Development and validation of a nomogram for predicting long-term overall survival in nasopharyngeal carcinoma
A population-based study

Jiayuan Wu, MD[a], Quan Zhou, MM[b], Zhenyu Pan, MD[c], Yufeng Wang, MM[d], Liren Hu, MM[d], Guanghua Chen, MD[e,*], Shengpeng Wang, MD[f,*], Jun Lyu, PhD[g,*]

Abstract

We aimed to develop a nomogram based on a population-based cohort to estimate the individualized overall survival (OS) for patients with nasopharyngeal carcinoma (NPC) and compare its predictive value with that of the traditional staging system.

Data for 3693 patients with NPC were extracted from the Surveillance, Epidemiology, and End Results dataset and randomly divided into two sets: training (n = 2585) and validation (n = 1108). On the basis of multivariate Cox regression analysis, a nomogram was constructed to predict the 3-, 5-, and 10-year survival probability for a patient. The performance of the nomogram was quantified with respect to discrimination, calibration, and clinical utility.

In the training set, age, sex, race, marital status, histological type, T stage, N stage, M stage, radiotherapy, and chemotherapy were selected to develop a nomogram for predicting the OS probability based on the multivariate Cox regression model. The nomogram was generally more discriminative compared with the American Joint Committee on Cancer 7th staging system. Calibration plots exhibited an excellent consistency between the observed probability and the nomogram's prediction. Categorical net classification improvement and integrated discrimination improvement suggested that the predictive accuracy of the nomogram exceeded that of the classic staging system. With respect to decision curve analyses, the nomogram exhibited preferable net benefit gains than the staging system across a wide range of threshold probabilities.

This proposed nomogram exhibits an excellent performance with regard to its predictive accuracy, discrimination capability, and clinical utility, and thus can be used as a convenient and reliable tool for prognosis prediction in patients with NPC.

Abbreviations: AJCC = American Joint Committee on Cancer, AUC = the area under curve, CCRT = concurrent radiochemotherapy, C-index = concordance index, DCA = the decision curve analysis, DNKC = differentiated non-keratinizing carcinoma, EBV = Epstein–Barr virus, ICD-O-3 = International Classification of Disease for Oncology, 3rd edition, IDI = integrated discrimination improvement, KSCC = keratinizing squamous cell carcinoma, M stage = distant metastasis, N stage = lymph node involvement, NPC = Nasopharyngeal carcinoma, NRI = the net reclassification improvement, OS = overall survival, ROC = the receiver operating characteristic, RT = radiotherapy, SEER = the Surveillance, Epidemiology, and End Results, T stage = the tumor size and extension, TNM = Tumor–Node–Metastasis, UNKC = undifferentiated non-keratinizing carcinoma, US = the United States, WHO = World Health Organization.

Keywords: AJCC staging system, nasopharyngeal carcinoma, nomogram, overall survival, SEER programs

[a] Department of Clinical Research, The Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, [b] Department of Science and Education, The First People's Hospital of Changde City, Changde, Hunan, [c] Department of Pharmacy, The Affiliated Children Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, [d] School of Public Health, Guangdong Medical University, [e] Department of Orthopedics, The Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, [f] Cardiovascular Research Center, School of Basic Medical Sciences, Key Laboratory of Environment and Genes Related to Diseases of Ministry of Education, Xi'an Jiaotong University Health Science Center, [g] Clinical Research Center, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China.

* Correspondence: Jun Lyu, Clinical Research Center, The First Affiliated Hospital of Xi'an Jiaotong University, No. 277, Yanta West Road (e-mail: lujun2006@xjtu.edu.cn); Shengpeng Wang, Cardiovascular Research Center, School of Basic Medical Sciences, Key Laboratory of Environment and Genes Related to Diseases of Ministry of Education, Xi'an Jiaotong University Health Science Center, Xi'an 710061, Shaanxi (e-mail: shengpeng.wang@xjtu.edu.cn); Guanghua Chen, Department of Orthopedics, The Affiliated Hospital of Guangdong Medical University, No. 57, South of Renmin Avenue, Zhanjiang 524001, Guangdong, China (e-mail: 404654885@qq.com).

1. Introduction

Nasopharyngeal carcinoma (NPC) is a specific malignance that originates in the epithelial lining of the nasopharynx, accounting for only 0.6% of newly diagnosed cancers per year.[1] Compared with other types of head and neck cancer, NPC has an uneven geographical distribution worldwide. NPC is uncommon in most area around the world, including the United States (US), with an incidence of <1 case per 100,000 person-years, but it is endemic in southern China and Southeast Asia, representing a peak incidence of 50 per 100,000 person-years.[2] The NPC pathogenesis is thought to be associated with Epstein–Barr virus (EBV) infection, family genetic factors, and environmental factors according to the current evidence.[3] Over the past three decades, the survival time of patients with NPC has prolonged because of the improvement of radiotherapy (RT) technology, the broad application of chemotherapy, and the accurate disease diagnosis. However, appropriately 30% of patients with NPC suffer a poor prognosis due to the development of recurrence or metastasis.[4] Given that patients with a high risk of poor prognosis may undergo additional treatment, early identification of these patients is necessary.[5]

To date, the standard treatment strategies for patients with NPC are RT alone for the early stage and concurrent radiochemotherapy (CCRT) for the advanced stage. These treatment are performed based on the current Tumor–Node–Metastasis (TNM) staging system.[6] However, an extreme variation of clinical outcomes has been reported among the patients with NPC with the same stage who receive similar treatment regimen.[7,8] This phenomenon suggests that the TNM staging system is far from a perfect tool for prognostic prediction and therapeutic decision, because it only accounts for the tumor size and extension (T stage), lymph node involvement (N stage), and distant metastasis (M stage), without considering other factors with prognostic values, such as demographic features, histological type, and clinical treatment. Moreover, the TNM staging system divides patients into various groups but fails to evaluate the individualized risk of survival outcomes.[9] Given that the prognosis of malignant patients is determined multifactorially, to develop an accurate tool that can help for the individualized risk classification and decision-making in clinic practice is urgent.

As a simple and convenient mathematical model, nomograms have been widely used in clinical practice through intuitive visual presentation. A nomogram can take the weight of each relevant factor into consideration and integrate the independent factors to predict a numerical probability of a special clinical event for individual patients over time.[10] Compared with the TNM staging system, several advantages have been found in nomograms, such as accurate estimation, strong discrimination, and user-friendliness. Several built nomograms are useful in the management of patients with NPC.[11–13] To the best of our knowledge, nomograms for patients with NPC based on the population-based data have not been reported. In the present study, we aimed to develop and validate a nomogram for the prognostic prediction of patients with NPC based on a multi-institution and multi-population data from the Surveillance, Epidemiology, and End Results (SEER) dataset. We also compared the performance of this nomogram with the currently used American Joint Committee on Cancer (AJCC) staging system for NPC.

2. Materials and methods

2.1. Patients

With the help of SEER*Stat software (version 8.3.5, National Cancer Institute, Bethesda, MD), we collected the detailed data on patients diagnosed with NPC (site recode International Classification of Disease for Oncology, 3rd Edition [ICD-O-3]/ World Health Organization [WHO] 2008 of "nasopharynx" and behavior recode ICD-O-3 of "malignant") from the SEER program of the National Cancer Institute.[14] The SEER program provides data on cancer incidence, prevalence, and mortality in the United States, and covers 28% of the US population from 18 cancer registries. We only included cases from 2004 to 2015 because the SEER database comprises detailed stage information (2004 AJCC 6th and 2010 AJCC 7th) collected since 2004. Patients with insufficient or unknown data were excluded. Given that the SEER database was publicly accessible, Institutional Review Board approval was not required for the present study. We have received permission from the SEER registry to access the data (authorization number: 15709-Nov2017).

2.2. Variables

Demographic, clinicopathologic, and therapeutic variables were retrieved from the SEER database, including age, sex, race, marital status, grade, histological type, tumor stage (T stage), nodal stage (N stage), metastatic stage (M stage), clinical stage (TNM stage), RT, chemotherapy, follow-up time, and survival outcome. The 7th edition of AJCC staging system was applied to the patients in this study, whereas patients reported on the 6th edition were also converted to the 7th edition. Histological types of the patients with NPC were divided into four groups according to the WHO classification scheme by using the ICD-O-3 codes: keratinizing squamous cell carcinoma (KSCC, ICD-O codes 8070 and 8071), differentiated non-keratinizing carcinoma (DNKC, ICD-O codes 8072 and 8073), undifferentiated non-keratinizing carcinoma (UNKC, ICD-O codes 8020, 8021, and 8082), and others (carcinoma not otherwise specified [NOS]; ICD-O code 8010).[15] The primary endpoint was overall survival (OS), defined as the interval from diagnosis of NPC to death from any cause or the last follow-up.

2.3. Construction of the nomogram

Eligible patients were randomly divided into either the training or validation set with the split ratio of 7:3. The data of the training set were used to perform the survival analysis and establish the nomogram, whereas those from the validation set were applied to validate the prediction model. We included age (continuous variable), sex (male or female), race (White, Black, Asian/Pacific Islander, or American Indian/Alaskan Native), marital status (married, single, or others), grade (well differentiated, moderately differentiated, poorly differentiated, or undifferentiated), histological type (KSCC, DNKC, UNKC, or others), T stage (T1, T2, T3, or T4), N stage (N0, N1, N2, or N3), M stage (M0 or M1), RT (yes or no), and chemotherapy (yes or no/unknown) as covariates in the regression model. Univariate and multivariate Cox regression analyses were conducted to identify the significant prognostic factors of OS by the backward stepwise method. Clinical stage (I, II, III, or IV) overlapping with the variables of T, N, and M stages were not included in the multivariate analysis. A nomogram for predicting 3-, 5-, and 10-year survival probability of patients with NPC was constructed based on the outcomes of the multivariate analysis.

2.4. Validation of the nomogram

The performance of the nomogram was first quantified in the training cohort and then in the validation cohort with respect to discrimination, calibration, and clinical utility.

The discrimination performances of the nomogram were quantitatively assessed by the concordance index (C-index) and the area under curve (AUC) of the receiver operating characteristic (ROC) curve.[16] Both C-index and AUC ranged from 0.5 to 1, with 1 indicating perfect discrimination and 0.5 indicating no discrimination. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to determine the overall improvement in the predictive accuracy of patients by using the nomogram in place of the traditional TNM staging system. NRI refers to the difference in proportions of patients with events correctly assigned a higher probability and patients without events correctly assigned a low probability by an updated model compared with the initial model.[17] IDI represents the improvement in average sensitivity (i.e., the true positive rate) without reducing the average specificity (i.e., the true negative rate) of a new model compared with that of a baseline model.[18] The nomogram calibration was investigated from the graphical representations of the consistency of the predicted probabilities and the observed outcomes based on 1000 bootstrap resamples.[19] Finally, we conducted the decision curve analysis (DCA) to validate the clinical values of the nomogram and the traditional TNM staging system, which is a method for assessing whether the clinical usefulness of prediction models increased the net benefits when realistic threshold probabilities were considered.[20,21] These analyses were conducted by using R version 3.5.1 (http://www.r-project.org/), and a two-sided P value < .05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

A total of 13,620 patients diagnosed with NPC as the primary cancer were retrieved from the SEER database. After a strict filtration, 9927 cases were excluded because of unknown clinicopathological information or inaccurate staging according to the AJCC TNM classification. Finally, 3693 patients were included in the present study, of which 2585 and 1108 cases comprised the training cohort and the validation cohort, respectively. Of the whole cohort, 1497 (40.5%) patients had died at the end of the follow-up with a median follow-up period of 34 months. The 3-, 5-, and 10-year survival rates of the entire cohort were 66.7%, 57.9%, and 44.2%, respectively. The age ranged from 7 years to 92 years with a median of 55 years. The majority of the patients were male (70.7%), married (61.4%), underwent RT (87.1%), and received chemotherapy (81.1%). With regard to grade, 115 (3.1%) patients were well differentiated, 519 (14.1%) patients were moderately differentiated, 1591 (43.1%) patients were poorly differentiated, and 1468 (39.7%) patients were undifferentiated. The most common histological type was KSCC (35.5%), followed by UNKC (22.7%), DNKC (21.5%), and others (20.3%). The proportion of Stage I, Stage II, Stage III, and Stage IV was 9.5% (351/3594), 23.6% (870/3693), 29.9% (1104/3693), and 37.0% (1368/3693), respectively. The characteristics of the patients in the training set and validation set are shown in Table 1.

3.2. Survival analysis and nomogram development

The outcomes of univariate and multivariate analyses in the training set were shown in Table 2. Based on the data of the

training set, the multivariate analyses showed that age, sex, race, marital status, histological type, T stage, N stage, M stage, RT, and chemotherapy were the key predictive factors for OS, indicating statistical significance (Table 2).

Table 1

Patient characteristics of the training cohort and the validation cohort (n = 3693).

Characteristics	Training cohort (n = 2585)		Validation cohort (n = 1108)	
	Number of patients	%	Number of patients	%
Age (years)				
≤19	81	3.1	30	2.7
20–39	286	11.1	158	14.3
40–59	1225	47.4	537	48.5
60–79	884	34.2	328	29.6
≥80	109	4.2	55	5.0
Sex				
Male	1817	70.3	793	71.6
Female	768	29.7	315	28.4
Race				
White	1290	49.9	525	47.4
Black	311	12.0	130	11.7
Asian/Pacific Islander	944	36.6	437	39.4
American Indian/ Alaska Native	40	1.5	16	1.4
Marital status				
Married	1594	61.7	674	60.8
Single	423	16.3	185	16.7
Others	568	22.0	249	22.5
Grade				
Well differentiated	80	3.1	35	3.2
Moderate differentiated	367	14.2	152	13.7
Poorly differentiated	1156	44.7	435	39.3
Undifferentiated	982	38.0	486	43.8
Histological type				
KSCC	932	36.1	378	34.1
DNKC	556	21.5	237	21.4
UNKC	558	21.6	282	25.5
Other	539	20.9	211	19.0
T stage				
T1	826	32.0	351	31.7
T2	648	25.1	273	24.6
T3	539	20.9	240	21.7
T4	572	22.0	244	22.0
N stage				
N0	737	28.5	297	26.8
N1	853	33.0	357	32.2
N2	681	26.4	313	28.3
N3	314	12.1	141	12.7
M stage				
M0	2301	89.0	1003	90.5
M1	284	11.0	105	9.5
Clinical stage				
I	248	9.6	103	9.3
II	613	23.7	257	23.2
III	758	29.3	346	31.2
IV	966	37.4	402	36.3
Radiation				
No	332	12.8	143	12.9
Yes	2253	87.2	965	87.1
Chemotherapy				
No/unknown	479	18.5	220	19.9
Yes	2106	81.5	888	80.1

DNKC = differentiated non-keratinizing carcinoma, KSCC = keratinizing squamous cell carcinoma, UNKC = undifferential non-keratinizing carcinoma.

Table 2

Univariate and multivariate Cox regression analyses of the training cohort.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (continuous variable)	1.036 (1.031–1.040)	<.001	1.035 (1.029–1.040)	<.001
Sex				
Male	Reference		Reference	
Female	0.838 (0.730–0.961)	.011	0.806 (0.701–0.928)	.003
Race				
White	Reference		Reference	
Black	1.014 (0.845–1.217)	.882	1.050 (0.870–1.267)	.612
Asian/Pacific Islander	0.603 (0.525–0.694)	<.001	0.810 (0.697–0.940)	.006
American Indian/Alaska Native	1.078 (0.674–1.723)	.754	1.266 (0.788–2.034)	.329
Marital status				
Married	Reference		Reference	
Single	1.160 (0.994–1.355)	.060	1.541 (1.306–1.819)	<.001
Others	1.909 (1.642–2.219)	<.001	1.653 (1.413–1.934)	<.001
Grade				
Well differential	Reference		Reference	
Moderate differential	1.162 (0.829–1.631)	.384	1.291 (0.915–1.823)	.146
Poorly differential	0.739 (0.536–1.020)	.066	1.052 (0.757–1.461)	.765
Undifferential	0.465 (0.334–0.646)	<.001	1.137 (0.791–1.634)	.490
Histological type				
KSCC	Reference		Reference	
DNKC	0.583 (0.493–0.689)	<.001	0.699 (0.585–0.836)	<.001
UNKC	0.409 (0.341–0.490)	<.001	0.569 (0.443–0.732)	<.001
Other	0.706 (0.602–0.829)	<.001	0.830 (0.695–0.990)	.038
T stage				
T1	Reference		Reference	
T2	1.331 (1.118–1.585)	.001	1.307 (1.95–1.559)	.003
T3	1.776 (1.491–2.116)	<.001	1.860 (1.553–2.226)	<.001
T4	2.343 (1.980–2.773)	<.001	2.469 (2.065–2.953)	<.001
N stage				
N0	Reference		Reference	
N1	1.133 (0.724–1.383)	.319	1.058 (0.895–1.251)	.510
N2	1.012 (0.917–1.043)	.108	1.158 (0.970–1.383)	.115
N3	1.261 (1.080–1.473)	<.001	1.459 (1.177–1.808)	.001
M stage				
M0	Reference		Reference	
M1	2.967 (2.538–3.468)	<.001	2.294 (1.932–2.724)	<.001
Clinical stage[*]				
I	Reference		–	–
II	1.056 (0.806–1.385)	.691	–	–
III	1.451 (1.122–1.877)	.005	–	–
IV	2.599 (2.031–3.325)	<.001	–	–
Radiotherapy				
No	Reference		Reference	
Yes	0.281 (0.242–0.326)	<.001	0.389 (0.328–0.461)	<.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.626 (0.542–0.723)	<.001	0.706 (0.592–0.842)	<.001

CI = confidence interval, HR = hazard ratio.

[*] We did not include clinical stage into the multivariate analysis because it overlapped with the T, N, and M stages.
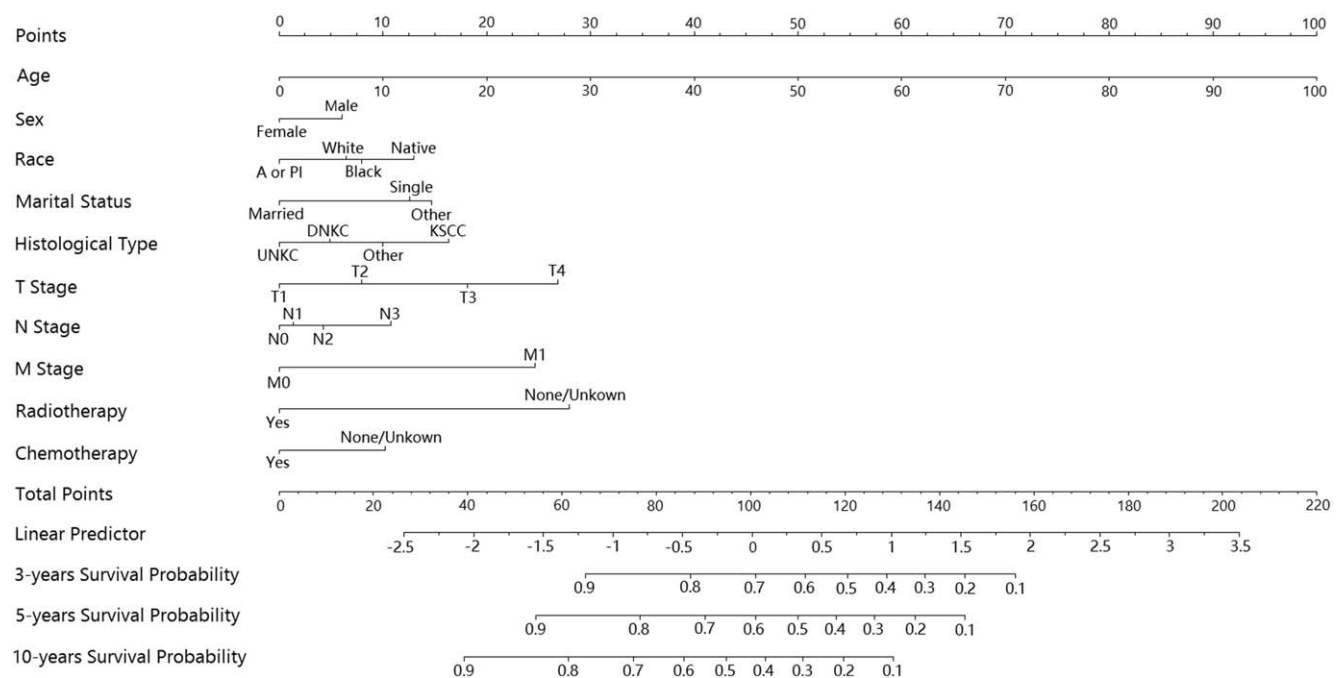
A nomogram for predicting 3-, 5-, and 10-year OS was constructed based on these significant variables in the training set (Fig. 1). By adding up the scores associated with each variable, and projecting total scores to the bottom scale, OS probabilities could be estimated at 3-, 5-, and 10-year time points.

3.3. Nomogram validation

With respect to the training cohort, the nomogram provided a higher C-index for OS prediction (0.754, 95% CI: 0.738–0.770)

than the AJCC 7th staging system (0.61, 95% CI: 0.59–0.63; *P* < .001). Similarly, the C-index of the validation set (0.763, 95% CI: 0.741–0.785) was also superior to that of the AJCC 7th staging system (0.61; 95% CI: 0.58–0.64; *P* < .001). These results implied that the nomogram was more robust than the existing AJCC staging system.

Moreover, we compared the predictive ability of these two models by calculating the AUC of the ROC curves. The outcomes demonstrated that the nomogram had a better predictive ability than the AJCC 7th staging system concerning the 3-, 5-, and 10-

Figure 1. Nomogram for predicting 3-, 5-, and 10-year overall survival of patients with nasopharyngeal carcinoma. A or PI = Asian/Pacific Islander, DNKC = differentiated nonkeratinizing carcinoma, KSCC = keratinizing squamous cell carcinoma, UNKC = undifferentiated nonkeratinizing carcinoma.

year OS in either the training set (Fig. 2A–2C) or the validation set (Fig. 2D–F).

The results of NRI and IDI calculations were depicted in Table 3. The usage of multiple variables to construct a comprehensive nomogram significantly improved the risk reclassification for 3-, 5-, and 10-year overall mortality prediction compared with the AJCC 7th staging system in both sets.

The calibration plots exhibited an excellent consistency between the observed probability and the nomogram's prediction with respect to the 3-, 5-, and 10-year OS in the training (Fig. 3A–3C) and validation sets (Fig. 3D–F). This finding suggested the appreciable reliability of the nomogram.

In addition, DCA exhibited preferable net benefit along with the threshold probability in the formulated nomogram compared with the AJCC 7th staging system at different time points (Fig. 4), indicating the favorable clinical utility of the nomogram.

4. Discussion

In this era of personalized cancer therapy, to determine whether an individual patient is at the risk of adverse clinical outcomes is important so that he/she can receive the most appropriate treatment. The practical application of the TNM staging system is restricted because it only provides risk stratification at a population level without offering an association between the individual patient and his/her corresponding prognosis. In contrast, the nomogram can serve as a scoring system and a visualized predicting tool to help physicians in easily matching patients with their expected OS through a simple calculation in clinical practice. In the present study, we establish a comprehensive and convenient nomogram to predict the OS probability at different time points for patients with NPC by using a large patient cohort from the SEER database. Validating the nomogram is essential to ensure that it can be applied generally and to

avoid overfitting. Compared with the commonly used AJCC 7th staging system, the current nomogram showed excellent predictive accuracy and discriminative ability. NRI and IDI also quantitatively proved that this comprehensive nomogram has a significantly increased likelihood of unfavorable OS identification, which is more effective than the traditional TNM classification. However, perfect predictive accuracy is not the same as usefulness in clinical practice. When the threshold probabilities of the net benefit are impractical, a model with good performance may also have limited applicability.[22] Therefore, we applied the DCA curves to investigate the clinic validity of our nomogram. In the DCA curve, the horizontal and vertical axes represent the probability threshold and the net benefit, respectively. The 3-, 5-, and 10-year DCA curves showed that the nomogram produces clinical net benefits in the training and validation cohorts, indicating that in can guide clinical interventions for patients.[23]

The classic TNM staging system depends purely on the anatomical extent of the malignancy and has ignored the effect of other variables on patients' survival. These issues can impair the predictive efficiency of NPC prognosis. The comprehensive model can completely reflect the intratumor heterogeneity of patients and quantify noninvasively and quantitatively the risk on a macroscopic scale by combining and illustrating the relative importance of various prognostic factors.[24] Thus, the nomogram represents a superior performance than the traditional staging system. Moreover, our nomogram can predict the survival probability at 3-, 5-, and 10-year time points that can be useful for a reasonable follow-up schedule.

Improved accuracy of a model comes at the expense of additional complexity. To balance the tradeoffs between comprehensiveness and comprehensibility during the modeling for nomograms is hard. Thus, we only collect practical variables with clinical importance, high reproducibility, and low time-
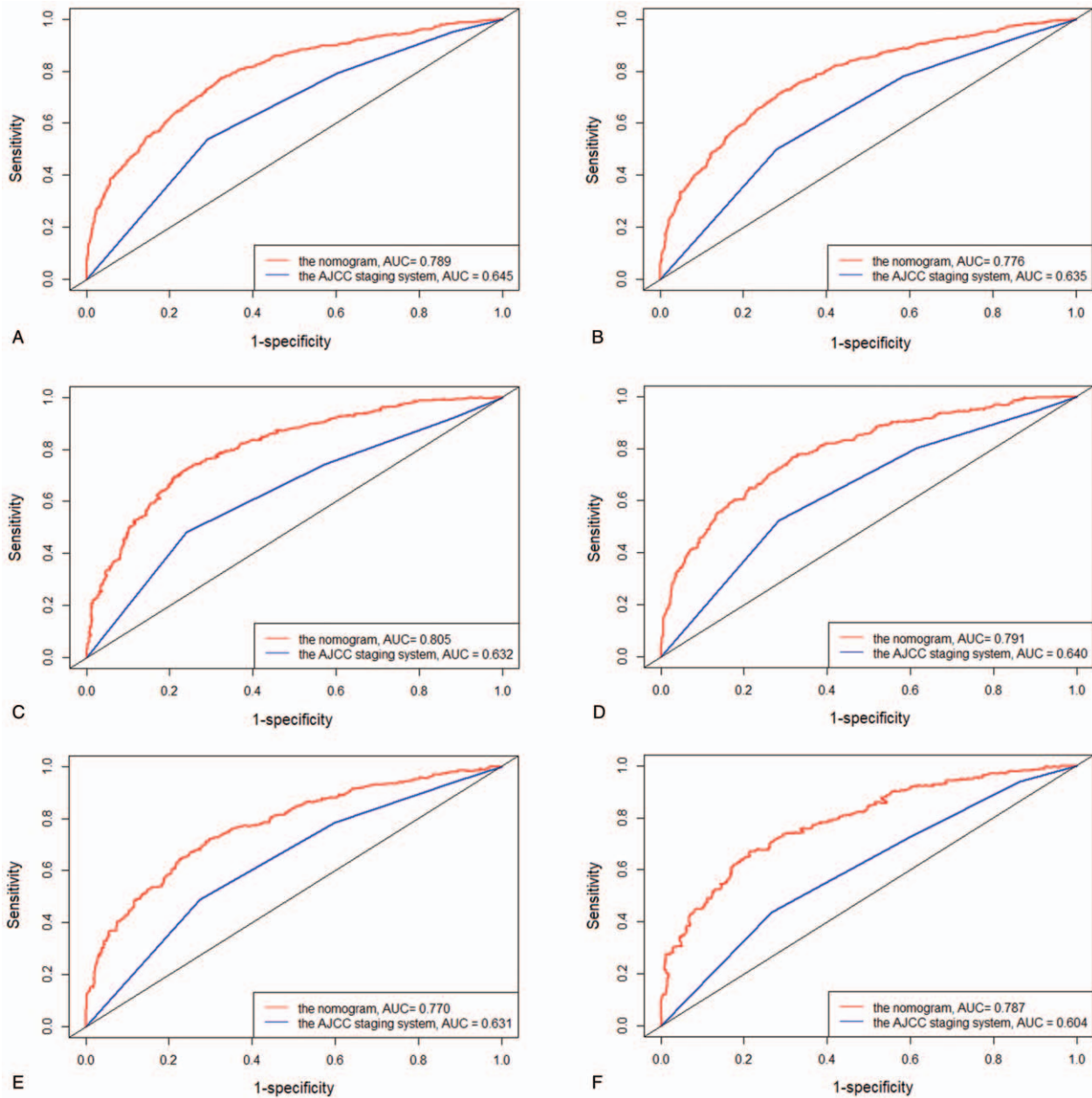
Figure 2. Time-dependent receiver operating characteristics curves of nomogram and AJCC staging system. (A) 3-year, (B) 5-year, (C) 10-year overall survival in training set; (D) 3-year, (E) 5-year, (F) 10-year overall survival in validation set.

Table 3

The net reclassification improvement and integrated discrimination improvement of the nomogram compared to the AJCC 7th staging system.

| Category	NRI (95% CI)	P	IDI (95% CI)	P
Training set				
3-year OS	0.692 (0.612–0.803)	<.001	0.165	<.001
5-year OS	0.658 (0.593–0.773)	<.001	0.176	<.001
10-year OS	0.740 (0.634–0.878)	<.001	0.174	<.001
Validation set				
3-year OS	0.732 (0.601–0.846)	<.001	0.180	<.001
5-year OS	0.682 (0.584–0.940)	<.001	0.199	<.001
10-year OS	0.764 (0.614–0.921)	<.001	0.194	<.001

CI = confidence interval, IDI = integrated discrimination improvement, NRI = net reclassification improvement, OS = overall survival.
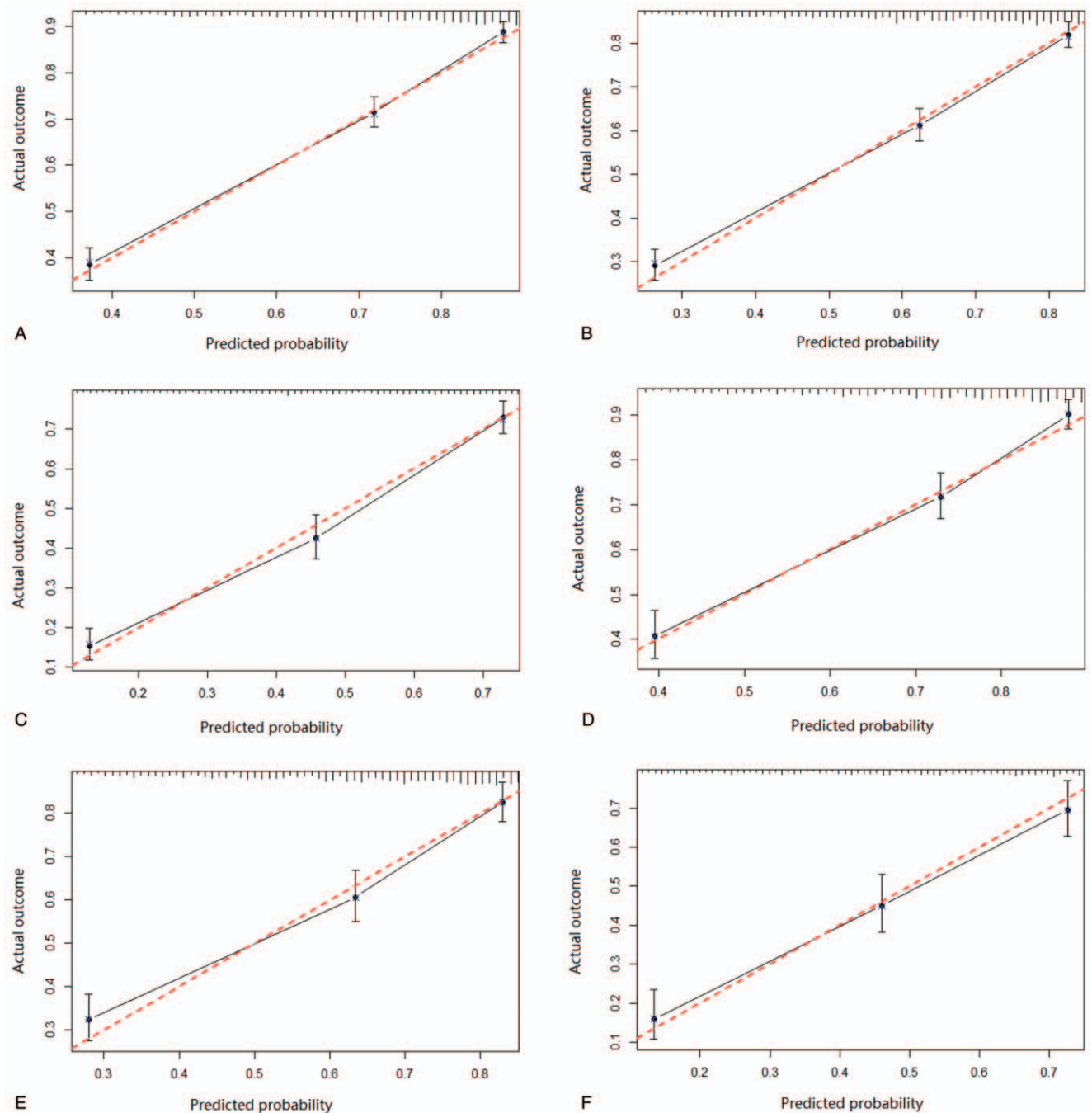
Figure 3. Calibration plots of nomogram. (A) 3-year, (B) 5-year, (C) 10-year overall survival in training set; (D) 3-year, (E) 5-year, (F) 10-year overall survival in validation set.

varying effects. After controlling for confounding factors, we have identified 10 independent prognostic factors, including age, sex, race, marital status, histological type, T stage, N stage, M stage, RT, and chemotherapy, to build the predictive model. Here, we declared several novel findings. First, the old patients with NPC signify the high risk of overall mortality, which is in line with previous studies.[25,26] However, these previous studies treated patients' age as a categorical variable, resulting in the loss of some valuable information to some degree. Second, Asian and Pacific Islander patients have a survival advantage compared with the other races, including the White and Black populations.

The epidermal growth factor receptor gene polymorphisms may help explain these racial differences.[27] Third, a married status induces a survival benefit that is often explained by psychosocial factors. Married individuals are likely to have a positive mode to overcome the mental pressure caused by an illness and exhibit high compliance and tolerance to anticancer therapy because their married status provides additional emotional and financial support.[28] Moreover, spousal supervision and family relations may help married patients in maintaining a positive lifestyle. Fourth, up to 35.5% of the patients with NPC in the US presented a histological type of keratinizing disease. This proportion was
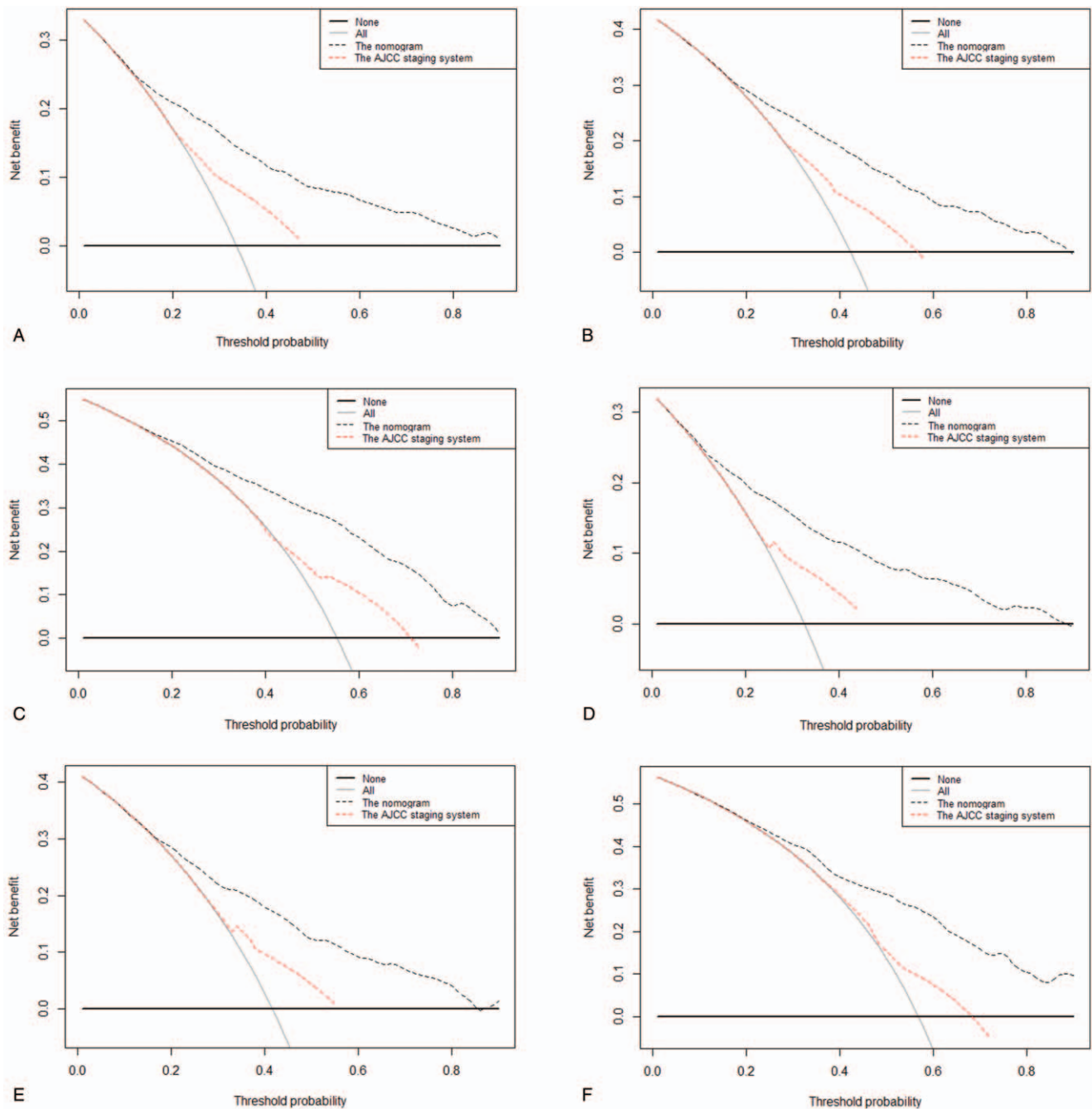
Figure 4. Decision curve analyses of nomogram and AJCC staging system. (A) 3-year, (B) 5-year, (C) 10-year overall survival in training set; (D) 3-year, (E) 5-year, (F) 10-year overall survival in validation set.

higher than that in the Chinese patients.[29] Finally, over 60% of the patients in our study were at advanced stages. This phenomenon may be attributed to the difficulty of early diagnosis in NPC.

As for NPC, several nomograms had been established based on different research objectives. Tang[30] enrolled 4630 patients with nondisseminated NPC to construct nomograms with or without plasma EBV DNA for predicting 3- and 5-year disease-free survival, and the proposed nomograms provided statistically significantly better discrimination than the TNM classification. Cho[31] designed nomograms in response to RT and OS based on

the clinical data of 270 NPC patients, and the nomograms showed perfect matches to the independent data set through an external validation process. Huang[32] included 7251 NPC patients undergoing intensity-modulated RT to create predictive models for the probabilities of NPC-related and other cause-specific mortality, respectively. These nomograms offered effective tools for the management of patients with NPC, providing patient counseling and clinical assessment. Compared with the abovementioned predictive models, the formulated nomogram in the present study showed the following strengths. First, this nomogram is the first established for NPC prognosis on

the basis of population-based data from multiple institutes rather than on the information of endemic patients from a single center of Eastern Asia. Second, the variables identified by our nomogram are easily obtained and can reflect the common status of patients and disease activity, providing clinically relevant information in NPC. Third, predicting the survival probability over 10 years is important for a nomogram because a large proportion of patients with NPC can achieve a relatively long survival time due to the improvement of medical technology. Fourth, this nomogram has a good ethnical representation because it was created based on the racially diverse population. Finally, our study is the first to consider marital status in nomogram construction.

The limitations of this study should be acknowledged. First, a selection bias might be observed due to the retrospective nature and the inclusion of patients with complete information. Second, several valuable variables that influence the survival outcome of patients with NPC, such as EBV infection, genetic predisposition, and tumor biomarkers, were unavailable from the SEER database, leading to a potential impairment of the nomogram effectiveness. Third, although we included the RT and chemotherapy as predictive factors into the nomogram, other important pieces of information, including therapeutic regimen, dosage, and duration time, were not provided by the SEER dataset. Thus, we were unable to evaluate their impact on the survival outcome. Fourth, local recurrence is the main cause of treatment failure for NPC, but the SEER database did not contain this information. Finally, the nomogram of our study was built based on the US population because of the lack of external validation. Its generalization to the global population, especially patients with NPC in epidemic areas, was still unclear.

5. Conclusion

We developed a nomogram to predict the probability of OS in patients with NPC based on a large, population-based cohort with long-term follow-up. Compared with the 7th edition of AJCC staging system, this nomogram had a perfect performance in predictive accuracy, discrimination capability, and clinical utility in inferring individuals' risk of all-cause mortality and guiding personalized treatment for those patients. Therefore, the nomogram could be used as a practical tool to predict prognosis at different time points. Owing to the limitations of this study, subsequent works must provide well-designed, multi-institutional, and prospective validation process to remedy the above-mentioned limitations and achieve a high level of evidence.

Author contributions

Conceptualization: Liren Hu, Jun Lyu.
Data curation: Jiayuan Wu, Quan Zhou, Yufeng Wang.
Formal analysis: Jiayuan Wu, Zhenyu Pan.
Methodology: Guanghua Chen, Jun Lyu, Shengpeng Wang.
Validation: Jiayuan Wu, Zhenyu Pan, Liren Hu, Guanghua Chen, Jun Lyu, Shengpeng Wang.
Visualization: Quan Zhou, Jun Lyu.
Writing – original draft: Jiayuan Wu, Quan Zhou.
Writing – review & editing: Zhenyu Pan, Yufeng Wang, Liren Hu, Jun Lyu.
Jun Lyu orcid: 0000-0002-2237-8771.
Shengpeng Wang orcid: 0000-0002-4818-4895.
Guanghua Chen orcid: 0000-0002-8877-1322.

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