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Correlation of neutrophil ratio to lymphocyte levels before therapy with the incidence of metastasis, lymph node involvements, in urothelial type muscle invasive bladder cancer in Indonesia

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ABSTRACT

Bladder cancer is cancer originated from the bladder mucosa or urothelium. Bladder cancer is the 9th most common malignancy worldwide and the most common malignancy of the urinary tract. Studies show that cancer triggers an inflammatory response, which causes changes in circulating inflammatory cells. Examination of neutrophils and lymphocytes is an inexpensive examination, reproducible, and easily obtained. Neutrophil to lymphocyte ratio (NLR) values have been used in several studies to evaluate the inflammatory response that occurs in tumors. In urology, the importance of NLR has been recognized in predicting progression and aggressiveness in urothelial bladder tumors, kidney cancer (RCC/renal cell carcinoma), and upper tract urothelial carcinoma (UTUC). This study was a cross-sectional study obtained retrospectively by evaluating the medical records of patients diagnosed with muscle-invasive bladder cancer (MIBC) at Dr. Sardjito General Hospital, Yogyakarta, Indonesia from January 2017 to December 2019. The NLR data were categorized into NLR < 2.5 and > 2.5. As much as 150 patients with bladder cancer were included in this study, with a mean age of 56.43 ± 13.60 years. In the comparison of NLR values and the incidence of metastasis, there were 15 people (20%) with NLR values < 2.5 who had metastasis while 32 people (42.7%) from the group with NLR > 2.5 had metastasis (p = 0.003). In the comparison of NLR values and nodule involvement, there were 25 (33.3%) patients with NLR < 2.5 and 39 (52%) patients with NLR > 2.5 (p = 0.021). This study showed that patients with metastatic bladder tumors and lymph node involvement had a significantly higher NLR value. It can be concluded the NLR value can be used to predict the metastatic level and lymph node involvement in patients with bladder tumors. Even though it is not a specific marker of inflammation, the NLR examination is simple, affordable, easy to obtain, and widely available.

ABSTRAK

Kanker kandung kemih adalah kanker yang berasal dari mukosa kandung kemih atau urothelium. Kanker kandung kemih adalah jenis keganasan urutan kesembilan yang paling umum terjadi di seluruh dunia dan merupakan jenis keganasan yang paling umum terjadi pada traktus urinarius. Penelitian menunjukkan bahwa kanker memicu proses inflamasi yang menyebabkan perubahan pada sirkulasi sel inflamasi. Pemeriksaan neutrofil dan limfosit merupakan pemeriksaan yang murah, reprodusibel dan mudah dilakukan. Nilai *neutrophil to lymphocyte ratio* (NLR) telah digunakan untuk melihat respon inflamasi yang terjadi pada tumor. Dalam urologi, NLR telah digunakan untuk memprediksi perkembangan dan agresivitas pada tumor kandung kemih urothelial, kanker ginjal (RCC/*renal cell carcinoma*) dan *upper tract urothelial carcinoma* (UTUC). Penelitian ini merupakan penelitian retrospektif menggunakan data rekam medis pasien yang didiagnosis kanker otot kandung kemih invasif (KKKIO) di RSUP Dr. Sarjito, Yogyakarta, Indonesia dari Januari 2017 hingga Desember 2019. Data NLR dikategorikan menjadi NLR < 2,5 dan > 2,5. Populasi pada penelitian ini yaitu 150 pasien dengan kanker kandung kemih, dengan usia rata-rata 56,43 ± 13,60 tahun. Perbandingan nilai NLR dengan kejadian metastasis yaitu terdapat 15 pasien (20%) dengan nilai NLR < 2,5 yang mengalami metastasis, sedangkan sebanyak 32 pasien (42,7%) dengan nilai NLR > 2,5 mengalami metastasis (0,003). Perbandingan nilai NLR dengan keterlibatan nodul, terdapat 25 pasien (33,3%) dengan NLR < 2,5 dan 39 pasien (52%) dengan NLR > 2,5 (0,021). Hasil penelitian menunjukkan bahwa pasien dengan tumor kandung kemih dengan metastasis dan ada keterlibatan kelenjar getah bening secara bermakna memiliki nilai NLR lebih tinggi. Dapat disimpulkan bahwa nilai NLR dapat digunakan untuk memprediksi tingkat metastasis dan keterlibatan kelenjar getah bening pada pasien dengan tumor kandung kemih. Meskipun bukan penanda inflamasi yang spesifik, pemeriksaan NLR merupakan pemeriksaan yang sederhana, terjangkau, mudah diperoleh dan tersedia secara luas.

Keywords:
NLR;
bladder cancer;
metastasis;
marker;
renal cell carcinoma;
inflammatory cells

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INTRODUCTION

Bladder cancer is cancer that originates from the bladder mucosa or urothelium.[1] Bladder cancer is the ninth most common malignancy worldwide and the most common malignancy of the urinary tract.[2] Urothelial bladder cancer has a high aggressiveness. To determine the appropriate management of patients with bladder cancer, accurate perioperative risk stratification is necessary.

Studies showed that cancer triggers an inflammatory response, which causes changes in circulating inflammatory cells. Tumor tissue in addition to inducing a systemic inflammatory response also causes a local inflammatory response due to disruption and destruction of tumors in the surrounding tissue.[3,4] Inflammation that occurs has an important role in the emergence and progression of tumors.

Currently, many systemic inflammatory mediators are investigated to evaluate the inflammatory response on tumors patients. Many inflammatory mediators are used as biomarkers to predict the prognosis of cancer, but most of these biomarkers are relatively expensive.[5,6] Examination of neutrophils and lymphocytes is an examination that is inexpensive, reproducible, and easily obtained examination.[4] Furthermore, meta analytic studies concerning the correlation between the neutrophil to lymphocyte ratio (NLR) and metastatic bladder cancer has been conducted in China, Australia, Korea, Japan and Canada.[7] However, the similar study on Indonesia population has not been conducted, yet. We hope our studies could shine a light to the Indonesian population's characteristic of NLR value to metastatic bladder cancer.

The NLR is obtained by dividing the absolute neutrophil level by the absolute lymphocyte level.[8] The NLR value has been used in several studies to assess the inflammatory response that occurs in tumors. Higher NLR values are associated with a poorer prognosis in bronchoalveolar carcinoma, melanoma, squamous cell carcinoma of the head and neck, as well as in kidney cancer. In urology, the importance of NLR has been recognized in predicting progression and aggressiveness in urothelial bladder tumors, kidney cancer (RCC/renal cell carcinoma), and upper tract urothelial carcinoma (UTUC).[9-12]

Previous studies have shown that NLR can be used as a biomarker for prognostic assessment, also can be used to help clinicians and patients in making decisions regarding their tailored treatment options for muscle invasive bladder cancer (MIBC).[13] Other studies also suggest that the use of NLR in predicting disease aggressiveness, the outcome of the disease oncology, and the response in the treatment of urothelial carcinoma management. Even though there were limitations of the study, such as the inter-study heterogenicity, bias of the publication possibility, the restricted number of studies, also there are no previous randomized controlled studies.[14]

This study aimed to investigate the correlation between NLR levels with the incidence of metastasis, lymph node involvement, in bladder cancer. The result of this study is expected to be a predictor of prognosis in patients with bladder cancer.

MATERIALS AND METHODS

Design of study

It was a cross-sectional study obtained retrospectively by reviewing the medical records of patients diagnosed with MIBC at Dr. Sardjito General

Hospital, Yogyakarta, Indonesia from January 2017 to December 2019. One hundred and fifty patients with MIBC were included in this study.

Procedure

Patients with incomplete medical record data and modalities were excluded. NLR data were categorized into NLR < 2.5 and > 2.5. Each patient and/or relative in charge of the research subject was given an explanation of the objectives, working methods, benefits, and risks of the research. If the prospective research subject or and/or relatives in charge understand and agree to participate in the research, they were asked to sign a written research agreement. NLR, demographic, clinical and pathological data including tumor staging, nodule staging, and metastasis were collected. Protocol of the study has been approve by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing/Dr. Sardjito General Hospital, Yogyakarta (ref. no. KE/FK/0524/EC/2021).

Statistical analysis

The data obtained were validated, coded, recapitulated, and tabulated.. The existing data were entered into a computer using the SPSS program for further statistical analysis. The relationship between the incidence of metastasis, lymph node involvement, and neutrophil-lymphocyte levels were analyzed by Chi-Square test or Fisher's Test, with p value < 0.05 was considered to be statistically significant.

RESULTS

Among 150 patients involving in this study, 118 were male (78.1%) while 32 were female (21.2%) with the mean age of patients was 56.43 ± 13.60 years. A total of 76 patients (50.7%) had tumors of the T2 category, while 51 (34%) had tumors of the T3 category, and 23 (15.3%) had tumors of the T4 category. Metastatic nodules were found in 64 patients (42.7%), while metastasis were found in 47 patients (31.3%). The mean absolute neutrophil level in the patients was 5.46 ± 6.50 with a range of values from 1.2 to 14.2. The mean absolute lymphocyte level in patients was 2.3 ± 11.50 with a range of values from 0.6 to 23.7. The characteristics of patients are shown in TABLE 1.

In the comparison of NLR values and the incidence of metastasis, there were 15 people (20%) with NLR values less than 2.5 who had metastasis while 32 people (42.7%) from the group with values above 2.5 had metastasis. A statistically significant relationship between NLR values and the incidence of metastasis in bladder cancer patients was observed (p=0.003) as shown in TABLE 2.

In the comparison of NLR values and nodule involvement, 25 (33.3%) patients with NLR < 2.5 had nodule involvement (N+), while 39 (52%) patients with NLR > 2.5 had nodule involvement (N+). A statistically significant relationship between NLR values and nodule involvement in bladder cancer patients was observed (p=0.021) as shown in TABLE 3.

TABLE 1. Sample characteristic

Variable	n (%)	Mean (SD)
Age (years)		56.43 ± 13.60
Gender		
• Male	118 (78.1%)	
• Female	32 (21.2%)	
Tumor staging		
• T2	76 (50.7%)	
• T3	51 (34%)	
• T4	23 (15.3%)	
Nodule staging		
• N1-3	86 (57.3%)	
• N0	64 (42,7%)	
Metastasis		
• M1	47 (31.3%)	
• M0	103 (68.7%)	
Neutrophil		5.46 ± 6.50
Lymphocyte		2.30 ± 11.50

TABLE 2. Univariate analysis of NLR

Variable	NLR		p
	< 2.5	> 2.5	
Metastasis [n (%)]			
• M1	15 (20.0)	32 (42.7)	0.003
• M0	60 (80.0)	43 (57.3)	
Nodule [n (%)]			
• N1-N3	25 (33.3)	39 (52.0)	0.021
• N0	50 (66.7)	36 (48.0)	

TABLE 3. Multivariate analysis logistic regression

Variable	Coefficient	S.E	Wald	df	p	OR	95% CI	
							Lower	Upper
Metastasis	1.051	0.371	8.029	1	0.005	2.86	1.38	5.91
Nodule	-0.076	0.539	0.020	1	0.888	0.92	0.32	2.66

DISCUSSION

Neutrophil to lymphocyte ratio can be used as an independent predictor that provides prognostic value, such as disease-free survival (DFS) and progression-free survival (PFS) in malignant tumors.[15] The NLR can be used as an independent prognostic factor in patients with bladder cancer undergoing

radical cystectomy.[16] The NLR is an important and useful parameter for predicting locally advanced organ-limited stage in MIBC so it needs to be part of clinical staging before radical cystectomy is performed.[17] Several studies reported that preoperative patients with elevated NLR can be up-staged and may benefit from neoadjuvant chemotherapy.[18-20] Recently, there is no standard cut-off value that is used as a standard in assessing NLR. Some studies use the NLR cut-off value ranging from 2-5.[21] In this study we used a cut-off value of 2.5.[4,22-24]

Patients with a higher NLR in bladder cancer are associated with a higher risk of developing bladder cancer with higher rates of cancer aggressiveness and more advanced disease. Higher disease stage, lymph node involvement, more number metastasis were found to have higher NLR.[18,19,21,25-28]

This study showed that there was a statistically significant difference where patients with metastatic bladder tumors (p=0.003), lymph node involvement (p=0.021), had higher NLR values. A previous study reported that patients with NLR 2.38 (p = 0.007) and metastatic lymph nodes (p = 0.030) have a high mortality risk.[16] In addition, a meta-analysis conducted by Gu *et al.*[22] regarding the relationship between NLR values and overall survival (OS) involving 9 studies with 2,300 patients showed that high NLR values are associated with lower OS (p=0.027). In line with the results of this study, which also showed a correlation of NLR values with the incidence of metastasis and lymph node involvement.

The hypothesized mechanism of NLR in relation to cancer is through the increase of growth factors, survival factors, pro-angiogenic factors, enzymes from the extracellular matrix, and induction of signals that cause epithelial to mesenchymal transition.[19,30-32] Patients with high NLR have relatively lower lymphocyte counts and higher neutrophil counts. This shows that the immune response by T lymphocytes against malignancy is not good where there is a decrease in cytotoxicity by T lymphocytes against malignant cells which ultimately causes tumor development. An increase of neutrophil count is associated with an increase in vascular endothelial growth factor (VEGF) which plays a role in tumor progression and angiogenesis.[6,18,22,33-37]

Inflammation has a role at every stage of tumor development starting from the initiation, promotion, malignant transformation, invasion, and metastasis phases.[38] Chemokines and cytokines produced by inflammatory cells as a result of interactions between tumor cells and immune cells have a role in tumor development by a way of regulating the growth, migration, and differentiation of all tumor cell types including neoplasms, fibroblasts, and endothelial cells.[39] Cancer cells will stimulate monocytes and neutrophils through myeloid growth factor and other pro-inflammatory mediators to secrete interleukin-6 (IL-6), VEGF which will stimulate tumor neovascularization, and transforming growth factor beta (TGF-ß) which will cause immunosuppression by inducing lymphocyte apoptosis and causing decreased lymphopoiesis.[4,8,15-17,40]

Some limitations in this study was identified. First, the data collected were obtained from a single clinical source, which is in Dr. Sardjito General Hospital,Yogyakarta. The data were limited from its confounding factors that will affect neutrophil to lymphocyte ratio, and factors that will affect metastasis in MIBC, such as the presence of other illnesses like congestive heart failure (CHF), atrial fibrillation (AF), anemia, or the presence of both high PTH, or low vitamin D.[41] Furthermore, this study also did not consider other confounding factors such as previous chronic bladder irritation and infections, personal history of bladder or urothelial

cancer, bladder birth defects, genetics, and family history, previous history of smoking, workplace exposures, and any history of chemotherapy or radiation therapy.[42,43]

Neutrophils affect the migration of cancer cells which ultimately play a role in the process of metastasis. Tumors induce neutrophil activation to release inflammatory mediators that promote malignant cell metastasis. Neutrophils residing in tumor cells (TANs/tumor-associated neutrophils) release enzymes that degrade the basement membrane and cause invasion of malignant cells across the basement membrane. The tumor cells then circulate. In the circulation, neutrophils play a role in helping tumor cells survive by inducing tumor cell aggregation. Circulating tumor cells adhere to the vascular endothelium and then cause tumor cell extravasation which ultimately plays a role in metastasis.

CONCLUSION

Neutrophil to lymphocyte ratio is a non-specific marker of inflammation that is simple, inexpensive, easy to obtain, and easy to calculate from peripheral blood tests. It can be used to predict the aggressiveness and extent of tumor invasion in patients diagnosed with MIBC.

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