ANTICANCER RESEARCH *41*: 5749-5759 (2021)
doi:10.21873/anticanres.15391

Survival Prediction by Baseline Systemic Immune-inflammation Index (SII) and its Changes During First-line Platinum-based Treatment in a Caucasian Population of Patients With Metastatic Urothelial Carcinoma (MUC)

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Abstract. *Background/Aim: Systemic immune-inflammation index (SII) predicts survival of patients with various malignancies. This study explored the prognostic value of SII in metastatic urothelial carcinoma (MUC) subjects. Patients and Methods: We evaluated 181 consecutive MUC patients treated with first-line platinum-based therapy. Karnofsky performance status <80% and visceral metastasis were present in 18.2% and 46.4% of patients, respectively. SII was based on platelet × neutrophil/lymphocyte counts. Study population was dichotomized by median into high and low SII groups before the initiation of chemotherapy and at week 6. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan–Meier method and compared with the log-rank test. Results: At median follow-up of 9.6 months, 174 patients experienced disease progression and 173 died. Patients with low SII at baseline and at week 6 had significantly better PFS (HR=0.58; p=0.0002 and HR=0.55; p<0.0001) and OS (HR=0.54; p<0.0001 and HR=0.54; p<0.0001) compared to patients with high SII. Independent prognostic value of SII was confirmed in a multivariate analysis. Conclusion: High SII before chemotherapy that persists at week 6 negatively affects survival. SII at baseline can be used in the stratification of patients within clinical trials and in clinical practice.*

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Key Words: Systemic immune-inflammation index, metastatic urothelial carcinoma, platinum-based chemotherapy, survival, response to treatment.

Bladder cancer is the tenth most common form of cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths in 2018 (1). Bladder cancer is more common in men than in women, with respective incidence and mortality rates of 9.6 and 3.2 per 100,000 in men, about 4 times those of women worldwide. Thus, the disease ranks higher among men, in whom it is the sixth most common cancer and the ninth leading cause of cancer-related death (1).

About 15% of patients with bladder cancer present with metastatic disease (2). Systemic platinum-based therapy has been the standard first-line treatment for inoperable, locally advanced, and metastatic urothelial carcinoma (MUC) for many years (3-5). The median overall survival (OS) following combined cisplatin-based chemotherapy is up to 15 months with objective response rates of 46%-49% (3, 4) and up to 9 months with carboplatin-based chemotherapy with objective response rates of less than 42% (5). Bajorin *et al*. established performance status and visceral metastases as independent factors for predicting survival in patients with MUC (6). However, there are no biomarkers that can predict which patients will not benefit from platinum-based chemotherapy and could therefore become candidates for different therapeutic approaches *e.g*., within clinical trials.

Inflammation plays a significant role in the process of tumorigenesis (7-9). Cells of the immune system secreting proinflammatory cytokines participate in cancer initiation, its development and metastatic spread (7). Through direct signaling to cancer cells, platelets induce an epithelial-mesenchymal-like transition and promote metastasis (8). Decrease and/or damage of lymphocytes promote these malignancies (9). Neutrophils secrete molecules promoting chronic inflammation as well as tumor angiogenesis and growth (9). Moreover, neutrophils, lymphocytes, and platelets affect survival of tumor cells in circulation (7).

Based on this data, various prognostic biomarkers such as platelet count (10) and neutrophil-to-lymphocyte ratio (11, 12) have been used to assess systemic inflammatory response in urothelial carcinoma. Recently, the systemic immune-inflammation index (SII) based on neutrophil, lymphocyte and platelet count has been developed and investigated as a prognostic indicator of poor outcome in various cancers (13, 14).

The objective of this retrospective unicentric study was to explore the prognostic value of the SII at baseline and its changes at week 6 during first-line platinum-based chemotherapy in a Caucasian population with metastatic urothelial carcinoma (MUC). We hypothesized that patients with high SII would have worse survival and treatment outcomes.

Patients and Methods

Study population. All patients enrolled into this retrospective study met the following inclusion criteria: Age ≥18 years, histologically proven carcinoma of the urothelium (renal pelvis, ureter, and bladder) with at least one measurable distant metastasis on computed tomography (CT) scan, white blood count $\geq 3.5\times10^9$/l, hemoglobin ≥10 g/dl, and platelets $\geq 100\times10^9$/l. Prior intravesical therapy, immunotherapy, or radiation therapy was allowed if completed at least 4 weeks before enrollment.

Exclusion criteria were as follows: Prior systemic chemotherapy, an active infection at time of blood count evaluation, second primary malignancy except basal cell skin carcinoma and/or in situ cervical carcinoma in the last 5 years, HIV infection/AIDS, or any immunodeficiency.

After obtaining the approval of the Ethical Committee at the National Cancer Institute (NCI) in Bratislava (Slovakia), pathologic, clinical, and radiologic data were entered by the physicians into electronic data files and their accuracy was validated for each patient by an independent investigator.

All patients were treated at the NCI in Bratislava (Slovakia) between January 2000 and December 2015 when they were managed in accordance with the guidelines for good clinical practice applicable at the time of their treatment. The standard first-line regimen comprised cisplatin (or carboplatin in cisplatin ineligible patients) with gemcitabine. After progression on platinum-based chemotherapy, there was no standard second-line option with an established effect on survival.

The most common combination of cytotoxic agents, cisplatin (70 mg per m^2 on day 1) and gemcitabine (1,000 mg per m^2 on days 1 and 8), with a new course on day 22 was administered to 133 patients (73.5%); carboplatin – area under the concentration-time curve (AUC) 5 on day 1 and gemcitabine (1,000 mg per m^2 on days 1 and 8), a new course on day 22 was administered to 28 patients (15.5%). All patients were treated with up to 8 courses of chemotherapy, depending on unacceptable toxicity, or disease progression. No patients received supportive care with granulocyte colony stimulating factor (G-CSF).

The response to treatment was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria Version 1.1 (15) with clinical and blood examinations, including complete blood counts in all patients at each course of chemotherapy. Radiologic response was obtained by computed tomography (CT) scan of the chest, abdomen, and pelvis at baseline and was repeated every 12 weeks during treatment.

Table I. *Patient characteristics*.

	n (%)
Study population	181 (100%)
Age	
Median (range)	66 (18-84)
Male/Female	135/45 (74.6%/25.4%)
Primary tumor site	
Bladder	148 (81.8%)
Upper GU tract	27 (14.9%)
Histology type	
Transitional cell carcinoma	181 (100.0%)
Chemotherapy	
Cisplatin + Gemcitabine	133 (73.5%)
Carboplatin + Gemcitabine	28 (15.5%)
Other platinum-based regimes	20 (11.0%)
Karnofsky performance status	
<80%	33 (18.2%)
Visceral metastasis	
Present	84 (46.4%)
Absent	97 (53.6%)
Response to treatment	
Objective response*	79 (43.7%)
No response	102 (53.3%)
Metastasis localization	
Lymph nodes	158 (87.3%)
Skeletal	45 (24.9%)
Lungs	60 (33.2%)
Liver	48 (26.5%)
Peritoneum	15 (8.3%)

n: Number of patients; *complete response or partial response.

An objective tumor response was reported in 79 of 181 evaluable patients (43.7%) including 24 complete responses (13.3%) and 55 partial responses (30.3%). Stable disease was recorded in 49 cases (27.1%); in 53 subjects (29.3%) cancer progressed on chemotherapy.

SII calculation. Systemic immune inflammation index (SII) was calculated taking into consideration the levels of platelets (P), neutrophils (N) and lymphocytes (L) determined on day 0 or day 1 before the first course of chemotherapy (SII baseline) and on day 0 or day 1 of the third course of treatment (SII at week 6) as suggested in the study of Lolli *et al*. (13). SII was defined as P×N/L (13). This study population was dichotomized by median into high SII and low SII groups at baseline (median 1,326) and at week 6 (median 705).

Statistical analysis. Data were summarized by frequency for categorical variables and by median and range for continuous variables. Differences were considered statistically significant when $p<0.05$. Progression-free survival (PFS) was calculated from the date of first-line chemotherapy (day 1 of the first course) until disease progression, last follow-up, or death for any reason. OS was calculated from the start of first-line chemotherapy (day 1 of the first course) until the last follow-up or death for any reason. The Kaplan–Meier method was used to estimate both PFS and OS. The

Table II. *Association between baseline SII and patient/tumor characteristics.*

	N	Mean	Median	SD	SEM	*p*-Value
SII	181	2,072.0	1,326.2	2,363.2	175.7	NA
Distant lymph node metastasis						
Absent	23	1,452.4	914.0	1,190.4	491.6	0.15
Present	158	2,162.1	1,421.9	2,477.8	187.6	
Bone metastasis						
Absent	136	2,064.7	1,156.1	2,551.9	203.2	0.06
Present	45	2,094.0	1,447.0	1,692.5	353.3	
Lung metastasis						
Absent	121	2,132.1	1,326.2	2,487.5	215.3	0.53
Present	60	1,950.7	1,319.2	2,104.8	305.7	
Liver metastasis						
Absent	133	1,969.3	1,178.0	2,341.8	204.9	0.19
Present	48	2,356.3	1,565.7	2,423.4	341.1	
Peritoneal metastasis						
Absent	166	2,033.6	1,277.9	2,372.00	183.7	0.42
Present	15	2,496.0	1,849.3	2,298.2	611.0	
Visceral metastasis						
Absent	97	1,955.9	1,178.0	2,292.4	240.3	0.62
Present	84	2,206.0	1,391.0	1,449.3	258.2	
KPS < 80%						
Absent	148	1,717.8	1,097.4	1,767.0	184.7	**0.00012***
Present	33	3,660.3	2,522.9	3,726.6	391.1	
Primary tumor site Bladder						
No bladder tumor	33	1,885.9	1,042.6	1,703.3	412.2	0.68
Bladder tumor	148	2,113.4	1,361.7	2,489.4	194.7	
Upper GU tract						
No upper GU tumor	154	2,121.2	1,421.9	2,449.8	190.7	0.30
Upper GU tumor	27	1,791.1	978.1	1,802.5	455.5	
Response to treatment						
No response	102	2,526.5	1,574.8	2,754.5	228.9	**0.00102***
Objective response**	79	1,485.1	974.3	1,563.3	260.1	

n: Number of patients; SD: standard deviation; SEM: standard error mean; NA: not applicable; KPS: Karnofsky performance status; *significant; **complete response or partial response. Bold values indicate statistical significance ($p<0.05$).

differences between the groups were determined by log rank test. Multivariate analysis was carried out by the Cox regression model and included Karnofsky performance status (KPS), visceral metastasis, and SII. Estimated hazard ratios (HR), their 95% confidence intervals (95%CI), and *p*-values were calculated from the Cox proportional hazard regression models. All statistical analyses were performed using NCSS 20 Statistical Software, Kaysville, UT, USA (16).

Results

Once patients were selected based on inclusion/exclusion criteria, a total of 181 MUC patients with median age of 66 years (range=18-84 years), who underwent first-line platinum-based chemotherapy, were enrolled in this study. Most patients were males (v=135; 74.6%). Of all subjects, 148 (81.8%) had bladder urothelial cancer and 27 (14.9%) upper genitourinary tract transition-cell carcinoma. At the time of chemotherapy initiation, 33 patients (18.2%) had a KPS less than 80% and visceral metastases were present in 84 (46.4%) of patients. The most common metastatic sites were distant lymph nodes in 158 (87.3%) patients, followed by lungs (n=60, 33.2%), liver (n=48, 26.5%), bones (n=45, 24.9%), and peritoneum (n=15, 8.3%). The demographic characteristics at baseline are shown in Table I.

Association between SII and patient/tumor characteristics. Median SIIs at baseline and week 6 were 1326 (range=83-17,870) and 705 (range=5-12,988), respectively. The association between baseline SII and patient/tumor characteristics are shown in Table II. In subjects with KPS <80% *vs.* KPS ≥80%, median SIIs significantly differed at baseline (median 2,523 *vs.* 1,097, $p=0.00012$) but not at week 6 (median 927 *vs.* 624, $p=0.06895$). A difference in median SIIs in responders to treatment *vs.* non-responders was significant at baseline (median 974 *vs.* 1574, $p=0.00102$) and at week 6 (median 601 *vs.* 842, $p=0.02752$).

Table III. *Subgroup analysis of prognostic value of baseline SII for progression-free survival.*

	n	HR	Lower 95%CI	Higher 95%CI	*p*-Value
SII	181				
Distant lymph node metastasis					
Absent	23	0.44	0.15	1.25	**0.0477***
Present	158	0.62	0.45	0.86	**0.023***
Bone metastasis					
Absent	136	0.55	0.38	0.80	**0.0004***
Present	45	0.85	0.47	1.54	0.5843
Lung metastasis					
Absent	121	0.57	0.39	0.83	**0.0015***
Present	60	0.61	0.36	1.03	**0.0499***
Liver metastasis					
Absent	133	0.53	0.37	0.77	**0.0002***
Present	48	0.92	0.51	1.65	0.7617
Peritoneal metastasis					
Absent	166	0.59	0.43	0.81	**0.0006***
Present	15	0.69	0.24	1.96	0.4637
Visceral metastasis					
Absent	97	0.50	0.32	0.78	**0.0006***
Present	84	0.71	0.46	1.11	0.1168
KPS < 80%					
Absent	148	0.65	0.46	0.91	**0.0079***
Present	33	0.58	0.28	1.19	0.1368
Primary tumor site Bladder					
No bladder tumor	33	0.65	0.32	1.33	0.1864
Bladder tumor	148	0.56	0.40	0.79	**0.0004***
Upper GU tract					
No upper GU tumor	154	0.55	0.39	0.76	**0.0001***
Upper GU tumor	27	0.67	0.29	1.54	0.281
Response to treatment					
No response	102	0.67	0.45	0.99	**0.0427***
Objective response**	79	0.62	0.37	1.03	**0.0387***

n: Number of patients; HR: hazard ratio; CI: confidence interval; KPS: Karnofsky performance status; *significant; **complete response or partial response. Bold values indicate statistical significance ($p<0.05$).

Prognostic value of SII at baseline. At median follow-up of 9.6 months (range=1.7-191.1 months), 174 patients (96.1%) experienced disease progression and 173 (95.6%) died. Median PFS for the entire cohort was 6.6 months (95%CI=5.4-7.4 months) and median OS was 9.6 months (95%CI=8.6-11.7 months).

When this study population was dichotomized by median baseline SII into high SII (>1326) and low (≤1,326), the median PFS was 7.8 months (95%CI=6.9-8.8) in patients with high SII and 4.8 months (95%CI=3.9-6.5 months) in those with low SII (HR=0.58, 95%CI=0.42-0.79; $p=0.0002$). Median OS was 7.6 months (95%CI=5.4-9.4 months) in patients with high SII and 13.1 months (95%CI=11.1-21.3 months) in subjects with low SII at baseline (HR=0.54, 95%CI=0.39-0.74; $p<0.0001$).

High SII at baseline was associated with significantly worse PFS in the subgroups of patients with and without distant lymph node metastasis, without bone metastasis, with and without lung metastasis, without liver metastasis, without peritoneal metastasis, without visceral metastasis, with KPS ≥80%, with bladder as the primary tumor site, without upper GU tract as the primary tumor site, with and without response to systemic treatment. The subgroups analyses for PFS are shown in Table III.

High SII at baseline was associated with significantly worse OS in the subgroups of patients with and without distant lymph node metastasis, without bone metastasis, with and without lung metastasis, without liver metastasis, without peritoneal metastasis, without visceral metastasis, with KPS ≥80% and KPS >80%, with bladder as the primary tumor site, with upper GU tract as the primary tumor site, and without response to systemic treatment. The subgroups analyses for OS are shown in Table IV.

A univariate analysis revealed that a significant predictor of PFS was KPS (HR=0.42, 95%CI=0.24-0.71; $p<0.0001$) but not visceral metastases (HR=0.76, 95%CI=0.56-1.03;

Table IV. *Subgroup analysis of prognostic value of baseline SII for overall survival.*

	n	HR	Lower 95%CI	Higher 95%CI	*p*-Value
SII	181				
Distant lymph node metastasis					
Absent	23	0.27	0.08	0.92	**0.0008***
Present	158	0.59	0.42	0.82	**0.0008***
Bone metastasis					
Absent	136	0.48	0.33	0.71	**<0.0001***
Present	45	0.83	0.46	1.51	0.544
Lung metastasis					
Absent	121	0.57	0.39	0.83	**0.0019***
Present	60	0.47	0.27	0.82	**0.0026***
Liver metastasis					
Absent	133	0.46	0.31	0.68	**<0.0001***
Present	48	0.93	0.52	1.68	0.8135
Peritoneal metastasis					
Absent	166	0.54	0.39	0.75	**0.0001***
Present	15	0.54	0.19	1.55	0.1799
Visceral metastasis					
Absent	97	0.48	0.30	0.75	**0.0002***
Present	84	0.62	0.40	0.97	0.0287
KPS <80%					
Absent	148	0.60	0.42	0.86	**0.021***
Present	33	0.50	0.24	1.01	**0.0424***
Primary tumor site Bladder					
No bladder tumor	33	0.54	0.26	1.12	0.0538
Bladder tumor	148	0.51	0.36	0.73	**<0.0001***
Upper GU tract					
No upper GU tumor	154	0.51	0.36	0.71	**<0.0001***
Upper GU tumor	27	0.52	0.21	1.26	0.0728
Response to treatment					
No response	102	0.53	0.36	0.79	**0.0011***
Objective response**	79	0.64	0.38	1.07	0.0607

n: Number of patients; HR: hazard ratio; CI: confidence interval; KPS: Karnofsky performance status; *significant; **complete response or partial response. Bold values indicate statistical significance ($p<0.05$).

$p=0.0678$). KPS and visceral metastasis present at time of treatment initiation were significant predictors of OS (HR=0.34, 95%CI=0.19-0.61; $p<0.0001$ for KPS and HR=0.73, 95%CI=0.54-0.99; $p=0.0386$ for visceral metastases). In a multivariate analysis, Karnofsky performance status, visceral metastasis presence, and SII at baseline remained significant predictors of PFS and of OS (Table V).

Prognostic value of SII at week 6. Study population was dichotomized again by median into high SII (>705) and low SII (≤705) groups at week 6. Median PFS was 4.8 months (95%CI=3.9-6.2 months) in patients with high SII and 8.2 months (95%CI=6.9-12.1 months) in subjects with low SII, (HR=0.55; 95%CI=0.41-0.76; $p<0.0001$). Median OS was 8.0 months (95%CI=6.1-9.2 months) in patients with high SII and 17.3 months (95%CI=12.1-22.4 months) in those with low SII (HR=0.54; 95%CI=0.39-0.74; $p<0.0001$). Kaplan–Meier estimates of probabilities of PFS and OS according to SII at week 6 are shown in Figure 1 and Figure 2, respectively.

Prognostic value of SII changes. When comparing four subgroups according to SII baseline and SII at week 6 (Figure 3), the most significant difference was between subgroups with low levels of inflammation determined by SII in both timepoints (median PFS 9.2 months, 95%CI=7.7-13.0) and high levels of inflammation before chemotherapy and at week 6 (median PFS 4.2 months, 95%CI=3.4-6.0). Median PFS for a subgroup with high level of inflammation before chemotherapy initiation and its low level at week 6 was 6.6 months (95%CI=4.4-9.9 months). Median PFS for a subgroup with low level of inflammation before chemotherapy initiation and its high level at week 6 was 6.1 months (95%CI=4.7-7.6 months).

Comparing four subgroups according to SII baseline and SII at week 6 (Figure 4), the most significant difference was

between subgroups with low levels of inflammation determined by SII before chemotherapy and at week 6 (median OS 20.9 months, 95%CI=13.0-24.2 months) and high levels of inflammation before chemotherapy and at week 6 (median OS 6.1 months, 95%CI=3.8-8.0). Median OS for a subgroup with high level of inflammation before chemotherapy initiation and its low level at week 6 was 9.6 months (3.5-14.5 months). Median OS for a subgroup with low level of inflammation before chemotherapy initiation and its high level at week 6 was 9.6 months (8.0-12.4 months).

Table V. *Multivariate (Cox regression) analyses of prognostic value of baseline SII for progression-free survival (A) and overall survival (B).*

A.

Variables	RR	95%CI Low	95%CI High	*p*-Value
SII				
>1,326 *vs.* ≤1,326	1.63	1.19	2.23	0.0024
KPS				
<80% *vs.* ≥80%	2.54	1.68	3.85	<0.00001
Visceral metastasis				
Present *vs.* absent	1.40	1.03	1.91	0.0332

B.

Variables	RR	95%CI Low	95%CI High	*p*-Value
SII				
>1,326 *vs.* ≤1,326	1.82	1.33	2.50	0.0002
KPS				
<80% *vs.* ≥80%	3.35	2.20	5.11	<0.00001
Visceral metastasis				
Present *vs.* absent	1.48	1.08	2.01	0.014

n: Number of patients; RR: risk ratio; CI: confidence interval; SII: systemic immune-inflammation index; KPS: Karnofsky performance status.

Discussion

This study draws attention to the final analysis of the association between systemic-immune inflammation index (SII) and both survival prediction and response to treatment with platinum-based regimens in a first-line setting in a Caucasian population of patients with metastatic urothelial carcinoma. High baseline SII levels were associated with poor survival in terms of PFS and OS, as well as poor response to treatment. Compared to baseline values, a level of systemic inflammation determined by SII was generally lower at week 6, which was equivalent to the application of two courses of chemotherapy. High SII at week 6 was associated with poor survival in terms of PFS and OS. The improvement of SII value at week 6 was associated with a better prognosis possibly as an effect of chemotherapy on the counts of peripheral blood cells secondary to a reduction of inflammation processes. A clinically significant difference was noted in PFS and OS between the subgroup of patients with a low level of SII both at baseline and at week 6 compared to a subgroup with a high level of SII at baseline and at week 6. While SII showed prognostic value in anti-PD-L1-treated patients with MUC after progression on first-line therapy (17), to the best of our knowledge, this is the first trial to demonstrate the significance of changes in SII during platinum-based chemotherapy in a Caucasian population.

Inflammation both systemic and in the local tumor microenvironment plays a critical role in tumorigenesis (18). The number and distribution of immune cell types, including neutrophils, macrophages, dendritic cells, natural killer (NK) cells, T cells and B cells, and proinflammatory cytokines produced by malignant and inflammatory cells in the tumor microenvironment are involved in the initiation, development, and metastatic spread (18). Therefore, changes in the balance between immune cells and cytokines can result in different responses of the immune system, as well as in the amount and ratio of cells detectable in peripheral blood.

Some types of cancers may accelerate the process of myelopoiesis, resulting in leukocytosis, characterized by increased numbers of immature myeloid cells in the bone marrow and blood (19). In this setting, accelerated myelopoiesis appears to result from the production of bone marrow-stimulating growth factors by tumor cells, most notably the cytokines granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor (GM-CSF) (18). Human-neutrophil proteins 1, 2, and 3 release cytokines, stimulate monocytes and inhibit the fibrinolytic system and, together with proinflammatory mediators, promote cell proliferation, survival, migration, angiogenesis, and metastasis (7, 20). Increases in numbers of neutrophils negatively impacts T-cell mediated adaptive immunity (21). CD4+T cells play key roles in tumor immunity through three different mechanisms (22). First, the provision of help for anti-tumor CD8+cytotoxic T lymphocytes (CTLs) through direct (activated CD4+ T cells secrete interleukin (IL)-2, which activates CD8+ CTLs) and indirect (by supporting and maintaining pro-inflammatory cross-presenting dendritic cells) mechanisms. Second, the production of effector cytokines such as interferon γ (IFNγ) and tumor necrosis factor-α (TNFα), both of which have direct anti-tumor activity. In addition, CD4+T cells can mediate direct cytotoxicity against tumor cells. Finally, the induction of humoral responses against tumor antigens drives differentiation and maturation of B cells into affinity-matured, class-switched plasma cells.

Among the causes of thrombocytosis is the capability of some tumor cells to produce thrombopoietin and an increase in platelets indicated by an up-regulation of platelet activation

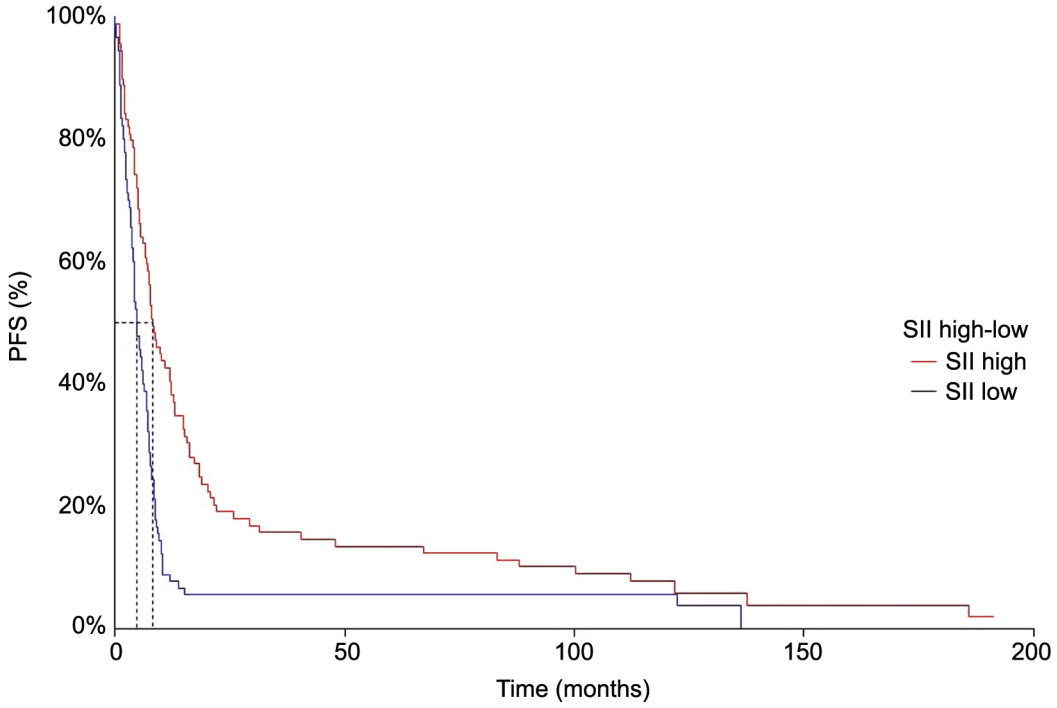

Figure 1. *Kaplan–Meier estimates of probabilities of progression-free survival (PFS) according to SII (705 median) at week 6 in metastatic urothelial carcinoma patients (n=179), HR=0.55, 95%CI=0.41-0.76, p<0.00001. Median PFS for SII high (red line) was 4.8 months (95%CI=3.9-6.2 months) and median PFS for SII low (blue line) was 8.2 months (95%CI=6.9-12.1 months). PFS: Progression-free survival; HR: hazard ratio; CI: confidence interval; SII: systemic immune-inflammation index.*

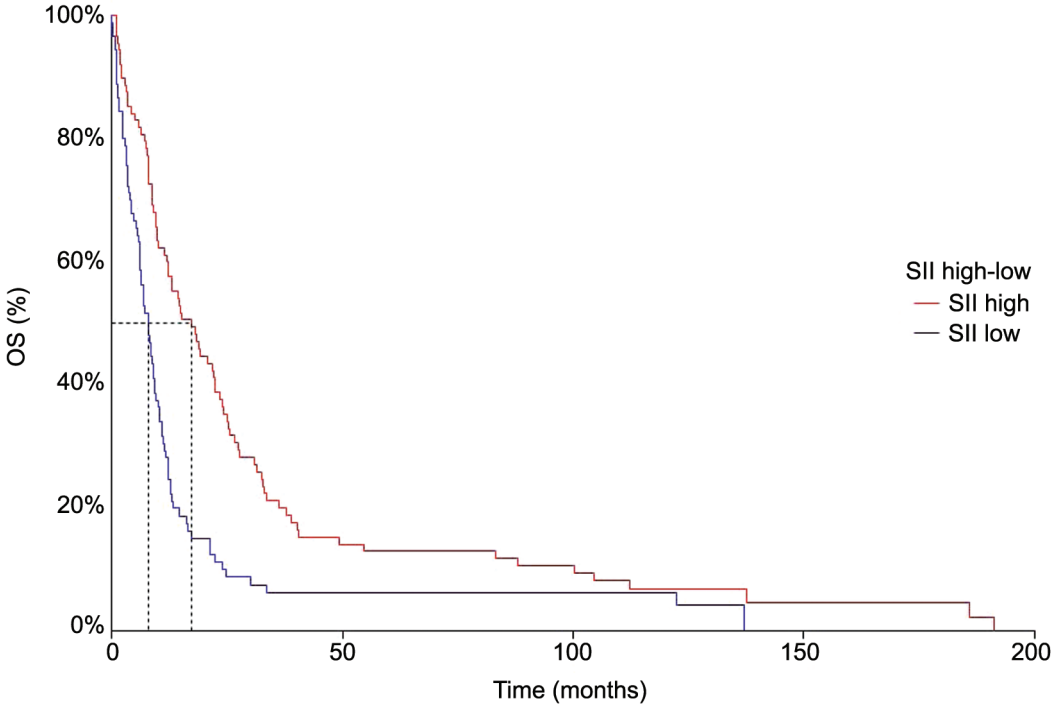

Figure 2. *Kaplan–Meier estimates of probabilities of overall survival (OS) according to SII (705 median) at week 6 in metastatic urothelial carcinoma patients (n=179), HR=0.54, 95%CI=0.39-0.74, p<0.00001. Median OS for SII high (red line) was 8.0 months (95%CI=6.1-9.2 months) and median OS for SII low (blue line) was 17.3 months (95%CI=12.1-22.4 months). OS: Overall survival; HR: hazard ratio; CI: confidence interval; SII: systemic immune-inflammation index.*

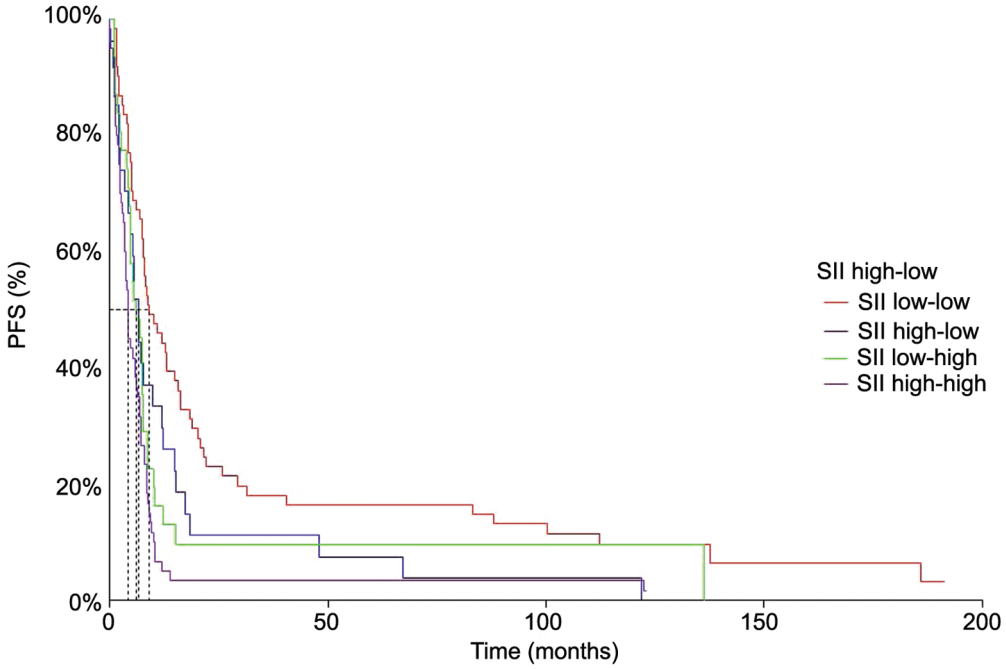

Figure 3. *Kaplan–Meier estimates of probabilities of progression-free survival according to SII at baseline (1326 median) and at week 6 (705 median) in metastatic urothelial carcinoma patients (n=179), p<0.00001. Median PFS for SII low-low (red line) was 9.2 months (95%CI=7.7-13.0 months), median PFS for SII high-low (blue line) was 6.6 months (95%CI=4.4-9.9 months), median PFS for SII low-high (green line) was 6.1 months (95%CI=4.7-7.6 months), and median PFS for SII high-high (violet line) was 4.2 months (95%CI=3.4-6.0 months). PFS: Progression-free survival; HR: hazard ratio; CI: confidence interval; SII: systemic immune-inflammation index.*

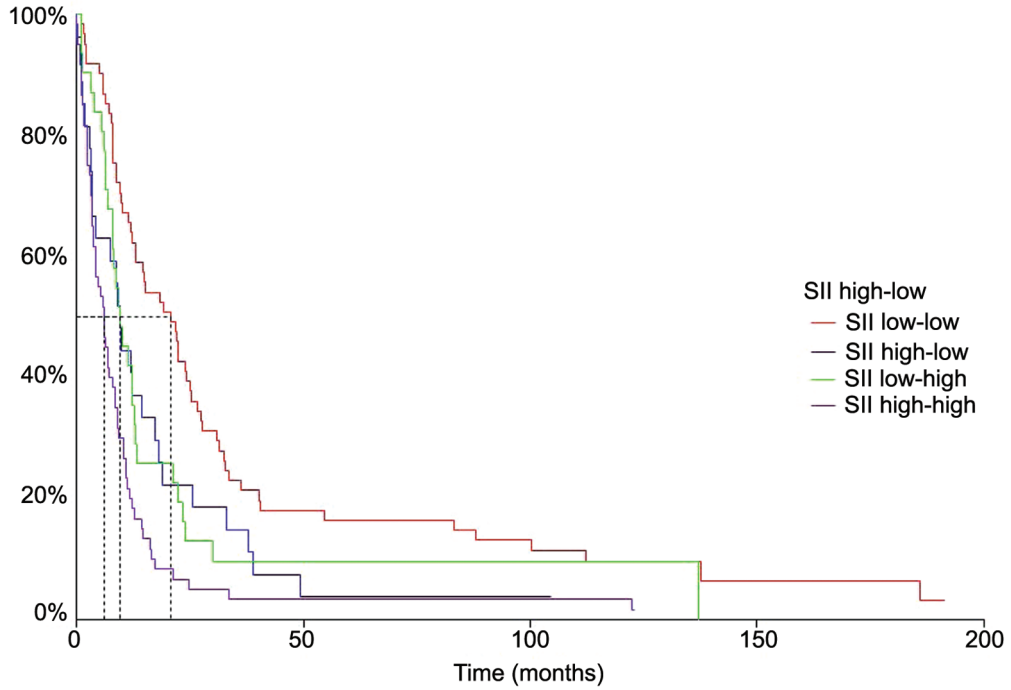

Figure 4. *Kaplan–Meier estimates of probabilities of overall survival according to SII at baseline and week 6 in metastatic urothelial carcinoma patients (n=179), p<0.00001. Median OS for SII low-low (red line) was 20.9 months (95%CI=13.0-24.2 months), median OS for SII high-low (blue line) was 9.6 months (95%CI=3.5-14.5 months), median OS for SII low-high (green line) was 9.6 months (95%CI=8.0-12.4 months), and median OS for SII high-high (violet line) was 6.2 months (95%=CI=3.8-8.0 months). OS: Overall survival; HR: hazard ratio; CI: confidence interval; SII: systemic immune-inflammation index.*

markers such as P-selectin, β-thromboglobulin or CD40 ligand (23). Thrombocytes also have a pro-metastatic effect by producing platelet-derived transforming growth factor β (TGF-β), which down-regulates NK group 2, member D (NKG2D) and results in protection of tumor cells from NK cells while promoting epithelial to mesenchymal transition by activation of TGF-β/smad and NF-κb signaling pathways (7) and promoting tumor cell extravasation (24). TGF-β is partially responsible for the transformation of neutrophils toward a pro-tumorigenic phenotype (25). Preoperative and postoperative thrombocytosis has been associated with worse outcomes in subjects with both bladder carcinoma and upper tract urothelial carcinoma (10, 26).

Several models (6, 11, 27-29) have been established in the effort to identify in advance a subpopulation of patients with inoperable locally-advanced and/or metastatic urothelial carcinoma, that has worse outcomes. Probably the most often used prognostic score derives from the Bajorin model (6), which is based on performance status and visceral metastasis sites of the disease. The Galsky model (27) considers the number of visceral metastases, the site of the primary tumor, performance status by Eastern Cooperative Oncology Group (ECOG), the presence or absence of lymph node metastases, and leukocyte count. The Glasgow prognostic score (28) incorporates an inflammation factor (C-reactive protein). Later, the neutrophil to lymphocyte ratio was confirmed as a prognostic index in the different stages of urothelial carcinoma including in the metastatic setting (11). In 2017, Su *et al*. (29) published a paper on the novel inflammation-based prognostic score incorporating absolute neutrophil count and the absolute lymphocyte count to predict survival of patients with metastatic urothelial carcinoma in Taiwan. A systemic immune-inflammation index (SII) combining neutrophil to lymphocyte ratio with platelet counts (13, 14) seems to be more objective in reflecting the balance between host inflammatory and immune response status than the previously mentioned neutrophil to lymphocyte ratio.

As was shown in this study, SII determined the prognosis of patients with metastatic urothelial carcinoma and their response to treatment. SII at baseline and its changes over time could be used for improved patient stratification. Early identification of subjects not responding to first-line platinum-based chemotherapy can spare them unnecessary toxicity while providing justification for the use of different therapeutic approaches within clinical trials and in clinical practice.

Among the limitations of this study are its non-randomized single-center retrospective design, the relatively low number of enrolled patients, and the lack of detailed analysis of chemotherapy toxicity. On the other hand, this study reflects a real-world population of patients with metastatic urothelial carcinoma and its treatment over the first 15 years of this millennium. However, validation with a larger prospective data set is necessary.

In previous studies, inoperable advanced urothelial carcinoma patients have been selected for treatment based on various criteria. In the JAVELIN study (30), subjects were randomized to avelumab maintenance or best supportive care considering their response to 4-6 courses of platinum-based chemotherapy with significantly better results in favor of immunotherapy. In the mono-immunotherapy arms of the phase 3 trial IMvigor130 (31) with atezolizumab and the phase 3 study KEYNOTE-361 (32) with pembrolizumab, only patients with programmed cell death ligand 1 (PD-L1) positive tumors were enrolled. However, none of the studies referred above has included data on SII at baseline and during treatment and, therefore, no conclusions can be drawn as to whether SII can act as a predictor for outcomes for these newer therapies in terms of survival and response to treatment.

One of the earliest immunotherapies for muscle-non-invasive urothelial bladder cancer is Bacille Calmette Guerin (BCG). Despite being used since 1970s, the exact mechanism of action has not been clarified for a long time. In 2019, Joseph and Enting published a review (33) about immunological cascade in BCG treatment with the key role of neutrophils, macrophages, and dendritic cells. Newer immunotherapies based on check-point inhibition have proved to offer some success in urothelial carcinoma over the last decade with response rates ranging from 10% to 50%. This limited efficacy may be explained by adaptations of the tumor and by their sole targeting of the CD8+ T lymphocytes that represent only the culmination of the activation of successive immune populations (33). Among the probable future directions in the urothelial carcinoma landscape are combinations of effective strategies, such as check-point inhibitors and BCG with some hypothetic treatment suppressing immunosuppressive tumor microenvironment and/or increasing the actions of innate immune cell subpopulations. New findings in urothelial carcinoma pathogenesis and novel therapeutics could also result from an increasing interest in urine microbiome research (34).

Conclusion

The systemic immune-inflammation index is an independent survival factor for Caucasian patients with metastatic urothelial carcinoma receiving first-line platinum-based chemotherapy. A high systemic immune-inflammation load before commencement of chemotherapy that persists at week 6 negatively affects PFS and OS, and correlates with response to treatment. Therefore, measuring and recording the systemic immune-inflammation index could be a useful tool for patient stratification as a routine part of clinical practice, as well as within clinical trials.

Conflicts of Interest

The Authors have no competing interests or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Authors' Contributions

PP and MM designed the study; PP drafted the manuscript. PP, JS, and JO collected data. PP and JS performed the statistical analysis. JM, MC, KR, and ZS contributed to clinical data collection. BK controlled the accuracy of data.

Acknowledgements

This study was supported by OncoReSearch, Slovakia. The first results of this retrospective study conducted at the National Cancer Institute of Slovakia were published in the form of an abstract at 2017 American Society of Clinical Oncology (ASCO) Annual Meeting. The Authors' gratitude also goes to Michael K. Hill who helped to improve the language and style of the final version of this manuscript.

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Received September 20, 2021
Revised October 10, 2021
Accepted October 12, 2021