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RESEARCH ARTICLE

Elevated neutrophil to lymphocyte ratio predicts poor prognosis in nasopharyngeal carcinoma

Xin An · Pei-Rong Ding · Feng-Hua Wang · Wen-Qi Jiang · Yu-Hong Li

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Abstract Elevated neutrophil to lymphocyte ratio (NLR) has been reported to be associated with worse survival in many malignancies, whereas its role in nasopharyngeal carcinoma (NPC) remains unclear. We retrospectively reviewed 363 consecutively, newly diagnosed, non-disseminated, and biopsy-proven NPC patients. Disease-specific survival (DSS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRFS) rates were compared according to NLR level. Multivariate analysis was performed to assess the prognostic value of NLR. The 5-year DSS, DMFS, and LRFS rates for patients with elevated or non-elevated NLR (> or ≤3.73) were 59.6% vs. 76.6% (p=0.03), 69.7% vs. 86.6% (p=0.002), and 78.5% vs. 87.3% (p=0.105), respectively. For patients with locoregionally advanced disease, NLR was not only an independent prognostic factor, but also a predictor of response to chemoradiotherapy. The 5-year DSS, DMFS, and LRFS rates for patients with elevated or non-elevated NLR were 47.2% vs. 73.7% (p<0.001), 59.2% vs. 85.1% (p<0.001), and 72.3% vs. 84.6% (p=0.041), respectively. Compared with radiation alone, chemoradiotherapy significantly improved DSS and LRFS for patients with non-elevated NLR, but not for those with elevated NLR. Pretreatment NLR is a strong prognostic factor for NPC patients. For patients with locoregionally advanced disease, NLR might also be a useful indicator for selection of treatment strategies.

Keywords Chemoradiotherapy · Neutrophil to lymphocyte ratio · Nasopharyngeal carcinoma · Radiotherapy · Prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common malignancies in southern China, especially in the region of Guangdong Province, where the incidence is 30 to 80 of 100,000 people per year [1]. Although NPC is sensitive to radiotherapy (RT), the long-term survival remains poor due to high incidence of distant metastasis and (or) local recurrences. Currently, the prognosis for NPC patients mainly relies on clinical staging. However, patients with the same clinical stage often present different clinical outcomes, indicating that the clinical staging is insufficient for precisely predicting prognosis of NPC. Various prognostic factors for NPC have been identified and evaluated retrospectively, most of these factors were identified by immunohistochemical staining of tumor tissue, such as apoptosis-related protein survivin and livin [2], angiogenetic factor vascular endothelial growth factor [3], and so

Xin An and Pei-Rong Ding contributed equally to this work.

X. An · P.-R. Ding · F.-H. Wang · W.-Q. Jiang · Y.-H. Li
State Key Laboratory of Oncology in South China,
651 Dongfeng East Road,
Guangzhou, Guangdong 510060, People's Republic of China

X. An · F.-H. Wang · W.-Q. Jiang · Y.-H. Li (✉)
Department of Medical Oncology, Cancer Center,
Sun Yat-sen Universisty,
Guangzhou, Guangdong 510060, People's Republic of China
e-mail: liyh@sysucc.org.cn

P.-R. Ding
Department of Colorectal Surgery, Cancer Center,
Sun Yat-sen Universisty,
Guangzhou, Guangdong 510060, People's Republic of China

on. However, few of these markers are currently in clinical application. It is therefore critical to explore valuable factors to predict outcome for NPC patients.

Recent studies have shown that systemic inflammatory response could promote tumor metastasis and progression by inhibition of apoptosis, promotion of angiogenesis, and damage of DNA [4]. Neutrophil to lymphocyte ratio (NLR), one of the inflammatory marker, has been shown to be associated with progression and metastasis of many kinds of malignancies, including colorectal cancer [5–7], gastric cancer [8], non-small cell lung cancer [9], ovarian cancer [10], intrahepatic cholangiocarcinoma [11], hepatocellular carcinoma [12, 13], and pancreatic cancer [14]. However, there is no report about the possible role of NLR in NPC patients. We therefore conducted this retrospective study to investigate whether NLR could serve as a prognostic factor in NPC patients.

Material and methods

Study population

A total of 381 consecutive newly diagnosed, histologically proven, and non- disseminated NPC patients were hospitalized and treated at the Sun Yat-sen University Cancer Center (Guangzhou, China) between November 2001 and July 2002. Of these patients, 18 were subsequently eliminated from the study, including ten patients who presented recurrence disease and had received RT therapy before, five patients who had residual disease after RT, and three patients who developed metastasis during the treatment. Thus, 363 patients were included in the analysis. There were 274 (75.5%) male patients and 89 (24.5%) female patients. The median age was 47 years (range, 12–76 years). The routine workup was done before the initiation of treatment, which included a complete physical examination, hematologic and biochemistry profiles, endoscopic examination of the nasopharynx, computed tomography (CT) or magnetic resonance imaging (MRI) scan of the nasopharynx and neck, chest plain film or CT scan, and abdominal sonography or CT scan. According to the 1997 AJCC staging system [15], 14 patients (3.9%) were classified as stage I, 81 patients (22.3%) as stage II, 165 patients (45.4%) as stage III, and 103 patients (28.4%) as stage IVA (M0) disease. Informed consent has been obtained, and procedures followed were in accordance with the institutional ethical standards of the responsible committee on human experimentation.

The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. All patients had no coexistent hematologic disorders or known active infection before treatment, ensuring that the white cell count was representative of normal baseline value.

Treatment and follow-up

All patients were treated with standard curative RT with or without chemotherapy. The median radiation dose was 70 Gy (range, 60–80 Gy) to the nasopharyngeal region and 60 Gy (range, 40–72 Gy) to the initially involved cervical node. For 268 locoregionally advanced stage III and IVA patients, 133 patients (49.6%) were treated with RT alone and 135 (50.4%) patients were treated with cisplatin and/or 5-FU-based neoadjuvant (28 patients) and/or concurrent chemotherapy (107 patients). Thirty-three (24.4%) patients received one cycle of chemotherapy, 88 (65.2%) patients received two cycles of chemotherapy, and 14 (10.4%) patients received three cycles of chemotherapy.

Patients were followed up at least every 3 months during the first 2 years; thereafter, patients were followed up every 5 months until death or until July 2009. The median follow-up period for the whole group was 62 months (range, 2–92 months). The following endpoints were assessed: disease-specific survival (DSS); distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRFS). Local recurrence was established by fiberoptic endoscopy and biopsy and/or MRI. Distant metastases were diagnosed based on clinical symptoms, physical examination, and imaging methods including chest plain film or CT scan, bone scan, and abdominal sonography or CT scan. Whenever possible, salvage treatments were given to patients after documented recurrence. The treatment employed included reirradiation, chemotherapy, and surgery.

Statistical analysis

Statistical analysis was performed by using SPSS statistical software (SPSS Inc, Chicago, IL, USA, version 12.0 for Windows). Receiver operating characteristic (ROC) curve analysis was performed to select the most appropriate cut-off point of NLR to stratify patients at a high risk of malignancy-related death. At each value, the sensitivity and specificity was plotted, thus generating an ROC curve. The score closest to the point with both maximum sensitivity and specificity (i.e., the point [0.0, 1.0] on the curve) was selected as the cut-off value. Chi-square tests were used to analyze differences among groups of patients with elevated or non-elevated NLR. The DSS, DMFS, and LRFS rates were calculated by the Kaplan–Meier method, and survivals were compared by using the log-rank test. Multivariate analyses with the Cox proportional hazards model were used to test independent prognostic impact of NLR. *P*

values of less than 0.05 were considered statistically significant.

Results

Recurrence and survival analysis

By July 2009, 49 patients (13.5%) developed locoregional recurrences, 72 patients (19.8%) developed distant metastases, and five patients (1.4%) developed both distant metastases and local–regional recurrences. Overall, the 5-year failure-free survival (FFS) rate was71.6%. The 5-year LRFS and DMFS rates were 87.4% and 82.5%, respectively. One hundred and one patients (27.8%) died of all causes, among which 96 (95.0%) died of recurrence disease. The 5-year DSS rate was 72.2%.

Determinants of NLR status

The mean NLR level was 3.07±1.65 (range, 0.72–11.0). An NLR value of 3.73 resulted in the most appropriate sensitivity of 0.66 and specificity of 0.55 for DSS. Using 3.73 as the cut-off point, we identified 92 patients (25.3%) as elevated NLR. None of the demographic and clinical characteristics, including age, gender, performance status (PS), T stage, N stage, and treatment modality, or serum lactate dehydrogenase (LDH) level was associated with elevated NLR.

NLR predicted survival for NPC patients

Various potential prognostic factors and NLR status were univariately analyzed by the log-rank test (Table 1). T status, N status, and NLR status were predictors of malignancy-related death. N status and NLR status were predictors of distant metastasis. T status and gender were predictors of local disease recurrence. Multivariate analysis showed that NLR status was an independent predictor of both malignancy-related death and distant metastasis. Other independent factors were advanced T and N status (predicted malignancy-related death), advanced N status (predicted distant metastasis) and advanced T status (predicted local disease recurrence) (Table 2).

Kaplan–Meier analysis showed that patients with an elevated pre-treatment NLR had a significant shorter DSS and higher distant metastatic rate than those with non-elevated NLR. The 5-year DSS rate was 59.6% in the elevated NLR group and 76.6% in the non-elevated NLR group (p=0.03). Five-year DMFS rate in the elevated NLR group and low NLR group were 69.7% and 86.6%, respectively (p=0.002). There was a trend of lower LRFS rate in patients with elevated NLR than in those with non-elevated NLR (78.5% vs. 87.3%, p=0.105) (Table 1 and Fig. 1).

NLR predicted response to chemoradiotherapy (CRT) for patients with locoregionally advanced stage

For 268 patients who had locoregionally advanced disease (stage III/IVA), 5-year DSS, FFS, DMFS, and LRFS rates were 66.7%, 66.0%, 78.6%, and 81.3%, respectively. Seventy out of 268 patients showed elevated NLR level (>3.73), whereas 198 patients showed non-elevated NLR level (≤3.73). The 5-year DSS, DMFS, and LRFS rates between elevated NLR group and non-elevated NLR groups were 47.2% vs. 73.7% ($p< 0.001$), 59.2% vs. 85.1% ($p<0.001$), and 72.3% vs. 84.6% (p=0.041), respectively (Fig. 2). For patients treated with RT alone (133 patients), the 5-year DSS rates between elevated NLR group and non-elevated NLR groups were 51.9% vs. 69.1 (p=0.014), while for patients treated with CRT (135 patients), the 5-year DSS rates between elevated NLR group and non-elevated NLR groups were 46.2% vs. 77.3% ($p<0.001$). (Fig. 3)

The efficacy of different treatment modality was also investigated. Among 198 patients with non-elevated NLR, 94 patients were treated by RT alone and 104 patients were treated by CRT. The events of patients dying from disease, developing distant metastasis, and developing local recurrence in RT alone group were 30, 22, and 17 cases, compared to 22, 19, and 14 cases in CRT group, respectively. The 5-year DSS, LRFS, and DMFS rates in RT alone and CRT group were 69.5% vs. 77.3% (p=0.049), 78.4% vs. 89.8% (p=0.021), and 84.9% vs. 85.2% (p= 0.588), respectively. Among 70 patients with elevated NLR, 39 patients were treated by RT alone and 31 patients were treated by CRT. The events of patients dying from disease, developing distant metastasis and local recurrence in RT alone group were 18, 16, and eight cases, compared to 17, 11, and eight cases in CRT group, respectively. The 5-year DSS, DMFS, and LRFS rates in the RT alone and CRT group were 51.9% vs. 46.2% (p=0.691), 56.3% vs. 62.9% (p=0.474), and 71.8% vs. 69.0% (p=0.438), respectively. (Fig. 4).

Discussion

In the current study, we demonstrated for the first time that pre-treatment NLR status was a strong prognostic factor for NPC patients. Patients with elevated NLR showed significantly worse DSS and DMFS, compared with patients with non-elevated NLR. Patients with elevated NLR also showed a tendency toward increased

Table 1 Univariate analysis of prognostic factors for patients with nasopharyngeal carcinoma

Factor	5-year disease-specific survival (%)	5-year distant metastasis-free survival (%)	5-year locoregional recurrence-free survival (%)
Gender			
Male	71.2	81.2	82.5
Female	74.9	86.5	93.0
P value	0.238	0.265	**0.031**
Age (years)			
≤50	73.3	80.3	85.5
>50	70.2	86.8	84.2
P value	0.489	0.171	0.548
PS			
0	72.5	82.4	86.3
1–2	70.9	82.3	81.0
P value	0.676	0.937	0.289
T status			
T1	89.3	92.3	96.0
T2	76.6	86.9	93.4
T3	70.8	81.4	80.1
T4	59.8	73.2	78.4
P value	**0.009**	0.137	**0.004**
N status			
N0	85.5	94.0	90.0
N1	74.5	84.6	83.5
N2	62.2	70.1	85.5
N3	42.1	68.4	82.2
P value	**0.000**	**0.000**	0.529
Treatment			
CRT	69.0	80.9	83.9
RT	74.3	83.4	85.9
P value	0.301	0.60	0.603
LDH			
≤245	72.4	82.9	85.1
>245	71.2	79.8	85.0
P value	0.637	0.66	0.44
NLR			
≤3.73	76.6	86.6	87.3
>3.73	59.6	69.7	78.5
P value	**0.003**	**0.002**	0.105

Data written in boldface mean that *P* values were statistically significant

Table 2 Multivariate analysis of independent prognostic factors for patients with nasopharyngeal carcinoma (n=363)

Variable	Disease-specific survival		Metastasis-free survival		Locoregional recurrence-free survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	–	–	–	–	0.43 (0.18–1.01)	0.052
T status	1.42 (1.12–1.80)	**0.004**	–	–	1.81 (1.28–2.56)	**0.001**
N status	2.59 (1.27–1.99)	**0.000**	2.01 (1.46–2.77)	**0.000**	–	–
NLR	1.74 (1.15–2.62)	**0.008**	2.37 (1.37–4.10)	**0.002**	–	–

HR hazard ratio, *CI* confidence interval

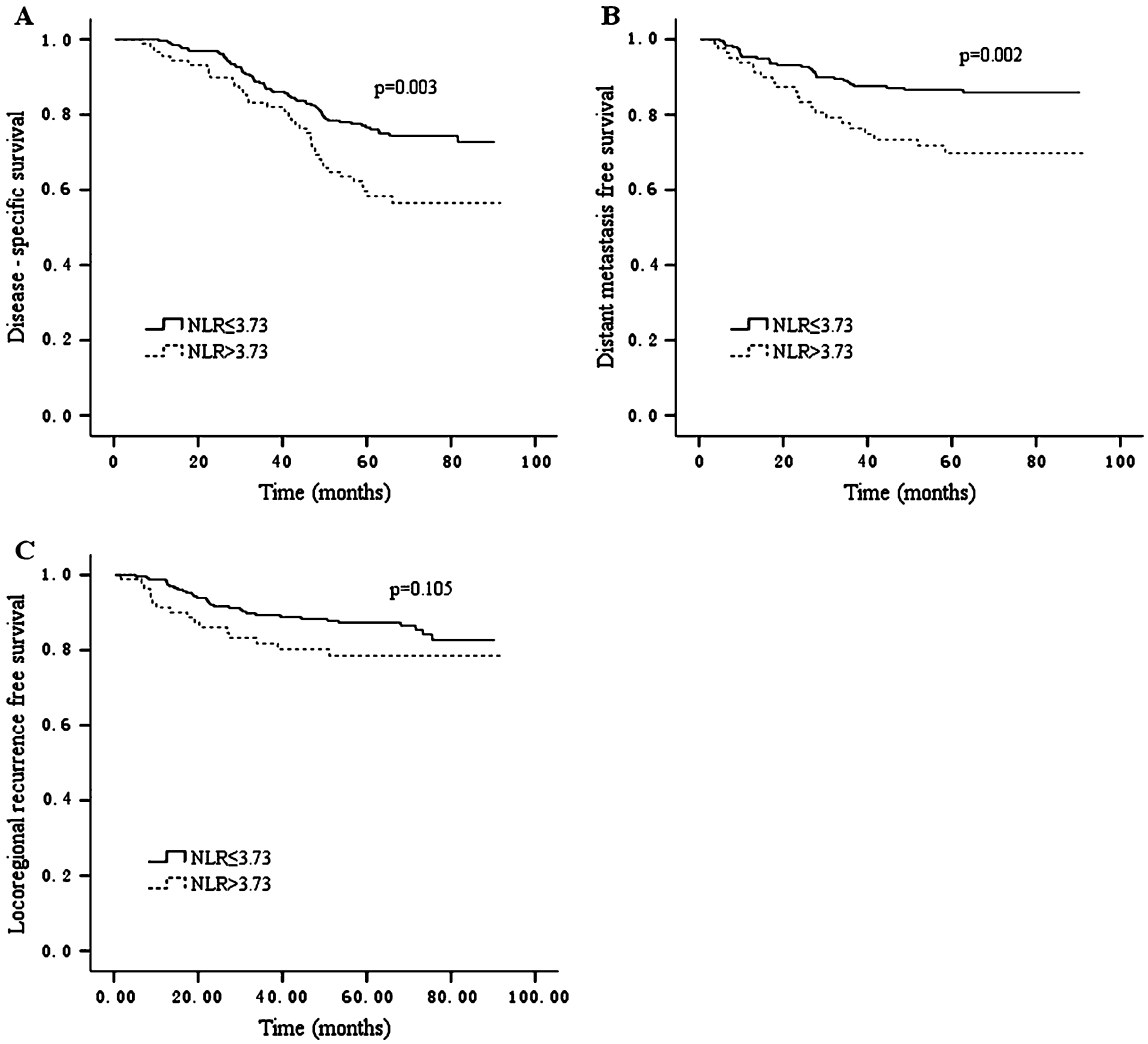

Fig. 1 Comparison of DSS (**a**), DMFS (**b**), and LRFS (**c**) according to pre-treatment NLR level for all the 363 patients

locoregional recurrence risk, although the difference was not statistically significant. For patients with locoregionally advanced stage disease in the same treatment modality, NLR remained a significant prognostic factor. On multivariate analysis, after adjusting T classification and N classification, NLR remained an independent prognostic factor for DSS and DMFS.

The association between elevated NLR and poor oncologic outcome is not clearly defined to date. Several possible mechanisms may explain it. First, the host's immune response to tumor is lymphocyte dependent. Early studies have shown an abundant infiltration of nonmalignant lymphocytes in the primary tumor of NPC [16, 17], which is linked with favorable prognosis [18]. Meanwhile, elevated peripheral blood lymphocyte counts have also been linked with improved survival in breast cancer patients undergoing curative resection, which is attributed to the pivotal role of lymphocytes in cytotoxic cell death and cytokines production that inhibit proliferation and metastatic activity of tumor cells [19]. Second, neutrophils are reported to be the primary source of circulating angiogenesis-regulating chemokines (e.g., CXCL8), growth factors (e.g., vascular endothelial growth factor), and proteases (e.g., tissue inhibitors of metalloproteinase) which are major contributors to tumor related angiogenesis [13, 20, 21]. Therefore, NLR can be considered as the balance between pro-tumor inflammatory status and anti-tumor immune status. Patients with elevated NLR have a relative lymphocytopenia and neutrophilic leukocytosis, which denotes that the balance is tipped in favor of pro-tumor inflammatory and is associated with poor oncologic outcome.

Currently, for patients with locally advanced disease, a number of randomized clinical trials have shown that

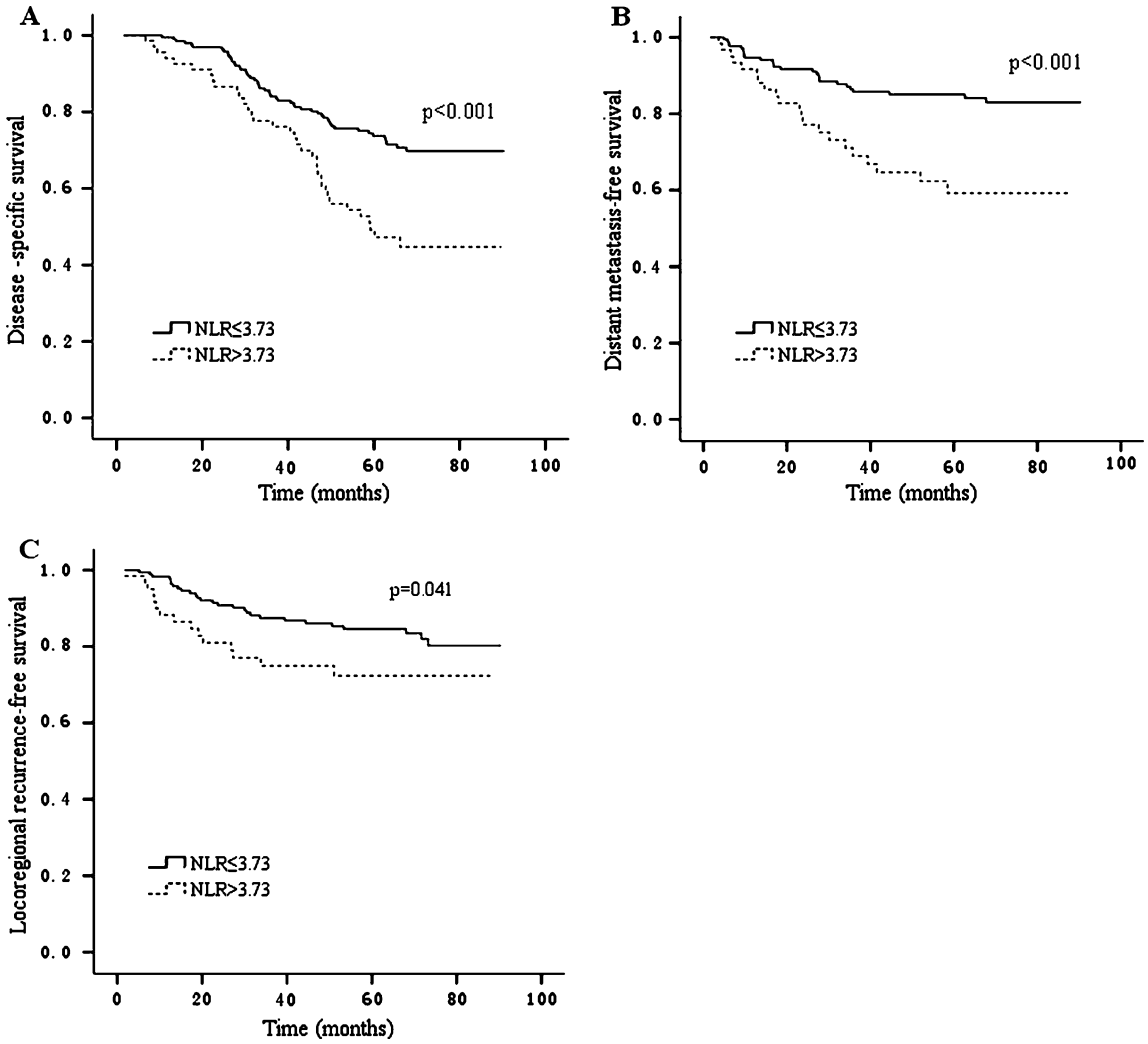

Fig. 2 Comparison of DSS (**a**), DMFS (**b**), and LRFS (**c**) curves according to pre-treatment NLR status for 268 locoregionally advanced patients

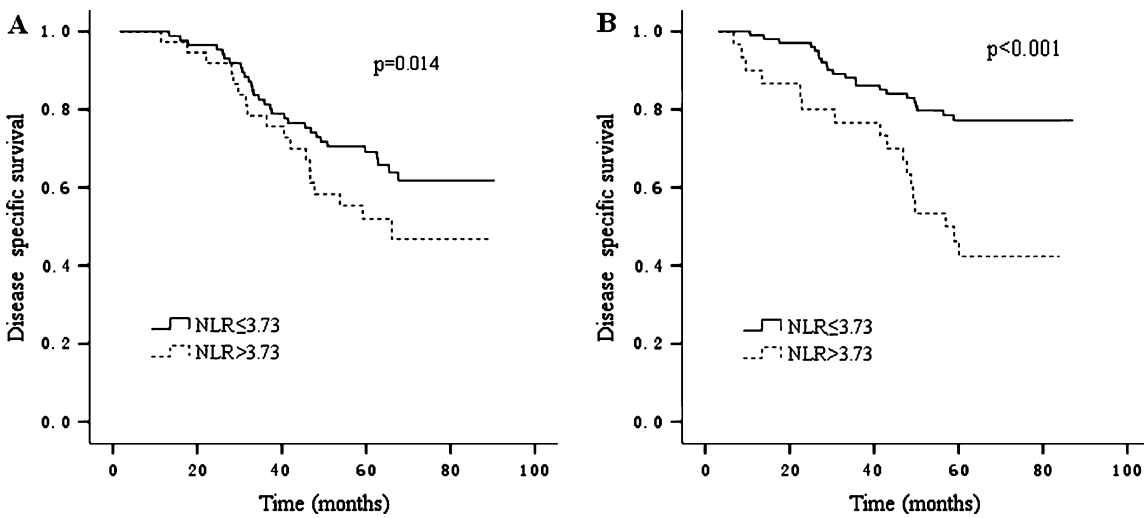

Fig. 3 Comparison of DSS of locoregionally advanced NPC patients treated by RT (**a**) or CRT (**b**) according to pre-treatment NLR status

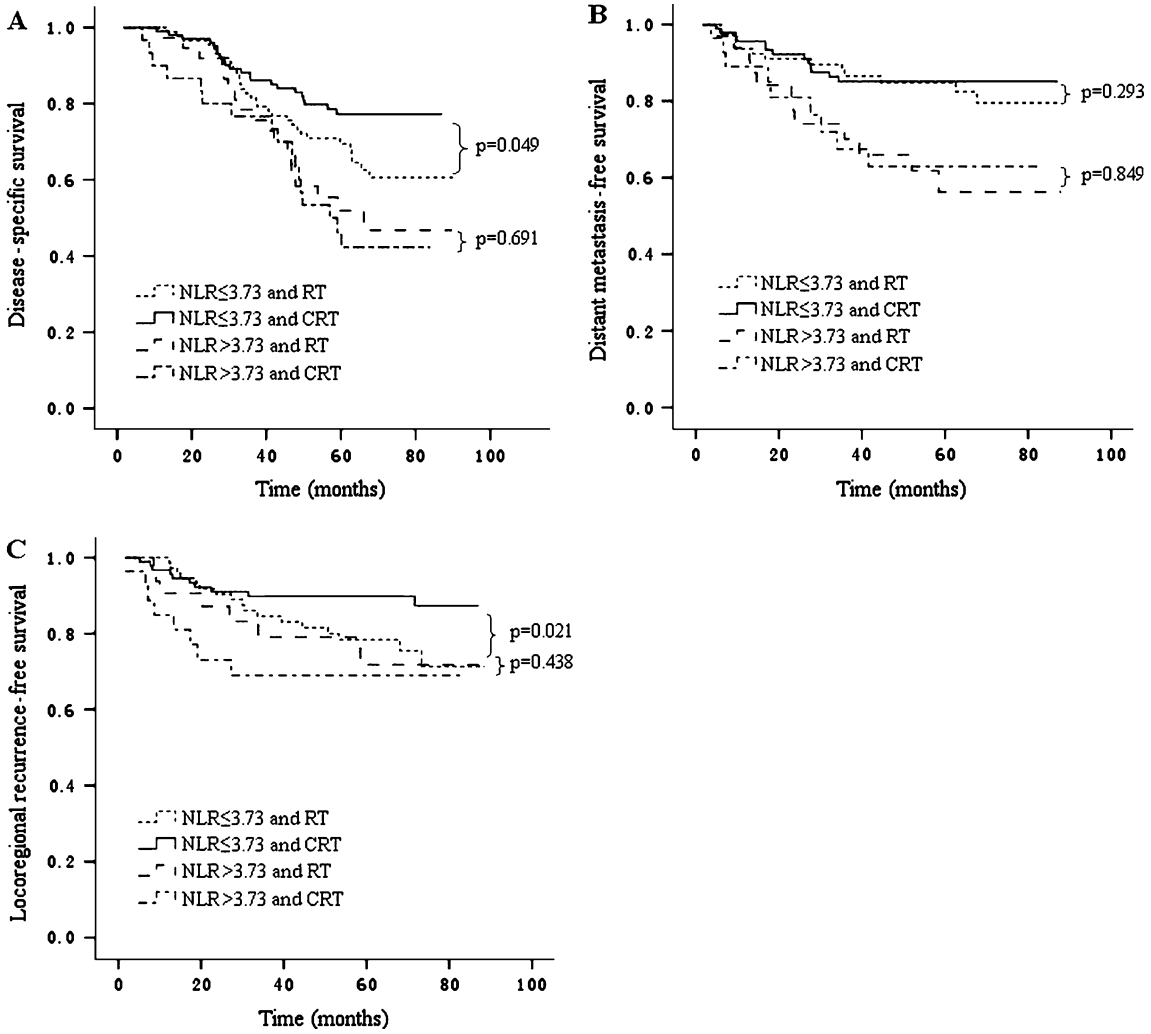

Fig. 4 Comparison of DSS (**a**), DMFS (**b**), and LRFS (**c**) of patients with locoregionally advanced NPC according to pre-treatment NLR status and different treatment modalities

concurrent chemoradiotherapy (CCRT) either with or without adjuvant chemotherapy could improve both overall and progression free survival [22–24]. However, not all the patients could benefit from CCRT. Lin et al. [25] reported that CCRT was superior to RT alone for low-risk patients but inadequate for high-risk patients according to their risk grouping system. Therefore, it is critical to identify patients who may benefit from more aggressive treatment modalities. According to our study, for patients with non-elevated NLR, CCRT is significantly better than RT alone in terms of OS and LRFS, while for patients with elevated NLR, CCRT failed to show significant survival benefits compared to RT alone. These findings suggest that NLR might be considered to be used as an indicator for decision making in the treatment of locoregionally advanced NPC patients.

NLR is an inexpensive, reproducible, and widely available blood test and adds no additional cost to routine pretreatment workup. This is especially relevant because NPC is endemic to many developing countries in which the healthcare budget is a major constraint. However, the interpretation of our results was hampered by the retrospective nature of the study. Various biases exist in the present study, such as among patient treated with CRT, only 79% of patients received CCRT and 24% of patients received only one cycle of chemotherapy. Therefore, further prospective study is warranted.

In summary, in the current study, we indicate that pre-treatment NLR level is a significant prognostic factor in patients with NPC. Furthermore, pre-treatment NLR level might be a useful indicator for decision making in the management of locoregionally advanced NPC.

Authors' disclosures of potential conflicts of interest The authors report no declarations of interest.

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