Original Article

Can Peripheral Blood Systemic Immune Response Parameters Predict Oncological Outcomes in Patients with Non-Muscle-Invasive Bladder Cancer?

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Abstract

Background: Many studies have investigated most cancer types - associations with systemic inflammatory response (SIR) parameters. **Aim:** This study investigated predictive values of SIR parameters in oncological outcomes and survival – to primary non-muscle-invasive bladder cancer (NMIBC) patients. **Materials and Methods:** We analyzed 74 primary NMIBC patients. Clinical features, laboratory results, and tumor characteristics were recorded. In addition, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), serum C-reactive protein, albumin-to-globulin ratio (AGR), and modified Glasgow prognostic scores (mGPS) were calculated. **Results:** The - mean age of the patients was - 67.41 ± 11.31 years, and the follow-up duration was 38.77 ± 19.53 months. We – found no significant NLR, CRP, and AGR – correlations with tumor characteristics and oncological outcomes. There were significant – correlations between MLR and pathological-T-stage and the PLR, pathological-T-stage, and tumor count. Carcinoma *in situ* was associated with a high mGPS. Multivariate analysis revealed no significant – correlations between systemic inflammatory response parameters and oncological outcomes. Patients with a high mGPS had poor cancer-specific survival. Increased NLR was associated with reduced overall survival. **Conclusions:** This study revealed no significant correlation between SIR parameters and oncological outcomes. Therefore, we need more reliable indicators than SIR parameters in NMIBC patients in clinical practice.

Keywords: *Non-muscle-invasive bladder cancer, outcome, progression, recurrence, systemic inflammatory response*

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Introduction

Bladder cancer is the ninth most commonly diagnosed cancer and thirteenth in cancer-related deaths worldwide. Approximately 70-75% of patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC), limited to mucosa or submucosa at initial admission.[1] However, 70% of patients have a high 5-year recurrence rate following initial TURBT except some parts of the world such as west African subregion.[2] Approximately 10-20% of NMIBC cases show progression to muscle-invasive bladder cancer (MIBC). The high progression and recurrence rates of pathological T1, grade 3, and high-risk NMIBC, together with the high 5-year cancer-related death rate (11.3%), have been documented. Patients diagnosed with primary NMIBC with progression have the poorest survival rates.[3] Even though a radical cystoprostatectomy is performed, approximately 50% die from the cancer. Managing such high-risk patients is crucial, regarding their treatment before disease progression.[3] Current

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risk estimation tools, such as the European Organization for Research and Treatment of Cancer (EORTC) scoring models, are based on clinicopathological features. Even though these estimation tools have improved NMIBC management, validation studies have reported their limited accuracy, particularly in high-risk groups.[4] Determining accurate biomarkers might help improve such models predictive capabilities in managing patients with a high risk of progression.[5]

The systemic inflammatory response (SIR) has been shown to play critical roles in tumorigenesis, proliferation, progression, and metastasis.[6] SIR markers such as monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have been used in prognosis prediction and anti-tumor assessment in many different types of malignancies, including urologic cancer.[7] Albumin and globulin are the main components of serum proteins. These proteins play essential roles in immunity and inflammation. The albumin-to-globulin ratio (AGR) has been reported to be a potential prognostic biomarker in various cancers.[8]

We could not find a study that had comprehensively investigated the relationship between SIR biomarkers and NMIBC outcome. This retrospective observational study aimed to investigate the predictive capability of a readily available blood-based SIR biomarker panel in the oncological outcome of NMIBC patients.

Materials and Methods

In this cross-sectional, observational study, we retrospectively analyzed the data of 74 patients diagnosed with primary high-risk non-muscle-invasive bladder cancer between January 2016 and August 2020 at the Aegean region of Turkey. After obtaining the local ethical committee approval (#323/303, date: 02/09/2021), the patient demographic characteristics and laboratory results including serum glucose, blood urea nitrogen, urea, alanine aminotransferase (ALT), alanine acetate transferase (AST), C-reactive protein (CRP), total protein, albumin, and complete blood count, characteristics of the tumor including tumor size and number, pathological stage, grade, presence of recurrence or progression, intravesical chemotherapy, follow-up duration, and survey were recorded. All patients underwent TURBT by a urologist. The surgeon made decisions for immediate intravesical chemotherapy and immunotherapy according to the tumor characteristics and guidelines on non-muscle-invasive bladder cancer. The second TURBT was performed in patients with a T1 or high-grade tumor identified in the initial TURBT. Postoperative immunotherapeutic instillation treatment was performed in all patients Postoperative follow-up measures adopted the recent EAU (European Association of Urology) guidelines on the non-muscle-invasive bladder cancer.[9] The urological pathologist evaluated all pathological specimens. The tumor stages were categorized according to the 2009 TNM classification approved by the Union International Contre le Cancer (UICC) tumor classification,[10] and the tumor grades were performed, following the WHO and the International Society of Urological Pathology (ISUP) tumor-grading system 2004.[11]

All tests for complete blood count (CBC) were collected from the antecubital vein at least seven days and not more than 30 days before surgery, between 08:00 AM and 10:00 AM, after fasting for at least eight hours. The neutrophil-to-lymphocyte ratio was calculated using the absolute neutrophil and lymphocyte counts, the monocyte-to-lymphocyte ratios by the absolute monocyte and lymphocyte counts, and the platelet-to-lymphocyte ratio by the platelet and absolute lymphocyte counts obtained in the peripheral blood count test. The modified Glasgow score (mGPS) was recorded as 0, 1, or 2 based on CRP and albumin levels measured in the blood samples. Recurrence-free survival was defined as the period between diagnosing the first non-muscle-invasive bladder cancer to the diagnosis time of recurrent non-muscle-invasive bladder cancer. Progression-free survival was defined as the period between the initial diagnosis of non-muscle-invasive bladder cancer and the time of tumor progression to pathological T2 stage or tumor grade increasing from low-grade to high-grade, or the presence of carcinoma in situ.

The study's exclusion criteria were a concomitant hematological or oncological disease, active urinary tract infection, history of chemotherapy/radiotherapy, recurrent or, incomplete tumor resection, and intravesical immunotherapy/chemotherapy.

We adjusted the cutoff values as 2.50 for NLR,[12] 5 mg/L for CRP,[12] 0.23 for MLR,[13] 123 for PLR,[14] and 1.41 for AGR[15] based on previously published studies.

All statistical analyses were performed using SPSS 26.0 (IBM Inc., Chicago, USA). Frequencies and percentages described categorical variables; continuous variables were described by means and standard deviations. The Kolmogorov–Smirnov test evaluated the normality of distributions. The Mann–Whitney- U test compared the groups regarding independent quantitative data, whereas the Chi-square test was used for independent qualitative data. Spearman's correlation analysis test was performed to determine correlations. All survival statistics were calculated with the Kaplan–Meier method and logistic regression analyses. Multivariate analyses were performed to confirm the statistical significance of the parameters.

ROC analysis was performed for the tested variables to interpret their sensitivities and specificities. A *P* value less than 0.05 was chosen for statistical significance.

Results

A total of 74 patients were included in the study. The demographic characteristics, comorbidities, the status of smoking and alcohol use, and the follow-up duration of the patients were presented in Table 1. The oncological tumor stages and grades, together with the recurrence and progression rates of the patients, with primary non-muscle-invasive bladder cancer are also presented in Table 1. Fifty-eight (78.4%) patients received immediate single-dose chemotherapy after primary TURBT. The second TURBT was performed in 26 (35.1%) patients after 2-6 weeks from initial TURBT.

When we divided the patients into subgroups according to the cutoff values regarding NLR, MLR, PLR, CRP, AGR, and mGPS there were no statistically significant relationships of NLR, CRP, and AGR with tumor characteristics, such as size, count, stage, and grade together with oncological outcomes such as recurrence, progression, and metastasis. On the other hand, we observed a statistically significant relationship between NLR and age (p = 0.002), MLR and pathological T stage (p = 0.008), and also between PLR and tumor count (p = 0.007), and pathological T stage (p = 0.007). Regarding the modified Glasgow prognostic score, the patients with an mGPS score of 2 had more CIS compared to the other patients (p = 0.011).

Spearman's correlation test revealed positive correlations of NLR with tumor size (r = 0.294) and pathological T stage (r = 0.342); MLR with tumor size (r = 0.382) and pathological T stage (r = 0.348); PLR with pathological T stage (r = 0.277) and tumor progression (r = 0.313); CRP with tumor size (r = 0.241) and pathological T stage (r = 0.260); AGR with tumor count (r = 0.283); and mGPS with the presence of CIS (r = 0.236). In addition, negative correlations of AGR were determined with tumor grade (r = -0.241) and CIS presence (r = -0.229).

In multivariate analysis, we did not identify any statistically significant relationships between systemic inflammation parameters and oncological outcomes when age, smoking status, and the presence of comorbidities were adjusted as confounding factors.

The areas under the ROC curve obtained through the performed ROC analysis with the variables tested are presented in Table 2.

Survival analysis

The mean overall survival (OAS) was 39.45 ± 19.03 months, recurrence-free survival (RFS)

Table 1: Distribution of demographic characteristics, tumor characteristics, and oncological outcomes of the patients with primary non-muscle-invasive bladder cancer

	Mean±SD
Age (years)	67.41±11.31
Follow-up duration (months)	38.77±19.53
	n (%)
Gender	
Male	64 (86.5)
Female	10 (13.5)
Smoking status	
Smoker	50 (67.6)
Non-smoker	24 (32.4)
Alcohol abuse	
Present	4 (5.4)
Absent	70 (94.6)
Comorbidities	
Coronary artery disease	13 (17.6)
Arterial hypertension	8 (10.8)
Type-2 diabetes mellitus	7 (9.5)
COPD/Asthma	3 (4.1)
More than one comorbidity	30 (40.5)
Oncological tumor stage	
Pathological Ta stage	49 (66.2)
Pathological T1 stage	25 (33.8)
Oncological tumor grade	
Low-grade	48 (64.9)
High-grade	26 (35.1)
Concomitant CIS	3 (4.1)
Tumor recurrence	
Present	32 (43.2)
Absent	42 (56.8)
Tumor progression	
Present	15 (20.3)
Absent	59 (79.7)

Table 2: Areas under the ROC curves for the tested parameters

Test result variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
MLR	0.674	0.123	0.158	0.433	0.915
NLR	0.629	0.105	0.219	0.423	0.835
PLR	0.723	0.120	0.064	0.487	0.959
AGR	0.420	0.189	0.674	0.049	0.792
mGPS	0.594	0.144	0.515	0.311	0.876
CRP	0.671	0.175	0.326	0.329	1.014

[a]Under the nonparametric assumption, [b]Null hypothesis: true area=0.5, MLR=Monocyte-to-lymphocyte ratio; NLR=Neutrophile-to-lymphocyte ratio; PLR=Platelet-to-lymphocyte ratio; AGR=Albumin-to-globulin ratio; mGPS=modified Glasgow Prognostic Score; CRP=C-reactive protein

was 22.91 ± 20.44 months, and progression-free survival (PFS) was 33.14 ± 23.70 months. The 5-year OAS, cancer-specific survival (CSS), PFS, and RFS rates were 82.6%, 95.8%, 80.8%, and 48.5%, respectively.

OAS

After patients were divided into subgroups taking the cut-off levels for NLR, MLR, PLR, CRP, AGR, and mGPS into consideration, survival analyses revealed that the 5-year OAS was 92.9% and 67.5% (p = 0.008) for NLR, 95.8% and 75.4% (p = 0.046) for MLR, 93.6% and 73.1% (p = 0.018) for PLR, 88.2% and 77.2% (p = 0.197) for CRP, 83.1% and 81.6% (p = 0.690) for AGR, 88%, and 69.8% and 88.9% (p = 0.152) for mGPS [Figure 1].

CSS

The 5-year CSS was 97.7% and 93.1% (p = 0.347) for NLR, 95.8% and 95.7% (p = 0.995) for MLR, 97.1% and 94.7% (p = 0.629) for PLR, 100% and 91.4% (p = 0.071) for CRP, 97.5% and 93.8% (p = 0.435) for AGR and 100%, and 84.2% and 100% (p = 0.012) for mGPS [Figure 2].

RFS

The 5-year RFS was 38.6% and 46.4% (p = 0.656) for NLR, 50% and 37.1% (p = 0.179) for MLR, 44% and 39.1% (p = 0.239) for PLR, 41.2% and 42.7% (p = 0.872) for CRP, 43.8% and 39.3% (p = 0.664) for AGR, and 45.3%, 34.2%, and 45.7% (p = 0.775) for mGPS [Figure 3].

PFS

The 5-year PFS was 74.1% and 74.5% (p = 0.712) for NLR, 84.2% and 66.2% (p = 0.244) for MLR, 85.3% and 63.9% (p = 0.050) for PLR, 80.4% and 66.4% (p = 0.296) for CRP, 68.1% and 80.6% (p = 0.959) for AGR, and 81.1%, 64%, and 57.1% (p = 0.434) for mGPS groups [Figure 4].

Discussion

This retrospective study investigated the predictive power of preoperative systemic inflammatory response parameters in oncological outcomes and survival of patients with NMIBC. In univariate analyses, the study revealed that MLR was associated with advanced pathological T stage, whereas PLR was associated with tumor count and pathological T stage. On the other hand, no statistically significant association was determined in multivariate analyses. Regarding survival, the patients with NLR >2.5 ng/dl, MLR <0.23, and PLR <123 had increased OAS. Additionally, the patients with an mGPS score of less than two had increased CSS. Moreover, a PLR value less than 123 was associated with an increased PFS rate. We found no association between systemic immune response parameters and the tumor's recurrence/progression in patients with NMIBC.

Inflammation plays a vital role in the local development and metastasis of malignant tumors. Until today,

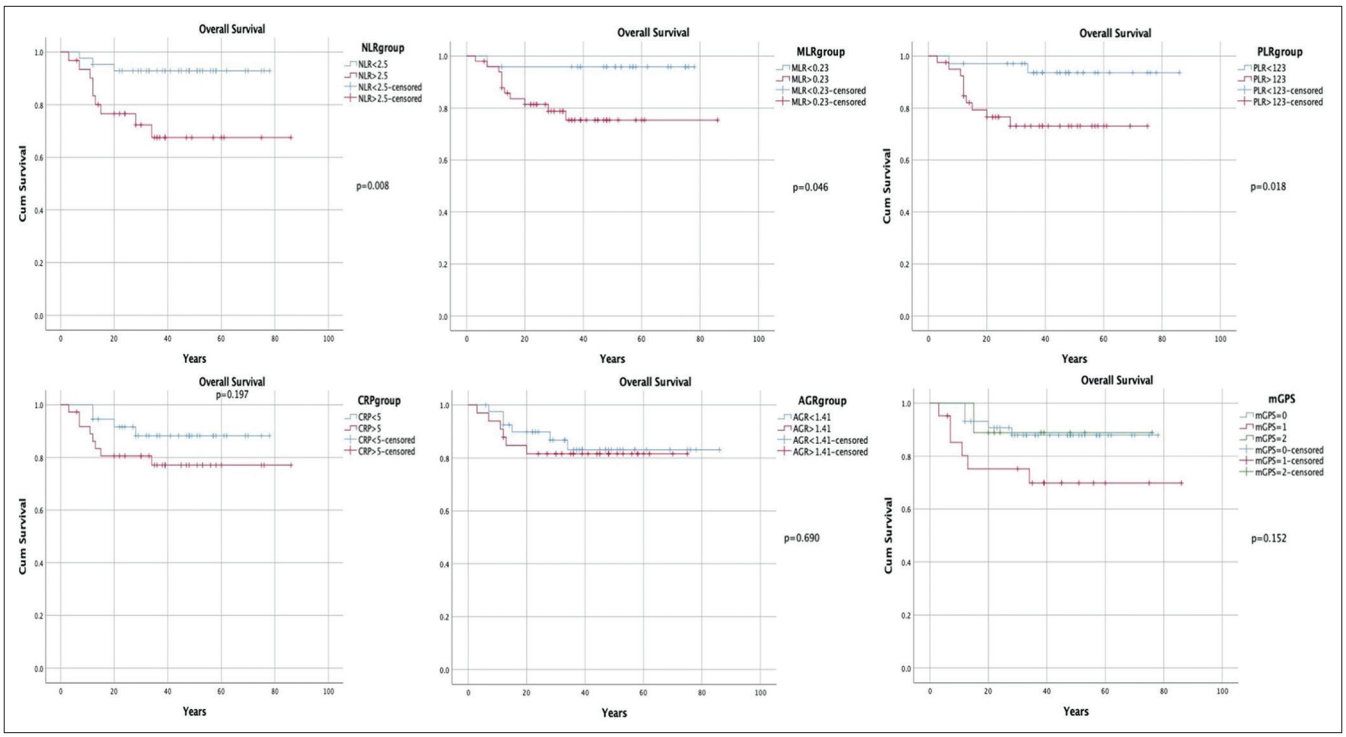

Figure 1: Overall survival Kaplan–Meier curves of patients according to the subgroups

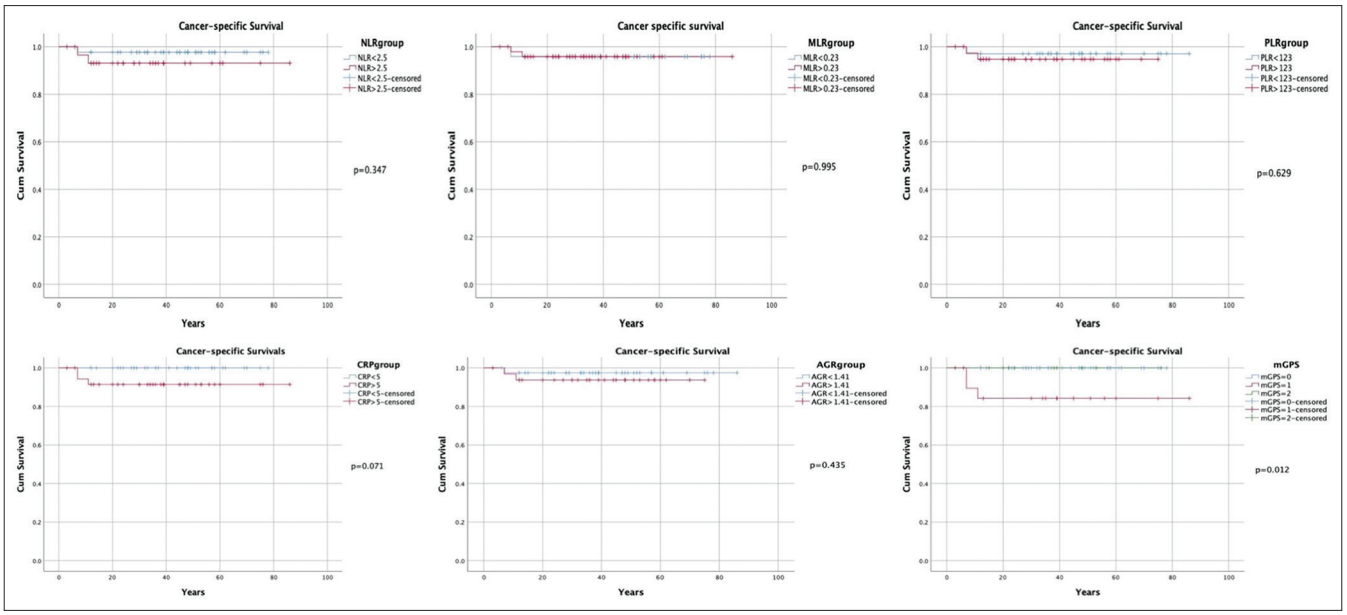

Figure 2: Cancer-specific survival Kaplan–Meier curves of the patients

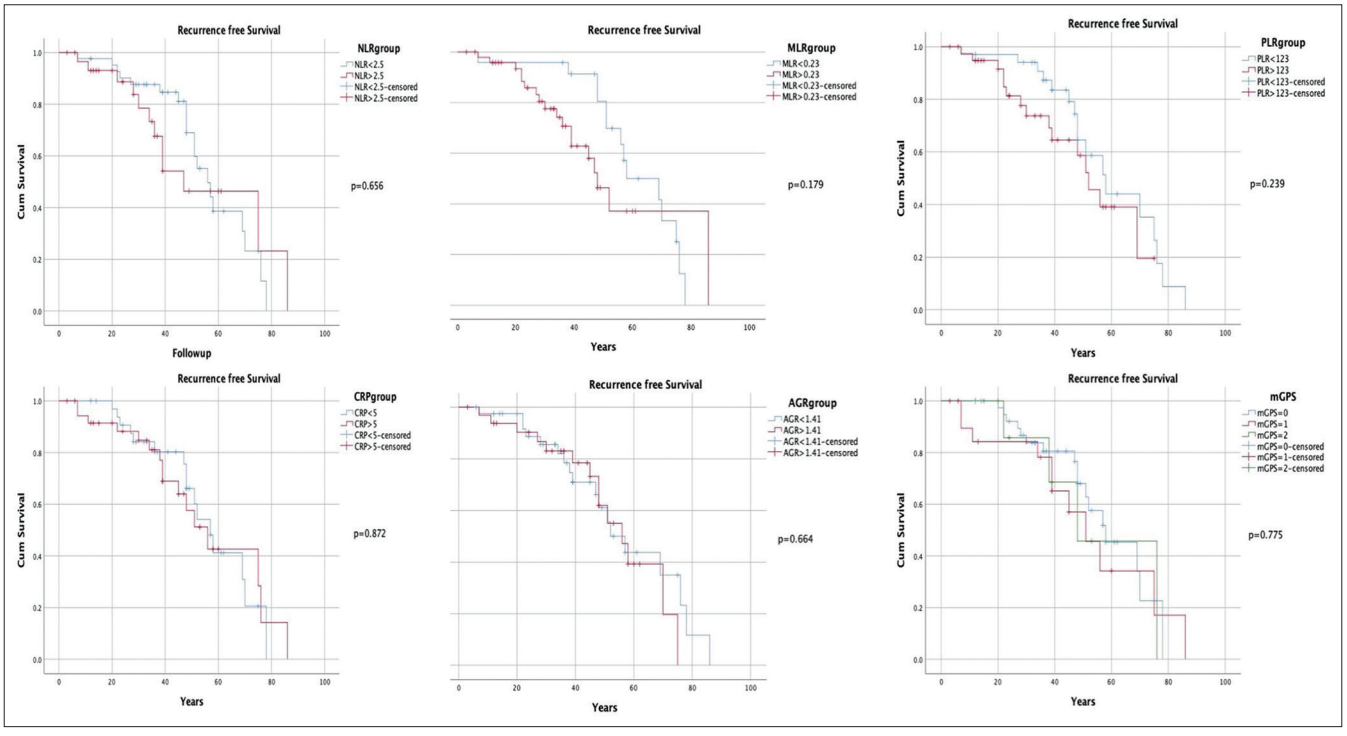

Figure 3: Recurrence-free survival Kaplan–Meier curves of the patients

the relationship between bladder cancer and chronic inflammation has been frequently investigated in several studies.[16] Systemic inflammation has been associated with tumor progression, recurrence, and metastasis, together with oncologic outcomes. The prognostic significance of inflammation markers, including the systemic immune-inflammatory index, has been demonstrated in many tumors, mainly prostate and colorectal cancers.[17] Currently, in evidence-based medicine, systemic inflammation markers do not exhibit a sufficient level of evidence regarding the evaluation and management of bladder cancers. The underlying pathophysiological mechanisms that the systemic inflammatory response markers cause biological changes in tumor tissues have not yet been clarified. Today, prognostic tools for patients with NMIBC have been primarily based on the tumor's pathological features.[18]

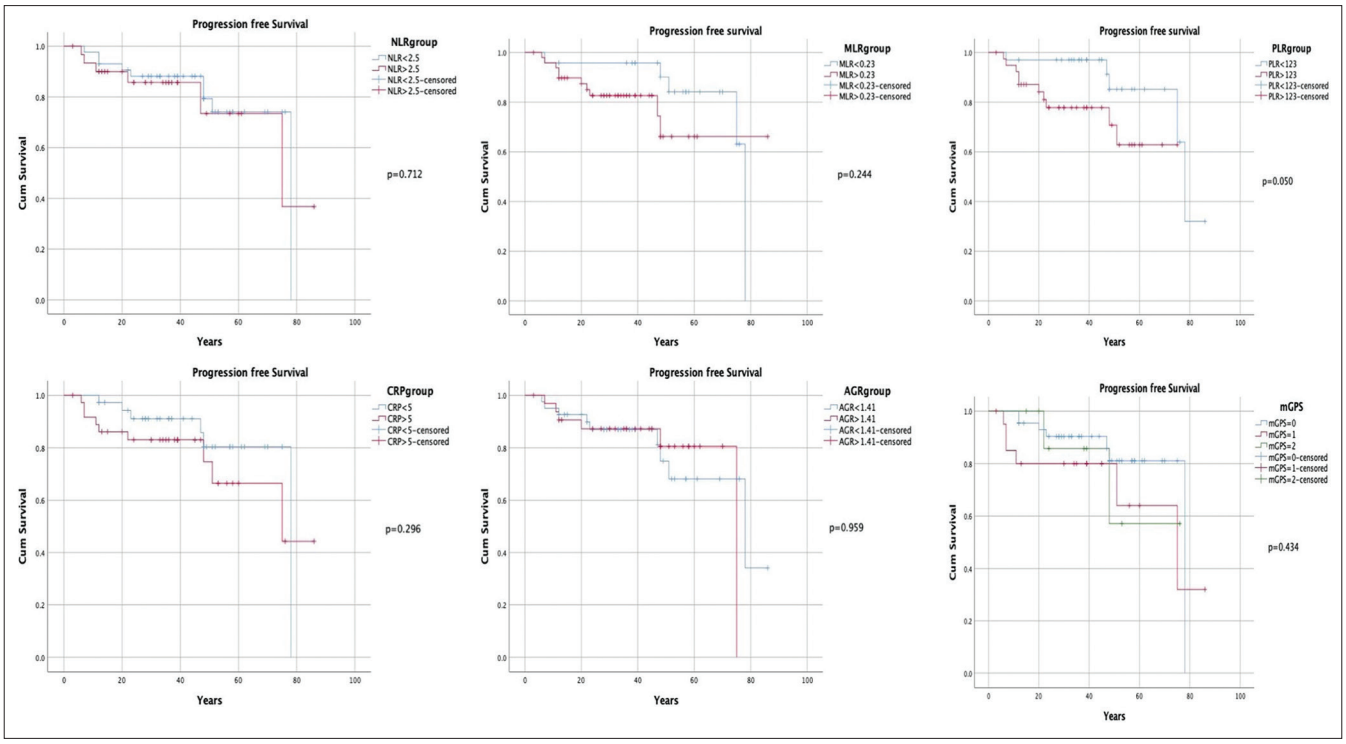

Figure 4: Progression-free survival Kaplan–Meier curves of the patients

An ideal biomarker should be able to detect possible occult micrometastasis, facilitate more accurate patient selection for perioperative systemic therapy, and have the potential to improve survival outcomes.[19] Unfortunately, patient heterogeneity in NMIBC still prevents the creation of a clinically useful, reproducible, inexpensive, and accurate biomarker. Introducing new biomarkers may help increase the prognostic impact of therapeutic models.[5] In our study, the systemic inflammatory response parameters were not related to oncological outcomes in patients with NMIBC. Therefore, we concluded that these parameters were not ideal biomarkers in patients with NMIBC.

Inflammatory blood cells such as neutrophils play crucial roles in producing high levels of reactive oxygen species (ROS), tumor necrosis factor-α (TNF-α), and macrophage migration inhibitory factor (MIF).[20] Also, neutrophils can secrete large amounts of arginase, ROS, and nitric oxide (NO), resulting in T-cell activation and impaired vascular endothelial growth factor (VEGF) production, eventually leading to tumor neovascularization.[21] As reported in studies with various cancer patients, high platelet counts can stimulate tumor angiogenesis and protect tumor cells from cytolysis, contributing to tumor recurrence and progression. Conversely, lymphocytes play an essential antitumor role by inhibiting tumor cell proliferation and metastasis and enhancing the patient's immune response to cancer.[22] Cancer may reflect decreased numbers of CD4+ T helper lymphocytes involved in cell growth, progression, and migration. Another potential cause of tumor-induced lymphocytopenia is the result of impaired lymphocyte homeostasis, together with increased apoptosis of lymphocytes. In addition, proapoptotic molecules such as Fas ligand can increase lymphocyte destruction by activating the extrinsic apoptosis pathway.[22] The retrospective study of Cantiello and colleagues[16] investigated three systemic inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) and their combinations in a multivariate predictive model. They reported that it could predict recurrence and disease progression risks in patients with high-risk NMIBC.[16]

Similarly, D'Andrea *et al*.[23] found that the preoperative neutrophil-to-lymphocyte ratio was associated with RFS and PFS. Our study did not find any relationship between NLR, tumor recurrence, and progression; however, NLR was associated with OAS in our patients with NMIBC. The univariate analyses revealed that the advanced pathological stage was associated with MLR and PLR. Additionally, PLR was associated with increasing tumor counts. As a result, we concluded that all these parameters involved reduced absolute lymphocyte count. Therefore, we suggest that lymphocytes might play an essential role in the oncological outcome. Moreover, platelets might contribute to tumor angiogenesis and be related to increased tumor count and advanced pathological stage.

Mbeuthcha reported that preoperative CRP, a marker of systemic inflammation, was associated with a high disease progression rate in NMIBC patients.[12] However, our study did not find any difference between the subgroups' preoperative CRP values regarding recurrence and progression in patients with NMIBC. Therefore, we suggest that CRP might indirectly contribute to increased CSS via mGPS.

Albumin has been reported to modulate the systemic inflammatory reaction and has antioxidant effects. Moreover, albumin plays a vital role in stabilizing cell growth and DNA replication. The globulin level increases due to the accumulation of acute-phase proteins and immunoglobulins, reflecting an immunological and inflammatory state.[24] Emerging evidence has shown that AGR could be a useful predictive tool for diagnosing cancer and determining its prognosis. However, this biomarker appears to have limited prognostic potential in patients with NMIBC. A low preoperative AGR value was associated with a higher risk of disease progression, but not disease recurrence in NMIBC patients.

On the other hand, AGR could not predict the risk of recurrence or progression in patients according to the EAU risk groups and those patients treated with BCG.[15] The study of Niwa, including 364 patients with primary NMIBC, found that low AGR was associated with a higher risk of both disease recurrence and progression.[25] In our study, we did not determine associations of AGR with increased risks of tumor progression and recurrence.

Limitations

This study had various limitations. First, because of the study's retrospective design, we could not investigate other systemic immunological parameters, such as interleukins, cytokines, macrophage migration inhibitory factors, IGF, TGF, VEGF, and reactive oxygen species, indicating inflammation. The study's second limitation was that we could not randomize the patients according to their pathological stages due to its small population.

İn conclusion**,** this study revealed no significant relationships between systemic inflammatory response parameters and oncologic outcomes regarding recurrence and progression in multivariate analysis. Although our study indicated that some components of systemic inflammatory response parameters might have been associated with improved survival in NMIBC patients, more reliable and valuable preoperative indicators than systemic immune response parameters are required in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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