and EBV DNA alone. This result demonstrated that the nomogram had significant clinical value for patients with LRRT, which is consistent with the results of the whole cohort.

From the above analysis, this nomogram can also predict the sensitivity of dmNPC patients to immunotherapy, aiding in identifying suitable candidates for chemotherapy plus immu-

Table2. Multivariate analyses in training cohort.

Variable	Multivariate HR (95% CI)	P Value
N stage		
N0-1	Reference	
N2-3	4.62 (1.42, 15.00)	0.01
Pretreatment EBV DNA (copies/mL)		
≤13400	Reference	
>13400	1.58 (0.94, 2.65)	0.09
LDH (U/L)		
≤458.70	Reference	
>458.70	2.68 (1.22, 5.90)	0.01
Tbil (umol/L)		
≤10.30	Reference	
>10.30	2.37 (1.39, 4.06)	<0.01
PLT (10^9/L)		
≤333	Reference	
>333	1.60 (0.94, 2.70)	0.08
No. of metastases		
≤3	Reference	
>3	1.80 (1.00, 3.19)	0.05
Liver involvement		
Yes	Reference	
No	0.65 (0.39, 1.10)	0.11
MTV (mL)		
≤300.54	Reference	
>300.54	1.35 (0.30, 6.01)	0.70
TLG (mL)		
≤2168.31	Reference	
>2168.31	8.80 (1.70, 45.66)	0.01

*Tumor stage was based on the American Joint Committee on Cancer, 8th edition. All statistical tests were two-sided. Abbreviations: HR, hazard ratio; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase; Tbil, bilirubin; PLT, platelets; MTV, metabolically tumor volume; TLG, total lesion glycolysis.

notherapy through an easy and relatively non-invasive method, particularly by using the PET-CT parameter TLG. By reflecting tumor metabolic activity and the dynamics of the tumor immune microenvironment, TLG is closely associated with immunotherapy sensitivity in dmNPC. Additionally, PD-L1 expression, CD8+ T-cell infiltration, and genetic variations (e.g., VAMP8) are factors influencing immunotherapy sensitivity [45]. Future efforts should integrate novel imaging technologies and multi-omics analyses to optimize personalized treatment strategies.

This study had several limitations. Firstly, it was retrospective in design; therefore, potential selection bias may have affected reliability and reproducibility. Secondly, owing to the limited follow-up time, the mPFS and overall survival time of the entire cohort were not fully established, and a longer follow-up period is needed. Thirdly, combined positive score (CPS) and tumor proportion score (TPS) consider the expression of PD-L1 in tumor cells and immune cells, which are related to the sensitivity of immunotherapy for cancers. Since this study is retrospective and lacks PD-L1 related data, this aspect will be explored in future research [46]. Fourthly, despite randomization, there were still differences in two of the 35 variables, HBG and PLT levels, between the training and validation cohorts. Fifthly, our study only included patients from a single centre and lacked external validation; thus, our model requires further validation in prospective studies and multicentre clinical trials.

Conclusion

The proposed nomogram integrating ^{18}F-FDG PET-CT parameters, peripheral blood indicators, and clinical characteristics provided statistically significantly better discrimination than the current TNM classification and served as a practical and easy-to-use tool for clinical assessments and guidance for individual treatment.

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Authorship contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by SYX, BBX, LPW. The first draft of the manuscript was written by LWG, YCL, SYX, BBBX, and DXW. The review and critical revision of the manuscript were performed by LTL, LG, LQT, ZX, YCL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

None.

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SUPPLEMENTARY MATERIAL

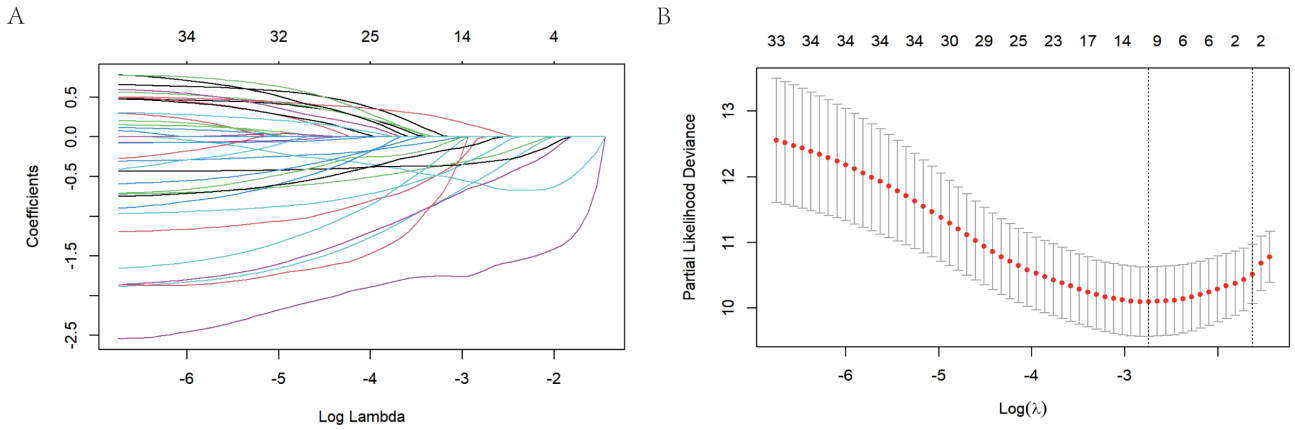

Figure S1. Relationship between Log(λ) and regression coefficients (A). Partial likelihood deviance curve with Log(λ) in Lasso regression (B).

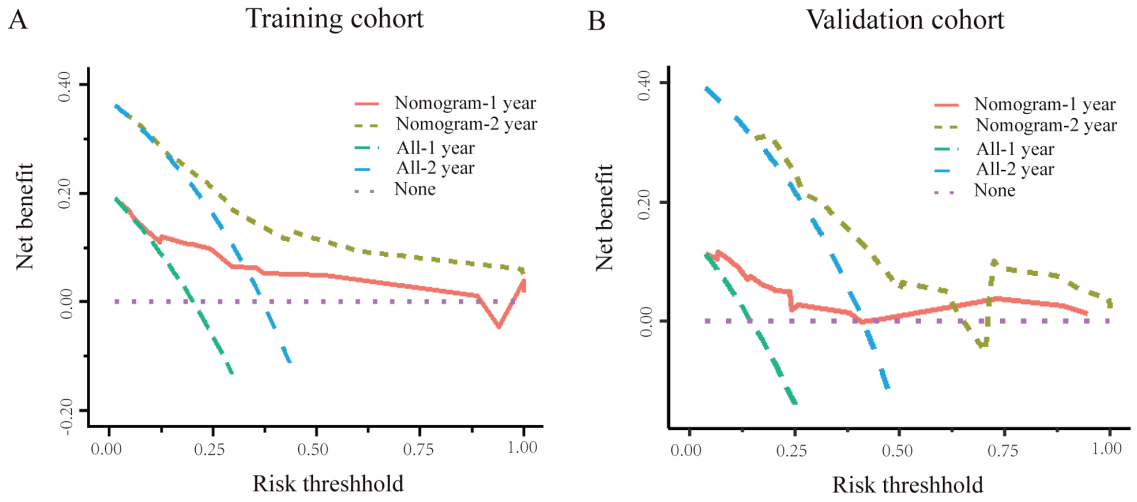

Figure S2. Decision curve analyses of the established nomogram predicting 1-year and 2-year PFS in patients with dmNPC who received chemotherapy plus PD-1 inhibitor in the training (A, B) and validation cohorts (C, D).

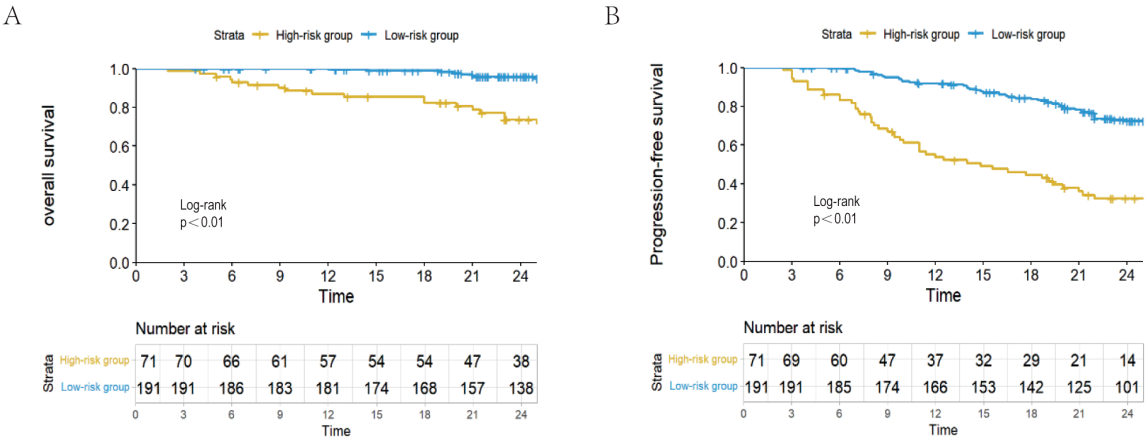

Figure S3. Survival curves of the low- and high-risk groups stratified using the nomogram for OS (A) and PFS (B) for the entire cohort. The log-rank test was used to calculate the p-values.

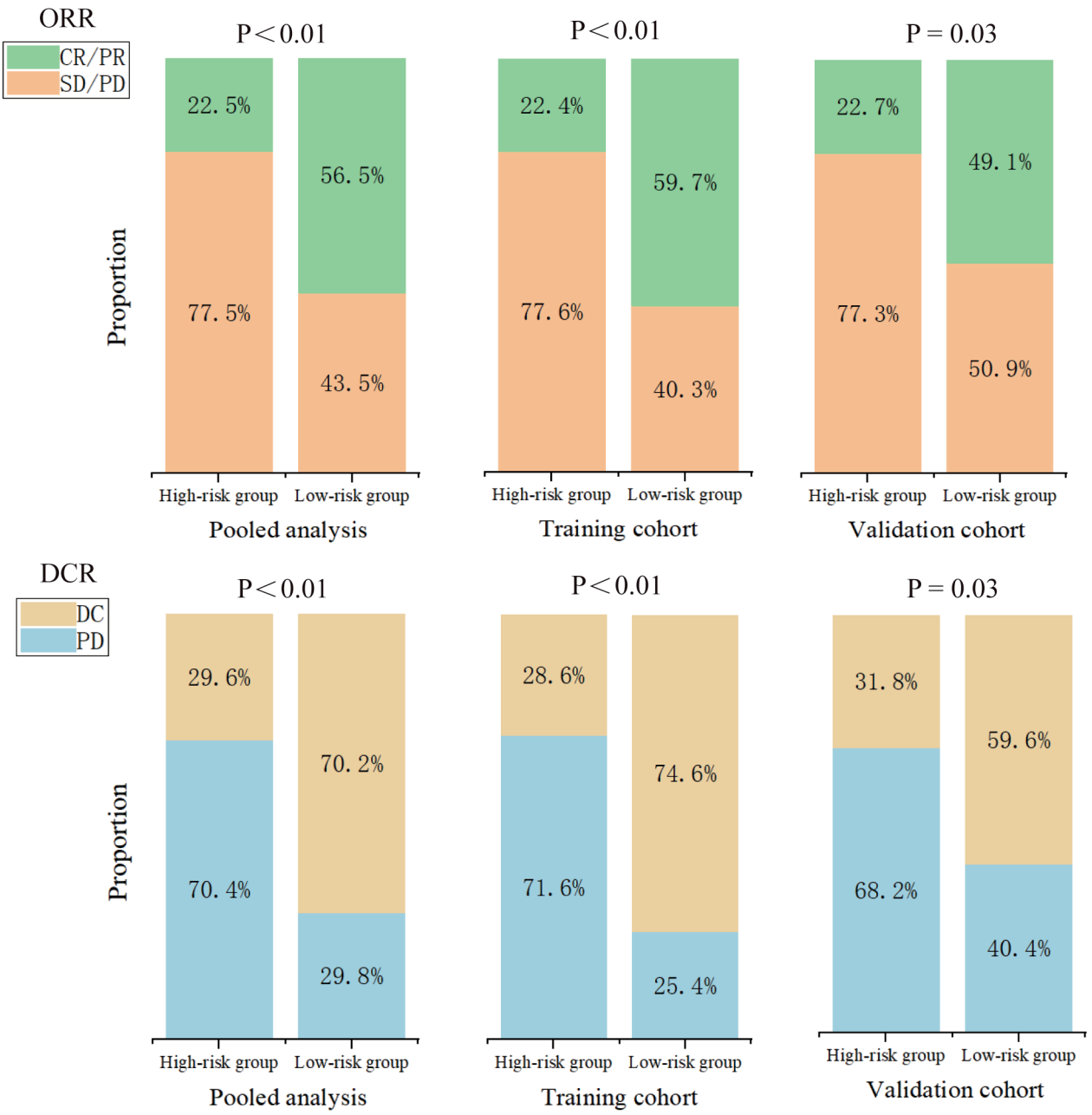

Figure S4. Distribution of ORR (A) and DCR (B) for low-and high-risk groups in the entire cohort, training cohort, and validation cohort. Chi-square tests were performed to compare the distribution between different prognosis groups. Abbreviations: ORR = objective response rate; DCR = disease control rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DC = disease control.

Table S1. The C-index of Nomogram, EBV DNA, TNM stage for prediction of OS in the training and validation cohort.

Variable	Training cohort		Validation cohort	
	C-index(95% CI)	P	C-index(95% CI)	P
All dmNPC patients				
Nomogram	0.75 (0.69, 0.81)	reference	0.74 (0.65, 0.82)	reference
EBV DNA	0.58 (0.53, 0.63)	<0.01	0.64 (0.56, 0.72)	<0.01
TNM stage	0.63 (0.57, 0.82)	<0.01	0.53 (0.44, 0.62)	<0.01
DmNPC patients receiving LRRT in subgroup analyses				
Nomogram	0.71 (0.62, 0.80)	reference	0.77 (0.67, 0.87)	reference
EBV DNA	0.62 (0.54, 0.70)	<0.01	0.68 (0.57, 0.79)	<0.01
TNM stage	0.60 (0.53, 0.67)	<0.01	0.52 (0.41, 0.63)	<0.01

*Nomogram included variables of TLG, number of metastases, EBV DNA level, N-stage, LDH level, Tbil level. Tumor stage was based on the American Joint Committee on Cancer, 8th edition. All statistical tests were two-sided. Abbreviations: C-index, concordance index; CI, confidence interval; dmNPC, de novo nasopharyngeal carcimoma; EBV, Epstein-Barr virus; LRRT, locoregional radiotherapy.

Table S2. Prognostic factors included in Lasso analyses.

Variable	Training cohort (N=183) No. (%)	Validation cohort (N=79) No. (%)	P Value
Age (years)			0.69
≤ 58	163 (89.1)	69 (87.3)	
> 58	20 (10.9)	10 (12.7)	
Sex			0.48
Male	146 (79.8)	66 (83.5)	
Female	37 (20.2)	13 (16.5)	
Smoking			0.11
Yes	82 (44.8)	27 (34.2)	
No	101 (55.2)	52 (65.8)	
Histologic findings			0.54
Keratinizing (type I)	1 (0.5)	1 (1.3)	
Nonkeratinizing differentiated (type II)	0 (0.0)	0 (0.0)	
Nonkeratinizing undifferentiated (type III)	182 (99.5)	78 (98.7)	
ECOG			0.18
0	12 (6.6)	2 (2.5)	
1	171 (93.4)	77 (97.5)	
BMI (kg/m^2)			0.84
<18.5	15 (8.2)	6 (7.6)	
18.5-24.0	102 (55.7)	44 (55.7)	
24.0-27.9	52 (28.4)	28 (35.4)	
≥28	14 (7.7)	1 (1.3)	
T stage			0.09
T1-2	10 (5.5)	9 (11.4)	
T3-4	173 (94.5)	70 (88.6)	
N stage			0.44
N0-1	30 (16.4)	10 (12.7)	
N2-3	153 (83.6)	69 (87.3)	

Table S2 *continued*. Prognostic factors included in Lasso analyses.

Variable	Training cohort (N=183) No. (%)	Validation cohort (N=79) No. (%)	P Value
Pretreatment EBV DNA (copies/mL)			0.80
≤ 13400	128 (69.9)	54 (68.4)	
> 13400	55 (30.1)	25 (31.6)	
CRP (mg/L)			0.95
≤ 17.75	150 (82.0)	65 (82.3)	
> 17.75	33 (18.0)	14 (17.7)	
LDH (U/L)			0.98
≤ 458.70	167 (91.3)	72 (91.1)	
> 458.70	16 (8.7)	7 (8.9)	
ALB (g/L)			0.64
≤ 37.70	9 (4.9)	5 (6.3)	
> 37.70	174 (95.1)	74 (93.7)	
SAA (mg/L)			0.75
≤ 50.60	138 (75.4)	18 (22.8)	
> 50.60	45 (24.6)	61 (77.2)	
Crea (umol/L)			0.22
≤ 95.10	179 (97.8)	75 (94.9)	
> 95.10	4 (2.2)	4 (5.1)	
Tbil (umol/L)			0.57
≤ 10.30	102 (55.7)	47 (59.5)	
> 10.30	81 (44.3)	32 (40.5)	
UA (umol/L)			0.09
≤ 311.70	61 (33.3)	18 (22.8)	
> 311.70	122 (66.7)	61 (77.2)	
WBC (10^9/L)			0.19
≤ 9.39	145 (79.2)	68 (86.1)	
> 9.39	38 (20.8)	11 (13.9)	
HGB (g/L)			0.01
≤ 147	123 (67.2)	48 (60.8)	
> 147	60 (32.8)	31 (39.2)	
PLT (10^9/L)			0.01
≤ 333	109 (59.6)	60 (75.9)	
> 333	74 (40.4)	19 (24.1)	
Neutrophil (10^9/L)			0.43
≤ 7.35	158 (86.3)	71 (89.9)	
> 7.35	25 (13.7)	8 (10.1)	
Monocyte (10^9/L)			0.77
≤ 0.52	117 (63.9)	49 (62.0)	
> 0.52	66 (36.1)	30 (38.0)	
Lymphocyte (10^9/L)			0.51
≤ 4.14	182 (99.5)	79 (100.0)	
> 4.14	1 (0.5)	0 (0.0)	

Table S2 *continued*. Prognostic factors included in Lasso analyses.

Variable	Training cohort (N=183) No. (%)	Validation cohort (N=79) No. (%)	P Value
No. of metastases			
≤ 3	80 (43.7)	31 (39.2)	
> 3	103 (56.3)	48 (60.8)	
Liver involvement			0.16
Yes	55 (30.1)	17 (21.5)	
No	128 (69.9)	62 (78.5)	
SUVmax			0.95
≤ 25.91	164 (89.6)	71 (89.9)	
> 25.91	19 (10.4)	8 (10.1)	
SUVpeak			0.96
≤ 5.86	92 (50.3)	40 (50.6)	
> 5.86	91 (49.7)	39 (49.4)	
SUVmean			1.00
≤ 16.04	146 (79.8)	63 (79.7)	
> 16.04	37 (20.2)	16 (20.3)	
MTV (mL)			0.74
≤ 300.54	169 (92.3)	72 (91.1)	
> 300.54	14 (7.7)	7 (8.9)	
TLG (mL)			0.92
≤ 2168.31	172 (94.0)	74 (93.7)	
> 2168.31	11 (6.0)	5 (6.3)	
NLR			0.07
≤ 4.42	156 (85.2)	60 (75.9)	
> 4.42	27 (14.8)	19 (24.1)	
MLR			0.50
≤ 0.61	175 (95.6)	74 (93.7)	
> 0.61	8 (4.4)	5 (6.3)	
PLR			0.70
≤ 277.27	159 (86.9)	70 (88.6)	
> 277.27	24 (13.1)	9 (11.4)	
NRI			0.36
≤ 91.34	6 (3.3)	1 (1.3)	
> 91.34	177 (96.7)	78 (98.7)	
PNI			0.76
≤ 61.60	172 (94.0)	75 (94.9)	
> 61.60	11 (6.0)	4 (5.1)	
SII			0.98
≤ 1504.66	155 (84.7)	67 (84.8)	
> 1504.66	28 (15.3)	12 (15.2)	

*Tumor stage was based on the American Joint Committee on Cancer, 8th edition. All statistical tests were two-sided. Abbreviations: LASSO, least absolute shrinkage and selection operator regression; No., number; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; EBV, Epstein-Barr virus; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALB, albumin; SAA, serum amyloid A; Crea, Creatinine; Tbil, bilirubin; UA, uric acid; WBC, white blood cell; HGB, hemoglobin; PLT, platelets; SUV, standard uptake value; MTV, metabolically tumor volume; TLG, total lesion glycolysis; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NRI, nutritional risk index; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Appendix S1

The patients underwent whole-body ^{18}F-FDG PET-CT scans using integrated PET-CT scanners (Discovery ST, GE Healthcare, Waukesha, WI, USA; or Biograph mCT; Siemens Healthcare, Henkestr, Germany). The patients fasted for at least 6 h before the ^{18}F-FDG PET-CT scan. Serum glucose levels were measured before the tracer injection (target serum glucose ≤11.1 mmol/l). A single-time-point PET scan (skull to mid-thigh) was performed with two-dimensional (2D) mode in Discovery ST or three-dimensional (3D) mode in Biograph mCT 60–90 min after the 18F-FDG injection (5.55 Mbq/kg for Discovery ST system and 3.7 Mbq/kg for Biograph mCT system), with 6–8 bed positions within a scan time of 1.5–3 min for each position. The low-dose CT scan was performed prior to PET scans using the following parameters: automatic tube current modulation, tube voltage 140 kV, collimation 16 × 1.25 mm, slice thickness 3.75 mm for the Discovery ST or tube current 80200 mAs, voltage 120 kV, collimation 32×1.25 mm, and slice thickness 3 mm for the Biograph mCT. Attenuation-corrected PET images and CT images without contrast enhancement were reconstructed using an ordered-subset expectation maximization iterative imaging reconstruction algorithm, with a slice thickness of 3.25 mm (2D) or with 2 mm (3D). Images were interpreted by two nuclear medicine physicians experienced in PET-CT diagnosis in the transaxial, coronal, and sagittal views.

Appendix S2

Dose and duration of PD-1 inhibitor administration

Patients received PD-1inhibitors every 3 weeks, including camrelizumab (200 mg), tislelizumab (200mg), toripalimab (3 mg/kg), pembrolizumab (200mg), nivolumab (3 mg/kg or 240 mg), or sintilimab (200 mg), until unacceptable toxicity developed, the disease progressed, the investigators decision, the patient withdrew informed consent, up to a maximum of 2 years.