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ORIGINAL RESEARCH

Neutrophil-to-lymphocyte ratio predicts the prognosis of stage II nasopharyngeal carcinoma

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Purpose: To assess the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in stage II nasopharyngeal carcinoma (NPC).

Methods: Stage II (2010 UICC/AJCC staging system) NPC patients treated between January 2007 and December 2014 were retrospectively analyzed. The NLR was calculated from peripheral blood cell counts before treatment. The optimal cut-off value of NLR was determined by receiver operating characteristic curve analysis. Survival rates were compared according to the NLR value. Multivariable Cox regression analyses were performed to assess the association between the NLR and overall survival (OS), locoregional-free survival (LRFS), and distant metastasis-free survival (DMFS).

Results: Two hundred and fifty-one stage II NPC patients were included in this study. The NLR was correlated with T stage (r=0.158, p=0.012). An NLR ≥2.92 was associated with poor 5-year OS (84.3% vs 97.4%, p=0.001) and LRFS (91.4% vs 98.4%, p=0.003). An NLR ≥2.82 was associated with poor 5-year DMFS (92.6% vs 98.2%, p=0.033). The multivariate Cox regression analysis showed that an NLR ≥2.92 was an independent prognostic biomarker in stage II NPC.

Conclusion: The NLR is an independent prognostic factor in stage II NPC.

Keywords: nasopharyngeal carcinoma, NPC, stage II, neutrophil-to-lymphocyte ratio, NLR

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers in Southern China.[1,2] With improvements in diagnosis, the incidence of stage II NPC has greatly increased. After treatment, the 5-year overall survival (OS) rate is nearly 90% for stage II NPC patients.[3,4] However, approximately 10% of patients experience recurrence, distant metastasis, or death. Hence, it is important to identify patients with a high risk of recurrence and metastasis to optimize adjuvant treatments.

Until now, the prognosis of NPC mainly depends on the TNM stage. However, the TNM stage is based on anatomical structures and does not reflect the biological heterogeneity of stage II NPC. At present, the Epstein-Barr virus (EBV) DNA titer is the only proven biomarker with clinical utility in NPC.[5–9] However, the EBV DNA test varies among different clinics. There is a critical need for additional prognostic biomarkers for stage II NPC.

Previous studies have indicated the association of the neutrophil-to-lymphocyte ratio (NLR) with prognosis in multiple tumor types.[10–12] Some studies have focused on the prognostic impact of the NLR in NPC.[13–16] However, the patients included in these studies were highly heterogeneous, mainly comprising those with locoregionally advanced NPC and metastatic disease. Moreover, the results differed between these

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studies. Hence, this study was conducted to assess the effect of the pretreatment NLR on prognosis in stage II NPC patients.

Materials and methods

Patients

We retrospectively analyzed stage II NPC patients (7th AJCC staging system[17]) treated at the Affiliated Tumor Hospital of Guangxi Medical University between January 2007 and December 2014. The inclusion criteria were as follows: (1) pathologically confirmed NPC; (2) no prior malignancy; (3) no current antitumor therapy; and (4) no infection or symptoms of inflammation. The exclusion criteria were as follows: (1) patients with a self-reported acute infection or hematologic disorder and (2) a synchronous malignancy. Peripheral blood was collected before treatment. Neutrophils and lymphocytes were counted using a Sysmex XE-5000 automated hematology analyzer (Sysmex, Kobe, Japan). This study was approved by the Affiliated Tumor Hospital of Guangxi Medical University's Ethics Committee. This study was performed according to compliance with the Declaration of Helsinki. But, informed consent was not available due to the retrospective nature. The data was anonymized or maintained with confidentiality.

Treatment, follow-up and endpoints

A detailed radiotherapy modality was published recently.[18] Concurrent chemotherapy was scheduled on days 1, 22, and 43 with 80–100 mg/m^2 of cisplatin for 1 or 3 days per cycle during radiotherapy. Adjuvant chemotherapy included 80–100 mg/m^2 of cisplatin for 1 or 3 days and 600–750 mg/m^2/d of 5-fluorouracil via continuous intravenous infusion for 96 hrs or 120 hrs in a cycle of 28 days for 2–3 cycles. Chemotherapy was postponed or discontinued in patients who experienced serious toxicity and could not recover before the next scheduled cycle.

Patients were followed up every three months throughout the first two years, every six months for the next three years, and then annually. Endpoints included OS, locoregional-free survival (LRFS), and distant metastasis-free survival (DMFS).

Statistical analysis

The NLR was defined as follows: NLR = N/L, where N and L were the neutrophil and lymphocyte counts before treatment, respectively.

The correlation of the NLR with different prognostic factors was assessed by Spearman's rank correlation coefficient. Prognostic factors were analyzed using the log-rank test in the univariate analysis; Cox regression analysis was used for the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the optimal cut-off points of the NLR for OS, LRFS, and DMFS. The Kaplan-Meier method was used to calculate survival rates. The log-rank test was used to assess differences between survival curves. Statistical analyses were performed using SPSS Statistics Version 23.0 software (IBM Co., Armonk, NY, USA). Two-tailed $p<0.05$ was considered statistically significant.

Results

Patient characteristics

Two hundred and fifty-one stage II NPC patients were included in this study. Ninety-four patients received radiotherapy alone, 103 patients received concurrent chemotherapy, and 54 patients received concurrent chemotherapy followed by adjuvant chemotherapy. The follow-up rate was 96.81%. The median follow-up time was 64 months (range, 12–116 months). Patient characteristics are shown in Table 1.

Correlation of the NLR with different prognostic factors

The cut-off points determined by the ROC curve of the NLR for OS, LRFS, and DMFS were 2.92, 2.92, and 2.82, respectively. A high NLR (≥2.92) was significantly correlated with T stage (r=0.158, p=0.012). However, the NLR did not correlate with age, sex, pathology, N stage, or AJCC stage (Table 1).

NLR is correlated with prognosis

An NLR ≥2.92 was associated with poor 5-year OS (84.3% vs 97.4%, p=0.001) (Figure 1) and LRFS (91.4% vs 98.4%, p=0.003) (Figure 2). The 5-year DMFS rate of the patients with an NLR ≥2.82 was significantly lower than that of the patients with an NLR <2.82 (92.6% vs 98.2%, respectively, p=0.033) (Figure 3).

In the univariate analysis, a high NLR was correlated with poor OS (Table 2), LRFS (Table 3), and DMFS (Table 4). To correct for possible confounding factors, we used multivariate Cox regression to assess the effect of the NLR. The results showed that a high NLR (≥2.92) was significantly correlated with poor OS (hazard ratio [HR]=6.674, 95% confidence interval [CI]: 1.871–23.799, p=0.003) (Table 2) and LRFS

Table 1 Patient characteristics and correlation of the NLR with different prognostic factors

	n	NLR	
		r	p
Age			
≥44	127 (50.60%)	0.026	0.676
<44	124 (49.40%)		
Sex			
Female	79 (31.47%)	−0.076	0.229
Male	172 (68.53%)		
Pathology			
WHO II	26 (10.36%)	−0.032	0.615
WHO III	225 (89.64%)		
T stage			
T1	46 (18.33%)	0.158	0.012
T2	205 (81.67%)		
N stage			
N0	56 (22.31%)	0.027	0.668
N1	195 (77.69%)		
AJCC			
T2N0	56 (22.31%)	0.103	0.104
T1N1	46 (19.52%)		
T2N1	149 (58.17%)		

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; r, Spearman's rank correlation coefficient.

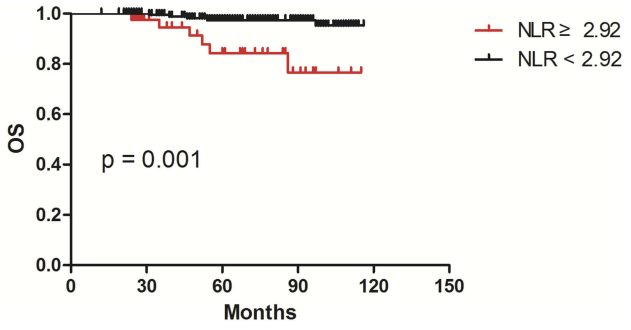

Figure 1 Kaplan-Meier survival curve of five-year overall survival according to the neutrophil-to-lymphocyte ratio.

(HR=4.651, 95% CI: 1.281–16.890, p=0.019) (Table 3). However, multivariate Cox regression revealed that the NLR (≥2.82) was not an independent prognostic biomarker (HR=4.399, 95% CI: 0.855–22.635, p=0.076) (Table 4).

Discussion

Our findings indicate that the NLR is an independent prognostic factor for stage II NPC patients. An elevated NLR

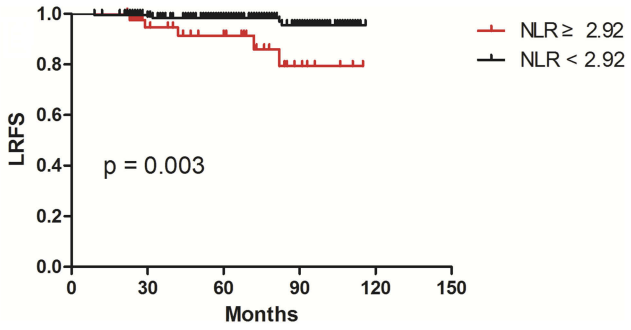

Figure 2 Kaplan-Meier survival curve of five-year locoregional-free survival according to the neutrophil-to-lymphocyte ratio.

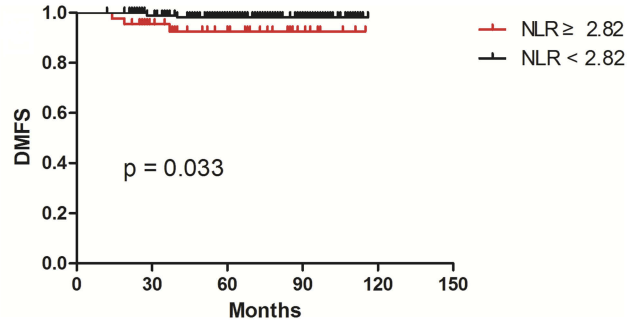

Figure 3 Kaplan-Meier survival curve of five-year distant metastasis-free survival according to the neutrophil-to-lymphocyte ratio.

was significantly associated with poor OS, LRFS, and DMFS. Patients with a high NLR were more likely to develop recurrence and metastasis. These high-risk patients should receive optimized adjuvant treatments and close follow-up.

The prognosis of NPC patients mainly depends on the TNM stage. Stage II NPC is divided into three subgroups (T1N1, T2N0, and T2N1). Several studies have indicated that patients with T2N1 have poor survival.[19,20] Xiao et al[20] revealed that the 5-year OS rate was 91.3%, 85.8%, and 73.1% (p<0.05) for T1N1, T2N0, and T2N1, respectively. Luo et al[19] reported that the 3-year OS rate was worse in T2N1 patients than in T1N1 and T2N0 patients (74.5 vs 100.0%, respectively; p=0.01). However, other studies have found that the survival rates were not different between the T1N1, T2N0, and T2N1 subgroups.[3,21–23] The prognosis of the three subgroups remains controversial. These studies suggest that the TNM stage does not reflect the biological heterogeneity of stage II NPC. Additional prognostic biomarkers are needed to identify high-risk patients.

Several recent studies have suggested that the level of EBV DNA in the plasma, serum, or peripheral blood cells is a useful prognostic factor for NPC patients.[5–9,24,25] However,

Table 2 Univariate and multivariate analyses of overall survival in stage II nasopharyngeal carcinoma patients

	n	Univariate (*p*)	Multivariate		
			HR	95% CI	*p*
Age		0.859	1.006	0.935–1.083	0.864
≥44	127 (50.60%)				
<44	124 (49.40%)				
Sex		0.724	1.360	0.340–5.445	0.664
Female	79 (31.47%)				
Male	172 (68.53%)				
Pathology		0.236	0.382	0.069–2.102	0.269
WHO II	26 (10.36%)				
WHO III	225 (89.64%)				
AJCC		0.165	4.088	0.882–18.949	0.072
T2N0	56 (22.31%)				
T1N1	46 (19.52%)				
T2N1	149 (58.17%)				
Technique		0.461	1.968	0.551–7.021	0.297
2D-CRT	73 (29.08%)				
IMRT	178 (70.92%)				
Treatment		0.867	0.637	0.264–1.537	0.361
RT	94 (37.45%)				
CCRT	103 (41.04%)				
CCRT+AC	54 (21.51%)				
NLR		0.001	6.674	1.871–23.799	0.003
≥2.92	41 (16.33%)				
<2.92	210 (83.67%)				

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; IMRT, intensity-modulated radiotherapy; 2D-CRT, two-dimensional conventional radiotherapy; HR, hazard ratio; CI, confidence interval.

Table 3 Univariate and multivariate analyses of locoregional-free survival in stage II nasopharyngeal carcinoma patients

	n	Univariate (*p*)	Multivariate		
			HR	95% CI	*p*
Age		0.074	1.065	0.0994–1.142	0.075
≥44	127 (50.60%)				
<44	124 (49.40%)				
Sex		0.754	1.114	0.282–4.398	0.877
Female	79 (31.47%)				
Male	172 (68.53%)				
Pathology		0.776	0.623	0.068–5.687	0.675
WHO II	26 (10.36%)				
WHO III	225 (89.64%)				
AJCC		0.588	1.331	0.457–3.876	0.600
T2N0	56 (22.31%)				
T1N1	46 (19.52%)				
T2N1	149 (58.17%)				

(*Continued*)

Table 3 (Continued).

	n	Univariate (*p*)	Multivariate		
			HR	95% CI	*p*
Technique 2D-CRT IMRT	 73 (29.08%) 178 (70.92%)	0.369	0.464	0.107–2.007	0.304
Treatment RT CCRT CCRT+AC	 94 (37.45%) 103 (41.04%) 54 (21.51%)	0.963	0.828	0.348–1.966	0.668
NLR ≥2.92 <2.92	 41 (16.33%) 210 (83.67%)	0.003	4.651	1.281–16.890	0.019

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; IMRT, intensity-modulated radiotherapy; 2D-CRT, two-dimensional conventional radiotherapy; HR, hazard ratio; CI, confidence interval.

Table 4 Univariate and multivariate analyses of distant metastasis-free survival in stage II nasopharyngeal carcinoma patients

	n	Univariate (*p*)	Multivariate		
			HR	95% CI	*p*
Age ≥44 <44	 127 (50.60%) 124 (49.40%)	0.568	0.992	0.907–1.086	0.868
Sex Female Male	 79 (31.47%) 172 (68.53%)	0.427	2.500	0.286–21.897	0.408
Pathology WHO II WHO III	 26 (10.36%) 225 (89.64%)	0.400	/	/	0.988
AJCC T2N0 T1N1 T2N1	 56 (22.31%) 46 (19.52%) 149 (58.17%)	0.500	1.408	0.369–5.380	0.617
Technique 2D-CRT IMRT	 73 (29.08%) 178 (70.92%)	0.373	0.449	0.048–4.154	0.480
Treatment RT CCRT CCRT+AC	 94 (37.45%) 103 (41.04%) 54 (21.51%)	0.328	1.065	0.366–3.104	0.908
NLR ≥2.82 <2.82	 44 (17.53%) 207 (82.47%)	0.033	4.399	0.855–22.635	0.076

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; IMRT, intensity-modulated radiotherapy; 2D-CRT, two-dimensional conventional radiotherapy; HR, hazard ratio; CI, confidence interval.

EBV DNA was not routinely tested in our hospital from 2007 to 2010. Moreover, the EBV DNA test varies among different clinics. Thus, this study did not assess the prognostic implication of the EBV DNA titer. On the other hand, several inflammatory biomarkers, including the NLR,[13–16] platelet-to-lymphocyte ratio (PLR),[16] lymphocyte-to-monocyte ratio (LMR),[26] prognostic nutritional index (PNI),[27] and Glasgow Prognostic Score (GPS),[15] were suggested to be associated with the prognosis of NPC patients. Among these inflammatory biomarkers, the NLR is simple to use in clinical practice, but the results varied between studies;[13–16] thus, the NLR needs to be further investigated. Thus, we only assessed the prognosis of the NLR in stage II NPC patients.

Experimental evidence to support the prognostic significance of the NLR with cancer was previously reported. An elevated NLR is a marker of upregulated inflammatory processes within the host microenvironment. Inflammation promotes tumor progression and metastasis via the inhibition of apoptosis, the promotion of angiogenesis, and damage to DNA.[28–30] Neutrophils support the initiation of metastasis by the preferential expansion of clones with high tumorigenicity.[31]

However, the practical application of the NLR still needs to be better defined, especially in NPC patients. Sun et al[32] reported that an NLR ≥2.7 was significantly associated with short progression-free survival. Similar results were also suggested by other studies,[13,15,16,33] although the NLR varied among these studies. On the other hand, Chua et al[14] found that an NLR ≥3.0 was not a prognostic factor in a pooled analysis of two randomized controlled trials. Possible explanations for previous contrary results include the following: (1) the patients included in these studies are highly heterogeneous; some studies included only metastatic NPC patients,[15,33] whereas others assessed I-IV stage patients as a whole group,[13,16] (2) the methods used to identify the value of the NLR were different; some studies used ROC curve analysis,[13,15,16] whereas Chua et al[14] used an NLR value of 3.0 directly, and/or (3) patients are also mostly retrospectively audited, thus likely having received nonstandardized treatments. The present study assessed the NLR only in stage II NPC patients. The patients included in this study were highly homogenous. Moreover, the optimal cut-off values of the NLR were determined by ROC curve analysis for different endpoints. Thus, the results of the current study are more credible.

The cut-off value of the NLR for OS was 2.92 for stage II NPC patients in our study. However, Jin et al[33] reported that an NLR of 3.6 was associated with survival in metastatic NPC patients. Moreover, our study revealed that the NLR was positively associated with T stage. These results indicate that the NLR could contribute to patient stratification by adding a layer of information on disease burden. It is possible that the NLR is associated with the TNM stage. However, the conclusion should be further assessed considering the small sample size of the group of patients in T1 stage. Moreover, the NLR was not associated with N stage or the overall tumor classification stage.

This study had several limitations. First, the risk of treatment failure was very low in stage II NPC patients, which might have reduced the statistical power. Second, confounding factors may still have influenced this retrospective cohort study. Multicenter, large-scale prospective studies will be necessary to assess the precise cut-off values of the NLR as a prognostic marker for NPC.

In conclusion, our study suggests that the NLR is an independent prognostic factor for stage II NPC patients.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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