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Blood cell count is not a significant predictor of survival in bladder cancer after radical cystectomy

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ABSTRACT

BACKGROUND

Radical cystectomy (RC) is the gold standard treatment for muscle-invasive bladder carcinoma. A predictive factor is needed for the aggressive approach as it could lead to overtreatment. Elevated blood cell count (BCC) markers are reported to have a significant association with poor outcomes in several types of malignancy. Neutrophil-to-lymphocyte-ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are well-known inexpensive and effective representative markers of inflammatory conditions. This study aimed to determine the BCC as a predictive factor of overall survival (OS) in patients with bladder carcinoma (BC) after RC.

METHODS

A retrospective cohort study was conducted involving 26 patients who had undergone RC. The demographic characteristics and BCC markers such as hemoglobin (Hb). NLR, PLR and lymphocyte/monocyte ratio (LMR) were collected. The patients were categorized based on the BCC marker value (≥ median and < median). Kaplan–Meier survival analysis was done to determine overall survival (OS) on BCC markers. The association between patient demographics and one-year survival was also determined using Mantel-Cox (Log-rank) method.

RESULTS

Among the 26 patients, the mean age was 55.6 ± 12.9 years. On univariate analysis, none of the demographic characteristics was found to be a significant predictor of one-year and overall survival ($p>0.05$). Hemoglobin, NLR, PLR and LMR were not significant predictors of one-year survival and OS ($p>0.05$).

CONCLUSIONS

The BCC was not a significant predictive factor of survival in patients with bladder cancer after radical cystectomy.

Keywords: Blood cell count, predictive factor, radical cystectomy, survival, retrospective cohort

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INTRODUCTION

Bladder carcinoma (BC) is the seventh most prevalent neoplasm worldwide and the most prevalent cancer of the urinary tract with an incidence of 550,000 every year.[1,2] In 2018, approximately 200,000 deaths were due to BC with 3.2 per 100,000 deaths among males and 0.9 per 100,000 deaths among females every year.[2]

Radical cystectomy (RC) is currently the gold standard treatment for muscle-invasive bladder carcinoma (MIBC) or recurrent high-grade non-muscle invasive bladder carcinoma (NMIBC). Radical cystectomy has also been found to be the most suitable treatment for stage II and stage III BC. Currently, 10-year cause-specific survival (CSS) rates after RC are only 70% for NMIBC and 40-60% for MIBC.[3–5] A systematic review and meta-analysis found 23.3% overall probability of tumor recurrence 1 year after RC, 38.3% at 5 years, 44.8% at 10 years, and 48.6% at 20 years.[6] The overall prognosis of the recurrent patients was also very poor with 80% of all the patients dying within 1 year and only 3.5% surviving for more than 5 years.[6] This indicates that a more aggressive approach is needed for oncological outcome improvement for both MIBC and recurrent high-grade NMIBC.[7] However, a non-selective aggressive treatment can lead to overtreatment of people with a good prognosis thus a predictive factor is needed.[7]

Current evidence assumes that systemic inflammatory response is triggered by the cancer, resulting in changes in inflammatory cells.[8] Neutrophilia with thrombocytosis and lymphocytopenia are the main cell changes found in cancer which along with inflammatory mediators promote the tumor microenvironment.[7] Several studies have found an association between several blood cell count (BCC) markers, such as preoperative lymphocyte-to-monocyte ratio (LMR), monocyte-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), with oncologic outcomes in several neoplastic diseases, including lung, renal, hepatic, breast, and bladder cancer [8] creating an inflammation-based scoring system to predict oncologic outcomes in cancer.[9]

Currently, several studies have found a significant association between BCC markers and invasive BC. Luo et al.[7] has found a significant difference in red cell distribution width (RDW), NLR, PLR, and MLR between BC patients and controls. This study has also found NLR to be an independent predictor for BC.

Our study differs from the previous study, in that we determined the association between preoperative CBC marker values and the overall survival in BC patients who have undergone RC. This study aimed to determine the BCC as a predictor factor of overall survival (OS) in patients with bladder carcinoma (BC) after RC.

METHODS

Research design

This was a retrospective cohort study and was conducted in the Haji Adam Malik North Sumatra General Central Hospital between 2014 and 2019.

Patients

A total of 26 patients were included in this study (19 male and 7 female) with median age of 57 years. Study subject enrollment followed a two-step method consisting of the selection of RC BC patients with available pre-treatment BCC biomarker reports and exclusion of patients with one of the following criteria: RC done for salvage, failed RC, and chemoradiation. All subjects were histologically diagnosed with BC.

Data collection

The data regarding patient characteristics (age, gender, T stage, N stage, M stage, histopathology, smoker status, hydronephrosis) and BCC were obtained from their medical records in 2014-2019. Pretreatment BCC was measured within a week before treatment initiation (median of 6 days, IQR 1/4 2-10 days).

The date of treatment initiation was defined as the date of RC. Every patient was treated with RC and none had a history of undergoing neoadjuvant therapy.

We then calculated the NLR, LMR, MLR and PLR based on the patient's BCC data. The NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Absolute lymphocyte count divided by absolute monocyte count was defined as the LMR. The PLR was calculated by dividing absolute platelet count by absolute lymphocyte count. The MLR was obtained by dividing absolute monocyte count by absolute lymphocyte count.

Clinical outcomes

Outcomes were measured by one-year and overall survival (OS). Overall survival was calculated as the time from the date of RC to the date of death regardless of cause. Surviving patients were censored at the date of last contact.

Statistical analysis

Patient characteristics and distributions of hematological parameters were summarized using descriptive statistics. All numerical variables were dichotomized based on the median of each variable. We then analyzed the association of patient demographics and hematological findings with one-year survival and overall survival using Mantel-Cox (Log-rank) test. All significantly associated variables will then be computed using Cox-regression analysis. Statistical analyses were performed using SPSS v23 for Windows. All tests were two-sided and a p-value of <0.05 was considered statistically significant.

Ethical clearance

The study has been approved for ethical clearance by the Ethical Committee, Faculty of Medicine, Universitas Sumatra Utara, under number 247/TGL/KEPKFKUSU-RSUPHAM/2020.

RESULTS

A total of 26 patients were included in this cohort (73% males, median age 57 years). Patient characteristics such as smoking status, hydronephrosis, histopathology, T stage, N stage, and CBC panel (leukocyte, lymphocyte, monocyte and platelet counts, NLR, MLR, LMR, PLR) are detailed in Table 1.

Overall survival analysis

The median survival time of male patients was 127 (9-658) days, relatively higher than that

Table 1. Demographic characteristics, pathological and hematological features of post-radical cystectomy patients (n=26)

Characteristic	n (%)
Gender	
Male	19 (73.1)
Female	7 (26.9)
Age (years) @	55.6 ± 12.9
Smoking	14 (60.9)
Hydronephrosis	10 (41.7)
Tumor (T) Stage	
T1/T2	7 (26.9)
T3/T4a	19 (73.1)
Node (N) involvement	9 (40.9)
Histopathological subtype	
Transitional cell carcinoma	20 (90.9)
Lympho-mucinous adenocarcinoma	1 (4.5)
Papillary urothelial carcinoma	1 (4.5)
Free tumor edge	13 (56.5)
Lympho-vascular invasion	10 (43.5)
Hemoglobin mg/dL $	10.2 (6.9-13.5)
Leukocytes $x10^3/\mu L$ $	8.4 (4.7-24.1)
Neutrophils $x10^3/\mu L$ $	60.2 (2.4-22.8)
Monocytes $x10^3/\mu L$ $	8.9 (2.9-13.3)
Lymphocytes $x10^3/L$ $	1.62 (0.4-3.1)
Platelets $x10^3/\mu L$ $	337 (109-712)
NLR $	3.89 (1.2-50)
MLR $	0.45 (0.2-4.4)
LMR $	2.21 (0.2-4.6)
PLR $	195.08 (87.9-818.9)

@Data presented as Mean ± SD; $ Median (Min-Max); NLR : neutrophile-to-lymphocyte ratio; MLR : monocyte-to-lymphocyte ratio-monocyte LMR : lymphocyte-to-monocyte-ration; PLR ; platelet-to-lymphocyte ratio

of female patients 102 (16-162). Patients <55 years of age had a longer median survival time than elderly patients [127 (9–658) versus 63.5 (9-620) days]. However, this difference was not found to be statistically significant (p>0.05). We also found that smoking status, hydronephrosis, T stage, lymph node involvement, carcinoma subtype, tumor margins, and lympho-vascular invasion were not statistically related to the overall patient survival rate (p>0.05).

Hematologic findings were not found to be significantly associated with overall patient survival. The group of patients with a higher one-year survival rate also had a longer median survival rate, except for the percentage of neutrophils. The median survival in patients with high neutrophil percentage was 83.5 (9-658) days, longer than in patients with low neutrophil percentage [71 (9 -569) days].

One-year survival analysis

There were no demographic factors associated with one-year survival. The one-year survival rate of female patients was 14.3%, while that of male patients was 26.7%. However, this difference was not statistically significant (p>0.05). In addition, there was no association between one-year survival rate and age, but the elderly had a relatively lower one-year survival rate. Details regarding the relationship between characteristics (demography) and patient survival are presented in Table 2. The percentage of patients who survived the first year after radical cystectomy was higher in patients with Hb 10.2 g/dL; leukocyte count $8.4x10^3/\mu L$; neutrophil, monocyte, and lymphocyte percentage less than 60.2%, 8.9%, and 1.62%, respectively; and platelet count less than $337x10^3/\mu L$, was statistically not significant (p>0.05) (Table 3).

DISCUSSION

Based on this study, we found that none of the hematological and demographic factors were associated with the survival of bladder cancer patients after radical cystectomy. Although no significant association was found, we note that median survival was relatively higher in patients with hemoglobin less than 10.200 g/dL, leukocyte count higher than $8.401x10^3/\mu L$, neutrophil count higher than 66.85%, monocyte count lower than 8.85%, lymphocyte count more than 18.7%, platelet count less than $364x10^3/\mu L$, NLR less than 3.576, MLR more than 0.447, LMR less than 2.238, and PLR more than 17.739.

We documented that patients with NLR <3.576 had a relatively higher median survival rate. According to previous studies, NLR and dNLR have prognostic value and can be used to predict survival in a large group of cancer patients.[10] Luo et al.[11] also reported a significant difference in RDW, NLR, PLR, and MLR between bladder cancer patients and controls. Furthermore, they found NLR to be an independent predictor for bladder cancer patients' survival. The present study confirmed that leukocyte values might hold important information for predicting bladder cancer severity and bladder cancer patient survival rate. Several inflammation-based prognostic scores that measure changes in circulating inflammatory cells using BCC markers, including preoperative NLR, PLR, MLR, and LMR, have been reported to have an association with oncologic outcomes in several cancers, including lung, renal, hepatic, breast, and colorectal cancer.[12]

The role of BCC as a potential predictive factor in cancer is based on the relationship between cancer and the inflammatory process.[13] The inflammatory process could promote carcinogenesis through oxidative and nitrative damage of macromolecules and epigenetic alterations.[14] Reactive oxygen species/reactive nitrogen species produced by inflammatory cells can lead to damage in biomacromolecules such as DNA, proteins, and lipids.[15,16] Epigenetic alteration in inflammation could cause an alteration in gene expression, such as aberrant DNA methylation and dysregulation of microRNA, which could lead to the promotion of carcinogenesis.[17] Several studies have also observed the induction of a systemic

Table 2. Univariate survival analysis on demographic characteristics and pathological features of post-radical cystectomy patients (n=26)

Characteristic	One year Rate (%)	95% CI	$\chi 2$ (df)	p-value*	Overall Rate (%)	95% CI	$\chi 2$ (df)	p-value	Median (min–max)
Gender			0.188 (1)	0.664			0.188 (1)	0.664	
Male	26.7	16.57; 36.83			6.7	1.63; 11.77			127 (9 - 658)
Female	14.3	6.89; 21.71			14.3	6.89; 21.71			102 (16 - 162)
Age (years)			0.662 (1)	0.416			1.235 (1)	0.266	
≤ 55	30.0	19.26; 40.74			10.0	3.8; 16.2			127 (9 - 658)
> 55	16.7	8.69; 24.71			8.3	2.65; 13.95			63.5 (9 - 620)
Smoking	30.8	19.92; 41.68	1.181 (1)	0.277	7.7	2.26; 13.14	1.181 (1)	0.277	127 (9 - 568)
Hydronephrosis	30.0	19.26; 40.74	0.224 (1)	0.636	20.0	11.23; 28.77	0.020 (1)	0.887	96 (9 - 475)
Tumor (T) Stage			0.078 (1)	0.781			0.078 (1)	0.781	
T1/T2	16.7	8.69; 24.71			16.7	8.69; 24.71			71 (25 - 162)
T3/T4a	25.0	15.2; 34.8			6.7	1.63; 11.77			121 (9 - 658)
Node involvement	33.3	21.99; 44.61	1.953 (2)	0.377	11.1	4.57; 17.63	0.995 (1)	0.319	218 (9 -658)
Histopathological subtype			0.192 (2)	0.908			0.161 (1)	0.688	
Transitional cell carcinoma	25.0	15.2; 34.8			10	3.8; 16.2			102 (9 - 568)
Lympho-mucinous adenocarcinoma	0.0	-			0	-			0 (0.00)
Papillary urothelial carcinoma	0.0	-			0	-			0 (0.00)
Free tumor edge [n (%)]	33.3	21.99; 44.61	0.176 (1)	0.675	16.7	8.69; 24.71	0.225 (1)	0.635	71 (9 - 658)
Lympho-vascular invasion [n (%)]	20.0	11.23; 28.77	0.010 (1)	0.922	0.0	-	0.029 (1)	0.865	86.5 (9 - 658)

* Log-rank test (95% CI); N/A: not applicable

Table 3. Univariate survival analysis on hematologic features of post-radical cystectomy patients (n=26)

Characteristic	One year Rate (%)	95% CI	$\chi 2$ (df)	p-value*	Overall Rate (%)	95% CI	$\chi 2$ (df)	p-value	Median (min–max)
Hemoglobin			0.970 (1)	0.325			0.970 (1)	0.325	
≥ 10.200	9.1	3.19; 15.01			9.1	3.19; 15.01			71 (9 -349)
< 10.200	36.4	24.57; 48.23			9.1	3.19; 15.01			121 (10 - 658)
Leukocytes			0.321 (1)	0.571			0.010 (1)	0.992	
≥ 8.401	12.5	5.57; 19.43			9.1	3.19; 15.01			47 (9 – 569)
< 8.401	28.6	18.12; 39.08			9.1	3.19; 15.01			157 (16 – 658)
Neutrophils			0.092 (1)	0.761			0.134 (1)	0.715	
≥ 66.850	18.2	9.84; 26.56			9.1	3.19; 15.01			83.5 (9 - 658)
< 66.850	27.3	17.06; 37.54			9.1	3.19; 15.01			71 (9 -569)
Monocytes			0.163 (1)	0.686			0.000 (1)	0.995	
≥ 8.850	22.2	12.97; 31.43			0.0	-			71 (9 -569)
< 8.850	25.0	15.2; 34.8			11.1	4.57; 17.63			86.5 (9 - 658)
Lymphocytes			0.067 (1)	0.795			0.104 (1)	0.747	
≥ 16.200	18.2	9.84; 26.56			9.1	3.19; 15.01			111.5 (9 -620)
< 16.200	27.3	17.06; 37.54			9.1	3.19; 15.01			47 (9- 658)
Platelets			0.359 (1)	0.549			0.069 (1)	0.792	
≥ 337.000	18.2	9.84; 26.56			0	-			44.5 (9 - 658)
< 337.000	27.3	17.06; 37.54			18.2	9.84; 26.56			121 (9 - 620)
NLR			0.067 (1)	0.795			0.104 (1)	0.747	
≥ 3.576	18.2	9.84; 26.56			9.1	3.19; 15.01			68 (9 - 658)
< 3.576	27.3	17.06; 37.54			9.1	3.19; 15.01			102 (9 -659)
MLR			0.054 (1)	0.816			0.020 (1)	0.887	
≥ 0.447	27.3	17.06; 37.54			9.1	3.19; 15.01			56 (9 -658)
< 0.447	18.2	9.84; 26.56			9.1	3.19; 15.01			121 (16 - 569)
LMR			0.054 (1)	0.816			0.020 (1)	0.887	
≥ 2.238	18.2	9.84; 26.56			9.1	3.19; 15.01			121 (16 - 569)
< 2.238	27.3	17.06; 37.54			9.1	3.19; 15.01			56 (9 - 658)
PLR			1.633 (1)	0.201			1.633 (1)	0.201	
≥ 17.739	36.4	24.57; 48.23			9.1	3.19; 15.01			116.5 (9 - 658)
< 17.739	9.1	3.19; 15.01			9.1	3.19; 15.01			71 (9 - 620)

* Log-rank test (95% CI); N/A: not applicable; NLR: neutrophile-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio-monocyte
LMR: lymphocyte-to-monocyte-ratio; PLR: platelet-to-lymphocyte ratio

inflammatory response by cancer leading to changes in circulating inflammatory cells which could trigger the growth, maturation, and differentiation of cells within the tumor microenvironment thus causing carcinogenesis.[18]

Previous studies have reported NLR as a predictive biomarker for recurrence-free post-radical cystectomy cancer-specific survival and overall survival as it has an essential role in immunity and inflammation in cancer development and progression.[19] A higher NLR means a higher innate immune response as compared to an adaptive immune response which leads to neutrophil overactivity that promotes carcinogenesis in pre-malignant lesions as a result of reactive oxygen species production, growth factor secretion, angiogenesis promotion, and metastasis promotion by the neutrophils.[8] On the other hand, T and B lymphocytes have an anti-tumor response thus a lower NLR would inhibit carcinogenesis as there are more inhibitory mechanisms compared to the promoting mechanisms.[15]

Although most studies suggests that NLR elevation is associated with worse clinical outcomes, some studies have also found a higher survival probability in patients with higher NLR.[20] A study done by Lee et al.[21] which includes patients with metastatic pancreatic cancer has found a significantly higher survival probability for NLR <1.89 compared to NLR ≥1.89. A systematic review and meta-analysis showed similar results, in that elevated pretreatment NLR predicted poorer OS in colorectal cancer.[22]

The imbalance in the patient's tumor stage demographics, as most samples have T3/T4a stage cancer, is thought to be the main reason for the different results. Cancer stage has been associated with worse survival, therefore, could create a sampling bias where most patients have a bad prognosis to start with. In our study, the age of the patients is normally distributed, thus it does not seem to be a bias even though it has been reported to be a bad prognostic factor in previous studies.

The limitation of this study was that it did not evaluate the contact length and height of the tumor. Increased in leukocyte value could be linear with tumor contact length and tumor height. The wider the tumor, the more the amount of inflammatory agents produced. This applies to tumor height (which reflects tumor degree of invasiveness) as well. Besides, the limited number of patients evaluated during the study might also have contributed to the results we reported. Therefore, future studies with a larger sample size should be conducted, and include ultrasound evaluation in the research to confirm this finding and hypothesis.

CONCLUSIONS

In this study, we found no significant association of hematological and demographic conditions with post-radical cystectomy patient survival.

CONFLICT OF INTEREST

Competing interests: no relevant disclosures.

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CONTRIBUTORS

A contributed to concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, and acted as the guarantor of this study. FFP contributed to design, manuscript

preparation, editing, and review. GPS contributed to concept, definition of intellectual content, data analysis and manuscript review. SMW contributed to concept, definition of intellectual content, manuscript editing, and manuscript review. BSH contributed to concept and definition of intellectual content. All authors have read and approved the final manuscript.

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