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ORIGINAL ARTICLE

The prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in nasopharyngeal cancer

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Summary

Purpose: *To investigate the prognostic value of pre-treatment neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and hemoglobin level in patients treated with definitive chemoradiotherapy (CRT) for nasopharyngeal carcinoma.*

Methods: *We retrospectively analyzed 97 patients who received definitive CRT for nasopharyngeal cancer. An NLR cut-off value of 4.42 was identified using receiver operating characteristic curve (ROC) analysis, an PLR cut-off value of 128.6 was identified using ROC analysis and a hemoglobin cut-off value of 13g/dl was identified using ROC analysis with overall survival (OS) as an endpoint.*

Results: *The 5-year progression-free survival (PFS) and overall survival (OS) for all patients were 67.1% and 72.6%, respectively. The patients with a high NLR (20.6%) had a significantly lower 5-year OS than those with a low NLR (79.4%) (OS: 46.9% vs. 79.7%, p<0.001). The patients with a high PLR (66.3%) had a borderline significant lower 5-year OS than those with a low PLR (32.7%) (OS: 66.1% vs. 87.9%, p=0.055). The patients with a low hemoglobin (18.4%) had a significantly lower 5-year OS than those with a high hemoglobin (80.6%) (OS: 46.6% vs. 78.9%, p<0.001). In univariate analysis, older age, IMRT technique, low hemoglobin and high NLR were prognostic factors. In multivariate analysis, high NLR, low hemoglobin and older age remained independent prognostic factors for OS.*

Conclusions: *Nasopharyngeal cancer tends to be more aggressive in patients with a high NLR and low hemoglobin. These patients should be treated more aggressively, given their unfavorable prognosis.*

Key words: *chemoradiotherapy, nasopharyngeal cancer, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, survival*

Introduction

Nasopharyngeal cancer (NPC) differs from other head and neck cancers in its relationship with Epstein-Barr virus (EBV) infection, demographic tendencies, clinical behavior and treatment. World Health Organization (WHO) statistic reports about 800,000 new NPC cases every year. They are 0.7% of all cancer cases in the world [1,2]. Basic treatment of NPC is radiotherapy with or without chemotherapy because of its radiosensitivity and anatomic localization [3]. Intensity modulated radiotherapy (IMRT) based treatments were found associated with long-term survival. Five-year local control of NPC-treated with IMRT ranges between 91.6-98.3% [2]. Thus, WHO recommends radiotherapy alone for stage I and concomitant chemoradiotherapy (CCRT) for stage II-IV non-metastatic NPC patients, using IMRT technique. Like the other solid tumors, prognosis of NPC primarily depends on TNM classification. But the TNM system is not enough to predict outcomes of treatment in NPC patients because in the same clinical stage patients with NPC generally present different treatment results [4,5]. Thus to get an optimal prediction in the NPC patients, we can combine TNM and biological

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markers to avoid the biological heterogeneity of cancer. Some of the biological markers have been shown in recently studies as additional prognostic factors including the EBV-DNA loads, micro-RNA signature, EGFR overexpression [6-8]. However, all these biological markers require large laboratory equipment and high cost. Peripheral blood check control gives some predictable values more practically and cheaper. In the last years pre-treatment elevated neutrophil count was found related with worse prognosis in many cancers. Especially for high neutrophil-lymphocyte ratios (NLR) there are lots of trials showing that higher ratio is correlated with poorer prognosis in different types of cancers [9,10]. In non-metastatic NPC, unfavorable outcomes have been associated with elevated total neutrophil counts [11], lymphocyte counts [11], C-reactive protein to albumin ratio [12], lymphocyte to monocyte ratio [13], Glasgow prognostic score [14], and decreased prognostic nutritional index [15].

Combination of these prognostic markers may give better prediction of prognosis but it's not clear which marker is definitely significant for prognosis in NPC. Thus, studies are going on to detect the most predictable marker for NPC.

The aim of our study was to find out the value of hematological parameters, especially NLR (neutrophil-lymphocyte ratio), PLR (platelet-lymphocyte ratio) and hemoglobin level, as prognostic factors in NPC.

Methods

Patient features

A group of NPC patients were included who were treated between 2010 and 2018 in Erciyes University Oncology Hospital. All patients were histopathologically confirmed with nasopharyngeal biopsy and had non-keratinizing undifferentiated pathological type (WHO II). Non-metastatic, stage II-IV patients were collected and all were treated by definitive chemoradiotherapy. The inclusion criteria were: 1) Histologically confirmed NPC; 2) Karnofsky performance status (KPS) >70; 3) No distant metastasis; 4) Adequate renal, cardiac and liver function; 5) Patients aged >16 years; 6) No immunological and hematological comorbid diseases; 7) No active infection at the beginning of treatment; 8) No previous treatment for NPC; 9) No previous cancer diagnosis. Ninety-seven patients with nasopharyngeal cancer were finally enrolled in the study.

Peripheral blood was collected 7 days before the beginning of treatment in all patients. According to these blood checks and clinical symptoms, infection was excluded in all patients. Hematological values of hemoglobin (hb), lymphocyte (lymp), neutrophil (neu) and platelet (plt) were assessed using hematology analyzer (Sysmex SE-9000, Kobe, Japan).

Peripheral neutrophil/lymphocyte ratio (NLR) was calculated as the ratio of absolute counts between the peripheral neutrophil and lymphocyte measurements. Peripheral platelet/lymphocyte ratio (PLR) was calculated as the ratio of absolute counts between the peripheral platelet and lymphocyte measurements. Hematological parameters were recorded by the medical staff during treatment and collected from patient's charts.

This study was approved by local ethics committee and all patients provided written informed consent.

Clinical staging

Staging was determined by clinical examination of head and neck, naso-endoscopy with direct fiberoptic system, magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET-CT). All patients were restaged according to 8th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) system [16].

Treatment

2/3D conformal technique was performed before 2012 and IMRT technique was performed after 2012. Standard dose and fractionation for 2/3D conformal RT was 70 Gy to primary tumor and 50-60 Gy to involved nodes in 35 daily fractions. The dose and fractions for IMRT were total 70Gy/2.12Gy per fraction to high risk planning target volume (primary tumor volume and involved nodes), total 60Gy/1.8Gy per fraction to intermediate risk planning target volume and total 54Gy/1.65Gy per fraction to low risk planning target volume. Cisplatin chemotherapy was administered as intravenous infusion of 100 mg/m^2 every 3 weeks or 50 mg/m^2 intravenous infusion weekly. Chemotherapy started in the first radiation treatment day in all patients.

Follow up

Patient follow up was assessed from the first day of treatment to the last examination or death. Both MRI and PET-CT were performed to evaluate treatment response on the 3rd month after the last treatment day. Treatment response evaluation was made according to Response Evaluation Criteria in Solid Tumors (RECIST criteria) [17]. The response to treatment was classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). If patients achieved a CR, they were monitored every 3 months for the first 2 years with MRI and the follow up examinations continued every 6 months thereafter. The location of the first clinical relapse in nasopharyx was accepted as local failure. The location of first clinical relapse was accepted as regional failure, if the relapse happened in the nodal area. If the relapse was beyond the above-mentioned areas it was accepted as distant failure. The duration of disease-free survival (DFS), time to locoregional failure (LRFS and RRRFS) and time to distant failure (DMFS) were calculated from day 1 of treatment until documented treatment failure. Overall survival (OS) was calculated from day 1 of treatment to the date of last follow up or death (Table 1).

Table 1. Comparison of patient characteristics between groups

	NLR<4,42 n (%)	*NLR≥4,42 n (%)*	*Total n (%)*	*p**	*PLR<128 n (%)*	*PLR>128 n (%)*	*Total n (%)*	*p**	*Hb<13 n (%)*	*Hb≥13 n (%)*	*Total n (%)*	*p**
Gender				0.41				0.63				<0.01
Female	24 (31.2)	4 (20)	28 (28.9)		8 (25)	20 (30.8)	28 (28.9)		10 (55.6)	18 (22.8)	28 (28.9)	
Male	53 (68.8)	16 (80)	69 (71.1)		24 (75)	45 (69.2)	69 (69.1)		84 (4.6)	61 (77.2)	69 (71.1)	
Age, years				0.8				0.27				1.00
<50	42 (54.5)	12 (60)	54 (56.1)		15 (46.9)	39 (60)	54 (55.7)		10 (55.6)	44 (55.7)	54 (55.7)	
≥50	35 (45.5)	8 (40)	43 (43.9)		17 (53.1)	26 (40)	43 (44.3)		8 (44.4)	35 (44.3)	43 (44.3)	
T category				0.45				0.01				0.79
T_{1-2}	36 (46.8)	7 (35)	43 (44.3)		20 (62.5)	23 (35.4)	43 (44.3)		7 (38.9)	36 (45.6)	43 (44.3)	
T_{3-4}	41 (53.2)	13 (65)	54 (55.7)		12 (37.5)	42 (64.6)	54 (55.7)		11 (61.1)	43 (54.4)	54 (55.7)	
N category				0.02				0.38				0.06
N_{0-1}	42 (54.5)	5 (25)	20 (20.4)		18 (56.3)	29 (44.6)	47 (48.5)		5 (27.8)	42 (53.2)	47 (48.5)	
N_{2-3}	35 (45.5)	15 (75)	38 (38.8)		14 (43.8)	36 (55.4)	50 (51.5)		13 (72.2)	3 (46.8)	50 (51.5)	
RT Technique				1.00				0.16				0.04
3D-RT	4 (5.2)	1 (5)	5 (5.2)		0 (0)	5 (7.7)	5		3 (16.7)	2 (2.5)		
IMRT	73 (94.8)	19 (95)	92 (94.8)		32 (100)	60 (92.3)	92		15 (83.3)	77 (97.5)		
TNM				0.20				0.24				0.01
II	17 (22.1)	1 (5)	18 (18.6)		9 (28.1)	9 (13.8)	18 (18.6)		0 (0)	18 (22.8)	18 (18.6)	
III	28 (36.4)	8 (40)	36 (37.1)		10 (31.3)	26 (40)	36 (37.1)		9 (50)	27 (34.2)	36 (37.1)	
IV_A	32 (41.6)	11 (55)	43 (44.3)		13 (40.6)	30 (46.2)	43 (44.3)		9 (50)	34 (43)	43 (44.3)	
Local recurrence				0.55				1.00				0.35
-	60 (77.9)	14 (70)	74 (76.3)		24 (75)	50 (76.9)	74 (76.3)		12 (66.7)	62 (78.5)	74 (76.3)	
+	16 (22.1)	6 (30)	23 (23.7)		8 (25)	15 (23.1)	23 (23.7)		6 (33.3)	17 (21.5)	23 (23.7)	
Regional recurrence				<0.01				0.26				0.63
-	74 (96.1)	15 (75)	89 (91.8)		31 (96.9)	58 (89.2)	89 (91.8)		16 (88.9)	73 (92.4)	89 (91.8)	
+	3 (3.9)	5 (25)	8 (8.2)		1 (3.1)	7 (10.8)	8 (8.2)		2 (11.1)	6 (7.6)	8 (8.2)	
Distant metastasis				0.11				0.16				0.08
-	66 (85.7)	14 (70)	80 (82.5)		29 (90.6)	51 (78.5)	80 (82.5)		12 (66.7)	68 (86.1)	80 (82.5)	
+	11 (14.3)	6 (30)	17 (17.5)		3 (9.4)	14 (21.5)	17 (17.5)		6 (33.3)	11 (13.9)	17 (17.5)	
Death				0.01				0.03				<0.01
-	64 (83.1)	11 (55)	75 (77.3)		29 (90.6)	46 (70.8)	75 (77.3)		9 (50)	66 (83.5)	75 (77.3)	
+	13 (16.9)	9 (45)	22 (22.7)		3 (9.4)	19 (29.2)	22 (22.7)		9 (50)	13 (16.5)	22 (22.7)	

NLR: Neutrophil/Lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, Hb: Hemoglobin, 3D-RT: Three-dimensional radiotherapy, IMRT: Intensity modulated radiotherapy; TNM: T and N categories are according to 8th edition American Joint Commission on Cancer staging system, *Fisher's Exact Test

Statistics

All data were expressed as mean ± SD unless otherwise stated and controlled for normality using Shapiro-Wilk test. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value. Chi-square and Fisher exact tests were used to compare categorical variables, such as different age, gender, T stage, N stage, NLR, PLR and hemoglobin level. To clarify the prognostic factors of survival, Cox regression model was applied to identify the best predictive variables using univariate and multivariate analysis. The predictors were estimated with relative risk and 95% CI in the regression model. Survival was estimated with Kaplan-Meier method and differences between groups were assessed by log-rank test. Differences were considered significant at $p<0.05$. The statistical analysis of the data was performed by using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA).

Results

Patient characteristics

From 2010 to 2018, a total of 97 (28 female and 69 male) eligible patients were evaluated. The median age was 49.5 years (range 16-75). Of the 97 patients, 16 (16.3%), 28 (28.6%), 20 (20.4%) and 33 (33.7%) had T1, T2, T3, and T4 disease stage, respectively. Of the 97 patients, 20 (19.6%), 28 (28.9%), 38 (39.2%) and 12 (12.4%) had N0, N1, N2, and N3 disease stage, respectively. Of the 97 patients, 18 (18.4%), 36 (36.7%) and 43 (43.9%) had stage II, stage III and stage IV_A disease, respectively. Five of 97 patients (5.1%) were treated with 2/3D conformal RT technique. Ninety-four of 97 patients (94.9%) were treated with IMRT technique. Median treatment duration was 48 days (range: 30-87). After chemoradiotherapy 79 patients (81.4%) were evaluated as complete responders and 18 (18.6%) as partial responders. Seventy-six (77.6%) of 97 patients were alive at the time of the last visit, 22 patients (22.4%) had died. The median NLR ratio was 2.68 (range: 0.21-28.36), the median PLR ratio was 156.8 (range: 6.8-424.7), and the median hemoglobin level was 14.3 g/dl (range: 10.7-17.3).

Cut-off values of parameters

ROC curves were used to identify the cut-off NLR, PLR and hemoglobin level. The patients were divided into groups. The best significantly cut-off

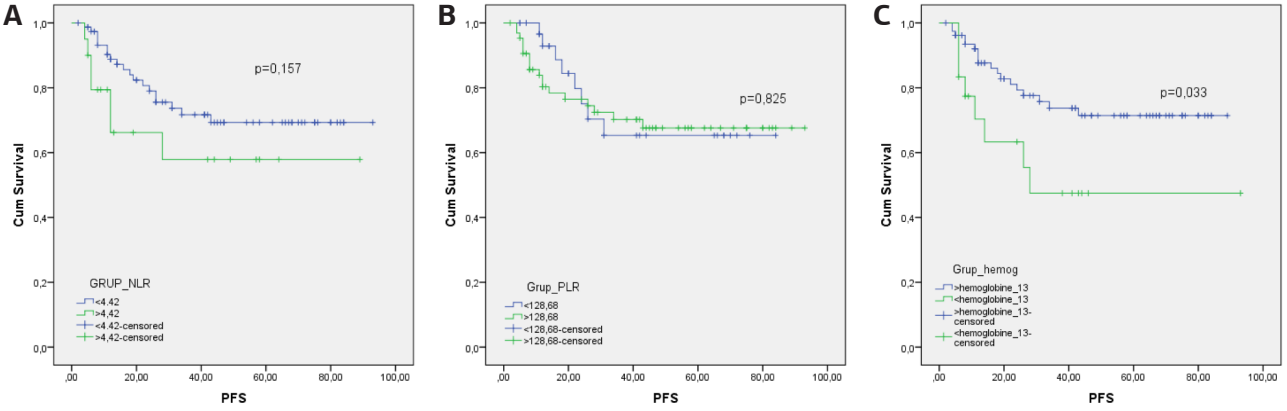

Figure 1. Progression-free survival between groups. **A:** lower group <4.42 and ≥4.42 higher group for NLR. **B:** lower group <128.6 and ≥128.6 higher group for PLR. **C:** lower group <13 g/dL and ≥13 g/dL higher group for hemoglobin levels.

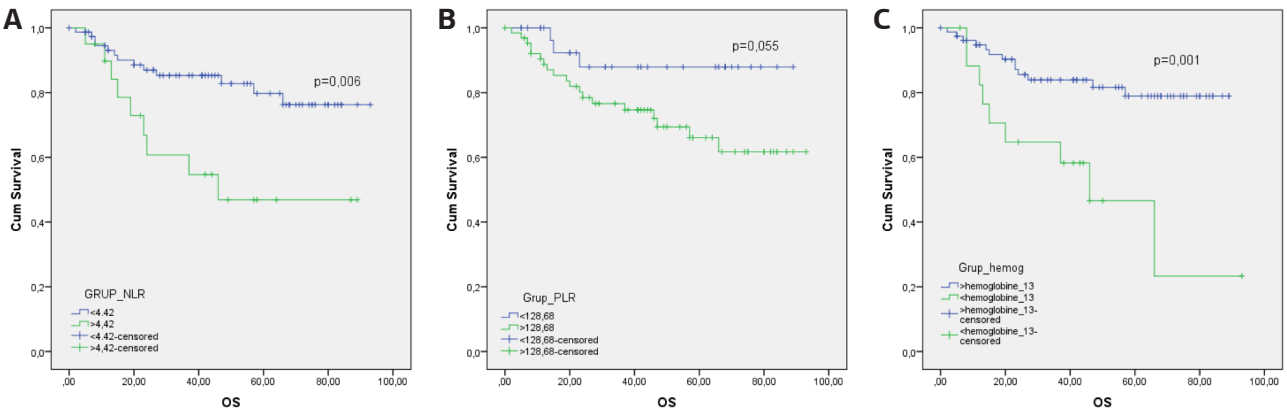

Figure 2. Overall survival between groups. **A:** lower group <4.42 and ≥4.42 higher group for NLR. **B:** lower group <128.6 and ≥128.6 higher group for PLR. **C:** lower group <13 g/dl and ≥13 g/dl higher group for hemoglobin levels.

Table 2. Univariate and multivariate analysis for progression-free survival

	Univariate analysis			*Multivariate analysis*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Gender						
Female						
Male	0.99	0.431 – 2.283	0.98			
Age, years						
<50						
≥50	2.98	1.328 – 6.692	<0.01	3.195	1.415-7.211	<0.01
T category						
T_{1-2}						
T_{3-4}	1.07	0.492 – 2.335	0.86			
N category						
N_{0-1}						
N_{2-3}	0.97	0.451 –2.102	0.94			
RT Technique						
3D-RT						
IMRT	0.21	0.075 – 0.634	<0.01	1.519	0.793 - 2910	0.20
TNM stage						
II	(ref)	(ref)	0.65			
III	0.562	0.193 – 1.817	0.36			
IV_A	0.839	0.358 – 1.964	0.68			
NLR						
<4.42						
≥4.42	1.84	0.775 -4.400	0.16			
PLR						
<128.6						
≥128.6	1.09	0.476 – 2.530	0.82			
Hb g/dL						
<13						
≥13	2.40	1.041 – 5.540	0.04	2.728	1.172 – 6.351	0.02

3D-RT:Three-dimensional radiotherapy, IMRT: Intensity modulated radiotherapy; NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, Hb: Hemoglobin, TNM: T and N categories are according to 8th edition American Joint Commission on Cancer staging system

value was 4.42 (area under the ROC curve: 0.592, p=0.19) for NLR. The best significantly cut-off value was 128.68 (area under the ROC curve: 0.599, p=0.17) for PLR. Statistically significant cut-off value was 13.0 (area under the ROC curve: 0.678, p=0.003) for hemoglobin. The patients were divided two groups (low-group and high-group) according to cut-off values.

Survival analysis

The 5-year OS rate of all patients was 72.6 months and 5-year PFS was 67.1 months. Five-year PFS rate for NLR group (low <4.42 and high>4.42) was 69% versus 57% and 5-year PFS rate for the PLR group (low<128 and high>128) was 65% versus 67%. There were no statistically significant differences between groups (p=1.57, p=0.47, p=0.82 respectively, Figure 1). Five-year PFS rate for the group of hemoglobin level (low<13g/dl and high>13g/dl) was 47% versus 71% with statistically significant difference (p=0.03, Figure 1). When the groups were evaluated in terms of OS, 5-year OS rate for NLR group (low<4.42 and high>4.42) was 79% versus 46% (p=0.006) and 5-year OS rate for the group of hemoglobin level (low<13 and high>13) was 46% versus 78% (p=0.001). There were statistically significant differences between groups. Five-year OS rate for the PLR group (low<128 and high>128) was 87% versus 66% with difference close to being statistically significant (p=0.055, Figure 2).

Univariate and multivariate analysis

Univariate analysis included gender, age, T stage, N stage, TNM stage, radiotherapy technique, NLR, PLR and hemoglobin level. High age (≥50), RT technique (IMRT), and low-hemoglobin (<13) were found as prognostic factors for PFS in univariate analysis (HR:2.98 95%CI:1.328-6.692

Table 3. Univariate and multivariate analysis for overall survival

	Univariate analysis			*Multivariate analysis*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Gender						
Female						
Male	0.99	0.431 – 2.283	0.98			
Age, years						
<50						
≥50	2.98	1.328 – 6.692	<0.01	3.195	1.415-7.211	<0.01
T category						
T_{1-2}						
T_{3-4}	1.07	0.492 – 2.335	0.86			
N category						
N_{0-1}						
N_{2-3}	0.97	0.451 –2.102	0.94			
RT Technique						
3D-RT						
IMRT	0.21	0.075 – 0.634	<0.01	1.519	0.793 - 2910	0.20
TNM stage						
II	(ref)	(ref)	0.65			
III	0.562	0.193 – 1.817	0.36			
IV_A	0.839	0.358 – 1.964	0.68			
NLR						
<4.42						
≥4.42	1.84	0.775 -4.400	0.16			
PLR						
<128.6						
≥128.6	1.09	0.476 – 2.530	0.82			
Hb g/dL						
<13						
≥13	2.40	1.041 – 5.540	0.04	2.728	1.172 – 6.351	0.02

3D-RT: Three-dimensional radiotherapy, IMRT: Intensity modulated radiotherapy; NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, Hb: hemoglobin, TNM: T and N categories are according to 8th edition American Joint Commission on Cancer staging system

p<0.01; HR:2.21, 95%CI:0.075-0.634, p<0.01; HR:2.40, 95%CI:1.041-5.540, p=0.04, respectively, Table 2). These were confirmed in multivariate analysis: high age (HR:3.19, 95%CI:1.415-7.211, p<0.01) and low-hemoglobin (HR:2.72, 95%CI:1.172-6.351, p=0.02) values were independent factors for PFS (Table 2).

In univariate analysis of risk factors for OS high age (≥50), NLR (≥4.42), hemoglobin (<13g/dl), RT technique (IMRT) were found as prognostic factors: HR:2.86, 95%CI:1.165-7.021, p=0.022; HR:3.10, 95%CI:1.320-7.295, p=0.009; HR:3.74, 95%CI:1.584-8.864, p=0.003; HR:2.569, 95%CI:1.088-6.067, p=0.031; HR:2.15, 95%CI:1.250-3.717, p=0.006, respectively. That was verified in multivariate analysis: high age (HR:3.81, 95%CL:1.508-9.656, p=0.003), high NLR (HR.3.25, 95%CI:1.354-7.801, p=0.007) and low-hemoglobin (HR:4.03, 95%CI:1.661-9.804, p=0.004) were independent prognostic factors for OS (Table 3).

Discussion

Neutrophils are the type of inflammatory cells considered to participate in different steps of tumor development via cytokine production [18]. During tumor progression, neutrophils can produce several cytokines, such as oncostatin-M, hepatocyte growth factor and transforming growth factor-β [18]. What's more, neutrophils are able to promote tumor angiogenesis by releasing angiogenic factors, such as vascular endothelial growth factor [19], angiopoietin-1 [20] and fibroblast growth factor 2 [21]. On the other hand, lymphocytes are responsible for immune surveillance resulting in the elimination of cancer cells. The presence of lymphocytes infiltrate in tumors is correlated with good prognosis and T cells have been utilized in order to target cancers [22,23]. Lymphocyte level in peripheral blood was associated with long survival

in NPC patients [11]. Several *in vitro* trials have shown that lymphocyte's and naturel killer's cytolytic activities were decreased when co-cultured with neutrophils. Besides, the level of suppression increased with additional neutrophils and this trial supported that high NLR level was correlated with worse prognosis [24-26].

In the literature, there are large ranges of cut off values (2,8-5) for NLR in NPC patients [27]. In our trial cut off value of NLR was found as 4.42 and this value is suitable according to the literature. There are so many trials for NLR. In the study by Wang et al [28] NLR cut off was 2.6 and that level was a statistically significant prognostic factor in terms of distant metastasis. In another study by Liew et al [29] cut off value of NLR was 2.99 and they suggested that it was an independent prognostic factor for DFS. In addition, in the trial by Sun et al [3] PLR and NLR were characterised as predictive factors for PFS, besides only high PLR was associated with poor OS. Chua et al [30] found that NLR ≥3 was related with AJCC T classification, AJCC N classification, overall tumor stage, pretreatment EBV-DNA titers, however there was no relation between NLR level and OS. He et al [11] observed NLR cut off value as 2.74 and found it as independent factor for OS and PFS. The patients with high level NLR (≥2.74) had worse survival in terms of PFS and OS. In this current study, we found that there were statistically significant differences between NLR≥4.42 and <4.42 for OS but not for PFS. High NLR (≥4.42) was associated with 3.1-fold increase in death risk.

Platelets are well known for their participation in thrombosis. They also trigger cells for tumor growth, dissemination and angiogenesis [31]. Activated platelets promote tumor cell growth and survival via interacting with cancer cells through paracrine signaling or direct contact. In several clinical trials, increasing platelet count was related with worse prognosis in different types of cancers [32-34]. In a meta-analysis for head and neck cancers, the cut off value of PLR ranged from 112 to 150.34. In the current study the cut off value of PLR was 128 and this value is suitable according to the literature. In this study we focused in PLR instead of platelet count. In meta-analysis which included head and neck cancers it was demonstrated that high PLR values were correlated with poor prognosis [35].

There is a limited number of published studies in the literature including patients with nasopharyngeal carcinoma [29,36-38]. In the study by Wei et al it was found that high-PLR (PLR ≥167.2 for PFS and PLR ≥163.4 for OS) was associated poorer PFS and OS in NPC patients [33]. Li et al observed that PLR ≥146.2 was a predictor for worse OS [36]. In the two studies by Bojaxhiu et al and Li et al, it was reported high-PLR was not associated with poor survival [37,38]. Hemoglobin is the most known predictive hematological parameter for all types of cancers. There are many studies about that and lower levels of hemoglobin mean worse prognosis. The reason of poor prognosis was probably the result of tumor hypoxia [39-41]. Similarly to literature, we proved that low hemoglobin (<13g/dl) was associated to poor OS.

Our study has some limitations to be considered. First, it was a retrospective trial and single-centered. Second, because of single-centered, the number of patient was limited. So, future researches should be carried out as multicenter, with more patient numbers and prospective. Third, smokers have leukocytosis that is also known smoker-leukocytosis [42]. Therefore, it's difficult to clarify whether failure of treatment is due to smoking during radiotherapy or because of high NLR. Additionally, patients with smoker-leukocytosis may have died from smoke-related comorbidities [37] that could not correlate with NLR and smoking in this study. Fourth, EBV-DNA is the most specific and prognostic marker in blood for NPC patients [43]. In addition, before and after treatment, EBV-DNA levels can play important role. Especially, post-treatment low EBV-DNA levels are correlated with good response to treatment [44-46]. In this study, we were not able to correlate NLR and EBV-DNA. A better equipped laboratory and a higher budget are needed to accurately measure EBV. The current article can be valuable because it provides information on prognosis without more advanced laboratory equipment and more costs. NLR obtained from the simple routine blood counts can also be used to predict survival. The role of PLR as a prognostic marker in nasopharyngeal cancer is still unclear according to our outcomes.

Conclusion

In this study we reported that high NLR, low hemoglobin and older age were independent prognostic variables for poorer OS in NPC patients treated with chemoradiotherapy. Patients with high NLR and low-hemoglobin should be treated more aggressively, given their unfavorable prognosis. Further research can help detect which marker is better in the prediction of prognosis in NPC patients.

Conflict of interests

The authors declare no conflict of interests.

Author contributions

Conception/design: Mete Gundog;
Provision of study material and patients: Hatice Basaran;
Collection and/or assembly of data: Mete Gundog, Hatice Basaran;
Manuscript writing: Mete Gundog, Hatice Basaran;
Final approval of manuscript: Mete Gundog, Hatice Basaran.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cance J Clin 2011; 61:69-90.
2. Zhang MX, Li J, Shen GP et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy; 10-year experience with a large cohort and long follow-up. Eur J Cancer 2015;51:2587-95.
3. Sun W, Zhang L, Luo M et al. Pre-treatment hematological markers as prognostic factors in patients with nasopharyngeal carcinoma: Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Head Neck 2015;38:e1332-40.
4. Xu J, Wan XB, Huang XF et al. Serologic antienzyme rate of Epstein- Barr virus DNase–specific neutralizing antibody segregates TNM classification in nasopharyngeal carcinoma. J Clin Oncol 2010;28:5202-09.
5. Wang HY, Sun BY, Zhu ZH et al. Eight-signature classifier for prediction of nasopharyngeal carcinoma survival. J Clin Oncol 2011;29:4516-25.
6. Lin JC, Wang WY, Chen KY et al. Quantification of plasma Epstein-Barr virus DNA in patients with nasopharyngeal carcinoma. N Engl J Med 2004;350:2461-70.
7. Liu N, Chen NY, Cui RX et al. Prognostic value of microRNA signature in nasopharyngeal carcinoma: a microRNA expression analysis. Lancet Oncol 2012;3:633-41.
8. Sun W, Long G, Wang J et al. Prognostic role of epidermal growth factor receptor in nasopharyngeal carcinoma: a meta-analysis. Head Neck 2014;36:1508-16.
9. Bozkurt O, Karaca H, Berk V et al. Predicting the role of the pre-treatment neutrophil to lymphocyte ratio in the survival of early triple-negative breast cancer patients. JBUON 2015;20:1432-9.
10. Kostakis ID, Vaiopoulos AG, Garoufalia Z et al. What can preoperative blood tests tell us about colorectal cancer? JBUON 2018;23:84-95.
11. He JR, Shen GP, Ren ZF et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head Neck 2012;34:1769-76.
12. Tao CJ, Chen YY, Jiang F et al. The C-reactive protein/albumin ratio is an independent prognostic factor for overall survival in patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy. J Cancer 2016;7:2005-11.
13. Li J, Jiang R, Liu WS et al. A large cohort study reveals the association of elevated peripheral blood lymphocyte to monocyte ratio with favorable prognosis in nasopharyngeal carcinoma. PLoS One 2013;8:e83069.
14. Li XH, Chang H, Xu BQ et al. An inflammatory biomarker-based nomogram to predict prognosis of patients with nasopharyngeal carcinoma: an analysis of a prospective study. Cancer Med 2017;6:310-19.
15. Yang L, Xia L, Wang Y et al. Low prognostic nutritional index (PNI) predicts unfavorable distant-metastasis free survival in nasopharyngeal carcinoma: a propensity score-matched analysis. PLoS One 2016;11:e158853.
16. Pan JJ, Ng WT, Zong JF et al. Proposal for the 8th Edition of the AJCC/UICC Staging System for Nasopharyngeal Cancer in the Era of Intensity-Modulated Radiotherapy. Cancer 2016;122:546-58.
17. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours; Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:225-47.
18. Tecchio C, Scapini P, Pizzolo G et al. On the cytokines produced by human neutrophils in tumors. Semin Cancer Biol 2013;23:159-70.
19. Webb NJ, Myers CR, Watson CJ et al. Activated human neutrophils express vascular endothelial growth factor (VEGF). Cytokine 1998;10:254-57.
20. Neagoe PE, Brkovic A, Hajjar F et al. Expression and release of angiopoietin-1 from human neutrophils: intracellular mechanism. Growth Factors 2009;27:335-44.
21. Tecchio C, Cassatella MA. Neutrophil-derived cytokines involved in physiological and pathological angiogenesis. Chem Immunol Allergy 2014;99:123-27.
22. Basso S, Zecca M, Merli P et al. T cell therapy for nasopharyngeal carcinoma. J Cancer 2011;2:341-46.
23. Duong CP, Yong CS, Kershaw MH et al. Cancer immunotherapy utilizing gene-modified T cells: From the bench to the clinic. Mol Immunol 2015;67:46-57.
24. Petri HT, Klassen LW, Kay HD et al. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. J Immunol 1985;134:230-34.
25. El-Hag A, Clark RA. Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. J Immunol 1987;139:2406-13.
26. Shau HY, Kim A. Suppression of lymphokine-activated killer induction by neutrophils. J Immunol 1988;141:4395-02.
27. Takenaka Y, Kitamura T, Oya R et al. Prognostic role of neutrophil-lymphocyte ratio in nasopharyngeal carcinoma: A meta-analysis. PLoS One 2017;12:e0181478.

28. Wang Y, Chen G. Identifying pretreatment baseline factors predictive of distant metastasis in patients with nasopharyngeal carcinoma after radiotherapy. Medicine 2017;96:e6692.
29. Liew KY, Zulkiflee AB. Neuthrophil-lymphocyte ratios in the prognostication of primary non-metastatic nasopharyngeal carcinoma. Braz J Otorhinolaryngol 2018;84:764-71.
30. Chua ML, Tan SH, Kusumawidjaja G et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: A pooled analysis of two randomised controlled trials. Eur J Cancer 2016;67:119-29.
31. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: a host factor that offers multiple potential targets in the treatment of cancers. J Cell Physiol 2014;229:1005-15.
32. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer 2013;109:401-07.
33. Rachidi S, Wallace K, Day TA, Alberg AJ, Li Z. Lower circulating platelet counts and antiplatelet therapy independently predict better outcomes in patients with head and neck squamous cell carcinoma. J Hematol Oncol 2014;27:65.
34. Gakis G, Fritsche HM, Hassan F et al. Prognostic relevance of postoperative platelet count in upper tract urothelial carcinoma after radical nephroureterectomy. Eur J Cancer 2014;50:2583-91.
35. Takaneka Y, Oya R, Kitamiura T et al. Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: Meta-analysis. Head Neck 2018;40:2714-23.
36. Li JP, Chen SL, Liu XM et al. A novel inflammation-based stage (I Stage) predicts overall survival of patients with nasopharyngeal carcinoma. Int J Mol Sci 2016;17:e1900.
37. Bojaxhiu B, Templeton AJ, Elicin O et al. Relation of baseline neutrophil-to-lymphocyte ratio to survival and toxicity in head and neck cancer patients treated with (chemo-) radiation. Radiat Oncol 2018;13:216.
38. Li XH, Chang H, Xu BQ et al. An inflammatory biomarker-based nomogram to predict prognosis of patients with nasopharyngeal carcinoma: an analysis of prospective study. Cancer Medicine 2017;6:310-19.
39. Biau J, Chautard E, Miroir J et al. Radioresistance parameters in head and neck cancers and methods to radiosensitize. Cancer Radiother 2015;19:337-46.
40. Narayanaswamy RK, Potharaju M, Vaidhyswaran AN, Perumal K. Pre-radiotherapy hemoglobin level is a prognosticator in locally advanced head and neck cancers treated with concurrent chemo-radiation. J Clin Diagn Res 2015;9:14-8.
41. Mai HQ, Mo HY, Hong MH et al. Impact of pre-radiotherapy hemoglobin level on local control of nasopharyngeal carcinoma. Ai Zheng 2005;24:727-30.
42. Kawada T. Smoking-induced leukocytosis can persist after cessation of smoking. Arch Med Res 2004;35:246-50.
43. Wang WY, Twu CW, Chenn HH et al. Long-term survival analysis of nasopharyngeal carcinoma by plasma Epstein-Barr virus DNA levels. Cancer 2013;119:963-70.
44. Leung SF, Tam JS, Chan AT et al. Improved accuracy of detection of nasopharyngeal carcinoma by combined application of circulation Epstein-Barr virus DNA and anti-Epstein-Barr viral capsid antigen IgA antibody. Clin Chem 2004;50:339-45.
45. 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;94:1614-19.
46. Zhang J, Shu C, Song Y et al. Epstein-Barr virus DNA level as a novel prognostic factor in nasopharyngeal carcinoma: A meta-analysis. Medicine 2016;95:e5130.