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Analysis of hematological parameters in bladder cancer in early and advanced stages at Dr. Sardjito Hospital

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ABSTRACT

Background: Bladder cancer (BC) is the tenth most common cancer in both males and females. Early detection can improve the patient's chances of survival, giving patients with BC a good prognosis. The hematological parameter determines the number of leukocytes, hemoglobin, platelets, and Neutrophil-Lymphocyte Ratio (NLR) in the body. The presence of abnormal values on hematological parameters indicates that the patient is in poor condition.

Objective: This study aims to compare hematological parameters between early-stage and advanced BC at Dr. Sardjito Hospital.

Methods: This study was a retrospective cross-sectional study using patient medical records. By using the results of the anatomical pathology, pre-operative hematology evaluated the influence on the bladder cancer stage. The sample used consisted of 130 bladder cancer patients. Chi-square and regression statistical tests were used to analyze the collected data.

Results: The advanced-stage group had considerably higher leukocytosis than the early-stage group (p = 0.000). Anemia predominated more in the later-stage group than in the earlier stage (p = 0.048). Additionally, the advanced-stage group experienced thrombocytosis more frequently than the early-stage group (p = 0.000). NLR was higher in the advanced compared to the early-stage group (p = 0.000).

Conclusion: Patients with advanced bladder cancer were more likely to experience abnormal hematological parameters levels than those with the earliest stages of the disease.

Latar Belakang: *Kanker kandung kemih adalah kanker paling umum kesepuluh yang terjadi pada populasi pria dan wanita. Deteksi dini dapat meningkatkan kelangsungan hidup, sehingga memberikan prognosis yang baik pada pasien kanker kandung kemih. Hematologi rutin adalah tes darah yang menentukan leukosit, hemoglobin, trombosit, dan Neutrophil-Lymphocyte Ratio (NLR) dalam tubuh. Adanya abnormalitas pada hematologi rutin menunjukkan bahwa pasien dalam kondisi yang tidak baik.*

Tujuan: *Penelitian ini bertujuan untuk mengetahui perbedaan hematologi rutin pada kanker buli stadium awal dan kanker buli stadium lanjut di RSUP Dr. Sardjito.*

Metode: *Penelitian ini merupakan penelitian cross-sectional retrospektif dengan menggunakan rekam medis pasien. Dengan menggunakan hasil patologi anatomi, hematologi pra-operasi dievaluasi pengaruhnya terhadap stadium kanker kandung kemih. Sampel yang digunakan sebanyak 130 pasien kanker kandung kemih. Uji statistik chi square dan analisis regresi digunakan untuk menganalisis data yang terkumpul.*

Hasil: *Kelompok stadium lanjut memiliki leukositosis yang jauh lebih besar daripada kelompok stadium awal (p = 0,000). Anemia lebih banyak terjadi pada kelompok stadium lanjut dibandingkan stadium awal (p = 0,048). Selain itu, kelompok stadium lanjut lebih sering mengalami trombositosis daripada kelompok stadium awal (p = 0,000). NLR lebih tinggi pada stadium lanjut dibandingkan dengan stadium awal (p = 0,000).*

Kesimpulan: *Pasien dengan kanker kandung kemih stadium lanjut lebih banyak menunjukkan nilai*

hematologi abnormal dibandingkan dengan stadium awal penyakit.

INTRODUCTION

Bladder cancer (BC) ranks tenth for both sexes accumulated, but it is the seventh most common cancer diagnosed in men worldwide. Incidence rates for males and women are 9.5 and 2.4 per 100.000 person/year individuals worldwide, respectively.[1] According to estimates, approximately 200.000 people died from BC in 2018, ranking it as the 13th most deadly malignancy. The number accounts for 2.1 percent of all cancer-related deaths.[2]

Currently, known risk factors for bladder cancer include tobacco, carcinogen exposure, Schistosomiasis chronic infection, bladder stones, radiotherapy, cyclophosphamide therapy, and pioglitazone treatment.[3-4] More than 80% of patients experience painless hematuria, the most prevalent symptom of BC. According to the tumor stage, there are two primary categories of BC: Non-Muscle Invasive Bladder Cancer (NMIBC) and Muscle Invasive Bladder Cancer (MIBC). Co-activation of the FGFR3 mutation, a high recurrence rate (50–70%), and a 5-year survival rate of >90% are the characteristics of NMIBC. Meanwhile, MIBC is characterized by a high metastasis rate, frequent TP53 mutations, and a 50% of 5-year survival rate. The patient's prognosis usually worsens after identification of BC development.[5]

Several prognostic markers for BC include deepness of invasion, lymph node metastases, TNM stage, and performance status.[1-2] Meanwhile, growing numbers of studies over the past few years have shown that inflammation and the survival of malignant tumors are related. Hematological parameters have been suggested as one of the prognostic indicators for many cancer-related diseases associated with inflammatory process.[6-7]

The hematological parameters assess leukocytes, hemoglobin, platelets, as well as Neutrophil-Lymphocyte Ratio (NLR).[7] Preoperative anemia predicts poor prognosis in malignancy, including overall survival and disease-free survival.[8] On the other hand, leukocytosis and thrombocytosis are observed in many cases of malignancy.[9-10] The NLR is calculated as the number of neutrophils divided by the number of lymphocytes. In pathogenic circumstances, neutrophil counts will rise while lymphocyte counts will fall. NLR is a simple parameter to assess the inflammatory status that occurs in individuals.[9-10] Because hematological parameters for patients are both required and affordable in clinical facilities, experimental data are generally simple to get. Since the overall survival rate has not changed significantly, how to assess a patient's prognosis has significant clinical implications for both clinicians and patients. The condition could enable clinicians to alter the treatment strategy while boosting patients' confidence in their ability to survive.

METHODS

Research Methods

This study is an observational cross-sectional study using a retrospective approach. The data were taken from medical records from January 2017 to May 2020. Total sampling is the approach in use. According to the protocol at Dr. Sardjito Hospital, all patients had full hematological parameters before surgery. The preoperative patient's hemoglobin, leukocyte, platelet, and NLR levels were recorded and linked to the bladder biopsy results.

Early stage (stage I and II) if the tumor has not reached the fatty tissue surrounding the bladder and has not spread to the regional lymph nodes or distant metastasis (≤ T2 and N0, M0). Meanwhile, the advanced stage if the tumor invades perivesical tissue and has spread to the lymph nodes or other organs (stages III and IV). The study was conducted for six months at Dr. Sardjito Hospital.

The Ethical Committee of the Faculty of Medicine, Universitas Gadjah Mada/ Sardjito Hospital, approved this study (KE/FK/1347/EC/2022).

Patient Study

The study involved 130 patients' medical record data who met the inclusion criteria, namely those who had a preoperative complete blood test and had the results of Anatomical Pathology-determined BC at Dr. Sardjito Hospital. Exclusion criteria include a history of previous surgery and pre-existing comorbidities such as pulmonary heart disease, neurological disorders, and synchronous and metachronous disease.

Data analysis

The statistical software SPSS was used to analyze this study. The Chi-square test determines whether there were differences in leukocytes, hemoglobin, platelets, and NLR between the early and advanced stages of BC. This study uses regression analysis to estimate the OR (Odds Ratio).

RESULTS

Characteristics

Table 1 shows the hematological parameter with normal leukocytes and platelets, a decreased hemoglobin level, and an increased NLR.

As shown in Table 2, the study's findings revealed that patients in the early and advanced stages had different numbers of leukocytes, hemoglobin, platelets, and NLR. The advanced-stage group had considerably higher leukocytosis than the early-stage group (p = 0.000). In the meantime, anemia was more common in the group with advanced stage than in the early stage (p = 0.048). Additionally, the advanced-stage group experienced thrombocytosis more frequently than the early-stage group (p = 0.000). Compared to the early-stage group, NLR was higher in the advanced stage (p = 0.000).

Table 3 shows the results of the regression analysis model for the association of hematological parameters with the bladder cancer stage. Leukocytes (OR, 2.981; 95% CI, 1.118 - 7.950), platelets (OR, 9.910; 95% CI, 2.400 - 40.909), and NLR (OR, 2.548; 95% CI, 1.051 - 6.175) all had p-value < 0.05, which meant the three variables are most affected on the stage of bladder cancer.

Table 1. Characteristics and hematological parameters of the subject

Variable	n (%)	Mean ± SD
Age (year)		60.07 ± 10.97
Gender		
Male	85 (65.4)	
Female	45 (34.6)	
Stage		
Early	68 (52.3)	
Advanced	62 (47.7)	
Leukocytes Count (10^3 /µL)		11.28 ± 5.93
Hemoglobin Count (g/dL)		10.28 ± 2.07
Platelets Count (10^3/µL)		368.68 ± 144.48
NLR		6.66 ± 8.45

SD: standard deviation;
NLR: neutrophil-lymphocyte ratio

Table 2. Bivariate analysis of hematological parameters in the bladder cancer

Variable		Early Stage	Advanced Stage	p-value
Leukocytes	Normal	56 (43.08%)	24 (18.46%)	0.000
	Leukocytosis	12 (9.23%)	38 (29.23%)	
Hemoglobin	Normal	25 (19.23%)	13 (10%)	0.048
	Anemia	43 (33.08%)	49 (37.69%)	
Platelets	Normal	65 (50%)	28 (21.54%)	0.000
	Thrombocytosis	3 (2.31%)	34 (26.15%)	
NLR	Normal	37 (28.46%)	15 (11.54%)	0.000
	High	31 (23.85%)	47 (36.15%)	

Table 3. Regression analysis to estimate the OR

Characteristics	OR	95% Cl	p-value
Gender	0.403	0.157 - 1.033	0.058
Age	0.983	0.942 - 1.025	0.414
Leukocytes	2.981	1.118 - 7.950	0.029*
Hemoglobin	1.145	0.437 - 2.997	0.783
Platelets	9.910	2.400 - 40.909	0.002*
NLR	2.548	1.051 - 6.175	0.038*

OR, odds ratio; Cl, confidence interval; * p<0.05

DISCUSSION

This study discovered that leukocytosis, anemia, thrombocytosis, and high NLR occurred more frequently in the advanced stage. These support previous findings that leukocytosis, anemia, thrombocytosis, and high NLR predict a poor prognosis in cancer patients.[11-13]

In the present study, we found a significant difference in leukocytes between the advanced and the early stage of BC. Leukocytosis is independently more common in the advanced stage than in the early stages of the disease, as shown by our data (Table 2). Besides, the advanced stage has a worse prognosis than the early stage. These results are consistent with previous studies that malignant lesions in the head, neck, lung, uterine/cervical, and urogenital systems are associated with inflammatory reactions. Chemokines mediate the tumor microenvironment that regulates leukocyte migration after reaching the tumor sites. Inflammatory cells, such as neutrophils, dendritic cells, macrophages, eosinophils, mast cells, and lymphocytes, are drawn to tumor cells by autocrine chemokines release. The cascade eventually increases the cell's survival, proliferation, and dissemination.[14] Neutrophils produce N-nitrosamines during the early stages of carcinogenesis, and the number of these cells in the tumor is significantly higher than in the normal mucosa. Immunosuppression brought on by inflammation creates a favorable environment for tumor growth. Through the recruitment and activation of inflammatory cytokines, tumor-intrinsic inflammation contributes to cancer mutation and malignant transformation. Necrosis factor (NF)-kappa B, the STAT3 pathway, reactive oxygen/nitrogen species, and prostaglandins are examples of cytokine mediators as the result of the inflammation process.[15]

In this study, we discovered a difference in hemoglobin levels between BC in its early and advanced stages. Our data shows that anemia is independently more prevalent in the advanced stages of the illness than it is in the early stages (Table 2). It is also well-recognized that the prognosis is worse for advanced ones than for early stages. Anemia in cancer patients can develop due to malnutrition or the lack of micronutrients. Other causes of anemia may include the suppression of trophic hormones such as erythropoietin. The mechanisms involve infection and inflammation, hematuria, tumor immunoreaction, and overexpression of inflammatory cytokines. These can reduce red blood cell survival, suppress erythroid progenitor cells, interfere with iron metabolism and utilization, and eventually disrupt normal erythropoiesis.[16]

Cancer-Related Anemia (CRA) is a symptom that appears as the disease progresses and is more frequent in patients with advanced cancer. This condition is due to chronic inflammation from the proinflammatory cytokines produced by immune cells and cancer cells.17 The primary cause of erythrocyte destruction is the activation of macrophages by various proinflammatory stimuli. The mechanisms for erythropoiesis suppression may involve chemical restriction and direct inhibition of erythropoietic progenitors. Therefore, increasing erythrocyte repair requires more than erythropoiesis alone.[18]

This study found that platelet levels varied between BC in its early and advanced stages. Our statistics reveal that thrombocytosis is more common in the advanced stages of the disease than in the earlier stages. The prognosis is likewise widely acknowledged to be worse for advanced-stage than for early stages. The mechanism of thrombocytosis in malignancy is not well understood. During endothelium activation, platelets release angiogenic growth factors. It

raises a hypothesis for platelet involvement in tumor-induced angiogenesis. Previous research has found an increase in vascular endothelial growth factor (VEGF) in cancer patients' platelets when compared to healthy patients.[19]

Platelets can be used by circulating tumor cells to shield them from immune system responses and to make it easier for them to connect to endothelial cells at metastatic sites. Due to their typical role in improving vascular integrity, platelets also play a part in carcinogenesis. It is well known that Transforming Growth Factor β (TGFβ) from platelets, through the signaling transcription factors Smad and NF-B, promotes the EMT (epithelial to mesenchymal transition) program in cancer cells.[20] EMT is a pathway that controls the mesenchymal phenotype of epithelial cells and promotes mobility and metastasis while safeguarding tumor cells against anoikis (apoptosis due to lack of adhesion). Platelet-derived TGFβ may also help tumors evade the immune system. VEGF levels are higher in cancer patient platelets than in healthy individuals. IL-6 signaling via STAT3 (signal transducer and activator of transcription 3) can trigger the expression of VEGF receptors (VEGFR2) in cancer cells; hence, IL-6, platelets, and VEGF are well-known as the pro-carcinogenic in cancer cells.[21]

The tumor may stimulate megakaryocytes in the bone marrow, increasing the number of platelets with higher VEGF levels. Platelets contain thrombopoietin (TPO), which is released when activated. TPO is a cytokine that stimulates megakaryocytes in the bone marrow to produce platelets while concurrently stimulating the release of VEGF from Nk cells. If the blood vessel wall is injured, the platelets will adhere to it and become activated, releasing their contents, including TPO. VEGF overexpression is the most common condition in malignancy and is involved in cancer progression.[19]

The NLR is the simple parameter that evaluates the ratio of neutrophils to lymphocytes to identify inflammatory disorders in people. The neutrophil is one of the most crucial cells for producing the inflammatory response in the acute phase. The immune system is mediated by T cells and humoral cells, with lymphocytes serving as its primary biological component. NLR reflects the occurring physiological stress, in which the level increases as physiological stress in the body increases. In addition, NLR may predict infection, postoperative complications, and mortality in a single, predictive factor for different forms of cancer. Increased NLR has been associated with higher mortality for cardiac disease. Results from this study are consistent with findings from earlier studies. Advanced bladder cancer is more likely to have a greater NLR, which indicates a poorer prognosis than bladder cancer in its early stages.[22]

However, this study has research limitations mainly due to the small sample size. Besides, this study did not examine additional hematological parameter compartments (such as the platelet-lymphocyte and hemoglobin-platelet ratio). Therefore further research is warranted to achieve more inclusive results. Based on the characteristics of leukocytes, hemoglobin, platelets, and NLR, the findings of this study may be utilized as a significant local reference for patients and urologists in Indonesia to assess the prognosis of BC.

CONCLUSION

Advanced BC is more likely to cause abnormal hematological parameters than BC in its early stages. Given these circumstances, it is clear that the prognosis gets worse as the disease progresses to the advanced stage. Leukocytosis, thrombocytosis and high NLR results are indicators of advanced bladder cancer and can help patients predict their prognosis.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest to the research, authorship, and/or publication of this article.

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REFERENCES

1. Witjes JA, Bruins HM, Carron A, Cathomas R, Comperat EM, Efstathiou JA, et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. European Urology. 2021; 79(1):82-104.
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Review Epidemiology of bladder cancer. Medical Sciences (Basel). 2020; 8(1): 15.
3. Cumberbatch MGK, Noon AP. Review Article

Epidemiology, aetiology and screening of bladder cancer. Translational Andrology and Urology. 2019; 8(1): 5–11.
4. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. World Journal of Urology. 2020; 38(8): 1895–1904.
5. Wang Y, Chen L, Ju L, Qian K, Liu X, Wang X, Xiao Y. Novel biomarkers associated with progression and prognosis of bladder cancer identified by co-expression analysis. Frontiers in Oncology. 2019 October; 11(9):1030.
6. Abide CY, Ergen EB, Cogendez E, Kilicci C, Uzun F, Ozkaya E, Karateke A. Evaluation of hematological parameters parameters to predict endometrial cancer. Journal of Clinical Laboratory Analysis. 2018;32(6):e22438.
7. Hoffman R, Benz E, Heslop H, Weitz J. 2017. Haematology: Basic Principles and Practice [7th ed.]. Elsevier
8. Huang XZ, Yang YC, Chen Y, Wu CC, Lin RF, Wang ZN, Zhang X. Preoperative anemia or low hemoglobin predicts poor prognosis in gastric cancer patients: a meta-analysis. Disease Markers. 2019: 7606128.
9. Zhang H, Lv H, Weng M, Wang H, Cata JP, Chen W, Miao C. Preoperative leukocytosis is associated with increased tumor-infiltrating neutrophil extracellular traps and worse outcomes in esophageal cancer. Annals of Translational Medicine. 2020; 8(7): 441.
10. Tang G, Zhen Y, Xie W, Wang Y, Chen F, Qin C, et al. Preoperative hemoglobin-platelet ratio can significantly predict progression and mortality outcomes in patients with T1G3 bladder cancer undergoing transurethral resection of bladder tumor. Oncotarget. 2018; 9(26): 18627–18636.
11. Schernberg A, Blanchard P, Chargari C, Ou D, Levy A, Gorphe P, et al. Leukocytosis, prognosis biomarker in locally advanced head and neck cancer patients after chemoradiotherapy. Clinical and Translational Radiation Oncology. 2018; 12: 8–15.
12. Li Y, Wu H, Xing C, Hu X, Zhang F, Peng Y, et al. Prognostic evaluation of colorectal cancer using three new comprehensive indexes related to infection, anemia and coagulation derived from peripheral blood. Journal of Cancer. 2020; 11(13): 3834–3845.
13. Nie D, Yang E, Li Z. Pretreatment thrombocytosis predict poor prognosis in patients with endometrial carcinoma: a systematic review and meta-analysis. BioMed Central Cancer. 2019;19(1):73.
14. Tavares-Murta BM, Candido-Murta EF. Systemic leukocyte alterations in cancer and their relation to prognosis. The Open Cancer Journal. 2008; 2(1): 53–58.
15. Hu X, Li YQ, Li QG, Ma YL, Peng JP, Cai SJ. Baseline peripheral blood leukocytosis is negatively correlated with T-cell infiltration predicting worse outcome in colorectal cancers. Frontiers in Immunology. 2018; 9: 2354.
16. Dowd AA, Ibrahim FI, Mohammed MM. Case report : Renal cell carcinoma as a cause of iron deficiency anemia. African Journal of Urology. 2014 March; 20(1): 25-27.
17. Madeddu C, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V, Macciò A. Pathogenesis and treatment options of cancer related anemia: perspective for a targeted mechanism-based approach. Frontiers in Physiology. 2018; 20(9):1294.
18. Chen C, Hu L, Li X, Hou J. Preoperative anemia as a simple prognostic factor in patients with urinary bladder cancer. Medical Science Monitor. 2017; 23: 3528–3535.
19. Bensalah K, Leray E, Fergelot P, Leclercq NR, Tostain J, Guillé F, Patard JJ. Prognostic Value of thrombocytosis in renal cell carcinoma. Journal of Urology. 2006;175(3):859-63.
20. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Preoperative thrombocytosis is associated with survival after surgery for colorectal cancer. Journal of Surgical Oncology. 2012;106(7):887-91.
21. Voutsadakis IA. Thrombocytosis as a prognostic marker in gastrointestinal cancers. World Journal of Gastrointestinal Oncology. 2014; 15;6(2):34-40.
22. Forget P, Khalifa C, Defour JP, Latinne D, Pel, MCV, Kock MD. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes. 2017; 10(1):1-4.