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The role of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in determining the prognosis of patients with testicular cancer

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ABSTRACT

Background: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as systemic inflammatory response markers, have been shown to play a role in prognostic factors for patients with malignancies in recent years. However, their application as the prognostic factors of testicular cancer remains unknown. This study aims to evaluate the prognostic role of testicular malignancies using preoperative hematological parameters, NLR and PLR, and their pre-diagnostic role in the staging of testicular cancer.

Methods: This was a cross-sectional retrospective study of thirty-nine patients who underwent radical orchiectomy due to testicular cancer at the Department of Urology Haji Adam Malik General Hospital between January 2014 and December 2018. For each patient, clinical features including age, sex, clinical stage, chemotherapy, radiology report, pre-treatment neutrophil count, lymphocyte count, platelet count, NLR, PLR, and postoperative histopathological report were collected. Then we analyzed the association between NLR, PLR and the testicular cancer metastasis incidence.

Result: The mean age of the patients was 27.56 ± 17.47 years. Seventeen patients had seminoma (42.5%), 16 others were yolk sac type of cancer (40.0%), and the rest six patients were teratoma (3 patients), lymphoma (2 patients), and embryonal carcinoma (1 patient). More than half (66.48%) of the patients received chemotherapy after radical orchiectomy, with 48.70% in clinical stage III. PLR was associated with testicular cancer metastases (p=0.024), while NLR was not (p=0.729).

Conclusion: High pre-treatment PLR levels are associated with the occurrence of metastasis in testicular cancer patients. Hematological parameters will become critical in the preoperative evaluation of such testicular cancer cases. The potential prognostic significance of NLR and PLR in testicular cancer should be tested with further studies.

Keywords: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, testicular cancer.
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INTRODUCTION

Testicular cancer is considered rare in men. It only accounts for 1% of all neoplasms. Testicular cancer is a significant research topic despite its low incidence since it affects 15-35 years males.[1] Physical examination and ultrasound results are the modalities to diagnose this tumor. Although there are some testicular tumor-specific indicators, they may be normal in some situations. Regional and international urological associations have developed guidelines to assist practitioners and caregivers in caring for and educating patients with testicular cancer. It is sometimes necessary to use other indicators and the available staging criteria to support medical judgments for the patient.[2]

Tumorigenesis and tumor invasion are both linked to inflammatory responses. There is an association between cancer cells and inflammation due to various mechanisms. Inflammation plays a key role in carcinogenesis at every stage.[3] In addition, prolonged inflammation has been shown to decrease immunological response and promote tumor growth.[2]

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as systemic inflammatory response markers, have played a role in prognostic factors for patients with malignancies in recent years. Tumor cells are associated with inflammation at almost every stage of carcinogenesis, including metastasis. The best part is that they can be easily estimated from routine complete blood counts.

Most studies have shown that an increase in NLR is linked to a poor prognosis in many malignancies. As a result, NLR can be used as a marker of systemic inflammatory response in various malignancies and inflammatory conditions. Simple blood tests like NLR are gaining popularity to predict the prognosis of cancer and inflammatory disorders. In

vast clinical settings, NLR and PLR can be used to predict the patient's prognosis.[3] However, the association of NLR and PLR to the prognosis of testicular cancer is still unclear. The purpose of this research is to evaluate the prognostic role of testicular malignancies using preoperative hematological parameters, NLR and PLR, and their pre-diagnostic role in the testicular cancer staging.

METHODS

This research uses a retrospective study design conducted at the Department of Urology at Haji Adam Malik General Hospital between January 2014 and December 2018. All patients diagnosed with testicular tumors who underwent radical orchiectomy were included in this study. Patients with acute infections, chronic inflammatory diseases, malignancies, or hematological disorders and patients with missing data were excluded.

Age, sex, clinical stage, chemotherapy, radiology report, pre-treatment count of neutrophils, lymphocytes, and platelets in peripheral blood samples during the preoperative period were collected. We used the SPSS 20 program to do the statistical analysis in this study. Descriptive statistical methods were used to present the study data that had been collected. The independent t-test was used to compare the means of numerical data in two independent groups with a normal distribution of data, while the Mann Whitney U test was used in the numerical data obtained were abnormally distributed. Those bivariate analyses evaluated the association between NLR, PLR, and the incidence of metastatic testicular cancer. The analysis is considered significant if $p < 0.05$.

RESULTS

Thirty-nine patients agreed to be subjects in this study. Table 1 shows the baseline characteristics of the study subjects. The mean age of the patients was 27.56 ± 17.47 years. The mean value of neutrophil counts was 5.7 ± 2.1 x 10^3 cells/µL, and the mean value of platelet counts was 263.3 ± 66.7 x 10^3 cells/µL. The NLR was 3.1 ± 1.4, and PLR was 141.3 ± 53.2.

Based on the types of testicular cancer, seminoma was identified in 17 patients (42.5%), yolk sac in 16 patients (40.0%), teratoma in 3 patients (7.5%), lymphoma in 2 patients (5.0%), and embryonal carcinoma in 1 (0.025%). Most (66.48%) of the patients received chemotherapy after radical orchiectomy. For the clinical stage, 19 patients were in stage III (48.7%), 11 patients were in stage I (28.2%), and nine patients were in stage II (23.1%) (Table 2).

PLR was associated with the incidence of testicular cancer metastasis (p=0.024), while NLR was not (p=0.729) (Table 3).

DISCUSSION

Tumor growth, progression, clinical presentation, and prognosis have been linked to the inflammatory process. It was involved in every stage of carcinogenesis.[1–3] The systemic inflammatory response to tumor cells differs depending on the form and prevalence of the malignancy. The interaction between the tumor and its host substantially impacts tumor growth. Currently, cytokines, C-reactive protein (CRP), leukocyte counts and the other blood markers as indicators of the systemic inflammatory response are considered independent prognostic variables in patients with malignancy.[4,5]

Based on the knowledge that has developed to date, the immune system can play a role in killing the cancer cells or can also increase tumor growth by increasing the invasive capacity of malignant cells and the ability to metastasize to distant organs. Many circulating neutrophils play an important role in tumor formation and angiogenesis.[1–3] A high neutrophils count can be associated with a bad prognosis. High NLR, which occurs because of the additional effect of enhanced neutrophils response to lymphocyte suppression, may aid cancer progression by suppressing the antitumor immune response. Neutrophilia can result from ectopic myeloid growth factors or a cancer-related inflammatory

Table 1. Baseline characteristics of the subjects.

Characteristics	Mean ± SD
Age (years)	27.56 ± 17.47
Neutrophil counts (10^3 cells/µL)	5.7 ± 2.1
Platelet counts (10^3 cells/µL)	263.3 ± 66.7
NLR	3.1 ± 1.4
PLR	141.3 ± 53.2

Table 2. Descriptive statistics of the subjects.

Characteristics	N (%)
Type of testicular cancers:	
Seminoma	17 (42.5%)
Yolk Sac	16 (40.0%)
Teratoma	3 (7.5%)
Lymphoma	2 (5.0%)
Embryonal carcinoma	1 (0.025%)
Regimen therapy:	
Chemotherapy post-radical orchiectomy	26 (66.48%)
Not having chemotherapy post radical orchiectomy	13 (33.52%)
Clinical stage:	
I	11 (28.2%)
II	9 (23.1%)
III	19 (48.7%)

Table 3. Association of NLR and PLR with the incidence of metastatic testicular cancers.

	Metastatic testicular cancer	p-value
NLR	3.5 ± 1.8	0.729
PLR	143.4 ± 54.2	0.024

response with cytokines because of tissue loss as part of paraneoplastic syndrome. Active neutrophils have been shown to, directly and indirectly, activate the growth of the tumor. Inflammatory mediators' molecular pathways can assist cancer cells' angiogenesis and metastasis, impacting treatment responses.[4,5]

Like neutrophils, platelets are also known to have an important role in tumorigenesis. By inducing VEGF cytokine, platelets stimulate tumor growth and angiogenesis. VEGF facilitates blood vessel development and contributes to cancer metastasis. Solid tumors have also been reported to produce IL-6, which encourages thrombocytosis. IL-6 will promote thrombopoietin, leading to an increased platelet count in patients with malignancy.[6] Research investigating the prognostic value of PLR in 1528 patients with renal cancer carcinoma has shown that elevated PLR was an independent indicator of poor overall survival and progression-free survival. The results of the subgroup study concluded that PLR could serve as a reliable marker for cancer prognosis.[7]

Calculation of NLR and PLR, which is known to have a role in determining the prognosis of cancer patients, has advantages in terms of cost-effectiveness compared to other markers such as examination of CRP levels.[6] Previous studies in patients undergoing transurethral resection–bladder due to bladder tumor surgery have identified that high NLR correlates with tumor grade and stage. In most studies examining the relationship between radical cystectomy outcomes and NLR, high NLR outcomes and worse ratios were found in disease-specific and overall survival.[1,5]

Most of the established studies were on the roles of NLR and PLR in the kidney, bladder, and upper urinary tract neoplasms. There are few studies regarding NLR and PLR in testicular cancer. In addition, regarding ethnicity and geographic location, there is high variability in the occurrence and clinical profile of testicular cancer.[8,9] A study by Yüksel et al. on localized testicular cancer patients found that the NLR value was higher than the control group.[1] Another study found that in patients with and without testicular cancer, the NLR values were 4.57 and 3.44. Despite the limitations in previous studies by which samples were obtained retrospectively, and concomitant inflammatory conditions such as infection or hematological disorders were not evaluated, NLR and PLR were still shown to be diagnostic biomarkers for testicular cancer patients.

Our present study evaluated the NLR and PLR on metastatic progression in testicular cancer patients. Although the mean of NLR in the metastatic cancer group (3.5 ± 1.8) was higher compared to the overall mean of NLR (3.1 ± 1.4), there was no significant association between the NLR and the metastatic testicular cancer group ($p = 0.729$). It is contrasted with the studies that showed a significant correlation between NLR and PLR in malignancy. Differences in the patient characteristics and the small sample size may alter the result. Two studies that assessed the association between the impact of radical cystectomy and NLR reported high NLR and worse overall survival ratios.[1,5]

Our study showed that the mean value of NLR was 3.5 ± 1.8. This result was higher than the NLR value in other cancers, as shown in a meta-analysis by Wei et al. in 2014.10 Wei's study concluded that high NLR (> 2.5) correlates with poor general survival in renal cell carcinoma, bladder cancer, and urothelial carcinomas. NLR and PLR found in the testicular cancer in this study are higher than in the early stage of cervical cancer.[11] Our findings were also aligned with Gokcen et al. research, which reported a higher NLR and PLR in testicular tumors than in other types of cancers.[12] Although, until now, many studies study the relationship of other cancers with hematological parameters, research on hematological parameters with testicular tumors is still relatively limited. The diagnosis of testicular cancer and its staging can be related to this practical and simple hematological parameter, but further research is needed to confirm this hypothesis.

Elevated pre-treatment PLR is associated with the incidence of metastasis in testicular cancer patients. In the preoperative assessment of such patients, hematological parameters will become essential.

The limitation of this study is the small number of samples, so this study cannot be applied in general. In order to resolve the possible prognostic importance of NLR and PLR in testicular cancer, further research should be performed.

CONCLUSION

Elevated pre-treatment PLR levels are associated with the occurrence of metastasis in testicular cancer patients. Hematological parameters will become critical in the preoperative evaluation of such patients. The potential prognostic significance of NLR and PLR in testicular cancer should be tested with further studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding this study.

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ETHICS APPROVAL

Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, has approved this study with letter number 1322/KEP/USU/2021.

CONSENT FOR PUBLICATION

The patient has given informed consent to extract data from medical records and publications.

AUTHORS CONTRIBUTION

Syah Mirsya Warli contributes to study conceptualization, methodology, manuscript writing and reviewing. David Ralph Lienhardt Ringoringo contributes to data collection, analysis, and manuscript writing. Bungaran Sihombing, Ginanda Putra Siregar, and Fauriski Febrian

Prapiska contribute to manuscript editing and reviewing.

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