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REVIEW

Predicting outcomes with pembrolizumab: A meta-analysis of pre-treatment hematological and clinical prognostic factors in advanced/metastatic urothelial carcinoma

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Summary ***Introduction: Recent studies have shown the therapeutic benefits of pembrolizumab in locally advanced or metastatic urothelial carcinoma (mUC). However, its high cost and variable patient responses remain challenges. This study aims to investigate the prognostic value of pre-treatment hematologic and clinical parameters in predicting outcomes in mUC patients.***

Methods: A comprehensive search was conducted across five databases for relevant articles. Studies that assessed the relationship between pre-treatment hematological and clinical parameters and either progression free survival (PFS) or overall survival (OS) were included and evaluated for bias.

Results: The literature search identified 27 studies encompassing a total of 4,731 patients. Several prognostic factors linked to OS were identified, with the most adverse survival outcomes associated with hypoalbuminemia (HR 3.13, 95% CI: 2.52-3.88), ECOG-PS ≥2 (HR 2.94, 95% CI: 2.65-3.26), and the presence of liver metastasis (HR 2.44, 95% CI: 2.16-2.76). Additionally, the presence of bone, liver, or lung metastases, ECOG-PS ≥ 2, surgical excision of the primary tumor, elevated C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR), and low hemoglobin levels were all correlated with unfavorable PFS and OS.

Conclusions: Patients with metastatic urothelial carcinoma and poor performance status, visceral metastases, high NLR or CRP, or low hemoglobin may have poorer survival, even with pembrolizumab. These factors may help guide clinical decisions for patients with advanced/metastatic urothelial carcinoma.

KEY WORDS: Urothelial; Pembrolizumab; Survival.

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INTRODUCTION

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is a type of cancer that originates in the urothelium. UC includes all tumors found in the bladder, upper urinary tract (including the renal pelvis and ureters), and proximal urethra, with bladder cancer constituting approximately 90% to 95% of these cases (1). It is the second most prevalent urological malignancy in men, with an estimated global mortality exceeding 200,000 (2).Current treatment options are dependent on the patient's tumor stage, grade, comorbidity, and performance. When the disease progresses to unresectable, locally advanced, or *metastatic UCs* (mUC), the administration of systemic therapy is generally recommended (3). For many years, cisplatin-based cytotoxic chemotherapy has been the standard treatment for mUC. However, as the disease advances, up to 50% of patients requiring chemotherapy may be considered unfit for cisplatin-based treatment due to the presence of comorbidities (4). Recently, immunotherapy using immune checkpoint inhibitors have emerged as alternative treatment options for individuals with mUC (5). One notable example of this class of drugs is pembrolizumab, a PD-1 inhibitor agent that functions by inhibiting the interaction between programmed cell *death protein-1* (PD-1) and its *ligand* (PD-L1) (6). Numerous ongoing studies are investigating these agents as first- and second-line therapies, both alone and in combination with chemotherapy or in a maintenance regimen, thereby signaling their steadily increasing importance (7).

Consequently, the *European Association of Urology* (EAU) has recently recommended the use of *Enfortumab vedotin* (EV) in combination with pembrolizumab as a first-line treatment for patients considered suitable for combination therapies, irrespective of their cisplatin eligibility, which significantly reduces treatment-related toxicity (3, 8). Despite these recommendations, EV may not be accessible in various countries. Furthermore, certain patients may be ineligible for EV treatment, including those with uncontrolled diabetes, peripheral neuropathy, and significant skin disorders (9). Therefore, for this patient population - comprising those who are either (1) ineligible for combination therapy or EV, (2) eligible for combination therapy but without access to EV, or (3) ineligible for both combination therapy and unfit for platinum-based chemotherapies - there exists uncertainty concerning the optimal treatment options available to them. For patients who are ineligible for platinum-based chemotherapies, current guidelines recommend assessing PD-L1 positivity status through immunohistochemistry. The *European Medicines Agency* (EMA) has approved pembrolizumab and atezolizumab for first-line treatment in patients with positive PD-L1 staining, while the U.S. *Food and Drug Administration* (FDA) has

approved pembrolizumab for use regardless of PD-L1 status (3). Despite these recommendations, the historical outcomes for this patient group have been unfavorable. Often, best supportive care is preferred over systemic therapy. This highlights the need for a biomarker to better predict which patient populations will benefit from these treatments. Several biomarkers have been proposed, including PD-L1 expression (10), *tumor mutational burden* (TMB), microsatellite instability (MSI), and mismatch repair deficiency (11). However, these biomarkers have been found to lack sufficient predictive accuracy. By systematically reviewing existing literature, we aim to identify the several hematological and clinical parameters that can better predict the population of mUC patients who are likely to benefit from pembrolizumab monotherapy.

Methods

This systematic review followed PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Cochrane handbook for systematic reviews of interventions. Our full protocol was registered in PROSPERO (registration number CRD42024608476).

Search strategy

A systematic literature data search was conducted in *PubMed*, *Scopus*, *ProQuest*, *Cumulative Index to Nursing and Allied Health Literature* (CINAHL) via EBSCO, and *Cochrane Central Register of Controlled Trials* (CENTRAL) for studies published up to November 2, 2024. We additionally performed a manual hand-search on Google and the reference lists of the included studies to maximize the search results. The following main keywords were initially established: "*pembrolizumab*", "*urothelial carcinoma*", along with prognostic factors such as "*hemoglobin*", "*neutrophil*", "*c reactive protein*" and "*lactate dehydrogenase*". We subsequently added several *Medical Subject Headings* (MeSH) and other free-text terms to construct database-specific search terms. The full search strings for each database are provided in ***Supplementary Table S1***. No publication date and language restrictions were set in all searches.

Eligibility criteria

We included clinical studies that examined the association between hematological parameters and outcomes in patients with advanced/metastatic UCs. To be included in this systematic review and meta-analysis, studies had to meet the following criteria: (1) the study population consisted of adults aged 18 years or older; (2) the study exclusively included UC patients receiving pembrolizumab monotherapy; (3) it assessed the relationship between prognostic factors and outcomes; and (4) it was either a clinical trial or an observational study (case-control or cohort studies). We accepted studies published in any language. Studies were excluded if: (1) the study was a review article, case report, case series, or conference abstract; (2) the full-text was irretrievable; or (3) raw data could not be separated.

Data extraction and quality assessment

Two independent investigators performed data extraction from each included study and recorded it within the pre-specified form, with discrepancies resolved by the consensus with an independent third investigator. The data extracted include the name of the first author and year of publication, study location (country and region), study design, sample size, pembrolizumab dose used, patients characteristics (age, sex), follow up duration, clinical characteristics (ECOG PS ≥ 2, site of primary tumor, metastatic sites), *overall response rate* (ORR), and relationship between prognostic factor and outcomes.

Risk of bias assessment

For the risk of bias assessment, *Quality in Prognosis Studies* (QUIPS) tool was used to assess the methodological quality of each study and subsequently judged to be yielding low, moderate, or high risk of bias (12). The visualization of the bias assessment's summary was generated using the Robvis tool (13). The methodological quality assessment of the included studies was conducted by two independent reviewers (NDF and JNR). Discordance in judgements was resolved simultaneously in a consensus with a third reviewer (KYU). We planned to conduct a funnel-plot and Egger's test to assess the possibility of publication bias across studies.

Statistical analysis

For the primary outcome of overall survival, we reported pooled *hazard ratios* (HRs) with their corresponding 95% *confidence intervals* (CIs). The initial quantitative synthesis was performed by comparing each prognostic factor, applying the generic inverse variance method within a DerSimonian-Laird fixed-effects model. In cases where significant heterogeneity was detected, a random-effects model was subsequently applied. In the case where two or more studies involved overlapping populations, analysis was prioritized to studies with larger sample sizes.

The presence of heterogeneity was analyzed using Cochran's Q and I^2 statistics, where heterogeneity was classified as negligible, low, moderate, or high to I^2 values of 0%, 25%, 50%, and 75%, respectively (14). Whenever appropriate (n ≥ 10), potential publication bias was evaluated visually by contour-enhanced funnel plot and quantitatively by Egger's and Begg's tests.

Whenever available, subgroup analyses were carried out based on the risk of bias. On the other hand, sensitivity analyses were conducted by leave-one-out analysis and the exclusion of studies with high-risk of bias. Meta-regression analyses were carried out for (1) year of publication, (2) % of males, (3) sample size; (4) mean age, (5) % of upper tract primary tumor site, and (6) follow up duration whenever possible. All analysis was conducted with R ver. 4.3.0 (*R Foundation for Statistical Computing, Vienna, Austria*). Conventional meta-analysis was conducted using the meta package, while meta-regression analyses were performed using the metafor package.

Results

Study selection

A PRISMA flowchart of the study selection process is depicted in Figure 1. Initial searches of the five databases yielded 4449 records. We identified duplicates, and a

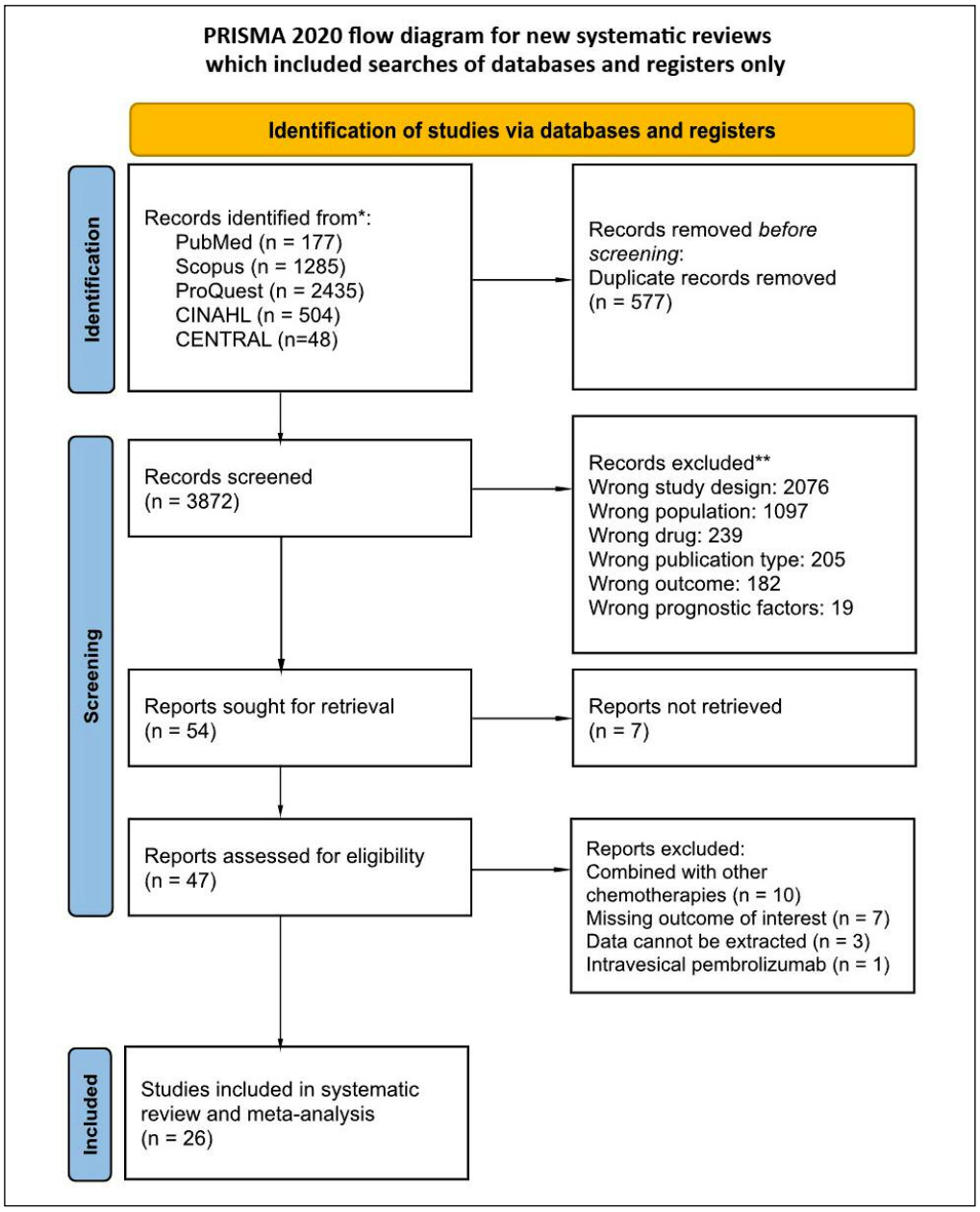


Figure 1.
PRISMA flowchart of the study selection process.

total of 577 records were removed. Of the remaining 3872 records, 3818 records were excluded. One conference abstract with unavailable full-text and six other articles were not retrieved. We then thoroughly reviewed forty-seven studies and further excluded twenty-one studies, due to the following: (1) combined with other chemotherapies (n = 10), missing outcome of interest (n = 7), data cannot be extracted (n = 3), and use of intravesical pembrolizumab (n = 1). Ultimately, the entire screening process led to the inclusion of twenty-six eligible studies in this systematic review.

Study characteristics

In our review, we analyzed a total cohort of 4,679 patients, with a median age ranging from 68.9 to 76 years. Among the total population, 3,092 patients were male, accounting for 71.5% of the participants. The majority of the research was conducted in Japan, with only one study taking place in the Netherlands. All studies used a retrospective comparative design. The median follow-up duration was quite variable, ranging from 5.7 to 34 months. Regarding ECOG *performance status* (PS), five studies did not disclose the percentage of patients with PS ≥ 2, while four studies only disclosed those with a PS of ≥ 1. In total, 604 patients (18.3%) were identified with a PS of ≥ 2. Among the studies that reported primary tumor sites, 1,863 patients (43.1%) had tumors in the upper urinary tract, while 2,212 patients (51.7%) had tumors originating from the bladder. The primary outcomes of our review were ORR, PFS, and OS. The values for each outcome are further reported in Table 1.

Quantitative analysis (meta-analysis)

Twenty-six studies with a total sample of 4,679 patients

Table 1.
Characteristics of included studies.

No	Author; Year	Location	Study Design	Sample size	Age (years)	Male	Follow up duration (months)	ECOG PS ≥ 2	Site of Primary Tumour	Outcome		
										ORR (%)	PFS (median)	OS (median)
1	*Akashi; 2023* (40)	Japan	Retrospective study	41	75 (58-81)	35 (85.4)	16.5 (1.0-47.8)	4 (10)	UTUC: 16 (40) BC: 25 (60)	29.3	4.9 (1.2-8.6)	17.8 (11.5-24.0)
2	*Fukata; 2022* (41)	Japan	Retrospective study	44	70 (54-80)	30 (68)	13.2 (1-40.8)	7 (16)	UTUC: 16 (36) BC: 28 (64)	54.5	NR	NR
3	*Furubayashi; 2021* (42)	Japan	Retrospective study	105	72 (67-77)	75 (71.4)	8.4 (4.1-15.7)	10 (9.5)	UTUC: 41 (39) BC: 42 (40) Both: 22 (21)	36.2	NR	NR
4	*Ito; 2020* (43)	Japan	Retrospective study	755	ECOG 0-1: 72.09 (66.3-77.23) ECOG 2: 72.01 (66.49-76.21) ECOG 3-4: 70.18 (63.5-75.72)	568 (75.2)	7.2	153 (20.26)	UTUC: 373 (49.4) BC: 382 (50.6)	26.2	NR	NR
5	*Kawashima; 2021(a)* (44)	Japan	Retrospective study	165	73 (28-93)	117 (70.9)	6.71 (0.26-37.0)	27 (16.3)	UTUC: 99 (60) BC: 61 (37) Both: 5 (3.0)	21.8 (2.32-2.88)	2.6	NR
5	*Kawashima; 2021(b)* (45)	Japan	Retrospective study	103	73 (30-86)	76 (73.8)	6.67 (0.99-36.1)	23 (22.3)	UTUC: 58 (56.3) BC: 45 (43.7)	30.1 (1.79-5.31)	3.55	NR
6	*Kita; 2022* (45)	Japan	Retrospective study	739	NR	554 (75)	34	150 (20.3)	UTUC: 352 (47.63) BC: 384 (51.9) Unknown: 4 (0.4)	27.2	3.5	NR
7	*Kobayashi; 2020* (46)	Japan	Retrospective study	463	71 (31-88)	357 (77.1)	17.7 (12.9-21.4)	90 (19.4)	UTUC: 179 (38.7) BC: 230 (49.7) Both: 27 (5.8) Unknown: 1 (0.2)	30.5	NR	10.2 (8.2-11.7)
8	*Komura; 2023* (47)	Japan	Retrospective study	100	70.30 (9.03)	78 (78)	NR	NR	UTUC: 18 (18) BC: 77 (77) Both: 5 (5)	22	NR	NR
9	*Kurashina; 2023* (18)	Japan	Retrospective study	75	NR	NR	7.3 (0.47-47.6)	NR	NR	21.3	NR	8.5 (6.4-10.7)
10	*Miyama; 2022* (48)	Japan	Retrospective study	50	71.9 (1.69)	31 (62)	NR	NR	UTUC: 23 (46) BC: 27 (54)	30	3.62	10.97
11	*Nagasaka; 2024* (49)	Japan	Retrospective study	48	76 (47-88)	31 (64.58)	NR	2 (4.17)	UTUC: 48 (100)	27.1	2.2	5.47
12	*Nishio; 2024* (50)	Japan	Retrospective study	220	NR	154 (70)	7.3	123 (56)*	UTUC: 85 (39) BC: 135 (61)	29.1	NR	NR
13	*Ogihara; 2020* (51)	Japan	Retrospective study	78	72.16 (9.29)	54 (69.23)	7.42 (0.9-17.9)	18 (23.07)*	UTUC: 35 (44.9) BC: 43 (55.1)	29.5	NR	NR
14	*Rijnders; 2023* (52)	Netherlands	Retrospective study	71	NR	51 (71.8)	NR	NR	UTUC: 21 (29.6) BC: 44 (61.9) Both: 6 (8.5)	NR	NR	NR
15	Sato; 202353	Japan	Retrospective study	101	71 (33-85)	71 (70.3)	19 (3-54)	17 (16.8)	UTUC: 35 (34.7) BC: 66 (65.3)	19.8	NR	13
16	Shimizu; 202054	Japan	Retrospective study	27	71.48 (7.51)	23 (85)	7.88 (4.76)	12 (44)	UTUC: 12 (44) BC: 15 (56)	37.0	4	7
17	Tamura; 202055	Japan	Retrospective study	41	68.91 ± 8.08	29 (70)	6.2 (4.4)	6 (15)	UTUC: 22 (54) BC: 19 (46)	14.6	2.5 (1.4-6.2)	11.9
18	Tanabe; 202415	Japan	Retrospective study	331	73 (68-78)	241 (73)	7.3 (3.4-16.5)	57 (17)	UTUC: 154 (47) BC: 177 (53)	32.3	3.3 (2.6-4.3)	9.6 (7.3-13.2)
19	Tomioka-Inagawa; 202216	Japan	Retrospective study	211	72.1 (1.63)	121 (57.3)	10	28 (13.4)	UTUC: 49 (23.2) BC: 89 (42.2)	25.1	5 (3-5)	17 (15-26)

20 Uchimoto; 202156	Japan	Retrospective study	212	72 (8.95)	151 (71.2)	8	120 (56.6)*	UTUC: 82 (38.7) BC: 130 (61.3)	26.4	NR	11.7
21 Uchimoto; 202257	Japan	Retrospective study	177	72 (66-78)	125 (70.6)	6	100 (56.5)*	UTUC: 68 (38.4) BC: 109 (61.6)	26.6	NR	14
22 Umeda; 202258	Japan	Retrospective study	115	75 (70-79)	29 (65.9)	7.4 (4.6-16.4)	NR	UTUC: 22 (50) BC: 21 (47.7) Both: 1 (2.3)	25.2	NR	NR
23 Yamamoto; 202259	Japan	Retrospective study	31	74 (70-82)	22 (71)	5.7 (3.4-16.3)	3 (10)	UTUC: 9 (29) BC: 22 (71)	35.5	NR	NR
24 Yamashita; 202360	Japan	Retrospective study	96	74 (70-79)	69 (72)	7 (4-17)	15 (15.6)	UTUC: 46 (48) BC: 41 (43) Both: 9 (9)	23	2	NR

Categorical data are shown as n (%), while numerical data are presented as mean (SD) or median (IQR).
NR: Not reported; ECOG-PS: Eastern Cooperative Oncology Group Performance Status Scale; UTUC: Upper urinary tract urothelial carcinoma; BC: Bladder urothelial carcinoma.
**ECOG PS >= 1.*

were included for meta-analysis. Pooled PFS and OS were measured using *hazard ratios* (HRs).

Demographic factors

The demographic factors chosen for this analysis are age and gender. Among these factors, age ≥ 70-75 years old are found to be associated with worse progression free survival (HR 1.21, 95%CI 1.04-1.41, n = 8 studies). Furthermore, our investigation revealed a lack of significant heterogeneity regarding these outcomes.

Clinical factors

Ten clinical factors are included in this analysis, consisting of metastasis sites (bone, liver, lung, and lymph node), ECOG-PS ≥ 2, UTUC primary site, prior surgical removal for primary site, pure UC pathological type, smoking, < 90 days from previous chemotherapy (Table 2). For PFS, we detected one factor with moderate amount of heterogeneity, which is UTUC primary site (I^2 = 58%). For OS, we detected three factors with moderate to high amounts of heterogeneity, including presence of bone (I^2 = 64%) or lymph node metastasis (I^2 = 73%), and ECOG-PS ≥ 2 (I^2 = 86%). All heterogeneity tests are performed using REM. Based on the HRs, there are six clinical factors that can be considered as prognostic factors. For PFS, five factors are linked with worse survival are as follows: (1) ECOG-PS ≥ 2 (HR 2.30, 95%CI 1.91-2.76); (2) pure UC pathological type (HR 2.33, 95%CI 1.20-4.54); (3) presence of liver metastasis (HR 1.70, 95%CI 1.35-2.14); (4) lung metastasis (HR 1.34, 95%CI 1.10-1.64); and (5) bone metastasis (HR 1.29, 95%CI 1.02-1.64). On the contrary, surgical removal of primary site (HR 0.80, 95%CI 0.65-0.99) is associated with better survival. Sensitivity analysis of PFS factors suggest that the provided overall effects are robust and not affected by any single study.

For OS, five factors are also associated with worse survival: (1) Presence of bone metastasis (HR 1.94, 95%CI 1.25-3.0); (2) Liver metastasis (HR 2.44, 95%CI 2.16-2.76); (3) Lung metastasis (HR 1.35, 95%CI 1.18-1.56); (4) ECOG-PS ≥ 2 (HR 3.38, 95%CI 2.17-5.28); (5) Time from previous chemotherapy < 90 days (HR 1.42, 95%CI 1.22-1.64). A leave-one-out sensitivity analysis was conducted for all prognostic factors showing significant heterogeneity. The analysis revealed that the presence of bone metastasis, upon removal of one study by *Tanabe et al.* (15) resulted in a shift of the pooled effect from significant to nonsignificant, and significant reduction of heterogeneity. The same result is found for C-reactive protein level. In contrast, the effects of all other clinical factors remained robust (***Supplementary Figures S2B, S2D***).

Hematological factors

We identified four potential hematological markers as prognostic factors: albumin, CRP, hemoglobin, and NLR. Most outcome analyses demonstrated nonsignificant heterogeneity, except for CRP's association with OS, which exhibited high heterogeneity (I^2 = 94%). For PFS, three markers showed a significant effect: elevated CRP (HR 1.94, 95%CI 1.54-2.45), low hemoglobin (HR 1.80, 95%CI 1.51-2.14), and high NLR (HR 1.65, 95%CI 1.44-1.89). For OS, we found four markers associated with poorer survival: hypoalbuminemia (HR 3.13, 95%CI 2.52-3.88), high CRP (HR 2.18, 95%CI 1.07-4.42), low hemoglobin (HR 2.08, 95%CI 1.85-2.35), and high NLR (HR 1.93, 95%CI 1.71-2.18). Sensitivity analysis was performed for all outcomes. For CRP, removing one study by Tomioka-Inagawa significantly reduced heterogeneity (16), while excluding a study by *Tanabe et al.* made the effect size nonsignificant (15). Given this, we advise interpreting these results with caution, while all other hematological markers showed stable outcomes.

Subgroup and meta-regression analyses

We performed subgroup and meta-regression analyses for prognostic factors with a sufficient number of studies: (1) age, (2) gender, (3) presence of liver metastasis, (4) ECOG-PS ≥ 2, and (5) UTUC primary site associated with OS. For most factors, we found no significant differences between subgroups. For ECOG-PS, results of the subgroup analysis of risk of bias are presented in the supplementary materials. Meta-regression analyses on the percentage of male (p = 0.01) suggest that this factor influenced the effect of ECOG-PS ≥ 2 on overall survival (***Supplementary Table S3 and Figure S4***). Additionally, subgroup comparisons based on risk of bias revealed no statistically significant differences in effect sizes between

Table 2.
Pooled hazard ratios of demographical, clinical, and hematological factors associated with PFS and OS.

Factors	Definition	Number of studies	Hazard ratio (95%CI)	Heterogeneity		Overall effect	
				I^2	p-value	Z-score	p-value
Progression free survival							
Demographic factors							
Age	≥ 70-75 years old	8	1.21 (1.04-1.41)	0	0.84	2.44	0.01
Gender	Male *vs.* female	8	0.99 (0.84-1.17)	1	0.42	-0.14	0.89
Clinical factors							
ECOG-PS	≥ 2 *vs.* < 2	8	2.30 (1.91-2.76)	39	0.12	8.9	< 0.01
Pathological type	Pure *vs* mixed UC	3	2.33 (1.20-4.54)	3	0.36	2.49	0.01
Liver metastasis	Yes *vs.* no	5	1.70 (1.35-2.14)	13	0.33	4.52	< 0.01
Lung metastasis	Yes *vs.* no	4	1.34 (1.10-1.64)	0	0.73	2.93	< 0.01
Lymph node metastasis	Yes *vs.* no	5	0.84 (0.70-1.01)	0	0.78	-1.82	0.07
Bone metastasis	Yes *vs.* no	3	1.29 (1.02-1.64)	0	0.89	2.12	0.03
Primary site	UTUC *vs* BC	8	1.05 (0.73-1.52)	58	0.02	0.32	0.76
Surgical removal of primary site	Yes *vs.* no	5	0.80 (0.65-0.99)	5	0.38	-2.07	0.04
Hematological parameters							
CRP	High *vs.* low	4	1.94 (1.54-2.45)	21	0.28	5.62	< 0.01
Hemoglobin	Low *vs.* high	5	1.80 (1.51-2.14)	0	0.69	6.52	< 0.01
NLR	High *vs.* low	6	1.65 (1.44-1.89)	13	0.33	7.22	< 0.01
Overall survival							
Demographic factors							
Age	≥ 70-75 years old	10	1.00 (0.99-1.01)	43	0.07	0.16	0.87
Gender	Male *vs.* female	10	0.97 (0.87-1.08)	30	0.17	-0.58	0.57
Clinical factors							
Bone metastasis	Yes *vs.* no	5	1.94 (1.25-3.00)	64	0.03	4.2	0.01
Liver metastasis	Yes *vs.* no	10	2.44 (2.16-2.76)	31	0.16	14.39	< 0.01
Lung metastasis	Yes *vs.* no	7	1.35 (1.18-1.56)	34	0.17	4.29	< 0.01
Lymph node metastasis	Yes *vs.* no	7	0.94 (0.67-1.33)	73	< 0.01	-0.4	0.7
ECOG-PS	≥ 2 *vs.* < 2	10	3.38 (2.17-5.28)	86	< 0.01	6.68	< 0.01
Pathological type	Pure *vs.* mixed UC	5	1.17 (0.88-1.55)	21	0.28	1.07	0.29
Primary site	UTUC *vs* BC	10	1.07 (0.97-1.18)	7	0.38	1.36	0.17
Smoking	Yes *vs.* no	6	1.03 (0.93-1.14)	0	0.44	0.57	0.57
Surgical removal of primary site	Yes *vs.* no	4	0.71 (0.58-0.88)	0	0.6	-3.21	< 0.01
Time from previous chemotherapy	< 90d *vs.* ≥ 90d	4	1.42 (1.22-1.64)	0	0.66	4.66	< 0.01
Hematological parameters							
Albumin	< 3.5-3.7	3	3.13 (2.52-3.88)	0	0.7	10.4	< 0.01
CRP	High *vs.* low	5	2.18 (1.07-4.42)	94	< 0.01	3.05	0.04
Hemoglobin	Low *vs.* high	8	2.08 (1.85-2.35)	23	0.24	12.05	< 0.01
NLR	High *vs.* low	8	1.93 (1.71-2.18)	46	0.07	10.52	< 0.01

ECOG-PS: Eastern Cooperative Oncology Group Performance Status Scale; UC: Urothelial carcinoma; UTUC: Upper urinary tract urothelial carcinoma; BC: Bladder urothelial carcinoma; CRP: C-reactive protein.

studies classified as low risk *versus* moderate-high risk (***Supplementary Figure S5***).

Publication bias and quality assessment of included studies

For outcomes with included studies ≥ 10, we performed publication bias assessment by generating funnel plots. For overall survival, one study each by *Tanabe et al.* (15), *Kobayashi et al.* (17), and *Kurashina et al.* (18) appeared as outliers in the funnel plots for age, gender, and liver metastasis, respectively. In contrast, a total of three studies assessing ECOG-PS fell outside the funnel plot, suggesting that ECOG-PS results may be particularly affected by publication bias. Nonetheless, Egger's test did not show statistically significant bias for any of the evaluated risk factors (***Supplementary Table S2 and Figure S3***).

Three reviewers assessed the risk of bias within individual studies using the QUIPS tool, given that all the included studies were studies evaluating prognostic factors (Figure 2). Among the studies reviewed, six were identified as having a high risk of bias due to attrition. All the included studies were retrospective in nature, and the high risk of attrition bias stemmed from either a lack of reporting on missing data or the exclusion of a significant portion of data (> 10%) from the final analysis. We identified three studies with a moderate risk of bias, while the remaining studies had a low risk of bias. Some studies were rated as having a moderate risk of bias related to participation, primarily because they failed to report details such as the study location or the recruitment period. Additionally, a few studies exhibited a moderate risk of bias due to confounding, as significant confounders were neither addressed in the study design nor adjusted for in the statistical analysis.

Figure 2 and 3 provides an in-depth visualization of the risk of bias assessment for each study.

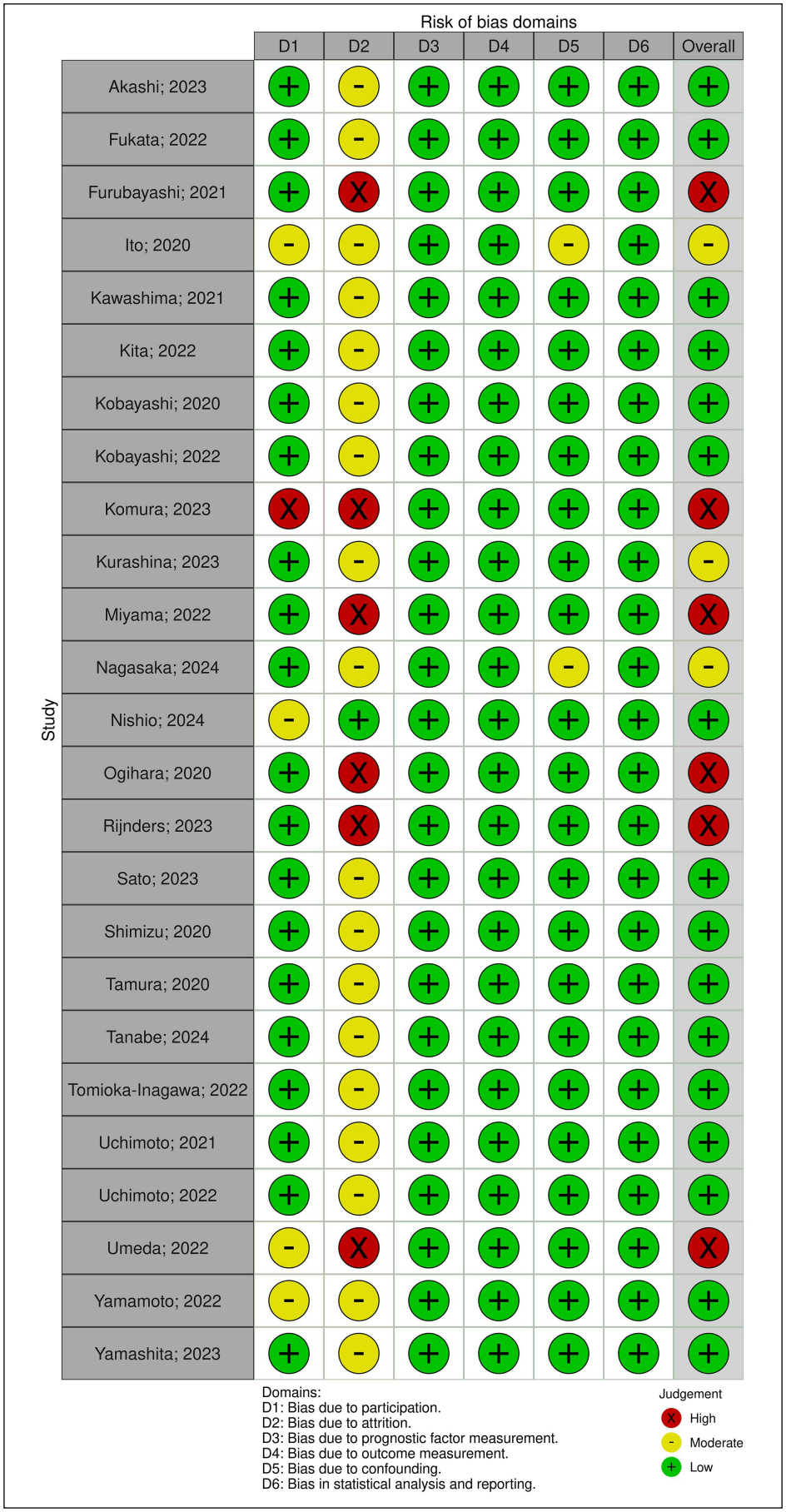
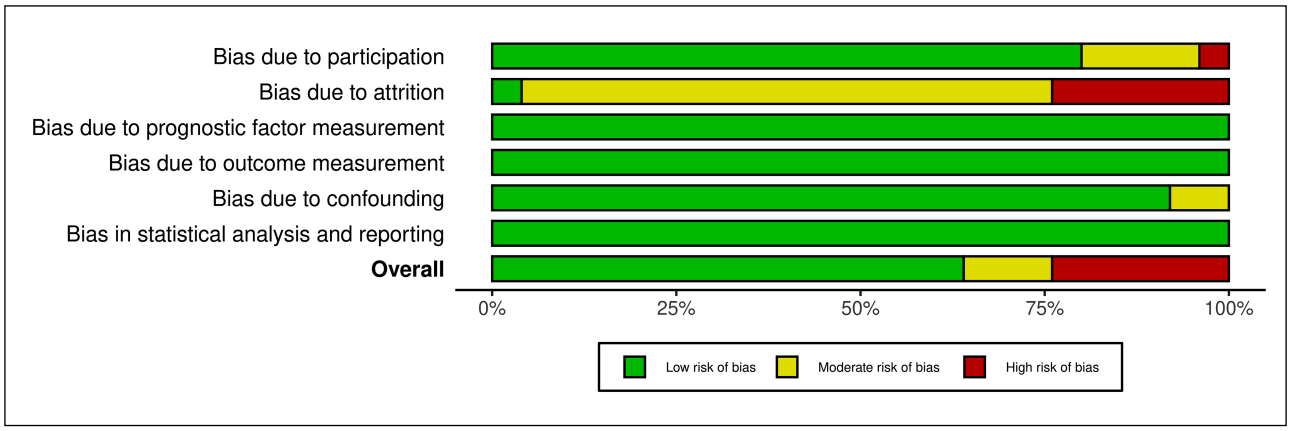


Figure 2.
Traffic plot of the included studies risk of bias assessed by QUIPS tool.

Figure 3.
Summary plot of the included studies risk of bias assessed by QUIPS tool.



Discussion

Given that only a small percentage of patients derive benefits from immunotherapy, numerous predictive biomarkers have been developed to improve outcome predictions. Current evidence indicates that PD-L1 expression serves as the most reliable biomarker for predicting which patients with advanced UC are likely to respond to anti-PD-1 or anti-PD-L1 therapies (19-21). However, pembrolizumab monotherapy showed comparable survival to platinum-based chemotherapy regardless of PD-L1 *combined positive score* (CPS) (22). That is why in this study, we identified several potential hematological and clinical risk factors linked to unfavorable outcomes in patients with advanced UC receiving pembrolizumab monotherapy.

The metastatic sites significantly associated with worse progression free survival and overall survival are the liver, lung, and bone. Lymph nodes are the most common site of metastasis in urothelial carcinoma, with other studies reporting an incidence of 69%-90% (23). In accordance with this study, patients with lymph-node-only metastasis tend to have better PFS and OS compared to those with visceral metastases. This better prognosis may be explained by the presence of immune cells within the lymph nodes, which may enhance the efficacy of *immune checkpoint inhibitors* (ICIs) and other therapies.

Additionally, lymph-node-only metastasis may represent an earlier stage of cancer progression, with less tumor heterogeneity or clonal evolution compared to visceral metastasis (24). In contrast, liver metastasis occurs less frequently, with an incidence ranging from 19% up to 47%, but is associated with the worst survival outcomes among metastatic sites, as this research demonstrates (25). Patients with liver metastases have a median overall survival of only seven months, highlighting its poor prognosis compared to other metastatic patterns (26). Liver metastases are often multiple and diffuse, indicating systemic disease with high tumor burden Hypotheses for the poor prognosis of liver metastases include the immunosuppressive microenvironment of the liver, increased tumor mutation burden, clonal evolution, and poor response to chemotherapy and ICIs (24, 25). Furthermore, small metastases in the liver might not be detected by imaging techniques and are only revealed later on during autopsy, such as in the study performed by *Wallmeroth* (27). Liver-directed therapies such as radiofrequency ablation may offer some survival benefit on top of systemic chemotherapy (26).

Bone metastases are reported in 32%-47% of patients with mUC (23, 27). Recent studies have reported a higher incidence of bone metastases, potentially due to advanced imaging techniques like bone scintigraphy and MRI, which have improved the detection of osseous lesions. Bone metastases often coexist with other metastatic sites and contribute to significant morbidity, including pain and fractures, further complicating the disease course (23). Lung metastases, present in 37%-45% of cases, are another common manifestation of advanced urothelial carcinoma (25). These metastases typically appear as pulmonary nodules, consolidation, or lymphangitic spread. Although lung metastases are less associated with poor survival outcomes than liver metastases, their presence often indicates advanced disease progression (25). The differences in prognosis among metastatic sites may be attributed to several factors. Organotropism and tumor biology likely play significant roles, as metastases to organs like the liver may reflect advanced clonal evolution, greater tumor heterogeneity, and a more unfavorable tumor microenvironment (24, 25). Immune heterogeneity across metastatic sites, such as variations in tumor-infiltrating lymphocytes, PD-L1 expression, and immune response, can further influence prognosis and treatment outcomes. Additionally, molecular factors, such as MTAP-deficient tumors, have been associated with an increased likelihood of visceral metastases and worse outcomes with ICIs (28).

Patients with an ECOG PS of ≥ 2 are clearly at a higher risk of poor outcomes. This is particularly significant as patients with a PS > 2 are typically considered unfit for platinum-based chemotherapy. In such cases, the European Association of Urology suggests that best supportive care may be the most appropriate approach to optimize quality of life and minimize treatment-related harm (3). For patients with a PS of 2, careful consideration of additional risk factors and overall organ function is essential, e.g. *glomerular filtration rate* (GFR) of less than 60mL/min. This decision should be made in close collaboration with experts to ensure a tailored and bal-

anced approach that takes into account the patient's comorbidities, disease burden, and treatment goals.

In contrast, patients with a PS of 0-1 represent a subgroup that may be better suited for more active treatment strategies. For these individuals, pembrolizumab monotherapy could be considered in two specific scenarios: (1) when *enfortumab-vedotin* (EFV) and platinum-based chemotherapy are unavailable, or (2) when the patient is deemed ineligible for platinum-based chemotherapy due to other contraindications. While pembrolizumab monotherapy may not be the first-line option in many cases, its role as an alternative should be weighed carefully, particularly in light of emerging evidence supporting its efficacy and safety in select patient populations. In a phase II single-arm trial involving 370 participants with cisplatin-ineligible urothelial carcinoma, pembrolizumab monotherapy achieved an objective response rate of 26% among 69 patients with metastatic UTUC (29).

Several prognostic blood- or serum-based parameters have been reported in advanced UCs, including CRP, LDH, *platelet-to-lymphocyte ratio* (PLR), and *neutrophil-to-lymphocyte ratio* (NLR). In our study, low hemoglobin and high NLR consistently demonstrated worse PFS and OS. *Hemoglobin* (HGB) level is one of the parameters that has been used as inclusion criteria in the original trials assessing pembrolizumab for advanced urothelial carcinoma (20). Several studies of other types of cancers have shown significantly longer OS and PFS in patients with higher HGB levels undergoing immunotherapy (30, 31). In one study, HGB levels were positively correlated with clinical outcomes in cancer patients receiving immunotherapy, but not in those not undergoing such treatment, suggesting a positive association between HGB levels and response to immunotherapy. Additionally, it was found that this effect was independent of other clinicopathological factors, including sex, age, tumor stage, and tumor mutational burden (TMB), as well as established biomarkers like PD-L1 expression and *microsatellite instability* (MSI) (32). It is thought that hypoxia induced by HGB reduction stimulates tumor growth and progression and decreases their sensitivity to anticancer treatments, eventually contributing to poor patient outcomes (33).

Pretreatment NLR and lymphocytopenia have been linked to increased mortality rates in patients with solid tumors, as well as in the general population (34, 35). This suggests that NLR is not a specific biomarker for patients with UCs. One study found that after adjusting for other prognostic factors, patients with a decrease in post-chemotherapy NLR experienced longer OS compared to those with merely low pretreatment NLR levels. These findings suggest a unique association between response to 1st-line chemotherapy with efficacy of pembrolizumab treatment (17). Furthermore, a trend was observed suggesting that high NLR is associated with worse OS, particularly in metastatic diseases. This suggests either a greater tumor burden or more prolonged chronic inflammatory process (36). The mechanisms linking high NLR to poor outcomes in cancer patients remain poorly understood. Research has indicated that neutrophils, along with other cells like macrophages, secrete various factors that promote tumor growth, likely contributing to an environment that stimulates tumor progression (34). A range of inflammatory cytokines play a role in the systemic inflammatory response. Notably, IL-6 specifically enhances the production of acute-phase proteins, such as C-reactive protein, while simultaneously reducing albumin synthesis in the liver (37). In this review, we also identified an association between high CRP levels and hypoalbuminemia with poor OS, although this was supported by fewer studies and significant heterogeneity. Interestingly, varying cutoff points for both hemoglobin and NLR across studies were documented. Despite these differences, given the relatively narrow range of hemoglobin and NLR cutoffs used in our analysis, we do not expect this variability to significantly affect the interpretation of our findings.

In our study, we found that higher CRP levels are associated with worse outcomes, although there is considerable heterogeneity. This variability may be attributed to the different cutoff values used in the studies included. The relationship between CRP and cancer prognosis is a complex interplay of cytokines. Tumor cells release cytokines and chemokines such as IL-6 and IL-8, which result in elevated serum CRP levels. Moreover, tumor growth and invasion can cause inflammation, contributing to further rise in CRP (38). High CRP levels have also been demonstrated to cause DNA damage and weaken immune function, further facilitating carcinogenesis and tumor progression (39).

To our knowledge, this is the first systematic review and meta-analysis that comprehensively assess prognostic value of pre-treatment hematologic and clinical parameters in predicting outcomes of patients with locally advanced or metastatic urothelial carcinoma. While we have made every effort to ensure the highest quality in this study, we recognize several limitations. First, the studies included in this review were quite heterogeneous, as they encompassed patients with different lines of chemotherapy. Second, most of the studies that met our inclusion criteria originated from Japan. These limitations underscore the necessity for standardized protocols and more rigorous studies to enhance our understanding of the predictive value of these prognostic factors in immunotherapy.

Conclusions

Our research revealed a number of important prognostic variables linked to survival in pembrolizumab-treated mUC patients. The occurrence of liver, lung, or bone metastases, low hemoglobin levels, high *neutrophil-to-lymphocyte ratio* (NLR), higher *C-reactive protein* (CRP) levels, and poor performance status (ECOG-PS ≥ 2) were all consistently associated with poorer outcomes. Although the analysis offers insightful information, the variety of included studies and the majority of data from Japan highlight the need for further systematic research to confirm these predictive markers and enhance clinical judgment for patients with mUC.

References

1. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer: A Review. JAMA. 2020; 324:1980-91.

2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020:

GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71:209-49.

3. Heijden AG van der, Bruins HM, Carrion A, et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. In Arnhem, The Netherlands: EAU Guidelines Office; 2025. Available from: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/

4. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006; 107:506-13.

5. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017; 389:67-76.

6. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017; 18:1483-92.

7. Merck Sharp & Dohme LLC. A Study of Efficacy and Safety of Pembrolizumab Plus Enfortumab Vedotin (EV) +/- Investigational Agents in First-Line Metastatic Urothelial Carcinoma (mUC) (MK-3475-04B/KEYMAKER-U04 [Internet]. 2025 Feb [cited 2025 Mar 1]. Report No.: NCT05845814. Available from: https://clinicaltrials.gov/study/NCT05845814.

8. Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. N Engl J Med. 2024; 390:875-88.

9. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2019; 37:2592-600.

10. Khunger M, Hernandez AV, Pasupuleti V, et al. Programmed Cell Death 1 (PD-1) Ligand (PD-L1) Expression in Solid Tumors As a Predictive Biomarker of Benefit From PD-1/PD-L1 Axis Inhibitors: A Systematic Review and Meta-Analysis. JCO Precis Oncol. 2017; 1:1-15.

11. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015; 372:2509-20.

12. Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Ann Intern Med. 2006; 144:427-37.

13. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12:55-61.

14. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557-60.

15. Tanabe K, Kobayashi S, Maezawa Y, et al. Gustave Roussy Immune score as a prognostic biomarker in patients with platinum-refractory metastatic urothelial carcinoma treated with pembrolizumab: YUSHIMA study. Int J Clin Oncol. 2024; 29:1302-10.

16. Tomioka-Inagawa R, Nakane K, Enomoto T, et al. The Impact of Neutrophil-to-Lymphocyte Ratio after Two Courses of Pembrolizumab for Oncological Outcomes in Patients with Metastatic Urothelial Carcinoma. Biomedicines. 2022; 10:1609.

17. Kobayashi T, Ito K, Kojima T, et al. Pre-pembrolizumab neutrophil-to-lymphocyte ratio (NLR) predicts the efficacy of second-line pembrolizumab treatment in urothelial cancer regardless of the pre-chemo NLR. Cancer Immunol Immunother. 2022; 71:461-71.

18. Kurashina R, Ando K, Inoue M, et al. Pretreatment Hemoglobin Levels and Platelet-to-Lymphocyte Ratio Predict Survival Benefit from Pembrolizumab in Advanced Urothelial Carcinoma. Cancer Diagn Progn. 2023; 3:230-5.

19. Plimack ER, Bellmunt J, Gupta S, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol. 2017; 18:212-20.

20. Bellmunt J, De Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017; 376:1015-26.

21. Huang J, Teng X. Expression of PD-L1 for Predicting Response to Immune Checkpoint Inhibitors in Metastatic Urothelial Carcinoma: A Systematic Review and Meta-Analysis. Curr Oncol. 2020; 27:656-63.

22. Powles T, Csoszi T, Özgüroglu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021; 22:931-45.

23. Shinagare AB, Ramaiya NH, Jagannathan JP, et al. Metastatic Pattern of Bladder Cancer: Correlation With the Characteristics of the Primary Tumor. Am J Roentgenol. 2011; 196:117-22.

24. Hsieh M-C, Chiang P-H, Rau K-M, et al. Metastatic Urothelial Carcinoma of the Bladder with Lymph Node-only Metastasis Treated with M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) has a Better Survival than GC (Gemcitabine and Cisplatin). Journal of Cancer Research and Practice 2014; 1; 197-207.

25. Shou J, Zhang Q, Zhang D. The prognostic effect of metastasis patterns on overall survival in patients with distant metastatic bladder cancer: a SEER population-based analysis. World J Urol. 2021; 39:4151-8.

26. Tatokoro M, Kihara K. Liver Metastases from Ureteral and Bladder Cancer. In: Di Carlo I, editor. Noncolorectal, Nonneuroendocrine Liver Metastases [Internet]. Cham: Springer International Publishing; 2015 [cited 2025 Jan 21]. p. 175-82. Available from: https://link.springer.com/10.1007/978-3-319-09293-5_14.

27. Wallmeroth A, Wagner U, Moch H, et al. Patterns of Metastasis in Muscle-Invasive Bladder Cancer (pT2-4): An Autopsy Study on 367 Patients. Urol Int. 1999; 62:69-75.

28. Makrakis D, Talukder R, Lin GI, et al. Association Between Sites of Metastasis and Outcomes With Immune Checkpoint Inhibitors in Advanced Urothelial Carcinoma. Clin Genitourin Cancer. 2022; 20:e440-52.

29. Vuky J, Balar AV, Castellano D, et al. Long-Term Outcomes in KEYNOTE-052: Phase II Study Investigating First-Line Pembrolizumab in Cisplatin-Ineligible Patients With Locally Advanced or Metastatic Urothelial Cancer. J Clin Oncol. 2020; 38:2658-66.

30. Gou M, Zhang Y, Liu T, et al. The Prognostic Value of Pre-treatment Hemoglobin (Hb) in Patients With Advanced or Metastatic Gastric Cancer Treated With Immunotherapy. Front Oncol. 2021; 11:655716.

31. Zhang Z, Zhang F, Yuan F, et al. Pretreatment hemoglobin level as a predictor to evaluate the efficacy of immune checkpoint inhibitors in patients with advanced non-small cell lung cancer. Ther Adv Med Oncol. 2020; 12:1758835920970049.

32. He Y, Ren T, Ji C, et al. The baseline hemoglobin level is a positive biomarker for immunotherapy response and can improve the predictability of tumor mutation burden for immunotherapy response in cancer. Front Pharmacol. 2024; 15:1456833.

33. Zhuang Y, Liu K, He Q, et al. Hypoxia signaling in cancer: Implications for therapeutic interventions. MedComm. 2023; 4:e203.

34. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014; 106:dju124.

35. Zidar DA, Al-Kindi SG, Liu Y, et al. Association of Lymphopenia With Risk of Mortality Among Adults in the US General Population. JAMA Netw Open. 2019; 2:e1916526.

36. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting Inflammatory Pathways for Prevention and Therapy of Cancer: Short-Term Friend, Long-Term Foe. Clin Cancer Res. 2009; 15:425-30.

37. Ohsugi Y. Recent Advances in Immunopathophysiology of Interleukin-6: An Innovative Therapeutic Drug, Tocilizumab (Recombinant Humanized Anti-human Interleukin-6 Receptor Antibody), Unveils The Mysterious Etiology of Immune-Mediated Inflammatory Diseases. Biol Pharm Bull. 2007; 30:2001-6.

38. Li W, Luo X, Liu Z, et al. Prognostic value of C-reactive protein levels in patients with bone neoplasms: A meta-analysis. PLoS One. 2018; 13:e0195769. doi: 10.1371/journal.pone.0195769.

39. Gao GD, Sun B, Wang XB, Wang SM. Neutrophil to Lymphocyte Ratio as Prognostic Indicator for Patients with Esophageal Squamous Cell Cancer. Int J Biol Markers. 2017; 32:409-14.

40. Akashi Y, Yamamoto Y, Hashimoto M, et al. Prognostic Factors of Platinum-Refractory Advanced Urothelial Carcinoma Treated with Pembrolizumab. Cancers. 2023; 15:5780.

41. Fukata S, Mizutani K, Yamamoto S, et al. Sarcopenia and the rate of change of the neutrophil/lymphocyte ratio as predictors of pembrolizumab efficacy in advanced urothelial carcinoma. Anticancer Drugs. 2022; 33:459-66.

42. Furubayashi N, Minato A, Negishi T, et al. The Eosinophil Changes, Efficacy and Safety of Pembrolizumab in Advanced Urothelial Carcinoma Patients with an Older Age and a Poor Performance Status. OncoTargets Ther. 2022; 15:1321-30.

43. Ito K, Kobayashi T, Kojima T, et al. Pembrolizumab for treating advanced urothelial carcinoma in patients with impaired performance status: Analysis of a Japanese nationwide cohort. Cancer Med. 2021; 10:3188-96.

44. Kawashima A, Yamamoto Y, Sato M, et al. FAN score comprising fibrosis-4 index, albumin-bilirubin score and neutrophil-lymphocyte ratio is a prognostic marker of urothelial carcinoma patients treated with pembrolizumab. Sci Rep. 2021; 11:21199.

45. Kita Y, Ito K, Kanda S, et al. Tolerability and treatment outcome of pembrolizumab in patients with advanced urothelial carcinoma and severe renal dysfunction. Urol Oncol Semin Orig Investig. 2022; 40:410.e11-410.e18.

46. Kobayashi T, Ito K, Kojima T, et al. Risk stratification for the prognosis of patients with chemoresistant urothelial cancer treated with pembrolizumab. Cancer Sci. 2021; 112:760-73.

47. Komura K, Tokushige S, Ishida M, et al. Tertiary lymphoid structure and neutrophil-lymphocyte ratio coordinately predict outcome of pembrolizumab. Cancer Sci. 2023; 114:4622-31.

48. Miyama Y, Kaneko G, Nishimoto K, Yasuda M. Lower neutrophil-to-lymphocyte ratio and positive programmed cell death ligand-1 expression are favorable prognostic markers in patients treated with pembrolizumab for urothelial carcinoma. Cancer Med. 2022; 11:4236-45.

49. Nagasaka H, Yamamoto S, Suzuki A, et al. C-reactive Protein Is a Prognostic Factor for Survival in Metastatic Upper Tract Urothelial Carcinoma Patients Receiving Pembrolizumab. In Vivo. 2024; 38:1823-8.

50. Nishio K, Higashio T, Komura K, et al. Predicting Objective Response of Pembrolizumab in Platinum-Refractory Urothelial Carcinoma Based on Neutrophil-Lymphocyte Ratio Fluctuation and Liver Metastases. Oncology. 2024; 102:457-64.

51. Ogihara K, Kikuchi E, Shigeta K, et al. The pretreatment neutrophil-to-lymphocyte ratio is a novel biomarker for predicting clinical responses to pembrolizumab in platinum-resistant metastatic urothelial carcinoma patients. Urol Oncol. 2020; 38:602.e1-602.e10.

52. Rijnders M, Robbrecht DGJ, Oostvogels AAM, et al. A blood-based immune marker for resistance to pembrolizumab in patients with metastatic urothelial cancer. Cancer Immunol Immunother. 2023; 72:759-67.

53. Sato R, Inamoto T, Matsushita Y, et al. Significance of second progression-free survival in patients with advanced urothelial cancer who received platinum-based combination chemotherapy followed by pembrolizumab. Int J Urol. 2023; 30:730-6.

54. Shimizu T, Miyake M, Hori S, et al. Clinical Impact of Sarcopenia and Inflammatory/Nutritional Markers in Patients with Unresectable Metastatic Urothelial Carcinoma Treated with Pembrolizumab. Diagnostics. 2020; 10:310.

55. Tamura D, Jinnouchi N, Abe M, et al. Prognostic outcomes and safety in patients treated with pembrolizumab for advanced urothelial carcinoma: experience in real-world clinical practice. Int J Clin Oncol. 2020; 25:899-905.

56. Uchimoto T, Komura K, Fukuokaya W, et al. Risk Classification for Overall Survival by the Neutrophil-Lymphocyte Ratio and the Number of Metastatic Sites in Patients Treated with Pembrolizumab—A Multicenter Collaborative Study in Japan. Cancers. 2021; 13:3554.

57. Uchimoto T, Nakamura K, Komura K, et al. Prognostic value of the fluctuation in the neutrophil-lymphocyte ratio at 6 weeks of pem-

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brolizumab treatment is specific to the clinical response in metastatic urothelial carcinoma. Urol Oncol Semin Orig Investig. 2022; 40:344.e11-344.e17.

58. Umeda K, Tanaka N, Yasumizu Y, et al. Site-Specific Differences in PD-1 Blockade Success and Biomarkers in Urothelial Carcinoma Treated with Pembrolizumab. Clin Genitourin Cancer. 2023; 21:128-35.

59. Yamamoto S, Fukushima H, Fukuda S, et al. Early cancer cachexia phenotype predicts survival of advanced urothelial cancer patients treated with pembrolizumab. Asia Pac J Clin Oncol. 2022; 18:410-8.

60. Yamashita S, Wada T, Deguchi R, et al. Prognostic significance of pre-treatment albumin-bilirubin grade in metastatic urothelial carcinoma receiving pembrolizumab. Jpn J Clin Oncol. 2023; 53:845-50.

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