ORIGINAL ARTICLE

De Ritis Ratio, Neutrophil-to-Lymphocyte Ratio, and Albumin Are Significant Prognostic Factors for Survival Even After Adjusted by the Treatment Duration in Metastatic Kidney and Bladder Cancer Treated With Immune-Checkpoint Inhibitors

Sung Han Kim¹, Eun Young Park², Hyung-Ho Lee¹, Jinsoo Chung¹, Ho Kyung Seo¹

¹Department of Urology, Urologic Cancer Center, Research Institute and Hospital of National Cancer Center, Goyang, Korea

²Biostatistics Collaboration Team, Research Institute and Hospital of National Cancer Center, Goyang, Korea

Purpose: This study aimed to determine the prognostic roles of several immune-related laboratory parameters in patients with metastatic kidney and bladder cancer treated with immune checkpoint inhibitors (ICIs).

Materials and Methods: Overall, 36 patients with either metastatic bladder (N=18) or kidney cancer (N=18) were enrolled retrospectively. Progression-free survival (PFS) and overall survival according to the pretherapeutic serum De Ritis ratio (DRR), neutrophil-to-lymphocyte ratio (NLR), and albumin level after ICI treatment, were analyzed. Treatment duration was adjusted using Contal and O'Quigley's method to explore the cutoff and maximize the log-rank test statistic. Cox proportional hazards model was used to analyze the laboratory parameters.

Results: A total of 9 patients received a combination therapy of multiple ICIs (N=9) and targeted agents (N=7). The median NLR, DRR, and albumin level at baseline were 1.7, 1.2, and 4.2 mg/dL, respectively. In the univariable analysis, combination of immunotherapies, total ICI cycles, baseline DRR, and albumin level were significant for PFS. Sex ratio, total ICI cycles, and baseline NLR and DRR were significant for cancer-specific survival (CSS). DRR and albumin levels, which were measured for up to 10 cycles, were significant in PFS and CSS. NLR was additionally significant in CSS. After adjusting total ICI cycles, DRR was significant in PFS and CSS, albumin level was significant only in PFS, and NLR was significant only in CSS in the multivariable analysis.

Conclusions: NLR, DRR, and albumin level are significant factors associated with the survival of patients with metastatic kidney and bladder cancer treated with ICI.

Key Words: Urinary bladder neoplasms, Immune checkpoint inhibitors, Kidney neoplasms, Prognosis

Received September 28, 2021

Revised October 18, 2021

Accepted October 25, 2021

Corresponding author:

Ho Kyung Seo

Email: seohk@ncc.re.kr

<https://orcid.org/0000-0003-2601-1093>

INTRODUCTION

Newly introduced immune checkpoint inhibitors (ICIs) have shifted a major therapeutic paradigm in cancer therapy, especially in metastatic settings, regardless of the cancer type.^{1,2} Checkpoint tar-

gets, such as cytotoxic T-lymphocyte antigen 4, programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1), are the most representative agents that not only improved the overall survival (OS) in patients with metastatic cancers despite the failure of existing systemic cancer

therapies but also resulted in long-term curable status, even in terminal cancer patients.

Bladder cancer (BC) and kidney cancer (KC) are immune-related cancers.^{3,4} Recent ICI trials in metastatic urological cancers have demonstrated some efficacious therapeutic outcomes of ICIs approved by the U.S. Food and Drug Administration (FDA), although some limitations were still observed. Moreover, the limited and modest efficacy of the overall response rates (10%–20%) in selected patients and the unpredictable adverse immunologic events during ICI treatment need to be studied further to discover any biomarkers indicative of the efficacy of these ICI agents.^{5,6}

Previous studies have sought several genetic biomarkers, such as DNA damage response pathway genes, as well as the PD-1/PD-L1 expression in either tumor cells or immune cells, using genome sequencing analysis by immune-based gene-targeting ICIs.⁷ The Cancer Genome Atlas and tissue-based analyses categorized metastatic BC and KC into several types. For example, the neuronal subtype of metastatic BC and KC has a favorable response (100%) to the PD-L1 inhibitor atezolizumab.⁸ However, the response rates across subtypes were still insufficient; thus, there is a need for identifying biomarkers that can predict responses and improve clinical outcomes.

Hematologic inflammatory parameters, such as neutrophils, lymphocytes, monocytes, and platelets, and their combined indices, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), can also reflect the immune status and have shown important predictive values for the prognosis of solid tumors in the past cytokine era, as well as in the recent ICI era.^{9–11}

The DRR, a combined laboratory parameter of hepatic enzymes, demonstrates the presence of hepatic injury and assesses the hepatic functional status, such as liver metastasis, which are significant factors associated with survival in

metastatic cancers.^{12,13} Albumin level also reflects various general conditions, including immune and nutritional states in patients treated with systemic therapies.^{14–16} Therefore, this study aimed to determine any potential significant prognostic markers among several systemic inflammatory parameters that were repeatedly obtained before each ICI cycle and evaluate their prognostic efficacy in progression-free survival (PFS) and cancer-specific survival (CSS) in patients with metastatic BC or KC treated with ICI for the first time in Korea.

MATERIALS AND METHODS

1. Ethical Statement

This retrospective study was approved by the Institutional Review Board of the National Cancer Center (IRB No. NCC2020-0211), and the requirement for informed consent was waived given the retrospective nature of the study. All patient data were anonymized and deidentified before the analysis. All study protocols were performed in accordance with the tenets of the Declaration of Helsinki.

2. Inclusion Criteria and Tissue Samples

A total of 36 patients with either metastatic bladder (N=19) or kidney (N=17) cancer who had undergone at least 2 cycles of ICI treatment with or without multitarget tyrosine kinase were enrolled in this study, and their medical records from 2016 to 2020 were reviewed retrospectively. Ten cycles were selected as the cutoff of ICI therapy because the analytical statistics of this study showed that the 10th cycle was the most appropriate time point to estimate the patients' survival prognoses using either the baseline or laboratory parameters during ICI therapy.

The patients received pembrolizumab, atezolizumab, avelumab, durvalumab, or nivolumab as second- or third-line therapy for either metastatic KC or BC. Among the 35 patients treated with ICIs, 30 received ICIs from the clinical trials at that period. The exclusion criteria were age <40 years, history of other cancers, no follow-up history, less than 3 months of follow-up, and <3 cycles of ICIs.

The immune-related parameters were collected retrospectively from the blood immune-related laboratory parameters measured before the ICI therapy. In the analyses, the parameters were collectively measured before each treatment cycle. These parameters included leukocytes, neutrophils, platelets, lymphocytes, hepatic enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), C-reactive protein, and albumin levels. The parameters combined among these immune-related parameters were NLR, PLR, and DRR. Before each cycle of ICI therapy, the body mass index (BMI, kg/m²) of the patients was classified according to the World Health Organization classification, which includes the following: underweight, <18.5 kg/m²; normal, 18.5–24.9 kg/m²; preobesity, 25.0–29.9 kg/m²; obese class I, 30.0–34.9 kg/m²; obese class II, 35.0–39.9 kg/m², and obese class III, ≥40 kg/m².

3. Statistical Analysis

The distribution of baseline clinicopathological variables was summarized as descriptive statistics (frequency with percent for categorical variables and mean with standard deviation (SD) or median with range for continuous variables). The PFS, which is the primary outcome, and CSS, which was calculated from the first ICI date, were analyzed.

The total ICI cycles ranged from 2 to 28, with a median value of 9.5, and showed a large difference in distribution between patients. To compensate for this, the Contal and O'Quigley's method was used

to find the cutoff for total ICI cycles that maximizes the difference in survival curves using log-rank test statistics. For both PFS and CSS, the prognosis was well distinguished based on 10 cycles. The BMI and blood immune-related variables for up to 10 cycles were considered as time-varying covariates in the Cox proportional hazards model.

The multivariable analysis for PFS was performed using backward selection after adjusting clinical variables with a univariable p-value <0.2 for each BMI and immune-related variables. For CSS, the number of events was only 7, and the most significant total ICI cycles were adjusted for multivariable analysis.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R ver. 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of less than 0.05 was considered significant.

RESULTS

The mean±SD patient age was 67.14±9.12 years. A total of 9 patients received combination therapy of multiple ICIs (N=9) and targeted agents (N=7) (Table 1). The median cutoff of the total number of ICI cycles was 9.5 (maximum, 28 cycles), and the 10 cycles showed significant survival differences (not shown in tables). Progression was noted in 24 patients (66.7%) after a median therapeutic duration of 7.0 months (0.8–35.0 months). The median NLR, DRR, and albumin level at baseline were 1.7, 1.2, and 4.2 mg/dL, respectively. Moreover, the median for average up to 10 cycles was 2.0, 1.2, and 4.1, respectively. Other patient characteristics are shown in Table 1.

In the univariable analysis, combination of immunotherapies (hazard ratio [HR], 0.31; 95% confidence interval [CI], 0.10–0.92), total ICI cycles (HR, 0.84; 95% CI, 0.78–0.90), DRR at baseline (HR, 3.39; 95% CI, 1.68–6.83), and albumin level

Table 1. Baseline patient characteristics (n=36)

Characteristic	No. (%)	Mean±SD	Median (range)
Age (yr)		67.14±9.12	67 (47–85)
Sex			
Male	23 (63.9)		
Female	13 (36.1)		
Body mass index (kg/cm ²)			
Low weight, <18.5	0 (0)		
Normal, 18.5–22.9	9 (28.1)	21.14±0.95	21 (19.8–22.7)
Preobesity, 23–24.9	9 (28.1)	24.18±0.52	24.3 (23.4–24.9)
Mild obesity			
Level 1, 25–29.9	13 (40.6)	26.91±1.41	26.8 (25.1–29.5)
Level 2, 30–34.9	0 (0)		
Level 3, ≥35	1 (3.1)		
Cancer type			
Kidney cancer	17 (47.2)		
Bladder cancer	19 (52.8)		
Clinical T stage (miss=24)			
T1+T2	4 (33.3)		
T3+T4	8 (66.7)		
Clinical N stage (miss=24)			
N0+1	6 (50.0)		
N2+N3	3 (25.0)		
Nx	3 (25.0)		
Nuclear grade (miss=9)			
2	6 (22.2)		
3	17 (63.0)		
4	4 (14.8)		
Target therapy			
No	29 (80.6)		
Sunitinib	1 (2.8)		
Axitinib	3 (8.3)		
Lenvatinib	3 (8.3)		
Immunotherapy drug			
Pembrolizumab	15 (41.7)		
Atezolizumab	3 (8.3)		
Avelumab	3 (8.3)		
Durvalumab	11 (30.6)		
Nivolumab	3 (8.3)		
Bevacizumab	1 (2.8)		
Combination of immunotherapies	9 (25)		
Immune-check point inhibitors cycle	36	12.97±8.90	9.5 (2.0–28.0)
Body mass index	32	24.80±3.30	24.5 (19.8–35.9)
Baseline laboratory parameters			
Neutrophil-to-lymphocyte ratio	36	2.02±1.05	1.7 (0.6–5.9)
De Ritis ratio	36	1.31±0.55	1.2 (0.6–3.3)
Albumin	36	4.10±0.35	4.2 (2.9–4.6)
Neutrophil	36	55.89±9.99	55.7 (32.2–77.4)
Lymphocyte	36	31.85±9.74	30.9 (11.4–57.7)
Platelet	36	247.69±85.67	232.5 (56.0–542.0)
Platelet volume	36	9.44±0.86	9.3 (8.0–11.6)
Platelet distribution width	36	10.01±1.64	9.7 (7.8–14.4)
Alanine aminotransferase	36	17.67±9.25	14 (6.0–47.0)
Aspartate aminotransferase	36	20.17±7.15	18.5 (9.0–40.0)
Treatment duration (mo)	36	11.12±9.54	7.0 (0.8–35.0)
Survival/death	29 (80.6)/7 (19.4)		
Progressive disease	24 (66.7)		

SD: standard deviation.

at baseline (HR, 0.09; 95% CI, 0.03–0.31) were significant factors for PFS ($p < 0.05$); whereas, sex ratio (HR, 15.53; 95% CI, 1.86–129.55), total ICI cycles (HR, 0.79; 95% CI, 0.67–0.94), NLR at baseline (HR, 2.19; 95% CI, 1.23–3.87), and DRR at baseline (HR, 5.48; 95% CI, 1.08–27.87) were significant factors for CSS ($p < 0.05$). The DRR (HR, 9.54; 95% CI, 3.99–22.80 for PFS, HR, 30.56; 95% CI, 4.35–214.6 for CSS) and albumin levels (HR, 0.04; 95% CI, 0.01–0.19 for PFS, HR, 0.03; 95% CI, 0.00–0.50 for CSS) were significant in both PFS and CSS, whereas NLR (HR, 1.31; 95% CI, 1.07–1.61) was significant only in CSS (Table 2).

After adjusting for total ICI cycles, albumin level (HR, 0.12; 95% CI, 0.02–0.62) was significant in PFS, whereas NLR (HR, 1.28; 95% CI, 1.02–1.61) was significant in CSS in the multivariable analysis. DRR (HR, 7.64; 95% CI, 2.76–21.14 for PFS, HR,

19.28; 95% CI, 2.08–178.52 for CSS) was the only significant factor in PFS and CSS (Table 3). The results of multivariable analysis using the variables showed the same tendency as those measured at baseline.

DISCUSSION

In the past decade, several ICI agents, including nivolumab, atezolizumab, pembrolizumab, avelumab, and durvalumab, have been approved by the FDA to treat patients with metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma (mUC).¹ ICI improved the OS by approximately 3 months in mUC and 6 months in mRCC. Significant durable responses were also observed compared to those observed after second-line chemotherapy, which has about 10%

Table 2. Univariable analysis of progression-free survival and cancer-specific survival

Variable	Progression-free survival			Cancer-specific survival		
	No. (event)	HR (95% CI)	p-value	No. (event)	HR (95% CI)	p-value
Age	36 (24)	1.04 (0.99–1.09)	0.114	36 (7)	1.01 (0.93–1.10)	0.883
Sex						
Male	23 (13)	1	-	23 (1)	1	-
Female	13 (11)	1.99 (0.89–4.45)	0.095	13 (6)	15.53 (1.86–129.55)	0.011
Cancer						
Kidney	17 (11)	1	-	17 (5)	1	-
Bladder	19 (13)	1.12 (0.49–2.54)	0.786	19 (2)	0.30 (0.06–1.53)	0.147
Combination of target and immunotherapies						
No	29 (20)	1	-	29 (6)	1	-
Yes	7 (4)	0.50 (0.16–1.52)	0.221	7 (1)	0.69 (0.08–5.73)	0.729
Combination of immunotherapies						
No	27 (20)	1	-	27 (6)	1	-
Yes	9 (4)	0.31 (0.10–0.92)	0.035	9 (1)	0.38 (0.05–3.15)	0.368
Total ICI cycles	36 (24)	0.84 (0.78–0.90)	<0.001	36 (7)	0.79 (0.67–0.94)	0.006
Baseline body mass index	32 (20)	0.94 (0.82–1.09)	0.416	32 (7)	0.93 (0.71–1.21)	0.568
Baseline neutrophil-to-lymphocyte ratio	36 (24)	1.41 (0.92–2.17)	0.116	36 (7)	2.19 (1.23–3.87)	0.007
Baseline De Ritis ratio	36 (24)	3.39 (1.68–6.83)	0.001	36 (7)	5.48 (1.08–27.87)	0.040
Baseline albumin	36 (24)	0.09 (0.03–0.31)	<0.001	36 (7)	0.11 (0.01–1.32)	0.081
Body mass index	-	0.93 (0.81–1.08)	0.354	-	0.82 (0.62–1.10)	0.180
Neutrophil-to-lymphocyte ratio	-	1.14 (1.00–1.31)	0.056	-	1.31 (1.07–1.61)	0.010
De Ritis ratio	-	9.54 (3.99–22.80)	<0.001	-	30.56 (4.35–214.6)	0.001
Albumin	-	0.04 (0.01–0.19)	<0.001	-	0.03 (0.00–0.50)	0.016

HR: hazard ratio, CI: confidence interval, ICI: immune-check point inhibitor.

Table 3. Multivariable analysis of progression-free survival and cancer-specific survival

Variable	BMI		NLR		DRR		Albumin	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Progression-free survival								
Combination of immunotherapies								
No	1	-	1	-	-	-	-	-
Yes	0.19 (0.04–0.83)	0.027	0.23 (0.06–0.91)	0.036	-	-	-	-
Total ICI cycles	0.78 (0.69–0.88)	<0.001	0.83 (0.77–0.90)	<0.001	0.87 (0.81–0.94)	<0.001	0.86 (0.79–0.93)	<0.001
Body mass index	1.11 (0.93–1.32)	0.245	-	-	-	-	-	-
NLR	-	-	1.03 (0.91–1.18)	0.623	-	-	-	-
DRR	-	-	-	-	7.64 (2.76–21.14)	<0.001	-	-
Albumin	-	-	-	-	-	-	0.12 (0.02–0.62)	0.012
Cancer-specific survival								
Total ICI cycles	0.78 (0.64–0.96)	0.018	0.78 (0.64–0.95)	0.013	0.84 (0.71–1.00)	0.045	0.82 (0.69–0.97)	0.020
Body mass index	1.06 (0.73–1.55)	0.753	-	-	-	-	-	-
NLR	-	-	1.28 (1.02–1.61)	0.033	-	-	-	-
DRR	-	-	-	-	19.28 (2.08–178.52)	0.009	-	-
Albumin	-	-	-	-	-	-	0.16 (0.00–9.59)	0.384

BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, DRR: De Ritis ratio, HR: hazard ratio, CI: confidence interval, ICI: immune-check point inhibitor.

higher objective response rate and 30% lower rate of adverse events.¹⁷ However, the unresponsiveness of a subset of patients to ICI is considered a major limitation in addition to immune-related adverse events. This has prompted researchers to search for biomarkers for response in patients with mUC and mRCC treated with ICI.

This study aimed to find significant prognostic factors, clinical data, and systemic inflammatory parameters that were obtained in each cycle of ICI in patients with either mRCC or mUC treated with ICI for the first time in Korea, regardless of urological cancer types. It was found that DRR and total ICI cycle were significant prognostic factors for both PFS and CSS, whereas baseline albumin level and NLR were significant factors for PFS and CSS, respectively; however, BMI was not ($p>0.05$) (Tables 2 and 3). Furthermore, the combination of immunotherapies was a significant prognostic factor for PFS. The study also cited that the prognoses of patients could be distinguished well based on the 10th cycle during ICI therapy. Inflammation and microenvironment are 2 major factors relating to the cancer therapeutic responses, tumor progression, and survival prognoses in

various cancer treatments with ICI.^{18,19} ICI affects the hematologic inflammatory cells to change the tumor and its microenvironment. The prognostic outcomes of therapies were dependent upon the complexity of the immune mechanism in each cancer patient. In addition, inflammation leads to the transport of bioactive molecules and other products of inflammation, which are potential biomarkers, to the tumor microenvironment.^{3,4,20}

The peripheral blood markers are noninvasive sources of potential biomarkers in patients receiving ICIs. Although associations of peripheral blood markers with clinical benefit and survival have already been noted, none have been validated as predictive biomarkers in prospective studies.²¹ Several ICI studies showed improved OS and PFS associated with baseline values, such as low NLR, low absolute monocyte count, low myeloid-derived suppressor cell count, high lymphocytes count, and high eosinophil count in inflammatory cells.²²

DRR, which is the ratio of ALT to AST (hepatic enzymes), provides information relating to survival and prognoses of hepatic reactions and hepatic conditions, such as liver cirrhosis, hepatic fibrosis, systemic inflammation, fatty liver, hepatitis, and

liver metastasis.^{13,17} Several studies have also implicated liver metastasis in the decreased response to ICI-based therapies in mRCC and mUC.^{13,17} Metastasis to the liver may disrupt the organ's immunomodulatory role, which can be correlated with the administration of anti-PD-1 agents that can lead to a decreased CD8+ T-cell density, thereby restricting the host's immune response to ICI-based treatments.¹³ The physiology of the tumor microenvironment with liver metastasis should further be explored.

The NLR was found to affect CSS remarkably.^{14,15} The NLR reflects the systemic inflammation relating to the lymphocytes. The host immune system plays a key role in the success of ICI therapy. Inflammatory cells have important effects on tumor development, and systemic inflammation markers can be of use in determining the prognosis.¹⁶ High NLR indirectly reflects immune dysregulation, suggesting a poor response to ICI treatment. The results of our analysis support the inclusion of an inflammatory biomarker in a prognostic model for patients with mUC and mRCC treated with ICI.

Albumin level was found to be a significant factor for PFS in this study. It reflects various conditions, such as nutritional status, hepatic function, and clinical inflammation, which are indicators of the severity of an illness and may play an important regulatory role in the immune system of patients with cancers, including mUC and mRCC.²³⁻²⁵ Furthermore, albumin level constitutes a major risk factor in the mRCC risk classification of Heng criteria, representing the prognostic outcome after targeted therapy. Our finding that low baseline albumin level predicts shorter OS and PFS is consistent with that of previous studies.²⁵

Longer treatment duration not only implies better survival outcome, but can also lead to an increased incidence of new or worsening adverse effects.^{26,27} This study showed that the increased number of ICI cycles was a significant favorable risk factor

for survival in mUC and mRCC (Tables 2 and 3). Adequate management of immune-related side events is important to continue ICI therapy for better survival outcomes. In this study, the 10th cycle, which was chosen as the most appropriate time point to estimate the survival prognoses for the first time in Korean patients, was adequately analyzed during ICI therapy. However, only 2%–7% patients demonstrated complete response following ICI therapy in metastatic cancer.¹⁷ This means that long-term treatment is observed only in selected patients. Researchers have been questioned regarding when ICI therapy must be stopped, or at what point the patient can be considered as showing complete remission, or whether the discontinuation of therapy leads to cancer recurrence and progression. Termination of long-term ICI therapy for favorable therapeutic outcomes is another interesting topic that should be discussed further.

This study had some limitations, including the retrospective design with a small number of patients treated with ICI, which prompts the need to further verify the results through a prospective study with adequate sample sizes. The study did not consider the adverse events and other factors, except immune inflammatory cells and BMI, that influence survival outcome and treatment. Despite these limitations, our findings will be helpful in setting a better therapeutic strategy for patients with metastatic BC and KC to predict the survival outcome with several laboratory and anthropometric parameters. To our knowledge, there are no data on the correlation between baseline multiple systemic inflammatory indices and the efficacy of ICIs in patients with metastatic RCC and BC.

CONCLUSIONS

The study found that the NLR, DRR, and albu-

min levels on the day of systemic infusion were significant factors associated with survival, regardless of the systemic therapy administered for metastatic KC and BC. Further large-scale prospective studies are needed to identify significant parameters as prognostic factors for survival in patients with metastatic urological cancer undergoing ICI treatment.

NOTES

- Conflicts of interest: No potential conflict of interest relevant to this article was reported.

- Funding: This study was supported by the Korean National Cancer Center Grants (nos. 1810241-3 & 2111080-1).

- Acknowledgments: We thank Ms. Jeung-eun Lee and Ae-na Jae for creating the database and performing the sorting processes.

- ORCID

Sung Han Kim: <https://orcid.org/0000-0002-1689-5203>

Eun Young Park: <https://orcid.org/0000-0003-2430-5282>

Hyung-Ho Lee: <https://orcid.org/0000-0003-4160-0216>

Jinsoo Chung: <https://orcid.org/0000-0003-2251-5331>

Ho Kyung Seo: <https://orcid.org/0000-0003-2601-1093>

REFERENCES

1. Seront E, Catala G, Dermine A, Lejeune S, Rys-selinck S. Immune checkpoint inhibitors as a real hope in advanced urothelial carcinoma. *Future Sci OA* 2018;4:FSO341.
2. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade Therapy. *Cancer Discov* 2018;8:1069-86.
3. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;140:883-99.
4. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860-7.
5. Shabto JM, Martini DJ, Liu Y, Ravindranathan D, Brown J, Hitron EE, et al. Novel risk group stratification for metastatic urothelial cancer patients treated with immune checkpoint inhibitors. *Cancer Med* 2020;9:2752-60.
6. Bellmunt J, Choueiri TK, Fougerey R, Schutz FA, Salhi Y, Winquist E, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol* 2010;28:1850-5.
7. Bellmunt J, Powles T, Vogelzang NJ. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. *Cancer Treat Rev* 2017;54:58-67.
8. Kim J, Kwiatkowski D, McConkey DJ, Meeks JJ, Freeman SS, Bellmunt J, et al. The cancer genome atlas expression subtypes stratify response to checkpoint inhibition in advanced urothelial cancer and identify a subset of patients with high survival probability. *Eur Urol* 2019;75:961-4.
9. Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. *Cancer Treat Rev* 2017;58:1-13.
10. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2014;23:1204-12.
11. Bilen MA, Dutcher GMA, Liu Y, Ravindranathan D, Kissick HT, Carthon BC, et al. Association between pretreatment neutrophil-to-lymphocyte ratio and outcome of patients with metastatic renal-cell carcinoma treated with nivolumab. *Clin Genitourin Cancer* 2018;16:e563-75.
12. Lalani AA, Xie W, Martini DJ, Steinharter JA, Norton CK, Krajewski KM, et al. Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immunother Cancer* 2018;6:5.
13. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo

- KL, Gubens MA, et al. Liver metastasis and treatment outcome with Anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. *Cancer Immunol Res* 2017;5:417-24.
14. Fest J, Ruiter R, Mulder M, Groot Koerkamp B, Ikram MA, Stricker BH, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer-A population-based cohort study. *Int J Cancer* 2020;146:692-8.
 15. De Giorgi U, Procopio G, Giannarelli D, Sabbatini R, Bearz A, Buti S, et al. Association of systemic inflammation index and body mass index with survival in patients with renal cell cancer treated with nivolumab. *Clin Cancer Res* 2019;25:3839-46.
 16. Anastasiou D. Tumour microenvironment factors shaping the cancer metabolism landscape. *Br J Cancer* 2017;116:277-86.
 17. Rijnders M, de Wit R, Boormans JL, Lolkema MPJ, van der Veldt AAM. Systematic review of immune checkpoint inhibition in urological cancers. *Eur Urol* 2017;72:411-23.
 18. Bonavita E, Bromley CP, Jonsson G, Pelly VS, Sahoo S, Walwyn-Brown K, et al. Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade. *Immunity* 2020;53:1215-29.e8.
 19. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;454:436-44.
 20. Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. *Nat Rev Cancer* 2005;5:263-74.
 21. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. *Lancet Oncol* 2016;17:e542-51.
 22. Ferrucci PF, Ascierto PA, Pigozzo J, Del Vecchio M, Maio M, Antonini Cappellini GC, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. *Ann Oncol* 2016;27:732-38.
 23. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J* 2010;9:69.
 24. Liu J, Dai Y, Zhou F, Long Z, Li Y, Liu B, et al. The prognostic role of preoperative serum albumin/globulin ratio in patients with bladder urothelial carcinoma undergoing radical cystectomy. *Urol Oncol* 2016;34:484.e1-484.e8.
 25. Li J, Cheng Y, Liu G, Ji Z. The association of pre-treatment serum albumin with outcomes in bladder cancer: a meta-analysis. *Onco Targets Ther* 2018;11:3449-59.
 26. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer* 2019;7:306.
 27. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. *J Am Diet Assoc* 2004;104:1258-64.