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Impact of concomitant medications on the oncologic efficacy of systemic therapy in patients with advanced or metastatic urothelial carcinoma: a systematic review and meta-analysis

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Abstract

Background Immune checkpoint inhibitors (ICI) and chemotherapy, including antibody-drug conjugates, are widely used for the treatment of patients with advanced unresectable or metastatic urothelial carcinoma (UC). The majority of elderly patients receive concomitant medications to address various comorbidities. We aimed to evaluate the impact of concomitant medications on oncological outcomes in patients with advanced unresectable or metastatic UC treated with systemic therapy.

Material & methods In August 2024, three datasets were queried for studies evaluating concomitant medications in patients with advanced unresectable or metastatic UC. The review protocol was registered in PROSPERO (CRD42024547335). The primary outcome was overall survival (OS). A fixed- or random-effects model was used for meta-analysis depending on the heterogeneity.

Results We identified 16 eligible studies (3 prospective and 13 retrospective) comprising 4,816 patients. Most reported concomitant medications included proton pump inhibitors (PPIs), antibiotics, steroids, and opioids. The use of concomitant PPIs, antibiotics, steroids or opioids during ICI therapy was associated with worsened OS (PPIs: HR: 1.43, 95% CI: 1.31–1.57, $p < 0.001$; antibiotics: HR: 1.2, 95% CI: 1.04–1.38, $p = 0.01$; steroids: HR: 1.45, 95% CI: 1.25–1.67, $p < 0.001$; and opioids: HR: 1.74, 95% CI: 1.46–2.07, $p < 0.001$). Concomitant use of antibiotics during chemotherapy did not impact OS (HR: 1.01, 95% CI: 0.67–1.51).

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Conclusions When treating advanced unresectable or metastatic UC with ICI therapy, we need to pay attention to concomitant medications, such as PPIs and antibiotics to avoid reducing the efficacy of ICI therapy. The mechanism of action of these drugs on ICI efficacy requires further examination.

Keywords Concomitant medications, Proton pump inhibitors, Antibiotics, steroids, Opioids, Histamine type-2 receptor antagonists, Immune checkpoint inhibitors, Urothelial carcinoma

Introduction

The combination of enfortumab vedotin (EV) plus pembrolizumab is the new first-line therapy and standard of care in patients with advanced unresectable or metastatic urothelial carcinoma (UC) [1, 2]. In cases patients unfit for EV but fit for cisplatin, the European Association of Urology (EAU) guidelines [3] and ESMO Clinical Practice Guideline [2] recommend switch maintenance treatment with avelumab after initial treatment with cisplatin-gemcitabine or nivolumab plus cisplatin-gemcitabine based on the results of JAVELIN bladder 100 and CheckMate 901 studies, respectively [4, 5]. Although ESMO Clinical Practice Guideline [2] do not recommend the routine use of immune checkpoint inhibitors (ICI) monotherapy, the EAU guidelines recommend pembrolizumab or atezolizumab monotherapy as first-line therapy for patients unfit for both EV and cisplatin who have positive programmed cell Death ligand 1 (PD-L1) expression, based on the results of two single arm phase II trials [6, 7]. Moreover, pembrolizumab or atezolizumab was recommended as second-line therapy by ESMO guidelines. Recent study revealed the effectiveness of second-line pembrolizumab even in mUC patients with Eastern Cooperative Oncology Group performance status (ECOG-PS) 2 [8]. Thus, the demand for and significance of ICI therapy for metastatic UC are increasing.

Patients with UC are often older and suffer from comorbidities. Disease-related and unrelated comorbidities are treated with medications that may interact with the cancer treatment, affecting efficacy and tolerability. Although various prognostic factors, such as neutrophil-to-eosinophil ratio and bone metastasis influence oncological outcomes in metastatic UC patients, it is also important to consider the impact of concomitant medications, as they may affect the efficacy and tolerability of standard therapies, in patients with metastatic UC treated with ICI [9, 10]. Therefore, in this systematic review and meta-analysis, we aimed to investigate the effect of concomitant medications on outcomes of patients with advanced unresectable or metastatic UC receiving standard systemic therapy.

Evidence acquisition

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024547335). The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and AMSTAR2 checklist (Supplementary Tables 1, 2 and Appendix 2) [11, 12].

Search strategy

In August 2024, PubMed (MEDLINE), Scopus, and Web of Science Core Collection databases were searched to identify studies investigating the effect of concomitant medications, including proton pomp inhibitors (PPIs), histamine type-2 receptor antagonists (H2RAs), ABx, bone targeted agents, antihypertensives, steroids, and opioids, on oncological outcomes in patients with advanced unresectable or metastatic UC treated with standard systemic oncologic therapies. The search strategy for each database is presented in the Supplementary Appendix 1. Two investigators independently performed an initial screening based on the titles and abstracts and noted the reasons of the exclusion of ineligible reports. Full texts were retrieved and evaluated for eligibility. In the case of discrepancies, the disagreements were solved by consensus among the authors.

Inclusion and exclusion criteria

We used the population, interventions, comparator, outcome, and study design (PICOS) framework to define the eligibility criteria (Supplementary Table 3) [13]. We included studies that reported on patients with advanced unresectable or metastatic urothelial carcinoma (population), who underwent systemic therapies, including ICI therapy, chemotherapy with concomitant medications (intervention), compared to those who underwent systemic therapies without concomitant medications (comparators), and assessed overall survival (OS) (primary outcomes). Both retrospective and prospective comparative studies were included (study design). We excluded studies that lacked original patient data, along with reviews, letters, editorial remarks, responses from authors, case reports, and articles not written in English. When encountering duplicate cohorts, we selected the one with the higher quality. We searched references of included manuscripts for additional studies of interest to identify further relevant studies.

Data extraction

Two reviewers independently extracted data on study and patient characteristics, including the first author's

Table 1 Characteristics of included studies

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Immune checkpoint inhibitors																			
Iida et al. 2024/ Retrospective	2018–2021	Pembrolizumab (100)/ 2nd line	PPI P-CAB	51	133	within 30 days before ICI initiation	T:73 C:72	6.6	T:67:33 C:84:16	≧2 T:27 C:20	T 43 C 49	51 39	6 12	24 29	27 20	NA	NA	49 51	Age/ Gender/ Primary site/ECOG-PS/Liver metastasis/ PPI/Antibiotics/ NSAIDs/ Metformin/ Steroids/ Opioids/ NLR/Alb/ Hb
Hong et al. 2024/ retrospective	2017–2020	Pembrolizumab (2) Nivolumab (6) Atezolizumab (92) 1st line (3%) 2nd line (72%) 3rd line (20%) ≥4th line (5%)	PPI Abx Steroid Opioid	247 356 308 491	960	within 30 days before ICI initiation	mean 68	NA	74:26	NA	NA	NA	NA	NA	NA	NA	NA	NA	Age/ Gender/ Number of comorbidities/Type of ICI/ICI treatment setting/ PPI/Antibiotics/ palliative radiation

Table 1 (continued)

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Sekito et al. 2024/ retrospective	2018–2022	Pembrolizumab (100)/ 2nd line	PPI	121	404	within 30 days before and after ICI initiation	72	8.3	73:23	≧2 T:12 C:7	T 53 C 50	45 48	2 1	58 59	20 12	37 36	21 13	NA	Age/ Gender/Primary site/ ECOG-PS/ Smoking/ Histology/T stage/Liver metastasis/ PPI/H2RA/ Antibiotics
Tomisaki et al. 2023/ retrospective	2003–2021	Pembrolizumab (100)/ NA	PPI	46	75	Within 60 days before and 30 days after ICI initiation	T:74 C:72	7.7	T:72:28 C:76:24	≧1 T:48 C:26	T 38 C 50	59 48	3 2	NA	31 15	NA	NA	NA	Age/Gender/ECOG-PS/Liver metastasis/ Hb/ Time from prior therapy/ PPi/Abx/ steroid/ H2RA
Fiala et al. 2023/ retrospective	2016–2022	Pembrolizumab (100)/ 2nd line	PPI	372	802	NA	Age > 65, 74%	15.3	I:74:26 C:73:27	≧2 I:20 C:15	T 71 C 75	29 25	0 0	71 70	19 17	32 34	31 26	NA	Age/ Gender/ Smoking/ Histology/ Primary site/ Metastatic site/ PPI/Metformin/ Statin

Table 1 (continued)

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Akashi et al. 2023/ retrospective	2018–2021	Pembrolizumab (100)/ 2nd line	ABx	16	41	NA	75	16.5	85:15	≧2 10	40	60	0	66	15	49	22	NA	Age/Gender/ECOG-PS/Surgical resection/ Any irAEs/ NLR/Hb/ CRP/Primary site/ metastasis site/Number of metastases/ Antibiotics
Santoni et al. 2023/retrospective	2016–2023	Pembrolizumab (100)/ 2nd line	Bone targeted agents	82	263	NA	70	22.7	76:24	≧2 28	76	24	0	61	22	35	100	NA	Age/ Gender/ Smoker/ ECOG PS/ Histology/ Primary site/ Synchronous BM (Y vs. N)/ Metastatic site/Radiotherapy /Bone targeted agents

Table 1 (continued)

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Okuyama et al. 2022/retrospective	2015–2021	Pembrolizumab (97)/ 2nd line	PPI	99	155	within 30 days before ICI initiation and during ICI therapy	71:73	NA	T:76:24 C:77:23	≧1 T:23 C:21	T 57 C 61	43 39	0 0	65 59	NA	NA	NA	NA	Age/ Gender/ Primary site/ ECOG-PS/ radiotherapy Number of metastatic sites ICI therapy treatment line/PPI/ ABx
Kunimitsu et al. 2022/retrospective	2017–2020	Pembrolizumab (100)/ 2nd line	PPI	34	79	administration for ≥ 30d within 60days before and/or 30days after ICI initiation	72:71	7.2	T:70:30 C:78:22	≧2 T:27 C:11	T 44 C 38	56 60	0 2	NA	21 18	NA	NA	NA	Age/ Gender/ ECOG-PS/ Smoking/ Hb/Alb/ NLR/Liver metastases

Table 1 (continued)

Author/year/Study design	Period	ICI treatment (%)/Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Fukuokaya et al. 2022/retrospective	2022	Pembrolizumab (100)/2nd line	PPI P-CAB	141	221	within 30 days before and after ICI initiation	Mean 69.6: 70.8	12.8	T:50:50 C:73:27	≧1 T:50 C:56.7	T 57 C 62	43 38	0 0	45 35	20 19	NA	NA	NA	Age/Gender/ECOG-PS/Smoking/Body mass index/Primary site/Metastatic site/Number of previous chemotherapies/Hb/NLR/Plt/Steroid/analgesic/PPI/ABx
Ruiz-Bañobre et al. 2021/retrospective	2016–2020	Atezolizumab (67) Pembrolizumab (24) Nivolumab (6) Duralumab (3)	PPI	54	119	within 30 days before ICI initiation	69	9.5	81:19	≧2 16	87	13	0	70	18	39	31	NA	ECOG-PS/Metastatic sites/LDH/Alb/Hb/NLR/PPI/ABx

Table 1 (continued)

Author/year/Study design	Period	ICI treatment (%)/Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Ishiyama et al. 2021/retrospective	2018–2020	Pembrolizumab (100)/2nd line	ABx	15	67	within 60days before and/or 30days after ICI initiation	67:65	8.6	T:73:27 C:65:35	≧2 I:40 C:19.2, $p=0.04$	T 27 C 35	73 65	0	80 65	47 23	20 40	13 8	NA	Age/Sex/ECOG-PS/Smoking/Primary site/Metastasis site/Hb/treatment line/Time since most recent chemotherapy/ABx
Kichenadasse et al. 2021/RCT*	2014–2016	Atezolizumab (100)	RASi	674	888	NA	66 And 67	11 And 17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Age/Gender/BMI/Primary site/ECOG/PS/PDL1 expression/Cardiovascular disorder/Diabetes/Hypertension/Renal failure

Table 1 (continued)

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Hokins et al. 2020/ RCT*	2014–2016	Atezolizumab (100)	ABx	653	888	within 30 days before and after ICI initiation	66 And 67	11 And 17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Age/Gender/BMI/ ECOG-PS/ histopathology/ smoking status/ Hb/PD-L1 expression/ Number of metastases/liver metastases
			PPI	286	888	within 30 days before and after ICI initiation	66 And 67	11 And 17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Age/Gender/BMI/ ECOG-PS/ histopathology/ smoking status/ Hb/PD-L1 expression/ Number of metastases/liver metastases
Drakaki et al. 2020/ retrospective	2011–2018	Atezolizumab (70) Pembrolizumab (24) Nivolumab (6)	Steroid	116	609	within 14days before and/or 30days after ICI initiation	74	5	74:26	≧2 23	NA	NA	NA	58	26	34	32		Hb/Liver metastases/chemotherapy prior to ICI therapy
Chemotherapy																			

Table 1 (continued)

Author/ year/ Study design	Period	ICI treatment (%)/ Treatment line	Concomitant medication	Number of medication user	Total patients	Definition of concomitant medication	Median Age, y	Median follow-up duration, mo	M: F	ECOG-PS, %	Primary site, %			Metastatic site, %					Controlled covariates
											Lower urinary tract	Upper urinary tract	Both	Lymph node	Liver	Lung	Bone	other	
Hokins et al. 2020/ RCT*	2014–2016	Docetaxel Paclitaxel Vinflunine	ABx	149	464	within 30 days before and after chemotherapy	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Age/Gender/BMI/ ECOG-PS/ histopathology/ smoking status/ Hb/PD-L1 expression/ Number of metastases/liver metastases
Tomisaki et al. 2023/ retrospective	2003–2021	Paclitaxel-gemcitabine	PPI	15	60	Within 60 days before and 30 days after chemotherapy	T:69 C:69	10.9	T:13:2 C:36:9	≧1 T:40 C:33	T 13 C 38	87 60	0 2	NA	20 13	NA	NA	NA	Age/Gender/ECOG-PS/Liver metastasis/ Hb/ Time from prior therapy/ PPi/Abx/ steroid/ H2RA

T: concomitant medication user C: non-concomitant medication user

ABx: Antibiotics, CRP: C-Reactive Protein, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, ICI: immune checkpoint inhibiters, PD-L1: programmed-death-ligand 1, PPI: proton pump inhibitor, NLR: neutrophil-to-lymphocyte ratio, RASi: renin-angiotensin system inhibitor

RCT*: These articles use the following data: IMvigor210 (single-arm atezolizumab) and IMvigor211 (phase III randomised trial of atezolizumab vs. chemotherapy)

name, publication year, country, study design, types of concomitant medications, definition of using concomitant medication, types of ICI therapy, treatment line, criteria for both inclusion and exclusion, the main endpoint, the number of participants, their median ages, sex, ECOG-PS, primary site of tumor, metastatic site, the median duration of follow-up, and OS. The adjusted hazard ratios (HR) and 95% confidence intervals (CI) were retrieved for OS. We also extracted the covariates used for adjusting the HR. All discrepancies were resolved by consensus with co-authors.

Quality assessment & risk of bias

Study quality and risk of bias were evaluated using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool to evaluate bias in non-randomized studies [14]. The ROBINS-I assessment of each study was performed by two authors independently. Finally, we evaluated potential publication bias by using funnel plot and Peters' linear regression test for funnel plot asymmetry was performed when at least ten studies were included in the meta-analysis.

Statistical analysis

All statistical analyses were performed using R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria, 2023; meta). To evaluate the impact of concomitant medication during ICI therapy in patients with advanced or metastatic UC, we generated and analyzed forest plots with adjusted HR and 95% CI. Cochran's Q test and the I^2 test were used to evaluate the heterogeneity. Significant heterogeneity was indicated by a p-value < 0.05 in Cochran's Q-tests and I^2 statistics greater than 50%. A random-effects model was utilized to calculate the pooled HR when significant heterogeneity existed. To reduce the impact of heterogeneity on the quantitative analysis, a subgroup analysis was performed according to the types of ICI therapy. When significant heterogeneity was observed, we attempted to investigate the causes of heterogeneity [15]. P-values at < 0.05 were considered significant.

Evidence synthesis

Study selection and characteristics

The search strategy is presented in Supplementary Fig. 1. According to our inclusion criteria, we identified 16 studies [16–31] (3 prospective trials and 13 retrospective studies) comprising 4,816 patients. The details of the studies characteristics are summarized in Table 1.

Risk of bias assessment

Authors' assessments of each domain for every study included are depicted in Supplementary Table 4. Funnel plots and Peter's Linear Regression analysis are depicted in Supplementary Fig. 2.

Meta-analysis

Forrest plots and funnel plots of each analysis on OS are shown in Figs. 1, as well as Supplementary Fig. 1.

Impact of concomitant use of PPIs

Ten studies [16–19, 21, 23–26, 30], comprising 3,836 patients, reported the impact of concomitant PPIs use on OS in patients with advanced unresectable or metastatic UC treated with ICIs. The patients who underwent ICI therapy with concomitant PPIs had significantly worse OS compared to those who did not use it (HR: 1.43, 95% CI: 1.31–1.57, $p < 0.001$, Fig. 1A). Subgroup analysis showed that patients who received pembrolizumab or atezolizumab with concomitant PPIs use had significantly worse OS compared to those who did not use concomitant PPIs (HR: 1.47, 95% CI: 1.29–1.67 and HR: 1.38, 95% CI: 1.2–1.58, respectively, Fig. 1A). Cochran's Q tests and I^2 statistics revealed no significant heterogeneity in analyses. Peters' linear regression test did not show a publication bias in adjusted OS ($p = 0.4$, Supplementary Fig. 2A).

Impact of concomitant use of antibiotics (ABx)

Eight studies [16, 18, 19, 23, 25, 26, 28, 29], comprising 3,413 patients, reported the impact of concomitant ABx use on OS in advanced unresectable or metastatic UC patients treated with standard systemic therapies. The patients who received systemic therapy with concomitant ABx had significantly worse OS compared to those who did not use (HR: 1.21, 95% CI: 1.06–1.39, $p < 0.001$ Fig. 1B). Subgroup analysis showed that the patients who received atezolizumab with concomitant ABx had significantly worse OS compared to those who did not (HR: 1.34, 95% CI: 1.15–1.55 Fig. 1B), while there was no significant difference in OS between those who received pembrolizumab with concomitant ABx and those without it (HR: 1.19, 95% CI: 0.75–1.89 Fig. 1B). Two studies [19, 29], comprising 524 patients, reported that the impact of concomitant ABx use on OS in advanced unresectable or metastatic UC patients treated with chemotherapies. There was no significant difference in OS between the two groups (HR: 1.01, 95% CI: 0.67–1.51, Fig. 1B). Peters' linear regression test did not show a publication bias in adjusted OS ($p = 0.6$, Supplementary Fig. 2B). Cochran's Q tests and I^2 statistics revealed significant heterogeneity in analyses. As we conducted sensitivity analysis and detected the cause of heterogeneity, the patients who received any ICIs with concomitant ABx had significantly worse OS compared to those who did not use (HR: 1.2, 95% CI: 1.04–1.38, $p = 0.01$, Supplementary Fig. 3).

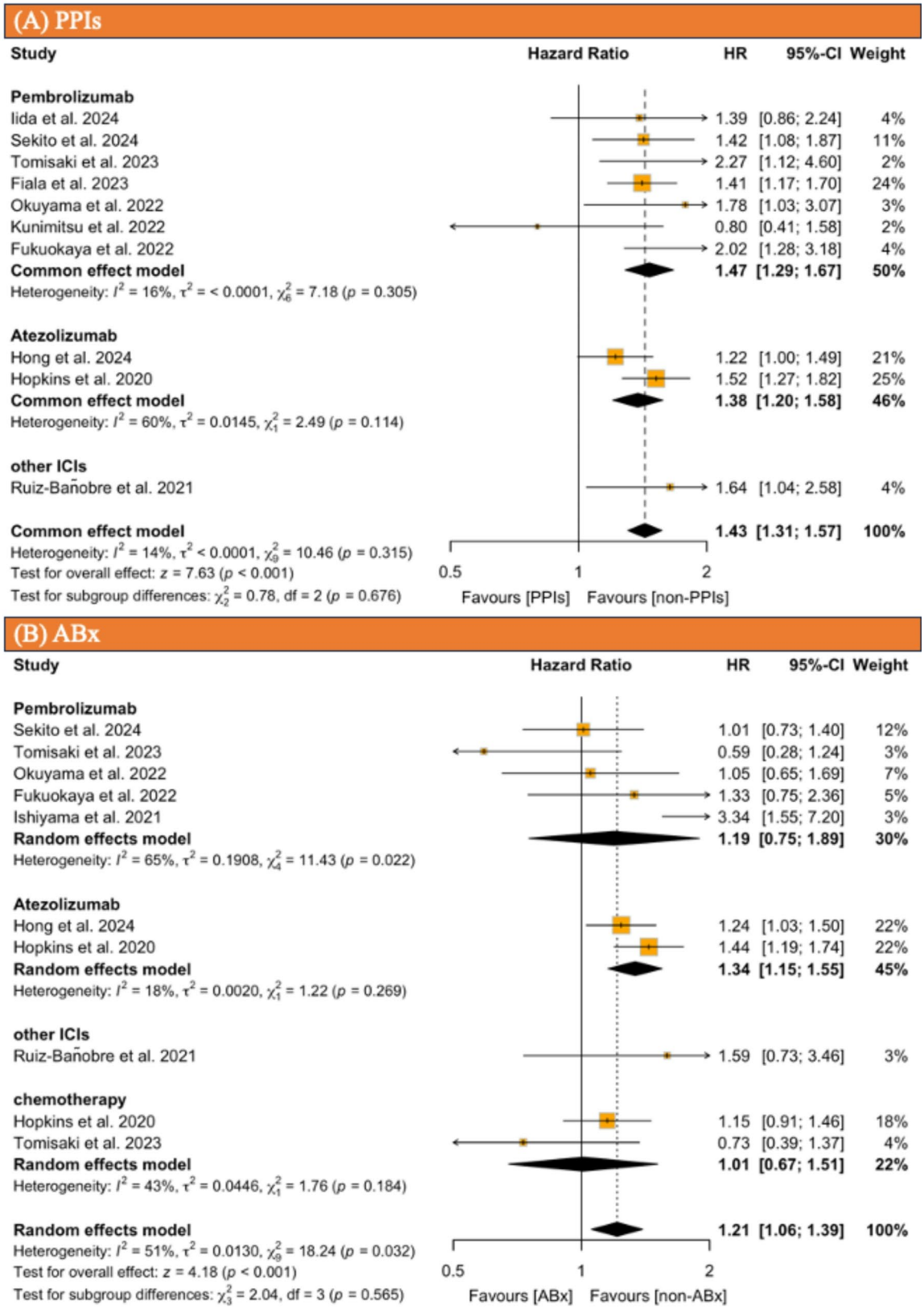

Fig. 1 Forest plots showing the comparison of oncological outcomes

Impact of concomitant use of steroids

Five studies [17, 19, 25, 29, 31], comprising 1,926 patients, reported the impact of concomitant steroids use on OS in patients with advanced unresectable or metastatic UC treated with ICIs. The patients who underwent ICI therapy with concomitant steroids had significantly worse OS compared to those who did not use (HR: 1.45, 95% CI: 1.25–1.67, $p < 0.001$ Supplementary Fig. 2C). Subgroup analysis revealed that no significant differences in OS between the patients who received pembrolizumab with concomitant steroids and those without (HR: 1.66, 95% CI: 0.95–2.90 Supplementary Fig. 2C). Cochran's Q tests and I^2 statistics revealed no significant heterogeneity in analyses.

Impact of concomitant use of opioids

Three studies [17, 18, 25], comprising 1,314 patients, reported a comparison of OS in advanced or metastatic UC patients treated with ICI between those who used concomitant opioids and those who did not. The patients who underwent ICI therapy with concomitant opioids had significantly worse OS compared to those who did not (HR: 1.74, 95% CI: 1.46–2.07, $p < 0.001$ Supplementary Fig. 2D). Subgroup analysis showed that there was no significant difference in OS between the patients who received pembrolizumab with concomitant opioids and those without it (HR: 2.12, 95% CI: 1.33–3.37 Supplementary Fig. 2D). Cochran's Q tests and I^2 statistics revealed no significant heterogeneity.

Effect of concomitant use of Histamine type-2 receptor antagonists (H2RAs)

Two studies [16, 19], comprising 479 patients, reported the impact of concomitant H2RAs on OS in advanced or metastatic UC patients treated with ICIs. There was no significant difference in OS between the two groups (HR: 1.02, 95% CI: 0.68–1.54, $p = 0.9$ Supplementary Fig. 2E). Cochran's Q tests and I^2 statistics revealed no significant heterogeneity.

Discussion

Enfortumab vedotin (EV) plus pembrolizumab is the standard first-line therapy for untreated metastatic UC, with alternative regimens available for selected patients [2, 32]. While ICI play a key role in metastatic UC treatment, their efficacy may be influenced by various clinical factors, including patient comorbidities and concomitant medications. Understanding these interactions is crucial, as patients with metastatic UC often receive multiple medications that could impact treatment outcomes. In addition to concomitant medications, other prognostic factors, such as bone metastases or neutrophil-to-eosinophil ratio, may significantly affect survival in metastatic UC [9, 10]. Given these complexities, a comprehensive approach is needed to optimize treatment outcomes in metastatic UC patients.

We found that the use of concomitant PPIs seems to negatively affect the efficacy of ICI therapy in patients with advanced or metastatic UC. Indeed, the OS was also negatively affected by concomitant PPIs use in patients treated with either pembrolizumab or atezolizumab. Although PPI use is considered safe, regarding the association between ICI therapy and PPIs, previous meta-analyses [33–35] revealed that concomitant use of PPIs was associated with worse OS in patients of lung cancer treated with ICIs. PPIs affect the gut microbiota due to changes in stomach acid and the direct effect of the medications. PPIs users exhibited a notable reduction in bacterial diversity and specific bacterial species, including *Bifidobacterium spp.*, along with a significant rise in pathogenic bacteria, such as *Clostridium difficile*, compared to non-users [36]. PPIs treatment decreased the populations of bacteria associated with a positive ICIs response, such as *Bifidobacterium*, while bacteria associated with ICIs resistance, like *Escherichia coli*, showed an increase with PPIs treatment [37]. These changes of gut microbiota due to PPIs could be considered to impair the efficacy of ICIs. Our analysis revealed that concomitant PPIs use was negatively associated with both OS and PFS in metastatic UC patients treated with ICIs, in accordance with the results of previous studies [33, 38, 39]. On the other hand, regarding concomitant H2RAs, our analysis revealed that no differences in OS. Although the detailed mechanisms remain unclear, previous reports suggested that H2RAs have less impact on the gut microbiota than PPIs [16]. Previous retrospective study, investigating the impact of concomitant H2RAs during ICI therapy in patients with lung cancer, melanoma, and renal cell carcinoma, revealed that concomitant use of H2RAs was not associated with OS [40]. Our analysis revealed the same result in the setting of metastatic UC patients. This suggests that if it is necessary to suppress gastric acid, one should consider H2RAs, and for those on PPIs, one should consider switching from PPIs to H2RAs to avoid compromising the effect of ICI therapy.

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the oncological impact of concomitant ABx during systemic therapy on oncological outcomes in patients with UC. ABx not only affect the bacteria causing the infection but also affect the resident microbiota. Changes in the microbiota due to antibiotic use can lead to the disruption of host immune homeostasis and heightened disease susceptibility [41]. Recently, some studies revealed that the use of ABx negatively affects the oncological outcomes of ICI treatment in patients with different types of cancer, such as renal cell carcinoma, non-small cell lung cancer, and esophageal squamous cell carcinoma [42–44]. However, the

impact of ABx on oncological outcomes in patients with UC treated with ICI therapy remains unclear and controversial. Although three studies [18, 28, 29] reported that patient using ABx had a significantly worse OS compared to those who did not, the other five studies [16, 19, 23, 25, 26] failed to show this. We found that the use of concomitant ABx significantly reduced the effect of ICI therapy in patients with UC. Conversely, concomitant use of ABx did not impair the efficacy of chemotherapy with a focus on OS, however, we only included two studies assessing the efficacy of concomitant ABx on chemotherapy efficacy.

We found that the concomitant use of steroids and opioids negatively affected OS. Some studies reported that both steroids and opioids may affect the gastrointestinal function and gut microbiota [45–47]. Furthermore, as the immunosuppressive mechanisms of steroids are multifactorial, patients receiving steroids at the initiation of ICIs can develop strong immune cascade effects, resulting in poor activation of the anti-tumor immune response. Additionally, previous study reported that the use of opioids can inhibit immune cells like natural killer cells and T-cells, diminishing their anti-tumor activity [48]. Previous meta-analyses [49, 50] revealed that the use of steroids or opioids was significantly associated with worsen OS in patients with non-small cell lung cancer treated with ICI therapy. Our analysis found that the use of both steroids and opioids were associated with poorer efficacy of ICI therapy in patient with metastatic UC. However, care should be taken in interpreting these results. It is important to recognize that patients requiring steroid or opioid for reasons, such as treatment for immune-related adverse events, palliative care due to multiple metastases, or brain edema secondary to brain metastases, for example, may have underlying conditions that contribute to poor prognoses, representing a confounding factor that could not be adjusted for in our analyses.

As we mentioned above, we believed that gut microbiota will play an important role in the efficacy of ICI therapy. Regarding metastatic renal cell carcinoma, a recent randomized phase I trial [51] investigated the efficacy of live bacterial supplementation (CBM588), including *Clostridium butyricum*, during nivolumab plus ipilimumab therapy. The metastatic renal cell carcinoma patients who received live bacterial supplementation were significantly associated with longer PFS compared to those who did not (12.7 mo vs. 2.5 mo, HR:0.15, 95%CI: 0.05–0.47, $p = 0.001$). Therefore, conducting similar studies in metastatic UC may be valuable. Additionally, further studies are needed to clarify the association between concomitant medications and the current standard of therapy, the combination therapy of EV and pembrolizumab.

Limitations

There are various limitations to our study. First, most of the included studies had retrospective design, which led to selection bias. Second, since PPIs may be prescribed to prevent the side effects of NSAIDs administered for cancer pain or to prevent the side effects of steroids for the treatment of immune-related adverse effects due to ICI therapy, these medications should also be considered as covariates. However, regrettably, only three studies [17, 19, 25] accounted for these covariates. Third, as mentioned above, we need to be cautious the regarding steroids and opioids. Although we only included the adjusted HR for our meta-analysis, there is a possibility that confounding factors have not been fully considered. Fourth, unfortunately, we only found two studies (one retrospective and one RCT) investigating the impact of concomitant medications on oncologic outcomes during chemotherapy. Furthermore, we were only able to conduct a meta-analysis on the oncological impact of concomitant ABx during chemotherapy. Fifth, we could not find and include a study investigating the association between EV and concomitant medication regarding the oncological outcomes. Finally, duration, types, and dose of concomitant medications, such as PPIs and ABx, could not be taken into consideration in our analysis due to lack of data.

Conclusions

We found that the use of concomitant medications, including PPIs, ABx, steroids, and opioids was significantly associated with worse OS in patients with advanced unresectable or metastatic UC treated with ICI therapy. Conversely, we did not find that concomitant ABx affects the efficacy of chemotherapy. One hypothesis explaining this relationship is that these concomitant medications reduce the diversity of the gut microbiota, thereby reducing the efficacy of ICI therapy. Taking our results into consideration, we believe that it is advisable to avoid unnecessary prescriptions whenever possible and to assess, using real-world data, the oncologic interactions of concomitant medications on each therapy, similar to drug-drug interaction safety.

Supplementary Information

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Supplementary Material 1

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Not allicable.

Author contributions
Authors' Contributions: Conception and design: ITData analysis and interpretation: ITDrafting the manuscript: ITRevision of the manuscript: AM, MKP, MM, TF, RS, EL, TK, SK, TI, KB, PR, KW, KO, PC, PKSupervision: MA, SFS.

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Data availability
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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