Risk Stratification and Individualized Chemotherapy for Elderly Patients with Locoregionally Advanced Nasopharyngeal Carcinoma

Jia Kou
Sun Yat-sen University Cancer Center
Lu-Lu Zhang
Sun Yat-sen University Cancer Center
Dan-Wan Wen
Sun Yat-sen University Cancer Center
Guan-Qun Zhou
Sun Yat-sen University Cancer Center
Chen-Fei Wu
Sun Yat-sen University Cancer Center
Si-Si Xu
Sun Yat-sen University Cancer Center
Xing-Li Yang
Sun Yat-sen University Cancer Center
Wei-Hong Zheng
Sun Yat-sen University Cancer Center
Zhen-Yu Qi
Sun Yat-sen University Cancer Center
Ying Sun
Sun Yat-sen University Cancer Center
Li Lin (linli@sysyucc.org.cn)
Sun Yat-sen University Cancer Center https://orcid.org/0000-0003-1052-1566

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Abstract

Backgroud: The optimal treatment strategy for elderly patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC) remains unclear. We aimed to develop individualized treatment strategies for such patients according to their pretreatment risk stratification and the degree of comorbidities.

Methods: A total of 583 elderly LA-NPC patients diagnosed between January 2011 and January 2018 were retrospectively studied. Based on prognostic factors confirmed by multivariate analysis, we constructed a nomogram for disease-free survival (DFS). The entire cohort was then divided into two groups according to the nomogram cutoff value determined by X-tile analysis. The degree of comorbidities was assessed by Charlson Comorbidity Index (CCI). We performed subgroup analysis based on the degree of complications in the low- and high-risk groups to compare the survival outcomes of different treatment regimens using the Kaplan-Meier method and the log-rank test.

Results: A nomogram for DFS was constructed with T/N classification, Epstein-Barr virus DNA and albumin. The high-risk group had significantly poorer survival compared with the low-risk group. The 3-year DFS and overall survival (OS) of the low-risk group and the high-risk group were 76.7% vs. 44.6%, 81.5% vs. 51.0% (both P<0.001) respectively. Only high-risk patients with fewer comorbidities (CCI =2) would benefit from induction chemotherapy combined with concurrent chemoradiotherapy, while patients in the low-risk group or the high-risk group with more comorbidities (CCI >2) would not have.

Conclusion: We constructed a prognostic nomogram for DFS and generated two risk groups. Combining risk stratification and degree of comorbidities can better guide individualized treatment for elderly LA-NPC patients.

Introduction

Nasopharyngeal carcinoma (NPC) is a special type of head and neck cancer with a high incidence in Southern China and Southeast Asia [1, 2]. The age distribution of NPC is unimodal in endemic areas (45–59 years old), while the age distribution is bimodal in non-endemic areas (15–24 years old, 65–79 years old) [3]. With an aging population and the extension of life expectancy, the number of elderly NPC patients will increase [4]. In addition, elderly patients have a higher risk of NPC-related mortality compared with younger patients [5]. Therefore, the management of this cohort needs to be taken seriously.

Despite the long-term survival for patients diagnosed in the early stages, up to 80% of patients with newly diagnosed NPC present with locoregionally advanced (LA) disease as the initial symptoms are innocuous and the location of the primary tumor is hidden. These patients have an unsatisfactory outcome with a 5-year OS of 70%-80% [6, 7]. Radiotherapy combined with platinum-based chemotherapy is recommended as the standard treatment regimen for LA-NPC patients. These treatment strategies are recommended by international guidelines from the results of several clinical trials [8–11]. However, limited elderly patients

were included in these trials due to strict inclusion criteria. Therefore, whether elderly patients with LA-NPC will benefit from such recommendations remains unclear.

Due to the intrinsic biological heterogeneity of tumors, accurate risk stratification prior to treatment is necessary for more considered decisions. At present, the most commonly used risk predictor for NPC is the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system [12]. However, the TNM staging system only takes anatomical information into account and does not fully reflect intra-tumor heterogeneity. More additional prognostic indicators need to be incorporated to improve the performance of the TNM staging system. In endemic areas, NPC is highly associated with Epstein-Barr virus (EBV) infection. Cell-free (cf) EBV DNA released into the circulatory system by tumor cells can be detected by real-time quantitative polymerase chain reaction (PCR)-based assays [13, 14]. Pretreatment cf EBV DNA load, can reflect tumor burden and is associated with patient survival [15–18], it is now widely used in clinical practice as an ideal prognostic indicator. Moreover, there are other hematological biomarkers (e.g. C-reactive protein [CRP], serum lactate dehydrogenase [LDH], hemoglobin [HGB], albumin [ALB]) that have demonstrated clinical utility for prognostication [19–23].

Comorbidities are also an important factor when developing treatment strategies, especially for the elderly, they are more likely to have co-existing ailments and decreasing organ function. Patients with severe comorbidities are unable to tolerate intensive treatment and are vulnerable to treatment-related complications and death from noncancerous diseases [22, 24, 25]. All of these issues affect the formulation of treatment strategies and the final survival outcome of patients.

Against this background, in this study, we constructed a pretreatment prognostic nomogram for elderly LA-NPC patients by combining the TNM staging system, cf EBV DNA and other clinical factors. We propose individualized treatment schemes according to the degrees of complications and risk classification determined by the nomogram.

Materials And Methods

Data extraction and patient selection

Since 2015, Sun Yat-sen University Cancer Center (SYSUCC) has established an automatic and dynamic big data intelligence platform that updates and integrates detailed electronic health record data extracted from daily healthcare systems. This allows oncologists to select eligible patients accurately, extract examination and therapeutic information, as well as, track the follow-up of patients. Using this platform, we reviewed a total of 804 elderly patients (³65 years old) with histologically proven and non-disseminated NPC who were newly diagnosed between January 2011 and January 2018. All patients were restaged according to the 8th edition of the AJCC/UICC staging system.

The inclusion criteria were: (a) stage III-IVa NPC patients undergoing radical radiotherapy (RT) ± induction chemotherapy (IC) / concurrent chemoradiotherapy (CCRT); (b) complete clinicopathologic and treatment

data; and (c) without adjuvant chemotherapy. This study was approved by the institutional review board, and informed consent waived as this retrospective study was based on an analysis of patients' routine clinical and treatment data.

Examinations and treatment protocols

All patients underwent baseline examinations before initiating treatment. The severity of comorbidity at diagnosis was determined by the Charlson Comorbidity Index (CCI), which was first introduced in 1987 and contains nineteen medical conditions, and age factors with a weighted score based on the adjusted risk of one-year mortality [26]. The sum of all the weighted scores give a single comorbidity score for each patient. A score of zero indicates no comorbidities were found. The higher the score, the more likely the predicted outcome will result in higher resource use or mortality. For every decade the patient was over 40 years old 1 point was added to risk and the “age points” added to the CCI score, no patient scored less than 2 in this study.

In this study, all patients received radical radiotherapy. The prescribed doses ranged from 60 to 70Gy with the daily fraction dose ranging from 2.00 to 2.43 Gy, five times a week for 6–7 weeks. Chemotherapy was not administered in some patients due to patient and family refusal or contraindication from medical comorbidities. Details of the examinations and chemotherapy protocols are described in the Supplementary Methods.

Follow-up and endpoints

Patients attended follow-up appointments at least every 3 months for the first 3 years after the end of treatment, and then every 6 months thereafter until death. Follow-up duration was calculated from the day of treatment initiation to last day of contact or death. The primary endpoint was disease-free survival (DFS, defined as the time from treatment initiation to the first failure or death from any cause). The secondary endpoint was overall survival (OS, defined as the time from the date of treatment initiation to death from any cause).

Statistical analysis

The CCI was divided into categorical variables based on a cutoff value determined by receiver operating characteristic (ROC) analysis. Other continuous variables were converted into categorical variables according to clinical cutoff points (ALB, LDH, HGB, and CRP) or findings reported in previous studies (cf EBV DNA load) [27, 28]. Cumulative survival rates were estimated using the Kaplan-Meier method and compared using the log-rank tests. Multivariate COX regression analysis was performed to define DFS predictors, then a forest plot was generated to demonstrate the results of the multivariate analysis.

The nomogram for DFS was then developed and based on significant prognostic factors from the multivariate Cox regression analysis. The calibration curves, which indicated the calibration ability of the nomogram, were assessed graphically by plotting the actual observed survival rates against the nomogram-predicted survival rates via a bootstrap method with 1,000 resamples. The discrimination

performance of the nomograms were measured quantitatively by Harrell's concordance indices (C-index), which were was measured using R software (version 3.4.3.) and the Hmisc package. Moreover, we compared the prognostic performance of the nomogram model, significant prognostic factors from the multivariate analysis and the 8th AJCC/UICC TNM staging system using C-index and the area under the ROC curve (AUC).

We used the X-tile software (version 3.6.1; Yale University School of Medicine, New Haven, CT, USA) to determine the optimal cutoff value of the nomogram and to divide the entire cohort into high-risk and low-risk groups. The Pearson χ2 test or Fisher's exact test was applied to assess the basic characteristics of the two groups. In order to develop the individualized treatment regimen for elderly LA-NPC patients, we performed a subgroup analysis according to the severity of complications in the two groups to compare RT alone, IC+RT, CCRT and IC+CCRT. All statistical analyses were performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) or the rms package in RStudio version 1.3.1093, unless otherwise specified. Statistical significance was set at a two-tailed P <0.05.

Results

Patient characteristics and follow-up

A total of 583 eligible patients were included in this retrospective analysis (the flowchart of patient inclusion is shown in **Figure 1**). The baseline characteristics of these patients are shown in **Table 1**. The median age at diagnosis was 68 years old (65-91 years old). Of the 583 patients, 42.7% (249/583) had a CCI score of 2 and 57.3% (334/583) had a CCI score above 2.

The median follow-up duration of the entire cohort was 47.1 months (2.7-149.5 months). During the follow-up period, 61 (10.5%) and 104 (17.8%) patients developed locoregional relapses and distant metastases, respectively; and 196 (33.6%) patients died from any cause. The detailed cause of death are described in the Supplementary Results. The 3-year and 5-year DFS for the entire cohort were 69.8% and 60.3%, respectively. The 3-year and 5-year OS for the entire cohort were 79.1% and 65.8%, respectively.

Development and validation of nomograms for DFS

Multivariate Cox regression analysis demonstrated that T classification, N classification, pretreatment cf EBV DNA load and ALB were significantly associated with DFS (**Figure 2**). The prognostic nomogram combining all of the aforementioned validated predictors for 3- and 5-year DFS in the 583 elderly LA-NPC patients are presented in **Figure 3a**. The point assignment is described in detail in **Table S1**. Calibration plots presented an excellent agreement between the nomogram predicted DFS and the actual observed DFS (**Figure 3b-c**). The C-index of the nomogram (0.668; 95% CI, 0.633-0.703) was significantly better than cf EBV DNA load (0.619; 95% CI, 0.587-0.652; *P* <0.001), the 8th edition of the TNM staging system (0.585; 95% CI, 0.552-0.618; *P* <0.001), T classification (0.561; 95% CI, 0.528-0.595; *P* <0.001), N classification (0.584; 95% CI, 0.548-0.620; *P* <0.001) and ALB (0.549; 95% CI, 0.520-0.578; *P* <0.001) in predicting DFS (**Table 2**).

The ROC analysis proved that the nomogram was superior to the other clinical factors in predicting DFS (**Table 2** and **Figure S1**). The AUC of the nomogram (0.710; 95% CI, 0.671-0.746) was higher than that of EBV DNA (0.656; 95% CI, 0.617-0.695; *P* <0.001), the 8th edition of TNM staging system (0.607; 95% CI, 0.567-0.647; *P* <0.001), T classification (0.588; 95% CI, 0.547-0.628; *P* <0.001), N classification (0.590; 95% CI, 0.549-0.630; *P* <0.001) and ALB (0.558; 95% CI, 0.517-0.599; *P* <0.001).

Risk stratification based on the nomogram

According to the results of X-tile software (**Figure S2**), a nomogram score of 114 was the optimal cutoff value for predicting DFS and the entire cohort was divided into high-risk (*n* =283) and low-risk groups (*n* =300). The clinical characteristics of patients in both groups are detailed in **Table S2**. The patients in the high-risk group presented poorer survival outcomes compared with those in the low-risk group at all survival endpoints. The 3-year DFS of the low-risk group and the high-risk group were 82.7% and 56.9%; and the 5-year DFS of the low-risk group and the high-risk group were 76.7% and 45.4% (*P* <0.001, **Figure 4a**). The 3-year OS of the low-risk group and the high-risk group were 89.5% and 69.2%; and the 5-year OS of the low-risk group and the high-risk group were 81.5% and 51.6% (*P* <0.001, **Figure 4b**).

Individualized therapeutic strategies based on the nomogram and CCI

A CCI score of 2 was determined as optimal cutoff value for DFS prediction by using ROC analysis, and CCI was converted into a categorical variable according to this threshold. Next, we performed subgroup analysis based on the severity of complications in the low- and high-risk groups to explore optimal treatment regimens. In the low-risk group with a CCI =2, no significant differences in survival outcome were observed among the RT alone, CCRT, IC+RT and IC+CCRT (3-year DFS: 82.3% *vs.* 82.5% *vs.* 71.4% *vs.* 77.8%, all *P* >0.05; 3-year OS: 85.6% *vs.* 86.1% *vs.* 85.7% *vs.* 90.0%, all *P* >0.05; **Figure 5a-b**). Similarly, in the low-risk group with a CCI >2, no significant differences in survival outcome were observed among the four treatment regimens (3-year DFS: 80.1% *vs.* 86.8% *vs.* 100.0% *vs.* 81.0%, all *P* >0.05; 3-year OS: 87.8% *vs.* 89.0% *vs.* 100.0% *vs.* 88.9%, all *P* >0.05; **Figure 5c-d**).

In the high-risk group, the patients with a CCI =2 who received IC+CCRT were significantly superior to those who received the other three treatment regimens in terms of DFS (3-year DFS: IC+CCRT *vs.* RT alone, 82.8% *vs.* 44.8%, *P* =0.002; IC+CCRT *vs.* IC+RT 82.8% *vs.* 60.2%, *P* =0.028; IC+CCRT *vs.* CCRT, 82.8% *vs.* 61.1%, *P* =0.022; **Figure 5e**); and significantly superior to RT alone and CCRT in terms of OS (3-year OS: IC+CCRT *vs.* RT alone, 86.9% *vs.* 62.1%, *P* =0.011; IC+CCRT *vs.* CCRT, 86.9% *vs.* 66.5%, *P* =0.009; **Figure 5f**). But there was no significant difference in OS between IC+CCRT and IC+RT (3-year OS, 86.9% *vs.* 81.1%, *P* =0.222; **Figure 5f**); and no significant differences in DFS and OS among the RT alone, CCRT and IC+ RT (3-year DFS: 44.8% *vs.* 61.1% *vs.* 60.2%, all *P* >0.05; 3-year OS: 62.1% *vs.* 66.5% *vs.* 81.1%, all *P* >0.05; **Figure 5e-f**). For the patients with a CCI >2, there were no significant differences among the RT alone, CCRT, IC+RT and IC+CCRT in term of DFS and OS (3-year DFS: 41.4% *vs.* 53.6% *vs.* 64.9% *vs.* 52.8%, all *P* >0.05; 3-year OS: 57.2% *vs.* 63.9% *vs.* 73.7% *vs.* 60.6%, all *P* >0.05; **Figure 5g-h**).

Discussion

Elderly patients with LA-NPC have an unsatisfactory survival outcome and current treatment guidelines have mostly been designed based on clinical trials with limited elderly patients inclusion [8, 29–31]. Therefore, whether elderly LA-NPC patients will benefit from treatment strategies recommended by guidelines remains unclear. In this study, we constructed a prognostic nomogram in elderly LA-NPC patients by incorporating the T classification, N classification, pretreatment cf EBV DNA load and other clinical prognostic factors that reflect intra-tumor heterogeneity and improve prognostic efficacy compared with the traditional staging system. We further explored optimal treatment strategies for elderly LA-NPC patients based on risk-stratification generated by the nomogram and the degree of comorbidities. To our knowledge, this is the first study to propose risk-adapted treatment for elderly LA-NPC patients by combining comorbidities of patients with pre-treatment prognostic models.

At present, cumulative retrospective studies have explored treatment strategies for elderly patients with LA-NPC. In the era of conventional two-dimensional radiotherapy (2D-RT), Liu and Zeng et al. reported that chemotherapy combined with radiotherapy improved survival for elderly LA-NPC patients compared with radiotherapy alone [32, 33]. However, with the development of radiotherapy technology and the wide application of IMRT in clinical practice, several retrospective studies have shown no survival benefit from the addition of chemotherapy in elderly LA-NPC patients receiving IMRT [34–36]. In terms of combination strategies of chemotherapy and radiotherapy, a retrospective study found no significant survival difference between CCRT and IC + RT [37]; and another study showed no significant survival benefit from adding IC to CCRT [38]. Notably, all the above retrospective studies were conducted in whole cohorts of elderly LA-NPC patients, thereby ignoring the intrinsic biological heterogeneity of tumors; which is an important factor influencing treatment decisions. Due to tumor heterogeneity, patients with the same TNM stage, who receive the same treatment regimen have markedly different survival outcomes; which reminds us that intra-tumor heterogeneity should be taken into account when identifying true high-risk patients who would benefit from a high-intensity treatment regimen.

Therefore, in this present study, the TNM staging system, pre-treatment cf EBV DNA load and various other clinical factors were comprehensively considered in order to create a risk classification to develop risk-adapted treatment strategies for elderly LA-NPC patients. Multivariate Cox regression analysis demonstrated that T classification, N classification, pretreatment cf EBV DNA load and ALB were independently associated with DFS. The TNM staging system, which well reflects tumor load, is widely recognized and the most commonly used pre-treatment risk stratification system. In addition, pretreatment cf EBV DNA load is a biomarker that can reflect tumor load and biological heterogeneity, and is considered complementary the TNM staging system [16]. A previous study by Lv et al. supported the concept of utilizing cf EBV DNA for individualization of chemotherapy intensity in patients with LA-NPC [39]. Our results suggest that lower ALB levels are associated with poorer survival in elderly LA-NPC patients. Low ALB levels, to some extent, reflect malnutrition and have been associated with poor outcomes in cancer patients [25, 40].

Next, we developed a prognostic nomogram by integrating T classification, N classification, pretreatment cf EBV DNA load and ALB. The high-risk and low-risk groups generated by the nomogram had significantly different survival outcomes. Compared with the TNM staging system and the above significant risk predictors, the prognostic nomogram model has better prognostic efficacy and could screen out high-risk patients who would benefit from intensive treatment.

It is well-known that elderly patients are associated with declining physiological function and an increasing comorbidity rate, which can alter the pharmacokinetics of many commonly used chemotherapeutic agents, thereby, decreasing sensitivity to radiotherapy and chemotherapy [41–44]. The value of comorbidities in guiding treatment decisions for patients with NPC has been determined in recent years [33, 45]. Based on the risk stratification generated by the prognostic nomogram, we further considered the influence of comorbidity on treatment decisions. In this study, we used CCI scores to describe degrees of patient's complications [26]. The results showed that only patients in the high-risk group with a CCI = 2 could benefit from the additional chemotherapy, and patients receiving the IC + CCRT had better survival than those receiving RT alone, CCRT and IC + RT. However, our results did not show improved survival benefit from additional chemotherapy for high-risk patients with a CCI > 2 and low-risk patients. A study by Liu et al. also reported that additional chemotherapy significantly improved the 5-year OS in elderly patients with LA-NPC, but not in those with more complications [33]. This is because severe comorbidities may increase the toxicity of specific treatments and shorten remaining life expectancy gained from therapy.

Our study has several limitations. Firstly, the treatment protocols of patients have a certain heterogeneity due to physician biases, which are unavoidable in retrospective studies. To best address this, we excluded patients who received a non-standard treatment regimen, and tried to keep the treatment intensity and regimens consistent. Yet, the advantages of retrospective studies is that they can reflect the treatments outcomes in real-world scenarios. Secondly, no data on treatment-related toxicity was reported in our study. Although our results show only 11% of elderly patients died from therapeutic toxicity, treatment-related toxicity is not negligible in determining chemotherapy due to fact that elderly patients may value quality of life over the extension of life. Taken together, our results should be treated cautiously and verified in a well-designed prospective clinical study.

Conclusion

In conclusion, we constructed a prognostic nomogram for DFS in elderly patients with LA-NPC by incorporating T classification, N classification, cf EBV DNA load and ALB. By combining risk stratification generated by the nomogram and degree of comorbidities, we can tailor individual risk-adaption treatment for elderly LA-NPC patients. High-risk patients with a CCI = 2 may benefit from IC + CCRT, while high-risk patients with a CCI > 2 and low-risk patients are unlikely to benefit from an intensive treatment regimen.

Abbreviations

LA-NPC, locoregionally advanced nasopharyngeal carcinoma; AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; TNM, tumor-node-metastasis staging system; ROC, receiver operating characteristic analysis; AUC, the are under the ROC curve; DFS, disease-free survival; OS, overall survival; CCI, Charlson Comorbidity Index; cf, Cell-free; EBV, Epstein-Barr virus; LDH, serum lactate dehydrogenase level; HGB, hemoglobin; CRP, C-reactive protein; ALB, albumin; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board, and the requirement to obtain informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets during the current study have been deposited in the Research Data Deposit public platform (www.researchdata.org.cn) and are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Study concept and design: Jia Kou, Li Lin, Ying Sun.

Data acquisition: Jia Kou, Li Lin, Guan-Qun Zhou, Ying Sun.

Data analysis and interpretation: Jia Kou, Li Lin, Cheng-Yang Jiao,, Meng-Qiu Tian, Xue Jiang.

Manuscript preparation: Jia Kou, Li Lin.

Critical revision: All authors.

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Tables

Table 1. Clinicopathologic characteristics and univariate analysis of DFS in the 583 elderly patients with locoregionally advanced nasopharyngeal carcinoma.

Characteristics	Entire cohort No. (%)	*P*-value	HR (95% CI)
Age, years			
Median (range)	68 (65-91)	-	-
≤ 68	336 (57.6%)	-	-
> 68	247 (42.4%)	-	-
Gender			
Male	463 (79.4)		Ref.
Female	120 (20.6)	0.373	0.86 (0.61-1.20)
Histological type (WHO) [a]			
Type I-II	18 (3.1)		Ref.
Type III	565 (96.9)	0.749	1.14 (0.51-2.57)
Smoking			
Yes	232 (39.8)		Ref.
No	351 (60.2)	0.992	1.00 (0.77-1.30)
Drinking			
Yes	92 (15.8)		Ref.
No	491 (84.2)	0.970	0.99 (0.70-1.42)
Family history of NPC			
Yes	115 (19.7)		Ref.
No	468 (80.3)	0.321	0.84 (0.60-1.18)
EBV DNA, copies/mL [b]			
< 4000	320 (54.9)		Ref.
³ 4000	263 (45.1)	< 0.001	2.65 (2.03-3.47)
LDH, IU/L [b]			
≤ 250	540 (92.6)		Ref.
> 250	43 (7.4)	0.243	1.32 (0.83-2.12)
HGB, g/L [b]			

≤ 120	51 (8.7)		Ref.
> 120	532 (91.3)	0.024	0.63 (0.42-0.94)
CRP, mg/L [b]			
≤ 3	349 (59.9)		Ref.
> 3	234 (40.1)	0.043	1.31 (1.01-1.69)
ALB, g/L [b]			
≤ 40	117 (20.1)		Ref.
> 40	466 (79.9)	< 0.001	0.59 (0.44-0.78)
T classification [c]			
T1	19 (3.3)		Ref.
T2	18 (3.1)	0.683	1.24 (0.44-3.55)
T3	385 (66.0)	0.878	0.94 (0.44-2.02)
T4	161 (27.5)	0.146	1.77 (0.82-3.82)
N classification [c]			
N0	92 (15.8)		Ref.
N1	265 (45.5)	0.362	1.22 (0.80-1.87)
N2	138 (23.7)	0.003	1.97 (1.26-3.08)
N3	88 (15.1)	< 0.001	2.34 (1.46-3.77)
Overall stage [c]			
III	358 (61.4)	-	-
IVa	225 (38.6)	-	-
CCI [d]			
= 2	249 (42.7)	-	-
> 2	334 (57.3)	-	-
Treatment modality			
RT alone	240 (41.2)	-	-
CCRT	154 (26.4)	-	-

IC+RT	72 (12.3)	-	-
IC+CCRT	117 (20.1)	-	-

Abbreviations*:* No., number; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; Ref., reference; WHO, World Health Organization; CCI, Charlson Comorbidity Index; EBV, Epstein-Barr virus; LDH, serum lactate dehydrogenase level; HGB, hemoglobin; CRP, C-reactive protein; ALB, albumin; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

[a] WHO Type I, keratinizing, WHO Type II, non-keratinizing (differentiated), WHO Type III, non-keratinizing (undifferentiated).

[b] All variables were measured before treatment.

[c] According to the 8th edition of the AJCC/UICC staging system.

[d] Each decade of age over 40 would add 1 point to risk and the “age points” would be added to the score from the Charlson Comorbidity Index. Therefore, no patient in our study had a CCI score below 2.

Table 2. C-index and AUC of prognostic model and single risk factors for predicting DFS in elderly patients with LA-NPC

Risk factors	C-index (95% CI)	*P*-value	AUC (95% CI)	*P*-value
Prognostic models				
Nomogram	0.668 (0.633-0.703)	Ref.	0.710 (0.671-0.746)	Ref.
8th TNM staging system [a]	0.585 (0.552-0.618)	< 0.001	0.607 (0.567-0.647)	< 0.001
Single risk factors				
EBV DNA	0.619 (0.587-0.652)	< 0.001	0.656 (0.617-0.695)	< 0.001
T classification [a]	0.561 (0.528-0.595)	< 0.001	0.588 (0.547-0.628)	< 0.001
N classification [a]	0.584 (0.548-0.620)	< 0.001	0.590 (0.549-0.630)	< 0.001
ALB	0.549 (0.520-0.578)	< 0.001	0.558 (0.517-0.599)	< 0.001

Abbreviations: DFS, disease-free survival; C-index, Harrell’s concordance indices; AUC, area under the receiver operator characteristic curve; CI, confidence intervals; Ref., reference; EBV, Epstein-Barr virus; ALB, albumin; LA-NPC, locoregionally advanced nasopharyngeal carcinoma;

[a] According to the 8th edition of the AJCC/UICC staging system.

Figures

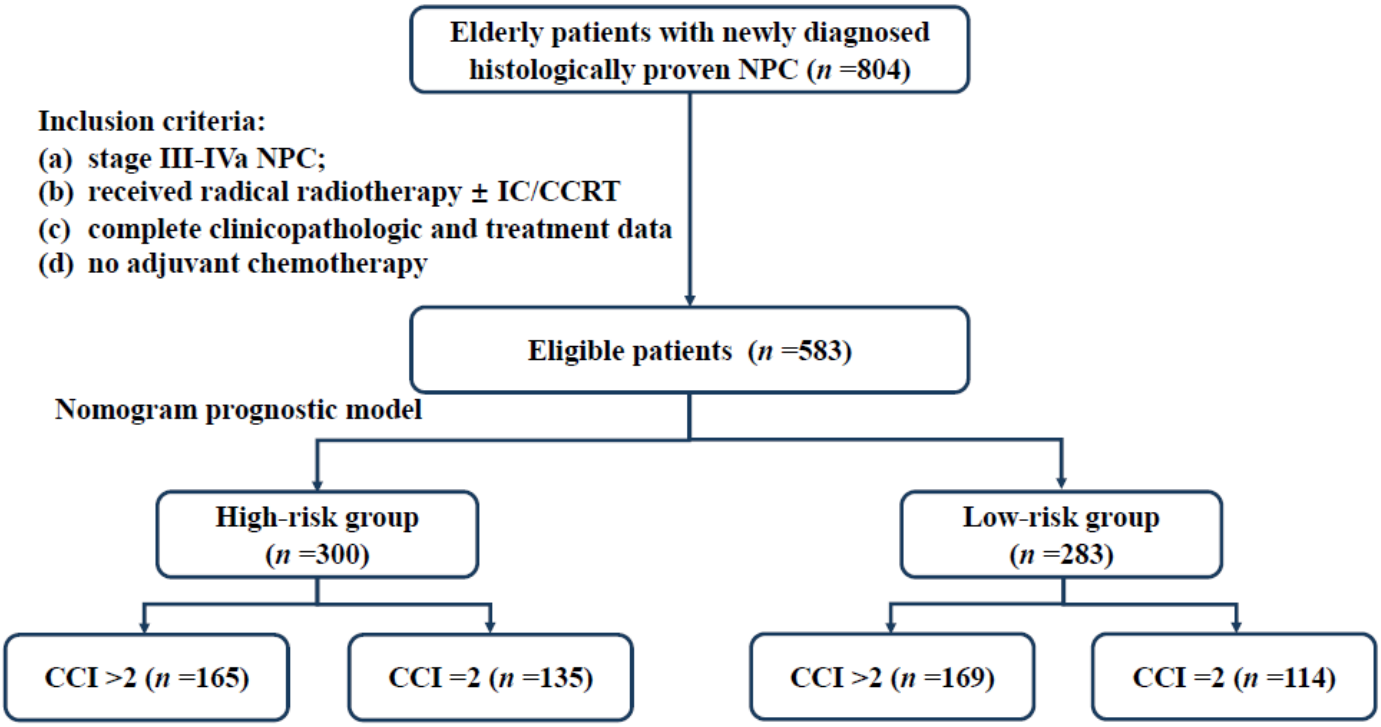

Figure 1

Flowchart of patients included in this study. NPC, nasopharyngeal carcinoma; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy.

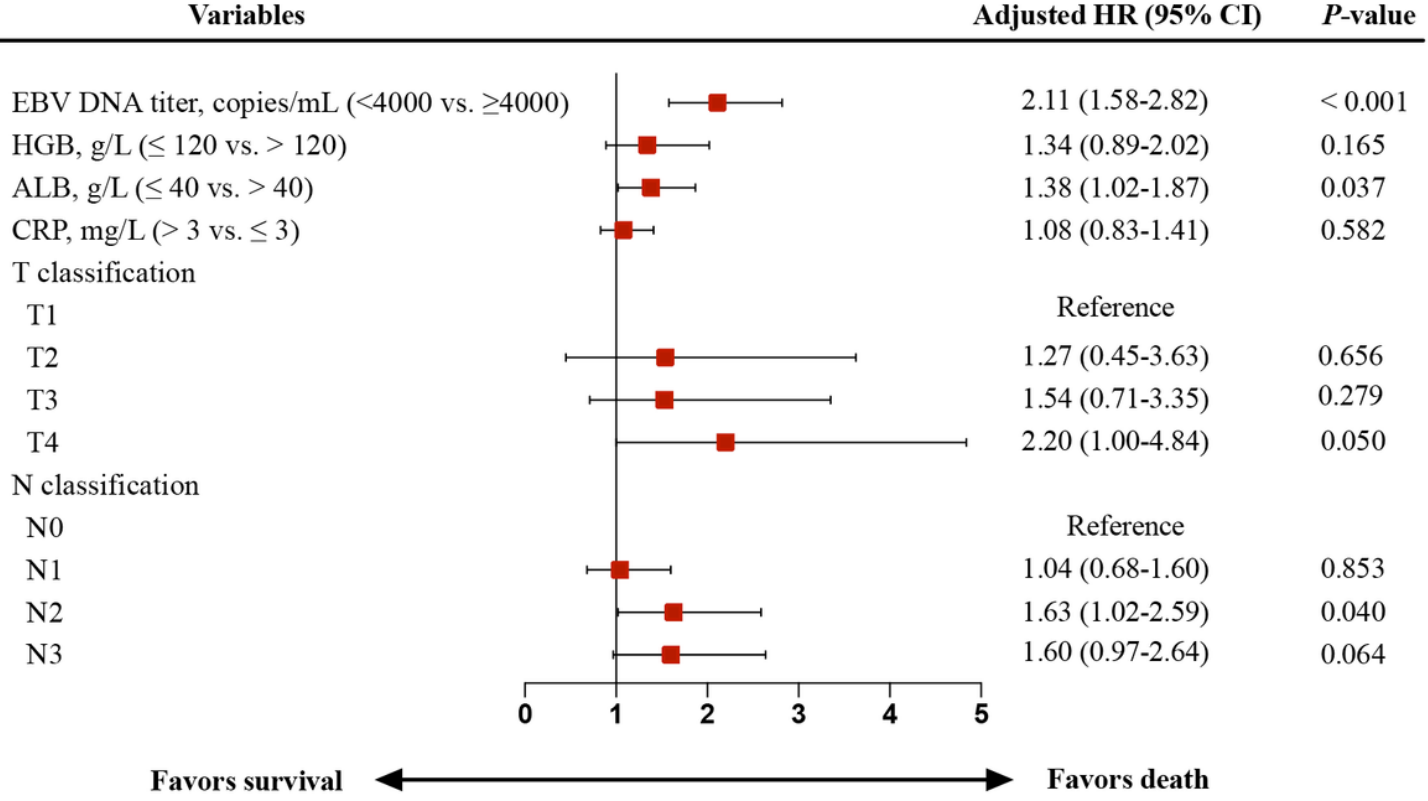

Figure 2

Forest plot showing the results of the multivariate analysis for DFS in elderly patients with LA-NPC. Red squares indicate HRs and horizontal bars indicate 95% CIs. LA-NPC, locoregionally advanced nasopharyngeal carcinoma; EBV, Epstein-Barr virus; DNA, deoxyribonucleic acid; HGB, hemoglobin; ALB, albumin; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval. DFS, disease-free survival.

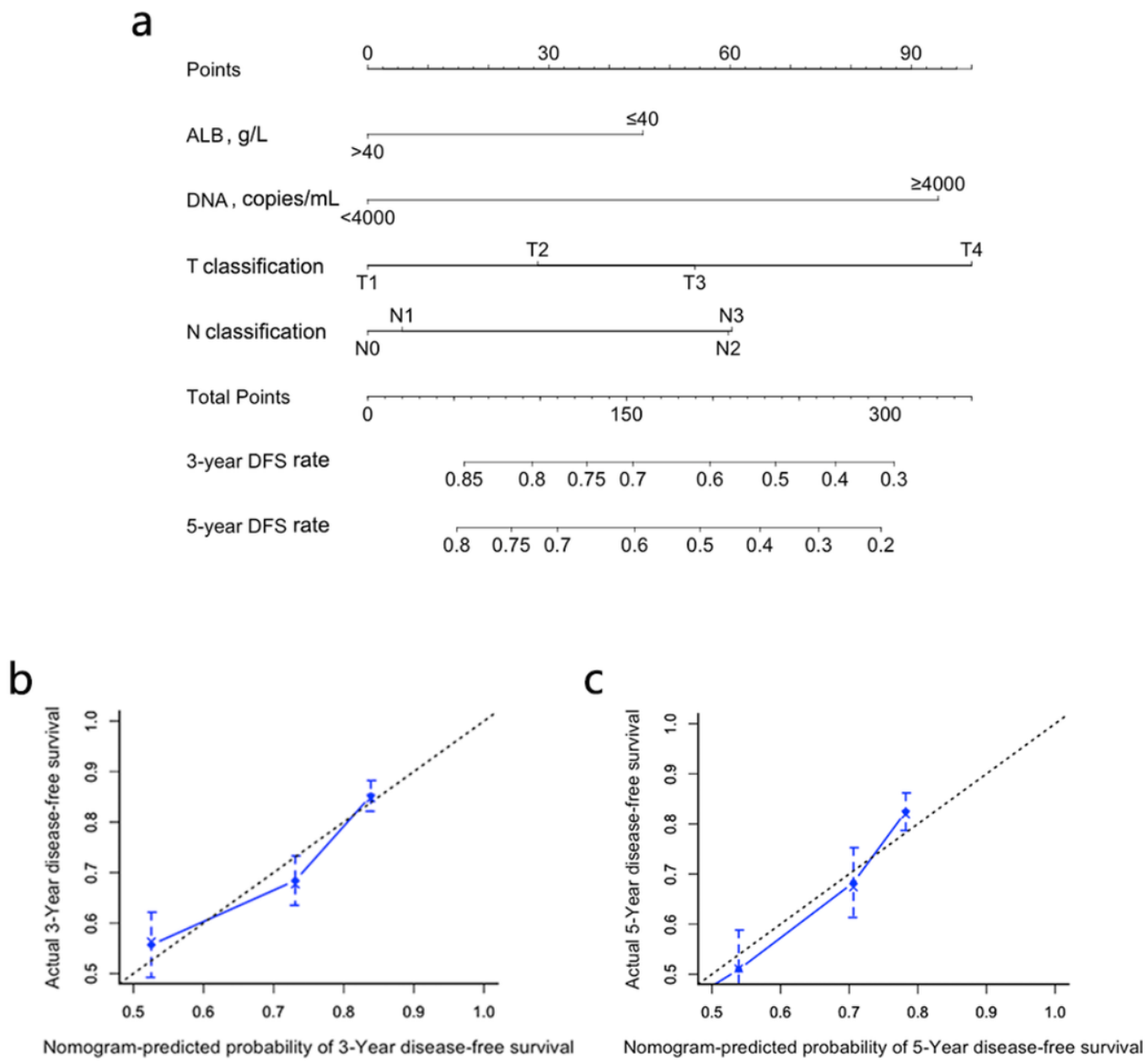

Figure 3

Prognostic nomogram (a) and calibration plots (b, c) for 3-year and 5-year DFS in elderly patients with LA-NPC. The X-axis represents the probability of 3-year DFS predicted by the nomogram, the Y-axis represents the actual observed probability of 3-year DFS. The dotted line indicates that the predicted and observed survival probability is consistent. NPC, nasopharyngeal carcinoma; EBV, Epstein-Barr virus; ALB, albumin; neutrophil-lymphocyte ratio; DFS, disease-free survival; OS, overall survival.

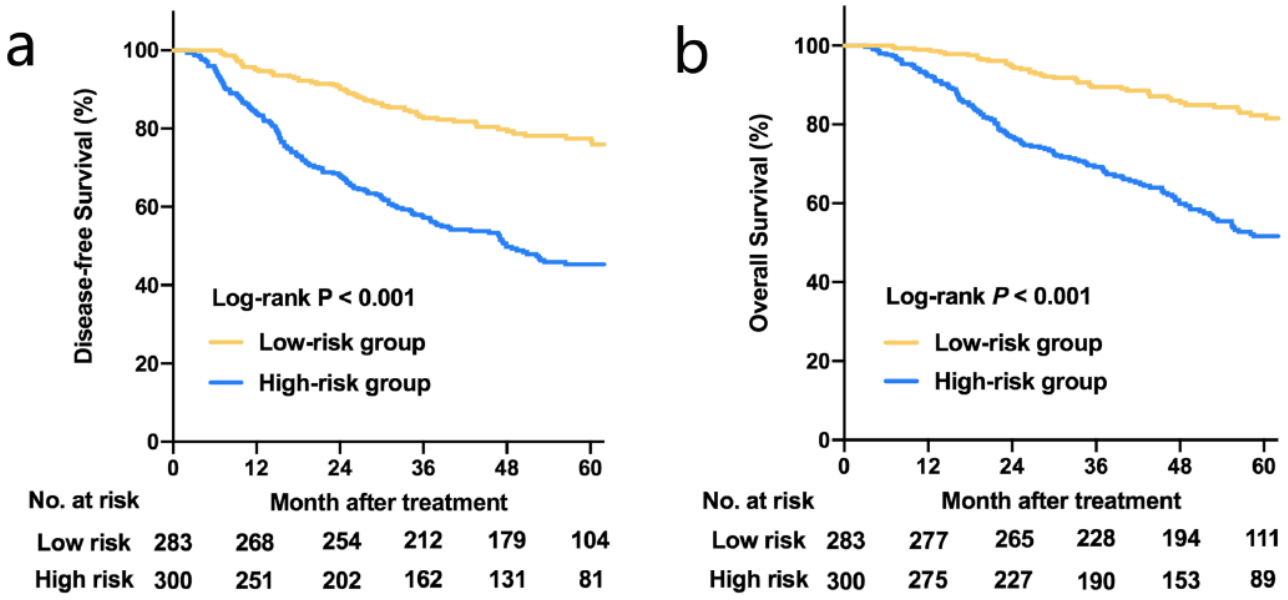

Figure 4

Survival outcomes of the high-risk and low-risk groups generated by the prognostic nomogram. Kaplan–Meier curves for DFS and OS for the two groups (a, b). RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy. DFS, disease-free survival; OS, overall survival.

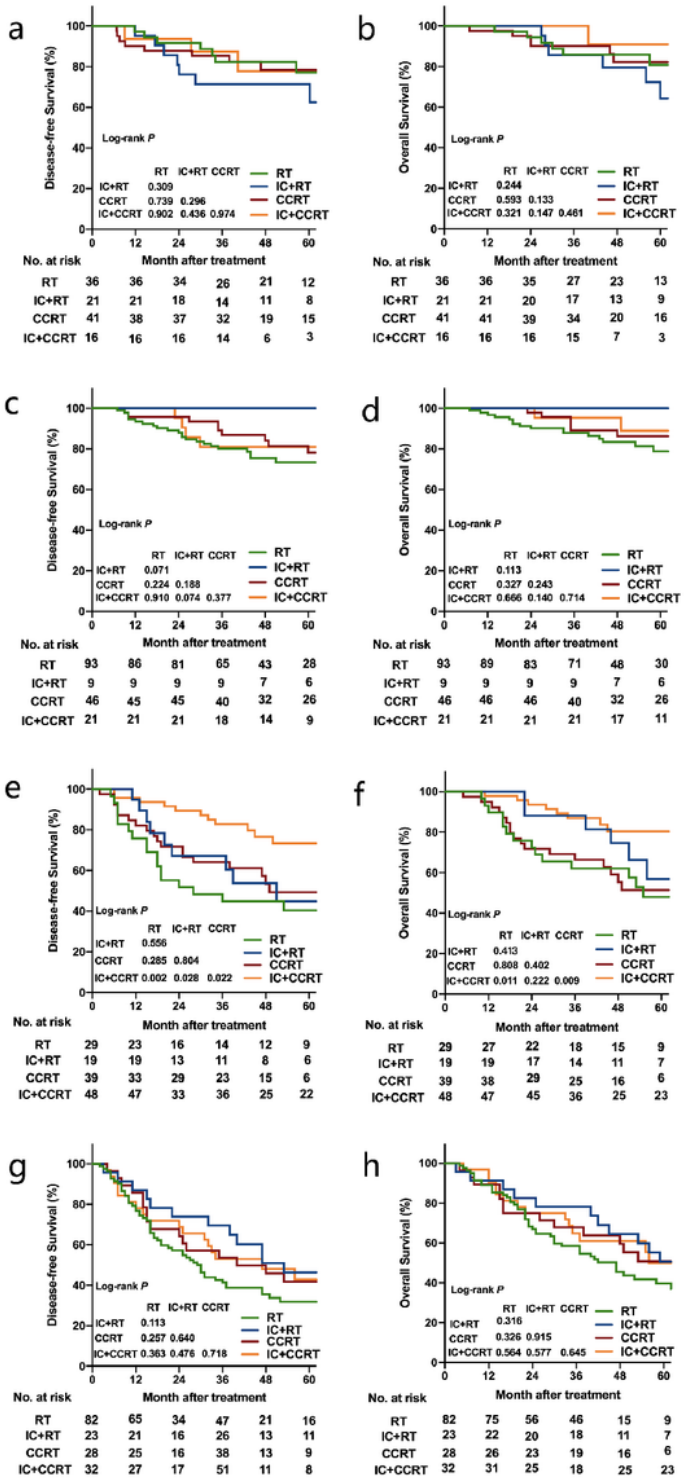

Figure 5

Kaplan-Meier DFS and OS curves of different treatment regimens in subgroups analysis. Survival outcomes of different treatment regimens in the low-risk groups with a CCI =2 (a, b), in the low-risk groups with a CCI >2 (c, d), in the high-risk groups with a CCI =2 (e, f) and in the high-risk groups with a CCI >2 (g, h); RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy. DFS, disease-free survival; OS, overall survival.

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