Original Article

Geriatric nutritional risk index as an independent prognostic factor in locally advanced nasopharyngeal carcinoma treated using radical concurrent chemoradiotherapy: a retrospective cohort study

Qing-Nan Tang[1,2#], Hui-Zhi Qiu[1,2#], Xiao-Qing Sun[1,3#], Shan-Shan Guo[1,2], Li-Ting Liu[1,2], Yue-Feng Wen[1,2], Sai-Lan Liu[1,2], Hao-Jun Xie[1,2], Yu-Jing Liang[1,2], Xue-Song Sun[1,2], Xiao-Yun Li[1,2], Jin-Jie Yan[1,2], Jin-Hao Yang[1,2], Dong-Xiang Wen[1,2], Ling Guo[1,2], Lin-Quan Tang[1,2], Qiu-Yan Chen[1,2], Hai-Qiang Mai[1,2]

[1]Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine; Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China; [2]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China; [3]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Contributions: (I) Conception and design: HQ Mai, QY Chen, LQ Tang, QN Tang; (II) Administrative support: HQ Mai, QY Chen, LQ Tang; (II) Provision of study materials or patients: QN Tang, HZ Qiu, XQ Sun, HQ Mai, QY Chen, LQ Tang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: QN Tang, HZ Qiu, XQ Sun, HQ Mai, QY Chen, LQ Tang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hai-Qiang Mai. Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China. Email: maihq@mail.sysu.edu.cn; Qiu-Yan Chen. Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China. Email: chenqy@sysucc.org.cn; Lin-Quan Tang. Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, China. Email: tanglq@sysucc.org.cn.

Background: Nutritional status is a key factor influencing the prognosis of patients with cancer. The Geriatric Nutritional Risk Index (GNRI) has been used to predict mortality risk and long-term outcomes. In this study, we aimed to evaluate the predictive value of pretreatment GNRI in patients with nasopharyngeal carcinoma (NPC).

Methods: A total of 1,065 patients with biopsy-proven non-disseminated nasopharyngeal carcinoma were included. Based on a cutoff value of pretreatment GNRI, patients were divided into two groups (low ≤107.7 and high >107.7). Combining GNRI and baseline Epstein-Barr virus (EBV) DNA, all patients were further stratified into three risk groups, namely, high-risk (high EBV DNA and low GNRI), low-risk (low EBV DNA and high GNRI), and medium-risk (except the above) groups. Multivariate analyses were performed using the Cox proportional hazards model to assess the predictive value of the GNRI.

Results: Among the 1,065 patients, 527 (49.5%) and 538 (50.5%) were divided into low and high GNRI groups, respectively. Within a median follow-up of 83 months, patients with a high GNRI score exhibited significantly higher overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS) compared to those with low GNRI scores (P<0.05). Multivariate analyses revealed that high GNRI is an independent prognostic factor for OS and PFS (hazard ratio, HR, 0.471, 95% CI, 0.270–0.822, P=0.008; HR 0.638, 95% CI, 0.433–0.941, P=0.023, respectively). Using a combination of baseline GNRI and EBV DNA, a satisfying separation of survival curves between different risk groups for OS, PFS, DMFS was observed. The survival rates of patients in the high-risk group were significantly lower than those in the low- and medium-risk groups (all P<0.001). The combined classification was demonstrated to be an independent prognostic factor for OS and PFS after adjustment using multivariate analysis.

Conclusions: Pretreatment GNRI is an independent prognostic factor for NPC patients. The combination of baseline GNRI score and EBV DNA level improved the prognostic stratification of

NPC patients.

Keywords: Nasopharyngeal carcinoma; Geriatric Nutritional Risk Index (GNRI); survival analysis; prognosis

Submitted Sep 18, 2020. Accepted for publication Jan 22, 2021.
doi: 10.21037/atm-20-6493
View this article at: http://dx.doi.org/10.21037/atm-20-6493

Introduction

Nasopharyngeal carcinoma (NPC) is an endemic malignancy of the head and neck that is prevalent in Southeast Asia and Southern China and is associated with high death rates (1,2). The mainstay treatment of NPC is radiotherapy. With the use of intensity-modulated radiation therapy (IMRT) and chemotherapy and the development of modern imaging techniques, the survival rate of patients with NPC has been significantly improved (3-6). However, a significant number of affected patients still exhibit locoregional relapse, adverse reactions to treatment, and distant metastasis, ultimately leading to death (7,8). Thus, the identification of prognostic factors as markers of risk stratification as well as the development of individualized therapeutic strategies may provide significant advances in the treatment of patients with NPC.

Epstein-Barr virus (EBV) DNA is correlated with high tumor burden and poor long-term survival of patients with NPC. Circulating cell-free EBV DNA has been established as a tumor marker and is used for screening, diagnosis, risk stratification, and predicting the prognosis of patients (9-11). Malnutrition is a prevalent clinical complication in patients with NPC, which has a negative impact on disease prognosis and quality of life (12). Screening patients with high nutrition risk is necessary to provide appropriate interventions to reduce malnutrition-related mortality and improve prognosis. The Geriatric Nutritional Risk Index (GNRI) is a straightforward nutrition measurement tool used in clinical practice (13) that integrates two parameters, namely, serum albumin concentration and current body weight, compared to the ideal body weight. Previous studies have reported that patients with low GNRI score (GNRI <98) exhibit a worse prognosis than those with a normal GNRI score (GNRI >98). Furthermore, the GNRI score is useful in the assessment of nutritional status and the prediction of long-term outcomes in patients with and without cancer (14-16). As GNRI was developed by modifying the nutritional risk index for elderly patients, most studies focus on the study of GNRI in the elderly. However, studies evaluating young adults have confirmed that GNRI assessment is valuable in the evaluation of the nutritional status in this population (15,17-20).

In this study, we aimed to evaluate the prognostic value of the GNRI score of patients with NPC and investigate the potential of GNRI as a reliable parameter in the management of these patients. Moreover, we studied the effect of EBV DNA in risk stratification to understand if the combined determination of GNRI and EBV DNA could improve risk stratification in patients with NPC.

We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6493).

Methods

Patients

Patient data were retrospectively analyzed and a total of 1,065 newly diagnosed patients with non-disseminated NPC from the Sun Yat-sen University Cancer Center (SYSUCC) between January 2009 and July 2014 were included in this study. The eligibility criteria included (I) newly-diagnosed patients with NPC without metastasis; (II) age ≥18 years; (III) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (IV) presence of NPC following the WHO histopathological type II or III grade; (V) treatment with IMRT and whole course concurrent chemotherapy (CCRT); (VI) availability of the complete medical history before treatment; (VII) availability of complete data with GNRI assessment and pretreatment plasma EBV DNA. Two patients with histopathological type I NPC, based on the WHO criteria, 9 patients who were lost to follow-up, and 11 patients with a history of other malignancies were excluded from this study. A total of 1,065 eligible patients were finally included. Categories are based on the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was

approved by ethics board of Sun Yat-sen University Cancer Center and individual consent for this retrospective analysis was waived.

Treatment

All patients were treated with CCRT. The concurrent chemotherapy regimen that was chosen was mainly platinum-based chemotherapy, with only cisplatin (80 mg/m^2) at weeks 1, 4, and 7 of the RT cycle or cisplatin 30–40 mg/m^2 weekly during radiotherapy, per the detailed regimens described as previous study (21). All patients received definitive radiotherapy in the form of IMRT. The IMRT plan followed the general design used at our institute (22). All patients were treated according to the treatment guidelines set for patients with NPC at SYSUCC.

GNRI calculation and EBV DNA detection

The data used for the calculation of the nutritional status were obtained within one week before treatment. GNRI was calculated as follows: 1.487 × serum albumin concentration (g/L) + 41.7 × present body weight/ideal body weight (kg). In this study, the ideal body weight was calculated from a body mass index (BMI) of 22 kg/m^2 and the patient's height as follows: ideal body weight = 22× square of height (m) (13). When the body weight of the patient exceeded the ideal body weight, the ratio between actual body weight and ideal body weight was set to 1. According to the median GNRI score, all patients were assigned to the low GNRI group (GNRI ≤107.7) or the high GNRI group (GNRI >107.7). Pretreatment peripheral blood was collected from patients for plasma EBV DNA detection. Blood was collected in ethylene diamine tetra-acetic-coated tubes and analyzed using real-time quantitative polymerase chain reaction as reported in previously published studies (23,24). Moreover, patients were assigned to two groups based on a cutoff value of 1,500 copies/mL as reported in a previous study (25).

Follow-up and clinical outcome assessment

After treatment, patients were assessed at outpatient clinics every three months for the first three years, and every six months, until death. The primary study endpoint was the overall survival (OS), and the secondary endpoints were progress-free survival (PFS), local-regional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). The definitions of these endpoints are as follows: OS, from the date of the first diagnosis of NPC to the date of death from any cause, or patient censoring at the date of the last follow-up; PFS, from the date of the first diagnosis of NPC to the date of the first progression at any site, or patient censoring at the date of the last follow-up; LRFS and DMFS, from the date of the first diagnosis of NPC to the date of locoregional relapse or distant metastasis, or patient censoring at the date of the last follow-up.

Statistical analysis

We classified categorical variables according to clinical findings and transformed continuous variables into categorical variables based on routine cutoff points or findings reported in previous studies (26,27). Chi-squared test or Fisher's exact test were used to analyze the clinical characteristics of the two GNRI groups. Kruskal-Wallis rank-sum test was used to analyze ranked data. PFS, OS, DMFS, and LRFS were calculated using the Kaplan-Meier method and the differences were compared using the log-rank test. Cox regression analysis was used to calculate both crude and adjusted hazard ratios with 95% confidence intervals. The covariates included gender, age, pathology, smoking history, the family of cancer, tumor stage, node stage, lactate dehydrogenase (LDH) levels, hemoglobin (HGB) levels, platelet (PLT) levels, serum albumin (ALB) levels, BMI, EBV DNA levels, and GNRI score. We used two-tailed tests and a P value <0.05 was considered statistically significant. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 25.0 software (IBM Corporation, Armonk, NY, USA).

Results

Clinical characteristics

Between January 2009 and July 2014, a total of 1,065 patients who were newly diagnosed with NPC were included in the study. The median duration of follow-up was 83 months (IQR, 72.1–90.5 months) and the median age of the whole study population was 45 years (IQR, 38–52 years). According to the median GNRI level (107.7, IQR, 104.1–110.6), patients were stratified into two groups with 527 (49.5%) in the high GNRI group and 538 (50.5%) in the low GNRI group. Patients in the low GNRI group had a higher proportion of women and the elderly (35.5% *vs.* 19.5%, 52.8% *vs.* 42.3%, respectively), higher levels of

plasm EBV DNA and T stage, lower levels of hemoglobin (HGB) and serum albumin (ALB), and lower body mass index (BMI) than those in the high GNRI group. The clinical background characteristics and laboratory findings of the patients are provided in *Table 1*.

Clinical outcomes

According to baseline EBV DNA level, patients were divided into two groups: high EBV DNA group (>1,500 copies/mL) and low EBV DNA group (≤1,500 copies/mL).

Table 1 NPC patient history and clinical features, according to GNRI

Variables	Low GNRI group n=538 (%)	High GNRI group n=527 (%)	P value
Gender			
Female	191 (35.5)	103 (19.5)	<0.001
Male	347 (64.5)	424 (80.5)	
Age			
≤45	254 (47.2)	304 (57.7)	0.001
>45	284 (52.8)	223 (42.3)	
Pathology			
Type II	13 (2.4)	20 (3.8)	0.194
Type III	525 (97.6)	507 (96.2)	
Smoking history			
No	357 (66.4)	338 (64.1)	0.447
Yes	181 (33.6)	189 (35.9)	
Family of cancer			
No	391 (72.7)	377 (71.5)	0.678
YES	147 (27.3)	150 (28.5)	
T stage			
T1	20 (3.7)	38 (7.2)	0.017
T2	98 (18.2)	113 (21.4)	
T3	330 (61.3)	307 (58.3)	
T4	90 (16.7)	69 (13.1)	
N stage			
N0	73 (13.6)	76 (14.4)	0.764
N1	230 (42.8)	230 (43.6)	
N2	195 (36.2)	190 (36.1)	
N3	40 (7.4)	31 (5.9)	
Clinical stage			
I	2 (0.4)	1 (0.2)	0.209
II	57 (10.6)	70 (13.3)	
III	354 (65.8)	360 (68.3)	
IVA	92 (17.1)	68 (12.9)	
IVB	33 (6.1)	28 (5.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Low GNRI group n=538 (%)	High GNRI group n=527 (%)	P value
LDH (U/L)			
≤245	519 (96.5)	506 (96.0)	0.697
>245	19 (3.5)	21 (4.0)	
HGB (g/L)			
≤113	19 (3.5)	4 (0.8)	<0.001
113–151	403 (74.9)	303 (57.5)	
≥151	116 (21.6)	220 (41.7)	
PLT (10^9/L)			
≤100	4 (0.7)	10 (1.9)	0.181
100–300	474 (88.1)	451 (85.6)	
≥300	60 (11.2)	66 (12.5)	
BMI			
≤22.9	340 (63.2)	199 (37.8)	<0.001
>22.9	198 (36.8)	328 (62.2)	
ALB (g/L)			
≤45.1	438 (81.4)	98 (18.6)	<0.001
>45.1	100 (18.6)	429 (81.4)	
EBV DNA (copies/mL)			
≤1,500	261 (48.5)	292 (55.4)	0.024
>1,500	277 (51.5)	235 (44.6)	

NPC, nasopharyngeal carcinoma; GNRI, geriatric nutritional risk index; LDH, lactate dehydrogenase; HGB, hemoglobin; PLT, platelets; BMI, body mass index; ALB, serum albumin; EBV, Epstein–Barr virus.

Patients in the high EBV DNA group showed worse OS (86.1% *vs.* 97.0%, P<0.001), PFS (78.8% *vs.* 91.6%, P<0.001), LRFS 91.9% *vs.* 95.3%, P=0.04), and DMFS (87.1% *vs.* 95.0%, P<0.001) compared to patients in the low EBV DNA group (*Figure 1*). Univariate Cox regression analysis revealed that gender, age, N stage, LDH levels, serum ALB levels, circulating EBV DNA levels, and GNRI score were significantly associated with OS. Furthermore, N stage, BMI, EBV DNA, and GNRI were significantly associated with PFS. Multivariate Cox regression analysis indicated that gender, age, N stage, LDH levels, PLT levels, circulating EBV DNA levels, and GNRI score could independently predict OS in NPC patients. Moreover, gender, N stage, circulating EBV DNA levels, and GNRI score could independently predict PFS (*Table 2*).

Prognostic value of pretreatment GNRI score

Compared to those in the low GNRI group, the five-year survival rate for OS, PFS, and DMFS was significantly higher in patients of the high GNRI group. However, there were no significant differences in the 5-year LRFS between the high and low GNRI groups (*Figure 2*). Multivariate analyses suggested that pretreatment GNRI score was an independent prognostic factor for OS and PFS (HR 0.471, 95% CI, 0.270–0.822, P=0.008; HR 0.638, 95% CI, 0.433–0.941, P=0.023, respectively) (*Table 2*). When analyzing the whole study population after adjusting for gender, age, pathology, smoking, the family of cancer, tumor stage, node stage, LDH levels, HGB levels, PLT levels, ALB levels, BMI, EBV DNA levels, and GNRI score, the interaction

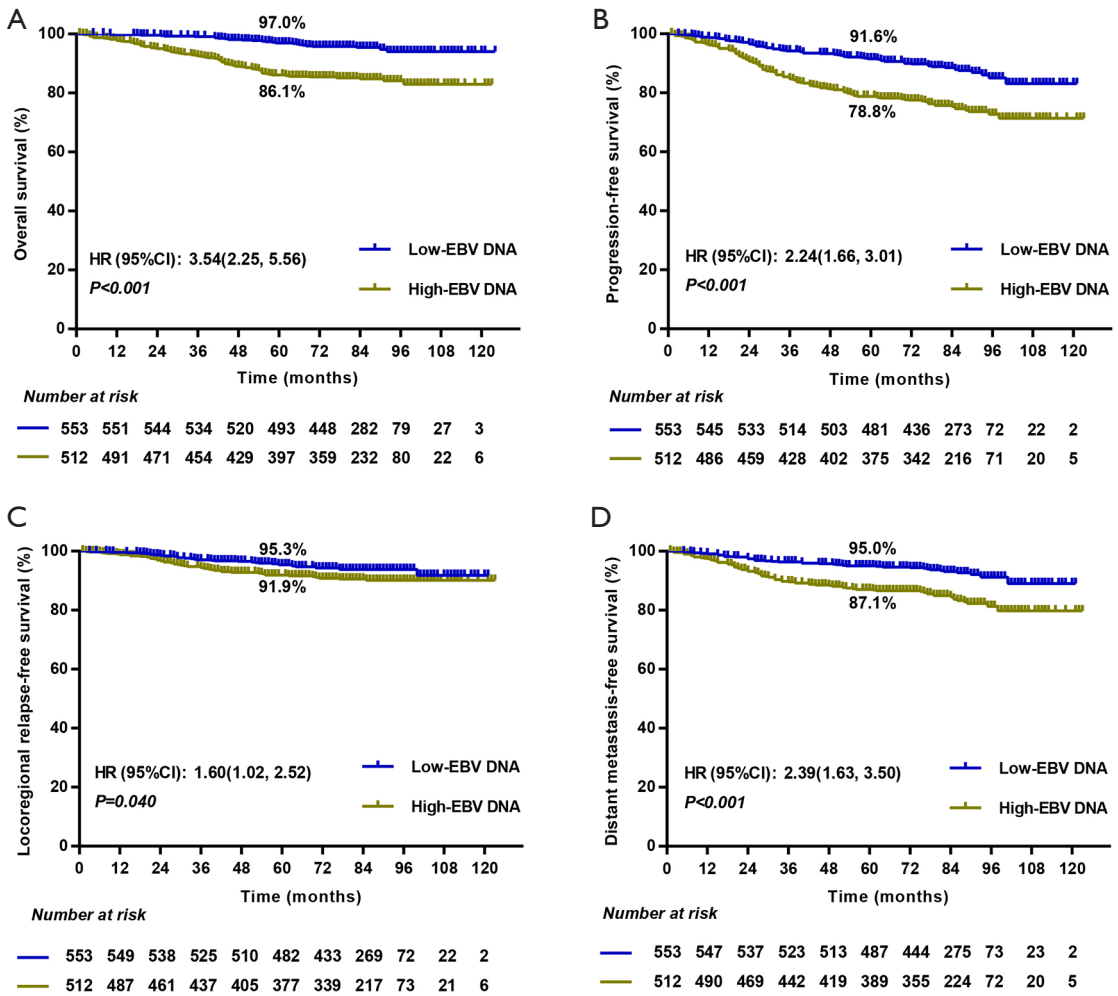

Figure 1 Kaplan-Meier survival curves for overall survival (A), progression-free survival (B), locoregional relapse-free survival (C), and distant metastasis-free survival (D) of patients with NPC stratified based on high and low baseline circulating EBV DNA levels. Categories are based on the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system. The cutoff value for baseline circulating EBV DNA levels was 1,500 copies/mL; five-year survival rates are presented.

Table 2 Univariate and multivariate Cox proportional hazards analysis of 1,065 patients with NPC

Variable	Univariate analysis			Multivariate analysis		
	HR*	95% CI	P value	HR*	95% CI	P value*
OS						
Gender	1.698	1.030–2.798	0.038	2.230	1.273–3.908	0.005
Age	1.867	1.246–2.796	0.002	1.726	1.130–2.637	0.011
Pathology	1.104	0.670–1.821	0.697	–	–	–
Smoking history	1.291	0.865–1.926	0.211	–	–	–
Family of cancer	0.893	0.571–1.396	0.619	–	–	–

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Univariate analysis			Multivariate analysis		
	HR*	95% CI	P value	HR*	95% CI	P value*
T stage	1.401	0.859–2.288	0.177	–	–	–
N stage	2.498	1.660–3.758	<0.001	2.011	1.317–3.069	0.001
LDH	2.222	1.031–4.792	0.042	2.419	1.103–5.305	0.027
HGB	0.918	0.599–1.408	0.696	–	–	–
PLT	1.629	0.978–2.713	0.061	2.431	1.377–3.981	0.002
ALB	0.593	0.396–0.887	0.011	–	–	–
BMI	0.742	0.499–1.104	0.141	–	–	–
EBV DNA	3.536	2.249–5.561	<0.001	2.932	1.836–4.683	<0.001
GNRI	0.490	0.324–0.741	0.001	0.471	0.270–0.822	0.008
PFS						
Gender	1.300	0.931–1.815	0.123	1.529	1.043–2.241	0.030
Age	1.305	0.984–1.732	0.065	–	–	–
Pathology	0.889	0.570–1.386	0.604	–	–	–
Smoking history	1.147	0.857–1.535	0.357	–	–	–
Family of cancer	0.868	0.628–1.201	0.393	–	–	–
T stage	1.145	0.820–1.599	0.426	–	–	–
N stage	1.572	1.185–2.086	0.002	1.356	1.009–1.822	0.043
LDH	1.401	0.717–2.736	0.323	–	–	–
HGB	0.930	0.684–1.265	0.644	–	–	–
PLT	1.106	0.727–1.684	0.638	–	–	–
ALB	0.782	0.589–1.039	0.090	–	–	–
BMI	0.729	0.548–0.970	0.030	–	–	–
EBV DNA	2.235	1.662–3.007	<0.001	1.998	1.469–2.717	<0.001
GNRI	0.639	0.479–0.853	0.002	0.638	0.433–0.941	0.023

*We calculated hazard ratios and P values with an adjusted multivariate Cox proportional hazards regression model, including gender (male *vs.* female), age (>45 *vs.* ≤45 years), pathology (type III *vs.* type II), smoking (yes *vs.* no), family of cancer (yes *vs.* no), tumor stage (T3 + T4 *vs.* T1 + T2), node stage (N2 + N3 *vs.* N0 + N1), LDH levels (>245 *vs.* ≤245 U/L), HGB levels (≥151 *vs.* <151 g/L), PLT levels (≥300 *vs.* <300 10^9/L), ALB levels (>45.1 *vs.* ≤45.1 g/L), BMI (>22.9 *vs.* ≤22.9 kg/m^2), EBV DNA (high-group *vs.* low-group), and GNRI (high-group *vs.* low-group) as covariates. Only variables that were significantly associated with survival are presented. NPC, nasopharyngeal carcinoma; GNRI, geriatric nutritional risk index; LDH, lactate dehydrogenase; HGB, hemoglobin; PLT, platelets; BMI, body mass index; ALB, serum albumin; EBV, Epstein–Barr virus; HR, hazard ratio; CI, confidence interval; PFS, progression–free survival; OS, overall survival.

analysis showed no significant interaction effect between the GNRI score and other significant prognostic factors of OS and PFS (all P>0.05) (*Table 3*).

Prognostic value of the combination of GNRI score and EBV DNA level

In this study, we combined the pretreatment GNRI score

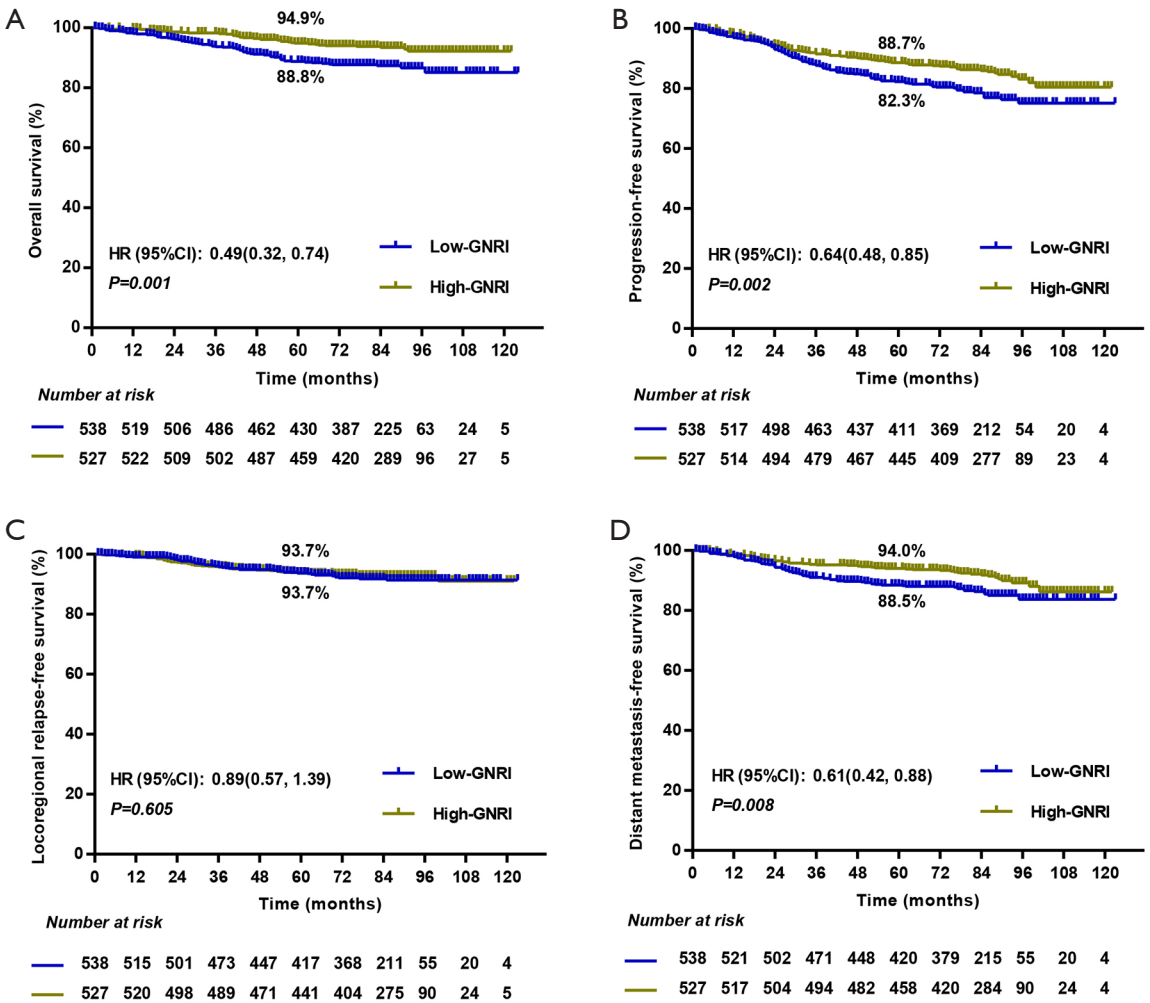

Figure 2 Kaplan-Meier survival curves for overall survival (A), progression-free survival (B), locoregional relapse-free survival (C), and distant metastasis-free survival (D) of patients with NPC stratified based on high and low baseline GNRI. Categories are based on the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system. The cutoff value for the baseline GNRI was 107.7; five-year survival rates are presented.

and baseline EBV DNA level to stratify patients into the high-risk (high EBV DNA level and low GNRI score), low-risk (low EBV DNA level and high GNRI score), and medium-risk (both high level and both low level) groups. Our analysis showed significant separations between the OS, PFS, and DMFS survival curves of different risk groups. Survival was significantly poorer in patients in the high-risk group than those in the low- and medium-risk groups (all P<0.001). However, no significant differences in LRFS were observed among these three groups (P=0.159). Kaplan-Meier curves, stratified according to the combination of GNRI score and EBV DNA level, is shown in *Figure 3*. In the multivariate analysis, the combined classification was demonstrated to be an independent prognostic factor for OS and PFS after adjustment. In addition, the HRs for OS and PFS for the high-risk group were considerably higher than those observed when only baseline EBV DNA level was assessed (*Table 4*).

Discussion

Radiotherapy and chemotherapy have been used as standard care in the treatment of NPC. Nevertheless, locoregional recurrence and distant metastasis occur frequently; hence,

Table 3 Interaction analysis between GNRI and other significant prognostic factors and its effect on overall survival and progression-free survival

	OS		PFS	
	Adjusted HR* (95% CI)	P value*	Adjusted HR* (95% CI)	P value*
GNRI and gender				
GNRI				
Low group	Reference		Reference	
High group	0.317 (0.033, 3.071)	0.321	0.468 (0.114, 1.922)	0.292
Gender				
Female	Reference		Reference	
Male	1.701 (0.348, 8.311)	0.512	1.221 (0.428, 3.479)	0.709
Interaction Effect				
High GNRI * male	1.243 (0.373, 4.135)	0.723	1.190 (0.557, 2.545)	0.654
GNRI and age				
GNRI				
Low group	Reference		Reference	
High group	0.846 (0.197, 3.636)	0.822	0.976 (0.371, 2.571)	0.961
Age				
≤45	Reference		Reference	
>45	2.906 (0.805, 10.485)	0.103	1.864 (0.762, 4.557)	0.172
Interaction Effect				
High GNRI * age>45	0.686 (0.287, 1.641)	0.397	0.753 (0.417, 1.362)	0.348
GNRI and N stage				
GNRI				
Low group	Reference		Reference	
High group	0.445 (0.095, 2.087)	0.304	0.594 (0.223, 1.581)	0.297
N stage				
N0–1	Reference		Reference	
N2–3	1.920 (0.560, 6.587)	0.300	1.272 (0.537, 3.012)	0.585
Interaction effect				
High GNRI * N2–3	1.035 (0.434, 2.470)	0.938	1.047 (0.586, 1.869)	0.877
GNRI and EBV DNA				
GNRI				
Low group	Reference		Reference	
High group	0.423 (0.073, 2.451)	0.337	0.951 (0.328, 2.760)	0.926
EBV DNA				
Low group	Reference		Reference	
High group	2.696 (0.684, 10.635)	0.157	2.832 (1.125, 7.084)	0.027
Interaction effect				
High GNRI * High EBV DNA	1.064 (0.410, 2.762)	0.899	0.785 (0.429, 1.436)	0.432

*The data was obtained from all 1,065 patients, a multivariable cox regression model adjusted for gender, age, pathology, smoking, family of cancer, tumor stage, node stage, LDH levels, HGB levels, PLT levels, ALB levels, BMI, EBV DNA levels, and GNRI score. GNRI, geriatric nutritional risk index; EBV, Epstein–Barr virus; HR, hazard ratio; CI, confidence interval; PFS, progression–free survival; OS, overall survival.

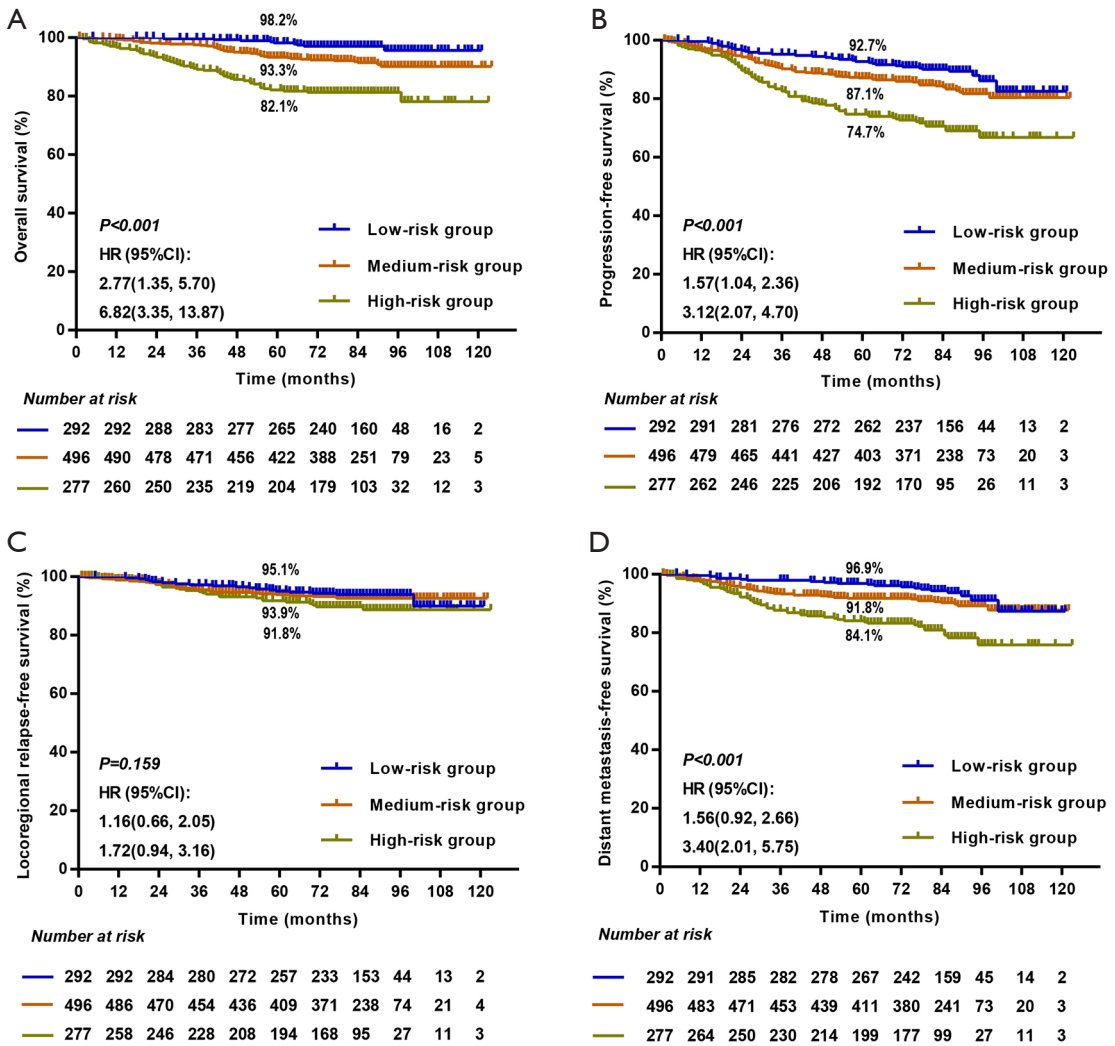

Figure 3 Kaplan-Meier survival curves for overall survival (A), progression-free survival (B), locoregional relapse-free survival (C), and distant metastasis-free survival (D) of patients with NPC stratified using a combination of GNRI and circulating EBV DNA levels. High-risk group: high EBV DNA and low GNRI; Low-risk group: low EBV DNA and high GNRI; Both high groups and both low groups were medium-risk group. Categories are based on the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system; five-year survival rates are presented.

it is of great importance to explore new prognostic factors, which would potentially help establish individualized treatment regimens. In this study, our findings indicated that patients with NPC in the high GNRI score group exhibited better OS, PFS, and DMFS than those in the low GNRI score group. Multivariate analyses showed that GNRI was an independent prognostic factor for OS and PFS. Using GNRI, we could distinguish patients with high nutritional risk and provide more intensive nutritional treatment to improve patient outcomes. Moreover, the combination of GNRI and EBV DNA levels showed increased prognostic value when compared to the GNRI or EBV DNA data alone. Thus, intense treatment in subsequent phases, such as the inclusion of adjuvant chemotherapy, better nutritional treatment, or close follow-up, is required for patients in the high-risk group.

Malnutrition is a frequent comorbidity in patients with cancer, which is known to be associated with an increased incidence of complications and to have an adverse effect on long-term survival (17,18,20,28). It has been reported that

Table 4 Multivariate Cox proportional hazards analysis of 1,065 patients with NPC for the combination of GNRI and EBV DNA levels

Variable	HR*	95% CI	P value*
OS			
Gender	2.261	1.291–3.960	0.004
Age	1.737	1.137–2.654	0.011
N stage	2.068	1.361–3.140	0.001
LDH	2.481	1.133–5.429	0.023
PLT	2.357	1.387–4.004	0.002
Medium-risk	2.767	1.308–5.857	0.008
High-risk	6.907	3.064–15.568	<0.001
PFS			
Gender	1.549	1.057–2.269	0.025
N stage	1.395	1.043–1.867	0.025
Medium-risk	1.590	1.032–2.451	0.036
High-risk	3.164	1.937–5.166	<0.001

*We calculated hazard ratios and P values with an adjusted multivariate Cox proportional hazards regression model, including gender (male *vs.* female), age (>45 *vs.* ≤45 years), pathology (type III *vs.* type II), smoking (yes *vs.* no), family of cancer (yes *vs.* no), tumor stage (T3 + T4 *vs.* T1 + T2), node stage (N2 + N3 *vs.* N0 + N1), LDH levels (>245 *vs.* ≤245 U/L), HGB levels (≥151 *vs.* <151 g/L), PLT levels (≥300 *vs.* <300 10^9/L), ALB levels (>45.1 *vs.* ≤45.1 g/L), BMI (>22.9 *vs.* ≤22.9 kg/m^2), and GNRI & EBV DNA (high-risk or medium-risk *vs.* low-risk) as covariates. Only variables that were significantly associated with survival are presented. NPC, nasopharyngeal carcinoma; GNRI, geriatric nutritional risk index; LDH, lactate dehydrogenase; HGB, hemoglobin; PLT, platelets; BMI, body mass index; ALB, serum albumin; EBV, Epstein–Barr virus; HR, hazard ratio; CI, confidence interval; PFS, progression–free survival; OS, overall survival.

malnutrition occurs in 35–60% of patients with NPC; a large proportion of these patients have problems related to nutrition before commencing treatment (29), which might significantly affect treatment responses. Previous studies show that anemia is associated with radiation resistance. Additionally, malnutrition reduces chemoradiotherapy tolerance, thereby prolonging treatment duration, which impairs immune function and increases the risk of secondary infections during treatment (15,30). Furthermore, poor nutritional status is often exacerbated during or after chemo- and radiotherapy. Adverse effects, such as nausea, vomiting, and radiation-induced oral mucositis, can decrease the food intake of patients and further worsen their nutritional status, which, in turn, can have an impact on treatment. Systematic nutritional monitoring and intervention in patients with head and neck cancer can significantly improve treatment outcomes. Subsequently, pretreatment nutrition screening and the identification of patients with NPC requiring nutritional interventions are essential to improve their treatment tolerance and survival.

Previous studies have demonstrated that low BMI, decreased hemoglobin, and serum albumin are markers of malnutrition. Those parameters have been used to identify patients suffering from nutritional deficits. However, their potential to assess nutritional status and predict prognosis is limited (20). The GNRI was originally developed to evaluate the nutritional status of elderly patients. Moreover, recent studies have confirmed the utility of GNRI to evaluate prognosis in patients with cancers, including esophageal carcinoma, lung cancer, and head and neck cancer (17-19,28,31). Hirahara *et al.* evaluated the impact of preoperative GNRI on clinical outcomes in 303 elderly patients with gastric cancer. Using preoperative GNRI level to categorize patients into low and normal GNRI groups, they found that GNRI is an important predictor of postoperative complications and overall survival in the elderly population afflicted with gastric cancer (28). Data from 248 patients with head and neck cancer (17) also showed that patients in the high-risk group had lower three-year survival rates compared to those in the intermediate- and normal-risk groups, and that the decreased GNRI score was significantly associated with an increased risk of

mortality. In this study, a similar prognosis value of GNRI was investigated in the population afflicted with NPC

To the best of our knowledge, this is the first study to evaluate the prognostic relevance of GNRI determination in patients with NPC and to report that GNRI was independently associated with the prognosis of patients with NPC. As a useful biomarker of NPC, circulating EBV-DNA levels are associated with the early screening of patients with NPC, which has been shown to correlate with tumor burden, clinical-stage, treatment response, and patient survival (24). Here, to assess the mortality-risk prediction, we investigated the potential of the combined determination of GNRI and circulating EBV DNA levels in our cohort. Our results suggested that the integration of GNRI and circulating EBV DNA levels had an increased value in risk stratification and mortality prediction. Additionally, given the unbalanced distribution of gender, age, EBV DNA levels, and N stage in different GNRI groups, we conducted an interaction analysis. The results revealed no interaction between GNRI and other significant factors. We determined that the levels of circulating EBV DNA in patients with NPC in the high GNRI group were lower than those in patients in the low GNRI group. Therefore, we hypothesized that such results might correlate with good nutritional and immune status of the high GNRI group.

Although our study benefits from a large sample size, long follow-up time, and uniform CCRT treatment patterns, we acknowledge the presence of several limitations. This was a retrospective, non-randomized, observational study conducted in a single institute that had potential selection bias. A larger multicenter prospective study would be necessary to establish the role of the GNRI as a tool for predicting the outcomes of patients with NPC. Moreover, we failed to analyze the relationship between pretreatment GNRI and treatment-related side effects; therefore, further investigations are warranted. Despite these limitations, the current study could serve as a valuable reference for the survival prediction of patients with NPC.

Conclusions

Based on the large sample size, uniform treatment modality, and long-term follow-up study, our results confirmed the pretreatment GNRI score as an independent prognostic predictor for patients with NPC. The combination of baseline GNRI score and EBV DNA level improved the prognostic stratification of these patients. Therefore, we suggest that the GNRI score should be evaluated in patients with NPC.

Acknowledgments

Funding: This study was supported by grants from the National Key R&D Programme of China (2017YFC1309003 and 2017YFC0908500), the National Natural Science Foundation of China (81425018, 81672868, and 81802775), the Sci-Tech Project Foundation of Guangzhou City (201707020039), the Sun Yat-sen University Clinical Research 5010 Programme, the Special Support Plan of Guangdong Province (2014TX01R145), the Natural Science Foundation of Guangdong Province (2017A030312003 and 2018A0303131004), the Natural Science Foundation of Guangdong Province for Distinguished Young Scholars (2018B030306001), the Sci-Tech Project Foundation of Guangdong Province (2014A020212103), the Health & Medical Collaborative Innovation Project of Guangzhou City (201400000001 and 201803040003), the Pearl River S&T Nova Programme of Guangzhou (201806010135), the Planned Science and Technology Project of Guangdong Province (2019B020230002), the National Science and Technology Pillar Programme during the Twelfth Five-Year Plan Period (2014BAI09B10), and the Fundamental Research Funds for the Central Universities.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6493

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-6493

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6493). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Sun Yat-sen University Cancer Center and individual consent for this retrospective analysis was waived.

Open Access Statement: This is an Open Access article

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Chen W. Cancer statistics: updated cancer burden in China. Chin J Cancer Res 2015;27:1.
3. Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral Oncol 2015;51:1041-6.
4. Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: Decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck 2016;38 Suppl 1:E1886-95.
5. Peng G, Wang T, Yang KY, et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 2012;104:286-93.
6. Chen YP, Chan ATC, Le QT, et al. Nasopharyngeal carcinoma. Lancet 2019;394:64-80.
7. Mao YP, Xie FY, Liu LZ, et al. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2009;73:1326-34.
8. Chan AT, Teo PM, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002;20:2038-44.
9. Chan KCA, Woo JKS, King A, et al. Analysis of Plasma Epstein-Barr Virus DNA to Screen for Nasopharyngeal Cancer. N Engl J Med 2017;377:513-22.
10. Ambinder RF. Plasma Epstein-Barr Virus DNA for Screening. N Engl J Med 2017;377:584-5.
11. Chan AT, Lo YM, Zee B, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. J Natl Cancer Inst 2002;94:1614-9.
12. Meng L, Wei J, Ji R, et al. Effect of Early Nutrition Intervention on Advanced Nasopharyngeal Carcinoma Patients Receiving Chemoradiotherapy. Journal of Cancer 2019;10:3650-6.
13. Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr 2005;82:777-83.
14. Wang H, Hai S, Zhou Y, et al. The Geriatric Nutritional Risk Index predicts mortality in nonagenarians and centenarians receiving home care. Asia Pac J Clin Nutr 2018;27:78-83.
15. Kubo N, Sakurai K, Tamura T, et al. The impact of geriatric nutritional risk index on surgical outcomes after esophagectomy in patients with esophageal cancer. Esophagus 2019;16:147-54.
16. Matsukuma Y, Tanaka S, Taniguchi M, et al. Association of geriatric nutritional risk index with infection-related mortality in patients undergoing hemodialysis: The Q-Cohort Study. Clin Nutr 2019;38:279-87.
17. Nakayama M, Gosho M, Adachi M, et al. The Geriatric Nutritional Risk Index as a Prognostic Factor in Patients with Advanced Head and Neck Cancer. Laryngoscope 2021;131:E151-6.
18. Shoji F, Matsubara T, Kozuma Y, et al. Preoperative Geriatric Nutritional Risk Index: A predictive and prognostic factor in patients with pathological stage I non-small cell lung cancer. Surg Oncol 2017;26:483-8.
19. Lee GW, Go SI, Kim DW, et al. Geriatric Nutritional Risk Index as a prognostic marker in patients with extensive-stage disease small cell lung cancer: Results from a randomized controlled trial. Thorac Cancer 2020;11:62-71.
20. Kanemasa Y, Shimoyama T, Sasaki Y, et al. Geriatric nutritional risk index as a prognostic factor in patients with diffuse large B cell lymphoma. Ann Hematol 2018;97:999-1007.
21. Sun X, Su S, Chen C, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. Radiother Oncol 2014;110:398-403.
22. Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre,

randomised controlled trial. Lancet Oncol 2016;17:1509-20.
23. Shao JY, Zhang Y, Li YH, et al. Comparison of Epstein-Barr virus DNA level in plasma, peripheral blood cell and tumor tissue in nasopharyngeal carcinoma. Anticancer Res 2004;24:4059-66.
24. Tang LQ, Chen QY, Fan W, et al. Prospective study of tailoring whole-body dual-modality [18F] fluorodeoxyglucose positron emission tomography/computed tomography with plasma Epstein-Barr virus DNA for detecting distant metastasis in endemic nasopharyngeal carcinoma at initial staging. J Clin Oncol 2013;31:2861-9.
25. Lin JC, Wang WY, Chen KY, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. The New England journal of medicine 2004;350:2461-70.
26. Zhou GQ, Tang LL, Mao YP, et al. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. Int J Radiat Oncol Biol Phys 2012;82:e359-65.
27. Tang LQ, Li CF, Li J, et al. Establishment and Validation of Prognostic Nomograms for Endemic Nasopharyngeal Carcinoma. J Natl Cancer Inst 2015;108:djv291.
28. Hirahara N, Tajima Y, Fujii Y, et al. Prediction of postoperative complications and survival after laparoscopic gastrectomy using preoperative Geriatric Nutritional Risk Index in elderly gastric cancer patients. Surg Endosc 2021;35:1202-9.
29. Zeng Q, Shen LJ, Guo X, et al. Critical weight loss predicts poor prognosis in nasopharyngeal carcinoma. BMC Cancer 2016;16:169.
30. de Pinho NB, Martucci RB, Rodrigues VD, et al. Malnutrition associated with nutrition impact symptoms and localization of the disease: Results of a multicentric research on oncological nutrition. Clin Nutr 2019;38:1274-9.
31. Hino H, Saito T, Matsui H, et al. Utility of Geriatric Nutritional Risk Index in patients with lung cancer undergoing surgery. Eur J Cardiothorac Surg 2020;58:775-82.

Cite this article as: Tang QN, Qiu HZ, Sun XQ, Guo SS, Liu LT, Wen YF, Liu SL, Xie HJ, Liang YJ, Sun XS, Li XY, Yan JJ, Yang JH, Wen DX, Guo L, Tang LQ, Chen QY, Mai HQ. Geriatric nutritional risk index as an independent prognostic factor in locally advanced nasopharyngeal carcinoma treated using radical concurrent chemoradiotherapy: a retrospective cohort study. Ann Transl Med 2021;9(7):532. doi: 10.21037/atm-20-6493