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ORIGINAL RESEARCH

Risk Signals of Antibody-Drug Conjugates in Bladder Cancer: A Real-World FAERS Study

Jinming Liu[1–3,*], Guowang Li[1,2,*], Jia Yang[1–3], Binxu Sun[1–3], Shanqi Guo[1–3]

[1]Department of Oncology, First Teaching Hospital, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; [3]Tianjin Cancer Institute of Traditional Chinese Medicine, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Binxu Sun; Shanqi Guo, Department of Oncology, First Teaching Hospital, Tianjin University of Traditional Chinese Medicine, Tianjin, 300380, People's Republic of China, Email sunbinxu@126.com; shanqi.guo@tmu.edu.cn

Background: Antibody-drug conjugates (ADCs) represent a transformative class of therapeutics for advanced bladder cancer. However, their real-world safety profiles are not yet fully characterized.

Methods: This retrospective pharmacovigilance study analyzed data from the FDA Adverse Event Reporting System (FAERS) from the first quarter of 2004 to the third quarter of 2024. Disproportionality analyses, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), and Bayesian confidence propagation neural network (BCPNN), were used to detect significant adverse drug event (ADE) signals for four ADCs in bladder cancer treatment: enfortumab vedotin (EV), sacituzumab govitecan (SG), trastuzumab deruxtecan (DS-8201), and trastuzumab emtansine (T-DM1).

Results: Among 494 analyzed reports, EV constituted the majority (91.7%). Distinct safety signals were identified for each ADC: EV was strongly associated with skin disorders and metabolic disturbances; SG was primarily linked to gastrointestinal events, with emerging signals of renal abnormalities; DS-8201 was associated with systemic administration-related issues; and T-DM1 showed signals for respiratory and bleeding events. Notably, oral candidiasis related to EV was not explicitly highlighted in the current prescribing information.

Conclusion: This study delineates the safety profiles of ADC therapies for bladder cancer, confirming known risks and identifying potential new signals. The findings highlight the need for ADC-specific monitoring strategies and proactive management protocols to mitigate toxicities, thereby providing essential evidence for clinical decision-making.

Keywords: FAERS database, antibody-drug conjugate, bladder cancer, adverse drug event, disproportionality analysis, real-world study

Introduction

Bladder cancer (BC) is a common malignant tumor of the urinary system, with a higher incidence in males than in females.[1] Globally, over 500,000 new cases of bladder cancer are diagnosed annually. This ranks bladder cancer ninth in incidence and thirteenth in mortality among all malignant tumors. Both incidence and mortality rates are increasing.[2,3] The most common pathological type of BC is urothelial carcinoma (UC), which accounts for more than 90% of cases, and the main treatments include surgery, radiotherapy, and chemotherapy. However, some patients experience post-operative recurrence and distant metastasis.[4] Furthermore, existing drug therapies are often limited in efficacy, associated with severe toxic side effects, and may lead to drug resistance.[5] Therefore, the search for novel, safe, and effective therapeutic approaches is of significant clinical importance for improving patient prognosis.

Antibody-drug conjugate (ADC) are a novel therapeutic approach that uses the specificity of monoclonal antibodies to target tumor-associated antigens and deliver cytotoxic agents to cancer cells.[6] By selectively delivering their payloads to tumor sites, ADCs can potentially reduce side effect severity, expand the therapeutic window, and improve pharmacokinetic and pharmacodynamic properties.[7] To date, the FDA has approved 15 ADCs, and over 80 additional ADCs are in

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clinical development worldwide.[8,9] Studies have shown that ADCs targeting specific tumor-associated antigens, such as Nectin-4 and HER2, are effective in treating bladder cancer.[10]

Despite these advancements, ADCs may face challenges during therapy. According to whether it specifically binds to the target, ADC drug therapy related toxicity can be divided into on target toxicity (target dependent) and off target toxicity (non target dependent).[11] The toxicity mechanism originates from the induction of antibodies, payloads, and linkers.[12] Different ADC drugs have different toxicity characteristics. For example, Enfortumab Vedotin has been associated with a 47.3% incidence rate of skin reactions, of which 14.9% were severe. Sacituzumab Govitecan has been linked to myelosuppression and gastrointestinal reactions, including nausea, vomiting, and diarrhea.[13,14] These findings from clinical trials are often limited. Therefore, real-world studies are essential for evaluating the adverse drug reactions of ADCs in bladder cancer treatment and for accurately assessing their potential risks in diverse patient populations.

The FDA Adverse Event Reporting System (FAERS) is a crucial database for monitoring the safety of drugs and biologics. It documents a wide range of adverse events, including drug side effects, drug interactions, allergic reactions, and other adverse events related to medication use.[15,16] This database is essential for identifying potential safety risks associated with drugs and reflects real-world scenarios across diverse populations and clinical settings. However, no retrospective analyses of ADCs for bladder cancer treatment have been reported in the FAERS database. Therefore, this study aims to conduct a statistical and comparative analysis of adverse event signals associated with ADC treatment for bladder cancer using the FAERS. Additionally, the study will compare the risk factors of ADC treatment for bladder cancer, providing valuable insights for their clinical use.

Materials and Methods

Data Source

This study is based on the FDA Adverse Event Reporting System (FAERS), using "Antibody drug conjugates" as search terms, to extract data reported from the first quarter of 2004 to the third quarter of 2024. The FAERS database consists of seven key data tables: demographics and administrative information (DEMO), drug information (DRUG), adverse event codes (REAC), patient outcomes (OUTC), report sources (RPSR), timing of drug therapy (THER), drug indications (INDI), and deleted case records (DELETED).[17]

Data Processing

To improve data accuracy, according to the official FDA guidelines, Primary ID (PRIMARYID) in the DEMO file is used as the unique field for association.[18] In this study, the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 preferred terms (PT) and systemic organ classifications (SOC) were used to standardize the description and nomenclature of ADEs.[19,20] For duplicate datasets, the FDA guidelines recommend the following deduplication procedure. First, the fields Case ID (CASEID), FDA Report Date (FDA_DT), and PRIMARYID are selected from the demographic table When multiple reports share the same CASEID, the record with the latest FDA_DT is retained. If both CASEID and FDA_DT are identical, the record with the largest PRIMARYID is kept. This process yields the final deduplicated dataset.

The study incorporated 21,712,563 reports of ADEs associated with ADCs from the FAERS. The exclusion criteria included: (1) Reports with IDs of ADEs related to ADCs treatment for bladder cancer that were officially deleted, duplicated, or missing by the FDA; (2) Reports with inaccurate information regarding gender, age, weight, or country of occurrence. A total of 494 participants were ultimately recruited (see Figure 1).

Data Analysis

Data Mining Algorithm

Potential ADE signals associated with ADCs were identified using three methods from disproportionality analysis: ROR, PRR and BCPNN. By integrating three distinct types of signal detection algorithms, this study aims to enhance the sensitivity and specificity of signal detection while reducing the potential bias associated with the use of a single algorithm.

Positive ROR signals are defined as: a≥3 reported target ADEs and a 95% CI lower limit>1.[21,22] The signal generation criteria for PRR are defined as follows:PRR≥2, at least three cases, and chi-square value ($\chi 2$)≥4.[23,24] For

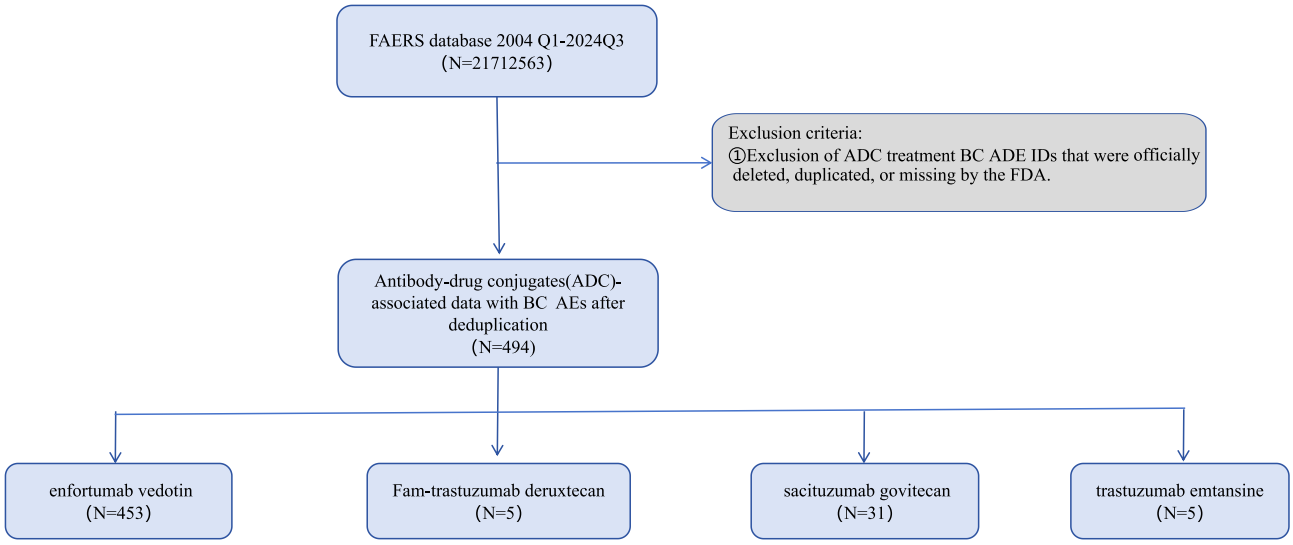

Figure 1 Data filtering flowchart.

the BCPNN method, a signal is generated when the lower limit of the 95% confidence interval (CI) of the Information Component (IC) value, denoted as IC_{025}, $IC_{025}>0$. In this study, the generation of a valid ADE signal is confirmed only when all the aforementioned conditions are met simultaneously.[25] The association between ADCs and BC was determined using the ROR, PRR, and BCPNN algorithms (Table 1).

Statistical Analysis

Initial data organization was performed using Microsoft Excel 2019, with collected information encompassing patient gender, age, ADE reporters, reporting countries, event severity, and event categories. Data management operations were conducted through MySQL 8.0 with Navicat Premium 15, while statistical analyses were carried out utilizing R 4.3.2 and GraphPad Prism 8. Non-normally distributed data are presented as median (quartile). Categorical data, including gender and age, are described using percentages (%). For continuous data, the Mann–Whitney *U*-test or the *t*-test was used to

Table 1 Fourfold Table of Measures of Disproportionality

Method	Formula	Threshold
ROR	$ROR = \frac{a/c}{b/d}$ $SE(lnROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%CI = e^{ln(ROR)\pm 1.96SE(lnROR)}$	$a \geq (lowerlimit)>1$
PRR	$PRR = \frac{a/(a+b)}{c/((c+d))}$ $SE(lnPRR) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$ $95\%CI = e^{ln(PRR)\pm 1.96SE(lnPRR)}$	$a \geq (lowerlimit)>1$ and $\chi^2>4$

(*Continued*)

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Table 1 (Continued).

Method	Formula	Threshold
BCPNN	$IC = log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC) = log_2 \frac{(a+1)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha)(a+c+\beta)}$ $V(IC) = \frac{1}{(ln2)^2}\left[\frac{(a+b+c+d)-a+\gamma-11}{(a+\gamma 11)(1+a+b+c+d+\gamma)} + \frac{(a+b+c+d-(a+b)+a-\alpha 1)}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)} + \frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}\right]$ $\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta)}$ $IC - 2SD = E(IC) - 2\sqrt{V(IC)}$	

Abbreviations: ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; BCPNN, Bayesian Confidence Propagation Neural Network.

evaluate group differences, while chisquare tests were applied for categorical data. Logistic regression analysis was employed to investigate the risk factors associated with ADCs. Results were considered statistically significant if $P<0.05$.

Results

Basic Information of ADE Reports for ADCs in BC

ADE reports related to ADCs used in the treatment of bladder cancer were analyzed using data spanning from Q1 2004 to Q3 2024. The analysis focused on five key variables: age (AGE), sex (SEX), weight (WT), reporter occupation (OCCP_COD), and country of occurrence (REPORTER_COUNTRY). Statistical analyses were performed using the *t*-test for continuous variables and the chi-square test for categorical variables. A total of 494 AEs related to bladder cancer were identified among patients treated with ADCs. The distribution of these AEs across different ADCs is as follows: Enfortumab Vedotin (EV) accounted for 91.7% (N=453), Sacituzumab Govitecan (SG) for 6.28% (N=31), Trastuzumab Deruxtecan (DS-8201a, T-DXd, ENHERTU) for 1.01% (N=5), and Trastuzumab Emtansine (T-DM1) for 1.01% (N=5). These findings indicate that EV is associated with a higher incidence of AEs in bladder cancer treatment. The majority of AE reports were from patients aged 65–85 years (49.8%). Among these, 76.1% were from male bladder cancer patients, which is over three times higher than that of females (24.3%), indicating that male patients are more susceptible to AEs during ADC treatment. Reports from consumer (CN) personnel constituted a significant proportion (41.1%). The largest number of reports originated from the United States (213 reports, 43.1%), followed by Japan (176 reports, 35.6%) (see Table 2).

Analysis of ADE Based on SOC Levels

Investigating the SOCs involved in the ADEs of the four aforementioned ADCs in bladder cancer, based on the criteria for effective signal determination outlined in Section 2.3.1. The four ADCs exhibited divergent distribution patterns across SOC categories of adverse events. EV was associated with 24 SOCs, DS-8201a with 4 SOCs, SG with 16 SOCs, and T-DM1 with 9 SOCs. Adverse events associated with EV are primarily concentrated in metabolism and nutrition disorders and skin and subcutaneous tissue disorders (see Table 3). DS-8201a is predominantly associated with general disorders and administration site conditions, as well as injury, poisoning and procedural complications (see Table 4). SG exhibits a focus on gastrointestinal disorders (see Table 5), while T-DM1 is mainly linked to respiratory, thoracic and mediastinal disorders (see Table 6).

Table 2 Summary of Basic Information on ADC-Related ADE Reports

	Group	Enfortumab Vedotin	Trastuzumab Deruxtecan	Sacituzumab Govitecan	Trastuzumab Emtansine
	Number of Reports	**N=453**	**N=5**	**N=31**	**N=5**
Age	<18	17 (3.8%)			
	>85	11 (2.4%)			
	18~64.9	68 (15.0%)	2 (40.0%)	8 (25.8%)	
	65~85	233 (51.4%)		10 (32.3%)	3 (60.0%)
	Missing	124 (27.4%)	3 (60.0%)	13 (41.9%)	2 (40.0%)
Sex	Female	99 (21.9%)	2 (40.0%)	8 (25.8%)	3 (60.0%)
	Male	350 (77.3%)	3 (60.0%)	21 (67.7%)	2 (40.0%)
	Missing	4 (0.9%)		2 (6.5%)	
W	<50 kg	13 (2.9%)			
	>100 kg	10 (2.2%)		3 (9.7%)	
	50~100 kg	76 (16.8%)	1 (20.0%)	2 (6.5%)	3 (60.0%)
	Missing	354 (78.1%)	4 (80.0%)	26 (83.9%)	2 (40.0%)
Occp_Cod	CN	192 (42.4%)		11 (35.5%)	
	HP	51 (11.3%)	1 (20.0%)	8 (25.8%)	
	MD	157 (34.7%)	3 (60.0%)	8 (25.8%)	4 (80.0%)
	PH	48 (10.6%)	1 (20.0%)	4 (12.9%)	
	OT				1 (20.0%)
	Missing	5 (1.1%)			
Reporter_Country	Argentina	2 (0.4%)			
	Australia	1 (0.2%)		1 (3.2%)	1 (20.0%)
	Austria	1 (0.2%)		1 (3.2%)	
	Belgium	1 (0.2%)		1 (3.2%)	
	Brazil	2 (0.4%)			
	Canada	2 (0.4%)			
	Czechia	1 (0.2%)			
	Finland	3 (0.7%)			
	France	25 (5.5%)			
	Germany	8 (1.8%)			
	Greece	2 (0.4%)			
	Israel	2 (0.4%)			
	Italy	2 (0.4%)		1 (3.2%)	
	Japan	176 (38.9%)			
	Korea, South	4 (0.9%)			3 (60.0%)
	Mexico	1 (0.2%)			
	Netherlands	2 (0.4%)			
	Poland	5 (1.1%)			
	Portugal	1 (0.2%)			
	Romania	1 (0.2%)			
	Russia	2 (0.4%)			
	Serbia	1 (0.2%)			
	Spain	10 (2.2%)		1 (3.2%)	
	Sweden	2 (0.4%)			
	Taiwan	2 (0.4%)			
	Thailand	1 (0.2%)			
	Turkey	4 (0.9%)		1 (3.2%)	
	Ukraine	1 (0.2%)			

(*Continued*)

Table 2 (Continued).

	Group	Enfortumab Vedotin	Trastuzumab Deruxtecan	Sacituzumab Govitecan	Trastuzumab Emtansine
	Number of Reports	**N=453**	**N=5**	**N=31**	**N=5**
	United Kingdom United States Vietnam Luxembourg Switzerland	2 (0.4%) 185 (40.8%) 1 (0.2%)	5 (100%)	22 (71.0%) 1 (3.2%) 1 (3.2%)	1 (20.0%)

Table 3 Signal Strength of AEs of Enfortumab Vedotin at the SOC Level in FAERS Database

System Organ Class (SOC)	Case Number	ROR (95%CI)	PRR	$\chi 2$	IC025
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	63	0.89 (0.69–1.16)	0.9	0.74	−0.52
General Disorders and Administration Site Conditions	195	0.66 (0.57–0.77)	0.7	28.29	−0.7
Hepatobiliary Disorders	34	1.16 (0.82–1.65)	1.15	0.67	−0.31
Metabolism and Nutrition Disorders	105	2.79 (2.26–3.46)	2.68	97.63	0.98
Infections and Infestations	97	0.58 (0.47–0.71)	0.6	27.3	−1
Investigations	93	0.78 (0.63–0.97)	0.8	4.96	−0.62
Respiratory, Thoracic and Mediastinal Disorders	64	0.79 (0.61–1.03)	0.8	3.12	−0.67
Nervous System Disorders	136	1.95 (1.62–2.34)	1.87	51.74	0.56
Cardiac Disorders	17	0.52 (0.32–0.84)	0.52	7.37	−1.59
Skin and Subcutaneous Tissue Disorders	302	5.98 (5.20–6.88)	5.05	787.23	1.84
Eye Disorders	24	1.00 (0.66–1.52)	1	0	−0.59
Gastrointestinal Disorders	148	1.30 (1.09–1.55)	1.28	8.84	0.08
Renal and Urinary Disorders	53	0.37 (0.28–0.49)	0.39	53.07	−1.7
Blood and Lymphatic System Disorders	90	1.19 (0.95–1.48)	1.17	2.29	−0.1
Injury, Poisoning and Procedural Complications	109	1.03 (0.85–1.26)	1.03	0.1	−0.25
Vascular Disorders	19	0.46 (0.29–0.73)	0.47	11.36	−1.7
Psychiatric Disorders	16	0.70 (0.42–1.16)	0.71	1.91	−1.2
Musculoskeletal and Connective Tissue Disorders	23	0.30 (0.20–0.46)	0.31	36.17	−2.23
Surgical and Medical Procedures	1	0.06 (0.01–0.43)	0.06	14.5	−6
Reproductive System and Breast Disorders	2	0.11 (0.03–0.44)	0.11	14.2	−4.76
Immune System Disorders	6	0.66 (0.29–1.50)	0.66	0.99	−1.68
Endocrine Disorders	6	0.90 (0.39–2.04)	0.9	0.07	−1.27
Social Circumstances	1	0.41 (0.06–3.01)	0.41	0.81	−3.31
Product Issues	5	0.26 (0.11–0.64)	0.27	10.1	−3.04

Table 4 Signal Strength of AEs of Trastuzumab Deruxtecan at the SOC Level in FAERS Database

System Organ Class (SOC)	Case Number	ROR (95%CI)	PRR	$\chi 2$	IC025
General Disorders and Administration Site Conditions	5	4.90 (1.42–16.94)	2.95	7.76	0.1
Injury, Poisoning and Procedural Complications	3	6.09 (1.57–23.57)	4.56	8.92	0.5
Surgical and Medical Procedures	1	11.48 (1.45–90.93)	10.43	8.58	1.15
Respiratory, Thoracic and Mediastinal Dilsorders	1	2.16 (0.27–17.04)	2.04	0.56	−1.19

Table 5 Signal Strength of AEs of Sacituzumab Govitecan at the SOC Level in FAERS Database

System Organ Class (SOC)	Case Number	ROR (95%CI)	PRR	χ2	IC025
Blood and Lymphatic System Disorders	5	1.87 (0.75–4.69)	1.8	1.84	−0.4
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1	0.39 (0.05–2.79)	0.4	0.96	−3.41
Gastrointestinal Disorders	9	2.33 (1.14–4.75)	2.12	5.75	0.1
Renal and Urinary Disorders	3	0.62 (0.19–1.98)	0.64	0.67	−2.14
Skin and Subcutaneous Tissue Disorders	2	0.74 (0.18–3.05)	0.75	0.17	−2.12
General Disorders and Administration Site Conditions	15	1.71 (0.95–3.08)	1.53	3.28	−0.2
Surgical and Medical Procedures	2	3.70 (0.90–15.23)	3.6	3.77	0.13
Injury, Poisoning and Procedural Complications	7	1.95 (0.88–4.30)	1.84	2.84	−0.21
Respiratory, Thoracic and Mediastinal Disorders	2	0.69 (0.17–2.84)	0.7	0.26	−2.22
Infections and Infestations	4	0.68 (0.25–1.89)	0.7	0.55	−1.85
Vascular Disorders	1	0.70 (0.10–5.07)	0.71	0.13	−2.58
Metabolism and Nutrition Disorders	2	1.30 (0.32–5.35)	1.29	0.14	−1.34
Investigations	2	0.46 (0.11–1.89)	0.48	1.21	−2.76
Cardiac Disorders	1	0.87 (0.12–6.32)	0.88	0.02	−2.27
Nervous System Disorders	1	0.35 (0.05–2.54)	0.36	1.18	−3.54
Eye Disorders	1	1.16 (0.16–8.43)	1.16	0.02	−1.86

Table 6 Signal Strength of AEs of Trastuzumab Emtansine at the SOC Level in FAERS Database

System Organ Class (SOC)	Case Number	ROR (95%CI)	PRR	χ2	IC025
General Disorders And Administration Site Conditions	2	0.75 (0.17–3.34)	0.79	0.14	−2.16
Respiratory, Thoracic and Mediastinal Disorders	3	4.86 (1.37–17.24)	4.09	7.34	0.41
Injury, Poisoning and Procedural Complications	2	2.18 (0.49–9.69)	2.03	1.11	−0.8
Renal and Urinary DISORDERS	1	0.81 (0.11–6.16)	0.82	0.04	−2.45
Investigations	2	1.99 (0.45–8.84)	1.86	0.86	−0.92
Gastrointestinal Disorders	2	1.95 (0.44–8.64)	1.82	0.8	−0.95
Infections and Infestations	1	0.66 (0.09–5.01)	0.68	0.17	−2.72
Blood and Lymphatic System Disorders	1	1.41 (0.19 −10.76)	1.39	0.11	−1.69
Reproductive System and Breast Disorders	1	6.70 (0.88–51.15)	6.32	4.51	0.49

Analysis of ADE Based on PT Levels

The criteria for effective signal determination described in Section 2.3.1 were reapplied to investigate the PTs associated with ADEs in the treatment of bladder cancer using the four aforementioned ADCs. The results were sorted based on the number of reports, with the top 20 findings presented. The results revealed that among the 504 detected PTs, 59 were identified as effective signals for ADEs related to EV therapy for bladder cancer (Figure 2A and Supplementary Table 1). For DS-8201a, ADEs were observed at 7 PTs, with 1 effective signal (Figure 2B and Supplementary Table 2). SG was associated with ADEs at 39 PTs, including 5 effective signals (Figure 2C and Supplementary Table 3). Conversely, T-DM1 was linked to ADEs at 14 PTs, but no effective signals were detected (Figure 2D and Supplementary Table 4).

Risk Analysis of PTs

The ROR was employed to assess the signal strength of ADE differences. Figure 3A shows that EV treatment for bladder cancer may be associated with 431 potential risks, of which 20 were selected for visualization. Among these, taste disorder (ROR: 44.86, 95% CI 20.82–96.67) and skin disorder (ROR: 36.96, 95% CI 17.47–78.19) had the highest risk levels. Figure 3B reports the risks related to DS-8201a, highlighting that among the seven identified risks, therapy change (ROR: 785.19, 95% CI 79.78–7728.17) was the most prominent. Figure 3C presents the 38 potential risks connected to

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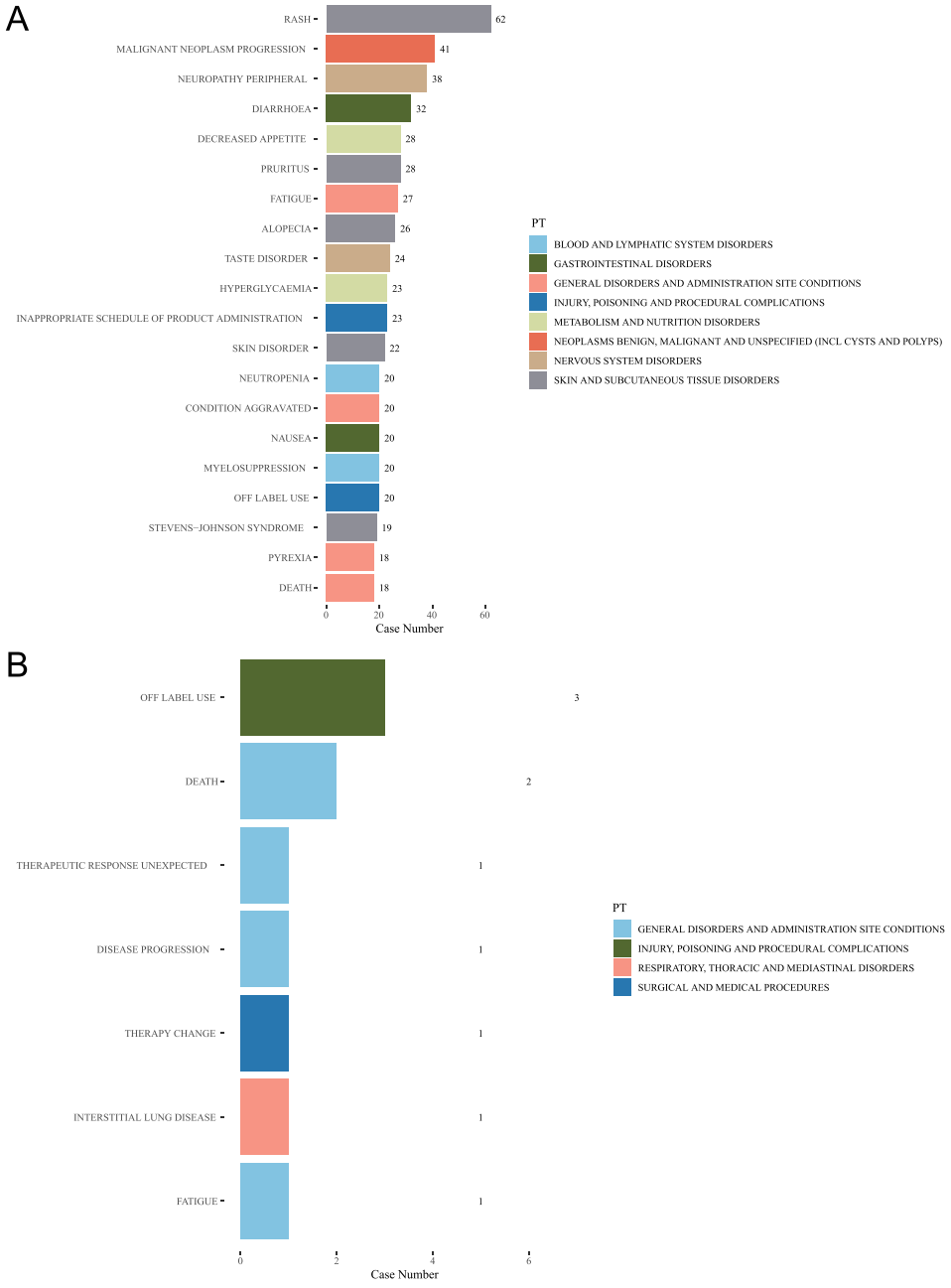
SG, with blood creatinine abnormal (ROR: 495.12, 95% CI 30.59–8012.99) having the highest proportion. Figure 3D indicates a relatively high risk of hematochezia (ROR: 134.53, 95% CI 16.62–1088.73) associated with T-DM1.

Discussion

This study presents the first systematic pharmacovigilance analysis of four antibody-drug conjugates (ADCs) used in bladder cancer treatment by mining the FDA Adverse Event Reporting System (FAERS) database. Using disproportionality analysis, we validated established toxicity profiles and identified novel potential safety signals. These findings are critical for optimizing ADC use in bladder cancer, a disease with substantial epidemiological burden. Our analysis demonstrates that each ADC exhibits a distinct organ-specific toxicity spectrum, largely determined by its unique target



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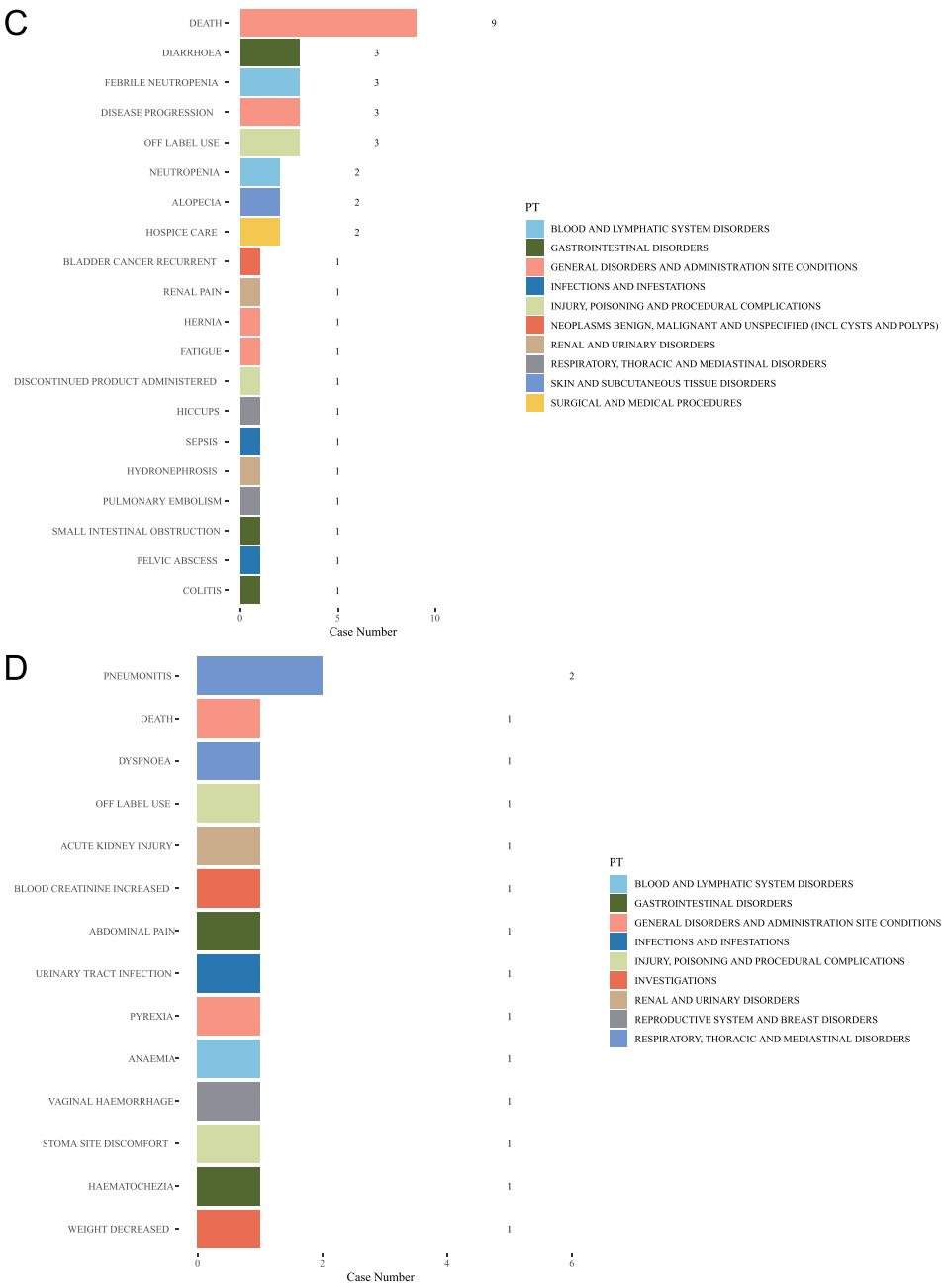

Figure 2 Distribution proportion of ADEs by PT. (**A**) Enfortumab Vedotin, (**B**) Trastuzumab Deruxtecan, (**C**) Sacituzumab Govitecan, (**D**) Trastuzumab Emtansine.

antigen and payload mechanism. The following sections interpret these results in the context of existing evidence and discuss their clinical and public health implications.

Clinical and Public Health Implications of Basic ADE Characteristics

Enfortumab vedotin (EV) accounted for more than 90% of the included adverse drug event (ADE) reports. This finding aligns with its rapid integration into clinical practice and widespread use, extending from later-line to first-line treatment for advanced urothelial carcinoma.[26,27] The landmark EV-302 trial demonstrated a significant survival benefit with EV therapy.[28] However, the high frequency of ADE reports in this study indicates that managing EV-associated toxicities in real-world populations remains challenging. Demographic analysis revealed that ADEs were predominantly reported in male patients aged 65 to 85 years. This demographic profile overlaps with the peak incidence of bladder cancer.[29] This

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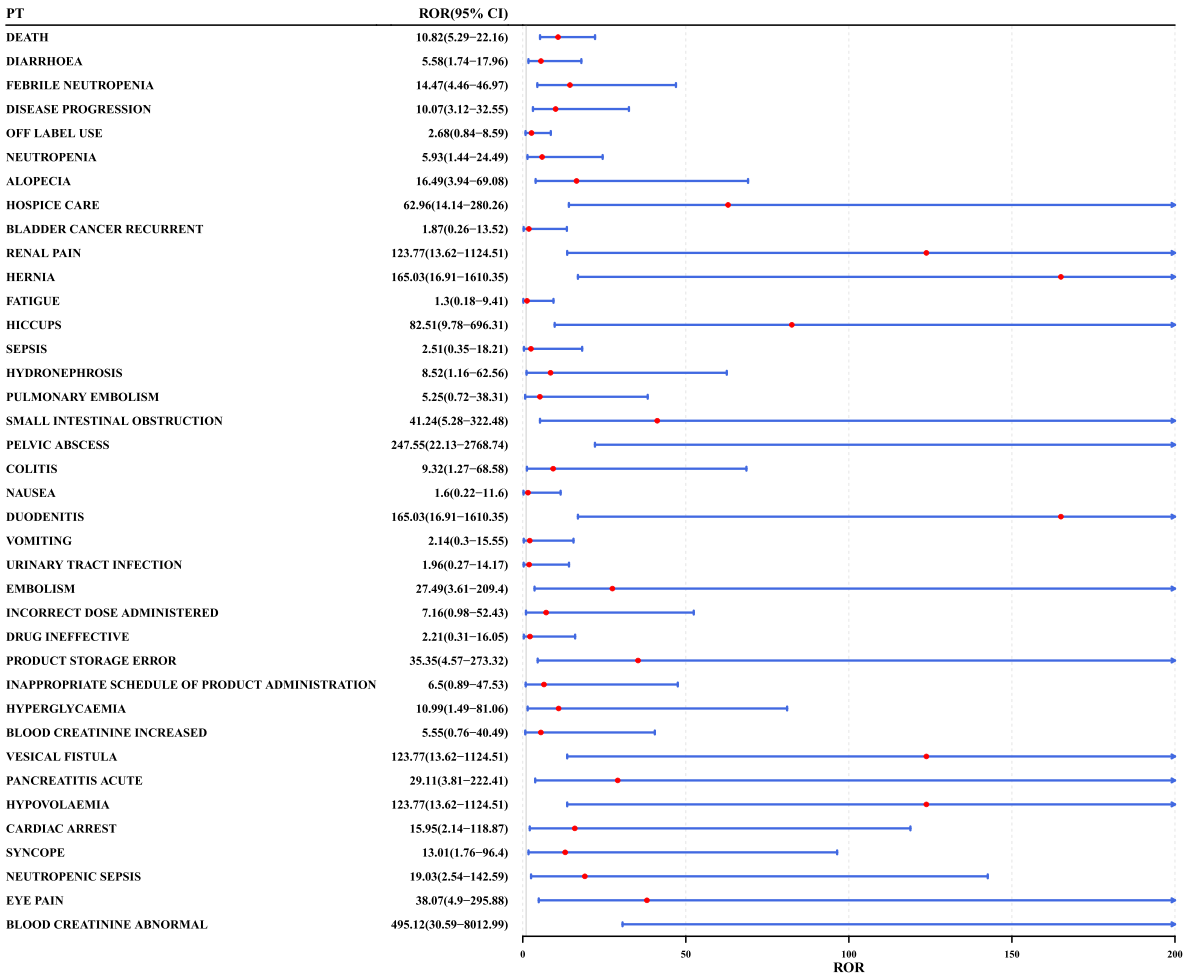
A



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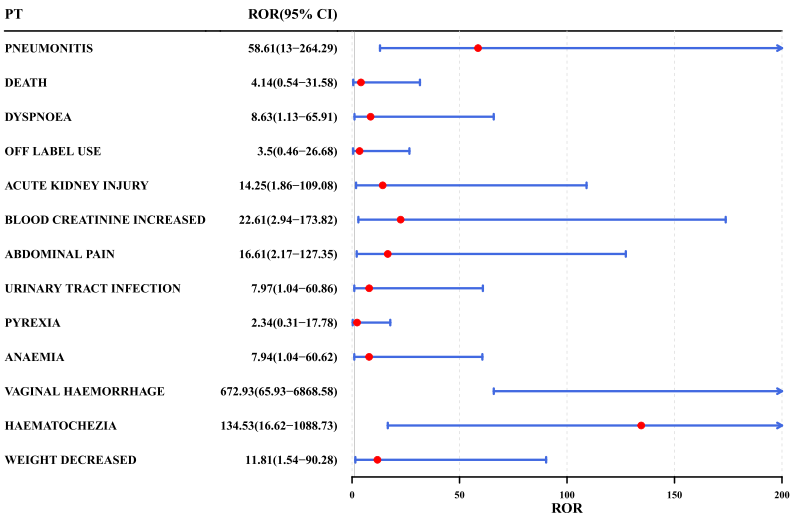

Figure 3 Continued.

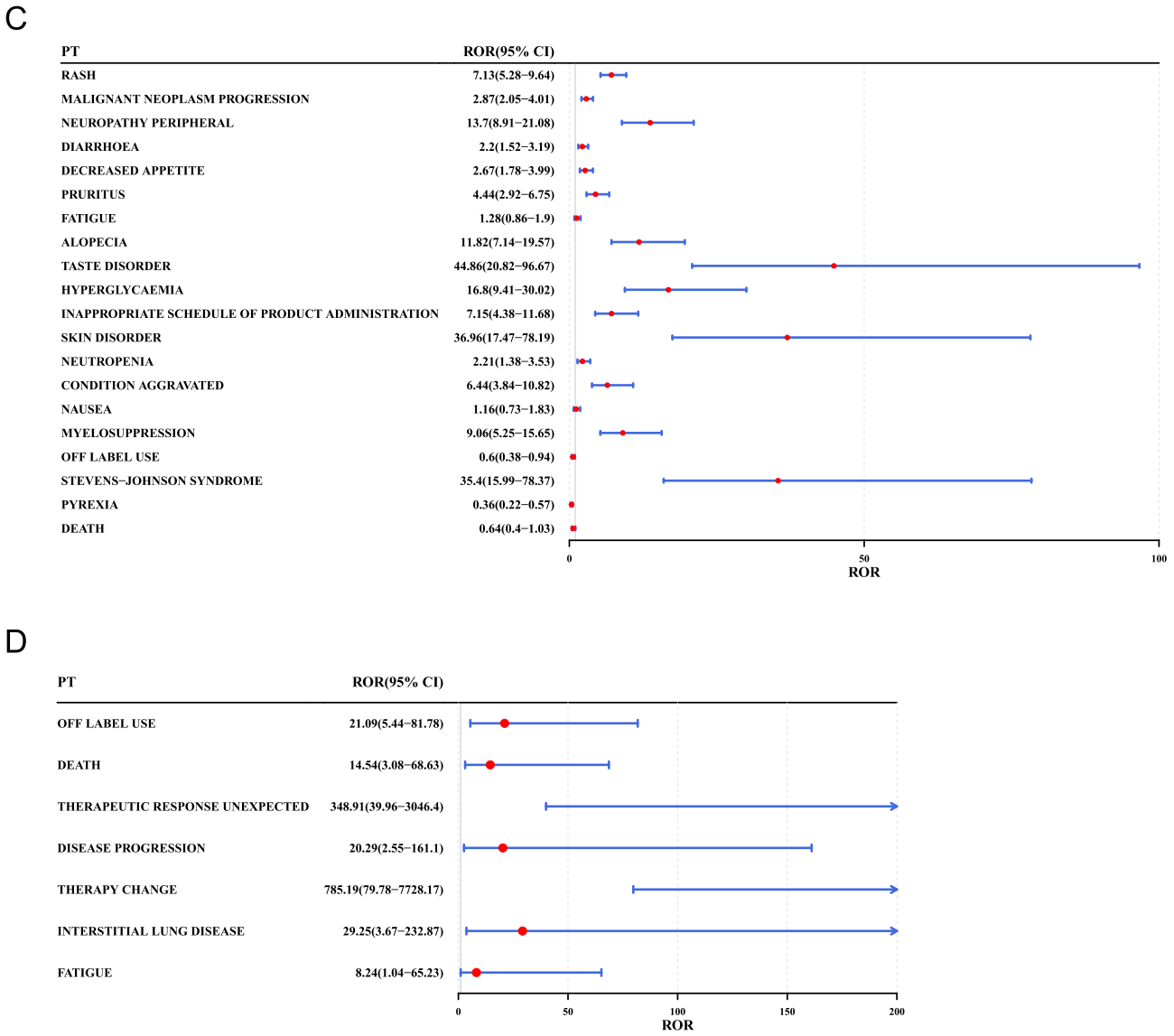

Figure 3 Signal strength of AE of four ADCs at the PT level in FAERS database. (**A**) Enfortumab Vedotin, (**B**) Trastuzumab Deruxtecan, (**C**) Sacituzumab Govitecan, (**D**) Trastuzumab Emtansine.

observation has critical clinical implications. Older adults often present with a higher burden of comorbidities and age-related decline in organ function. This population may be more susceptible to ADC toxicities, which can compromise treatment tolerance and persistence. Consequently, treatment-related toxicities may limit the translation of survival benefits observed in clinical trials to real-world practice.

From a public health perspective, the high concentration of reports from the United States and Japan, alongside a substantial proportion of consumer reports, highlights disparities in healthcare systems, drug accessibility, pharmacovigilance practices, and patient engagement across regions.[30] Such heterogeneity in reporting may introduce bias into the global understanding of ADC safety profiles. Therefore, establishing unified and proactive international pharmacovigilance frameworks is essential for comprehensively evaluating ADC safety across diverse populations.

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Insights for Clinical Practice from Organ-Specific Toxicity Profiles

Enfortumab Vedotin: Managing Dermatologic and Metabolic Toxicities

This study confirms that skin and subcutaneous tissue disorders are the most prominent toxicities associated with enfortumab vedotin (EV), consistent with findings from pivotal clinical trials.[13,31] Most of these reactions manifest shortly after the first treatment cycle. The underlying mechanism may involve high Nectin-4 expression in the skin,[32] which disrupts intercellular adhesion and induces apoptosis.[33] Notably, quantitative signal detection identified oral candidiasis as an adverse event not previously emphasized in the EV prescribing information. This complication may arise from EV-induced neutropenia, which compromises oral mucosal immunity.[13] In clinical practice, preventive education and early intervention for oral candidiasis should be considered for patients who develop neutropenia during EV treatment. This proactive approach helps maintain patients' quality of life and prevent more severe secondary infections.

Furthermore, EV-associated metabolic disorders—particularly hyperglycemia and the risk of diabetic ketoacidosis (DKA)—require heightened vigilance.[34,35] The proposed mechanism involves the payload monomethyl auristatin E (MMAE) disrupting microtubule-dependent trafficking of the glucose transporter GLUT4.[36] Severe metabolic disturbances can lead to significant clinical consequences, including treatment interruption, hospitalization, or even death. Consequently, strict baseline glucose assessment, regular monitoring during treatment, and comprehensive patient education should be integral components of the standard EV treatment pathway. These measures are critical for safely maintaining effective therapy and achieving optimal long-term survival outcomes.

Sacituzumab Govitecan: Balancing Gastrointestinal and Potential Renal Toxicity

The toxicity profile of SG was predominantly characterized by gastrointestinal reactions, consistent with the known toxicity of its SN-38 payload.[37,38] However, our analysis identified elevated blood creatinine as a significant signal of potential risk. Although a direct causal relationship cannot be confirmed, dehydration resulting from recurrent or severe diarrhea may induce prerenal acute kidney injury, which can manifest as elevated creatinine levels. This finding offers a critical insight for clinical management. For patients treated with SG, particularly elderly individuals or those with a poor performance status, proactive management of diarrhea and maintenance of adequate hydration are essential beyond symptomatic control.[39] These measures are crucial for preserving renal function and enabling the continuation of therapy. Although the ASCENT trial reported that gastrointestinal toxicity is generally manageable, real-world populations exhibit greater patient heterogeneity.[38] Therefore, our results support the need for enhanced renal function monitoring in clinical practice.

Trastuzumab Deruxtecan: Focusing on ILD and Treatment Modifications

Although data for DS-8201a in bladder cancer are limited, "therapy change" emerged as a key signal in our analysis. This finding indirectly yet strongly suggests that toxicity, particularly interstitial lung disease (ILD), is a major cause of treatment disruption or dose adjustment in real-world practice.[40,41] ILD is a well-established, serious, and potentially fatal adverse reaction to DS-8201a.[42] This finding underscores that when DS-8201a is used for bladder cancer (particularly in off-label settings), the proactive monitoring and management protocols for ILD established in other cancers (eg, breast, gastric cancer) must be rigorously implemented. Early identification and management of ILD are crucial for preventing progression to fatal outcomes, thereby ensuring that patients can derive sustained benefit from this effective therapy.

Trastuzumab Emtansine: Heeding Pulmonary and Bleeding Signals

T-DM1 is rarely used in the treatment of bladder cancer. However, the detected signals for respiratory disorders and bleeding events (eg, hematochezia, vaginal hemorrhage) are consistent with its known risks of pulmonary toxicity and thrombocytopenia.[43,44] Consequently, for bladder cancer patients under consideration for T-DM1 therapy, baseline assessment of pulmonary function and bleeding risk is recommended. Although these signals require further confirmation, incorporating patient education regarding potential risks and establishing a monitoring plan during treatment strategy development are aligned with the principles of precision medicine and patient safety.

Limitation

Although the FAERS provides extensive adverse event data, its utility is limited by several methodological constraints. First, as a voluntary reporting system, FAERS is susceptible to underreporting, duplicate entries, and incomplete case information, potentially compromising data representativeness. For example, the number of adverse drug event (ADE) reports for trastuzumab deruxtecan and trastuzumab emtansine was extremely limited (five cases each). This small sample size may affect signal stability and reproducibility, as individual anomalous reports could increase false-positive and false-negative risks. Second, the signal detection algorithms employed—including the ROR, PRR, and BCPNN—identify statistical associations but cannot establish causality. Future studies should incorporate spontaneous reports from diverse sources or integrate clinical trial data with real-world evidence to improve the comprehensiveness of ADC safety evaluations and enhance the accuracy and reliability of ADE signal detection.

Moreover, several potential biases and confounding factors may affect the study findings. Media attention may artificially inflate reporting rates for specific adverse events, potentially generating spurious signals. Future analyses could apply time-series analysis to correlate reporting rates with major media events, thereby helping to quantify and mitigate this bias. Indication bias poses a particular challenge in this population, as patients with advanced bladder cancer often have significant comorbidities and receive concurrent treatments, complicating the distinction between drug-related events and manifestations of underlying disease or other therapies. For instance, renal abnormalities associated with sacituzumab govitecan could reflect drug toxicity or disease progression. This finding emphasizes the importance of incorporating drug indications and patient characteristics during signal detection to identify and control for this bias. Additional biases, including selection bias and heterogeneity in reporting quality, may also influence the results. Therefore, all detected signals should be interpreted as hypothesis-generating rather than definitive evidence of causation.

Conclusion

In summary, this study identified several clinically significant safety signals requiring attention: enfortumab vedotin was associated with skin toxicity and metabolic abnormalities; sacituzumab govitecan commonly induced gastrointestinal reactions; and trastuzumab deruxtecan primarily manifested systemic and administration-site-related symptoms. Trastuzumab emtansine was predominantly associated with respiratory symptoms. Furthermore, novel adverse event signals were identified, including oral candidiasis, elevated blood creatinine, and hematochezia. Despite these limitations, the findings support optimizing personalized ADC therapy through enhanced real-world monitoring and early intervention, thereby maximizing efficacy and controlling toxicity. Future research should utilize well-designed prospective observational or registry studies to quantify the incidence of these identified risks and their impact on key clinical endpoints, including progression-free survival, overall survival, and quality of life. Concurrently, exploration of biomarkers predictive of toxicity susceptibility is warranted to advance precision medicine and enhance medication safety.

Abbreviations

ADC, Antibody-Drug Conjugate; BC, Bladder Cancer; ADE, Adverse Drug Event; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; BCPNN, Bayesian Confidence Propagation Neural Network; PT, Preferred Terms; SOC, Systemic Organ Classifications; EV, Enfortumab Vedotin; SG, Sacituzumab Govitecan; DS-8201a, Trastuzumab Deruxtecan; T-DM1, Trastuzumab Emtansine.

Data Sharing Statement

The datasets generated or analysed for this study can be found here: FDA Adverse Event Reporting System (FAERS) (https://www.fda.gov/).

Ethics Approval and Informed Consent

This study involved the analysis of anonymized data from the publicly available FDA Adverse Event Reporting System (FAERS) database. In accordance with Article 32 of China's "Notice on the Issuance of Measures for the Ethical Review of Human Life Science and Medical Research" (2023), which permits the waiver of ethical review for studies utilizing public, anonymized data that do not involve harm to individuals, sensitive personal information, or commercial interests,

this research was deemed exempt from formal institutional ethical approval. The Ethics Committee of First Teaching Hospital of Tianjin University of Traditional Chinese Medicine reviewed the research protocol and data handling procedures and confirmed that the study complied with the above regulations and was exempt from ethical review.

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Disclosure

The authors report no conflicts of interest in this work.

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