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Original Article

Peripheral neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic factors in patients with nasopharyngeal carcinoma

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Abstract

Background: This study aimed to evaluate the prognostic value of pretreatment peripheral neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in nasopharyngeal carcinoma (NPC).
Methods: A total of 450 NPC patients in Dr. Sardjito hospital, Yogyakarta were recruited. Kaplan-Meier was used to analyze patients' survival while association of pretreatment NLR and PLR with overall survival (OS) were examined with Cox proportional hazards regression model (adjusted for age, gender, WHO pathological classification, clinical staging, and therapy).
Results: Cut-off values of 5.35 and 339.23 for pretreatment NLR and PLR respectively were used to sort NPC patients into high- and low-level groups. NLR and PLR are associated with tumor size (P=0.015 : P=0.012). High NLR and PLR are significantly associated with lower OS (median OS±SE high-level NLR vs. Low-level NLR: 20.18 ± 2.68 vs. 33.29 ± 2.38 months, P< 0.001; median OS±SE high-level PLR vs. low-level PLR: 20.29 ± 1.89 vs. 32.86 ± 2.27 months, P<0.001). NLR, clinical stage and therapy are independent prognostic factors in NPC (NLR: HR, 1.84; 95% CI, 1.26–2.7).
Conclusion: Pretreatment NLR is an independent prognostic factor and may serve as clinically useful biomarker for OS of NPC patients.

***Keyword**: nasopharyngeal carcinoma, neutrophil, lymphocyte, platelet, prognosis*

Abstrak

Latar belakang: Tujuan dari penelitian ini adalah untuk mengevaluasi nilai prognostik rasio jumlah neutrofil terhadap limfosit (NLR) dan rasio jumlah trombosit terhadap limfosit (PLR) darah tepi sebelum terapi pada karsinoma nasofaring (KNF).
Metode: Penelitian ini terdiri dari 450 pasien KNF di rumah sakit Dr. Sardjito. Analisis Kaplan-Meier digunakan untuk menghitung dan menggambarkan kurva kesintasan hidup pasien. Hubungan NLR dan PLR dengan kesintasan hidup (OS) diperiksa lebih lanjut dengan pemodelan regresi proporsional Cox, dengan penyesuaian usia, jenis kelamin, klasifikasi patologis WHO, stadium klinis, dan terapi.
Hasil: Nilai batas NLR dan PLR masing-masing adalah 5,35 dan 339,23, dan digunakan untuk membagi pasien KNF menjadi kelompok tingkat tinggi dan rendah. NLR dan PLR berhubungan dengan ukuran tumor pasien KNF (P=0.015: P=0.012). NLR tinggi berkaitan dengan kesintasan hidup yang pendek (median OS±SE NLR > 5,35 vs. NLR ≤ 5,35: 20,18 ± 2,68 vs. 33,29 ± 2,38 bulan, P < 0,001). PLR tinggi berkaitan dengan kesintasan hidup yang pendek (median OS±SE PLR > 339,23 vs. PLR ≤ 339,23: 20,29 ± 1,89 vs. 32,86 ± 2,27 bulan, P < 0,001). Analisis multivariat regresi proporsional Cox menunjukkan bahwa NLR, stadium dan terapi adalah faktor prognostik independen pada pasien KNF (NLR rasio hazard [HR], interval kepercayaan 95% [IK] untuk kesintasan hidup, HR, 1.84; 95% IK, 1.26–2.7).
Kesimpulan: NLR adalah faktor prognostik independen dan dapat berfungsi sebagai biomarker yang berguna secara klinis untuk menilai kesintasan hidup pasien KNF.

***Kata kunci**: karsinoma nasofaring, neutrofil, limfosit, trombosit, prognosis*

Background

Nasopharyngeal carcinoma (NPC) is a malignancy which originates from nasopharyngeal epithelium and is frequently found in the pharyngeal recessus (fossa Rosenmüller) located posteromedial to the ostium of Eustachian tube in the nasopharynx.[1] Generally, the prevalence of NPC is rare worldwide with a rate of less than 1/100,000 population.[2] The incidence of NPC in the world is approximately 86,000 per year with a mortality rate of 50,000 annually.[3] However, in certain countries, NPC is quite common. In Indonesia NPC is the fifth most frequently found head and neck cancer among males. The incidence of NPC in Indonesia is 6.6/100,000 population with a mortality rate as high as 4.3/100,000 population.[4]

Currently, prognosis evaluation of NPC is based on the cancer's stage (tumor size, involvement of lymph nodes and occurrence of distant metastasis).[5] Several molecular biomarkers, such as the Epstein-Barr virus' DNA in plasma had been found to have prognostic value [6,7]. However, their application in clinical setting is limited by high cost and technical requirements. Therefore, a novel low-cost prognostic biomarker is very much anticipated. Recent studies have shown that inflammatory cells play important roles in the occurrence and development of cancer.[8,9] In tumor microenvironment, inflammatory cells release multiple cytokines which promote cancer development while the body immune response system regulates the number and activity of lymphocytes to attack cancer cells.[9]

Neutrophil-to-lymphocyte ratio (NLR) is easily measured and reflected host inflammatory response. Previous studies have shown that NLR is a significant prognostic marker for several solid tumor, including lung cancer, hepatocellular carcinoma, breast cancer, gastric cancer and prostate cancer. [10,11,12,13,14]

Platelets play different roles in the body's physiological and pathological pathways. Concerning oncological process, platelets are involved in the metastasis of tumors.[15] Thrombocytosis has been identified as poor prognostic marker in solid tumors including oral and esophageal squamous cell carcinoma, bronchial and lung carcinoma, gastric cancer and breast cancer. [16,17,18,19,20] Hence, aim of this study is to evaluate the prognostic values of peripheral neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in NPC.

Methods

663 patients' data were collected during 2007-2015 from Dr. Sardjito Hospital data registry. Patients need to meet the following inclusion criteria: patient with newly diagnosed NPC and confirmed histologically who received therapy in Dr. Sardjito Hospital. Exclusion criteria, any of the following: missing data, history of other malignancy and history of infection or autoimmune disease. A retrospective analysis of 450 patients was performed for patients who fulfilled inclusion and did not meet exclusion criteria in Dr. Sardjito Hospital.

Routine blood count test was conducted prior to treatment initiation in these patients, which included neutrophil, lymphocyte and thrombocyte count. Laboratory data were obtained from medical record retrospectively from patient's medical record. The TNM staging used in this study was American Joint Cancer Committee (AJCC) sixth edition (Greene *et al*, 2002). Selected patients were monitored until death or for a minimum of 3 years. This study was approved by Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine Universitas Gadjah Mada, Yogyakarta.

NLR is defined by the absolute number of neutrophils divided by the absolute number of lymphocytes. PLR is defined by the absolute number of platelets divided by the absolute number of lymphocytes which obtained from routine blood count test before treatment initiation. The cut-off value of NLR and PLR is determined by analysis of receiver operating characteristic (ROC) curve and the value is expressed using the Youden index. Data were divided into 2 groups, which are high and low based on the cut-off value. Data frequency was recorded in form of proportion and then analyzed using chi-squared method. The endpoint of study was to evaluate overall survival (OS) of patients. OS is defined as the time from diagnosis to death, while patients who were still alive or loss to follow up were categorized into sensor group. The overall survival curve was estimated using Kaplan-Meier method and compared statistically using log-rank test. Univariate and multivariate analysis based on the Cox proportional regression model were conducted to identify prognostic factors. Other potential prognostic factors were used as modifiers in multivariate analysis including sex (male vs female), age (<50 years old vs ≥ 50 years old), histologic confirmation of nasopharyngeal carcinoma based on WHO (type I,II and III), clinical staging (I, II, III, IVA, IVB, IVC) and treatment (without treatment, chemo-therapy, radiotherapy and chemoradiotherapy). All

statistical analyses were 2-tailed with and p < 0,05 was determined statistically significant. All statistical analysis were performed using SPSS v16.0 (SPSS, Chicago, IL).

Results

There was a total of 450 NPC patients in this study with median age 49 years (minimum age 11 years, maximum age 76 years). The median survival rate of the 450 subjects is 29.7 months (95% CI (confidence interval): 26,02–33,39) with 3 years survival rate of 40.8%. Median follow up in this study is 30.3 months (95% CI: 27,9 - 32,7). Loss to follow up in this study is 34.7%.

The cut-off value of NLR, as determined by ROC curve, in this study is 5.35. Area under curve (AUC) is 0.56 with 95% CI: 0,51-0,6 and P = 0,048. The value 5.35 was chosen because it has the highest Youden index (index 0.143). This cut-off value of 5.35 has 35.2% sensitivity and 78.2% specificity. The cut-off value of PLR used in our study is 339.23 with AUC 0.55 (95% CI: 0,5-0,6 and P = 0,11). This value was chosen as it has the highest Youden index (index 0.11). This cut-off value of 339.23 has 28.7% sensitivity and 82.3% specificity.

The association between NLR and PLR with clinical characteristic in patients with NPC is shown in Table 1. NLR and PLR were found to be significantly associated to tumor size (T) (P = 0,015: P = 0,012). Age, sex, histopathology, involvement of lymph node (N), distant metastasis (M) and clinical stage were found to be not associated to NLR and PLR.

Table 1. Association between NLR and PLR with clinical characteristics in patients with NPC

Characteristics		Case (%)	NLR			PLR		
			≤ 5.35	> 5.35	*P*	≤ 339.23	> 339.23	*P*
Age (year)								
	<50	51.1	168	62	0.412	180	50	0.553
	≥50	48.9	153	67		167	53	
Sex								
	Male	69.3	226	86	0.437	247	65	0.119
	Female	30.7	95	43		100	38	
Pathology								
	Type I/II	5.6	18	7	0.940	22	3	0.182
	Type III	94.4	303	122		325	100	
T class								
	Tis-T2	36.7	129	36	0.015	138	27	0.012
	T3-T4	63.3	192	93		209	76	
N class								
	N0-N1	33.6	110	41	0.614	119	32	0.543
	N2-N3	66.4	211	88		228	71	
Distant Metastatic								
	No	82.4	265	106	0.923	287	84	0.787
	Yes	17.6	56	23		60	19	
Overall Stage								
Stage	I	0.4	1	1	0.227	1	1	0.32
	II	5.7	23	3		24	2	
	III	20.8	72	22		76	18	
	IVA	19.3	59	28		65	22	
	IVB	36	110	52		121	41	
	IVC	17.8	56	23		60	19	
Therapy								
	None	12.6	30	27	0.002	39	18	0.003
	Chemotherapy	24.5	79	31		83	27	
	Radiotherapy	3.5	9	7		9	7	
	Chemoradiotherapy	59.4	203	64		216	51	

NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Based on the univariate analysis with Cox regression, NLR has hazard ratio (HR) of 2.08 (95% CI: 1,56-2,7, P < 0,001) while PLR has HR of 2.02 (95% CI: 1,48-2,7, P < 0,001) for survival of NPC patients. High NLR is significantly associated to lower survival rate (median OS±SE NLR > 5.35 vs. NLR ≤ 5.35: 20.18 ± 2.68 vs. 33.29 ± 2.38 months, P < 0.001) (Figure 1). High PLR is significantly associated to lower survival rate (median OS±SE PLR > 339.23 vs. PLR ≤ 339.23: 20.29 ± 1.89 vs. 32.86 ± 2.27 months, P < 0.001) (Figure 2).

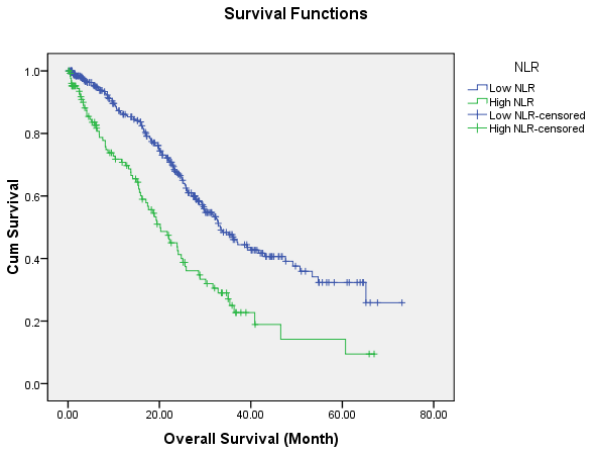

Figure 1. Kaplan Meier curve for NLR and survival rate

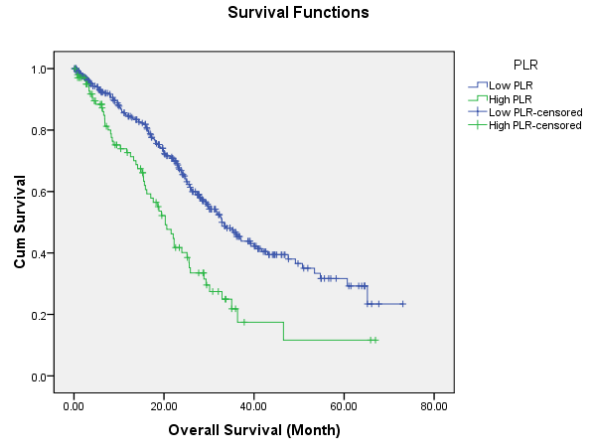

Figure 2. Kaplan Meier curve for PLR and survival rate

Based on the multivariate analysis with Cox regression, NLR, clinical stage and treatment are independent prognostic factors for overall survival of NPC patients (NLR's HR 1.84; 95% CI: 1.26 – 2.7). From multivariate analysis, PLR is not an independent prognostic factor for overall survival of NPC patients. (Table 2)

Table 2. Multivariate analysis on prognostic factors for overall survival of NPC patients

Endpoint	Hazard ratio (95% CI)	*P*
Overall survival		
Stage	1.245 (1.098-1.412)	0.001
Age (< 50 vs. ≥ 50)	1.26 (0.948-1.675)	0.111
Sex (Female vs. Male)	0.872 (0.641-1.185)	0.38
Therapy	0.629 (0.549-0.721)	<0.001
Pathology	1.568 (0.766-3.211)	0.218
NLR level (≤ 5.35 vs. > 5.35)	1.848 (1.261-2.709)	0.002
PLR level (≤ 339.23 vs.> 339.23)	1.11 (0.733-1.681)	0.623

Discussion

All cancer cells induce inflammation regardless before or after cancer development, which provides favorable condition for these cells.[21] Immune cells in the body participate in all stages of neogenesis and immuno-surveillance. This is illustrated by the fact that inflammatory microenvironment contributes in tumor initiation through mutation, genomic instability and epigenetic modification.[22]

Neutrophilia is associated with poor prognostic value in several cancers, such as lung cancer, melanoma and renal carcinoma.[23,24,25] Tumor-associated neutrophils (TANs) help tumor progression in multiple ways, one of which is by releasing matrix metalloproteinase-9 (MMP-9), cytokines (IL-1β, TNF-α, IL-6, and IL-12) dan arginase 1. TANs also produce reactive oxygen species (ROS) and serine proteases which facilitates tumor development.[26]

Acute inflammation can trigger antitumor immunity. Immunogenic cell death (ICD) as a result of injury, stress and certain chemotherapy may induce the expression of surface calreticulin and high-mobility group box 1 (HMGB1) protein in cancer cells, hence activating innate immunity via pattern recognition receptors (PRRs). Dendritic cell maturation and antigen cross-presentation, together with secretion of inflam-matory cytokines, can efficiently produce cytotoxic T cells, which triggers effective anti-tumor immunity responses.[21]

In this study, we found that higher stage of tumor size (T) is associated to higher NLR. High NLR signifies higher neutrophil count compare to lymphocyte in NPC patients. The increase in NLR is also significantly

associated to lower overall survival rate of NPC patients. The prognostic role of NLR in NPC patient is independent and is not affected by age, sex, stage, tumor histopathology, treatment and PLR of NPC patients.

A previous study had shown that NLR is a serum-based parameter which could reflect the immune response status of patients with solid tumor. NLR can represent the activity index of pro-tumor and anti-tumor in solid tumor patients.[27] NLR is relatively easy to obtain and cost efficient as it can be measured from routine blood count test result, which is carried out prior to treatment intiation. Hence, NLR can be used as biomarker to evaluate prognosis of NPC patients.

Thrombocytosis occurs in 10-57% of cancer patients.[28] Other studies had shown that thrombocyte count is inversely proportional to survival rate and thrombocytosis is known as a poor prognostic indication.[29,30,31] The main trigger of thrombocytosis in malignancy is the release of cytokines by cancer cells including IL-1, GM-CSF, G-CSF and IL-6, which stimulates thrombopoiesis through a mechanism dependent of thrombopoietin and affects growth and differentiation of megakaryopoiesis.[32,33]

Thrombocyte contributes to metastasis of cancer by facilitating migration of tumor cells, invasion and infiltration of blood vessels.[34,35] Tumor cells recruit thrombocytes before activating the thrombocytes' membrane which causes the release of their contents into peritumoral area, encouraging extravasation of tumor cells and eventually metastasis.[36]

In this study, we found higher stage of tumor size (T) is also associated to higher PLR value. High PLR signifies higher thrombocyte count compare to lymphocyte in NPC patients. In the univariate analysis, the increase in PLR is significantly associated to lower overall survival rate of NPC patients, however, the prognostic role of PLR in NPC patient is not independent and is affected by other prognostic factors including age, sex, stage, tumor histopathology, treatment and NLR of NPC patient.

The limitations of this study include the relatively high number of loss to follow up data and the fact that this research utilizes secondary data, which is very dependent on the completeness of medical record, such that any incomplete record will exclude a large number of patients as subject. However, this research has comparatively high number of subjects (450 NPC patients) which covers clinical stage I until IVC.

Conclusion

NLR is an independent prognostic factor dan can be used as biomarker to evaluate overall survival of NPC patients clinically. High NLR is associated to lower overall survival in many solid tumor patients including NPC patients. NLR can serve as a cost efficient and easily accessible prognostic biomarker. Further research should be conducted to measure the significance of NLR in treatment decision-making for solid tumor patients including those with NPC.

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Conflict of Interest

The authors have no conflict of interest.

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