ELMER PRESS

Original Article

World J Oncol. 2023;14(5):423-429

Tumor Markers as Predictors of Acute Kidney Injury Incidence and Staging of the Muscle-Invasive Bladder Cancer Receiving Chemoradiation Therapy

Syah Mirsya Warli[a, b, e], Fauriski Febrian Prapiska[b], Dewi Indah Sari Siregar[c], Ilham Ari Seja[d]

Abstract

Background: Bladder cancer, as one of types of cancers within the urinary tract, is associated with a greater risk of acute kidney injury (AKI), resulting in a poorer prognosis, discontinuation of effective oncological treatments, longer hospitalization, and higher expenses. There is no discussion yet on tumor markers in bladder cancer. With the revolutionary advances in bladder cancer molecular subtyping over the past decade, the presence of tumor markers to assess the staging of bladder cancer has yet to be discussed. In this study, we intended to assess the relationship between tumor markers and incidence of AKI, also between tumor markers and the cancer staging.

Methods: This retrospective cross-sectional study utilized secondary data from 26 medical records of patients diagnosed with bladder cancer at the Adam Malik and Universitas Sumatera Utara Hospital between 2021and 2022. This study included all patients with bladder cancer who met the inclusion criteria. Continuous variables were reported as mean (standard deviation (SD)) and examined using an independent *t*-test. Categorical variables were reported as proportions, examined using Chi-square or Fisher's exact test. Pre- and post-tumor marker data were evaluated with dependent sample *t*-test for normal variance data, and Wilcoxon test for data with atypical distribution. P values were set at 0.05.

Results: CD44 (P = 0.003) and programmed cell death 1 (PD-1) (P = 0.030) were the only significant markers in their pre- and post-chemoradiation states among the four investigated tumor markers in this study. Meanwhile, PD-1 tumor marker levels were only found to be significant between AKI and pre-chemoradiation (P = 0.011). Even though the multivariate study of tumor staging did not show any statistical significance, both tumor markers CD44 and PD-1 showed a significant effect on the incidence of acute renal damage (P = 0.034).

Conclusions: Pre-chemoradiation PD-1 tumor markers showed promise as good predictive indicators for staging and AKI incidence in muscle-invasive bladder cancer patients undergoing chemoradiation therapy.

Keywords: Muscle-invasive bladder cancer; Acute kidney injury; Tumor marker; Staging; Chemoradiation; Tumor marker

Introduction

Bladder cancer is one of many malignancies of the urinary tract. In 2020, there is an estimation of 80,000 novel cases and 17,980 deaths [1]. The majority of patients (70%) had non-muscle-invasive bladder cancer (NMIBC) with high recurrence risk (50-70%) and can further advance to muscle-invasive bladder cancer (MIBC) in approximately 10-20% of patients. Bladder cancers are staged according to the eighth edition of the tumor, node, metastasis (T, N, and M) by the American Joint Commission on Cancer (AJCC) and graded according to the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system from 2004 [2]. It is known that cancer patients undergoing treatment might experience acute obstructive renal failure (AORF) which is a frequent complication associated with bladder cancer and will develop acute kidney injury (AKI). AKI that originated from pre-, renal, or post-renal causes, possesses significant complexity in patients, resulting in a poorer prognosis, cessation of oncological treatments, longer hospital stays, and higher expenses [3]. Chemoradiation-associated nephrotoxicity, hypercalcemia, tumor lysis syndrome, and obstructive nephropathy are some of the causes of AKI [4]. Knowledge of specific risk factors and their modification is essential for the prevention of AKI, as there are currently no effective treatments for this condition. This is especially true considering the significant increase in AKI among critically ill and noncritically ill cancer

Manuscript submitted August 1, 2023, accepted August 23, 2023
Published online September 20, 2023

[a]Division of Urology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara - Haji Adam Malik General Hospital, Medan, Indonesia
[b]Department of Urology, Faculty of Medicine, Universitas Sumatera Utara Hospital - Universitas Sumatera Utara, Medan, Indonesia
[c]Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara Hospital - Universitas Sumatera Utara, Medan, Indonesia
[d]Department of Urology, Faculty of Medicine, Universitas Indonesia - Haji Adam Malik General Hospital, Medan, Indonesia
[e]Corresponding Author: Syah Mirsya Warli, Division of Urology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara - Haji Adam Malik General Hospital, Medan, Indonesia. Email: warli@usu.ac.id

doi: https://doi.org/10.14740/wjon1676

patients [5, 6].

CD44 is a cell surface glycoprotein that plays a crucial role in cell adhesion, migration, and signaling. It is involved in a variety of physiological and pathological processes, including immune responses, tissue development, wound healing, and cancer progression. CD44 exists in multiple isoforms due to alternative splicing of its gene, resulting in different forms of the protein with varying functions and properties. CD44v3, one of variant isoforms from CD44, decreases tubular damage during obstructive nephropathy, decreases apoptosis and increases tubular epithelial cell proliferation, also prevents the development of renal fibrosis, while CD44s expression performs the opposite [7]. Epidermal growth factor receptor (EGFR) family (also known as ErbB family) is a significant class of tyrosine kinase proto-oncogenes receptor which are crucial in a variety of cellular processes, including cell proliferation, migration, adhesion, and potentially cellular transformation, including urothelial carcinogenesis. There are four members of the EGFR family: human epidermal growth factor receptor 1 (HER1) (EGFR and ErbB1), HER2 (ErbB2 and HER2/neu), HER3 (ErbB3), and HER4 (ErbB4). HER2 expression significantly correlated with higher stage cancer, not with tumor grade especially in cancer recurrence in the urinary bladder after the primary treatment of upper tract urothelial carcinoma (UTUC) and lymph node metastasis [8]. There are no current studies examining the relationship between elevated HER2 and AKI, but it has been established that the use of HER2 inhibitors elevates the possibility of kidney disease development due to their nephrotoxic effects, which occurs with minimal frequency [9]. The programmed cell death 1 (PD-1) pathway (PD-1/programmed cell death ligand 1 (PD-L1)) functions as immunological negative regulators and is used as immune checkpoint inhibitors (CPIs). Inhibiting these pathways enhances the antitumor response of adaptive immune system, although accompanied by immune-related adverse events due to nonspecific immunologic activation. However, there are no studies discussing the correlation between an elevated PD-1/PD-L1 ratio and AKI incidence, even though individuals utilizing PD-1/PD-L1 inhibitor face a heightened chance of experiencing AKI as a result of interstitial nephritis [10].

The aim of this study was to understand more and analyze tumor markers CD44, ErbB2/HER2, PD-1 and PD-L1 as predictors of AKI incidence and staging of the MIBC in patients who underwent chemoradiation therapy. We believe this research will especially benefit chemoradiation therapy in the future.

Objectives

We intended to study the correlation of tumor markers in predicting AKI incidence and staging of bladder cancer.

Materials and Methods

This was a retrospective cross-sectional analysis where the data were obtained from the Adam Malik General Hospital and Universitas Sumatera Utara Hospital. We used secondary data from medical records of bladder cancer patients between 2021 and 2022. This study has been authorized by the Ethics Committee with approval number 1268/KEP/USU/2021. We include all bladder cancer patients that underwent chemotherapy with the same regimen using gemcitabine and cisplatin without any differentiation based on subtypes ranging from stage I to IV with various TNM staging from both hospitals with the criteria for inclusion including: 1) bladder cancer confirmed through histopathology; 2) thorough staging based on AJCC criteria encompassing tumor (T), lymph nodes (N), and metastasis (M); 3) assessment of tumor markers including CD44, ErbB2/HER2, PD-1, and PD-L1. The exclusion criteria for our study included individuals who had AKI or had previously undergone procedures like nephrostomy or the insertion of a double-J stent. All parameters were measured using standardized methods and examined by certified attending doctors in each department. The laboratory staff who performed the laboratory examinations did not know the clinical staging or outcomes of the patient. Sample matching was performed based on risk factors and age. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Chi-square or Fisher's exact tests were applied to evaluate categorical variables reported as proportions. Fewer than 50 participants were evaluated for normality using the Shapiro-Wilk test. The pre- and post-tumor marker data were evaluated using *t*-test dependent for data with normal variances and Wilcoxon test for data with an atypical distribution. Data were examined using SPSS 24. P value was set at 0.05. Continuous variables were described as mean (standard deviation (SD)) and examined with *t*-test for independent samples.

Results

Initially, 45 records were identified and assessed for eligibility. After the assessment, 19 records were excluded for various reasons. We ultimately included 26 records for analysis in this study. The subjects' demographic profiles are presented in Table 1.

The subject's clinical information showed that 92.3% of the patients were male, with mean age of 58.88 years. Most were found to be in stage II bladder cancer with the majority in the T2 staging.

CD44 marker increased from 299.24 (91.45) to 360.39 (84.28) with P value of 0.003 while PD-1 also increased from 245.50 (114.20 - 562.58) to 311.09 (137.80 - 1529.30) with P value of 0.030. ErbB2/HER2 and PD-L1 showed no significant difference between the pre- and post-chemoradiation values, which are presented in Table 2.

According to the results from one-way analysis of variance (ANOVA) test between tumor markers and staging (Table 3), pre-chemoradiation PD-1 tumor marker levels were shown to have significance in the two groups (F (1, 24) = (9.230), P = 0.006). Additionally, the effect size can be categorized as large (η^2 = 0.278). On the other hand, the differences among the other tumor markers were not statistically significant. CD44

Table 1. Subject Characteristics

Variable	Frequency (%)/mean (SD)
Gender	
Male	24 (92.3%)
Female	2 (7.7%)
Age	58.88 (11.48)
Bladder cancer staging	
Stage I	0 (0%)
Stage II	12 (46.20%)
Stage III	6 (23.1%)
Stage IV	8 (30.7%)
T staging	
T1	0 (0%)
T2	12 (46.2%)
T3	8 (30.8%)
T4	6 (23.1%)
N staging	
N0	18 (69.2%)
N1	3 (11.5%)
N2	5 (19.2%)
N3	0 (0%)
M staging	
M1	24 (92.3%)
M2	2 (7.7%)

SD: standard deviation.

Table 2. Comparison of Tumor Marker CD44, Erb2/HER2, PD-1 and PD-L1 Pre- and Post-Chemoradiation

Tumor markers	Pre-chemoradiation (mean (SD)/ median (min - max))	Post-chemoradiation (mean (SD)/median (min - max))	P value
CD44	299.24 (91.45)	360.39 (84.28)	0.003[a*]
Erb2/HER2	3,364.12 (960.69)	3,264.46 (904.27)	0.719[a]
PD-1	245.50 (114.20 - 562.58)	311.09 (137.80 - 1,529.30)	0.030[b*]
PD-L1	98.57 (57.72 - 208.74)	127.47 (47.06 - 9,343)	0.143[b]

[a]Paired *t*-test. [b]Wilcoxon test. *P < 0.05. SD: standard deviation; min: minimum; max: maximum; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; HER2: human epidermal growth factor receptor 2.

Table 3. One-Way ANOVA for Tumor Staging and Tumor Marker CD44, Erb2/HER2, PD-1 and PD-L1 Pre- and Post-Chemoradiation

Tumor markers	Pre-chemoradiation			Post-chemoradiation		
	Eta-squared	F	Sig.	Eta-squared	F	Sig.
CD44	0.11	0.256	0.618	0.73	1.884	0.183
Erb2/HER2	0.31	0.761	0.392	0.00	0.002	0.966
PD-1	0.278	9.230	0.006*	0.137	3.801	0.063
PD-L1	0.007	0.166	0.687	0.018	0.430	0.518

*P < 0.05. ANOVA: analysis of variance; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; Sig.: significance; HER2: human epidermal growth factor receptor 2.

Table 4. One-Way ANOVA for Acute Kidney Injury and Tumor Marker CD44, Erb2/HER2, PD-1 and PD-L1 Pre- and Post-Chemoradiation

Tumor markers	Pre-chemoradiation			Post-chemoradiation		
	Eta-squared	F	Sig.	Eta-squared	F	Sig.
CD44	0.129	3.557	0.071	0.049	1.228	0.279
Erb2/HER2	0.035	0.883	0.357	0.000	0.000	0.983
PD-1	0.241	7.620	0.011*	0.000	0.007	0.933
PD-L1	0.152	4.306	0.049	0.046	1.164	0.291

*P < 0.05. ANOVA: analysis of variance; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; Sig.: significance; HER2: human epidermal growth factor receptor 2.

and PD-1 were the only two markers that were statistically significant in their pre- and post-chemoradiation state out of the four tumor markers being studied.

Furthermore, a one-way ANOVA test was conducted between tumor markers and the prevalence of AKI (Table 4). The results showed that a significant difference was only discovered between AKI and pre-chemoradiation PD-1 tumor marker levels (F (1, 24) = (7.620), P = 0.011). The effect size can also be categorized as large ($\eta^2 = 0.278$). Similarly, no significant difference was found among both pre-and post-chemoradiation tumor levels regarding AKI.

Multivariate analysis using multivariate analysis of variance (MANOVA) was further conducted for tumor markers CD44 and PD-1 due to their statistical significance between pre- and post-chemoradiation on bivariate analysis (Table 5). Based on the results, the assumption of homogeneity of covariance only held for the incidence of AKI but not for tumor staging. Nevertheless, multivariate analysis on tumor staging showed statistically insignificant results. For AKI, Levene's test for equality of variances showed P > 0.05 in all the four independent variables, thus validifying the multivariate result. A P value of 0.034 indicated a significant influence of both tumor markers CD44 and PD-1 on the incidence of AKI.

Discussion

Based on our study, we tried to investigate thoroughly the incidence of AKI in bladder cancer patients who were treated with chemotherapy in our center, and we found that tumor marker CD44 is an independent marker for AKI (P = 0.034) with a significant difference shown pre- and post-chemoradiation (P = 0.003). The stem cell identifier CD44, which functions as surface adhesion, is suggested as a possible marker. *CD44* is a significant gene found in several areas of cancer progression and development, particularly in bladder cancer cells. An increased expression has been found to be correlated with more advanced clinical tumor stage, lymph node participation, local recurrence, and decreased survival rates among individuals with bladder cancer [11]. In an *in vitro* study by Matsushita et al, using rats with an AKI model, CD44 was present in expanded renal tubules, while in rats with a renal fibrosis model, it was observed in tubules located in fibrotic regions, indicating the CD44 presence in renal tubules undergoing maladaptive repair. As a result, these elements may serve as valuable indicators for detecting impairments in the regenerative processes of renal tubules [12].

Table 5. MANOVA for Acute Kidney Injury and Tumor Staging for Tumor Marker CD44 and PD-1 Pre- and Post-Chemoradiation

MANOVA	Box	Pillai	Wilk's	F value	P
AKI	0.12	0.377	0.623	3.181	0.034*
Tumor staging	0.034	0.342	0.658	2.73	0.057

*P < 0.05. MANOVA: multivariate analysis of variance; PD-1: programmed cell death 1; AKI: acute kidney injury.

According to the findings from clinical specimens, CD44 staining was strongly related with higher clinical stage, increased incidence of localized region failure, and reduced rate of disease-specific survival for MIBC patients. Through cellular and orthotopic models, we demonstrated CD44 presence has a greater capacity for invasion, as well as an enhanced epithelial-mesenchymal transition (EMT) in bladder cancer cells, in comparison to other types of CD44. The levels of CD44 that were measured in clinical samples were shown to have a substantial association with those found in *in vitro* tests. In both *in vitro* and *in vivo* testing, a reduction in the expression of CD44 was observed, as well as in cancer stem-cell-like characteristics and aggressive tumor behavior. The associated modifications included a reduction in PD-L1-mediated T-cell suppression as well as a dampening of STAT3 activation and EMT [13]. This marker has also shown its applicability in other cancers. A systematic review conducted by Li et al [14] has also discussed the use of CD44 as a marker for the prognosis of renal cell carcinoma, where high levels of CD44 positively correlate with a higher Fuhrman grade, recurrence rate, microvascular invasion, and worse prognosis. CD44 overexpression may also indicate poorer prognosis in colorectal cancer, alongside with worse lymph node and/or distant metastasis. CD44, which is essentially a hyaluronan (HA) receptor, activates stem cell regulatory genes. When tightly bound with HA, CD44 aids in the homing and adhesion of cancer stem cells, subsequently triggering migration of cancer cells. Moreover, the HA-CD44 bond is also important in activating the anti-apoptotic pathways through the receptor tyrosine-kinase pathway.

Even though our study mentioned otherwise, a meta-analysis by Gan et al [15] described that both transcriptional and

translational levels of HER2 expression were significantly elevated in bladder cancer compared to normal tissue. This was the case across both levels. In addition, HER2 protein tends to be overexpressed in carcinoma *in situ* (CIS) as well as multifocal malignancies. A study by Soria et al [16] has also discussed the effect of HER2 status in invasive bladder cancer patients. Despite the fact that one-third of those who were treated with radical cystectomy had an overexpression of HER2, it was not significantly correlated with oncological outcomes. Conflicting results in literature suggests more research and reviews should be established to reach a common ground.

As one of the many EGFR, HER2 plays a role in cell proliferation, migration, and survival through the activation of intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK) pathway and phosphoinositide 3-kinase pathway. The protein itself is coded by the associated oncogene, precisely located in chromosome 17, and mutation in this gene leads to overexpression. HER2 also serves as a common tumor marker in other cancer types, such as breast cancer. The amount of HER2 protein in tumor was directly correlated with tumor size, grade, and stages of breast cancers. Additionally, we discovered that the expression of the *HER2* gene was linked to the tumor stage by evaluating the data from The Cancer Genome Atlas (TCGA) that was collected on breast cancer. More research is required to verify the specifics of the relevant mechanism. A study has shown a correlation between the *HER2* gene and protein and lymph node metastases in breast cancer. However, the study failed to find a correlation between the expression and survival time, whether it would be overall survival (OS), disease-specific survival, or progression-free survival (PFS) [15].

The PD-1 (CD279) pathway initiates a series of reactions that restrict immune activity, resulting in reduced cytokine secretion and autoimmunity, thereby preventing inadvertent tissue damage. The pathway is filled with PD-1 receptor and its two ligands: PD-1 ligand 1 (PD-L1, B7-H1, and CD274) and PD-1 ligand 2 (PD-L2, B7-DC, and CD273). PD-L1 is generated in human antigen-presenting cells, T and natural killer (NK) cells, as well as stem cells and various non-hematopoietic cells [17]. In this study, PD-1 was found to be an independent marker for AKI ($P = 0.034$) and showed significant difference between pre- and post-chemoradiation ($P = 0.030$). The pre-chemoradiation PD-1 level was also significantly associated with an incidence of AKI and a higher tumor staging. This association could be used as a marker to observe and prevent the development of AKI among these groups of patients. A review by Han et al [18] reported high PD-1 expression on tumor-specific T cells. An increase in this expression as seen in this study correlates to two contrasting functions where it has the potential to be either advantageous or detrimental. In terms of its favorable effects, it plays a crucial part in controlling inefficient or detrimental immune responses and sustaining immune tolerance. On the other hand, PD-1 catalyzes the development of cancerous cells through disturbing protective immune responses, subsequently promoting the proliferation of cancerous cells [18]. Pathways with PD-1 also aid in the maintenance of T-cell homeostasis and exaggeration of self-tolerance, supporting the juggle of stimulatory and inhibitory signals, exerting unfavorable conditions and cancer growth.

PD-L1 as prognostic marker has been used in a variety of different urologic malignancies. According to several research, PD-L1 on tumor cells is linked to a higher grade and stage of the disease as well as a poorer prognosis. Nevertheless, the overall effect of the expression on prognosis in urothelial carcinoma (UC) is still a matter of debate at this time [19]. In a review by Zhou et al [17], although tumor cells expressed significantly higher levels of PD-L1 and its receptor PD-1 than the normal adjacent urothelium, no correlation was found with pathological staging, recurrence of disease, cancer-type specific, or overall mortality among patients who underwent radical cystectomy. However, in a subgroup of patients with organ-confined disease, the expression was linked with significantly elevated risk of all-cause mortality in univariate analysis, despite the trend towards elevated mortality risk observed in multivariate analysis that was not statistically significant [17]. Nakanishi et al were among the first researchers to identify an association between PD-L1 expression in tumor cells and a poorer clinical result with a higher probability of recurrence and a shorter OS in a group of 65 subjects diagnosed with UC [20].

Based on the research of Ferro et al addressing randomized controlled trial of PD1/L1 inhibitors alone or in combination with chemotherapy resulted that the treatment with an ICI-containing regimen was associated with a reduced risk of death in metastatic urothelial carcinoma (mUC) patients, which was associated with PD-L1 expression and metastatic site [21]. A new novel therapeutic opportunity was conducted by Lacovino et al [22], suggesting that the analysis of circulating tumor DNA (ctDNA) could offer valuable biomarkers, as evidenced by the Imvigor010 trial. Notably, ctDNA analysis yielded intriguing results. ctDNA levels have demonstrated efficacy in predicting complete tumor response in diverse cancer types. Patients with positive ctDNA results in the immunotherapy arm exhibited superior OS and PFS compared to the observation arm. These findings have the potential to impact neoadjuvant therapy practices, but further trials and evaluation of molecular biomarkers are imperative for refining patient selection [22].

Moreover, trials have been conducted on drugs formulation targeting PD-1 and PD-L1. The feedback on phase 1 trial on anti-PD-L1/PD-1 drugs have been positive in heavily pretreated patients with metastatic bladder cancer, demonstrating that the protein is useful for many other purposes other than its prognostic value. Monoclonal antibodies manipulating the PD-1/PD-L1 interaction may also prevent tumors from inducing T-cell tolerance and evading immune checkpoints. This treatment method has been promising towards metastatic renal cell carcinoma.

Limitations

Although showing potential, this research bears certain constraints. Firstly, the limited number of participants significantly restricted the scope of this study. Secondly, the study's retrospective approach led to the exclusion of some subjects due to incomplete data. Subsequent investigations, employing

more rigorous frameworks and methodologies, are essential to validate and build upon the current study's outcomes.

Conclusions

Tumor markers PD-1 pre-chemoradiation showed promising results as favorable prognostic factors to predict staging and AKI incidence in MIBC receiving chemoradiation therapy.

Acknowledgments

The authors thank the Ministry of Research and Technology, Higher Education of Indonesia for the research grant DRPM-PDUPT and PT. Prodia Widyahusada Tbk for the support. The authors acknowledge the role of Ignatius Ivan Putrantyo, MD, from Department of Urology, Faculty of Medicine, Universitas Indonesia - Haji Adam Malik General Hospital, Medan, Indonesia who is also an alumnus of Master of Science Program in Nanotechnology and Regenerative Medicine in University College London for his suggestion during this work preparation, especially in conducting its methodological reasoning and statistical interpretation.

Financial Disclosure

This research was supported by the Ministry of Research and Technology, Higher Education of Indonesia, with the research grant DRPM-PDUPT for the year 2021 (No.44/UN5.2.3.1/PPM/KP-DRPM/2021).

Conflict of Interest

The authors have declared that no competing interests exist.

Informed Consent

Written informed consent was obtained from the patient for publication of this article and accompanying images.

Author Contributions

Warli SM: concept of article, data collection, and text editing. Prapiska FF: concept of article, data collection, and text editing. Siregar DIS: concept of article, and data collection. Seja IA: data collection and analysis, writing the text of manuscript. All authors read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

References

1. Hu X, Li G, Wu S. Advances in diagnosis and therapy for bladder cancer. Cancers (Basel). 2022;14(13):3181. doi pubmed pmc
2. Ahmadi H, Duddalwar V, Daneshmand S. Diagnosis and staging of bladder cancer. Hematol Oncol Clin North Am. 2021;35(3):531-541. doi pubmed
3. Braet P, Sarto GVR, Pirovano M, Sprangers B, Cosmai L. Treatment of acute kidney injury in cancer patients. Clin Kidney J. 2022;15(5):873-884. doi pubmed pmc
4. Kitchlu A, McArthur E, Amir E, Booth CM, Sutradhar R, Majeed H, Nash DM, et al. Acute kidney injury in patients receiving systemic treatment for cancer: a population-based cohort study. J Natl Cancer Inst. 2019;111(7):727-736. doi pubmed pmc
5. Cosmai L, Porta C, Foramitti M, Perrone V, Mollica L, Gallieni M, Capasso G. Preventive strategies for acute kidney injury in cancer patients. Clin Kidney J. 2021;14(1):70-83. doi pubmed pmc
6. Lameire N, Vanholder R, Van Biesen W, Benoit D. Acute kidney injury in critically ill cancer patients: an update. Crit Care. 2016;20(1):209. doi pubmed pmc
7. Rampanelli E, Rouschop KM, Claessen N, Teske GJ, Pals ST, Leemans JC, Florquin S. Opposite role of CD44-standard and CD44-variant-3 in tubular injury and development of renal fibrosis during chronic obstructive nephropathy. Kidney Int. 2014;86(3):558-569. doi pubmed
8. Chen CH, Tsai YS, Tzai TS. Significance of HER2 expression in patients with upper tract urothelial carcinoma: A meta-analysis. Urological Science. 2016;27(4):238-243.
9. Cosmai L, Gallieni M, Porta C. Renal toxicity of anticancer agents targeting HER2 and EGFR. J Nephrol. 2015;28(6):647-657. doi pubmed
10. Manohar S, Kompotiatis P, Thongprayoon C, Cheungpasitporn W, Herrmann J, Herrmann SM. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. Nephrol Dial Transplant. 2019;34(1):108-117. doi pubmed
11. Wu CT, Lin WY, Chang YH, Chen WC, Chen MF. Impact of CD44 expression on radiation response for bladder cancer. J Cancer. 2017;8(7):1137-1144. doi pubmed pmc
12. Matsushita K, Toyoda T, Yamada T, Morikawa T, Ogawa K. Specific expression of survivin, SOX9, and CD44 in renal tubules in adaptive and maladaptive repair processes after acute kidney injury in rats. J Appl Toxicol. 2021;41(4):607-617. doi pubmed
13. Wu CT, Lin WY, Chen WC, Chen MF. Predictive value of CD44 in muscle-invasive bladder cancer and its relationship with IL-6 signaling. Ann Surg Oncol. 2018;25(12):3518-3526. doi pubmed
14. Li X, Ma X, Chen L, Gu L, Zhang Y, Zhang F, Ouyang Y, et al. Prognostic value of CD44 expression in renal cell carcinoma: a systematic review and meta-analysis. Sci Rep. 2015;5:13157. doi pubmed pmc
15. Gan K, Gao Y, Liu K, Xu B, Qin W. The clinical significance and prognostic value of HER2 expression in blad-

der cancer: a meta-analysis and a bioinformatic analysis. Front Oncol. 2021;11:653491. doi pubmed pmc
16. Soria F, Moschini M, Haitel A, Wirth GJ, Gust KM, Briganti A, Roupret M, et al. The effect of HER2 status on oncological outcomes of patients with invasive bladder cancer. Urol Oncol. 2016;34(12):533.e1-e10. doi pubmed
17. Zhou TC, Sankin AI, Porcelli SA, Perlin DS, Schoenberg MP, Zang X. A review of the PD-1/PD-L1 checkpoint in bladder cancer: From mediator of immune escape to target for treatment. Urol Oncol. 2017;35(1):14-20. doi pubmed
18. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020;10(3):727-742. pubmed pmc
19. Gadiot J, Hooijkaas AI, Kaiser AD, van Tinteren H, van Boven H, Blank C. Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer. 2011;117(10):2192-2201. doi pubmed
20. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother. 2007;56(8):1173-1182. doi pubmed
21. Ferro M, Crocetto F, Tataru S, Barone B, Dolce P, Lucarelli G, Sonpavde G, et al. Predictors of efficacy of immune checkpoint inhibitors in patients with advanced urothelial carcinoma: a systematic review and meta-analysis. Clin Genitourin Cancer. 2023. doi pubmed
22. Iacovino ML, Miceli CC, De Felice M, Barone B, Pompella L, Chiancone F, Di Zazzo E, et al. Novel therapeutic opportunities in neoadjuvant setting in urothelial cancers: a new horizon opened by molecular classification and immune checkpoint inhibitors. Int J Mol Sci. 2022;23(3):1133. doi pubmed pmc