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ORIGINAL RESEARCH

Predictive Value of Some Inflammatory Indexes in the Survival and Toxicity of Nasopharyngeal Carcinoma

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Objective: The present study aimed to investigate the predictive value of some inflammatory indexes, such as the ratio of C-reactive protein-to-albumin (CAR), high-sensitivity C-reactive protein-to-albumin (HCAR), C-reactive protein-to-lymphocyte (CLR), and high-sensitivity C-reactive protein-to-lymphocyte (HCLR) in the survival and toxicity of nasopharyngeal carcinoma and provide reference for the development of treatment.

Methods: A retrospective analysis was conducted on 162 patients from 2013 to 2018. The value of the indexes before the treatment was calculated. SPSS 25.0 software was used for the analysis, and the cutoff values of the indexes were determined by the receiver operating characteristic curve (ROC). The prognostic value of the indexes was evaluated according to the overall survival rate (OS), progression-free survival rate (PFS), and the incidence of toxic side effects.

Results: The index CLR was found to be the predictor of mortality of nasopharyngeal carcinoma but not the indicator for toxicity.

Conclusion: The index CLR can be used for risk-stratification. However, whether the risk-stratification treatment based on these indicators can improve the prognosis subsequently needs further prospective study.

Keywords: nasopharyngeal carcinoma, C-reactive protein/albumin ratio, high-sensitivity C-reactive protein/albumin ratio, C-reactive protein/lymphocyte ratio, high-sensitivity C-reactive protein/lymphocyte ratio, survival, toxicity

Introduction

Nasopharyngeal carcinoma is one of the most common malignant tumors in China. The annual incidence of the tumor in southern and southeast Asia is about 30/100,000.[1] However, geographical and ethnic differences are observed.[2] Although radiation therapy is the primary treatment for nasopharyngeal carcinoma, comprehensive treatment has been advocated in recent years, which has improved the therapeutic effect and prognosis of the disease. The 5-year survival rate of patients with stage I and II nasopharyngeal carcinoma is 95%. Nonetheless, recurrence and metastasis are still the main reasons for the failure of the treatment of nasopharyngeal carcinoma. Some patients exhibit serious adverse reactions after and during treatment, which affects the survival and quality of life of the patients. Reportedly, the incidence of local recurrence and distant metastasis in nasopharyngeal carcinoma patients at 5 years is 8.2–22.0%,[3] and the therapeutic effects need further improvement.

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Several studies have proved that tumor staging is the main risk factor affecting prognosis. Most of the clinical screening is effectuated via tumor staging and treatment planning. Tumor staging is based on anatomical factors and neglects biological characteristics of tumor cells. Thus, the predictive effect of tumor staging on nasopharyngeal carcinoma has some limitations. Accumulating evidence has confirmed that inflammation is a hallmark of cancer and plays a major role in the development of tumors.[4] Indicators based on inflammatory response, such as Glasgow prognostic score (GPS),[5–8] C-reactive protein-to-albumin ratio (CAR),[9–14] neutrophil-to-lymphocyte ratio (NLR),[15–17] and platelet-to-lymphocyte ratio (PLR)[18–20] are crucial while evaluating the survival and toxicity of several cancers.[21] However, the effect of CAR, high-sensitivity CAR (HCAR), C-reactive protein-to-lymphocyte ratio (CLR), and high-sensitivity CLR (HCLR) on the prognosis of nasopharyngeal carcinoma is unclear. Therefore, the present study aimed to evaluate the predictive value of CAR, HCAR, CLR, and HCLR for the survival and toxicity outcomes in patients with nasopharyngeal carcinoma intensity-modulated radiation therapy (IMRT).

Methods

Information

The information on the cases of nasopharyngeal carcinoma from 2013 to 2018 was collected. The follow-up deadline was June 2019. This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital (LW2020027), in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Enrollment criteria for the study: (1) age 6–75 years; (2) pathological diagnosis of nasopharyngeal carcinoma; (3) intensity-enhanced radiotherapy for nasopharyngeal carcinoma, combined with or without chemotherapy; (4) received anti-tumor therapy previously, and peripheral blood inflammation markers could be obtained; (5) KPS ≥70 points. The exclusion criteria were as follows: (1) other histologically derived malignant tumors; (2) nasopharyngeal carcinoma patients with newly diagnosed metastasis or newly diagnosed patients suspected of distant metastasis; (3) KPS <70 points; (4) severe infection, requiring intravenous antibiotics and antifungal or antiviral therapy; (5) failure to retrieve pretreatment peripheral blood inflammatory markers; (6) severe blood system, infectious, cardiac, and cerebrovascular diseases.

This study was approved by the ethics committee of our center. A total of 162 patients who met the above criteria were included in the present study. Baseline data, including the general information, related medical history, hematological parameters, staging (AJCC 8th edition staging), treatment plan, radiotherapy dose, survival, and various toxic side effects, were collected. Also, CAR, HCAR, CLR, and HCLR were calculated. The general characteristics of the patients and diseases are shown in Table 1.

Statistical Methods

All indicators were analyzed by the Kolmogorov–Smirnov test (K-S). Except for the age distribution, which is a homogeneous distribution of normal variance, other indicators showed non-normal distribution.

Correlation Analysis

The continuous normal distribution data were analyzed by bivariate Pearson's correlation analysis. The continuous non-normal distribution data or the non-normal distribution grade data were selected by bivariate Spearman correlation analysis, and the bivariate Kendall correlation analysis was used to assess the classification and grade data.

Determination of Cutoff Values

The optimum cutoff values of CAR, HCAR, CLR, and HCLR for the prediction of survival and toxicity were determined through the receiver operating characteristic (ROC) curve analysis. ROC curves were generated to select the optimal cutoff point with the highest Youden's index for OS and PFS.

Univariate and Multivariate Analysis

In this study, the survival rate was calculated using the Kaplan–Meier method, and univariate and multivariate analyses (Cox proportional hazards model) were used to identify the factors significantly associated with prognosis. However, to determine the risk factors affecting the occurrence of bone marrow suppression, gastrointestinal tract reactions, radioactive skin and mucosal reaction. The comparisons between groups were performed using the Mann–Whitney *U*-test and Student's *t*-test for continuous variables, Kruskal–Wallis *H*-test was used to compare the differences between 3 groups and above and multivariate analysis (Logistic regression) was performed on the significant indicators in univariate analysis.

Table 1 Patients' and Disease Characteristics

Variables	Cases (%)
Age (years)	<18:1 (0.6%) 19–60:146 (90.1%) >60:15 (9.3%)
Gender	Male 118 (72.8%) Female 44 (27.2%)
Smoking	Yes 59 (36.4%) No 103 (63.6%)
Nasopharyngeal carcinoma family inheritance	Yes 11 (6.8%) No 151 (93.2%)
Family history of malignant tumors	Yes 14 (8.6%) No 148 (91.4%)
T stage (1/2/3/4)	T1:13 (8.0%) T2:71 (43.8%) T3:49 (30.3%) T4:29 (17.9%)
N stage (0/1/2/3)	N0:7 (4.3%) N1:43 (26.6%) N2:83 (51.2%) N3:29 (17.9%)
Tumor stage	I:1 (0.6%) II:26 (16.0%) III:78 (48.2%) IV:57 (35.2%)
Treatment	Radiotherapy alone:12 (7.4%) Synchronous chemoradiotherapy: 49 (30.3%) IMRT+ Adjuvant chemotherapy: 101 (62.3%)
Radiotherapy dose (GTV)	<70.4Gy:34 (21%) 70.4–70.94Gy:18 (11.1%) 70.95–72.6Gy:105 (64.8%) >72.6Gy:5 (3.1%)
Myelosuppression	I: 40 (24.7%) II: 74 (45.7%) III: 37 (22.8%) IV: 11 (6.8%)
Gastrointestinal reaction	0: 81 (50%) I: 17 (10.5%) II: 50 (30.9%) III: 13 (8.0%) IV: 1 (0.6%)
Radioactive skin and mucosal reaction	I: 65 (40.1%) II: 67 (41.4%) III: 30 (18.5%)

Notes: Grading was performed according to the AJCC 8th edition staging, RTOG Acute Radiation Injury Grading Criteria and Adverse Event General Terminology Criteria (CTCAE) v4.03. GTV refers to clinically visible or accessible tumor sites and tumor areas that can be confirmed by means of diagnostic tests.
Abbreviation: GTV, gross tumor volume.

Survival Analysis

Survival curves were plotted using the Kaplan–Meier method, and the Log rank test was applied to assess the differences between survival rates. The prognostic value of CAR, HCAR, CLR, HCLR, and other variables (age and smoking) was assessed by multivariate Cox regression analysis.

P<0.05 indicated statistically significant difference. All the analyses were carried out using SPSS version 25.

Results

Survival Outcomes

The median survival time was 32.5 (4–48) months, The median follow-up time was 50 (9–99) months. In the cohort, 20 patients died, 6 patients had a local recurrence (1 death), and 19 patients (11 deaths) had distant metastasis during and after treatment. The specific survival time could not be estimated by the K-M curve due to the small number of deaths in this study. The OS and PFS rate was 87.7% and 84.6%, respectively, the 1-year survival rate was 96.9%, and the 3-year OS rate was 68.5%, respectively.

Correlation Analysis

CAR, CLR, and HCLR were weakly correlated with T, N, and tumor stage (P<0.05, r<0.3); HCAR was weakly correlated with T, N staging, and radiation skin mucosal reaction (P<0.05, r<0.3). In order to further verify whether the model was successfully established, we performed a collinear analysis. Obvious collinearity was detected between the four indicators of CAR, HCAR, CLR, and HCLR (variance inflation factor, VIF, 15.762–26.189); however, none was observed between CAR, HCAR, CLR, HCLR, and other indicators (VIF<5).

Cutoff Values for CAR, HCAR, CLR, and HCLR

The optimal cutoff value for the survival prediction was determined by ROC curve analysis. When OS was taken as the endpoint of CAR, HCAR, CLR, and HCLR, the critical value of CAR was 0.08 (P<0.001, sensitivity 85.0%, specificity 72.5%), the HCAR cutoff value was 0.03 (P<0.001, sensitivity 90.0%, specificity 75.4%), the CLR cutoff value was 1.41 (P<0.001, sensitivity 95.0%, specificity 58.5%), and the HCLR threshold was 0.45 (P<0.001, sensitivity 95.0%, specificity 64.8%) (Figure

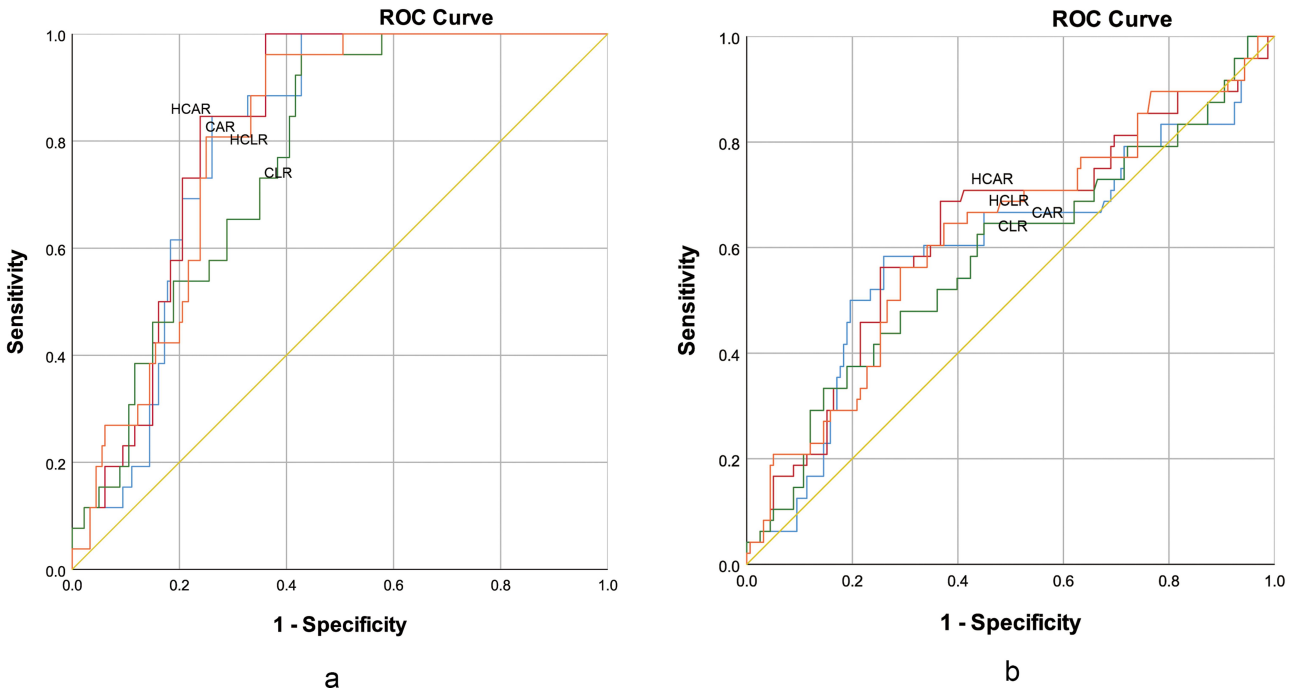

Figure 1 The ROC curve of CAR, HCAR, CLR, HCLR based on the overall survival (OS) (**a**) and the progression-free survival (PFS) (**b**).
Abbreviations: ROC, receiver operating characteristic; CAR, C-reactive protein-to-albumin ratio; HCAR, high-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, hypersensitive C-reactive protein-to-lymphocyte ratio.

1A). When PFS was used as the endpoint, the CAR threshold was 0.08 (P<0.05, sensitivity 63.6%, specificity 72.9%), the HCAR cutoff was 0.02 (P<0.01, sensitivity 75.8%, specificity, sexuality 64.3%), the CLR threshold was 2.01 (P<0.05, sensitivity 51.5%, specificity 76%), and the HCLR cutoff value was 0.62 (P<0.01, sensitivity 63.6%, specificity 71.3%) (Figure 1B).

Kaplan–Meier Curves

The Kaplan–Meier survival curves of CAR (Figure 2A), HCAR (Figure 2B), CLR (Figure 2C), and HCLR (Figure 2D) based on total OS and the Kaplan–Meier survival curves of CAR (Figure 3A), HCAR (Figure 3B) and HCLR (Figure 3D) based on PFS showed statistical significance (P<0.05), however, the K-M curve of CLR (Figure 3C) based on PFS showed no significant statistical significance (P > 0.05), indicating that the OS and PFS rate of low-level CAR, HCAR, and HCLR was significantly higher than that of high-level CAR, HCAR, HCLR. A high level of CLR predicted poor OS.

Univariate and Multivariate Analysis

Table 2 summarizes the results of univariate analysis. Univariate analysis revealed that radiotherapy dose (P=0.015), CAR (≤0.08/>0.08) (P<0.001), HCAR (≤0.03/>0.03) (P=0.001), CLR (≤1.41/>1.41) (P=0.002), and HCLR (≤0.45/>0.45) (P<0.001) were significantly associated with OS. N stage (P=0.002), tumor stage (P=0.029), treatment (P=0.007), radiotherapy dose (P=0.044), CAR (≤0.08/>0.08) (P=0.017), HCAR (≤0.02/>0.02) (P=0.015), HCLR (≤0.62/>0.62) (P=0.043), and gastrointestinal reaction (P=0.060) were significantly associated with PFS. In order to identify the optimal influencing factors, the variables that were significant in univariate analysis (P<0.1) were subjected to multivariate analysis to identify the independent prognostic indicators for OS and PFS. Multivariate analysis suggested that CLR (HR 11.763; 95% CI, 1.257–110.050; P=0.031) was an independent indicator affecting OS. Gender (HR 3.152; 95% CI: 1.501–6.618; P=0.002), treatment (P=0.017), and gastrointestinal reaction (P=0.006) were independent indicators affecting PFS.

Toxicity

Univariate and multivariate analysis of toxic side effects showed that gender, T stage, N stage, and treatment plan were related to the occurrence of myelosuppression. The choice of the treatment plan was related to the occurrence of gastrointestinal reaction and radioactive skin and mucosal reaction. Univariate analysis suggested that the index

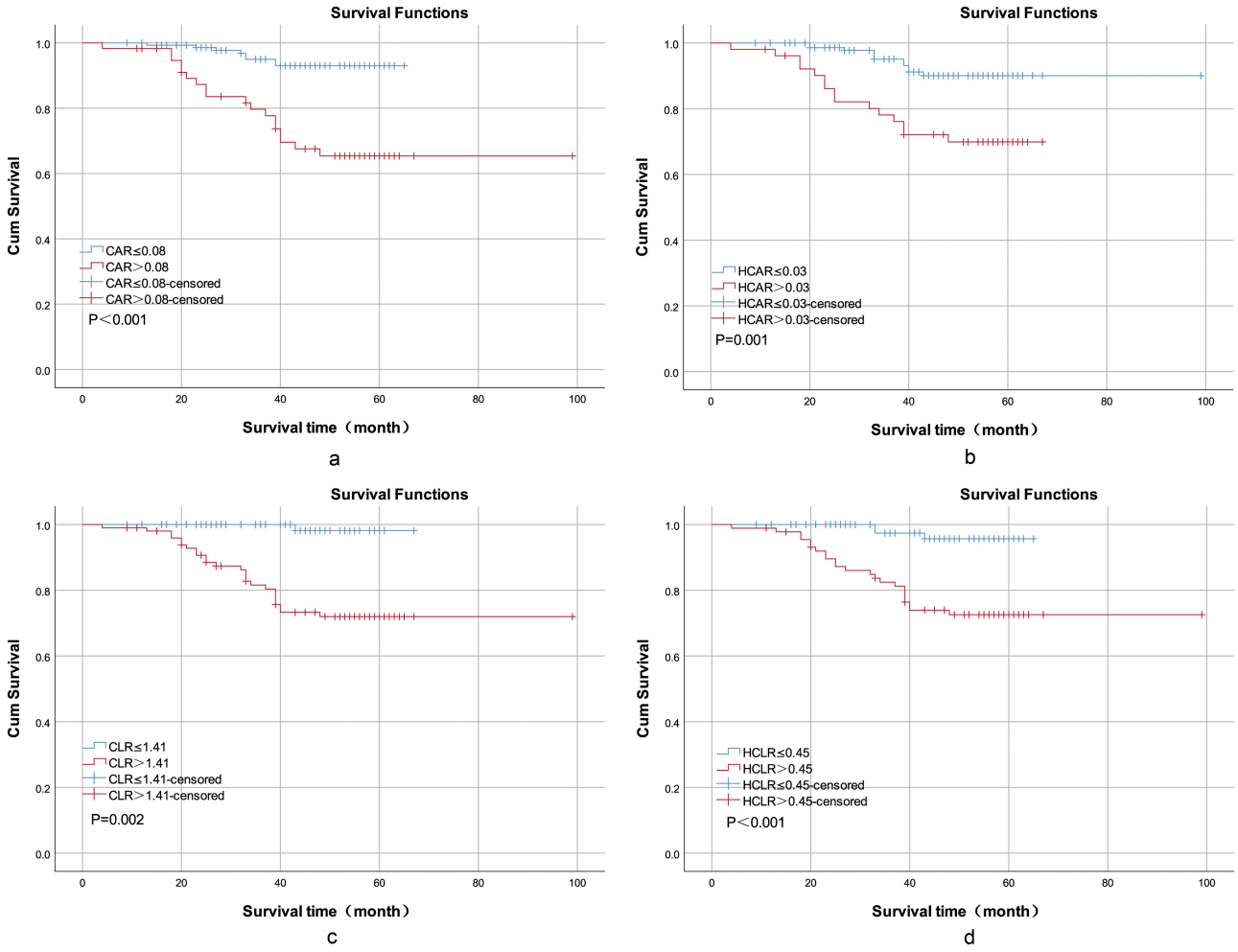

Figure 2 The Kaplan–Meier survival curves of CAR (**a**), HCAR (**b**), CLR (**c**), HCLR (**d**) based on the overall survival (OS).
Abbreviations: CAR, C-reactive protein-to-albumin ratio; HCAR, high-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, hypersensitive C-reactive protein-to-lymphocyte ratio.

of CAR predicted the occurrence of gastrointestinal reaction but not in a multivariate analysis. However, no significant difference was detected in HCAR, CLR, and HCLR in myelosuppression, gastrointestinal reaction, and radiation skin damage (Table 3).

Discussion

Nasopharyngeal carcinoma refers to malignant tumor that occurs on the top and side walls of the nasopharyngeal cavity. It is one of the high-grade malignant tumors in China detected in the ear, nose, and throat. It is moderately sensitive to radiation therapy, which is the preferred treatment for nasopharyngeal carcinoma. However, due to the easy recurrence and early metastasis of the tumor, the prognosis is still poor. Reportedly, the incidence of local recurrence and distant metastasis in nasopharyngeal carcinoma patients at 5 years is 8.2–22.0%.[3] Consecutively, the adverse reactions, such as myelosuppression, gastrointestinal reactions, radioactive skin, and mucosal damage post-radiotherapy and chemotherapy severely affect the quality of life of patients. Therefore, by studying the risk factors associated with the prognosis of patients with nasopharyngeal carcinoma, screening high-risk patients and their systematic treatment is of great clinical significance for improving the prognosis and quality of life.

Inflammation is closely related to tissue damage and infection. In recent years, exploring the correlation between inflammation and cancer has been a hot topic of research in clinical oncology. Accumulating evidence confirms that inflammation is a hallmark of cancer and plays a major role in the development of tumors.[4] First, chronic inflammation promotes the development of tumors, such as hepatitis-related liver cancer, *Helicobacter pylori* infection caused by gastric cancer, repeated esophageal

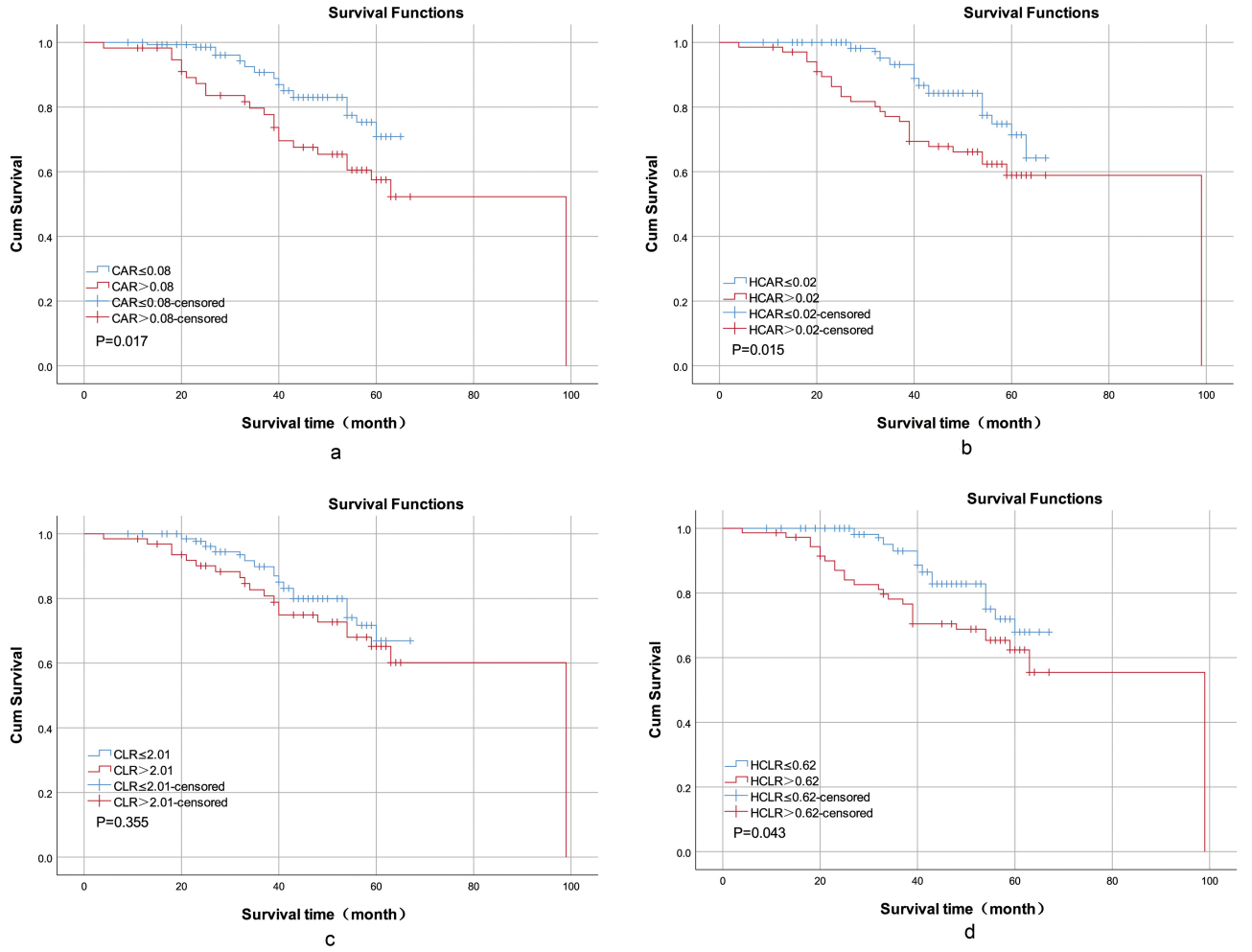

Figure 3 The Kaplan–Meier survival curves of CAR (**a**), HCAR (**b**), CLR (**c**), HCLR (**d**) based on the progression-free survival (PFS).
Abbreviations: ROC, receiver operating characteristic; CAR, C-reactive protein-to-albumin ratio; HCAR, high-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, hypersensitive C-reactive protein-to-lymphocyte ratio.

inflammatory lesions, and esophageal cancer. Second, inflammation is a vital part of tumor development as it changes the tumor microenvironment and could be involved in tumor invasion, migration, and metastasis.[22] C-reactive protein (CRP) is a typical acute phase protein that is a nonspecific, acute inflammatory marker. The plasma concentration rises rapidly with inflammation, infection, tissue damage, and the development of cancer. Therefore, CRP and CAR and other inflammatory markers are associated with poorer survival in many malignancies. A meta-analysis[13] showed that in addition to colorectal cancer, high-level CAR is associated with poor prognosis of other malignancies, suggesting that it can be used as a prognostic indicator for human malignancies in a clinical setting. Thus, the present study aimed to investigate the predictive value of some inflammatory indexes based on CRP (CAR, HCAR, CLR, and HCLR) in the survival and toxicity of nasopharyngeal carcinoma and provide reference for the development of treatment.

In this study, univariate analysis showed that CAR, HCAR, CLR, and HCLR significantly affected the total OS. Furthermore, CAR, HCAR, and HCLR indexes exerted statistically significant influence on PFS. The Kaplan–Meier survival curve showed that the OS and PFS of low-level CAR, HCAR, CLR, and HCLR were better than those of the high-level group. However, multivariate analysis suggested that only CLR index had statistically significant influence on OS. No significant differences were noted in the toxicity.

The results showed that CLR is a critical indicator for predicting the survival rate of patients with nasopharyngeal carcinoma. However, CAR, HCAR, CLR, and HCLR were not significantly associated with the occurrence of recent toxic side effects in the carcinoma. These results

Table 2 Univariate and Multivariate Analysis Results of OS and PFS

Variables	OS				PFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95.0% CI)	P	HR (95.0% CI)	P	HR (95.0% CI)	P	HR (95.0% CI)	P
Age (years)	1.031 (0.992–1.072)	0.122			1.011 (0.983–1.014)	0.444		
Gender (male/female)	0.601 (0.336–1.077)	0.087	1.003 (0.453–2.221)	0.995	1.663 (0.928–2.980)	0.087	3.152 (1.501–6.618)	0.002
Smoking	0.789 (0.317–1.964)	0.610			0.654 (0.316–1.355)	0.253		
NPC family inheritance	0.537 (0.073–3.963)	0.542			0.266 (0.037–1.933)	0.191		
Family history of malignant tumors	0.046 (0–101.123)	0.433			0.771 (0.187–3.182)	0.719		
T stage		0.675				1		
T1	1.664 (0.213–13.008)	0.627			1.013 (0.300–3.415)	0.983		
T2	2.411 (0.308–18.848)	0.402			1.058 (0.307–3.655)	0.928		
T3	2.642 (0.308–22.636)	0.375			1.120 (0.289–4.339)	0.870		
T4	1				1			
N stage		0.147				0		0.094
N0	1				1		1	
N1	0.154 (0.010–2.460)	0.186			0.276 (0.046–1.660)	0.160	2.290 (0.317–16.550)	0.412
N2	1.352 (0.180–10.163)	0.769			1.199 (0.282–5.092)	0.806	0.154 (0.019–1.236)	0.078
N3	1.797 (0.221–14.612)	0.584			2.597 (0.592–11.383)	0.206	0.796 (0.288–2.204)	0.661
Tumor stage		0.664				0.029		0.763
I	0.001 (0–0.001)	0.988			175.702 (0–1.138*10^77)	0.953	244.026 (0–1.359*10^64)	0.940
II	0.311 (0.040–2.411)	0.264			363.035 (0–2.343*10^77)	0.947	107.972 (0–6.028*10^63)	0.949
III	0.729 (0.333–1.600)	0.431			749.971 (0–4.840*10^77)	0.940	162.547 (0–9.077*10^63)	0.944
IV	1				1		1	
Treatment		0.612				0.007		0.017
Radiotherapy alone	0.926 (0.187–4.592)	0.926			0.791 (0.159–3.934)	0.775	0.819 (0.120–5.574)	0.838
Synchronous chemoradiotherapy	1.436 (0.333–6.191)	0.627			2.854 (0.688–11.844)	0.149	3.493 (0.549–22.225)	0.185
IMRT+ Adjuvant chemotherapy	1				1		1	
Radiotherapy dose	1.720 (1.112–2.660)	0.015	1.484 (0.950–2.316)	0.082	1.372 (1.008–1.868)	0.044	1.301 (0.913–1.852)	0.145
CAR	5.715 (2.484–13.147)	0.000	1.688 (0.661–4.310)	0.274	2.047 (1.139–3.679)	0.017	0.738 (0.293–1.860)	0.519
HCAR	3.773 (1.731–8.221)	0.001	1.480 (0.580–3.776)	0.412	2.070 (1.155–3.711)	0.015	2.952 (0.628–13.877)	0.170
CLR	25.381 (3.439–187.34)	0.002	11.763 (1.257–110.050)	0.031	1.327 (0.729–2.417)	0.355		
HCLR	8.799 (2.640–29.332)	0.000	1.300 (0.293–5.768)	0.730	1.832 (1.018–3.296)	0.043	1.083 (0.234–5.009)	0.918

(*Continued*)

Table 2 (Continued).

Variables	OS				PFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95.0% CI)	P	HR (95.0% CI)	P	HR (95.0% CI)	P	HR (95.0% CI)	P
Myelosuppression		0.313				0.197		
I	0.608 (0.244–1.513)	0.284			0.816 (0.349–1.911)	0.640		
II	0.337 (0.101–1.122)	0.076			1.124 (0.475–2.659)	0.791		
III	0.922 (0.244–3.480)	0.904			2.170 (0.784–6.003)	0.136		
IV	I				I			
Gastrointestinal reaction		0.301				0.060		0.006
0	I				I		I	
I	0	0.975			0.389 (0.117–1.293)	0.123	0.338 (0.089–1.283)	0.111
II	0.379 (0.140–1.029)	0.057			0.455 (0.219–0.948)	0.035	0.345 (0.158–0.754)	0.008
III	1.471 (0.495–4.374)	0.487			1.209 (0.463–3.155)	0.698	2.996 (0.972–9.231)	0.056
IV	0	0.991			2.412 (0.569–10.221)	0.232	0.289 (0.058–1.433)	0.129
Radioactive skin and mucosal reaction		0.273				0.456		
I	1.764 (0.704–4.421)	0.226			1.359 (0.705–2.621)	0.360		
II	2.375 (0.798–7.073)	0.120			1.650 (0.722–3.772)	0.235		
II	I				I			

Abbreviations: NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; CAR, C-reactive protein-to-albumin ratio; HCAR, high-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, hypersensitive C-reactive protein-to-lymphocyte ratio.

Table 3 Univariate and Multivariate Analysis of Myelosuppression, Gastrointestinal Reactions, Radioactive Skin and Mucosal Reaction

Toxicity	Myelosuppression		Gastrointestinal Reaction		Radioactive Skin and Mucosal Reaction	
n	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
	(P)	(P)	(P)	(P)	(P)	(P)
Age (years)	0.305		0.552		0.083	
Gender (male/female)	0.003	0.000	0.537		0.696	
Smoking (yes/no)	0.236		0.788		0.722	
NPC family inheritance (yes/no)	0.046		0.572		0.302	
Family history of malignant tumors (yes/no)	0.410		0.801		0.056	
T stage (T1/2/3/4)	0.021	0.005	0.390		0.175	
N stage (N0/1/2/3)	0.017	0.044	0.249		0.096	
Tumor stage (I/II/III/IV)	0.000		0.173		0.278	
Treatment	0.000	0.000	0.003	0.000	0.006	0.008
Radiotherapy alone						
Synchronous chemoradiotherapy						
IMRT+Adjuvant chemotherapy						
Radiotherapy dose	0.008		0.142		0.202	
CAR (≤0.08/>0.08)	0.720		0.034		0.073	
HCAR (≤0.03/>0.03)	0.842		0.050		0.520	
CLR (≤1.41/>1.41)	0.877		0.448		0.094	
HCLR (≤0.45/>0.45)	0.515		0.062		0.271	

Abbreviations: NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; CAR, C-reactive protein-to-albumin ratio; HCAR, high-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, hypersensitive C-reactive protein-to-lymphocyte ratio.

differed from those of the meta-analysis by Xu et al (high pretreatment CAR indicates poor prognosis in human malignancies except colorectal cancer).[13] Moreover, the recent occurrence of the toxic side effects in the pharyngeal cancer was different from the results of the study by Tominaga et al (CAR as a significant determinant of severe side effects of adjuvant chemotherapy with stage III colorectal cancer).[10] However, our study did not find significant effects of CAR on prognosis and toxic and side effects of inflammatory markers, which might be attributed to a variety of confounding factors as well as limited number of samples.

First, this is a retrospective analysis that may have selection bias and aliasing variables. When the recent toxic side effects occurred, due to the timely clinical detection and effective treatment, only a few cases of grade 4 adverse reactions were observed in this study. In addition, the patients with the KPS score >70 exhibited a satisfactory nutritional status based on albumin and other nutrition. Intriguingly, the effects of low levels of CAR, HCAR, CLR, and HCLR were excluded, and selection biases were inevitable. Secondly, the correlation analysis revealed that CAR, CLR, and HCLR were weakly correlated with T, N, and tumor stage, while HCAR was weakly correlated with T, N staging, and radiation skin mucosal reaction. Thus, we performed a collinear analysis. Since CAR, HCAR, CLR, and HCLR are calculated based on albumin, lymphocytes, and two common indicators, distinct collinearity was observed. However, no obvious collinearity was detected with other indicators, suggesting that the model was established successfully. Thirdly, this experiment does not systematically describe the individual

treatment plan, the dosage, and the treatment cycle. Thus, the possibility that the specific choice of treatment options and other factors leads to different degrees of toxic side effects cannot be excluded. Nevertheless, the present study has certain limitations. This study included a total of 162 cases constituting a small sample size, thereby necessitating large-scale studies for further validation. Also, a retrospective, single-center study on high-risk for nasopharyngeal carcinoma is required to evaluate the treatment effect and survival prognosis.

The current study clarified not only the CAR indicators for nasopharyngeal carcinoma associated with poor prognosis, but the predictive role of HCAR, CLR, and HCLR is yet unclear in patients with nasopharyngeal carcinoma. To the best of our knowledge, no previous report has examined the correlation between inflammation-based indexes and the side effects of chemotherapy in nasopharyngeal cancer. In addition, compared with previous studies, this study includes four indicators (CAR, HCAR, CLR, and HCLR), which are of certain novelty. Our data suggested that in nasopharyngeal cancer patients treated with IMRT, CLR, but not PFS or toxicity, is an independent predictor of mortality. CLR is a readily available biomarker that could improve the pretreatment prognostication and may be used for risk-stratification. This finding could be attributed to CLR that is composed of CRP and lymphocytes, both of which are closely related to the state of inflammation. Tumor-related inflammation causes suppression of antitumor immunity by recruiting regulatory T cells and activating chemokines, which in turn, result in tumor growth and metastasis. CRP is a typical acute phase protein; its plasma concentration increases rapidly with the development of inflammatory tissue damage and cancer; also, it is a non-specific inflammatory marker in the acute phase. Therefore, CRP and CRP-based inflammatory markers, such as CAR and CLR, have been shown to predict poor survival in previous studies of multiple malignancies. CLR is an inexpensive and easily measurable indicator of inflammation that can help clinicians develop personalized treatment and follow-up strategies for patients with non-metastatic nasopharyngeal cancer.

Conclusion

This study showed that CLR is a novel and promising inflammatory score for the survival prognosis in patients with nasopharyngeal carcinoma treated with IMRT. However, it could not be concluded that CAR, HCAR, and HCLR have no predictive effect on survival prognosis, thereby necessitating stringent standards for a large-scale study in the future.

Abbreviations

CAR, C-reactive protein-to-albumin ratio; HCAR, High-sensitivity C-reactive protein-to-albumin ratio; CLR, C-reactive protein-to-lymphocyte ratio; HCLR, Hypersensitive C-reactive protein-to-lymphocyte ratio; IMRT, Intensity-modulated radiation therapy; OS, Overall survival; PFS, Progression-free survival; K–S test, Kolmogorov–Smirnov test; ROC, Receiver operating characteristic; GTV, Gross tumor volume; NPC, nasopharyngeal carcinoma; KPS, Karnofsky Performance Status; AJCC, American Joint Committee on Cancer; VIF, variance inflation factor.

Ethical Approval

This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital (LW2020027), in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

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Disclosure

The authors declare no conflicts of interest.

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