The prognostic value of routine preoperative blood parameters in muscle-invasive bladder cancer

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Abstract

Background A routine blood examination is one of the most rapid, convenient and inexpensive clinical examinations that can reflect a patient's inflammatory status and other blood conditions, and the prognostic value of routine preoperative blood parameters in MIBC patients is still unclear, so we evaluated the prognostic value of routine preoperative blood parameters in muscle-invasive bladder cancer (MIBC) following radical cystectomy (RC). **Methods** Data on 272 patients with MIBC who underwent RC at our institution were retrospectively collected between March 2006 and August 2018. The median preoperative neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and hemoglobin (HGB) values were used as cutoffs to form the low and high NLR, low and high PLR, and low and high HGB groups, respectively. The clinicopathologic characteristics of each group were compared by chi-square and t tests. Kaplan-Meier survival and multivariate Cox regression analyses were used to analyze prognosis. **Results** The median NLR, PLR and HGB values were 2.48, 115 and 125, respectively. Kaplan-Meier results showed that the high NLR and low HGB groups had poor progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). A high PLR correlated only with poor OS. Multivariate Cox analyses showed that pathologic T4 stage, positive lymph node status and low HGB were independent risk factors for PFS, CSS and OS, and pathologic T3 stage was an independent risk factor for PFS and CSS; however, age was the only independent risk factor for OS. **Conclusion** Preoperative peripheral blood HGB is an independent risk factor for the prognosis of MIBC patients. These data suggest that HGB may be a useful prognostic marker for MIBC patients undergoing RC.

Background

Bladder cancer is the ninth most common malignant tumor in the world and the most common malignant tumor of the urinary system [1], of which muscle-invasive bladder cancer (MIBC) accounts for approximately 25%-30%. Currently, radical cystectomy (RC) is the standard treatment for MIBC, with a 5-year survival rate of 50%-66% [2-4]. In recent years, there has been an urgent need to find sensitive and specific molecular markers for risk stratification in cancer patients due to the goal of individualized precision therapy. In the past, most biomarkers were determined based on PCR or immunohistochemistry, while a routine blood examination is one of the most rapid, convenient and inexpensive clinical examinations that can reflect a patient's inflammatory status and other blood conditions through neutrophils, lymphocytes, platelets, hemoglobin and other indicators. Studies have shown that systemic inflammatory reactions associated with tumors can affect tumor progression, metastasis and prognosis [5-6]. A number of inflammatory indicators, such as the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), have been paid attention to in breast cancer, colorectal cancer and gastric cancer [7-9]. In addition, studies have shown that colorectal cancer patients have poor prognoses with low preoperative hemoglobin (HGB) levels [10]. At present, the prognostic value of routine preoperative blood parameters in MIBC patients is still unclear. Therefore, our study aimed to evaluate the prognostic value of routine preoperative blood parameters in MIBC patients by analyzing the relationship between

routine preoperative blood parameters and the clinicopathologic features and prognosis of MIBC patients following RC.

Methods

Clinical data

Clinical data and postoperative follow-up results of bladder cancer patients admitted to the Urology Department of the First Affiliated Hospital of Army Medical University were retrospectively collected between March 2006 and August 2018. The inclusion criteria were as follows: ① the patient underwent RC; ② the patient was pathologically diagnosed with muscle-invasive urothelial carcinoma of the bladder; ③ the preoperative imaging examination excluded distant metastasis; and ④ perfect patient information. The exclusion criteria were as follows: ① the patient suffered from other malignant tumors; and ② the presence of acute and chronic inflammation or diseases of the blood or immune system before the preoperative blood draw. A total of 272 patients were enrolled, including 169 patients in stage T2, 53 patients in stage T3, and 50 patients in stage T4.

The research group

The NLR and PLR were calculated by determining the ratio of the neutrophil absolute value to the lymphocyte absolute value and the platelet absolute value to the lymphocyte absolute value, respectively. The median NLR, PLR and HGB values were 2.48, 115 and 125, respectively, which were chosen as cutoffs to form the low and high NLR, low and high PLR, and low and high HGB groups, respectively. The relationship between the three groups and the clinicopathologic features and prognosis of MIBC patients was further analyzed.

Clinical variables and follow-up results

General information and the pathologic stage, pathologic grade, lymph node status, preoperative neutrophil value, preoperative lymphocyte value, preoperative platelet value and preoperative hemoglobin value of MIBC patients were recorded in detail. The pathologic staging of bladder cancer followed the tumor node metastasis (TNM) staging of the American Joint Committee on Cancer (AJCC), and pathologic grading was adopted by the World Health Organization (WHO) in 2004. The main outcome index of this study was CSS, and the secondary indexes were PFS and OS. The follow-up deadline was December 1, 2018.

Statistical analysis

IBM SPSS 20.0 software was used for statistical analyses. Continuous variables are presented as the mean $\pm$ standard deviation, and were compared by the t test. Categorical variables are expressed as cases and percentages, and were compared by the χ^2 test. Kaplan-Meier survival and multivariate Cox regression analyses were used to analyze prognosis. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

The follow-up time of the patients ranged from 1-151 months, and the median follow-up time was 25 months. The median age was 64.33 ± 10.17 years, and the male to female ratio was 4.8:1.

Results of single factor analysis

A t test was conducted to examine the continuous variables of the low and high NLR, low and high PLR, and low and high HGB groups, and test was conducted to examine the categorical variables. There were statistically significant differences in age, sex, pathologic grade, pathologic T stage and positive lymph node status between the low and high NLR groups. There were statistically significant differences in pathologic T stage and positive lymph node status between the low and high PLR groups. There were statistically significant differences in age, sex and positive lymph node status between the low and high HGB groups. Specific single factor analysis results are shown in table 1.

Survival analysis

Kaplan-Meier analysis was performed to examine the PFS, CSS and OS of the three groups, namely, the low and high NLR, low and high PLR, and low and high HGB groups, and the log-rank test was performed on the survival curves. The log-rank test results showed that the P values of the PFS, CSS and OS curves of the low and high NLR groups were 0.007, 0.005 and 0.005, respectively, and the P values of the low and high PLR groups were 0.104, 0.051 and 0.026, respectively. The P values of the low and high HGB groups were all 0.000. Specific survival curve analysis results are shown in figure 1.

Univariate and multivariate Cox regression results

The univariate Cox analysis showed that pathologic T stage, positive lymph node status, low HGB and high NLR were risk factors influencing the PFS, CSS and OS of MIBC patients, while age and high PLR were the only risk factors for OS. Univariate Cox regression results are shown in table 3. These significantly different variables and clinically significant pathologic grades were included in the multivariate Cox regression analysis, and the results showed that the independent risk factors influencing PFS, CSS and OS were pathologic T4 stage, positive lymph node status and low HGB. Pathologic T3 stage was identified as an independent risk factor affecting PFS and CSS. Age was identified as the only independent risk factor affecting OS. Multivariate Cox regression results are shown in table 4.

Discussion

A routine blood examination is one of the most commonly used tests in clinical practice. It mainly measures the white blood cell system, the platelet system and the hemoglobin system and can quickly provide information about the states of inflammation and anemia. Evidence suggests that peripheral blood analysis can reflect the microenvironmental status of tumors [11-12]. For example, the NLR, PLR

and other inflammatory indicators can be used to predict the prognosis of tumors. In addition, tumor-related anemia has gradually been paid attention to because the hypoxic environment of the body is likely to promote tumor growth and invasion [13]. Currently, the prognostic value of these routine blood indexes in MIBC patients is still unclear. Therefore, this study further explored the value of routine preoperative blood indexes in MIBC patients by analyzing the relationship between the preoperative NLR, PLR and HGB and clinicopathologic characteristics and prognosis.

The univariate analysis performed in this study revealed statistically significant differences in age, sex, pathologic grade, pathologic T stage and positive lymph node status between the low and high NLR groups. There were statistically significant differences in pathologic T stage and positive lymph node status between the low and high PLR groups. There were statistically significant differences in age, sex and positive lymph node status between the low and high HGB groups. Kaplan-Meier analysis revealed significant differences in the PFS, CSS and OS of the NLR and HGB groups and significant differences only in the OS of the PLR group. The univariate Cox analysis showed that pathologic T stage, positive lymph node status, low HGB and high NLR were risk factors affecting the PFS, CSS and OS of MIBC patients, while age and high PLR were risk factors only for OS. The multivariate Cox analysis also showed that the independent risk factors affecting PFS, CSS and OS were pathologic T4 stage, positive lymph node status and low HGB; pathologic T3 stage was identified as an independent risk factor affecting PFS and CSS; age was identified as the only independent risk factor affecting OS. However, a high NLR and a high PLR were not identified as independent risk factors affecting PFS, CSS and OS and may be removed by the interference of other factors in the multivariate Cox regression analysis. Therefore, the value of the NLR and PLR needs to be evaluated by multicenter and large sample studies.

Studies have shown that inflammation affects the occurrence, development and metastasis of tumors [11], and cancer-related inflammation is a key determinant of prognosis in cancer patients, while tumor patients with systemic inflammation have a poor prognosis [6]. The systemic inflammatory response can affect the nutritional status, immune function and psychological fluctuations of patients, and an imbalance in the above factors will affect prognosis. In recent years, a number of studies have been looking for factors that can truly reflect the systemic inflammatory response in patients and exploring their value in risk stratification in tumor patients, such as C-reactive protein, the NLR, the PLR and the scoring system (GPS score) formed by combining multiple inflammatory factors [14-15]. Guthrie et al. [16] found that the NLR was increased in patients with advanced or invasive diseases, manifested by increased tumor and lymph node staging and an increased number of metastatic lesions. In addition, preoperative increases in the NLR and PLR in patients with RC are associated with a poor prognosis [17-19]. Leibowitz-Amit [20] found that MIBC patients with a high lymphocyte absolute value before neoadjuvant chemotherapy were associated with a high complete response rate, while the complete response rate in patients with a high NLR and PLR was low, which suggests that the inflammatory response affects the body's sensitivity to chemotherapy and that anti-inflammatory treatment before chemotherapy may play an auxiliary role.

The prognosis of cancer patients is dependent not only on the biological characteristics of tumors but also, to a greater extent, on host reactions [5-6]. Motomura et al. [21] found that a high NLR was associated with increased serum and peritumor IL-17 and VEGF levels, suggesting that the systemic inflammatory response may further affect tumor development through the upregulation of proinflammatory cytokines. Grivennikov et al. [11] concluded that immune cells can affect tumor cells by producing cytokines, chemokines, growth factors, prostaglandins, reactive oxygen species, etc. Studies have also examined the relationship between macrophages and tumor cells. Chen et al. [22] found that PTEN mutation or deletion can promote the infiltration of macrophages in glioblastoma, while macrophages migrating to the tumor can secrete the SPP1 factor to promote the survival of tumor cells and the formation of new blood vessels, thereby promoting tumor progression. In conclusion, further studies on the regulation of systemic inflammatory responses by the tumor and host-derived factors may provide new therapeutic strategies for cancer patients.

A previous epidemiological investigation found that 67% to 80% of patients with bladder cancer presented with a painless gross hematuria [23], which was one of the main reasons for the decrease in HGB before surgery. In addition, bone marrow suppression caused by neoadjuvant chemotherapy and tumor invasion also led to a decrease in HGB. A meta-analysis showed that low preoperative HGB levels were considered prognostic factors for MIBC patients with RC [24]. Grimm et al. [25] found that low preoperative HGB levels were independent risk factors for CSS and OS after RC. Bi et al. [26] found that patients with high preoperative HGB levels and a high body mass index (BMI) had a good postoperative prognosis after RC, and one study showed that HGB was positively correlated with BMI [27]. Preoperative low hemoglobin levels can lead to tumor hypoxia, which promotes tumor growth by stimulating angiogenesis, acquiring genome mutations, and increasing resistance to apoptosis [13, 28] and further leads to increased staging and a poor prognosis. On the other hand, it is speculated that tumor-related inflammation may result in the release of various inflammatory factors, which may affect erythropoietin synthesis and lead to the decrease in HGB [29]. Currently, hemoglobin is not commonly used in various risk prediction tools, so the results of this study suggest that we need to improve our understanding of the impact of preoperative anemia or low hemoglobin levels on postoperative survival.

There are still some limitations to this study. (1) This study was a retrospective study, and patient selection may cause bias; (2) Some patients were followed up by telephone with the possibility of inaccurate outcomes; (3) Only the NLR, PLR and HGB were examined in this study, while other blood indicators may be of greater value in the prognosis of bladder cancer.

Conclusion

The preoperative peripheral blood HGB level is an independent risk factor for the prognosis of MIBC patients, and it can be used as a prognostic indicator for MIBC patients following RC.

Abbreviations

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; HGB: hemoglobin; BMI: body mass index; PFS: progression-free survival; CSS: cancer-specific survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; MIBC: muscle-invasive bladder cancer; RC: radical cystectomy.

Declarations

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Availability of data and materials

The datasets analyzed during the current study is available from the corresponding author on reasonable request.

Authors' contribution

Project development: ZWC. Data collection or management: JQZ, LWW, HD, SL. Data analysis and interpretation: JQZ and XZZ. Manuscript writing: JQZ. Final approval of manuscript: ZWC.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors have no potential conflicts of interest to declare.

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Tables

Table1-Clinicalpathologic characteristics of cohort

Factors	NLR			PLR			HGB		
	High NLR (n=136)	Low NLR (n=136)	<i>P</i>	High PLR (n=137)	Low PLR (n=135)	<i>P</i>	High HGB (n=140)	Low HGB (n=132)	<i>P</i>
Age(x±s) /years	65.6 ±9.3	63.1±10.9	0.046*	64.7±10.2	63.9 ±10.2	0.508	63.1 ±9.7	65.6±10.5	0.041*
BMI(x±s) /kg.m ⁻²	22.8 ±3.4	23.2 ±2.9	0.308	22.7 ±3.4	23.3 ±2.8	0.102	23.3±3.0	22.7±3.2	0.102
Gender [n(%)]			<0.001*			0.829			<0.001*
Male	124(91.2)	101(74.3)		114(83.2)	111(82.2)		127(90.7)	98(74.2)	
Female	12(8.8)	35(25.7)		23(16.8)	24(17.7)		13(9.3)	34(25.8)	
Smoking [n(%)]			0.179			0.336			0.951
yes	82(60.3)	71(52.2)		81(59.1)	72(53.3)		79(56.4)	74(56.1)	
no	54(39.7)	65(47.8)		56(40.9)	63(46.7)		61(43.6)	58(43.9)	
Pathologic grading [n(%)]			0.004*			0.258			0.315
Low grade	17(12.5)	36(26.5)		23(16.8)	30(22.2)		24(17.1)	29(22.0)	
High grade	119(87.5)	100(73.5)		114(83.2)	105(77.8)		116(82.9)	103(78.0)	
Pathologic T stage [n(%)]			0.006*			0.004*			0.078
T2	72(52.9)	97(71.3)		72(52.5)	97(71.9)		96(68.6)	73(55.3)	
T3	31(22.8)	22(16.2)		32(23.4)	21(15.5)		23(16.4)	30(22.7)	
T4	33(24.3)	17(12.5)		33(24.1)	17(12.6)		21(15.0)	29(22.0)	
Lymph node [n(%)]			0.025*			0.030*			0.013*
Positive	36(26.5)	21(15.4)		36(26.3)	21(15.6)		21(15.0)	36(27.3)	
Negative	100(73.5)	115(84.6)		101(73.7)	114(84.4)		119(85)	96(72.7)	

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; HGB: hemoglobin; BMI: body mass index; * P<0.05.

Table 2-Surval rate of NLR, PLR and HGB grouping

Grouping	Years	Progression-free survival rate	Cancer-specific survival rate	Overall survival rate
Low NLR	1	76.1%	84.0%	81.4%
	2	67.8%	74.7%	72.4%
	5	62.4%	62.7%	57.3%
High NLR	1	63.8%	68.8%	65.6%
	2	57.5%	59.2%	55.7%
	5	48.7%	50.3%	47.4%
Low PLR	1	72.2%	81.1%	79.5%
	2	67.6%	71.5%	69.3%
	5	60.3%	62.5%	58.4%
High PLR	1	67.7%	71.4%	67.2%
	2	57.8%	62.0%	58.3%
	5	50.6%	49.7%	45.7%
Low HGB	1	60.9%	68.7%	65.5%
	2	50.8%	56.6%	53.2%
	5	43.9%	45.7%	41.6%
High HGB	1	78.1%	83.2%	80.7%
	2	73.6%	76.3%	74.0%
	5	65.9%	66.3%	62.3%

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; HGB: hemoglobin.

Table 3-Univariate Cox analysis of PFS, CSS and OS of MIBC patients

Variate	PFS		CSS		OS	
	HR(95%CI)	P	HR(95%CI)	P	HR(95%CI)	P
Age	1.013(0.993-1.034)	0.191	1.015(0.995-1.036)	0.132	1.029(1.009-1.049)	0.004*
BMI	0.980(0.921-1.043)	0.528	0.973(0.914-1.036)	0.395	0.980(0.925-1.039)	0.500
Gender(male)	1.358(0.798-2.312)	0.259	1.353(0.794-2.304)	0.266	1.310(0.802-2.139)	0.280
Smoking(yes)	1.068(0.728-1.566)	0.737	1.107(0.755-1.624)	0.602	1.034(0.725-1.477)	0.852
Pathologic grade	1.307(0.801-2.131)	0.284	1.414(0.863-2.316)	0.169	1.437(0.905-2.282)	0.124
(high grade)						
Pathologic T stage						
T2	reference		reference		reference	
T3	2.385(1.472-3.864)	<0.001*	2.329(1.438-3.774)	0.001*	2.078(1.327-3.255)	0.001*
T4	4.572(2.915-7.173)	<0.001*	4.812(3.060-7.568)	<0.001*	4.012(2.618-6.149)	<0.001*
Lymph node (positive)	3.811(2.565-5.661)	<0.001*	3.919(2.632-5.835)	<0.001*	3.316(2.269-4.846)	<0.001*
HGB≥125	0.482(0.327-0.712)	<0.001*	0.488(0.331-0.719)	<0.001*	0.520(0.363-0.746)	<0.001*
NLR≥2.48	1.682(1.141-2.480)	0.009*	1.734(1.173-2.562)	0.006*	1.676(1.164-2.414)	0.006*
PLR≥115	1.366(0.932-2.001)	0.110	1.456(0.993-2.137)	0.055	1.493(1.043-2.138)	0.029*

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; HGB: hemoglobin; BMI: body mass index; PFS: progression-free survival; CSS: cancer-specific surviva; OS: overall survival; HR: hazard ratio; CI: confidence interval; * P<0.05.

Table 4- Mutivariate Cox analysis of PFS, CSS and OS of MIBC patients

Variate	PFS		CSS		OS	
	HR(95%CI)	<i>P</i>	HR(95%CI)	<i>P</i>	HR(95%CI)	<i>P</i>
Age	---	---	---	---	1.032(1.012-1.052)	0.002*
Pathologic T stage						
T2	reference		reference		reference	
T3	1.716(1.025-2.873)	0.040*	1.707(1.023-2.847)	0.041*	1.558(0.959-2.529)	0.073
T4	3.496(2.165-5.647)	<0.001*	3.619(2.238-5.854)	<0.001*	3.225(2.034-5.113)	<0.001*
Pathologic grade	0.778(0.454-1.335)	0.363	0.845(0.491-1.457)	0.545	0.934(0.564-1.545)	0.790
(high grade)						
Lymph node (positive)	2.734(1.756-4.257)	<0.001*	2.687(1.715-4.209)	<0.001*	2.414(1.579-3.691)	<0.001*
HGB≥125	0.594(0.400-0.884)	0.010*	0.631(0.423-0.941)	0.024*	0.650(0.447-0.946)	0.024*
NLR≥2.48	1.211(0.809-1.815)	0.352	1.231(0.820-1.847)	0.316	1.149(0.756-1.747)	0.515
PLR≥115	---	---	---	---	0.995(0.660-1.500)	0.982

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; HGB: hemoglobin; BMI: body mass index; PFS: progression-free survival; CSS: cancer-specific survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; * P<0.05.

Figures

Figure 1

Kaplan-Meier results of PFS, CSS and OS grouped by NLR, PLR and HGB (A)(B)(C): NLR's relationship with PFS, CSS and OS, respectively; (D)(E)(F): PLR's relationship with PFS, CSS and OS, respectively; (G) (H)(I): HGB's relationship with PFS, CSS and OS, respectively.