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Research article

Predictive value of inflammatory indices LMR, PLR and NLR in patients with muscle-invasive bladder cancer

Andrey I. Gorelov[1, 2], Dmitriy A. Zhuravskii[1], Anna A. Gorelova[1, 3]

[1] Saint Petersburg State University, Saint Petersburg, Russia;
[2] City Pokrovskaya Hospital, Saint Petersburg;
[3] St. Petersburg Research Institute of Phthisiopulmonology, Saint Petersburg, Russia

BACKGROUND: Increasing the efficiency of predicting the results of treatment of patients with bladder cancer is one of the important tasks of modern urology.

AIM: Our aim was to identify and evaluate the association between the most significant clinical, morphological and immunological markers and survival of muscle-invasive bladder cancer patients treated with radical cystectomy. We also developed an algorithm for diagnosis and treatment of patients with muscle-invasive bladder cancer.

MATERIALS AND METHODS: This retrospective study included 100 muscle-invasive bladder cancer patients, who underwent radical cystectomy between 1995 and 2013. The study endpoints were overall survival.

RESULTS: Univariable analysis revealed that continuous (Lymphocyte-monocyte ratio), PLR (platelet-lymphocyte ratio) и NLR (neutrophil-lymphocyte ratio) were significantly associated with overall survival. On multivariable regression model analysis, continuous LMR, NLR, and PLR independently predicted both endpoints.

CONCLUSIONS: Our findings indicate that the cheap and simple blood-based biomarkers may be valuable in identifying muscle-invasive bladder cancer patients treated with radical cystectomy, who are at higher risk of all-cause mortality.

Keywords: bladder cancer; inflammatory markers; radical cystectomy.

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Научная статья

Прогностическое значение воспалительных индексов LMR, PLR и NLR у пациентов с мышечно-инвазивным раком мочевого пузыря

А.И. Горелов[1, 2], Д.А. Журавский[1], А.А. Горелова[1, 3]

[1] Санкт-Петербургский государственный университет, Санкт-Петербург, Россия;
[2] Городская Покровская больница, Санкт-Петербург, Россия;
[3] Санкт-Петербургский научно-исследовательский институт фтизиопульмонологии, Санкт-Петербург, Россия

Актуальность. Повышение эффективности прогнозирования результатов лечения больных раком мочевого пузыря — одна из важных задач современной урологии.

Цель. Оценить прогностическую ценность периоперационных иммунологических маркеров LMR (lymphocyte-monocyte ratio — лимфоцитарно-моноцитарный индекс), PLR (platelet-lymphocyte ratio — тромбоцито-лимфоцитарный индекс) и NLR (neutrophil-lymphocyte ratio — нейтрофильно-лимфоцитарный индекс) у пациентов с мышечно-инвазивным раком мочевого пузыря, которым была выполнена радикальная цистэктомия.

Материалы и методы. В ретроспективное исследование были включены 100 пациентов с мышечно-инвазивным раком мочевого пузыря, перенесших радикальную цистэктомию в период с 1995 по 2013 г. Конечной точкой исследования была общая выживаемость.

Результаты. Пятилетняя общая выживаемость была достоверно ниже ($p < 0{,}0001$) в группах высокого риска при всех воспалительных индексах и составила 52, 57 и 45 % для PLR-, NLR- и LMR-высоких рисков соответственно. Проведение множественного регрессионного анализа показало, что анализируемые иммунологические маркеры могут использоваться для прогнозирования исходов хирургического лечения.

Выводы. Наши результаты показывают, что дешевый и простой анализ маркеров воспаления могут быть ценными для выявления пациентов высокого и низкого риска с мышечно-инвазивным раком мочевого пузыря, предсказывая эффективность хирургического лечения.

Ключевые слова: рак мочевого пузыря; воспалительные маркеры; радикальная цистэктомия.

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ЭКО•ВЕКТОР

BACKGROUND

Bladder cancer (BC) is the ninth most common cancer and is four times more common in men than in women [1]. More than 130,000 people die from BC each year, accounting for 2.1% of all cancer deaths. Over the past 10 years, BC patients in Russia increased to 58.6% [2]. About 85% of all cases are of patients >55 years old [3].

Currently, radical cystectomy is the gold standard for the treatment of patients with muscle-invasive bladder cancer (MIBC), despite a high percentage of postoperative complications and unsatisfactory long-term results [4]. Unfortunately, readily available biomarkers to assess the prognosis of patients remains to be developed. As early as the beginning of 1889, Rudolf Virchow put forward the hypothesis that cancer arises from foci of chronic inflammation. Since then, several research studies focused on establishing a link between the inflammatory microenvironment of malignant tissues and prevention or treatment of cancer. The accumulated evidence supported Virchow's hypothesis. Inflammation serves as a crucial defense mechanism of the body against cellular damage in response to stress, by which the immune system attempts to neutralize or eliminate harmful stimuli and initiate regenerative or healing processes. However, it has been proven that excessive or persistent inflammation contributes to carcinogenesis and tumor progression by activating inflammatory molecules and signals [5].

Numerous studies have demonstrated the relationship between inflammatory indices and well-known inflammatory proteins such as procalcitonin, C-reactive protein, and interleukins [6–8]. Moreover, routine blood count and inflammatory indices have been revealed as prognostic factors in patients suffering from systemic inflammatory diseases, acute coronary syndrome, heart failure, and Behcet's disease [9–11]. The relationship between inflammation and the pathophysiology of cancer has been demonstrated by the action of non-steroidal anti-inflammatory drugs, such as inhibitors of COX 2 (cyclooxygenase 2). This group of drugs stimulates apoptosis and tumor shrinkage [12].

It has been proven that a malignant tumor induces a network of interactions between immune cells and the tumor [13]. Lymphocytes represent the basis of the antitumor activity of the immune system [14]. A decrease in the number of lymphocytes is associated with the progression of BC [15]. Sharma et al. [16] have shown that the presence of a large number of $CD8^+$ lymphocytes improved the prognosis of patients with MIBC.

Cells of the tumor microenvironment stimulate monocytes and neutrophils to secrete interleukin 6 (IL 6), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF-β), which determine systemic immunosuppression, reducing lymphopoiesis. These mediators stimulate myelopoiesis with polarization of neutrophils and monocytes into protumor cells. Additionally, neoplasms induce the recruitment of neutrophils and monocytes that reside in the tumor microenvironment. These cells, known as tumor-associated macrophages and tumor-associated neutrophils, cause tumor progression [17]. Platelets are involved in the recruitment of monocytes and neutrophils and are the main source of TGF-β. Platelets through VEGF activation stimulate tumor angiogenesis.

The notable markers include lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR). They can be easily identified using a clinical blood test. These indicators serve as additional markers of the systemic inflammatory response and correlate with stage progression and poor prognosis [18]. The preoperative neutrophil-lymphocyte ratio may be a prognostic biomarker for patients with a history of radical cystectomy for bladder urothelial carcinoma [19]. An increase in blood neutrophil-lymphocyte ratio during follow-up after radical cystectomy is a potential marker for the early detection of recurrence [20]. Furthermore, NLR is associated with a pathological response in MIBC patients receiving neoadjuvant chemotherapy [21]. However, the reasons of increase of this ratio in most patients are unclear.

The study of the role of platelets in the mechanism of inflammation and oncogenesis determined the prognostic significance of PLR in BC. Thus, a meta-analysis by Tamura et al. [22] has revealed a relationship between elevated LMR and poor prognosis. Moreover, Zhang et al. [23] have established that high PLR numbers correlated with low overall survival rate.

The present study aimed to evaluate the prognostic value of the LMR, PLR, and NLR factors in MIBC patients after radical cystectomy.

MATERIALS AND METHODS

A retrospective analysis of the case histories of 100 patients (89 men and 11 women aged 35–75 years; mean age, 59.21 ± 8.54 years) with MIBC, who underwent radical cystectomy with various methods of urinary diversion, was performed in 1995–2013 in Multidisciplinary Hospital 2, St. Petersburg City, and Pokrovskaya Hospital, St. Petersburg City.

The inclusion criteria were the presence of urothelial carcinoma, muscle-invasive form, and radical cystectomy with lymph node dissection as the only treatment method.

Contrastingly, *the exclusion criteria were* non-urothelial carcinoma, distant metastases, concomitant systemic inflammatory diseases, patients with concomitant tumor diseases of other localization, hematological pathology, and patients receiving neoadjuvant chemotherapy.

In the distribution of patients according to the TNM system, stage T2 was detected in 64 (64.4%) patients, T3 in 16 (16.2%) patients, and T4 in 19 (19.2%) patients. Depending on involvement of regional lymph nodes, the patients were distributed with N+ for 24 (24.0%) patients and N0 for

76 (76.0%) patients. The G2 degree of differentiation for 62 (62.6%) patients prevailed. Highly differentiated cancer (G1) was revealed in 22 (22.2%) patients and low-differentiated tumor (G3) in 15 (15.2%) patients. In 62 (62.0%) patients, the size of the primary tumor was >3 cm, and in 38 (38.0%) patients, it was <3 cm.

All the patients underwent a complete urological examination in the preoperative period. A preoperative blood test was performed, at an average of 3 days before the surgery, by collecting peripheral venous blood in ethylenediaminetetraacetic acid tubes. The LMR, PLR, and NLR indices were derived by dividing the absolute count of monocytes, platelets, and neutrophils by the absolute count of lymphocytes, respectively.

Statistical analysis was performed using Statistica 12 with Medical Bundle (StatSoft Inc., Tulsa, OK, USA) and MedCalc Statistical Software v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium). The relationship between groups and 5-year overall survival was determined using the Kaplan–Meier curves and log-rank test. The Cox regression model was used for univariate multivariable analysis. Variables included in univariate analysis were gender, age, tumor size, stage T, lymph node involvement, PLR, NLR, and LMR.

RESULTS

To achieve our aim, we studied the relationship of RLR, NLR, and LMR levels with gender differences, age, T and N stages, G malignancy, and overall survival rate.

To assess the significance of the studied clinical and laboratory parameters, all the patients were distributed into the high and low risk groups depending on inflammatory indices. High and low PLR and NLR values were defined as high and low risk of disease progression, respectively. Low and high LMR levels were rated as high and low risk groups, respectively.

To calculate the optimal value of the cutoff threshold and its representation in graphical form, the ROC-analysis method (receiver operator characteristic) was used. The relationship between the value of inflammatory indices and overall survival rate was determined. The optimal threshold value of inflammatory markers in this study in accordance with the Youden index were PLR ⩾ 110.15; LMR < 4.97; and NLR ⩾ 2.15 (Table 1). The criterion for determining the cut-off points was the overall survival of patients.

Statistically significant data were obtained, indicating the high specificity and sensitivity of these markers in terms of prognosis for MIBC patients (Fig. 1, Table 2) ($p > 0.0001$).

When evaluating clinical and laboratory parameters in groups of high and low risk patients, the groups were found to be homogeneous ($p = 0.067$). There were no significant differences between the level of inflammatory indices (PLR, NLR, LMR) and gender ($p > 0.05$). The relationship between the level of PLR, NLR, and LMR indices and age is presented in Tables 2–4 and Fig. 1.

In this study, the patients were classified into two groups depending on age, with 54 (54%) patients aged <60 years and 46 (46%) patients aged ⩾60 years. The mean values of the NLR and PLR indices were significantly higher (<0.0001) in the group of patients aged ⩾60 years (2.78 and 147.60 versus 2.30 and 122.86, respectively). In the group of patients <60 years of age, the LMR ratio was significantly higher than in patients >60 years of age (4.68 versus 4.13) (Table 3).

To assess the sensitivity and specificity of the age of patients in relation to the overall survival rate of MIBC patients, an ROC analysis was performed. Sensitivity and specificity were 71.88% and 50%, respectively, AuROC was 0.58, efficiency was 60.94%, and chi-square was 4.7852. A table summarizing the ROC analysis for age and inflammation indices depending on mortality is presented in Fig. 1.

Assessment of age differences revealed that patients <60 years of age had low-risk NLR, PLR, and LMR indices significantly. These data are presented in Table 4.

The relationship between inflammatory indices (NLR, PLR, LMR) and the degree of tumor invasion of the urinary wall (category T) is presented in Table 5.

In our study, patients were most often diagnosed with category T2 (64%) and less often T3 and T4 (16% and 19% of patients, respectively). Table 5 shows that with the degree of prevalence of the T2 tumor, the values of inflammatory indices prevailed, corresponding to a low risk of

Table 1. Sensitivity and specificity of various indices of inflammation in relation to the overall survival of patients with muscle-invasive bladder cancer, according to the Youden's index

Таблица 1. Чувствительность и специфичность различных индексов воспаления в отношении общей выживаемости больных мышечно-инвазивным раком мочевого пузыря, в соответствии с индексом Юдена

Inflammation index	Cutoff point	Sensitivity, %	Specificity, %	Area under the curve (AuROC)
PLR	⩾110.15	98.44	100	1.00
LMR	<4.97	100	94.44	0.99
NLR	⩾2.15	93.75	88.89	0.95

Note. Here and in Tables 2–6. PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; NLR, neutrophil-lymphocyte ratio.

Table 2. Mortality of patients with muscle-invasive bladder cancer at the 5-year follow-up stage depending on the values of inflammation indices and the age of patients

Таблица 2. Смертность больных мышечно-инвазивным раком мочевого пузыря на 5-летнем этапе наблюдения в зависимости от значений индексов воспаления и возраста больных

	Factor	Absolute value	Mortality rate, *n* (%)	χ^2	*p* (df = 1)
PLR	High risk ⩾110.15	63	63 (100)	95.7770	<0.0001
	Low risk <110.15	27	4 (14.8)		
LMR	High risk <4.97	64	58 (96.97)	91.5825	<0.0001
	Low risk >4.97	26	4 (15.4)		
NLR	High risk ⩾2.15	60	55 (93.75)	68.2919	<0.0001
	Low risk <2.15	40	6 (15)		
Age	<60 years	56	31 (55.56)	4.7852	0.0287
	>60 years	46	33 (71.88)		

Table 3. Inflammatory indices NLR, PLR, LMR in patients with muscle-invasive bladder cancer depending on age

Таблица 3. Значения воспалительных индексов NLR, PLR, LMR больных мышечно-инвазивным раком мочевого пузыря в зависимости от возраста

Index	NLR		PLR		LMR	
	up to 60 years	60 years and more	up to 60 years	60 years and more	up to 60 years	60 years and more
Quantity, *n*	54	46	54	46	54	46
Average	2.30	2.78	122.86	147.60	4.68	4.13
Standard deviation	0.48	0.47	24.67	30.32	0.76	0.75
Maximum	3.30	3.48	180.22	180.22	5.72	5.70
Upper quartile	2.57	3.14	139.38	173.86	5.43	4.73
Median	2.14	2.89	119.51	159.28	4.55	3.79
Lower quartile	1.91	2.53	99.67	106.94	4.03	3.54
Minimum	1.67	1.79	98.21	99.75	3.35	3.30
p	<0.0001		<0.0001		0.0002	

mortality. For all considered indices (NLR, PLR, and LMR) in the T2 category, 56.25% of patients corresponded to the degree of low risk. A tendency toward an increase in the number of high-risk patients with an increase in T category was revealed. Thus, in the NLR group, categories T3 and T4 were established in 68.75% and 73.68% of high-risk patients, respectively. In the PLR group, categories T3 and T4 were noted in 75% and 63.16% of high-risk patients, respectively. However, in the LMR group with the T4 category, low-risk patients were more common (68.42%). Significant differences between low- and high-risk groups for different T categories were revealed only in the PLR group ($p = 0.0479$).

The results of the study of the relationship between the values of the inflammatory indices NLR, PLR, and LMR and the presence of metastatic lesions of regional lymph nodes are presented in Table 6.

Table 6 shows that high-risk PLR and NLR indices were significantly noted in patients with metastatic lesions of regional lymph nodes and that the level of the LMR index did not depend on its condition.

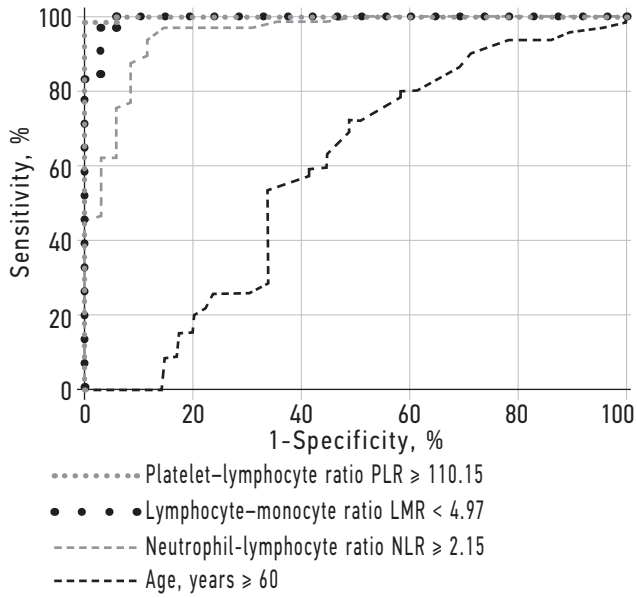

Fig. 1. ROC curve for overall survival of patients with muscle-invasive bladder cancer

Рис. 1. ROC-кривая для общей выживаемости больных мышечно-инвазивным раком мочевого пузыря

Table 4. Relationship between the values of inflammatory indices NLR, PLR, LMR and the age of patients with muscle-invasive bladder cancer

Таблица 4. Зависимость между значениями воспалительных индексов NLR, PLR, LMR и возрастом больных мышечно-инвазивным раком мочевого пузыря

Indices	Age, years		*p*
	up to 60	60 and more	
PLR, *n* (%):			
Low risk (<110.15)	35 (64.81)	13(28.26)	<0.0001
High risk (>110.15)	19 (35.19)	33 (71.74)	
NLR, *n* (%):			
Low risk (<2.15)	29 (53.7)	10 (21.74)	<0.0001
High risk (>2.15)	25 (46.3)	36 (78.26)	
LMR, *n* (%):			
Low (>4.97)	38 (70.3)	17 (36.96)	0.0002
High (<4.97)	16 (29.63)	29 (63.04)	

Table 5. The relationship between the values of the inflammatory indices NLR, PLR, LMR and the degree of tumor invasion of the bladder wall (category T)

Таблица 5. Зависимость между значениями воспалительных индексов NLR, PLR, LMR и степенью опухолевого прорастания стенки мочевого пузыря (категория T)

Group	T2, *n* = 64	T3, *n* = 16	T4, *n* = 19	*p* (df = 2)
NLR:				
Low risk, *n* (%)	36 (56.25)	5 (31.25)	5 (26.32)	0.3177
High risk, *n* (%)	28 (43.75)	11 (68.75)	14 (73.68)	
PLR:				
Low risk, *n* (%)	36 (56.25)	4 (25.00)	7 (36.84)	0.0479
High risk, *n* (%)	28 (43.75)	12 (75.00)	12 (63.16)	
LMR:				
Low risk, *n* (%)	36 (56.25)	5 (31.25)	13 (68.42)	0.0800
High risk, *n* (%)	28 (43.75)	11 (68.75)	6 (31.58)	

Table 7 presents the relationship between the values of the inflammatory indices NLR, PLR, and LMR and the degree of differentiation of the bladder tumor.

Analysis of Table 7 reveals that the low-risk PLR index in patients with a high-differentiated tumor (G1) was registered significantly more often than the high-risk index ($p = 0.0384$). The same tendency was noted for the NLR and LMR indices; however, no significant differences were revealed. When comparing the indices of the PLR index, based on the degree of tumor differentiation, significant differences were noted between categories G1 and G3 ($p = 0.01$). Analysis of NLR and LMR indices depending on the degree of tumor malignancy showed the same tendency as the PLR index; however, the differences are not significant.

Thus, it can be concluded that patients had a uniform distribution regarding inflammatory indices and the degree of tumor differentiation. Thus, patients with high-risk inflammatory markers NLR, PLR, and LMR more often had moderately and low-differentiated tumors. However, a significant difference was noted only when analyzing the PLR index ($p = 0.0384$).

The main criterion for the outcome of treatment of patients with BC is survival rate. In our study, overall survival was assessed using the Kaplan–Meier method.

An analysis of the cumulative survival rate of patients showed a significant difference ($p > 0.0001$) in mortality rate in high- and low-risk patients regarding the level of inflammatory markers NLR, PLR, and LMR (Fig. 2). Thus, the 5-year overall survival rate was significantly lower (<0.0001) in high-risk groups for all inflammatory indices and amounted to 52%, 57%, and 45% for high-risk PLR, NLR, and LMR, respectively.

DISCUSSION

To date, only a few studies have analyzed the prognostic value of several inflammatory indices simultaneously, namely, LMR, PLR, and NLR in patients with BC. In the studies by Ma et al. [24] and Neal et al. [25], it was demonstrated that a high level of the NLR index before surgery was an independent prognostic factor in all patients with localized kidney cancer and colorectal cancer with liver metastases.

The results of our study confirmed the data obtained by D'Andrea et al. [26]. These authors conducted a major multicenter study and obtained results that allowed them to indicate LMR and NLR as independent prognostic factors for the survival of MIBC patients. Zhang et al. [27]

Table 6. Relationship between the values of the inflammatory indices NLR, PLR, LMR and the presence of lesions of regional lymph nodes (category N)

Таблица 6. Зависимость между значениями воспалительных индексов NLR, PLR, LMR и наличием поражений регионарных лимфатических узлов (категория N)

Group	N0, *n* = 76	N+, *n* = 24	*p*
PLR, *n* (%):			
Low risk (<110.15)	42 (55.26)	6 (25.00)	0.0097
High risk (>110.15)	34 (44.74)	18 (75.00)	
NLR, *n* (%):			
Low risk (<2.15)	36 (47.37)	3 (12.50)	0.0023
High risk (>2.15)	40 (52.63)	21 (87.50)	
LMR, *n* (%):			
Low risk (>4.97)	44 (57.89)	11 (45.83)	0.3005
High risk (<4.97)	32 (42.10)	13 (54.17)	

Table 7. Relationship between the values of the inflammatory indices NLR, PLR, LMR and the degree of differentiation of the bladder tumor (category G)

Таблица 7. Зависимость между значениями воспалительных индексов NLR, PLR, LMR и степенью дифференцировки опухоли мочевого пузыря (категория G)

Index	G1, *n* = 22	G2, *n* = 62	G3, *n* = 15	*p*
PLR, *n* (%):				
Low risk (<110.15)	15 (68.18)	28 (45.16)	4 (26.67)	0.0384
High risk (>110.15)	7 (31.82)	34 (54.84)	11 (73.33)	
NLR, *n* (%):				
Low risk (<2.15)	13 (59.09)	22 (35.48)	4 (26.67)	0.1698
High risk (>2.15)	9 (40.91)	40 (64.52)	11 (73.33)	
LMR, *n* (%):				
Low risk (>4.97)	14 (63.64)	35 (56.45)	5 (33.33)	0.0825
High risk (<4.97)	8 (36.36)	27 (43.55)	10 (66.67)	

Fig. 2. Cumulative overall survival of patients with muscle-invasive bladder cancer at different values of inflammatory indices: *a* – overall survival of patients with high and low risk NLR (<0.0001); *b* – overall survival of patients with high and low risk PLR (<0.0001); *c* – overall survival of patients with high and low risk LMR (<0.0001)

Рис. 2. Кумулятивная общая выживаемость больных мышечно-инвазивным раком мочевого пузыря при различных значениях воспалительных индексов: *a* — общая выживаемость пациентов с NLR высокого и низкого риска (<0,0001); *b* — общая выживаемость пациентов с PLR высокого и низкого риска (<0,0001); *c* — общая выживаемость пациентов с LMR высокого и низкого риска (<0,0001)

revealed that low LMR was a more reliable predictor of overall survival than high PLR and NLR. Bhindi et al. [28], in turn, showed that PLR is an independent factor determining overall survival rate. The degree of malignancy and tumor necrosis differed significantly between the groups of the parameters analyzed, indicating that biomarkers reflected adequately the non-differentiation and aggressiveness of tumor cells.

The search for independent prognostic markers led to the consideration of immunological parameters. In the present study, we used the three inflammation indices most commonly available in everyday practice: NLR, PLR, and LMR. To determine their prognostic significance, the results of these markers were analyzed in all 100 patients included in the study. All patients were distributed into groups depending on the effect of inflammatory markers on overall survival, namely, PLR, NLR, and LMR of high and low risk. The optimal threshold value for inflammatory markers in this study were PLR ⩾ 110.15; LMR < 4.97; and NLR ⩾ 2.15. Patients <60 years of age had low-risk NLR, PLR, and LMR indices significantly more often. Regional metastases (N) were more common in patients with high-risk PLR, NLR, and LMR. Low-risk PLR and LMR were registered more often in patients with T2 tumor, whereas high-risk PLR and NLR were noted more often in patients with T3–4 tumor. The moderately differentiated tumors (G2) were most common (62 patients; 62%). Patients with category G3 had high-risk inflammatory indices more often, and 5-year overall survival rate was significantly lower for all high-risk inflammatory indices.

Multiple regression analysis showed that the immunological markers analyzed can be used to predict the outcomes of surgical treatment. We acknowledge that the retrospective nature of our research is a relative disadvantage in the quality of the work performed. Due to the lack of complete information on preoperative levels of C-reactive protein, procalcitonin, and interleukins, we were unable to compare biomarkers based on complete blood count with these well-known markers of inflammation. However, despite these limitations, this study is the first to analyze the predictive value of the LMR, PLR, and NLR scores in one cohort of MIBC patients with the history of radical cystectomy. Multicenter and prospective studies are required to clarify further the predictive value of LMR, PLR, and NLR in MIBC patients after radical cystectomy.

CONCLUSIONS

Our results show that low-cost and simple analysis of inflammatory markers holds promise for identifying high- and low-risk patients with MIBC, predicting the efficiency of surgical treatment.

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AUTHORS' INFO

***Anna A. Gorelova,** Cand. Sci. (Med.), Assistant Professor of the Department of Hospital Surgery with a Course of Urology;
address: 7–9, Universitetskaya embankment, Saint Petersburg, 199034, Russia; ORCID: https://orcid.org/0000-0002-7010-7562;
eLibrary SPIN: 8568-9004; Scopus: 57202812074;
e-mail: gorelovauro@gmail.com
Andrey I. Gorelov, Dr. Sci. (Med.), Professor of the Department of Hospital Surgery with a Course of Urology, Head of Urological Unit;
ORCID: https://orcid.org: 0000-0002-2858-5317;
eLibrary SPIN: 5070-9526; Scopus: 7005253173;
e-mail: gorelov_a_i@mail.ru
Dmitriy A. Zhuravskii, Postgraduate student;
ORCID: https://orcid.org: 0000-0002-2556-3390;
eLibrary SPIN: 3748-7129; e-mail: zhuravskiy.spbu@gmail.com

ОБ АВТОРАХ

***Анна Андреевна Горелова,** канд. мед. наук, ассистент кафедры госпитальной хирургии с курсом урологии, ст. н. с.; адрес: Россия, 199034, Санкт-Петербург, Университетская наб., д. 7–9;
ORCID: https://orcid.org/0000-0002-7010-7562;
eLibrary SPIN: 8568-9004; Scopus: 57202812074;
e-mail: gorelovauro@gmail.com
Андрей Игоревич Горелов, д-р мед. наук, профессор кафедры госпитальной хирургии с курсом урологии, заведующий отделением урологии; ORCID: https://orcid.org:0000-0002-2858-5317;
eLibrary SPIN: 5070-9526; Scopus: 7005253173;
e-mail: gorelov_a_i@mail.ru
Дмитрий Александрович Журавский, аспирант;
ORCID: https://orcid.org:0000-0002-2556-3390;
eLibrary SPIN: 3748-7129; e-mail: zhuravskiy.spbu@gmail.com

* Corresponding author / Автор, ответственный за переписку