THE RELATIONSHIP OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) WITH LOCALIZED AND NON-LOCALIZED TESTICULAR GERM CELL TUMORS

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ABSTRACT

Objective: *This study aim to reveal the relationship preoperative neutrophil-to-lymphocyte ratio (NLR) with testicular germ cell tumors (GCT).* ***Material & Methods:*** *A total of twenty-six patients diagnosed with TGCT from 2017 to 2022 in Saiful Anwar Hospital, Malang were included in this retrospective study. Patients were grouped as localized and non-localized. Hematological and biochemical blood measured the days before radical orchiectomy.* ***Results:*** *Eleven patients (42.3%) had seminomas and fifteen patients (57.7%) had non-seminomatous testicular cancer. Six patients (23.1%) had localized and twenty patients (76.9%) had non-localized testicular cancer. There was a statistically significant difference between mean NLR of the localized patients and non-localized patients (localized NLR: 1.7±0.84, non-localized: 3.65±0.97, p=0.000). The optimal cut-off value for localized and non-localized TGCT was 3.05 with sensitivity 83.33% and specificity 75%. That was statistically significant between cut-off value NLR with localized and non-localized TGCT (correlation coefficient 0.505, p=0.008).* ***Conclusion:*** *NLR appears to be a useful marker for TGCT. It is successful in predicting localized and non-localized disease in early preoperative period.*

Keywords: *Neutrophil-to-lymphocyte ratio, testicular cancer, testicular germ cell tumors.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk mengungkap hubungan rasio neutrofil terhadap limfosit (NLR) pra operasi dengan tumor sel germinal testis (GCT).* ***Bahan & Cara:*** *Sebanyak dua puluh enam pasien yang didiagnosis dengan TGCT dari tahun 2017 hingga 2022 di Rumah Sakit Saiful Anwar, Malang diikutsertakan dalam penelitian retrospektif ini. Pasien dikelompokkan sebagai terlokalisasi dan tidak terlokalisasi. Darah hematologi dan biokimia diukur beberapa hari sebelum orkiektomi radikal.* ***Hasil:*** *Sebelas pasien (42,3%) memiliki seminoma dan lima belas pasien (57,7%) memiliki kanker testis non-seminomatosa. Enam pasien (23,1%) memiliki kanker testis terlokalisasi dan dua puluh pasien (76,9%) memiliki kanker testis tidak terlokalisasi. Ada perbedaan yang signifikan secara statistik antara NLR rata-rata pasien terlokalisasi dan pasien tidak terlokalisasi (NLR terlokalisasi: 1,7±0,84, tidak terlokalisasi: 3,65±0,97, p=0,000). Nilai batas optimal untuk TGCT terlokalisasi dan non-lokalisasi adalah 3,05 dengan sensitivitas 83,33% dan spesifisitas 75%. Nilai batas tersebut signifikan secara statistik antara nilai batas NLR dengan TGCT terlokalisasi dan non-lokalisasi (koefisien korelasi 0,505, p=0,008).* ***Simpulan:*** *NLR tampaknya merupakan penanda yang berguna untuk TGCT. NLR berhasil memprediksi penyakit terlokalisasi dan non-lokalisasi pada periode pra operasi dini.*

Kata kunci: *Rasio neutrofil terhadap limfosit, kanker testis, tumor sel germinal testis.*

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INTRODUCTION

Testicular cancer is a rare malignancy which forms 1% of all male cancers globally. Testicular cancer is the most common type of malignancy in men between ages of 15 and 44 years.[1] The incidence of testicular cancer has increased in the Caucasian populations with a 7.8 and 6.7 in 100,000 men incidence rate in Western and Northern Europe, respectively, compared to Northern Africa which accounted for 0.6 in 100,000 men.[2] The predominant histology is testicular germ cell tumours (90-95% of cases) which divided into two groups as seminoma and non-seminoma germ cell tumors.[3]

The development of cancer progression was influenced by the tumor microenvironment and host inflammatory response.[4] Inflammatory cells produce several mediators and cytokines that can induce or

promote angiogenesis, tumor growth, invasion and metastasis.[4-5] Also, it has been hypothesized that synthesis of inflammatory cytokines can be triggered by the tumor microenvironment resulting in alterations of acute phase reactants such as serum neutrophil and lymphocyte counts.[6] Cumulative evidence has supported the role of inflammation in cancer development and progression, and the neutrophil-to-lymphocyte ratio (NLR), represents an inexpensive, easily measured and reproducible marker of systemic inflammation that correlates with tumour activity.[7] However, limited data exist regarding the potential prognostic role of NLR in testicular cancer.

OBJECTIVE

In this study, we aimed to reveal the relationship between testicular germ cell tumors (TGCT) and neutrophil-to-lymphocyte ratio (NLR) and to determine whether this ratio can be used as a serum tumor marker for TGCT.

MATERIAL & METHODS

Data of the patients in the Saiful Anwar General Hospital who underwent radical orchiectomy due to testicular cancer between 2017 to 2022 were analyzed retrospectively. Twenty-six patients with testicular germ cell tumor were included in the study whose underwent radical orchiectomy. Patients with infectious or inflammatory conditions, hematological disease, other malignancies, diabetes mellitus, cardiovascular diseases, end-stage renal disease, and patients with incomplete data including complete blood count, HCG, AFP, LDH and abdominal tomography were excluded.

Twenty-six patients with testicular germ cell tumor were included in the study. Hematological and biochemical blood measured the days before radical orchiectomy, as part of our routine pre-operative examination. Tumour markers were collected before radical orchiectomy. No patient received chemotherapy prior to these blood results. Patients with no regional lymph nodes or distant metastasis on computed tomography and no elevated serum markers following orchiectomy (stage 1A and stage 1B) were categorized as localized and patients with regional lymph nodes or distant metastasis or elevated serum markers following orchiectomy (stage 1S, stage 2 and stage 3) were categorized as non-localized. Histologically, patients were categorized as seminoma and non-seminoma germ cell tumors.

Data analysis was performed using SPSS 22.0 computer software (Statistical Package for Social Sciences, Chigaco, IL, USA). Study data were evaluated using descriptive statistical methods. Independent t-tests was used for comparisons of quantitative data with normal distribution. Receiver operating characteristics curve analysis was performed to find cut-off levels for NLR as a predictor of localized and non-localized TGCT. The relationship between clinicopathological features and NLR was calculated with chi-square test. All tests were two-sided with $p<0.05$ considered to be statistically significant.

RESULTS

A total of twenty-six patients diagnosed with TGCT were included in this retrospective study. Table 1 showed the summary of clinical characteristics of the patients. Mean age of the patients was 33.5±13.5 years. Eleven patients (42.3%) had seminomas and fifteen patients (57.7%) had non-seminomas testicular cancer. Six patients (23.1%) had localized and twenty patients (76.9%) had non-localized testicular cancer. All of the non-seminomas tumors were mixed germ cell tumors; 9 patients had yolk sac tumor, 1 patients had embryonal carcinoma, 4 patients had teratoma, and 1 patient had adenocarcinoma.

Table 1. Demographic characteristic of the patients.

	Frequency	%
Age (mean±SD), years	33.5±13.5	(3-64)
Histology		
Seminoma	11	42.3%
Non-seminoma	15	57.7%
Staging		
Localized	6	23.1%
Non-localized	20	76.9%
Neutrophils (mean±SD)	6.4±3.0	(2.21-12.4)
Lymphocytes (mean±SD)	2.1±0.8	(1.2-4.56)
NLR (mean±SD)	3.2±1.2	(0.48-5.37)

There was a statistically significant difference between mean NLR of the localized patients and non-localized patients (localized NLR: 1.7±0.84, non-localized: 3.65±0.97, p=0.000) (Table 2). Mean NLR was significantly higher in non-localized patients compared to localized patients.

Table 2. Comparison of Neutrophil-to-Lymphocyte Ratio Between Localized and Non-localized TGCT.

	Localized		Non-localized		P-value
	Mean	SD	Mean	SD	
Neutrofil	3.94	0.50	7.08	3.02	0.000
Limfosit	1.94	0.59	2.12	0.79	0.609
NLR	1.70	0.84	3.65	0.97	0.000

NLR of localized and non-localized TGCT were used to define an optimal cut-off value for the presence of non-localized TGCT. The optimal cut off value for localized and non-localized TGCT was 3.05 with sensitivity 83.33% and specificity 75%, area under the receiver operating characteristics curve was 95.8% (95% CI:87.2%-104.4%) (Figure 1).

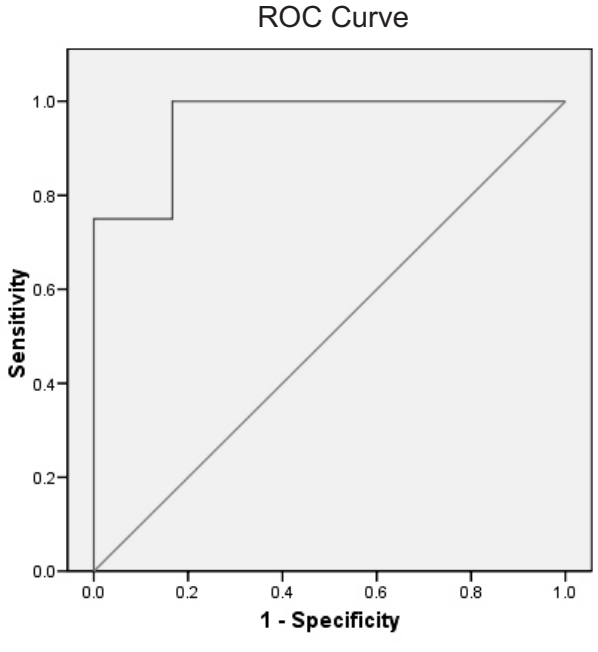

Figure 1. Receiver Operating Characteristic (ROC) Curve.

Spearman correlation coefficient was calculated as 0.505 indicating a positive correlation between cut off value NLR with localized and non-localized TGCT that was statistically significant (p=0.008) (Table 3). The value of the correlation coefficient is positive, meaning that the higher the NLR with the cut off of the ROC results, the tendency is that the patient is in the non-localized group, while for the lower NLR there is a tendency that the patient is in the localized group.

Table 3. Correlation of Neutrophil-to-Lymphocyte with Localized and Non-localized TGCT.

	Localized	non-localized	Spearman correlation and P-value
NLR < 3.05	5 (50%)	5 (50%)	r = 0.505
NLR = 3.05	1 (6.3%)	15 (93.8%)	p = 0.008

DISCUSSION

Testicular cancer represents 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies.[8] The predominant histology is testicular germ cell tumours (TGCT) (90-95% of cases) and serum tumor markers play a crucial rule in diagnosis, treatment and follow-up of patient with TGCT.[3] Regarding response and prognosis, inflammation plays a role in the progressivity and prognosis of TGCT.[3,9] One of the markers was NLR. NLR is an inexpensive and easily acquired inflammatory marker.[7] Inflammatory cells produce mediators and cytokines that can induce or promote angiogenesis, tumor growth, invasion, and metastasis.[10] Systemic inflammation has an essential role in all tumorigenesis stages. It may induce the process via genetic mutations and genomic instability. Inflammation can also activate tissue repair, inducing the proliferation of premalignant cells.[11] Schepisi et al. presented a comprehensive discussion on the strong relationship between the role of immune system and inflammatory processes in tumour biology. A heightened circulating neutrophil level is associated with increased cytokines, particularly interleukins (IL-1, IL-6) and pro-angiogenic vascular endothelial growth factor which promote tumour migration and proliferation.[12] IL-6 protects the cancer cells from therapy-induced DNA damage, oxidative stress and apoptosis, hence promoting tumourigenesis.[13]

Templeton et al, in his meta-analysis of 100 studies, comprising 40,559 patients, demonstrated the strong relationship between NLR and over 20 solid tumours. Although the analysis involved a very heterogeneous group of malignancies, the sheer patient size and consistent results reflect the fundamental role of inflammation and immune suppression, as represented by NLR, in cancer biology.[14] Since then, further independent studies, each focusing primarily on individual malignancy, or in particularly, urological malignancies, similarly

established the significance of NLR. Jankovich et al, in his review of 103 patients, commented a higher prevalence of non-metastatic disease in patients with NLR <4. A NLR cutoff of 4 was arbitrarily determined to stay consistent to Templeton et al. meta-analysis.[15] Tan et al, in his studies in a larger cohort of patients, with an extended follow-up time and more detailed clinicopathological features to evaluate the association between NLR and testicular cancer, demonstrated that a higher preoperative NLR (≥ 3.0) predicts lymph node involvement and metastatic disease, which hence represent an advanced cancer staging in both seminoma and non-seminoma germ cell tumors.[9]

In this study, we observed a higher level of NLR in localized patients compared with non-localized patients, it was seen that NLR of non-localized TGCT patients was significantly higher (localized NLR: 1.7±0.84, non-localized: 3.65±0.97, p=0.000). We performed receiver operating characteristics curve analysis to define cut-off levels for NLR as a predictor of localized and non-localized TGCT. The optimal cut off value in this study was 3.05. In their study, Yuksel et al. defined a cut off value of 2.06 for NLR and Jankovich et al, in his review of 103 patients, showed a higher prevalence of non-metastatic disease in patients with NLR <4).[15-16] Eventhough this study showed that NLR seemed to be higher in non-localized patients, a definitive conclusion still could not be made until a prospective cohort study with larger sample size is performed.

CONCLUSION

NLR appears to be a useful marker for TGCT. It is successful in predicting localized and non-localized disease in early preoperative period. This study has several limitations. We had a small group of patients and single-center study. We did not evaluate relationship of NLR with recurrence and prognosis. Further large-scale and prospective cohort studies are required.

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