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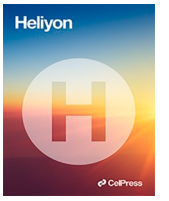

Research article

Risk analysis of enfortumab vedotin: A real-world approach based on the FAERS database

Fuchun Zheng [a,b,1], Yuanzhuo Du [a,b,1], Yuyang Yuan [a,b], Zhipeng Wang [a,b,1], Sheng Li [a,b], Situ Xiong [a,b], Jin Zeng [a,b], Yifan Tan [a,b], Xiaoqiang Liu [a,b], Songhui Xu [a,b], Bin Fu [a,b], Wei Liu [a,b,*]

[a] Department of Urology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, 330000, China
[b] Key Laboratory of Urinary System Diseases of Jiangxi Province, Nanchang, China

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ABSTRACT

Purpose: To analyze the risk of enfortumab vedotin (EV), a targeted therapy for advanced bladder cancer, using real-world data from the U.S. Food and Drug Administration's Federal Adverse Event Reporting System (FAERS).

Methods: A retrospective pharmacovigilance analysis was conducted using FAERS data from Q1 2020 to Q1 2024. Adverse drug events (ADEs) related to EV were identified and categorized according to the System Organ Classes (SOCs) and specific events. Statistical methods, such as the proportional reporting ratio, reporting odds ratio (ROR), Bayesian confidence propagation neural network, and empirical Bayesian geometric mean were used to detect safety signals.

Results: Of the 7,449,181 FAERS case reports, 1,617 EV-related ADEs were identified, including 101 preferred terms and 22 SOCs. The key SOCs included skin and subcutaneous tissue, metabolic, and nutritional disorders. Rare ADEs, such as lichenoid keratosis (n = 4; ROR 26.89), small intestinal perforation (n = 3; ROR 24.51), pigmentation disorder (n = 9; ROR 18.16), and cholangitis (n = 8; ROR 17.48), showed significant disproportionality.

Conclusion: While most findings aligned with the existing data, new signs such as lichenoid keratosis and small intestinal perforation were identified. Further studies are necessary to validate these findings and emphasize the need for the clinical monitoring of EV-related ADEs.

1. Introduction

In 2023, bladder cancer (BC) was the seventh most common malignant tumor in the United States, with approximately 82,290 new cases and 16,710 estimated deaths [1]. While most urothelial carcinomas are non-muscle invasive and can be effectively managed through bladder treatment and/or surgical resection, approximately half of the patients experience recurrence following cystectomy. Distant metastases are more common than local recurrence [2]. In addition, approximately 4 % of the patients are diagnosed with locally advanced or metastatic disease [3].

Historically, cisplatin-based regimens have served as the first-line chemotherapy for locally advanced or metastatic urothelial

* Corresponding author. Department of Urology, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, 330000, China.
E-mail addresses: urofubin@126.com (B. Fu), doctorleo1990@163.com (W. Liu).
[1] These authors contributed to the work equally and should be regarded as co-first authors.

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carcinoma (la/mUC), with an overall response rate (ORR) of 50 % and a median progression-free survival of 7 months [4]. However, nearly half of these patients are unable to undergo cisplatin chemotherapy because of renal insufficiency and poor treatment responses [5]. The treatment options for mUC patients who have previously received platinum-containing regimens and immunotherapies are limited [6]. Recently, erdafitinib has received accelerated Food and Drug Administration (FDA) approval for the treatment of patients with fibroblast growth factor receptor 3 or fibroblast growth factor receptor 2 alterations. Such cases account for approximately 20 % of bladder urothelial carcinoma cases and nearly 40 % of urothelial carcinoma cases in the upper urinary tract. Other chemotherapeutic drugs, such as taxanes, can also be utilized in these scenarios[7–9]. Other monotherapy chemotherapy treatments have demonstrated low ORR and short response durations. Antibody-drug conjugates (ADCs) represent a rapidly growing class of cancer therapies. These therapies consist of antibodies chemically linked to potent cytotoxic agents, also known as "payloads." ADCs are widely used for the treatment of various malignant tumors [10].

Enfortumab vedotin (EV) is a nectin-4-targeting ADC that received its first global approval from the FDA in December 2019. EV specifically targets nectin-4, delivering a toxic microtubule inhibitor as its payload. It is indicated for the treatment of la/mUC in patients who have previously received programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors and platinum-based chemotherapy in neoadjuvant/adjuvant, locally advanced, or metastatic settings [6]. The effectiveness and safety of EV in this group of patients were evaluated in a multicenter open-label Phase 2 trial (EV-201). The most common treatment-related adverse events (AEs) observed were fatigue (50 % overall, 6 % grade $\geq$3), hair loss (49 % overall, no grade $\geq$3), decreased appetite (44 % overall, 1 % grade $\geq$3), taste disorders (40 % overall, no grade $\geq$3), and peripheral sensory neuropathy (40 % overall, 2 % grade $\geq$3). The most frequent grade 3 or higher treatment-related AEs were neutropenia (8 %), anemia (7 %), and fatigue (6 %) [11].

Previous studies on EV primarily stemmed from clinical trials conducted under controlled conditions, featuring limited sample sizes and follow-up periods, potentially overlooking a range of AEs [6]. The onset timing of EV-related Adverse drug events (ADEs) remains unclear. Therefore, it is vital to explore potential ADEs signals in large risk analysis samples using data mining algorithms. The Federal Adverse Event Reporting System (FAERS), the world's largest pharmacovigilance database, is a robust tool for monitoring drug-related ADEs [12]. This study aimed to investigate the safety profile of EVs using FAERS data, focusing on the incidence and types of reported AEs and identifying any novel or unexpected safety concerns. These insights are invaluable for healthcare providers, patients, and regulatory agencies to ensure the safe and effective clinical use of EV.

2. Methods

2.1. Data collection

The FAERS database comprises reports divided into seven primary sections: patient demographics, drug information, adverse event (AE) details, patient outcomes, report sources, treatment dates, and drug indications [13]. For this study, we extracted ASCII report files from the FAERS database, covering data from Q1 2020 to Q1 2024. This period was selected to capture recent and relevant data for EV. The total number of ADE reports analyzed was 6,409,164. Data analysis was conducted using R software (version 4.3.1, https://www.r-project.org), ensuring robust statistical handling of this large dataset.

2.2. Data extraction and analysis

Duplicate reports were eliminated by selecting only the most recent report from the DEMO table, based on the date of data sharing for the same case. A primary ID field was used to link the datasets. The adverse event reports in the FAERS database were carefully categorized using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The MedDRA framework is structured into five levels: system organ class (SOC), high-level group term, high-level term, preferred term (PT), and lowest-level term [14]. Drug names were standardized using MedDRA 26.1 system. Only reports that identified EV as the primary drug associated with ADEs were included, resulting in 1,617 EV-related ADE reports involving 101 PTs. Clinical characteristics such as sex, age, reporting region, reporter type, reporting time, and patient outcomes related to EV-associated AEs were collected. Ethical approval was not required because identification of individual patients was not feasible.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product [15]. AEs are primarily evaluated using the following algorithms: proportional reporting ratio (PRR) [16], reporting odds ratio (ROR) [17], Bayesian confidence propagation neural network (BCPNN) [18], and the empirical Bayesian geometric mean (EBGM) [19]. PRR estimates the relative risk but can be sensitive and prone to false positives, especially with low reported case numbers. Conversely, the ROR offers a dependable estimate of the rate or hazard ratio, exhibiting less bias than the other indices. The BCPNN is considered stable, even with limited reports, whereas the EBGM excels in identifying signals from infrequent occurrences. This study strategically combined the ROR, PRR, BCPNN, and EBGM algorithms to leverage their strengths, broaden the detection scope, and ensure diverse perspectives for result verification. Through this combined approach, cross-validation was achieved, reducing false positives, and enhancing the detection of potentially rare adverse reactions via threshold and variance adjustments. The algorithms employed 2×2 contingency tables, as detailed in Table S1, with the specific formulas and threshold values outlined in Table S2. Higher values in these tables indicate a stronger signal strength, implying a robust association between the target drug and AEs. The validated drug reaction findings adhered to the positive signal selection criteria established by these algorithms. EV data were meticulously handled and statistically analyzed using Excel and R Studio software, as illustrated in the study's flowchart (Fig. 1).

3. Results

3.1. ADE reports and clinical information

A total of 6,409,164 ADE reports were identified from the FAERS database between Q1 2020 and Q1 2024. Among these, 1,617 ADE reports identified EV as the primary suspected drug, involving 101 PTs. The number of reports of this drug has increased annually; the number of reports was notably higher for men (1,184 reports, 73.22 %) than for women (363 reports, 22.45 %). The predominant age group affected was 75 years and older, with 505 reports (31.23 %). Physicians submitted the majority of the reports (663 reports, 41.00 %), and the primary reporting country was the United States (772 reports, 47.74 %) (Fig. 2). With regard to clinical outcomes, hospitalization was the most frequent (436 reports, 22.38 %), followed by death (326 reports, 16.74 %). Additional details are presented in Table 1.

3.2. Signal detection associated with EV

3.2.1. Signal detection based on SOC levels

Signal detection based on SOC levels revealed that EV-induced ADEs primarily affected 22 SOCs. The SOCs were reordered based on the ROR results. The SOC with the highest number of AEs and highest ROR values was skin and subcutaneous tissue disorders (949 reports, ROR 4.24, PRR 3.59, IC 1.84, and EBGM 3.59). Additionally, metabolic and nutritional disorders (307 reports, ROR 3.5, PRR 3.34, IC 1.74, and EBGM 3.34) and blood and lymphatic system disorders (226 reports, ROR 2.82, PRR 2.73, IC 1.45, and EBGM 2.73) demonstrated high ROR values, indicating strong associations across all four algorithms. Some findings matched the common adverse reactions listed in the drug inserts, thereby enhancing the data credibility. However, certain SOCs with notable adverse reactions, such as psychiatric disorders (41 reports, ROR 0.15, PRR 0.15, IC -2.71, and EBGM 0.15) and immune system disorders (eight reports, ROR 0.14, PRR 0.15, IC -2.78, and EBGM 0.15), were not documented in the drug labelling (Table 2).

3.2.2. ADE frequency analysis

Table 3 displays the top 50 EV-associated ADEs, ranked by signal strength. Notably, malignant neoplasm progression (179 reports; ROR 21.29, PRR 20.53, IC 4.35, and EBGM 20.43), peripheral neuropathy (176 reports; ROR 22.99, PRR 22.17, IC 4.46, and EBGM 22.06), and hyperglycemia (78 reports; ROR 34.16, PRR 33.62, IC 5.06, and EBGM 33.35) exhibited relatively high frequency rates and signal strengths. Additionally, ADEs such as lichenoid keratosis (four reports; ROR 26.89, PRR 26.87, IC 4.74, and EBGM 26.7),

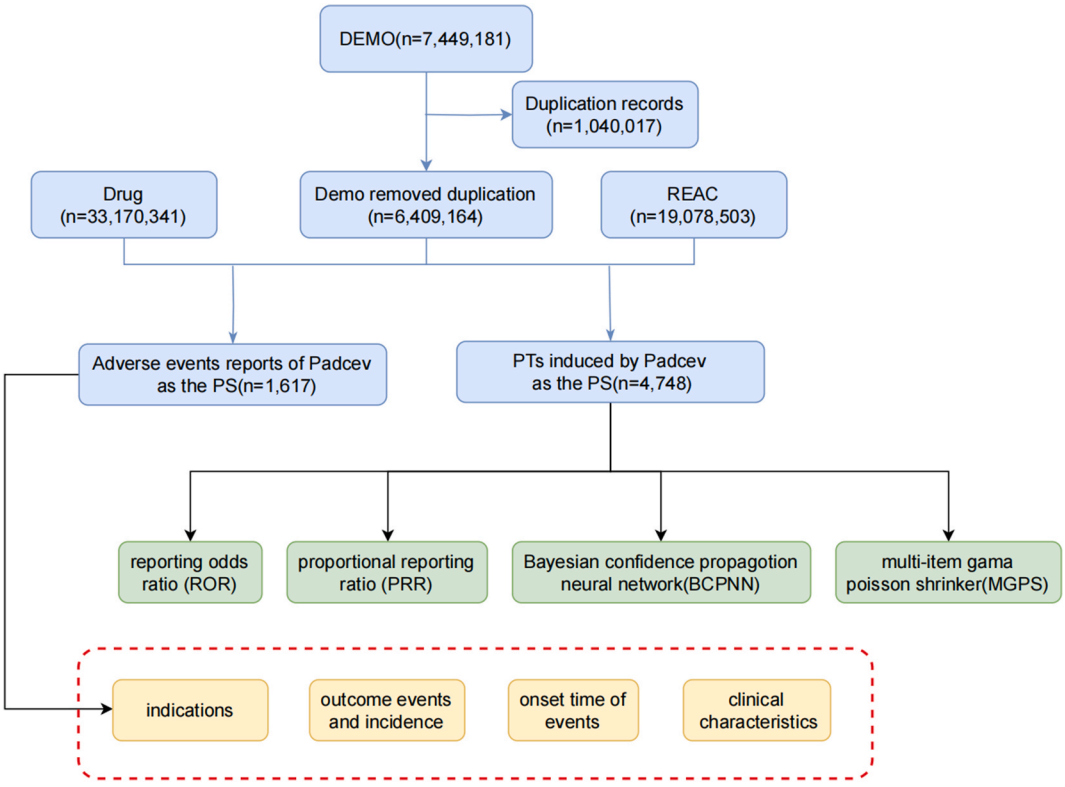

Fig. 1. The flow diagram of selecting enfortumab vedotin-related adverse events (AEs) from FDA Adverse Event Reporting System (FAERS) database.

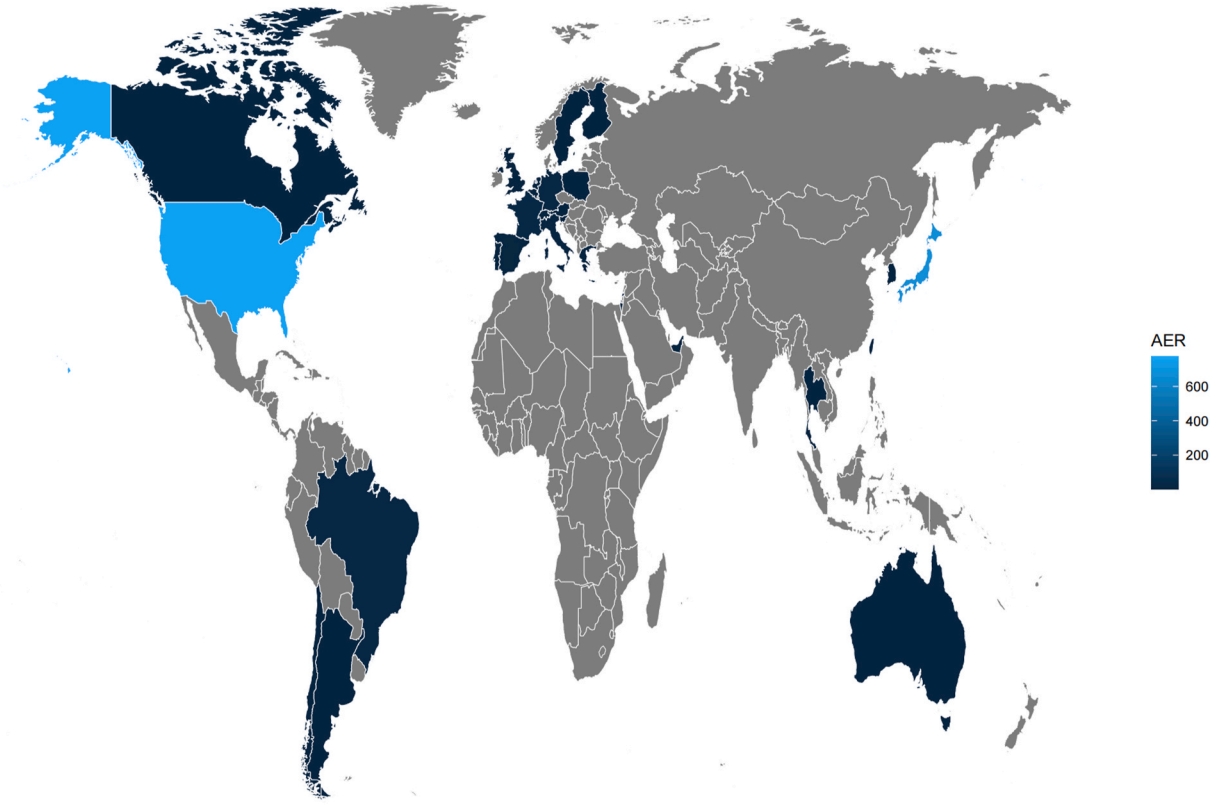

Fig. 2. World map of the adverse reaction reports for enfortumab vedotin. Abbreviations: AER, Adverse Event Reporting.

small intestinal perforation (three reports; ROR 24.51, PRR 24.50, IC 4.61, and EBGM 24.35), pigmentation disorder (nine reports; ROR 18.16, PRR 18.13, IC 4.17, and EBGM 18.05), cholangitis (eight reports; ROR 17.48, PRR 17.46, IC 4.12, and EBGM 17.39), ileus (11 reports; ROR 16.18, PRR 16.15, IC 4.01, and EBGM 16.08), compression fracture (four reports; ROR 15.8, PRR 15.78, IC 3.98, and EBGM 15.73), hydronephrosis (eight reports; ROR 15.39, PRR 15.36, IC 3.94, and EBGM 15.31), and gastric ulcer hemorrhage (three reports; ROR 10.19, PRR 10.19, IC 3.35, and EBGM 10.16) were identified as potential new ADE signals not mentioned in the package insert.

4. Discussion

Nectins are type I transmembrane proteins belonging to the immunoglobulin superfamily that function as cell-adhesion molecules. Closely related to, but distinct from, nectin-like molecules, the nectin family consists of four primary members (nectin-1 to nectin-4) [20]. EV is a monoclonal antibody targeting nectin-4; it was approved by the US FDA in 2019 for the treatment of la/mUC [21]. This antibody-drug conjugate comprises a fully human monoclonal antibody specific for nectin-4 and monomethyl auristatin E, a microtubule-disrupting agent. The targeted delivery of this agent induces cell cycle arrest and apoptosis [11,22]. In a Phase 3 clinical trial, EV significantly prolonged survival compared to standard chemotherapy in patients with la/mUC who had previously received platinum therapy and PD-1/L1 inhibitors [23]. EV is generally considered a safe and well-tolerated drug; however, common adverse reactions still occur after its use. The most frequent ($\geq$20 %) all-grade AEs associated with its use include fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus, and dry skin. Additionally, hyperglycemia, peripheral neuropathy, ocular disorders, skin reactions, infusion site extravasations, and embryo-fetal toxicity are specifically labelled as warnings and precautions for EV [6]. As a recently marketed drug, monitoring the real-world usage of EV-related AEs is crucial for ensuring its safety and efficacy. This study systematically evaluated the adverse reactions related to EV via an in-depth analysis of the FAERS database from Q1 2020 to Q1 2024. The results confirm existing safety information, uncover potential new risks, and provide essential data to support medical decision-making and public health policies.

Our study identified a substantial number of AEs associated with EV, with 1,617 reports indicating EV as the primary suspected drug. This underscores the importance of the continuous monitoring and evaluation of drug safety in real-world clinical settings. The predominance of male patients and the higher frequency of AEs in older age groups align with the established clinical indications for EV, such as the treatment of BC, which is more common in elderly men compared to women [24,25]. It is noteworthy that physicians submitted the most adverse reaction reports (41.00 %), rather than consumers themselves. This is likely because physicians are more

Table 1
Basic information on ADEs related to enfortumab vedotin from the FAERS database.

Variable	Total
Number of events	1617
Year	
2020	177 (10.95)
2021	242 (14.97)
2022	356 (22.02)
2023	631 (39.02)
2024	211 (13.05)
Sex	
Female	363 (22.45)
Male	1184 (73.22)
Unknown	70 (4.33)
Age	
<65	189 (11.69)
65~75	351 (21.71)
≥75	505 (31.23)
Unknown	572 (35.37)
Reporter	
Physician	663 (41.00)
Consumer	564 (34.88)
Pharmacist	385 (23.81)
Unknown	5 (0.31)
Reported countries	
United States	772 (47.74)
Japan	669 (41.37)
Other	176 (10.88)
Outcomes	
Other serious	1139 (58.47)
Hospitalization	436 (22.38)
Death	326 (16.74)
Life threatening	33 (1.69)
Disability	13 (0.67)
Required Intervention to Prevent Permanent Impairment/Damage	1 (0.05)

Abbreviations: ADEs, Adverse drug events; FAERS, FDA Adverse Event Reporting System.

familiar with the reporting process, understand the clinical significance of AEs, and are more aware of the potential side effects of drugs. Additionally, patients may not recognize certain symptoms as adverse reactions or may lack awareness of how to report them. Furthermore, with most reports originating from the United States. (47.74 %), regional or cultural reporting trends may have influenced these findings, warranting further investigation to identify potential biases. With regard to adverse outcomes, besides unknown events, death and hospitalization were the most prevalent. This is crucial because it may be related to the indications for EV, given that patients with mUC generally have a poor prognosis [26].

The present study uncovered certain AEs associated with EV, such as psychiatric and immune system disorders, which were not previously mentioned in the instructions for the use of this drug. This suggests the need to update these instructions so as to provide more comprehensive AE-related information. Additionally, commonly occurring AEs, such as hyperglycemia, skin disorders, and peripheral neuropathy, aligned with the existing information, underscoring their significance. Although relatively rare, AEs such as lichenoid keratosis, small intestinal perforation, pigmentation disorder, cholangitis, ileus, compression fracture, hydronephrosis, and gastric ulcer hemorrhage exhibit high signal strength, indicating their potential importance. Although this study highlighted these new EV-related AEs, further research is necessary to understand their potential connections and mechanisms.

Lichenoid keratosis is a rare chronic inflammatory skin disease characterized by asymptomatic hyperkeratotic papules on the trunk and limbs [27]. Although some studies have shown that immune checkpoint inhibitors can cause lichenoid keratosis [28], current evidence does not indicate that ADC-related drugs can cause this condition. This warrants serious attention from healthcare professionals. The use of EV may cause gastrointestinal reactions [29], but no previous studies have reported the occurrence of EV-induced small intestinal perforations. Although the exact mechanism underlying this phenomenon is not yet clear, we speculate that the drug may reduce blood supply to the intestinal wall, leading to ischemia. Additionally, in some cases, the destruction of tumors may compromise the stability of the intestinal wall, thereby increasing the risk of perforation [30]. Skin toxicity is one of the most common adverse reactions to EV and primarily manifests as rashes or itching. Rare but potentially life-threatening or fatal manifestations, such as Stevens-Johnson syndrome, have also been reported [31]. However, there are currently no reports on pigmentation disorders, highlighting the relative limitations of clinical trials.

Drug-induced bile duct injury can be caused by various drugs used outside medical settings, including herbal supplements, carbapenems, and ketamine. In most cases, the damage is caused by T cell-mediated immune responses. Bile duct injury caused by immune checkpoint inhibitors results from excessive stimulation or inadequate regulation of the immune system [32]. Given that these drugs can cause immune-related adverse reactions, it is plausible that cholangitis associated with EV may be related to similar mechanisms. Intestinal obstruction is primarily caused by anticholinergic drugs such as olanzapine [33]. However, there are no reports

Table 2
The signal strength of ADEs of enfortumab vedotin at the SOC level in FAERS database.

System organ class	Case Reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC(IC025)	EBGM (EBGM05)
skin and subcutaneous tissue disorders	949	4.24 (3.95, 4.55)[a]	3.59 (3.38, 3.81)[a]	1877.3	1.84 (1.74)[a]	3.59 (3.38)[a]
metabolism and nutrition disorders	307	3.5 (3.12, 3.93)[a]	3.34 (2.97, 3.76)[a]	512.47	1.74 (1.57)[a]	3.34 (3.03)[a]
blood and lymphatic system disorders	226	2.82 (2.46, 3.22)	2.73 (2.43, 3.07)[a]	252.02	1.45 (1.26)[a]	2.73 (2.44)[a]
hepatobiliary disorders	91	2.33 (1.89, 2.86)	2.3 (1.89, 2.8)[a]	67.38	1.2 (0.9)[a]	2.3 (1.93)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	333	1.69 (1.52, 1.89)	1.65 (1.5, 1.82)	88.04	0.72 (0.56)[a]	1.65 (1.5)
endocrine disorders	17	1.33 (0.83, 2.15)	1.33 (0.83, 2.13)	1.42	0.42 (-0.25)	1.33 (0.9)
nervous system disorders	457	1.33 (1.21, 1.47)	1.3 (1.2, 1.41)	34.59	0.38 (0.24)[a]	1.3 (1.2)
renal and urinary disorders	112	1.25 (1.04, 1.51)	1.24 (1.04, 1.48)	5.49	0.32 (0.05)[a]	1.24 (1.06)
eye disorders	100	1.08 (0.88, 1.31)	1.07 (0.88, 1.3)	0.52	0.1 (-0.18)	1.07 (0.91)
investigations	295	1.04 (0.93, 1.17)	1.04 (0.92, 1.17)	0.51	0.06 (-0.11)	1.04 (0.94)
gastrointestinal disorders	380	1.01 (0.91, 1.12)	1.01 (0.92, 1.11)	0.02	0.01 (-0.14)	1.01 (0.92)
infections and infestations	231	0.83 (0.73, 0.95)	0.84 (0.75, 0.94)	7.41	−0.25 (-0.44)	0.84 (0.75)
general disorders and administration site conditions	662	0.73 (0.67, 0.79)	0.77 (0.71, 0.83)	57.81	−0.38 (-0.5)	0.77 (0.72)
respiratory, thoracic and mediastinal disorders	151	0.68 (0.58, 0.8)	0.69 (0.59, 0.81)	21.94	−0.53 (-0.77)	0.69 (0.6)
vascular disorders	41	0.45 (0.33, 0.62)	0.46 (0.34, 0.63)	26.8	−1.13 (-1.56)	0.46 (0.35)
cardiac disorders	42	0.44 (0.32, 0.6)	0.44 (0.33, 0.59)	29.71	−1.17 (-1.6)	0.44 (0.34)
injury, poisoning and procedural complications	227	0.35 (0.31, 0.4)	0.38 (0.34, 0.43)	262.54	−1.4 (-1.59)	0.38 (0.34)
musculoskeletal and connective tissue disorders	66	0.25 (0.2, 0.32)	0.26 (0.21, 0.33)	142.51	−1.92 (-2.27)	0.26 (0.22)
reproductive system and breast disorders	6	0.21 (0.09, 0.47)	0.21 (0.09, 0.47)	17.88	−2.25 (-3.32)	0.21 (0.11)
psychiatric disorders	41	0.15 (0.11, 0.2)	0.15 (0.11, 0.21)	203.34	−2.71 (-3.14)	0.15 (0.12)
immune system disorders	8	0.14 (0.07, 0.29)	0.15 (0.08, 0.3)	40.67	−2.78 (-3.73)	0.15 (0.08)
surgical and medical procedures	5	0.07 (0.03, 0.17)	0.07 (0.03, 0.17)	62.23	−3.83 (-4.98)	0.07 (0.03)

[a] Indicating statistical significance. Abbreviations: ADEs, Adverse drug events; SOC, system organ classe; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; EBGME, mpirical Bayesian Geometric Mean; CI, confidence interval; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM05, the lower limit of 95 % CI of EBGM; χ2,chi-squared.

of intestinal obstruction caused by EV. Compression fractures can be induced by various medications, particularly those that affect bone density and strength. For example, corticosteroids increase the risk of such fractures by suppressing bone formation and increasing bone resorption, leading to osteoporosis [34]. Therefore, EV-induced compression fractures may be attributed to the changes in bone density and strength caused by EV. Hydronephrosis, or swelling of the kidney due to build-up of urine, can sometimes be caused by certain medications. Drugs that affect urinary outflow, such as anticholinergics and opioids, can cause urinary retention and subsequent hydronephrosis [35]. Although the use of EV can damage renal function [35], adverse reactions specifically involving hydronephrosis have not yet been described. Gastric ulcer hemorrhage can be caused by nonsteroidal anti-inflammatory drugs and corticosteroids [36]. These drugs can damage the protective lining of the stomach, leading to ulcer formation and subsequent bleeding. Although gastric ulcer hemorrhage has not been reported among the gastrointestinal adverse reactions caused by EV [37], it remains a life-threatening condition that warrants the attention of clinical physicians.

The risk analysis of EV based on the FAERS database has several limitations. First, the FAERS database relies on voluntary reporting, which can lead to under-reporting or incomplete data, potentially skewing the results. Second, the database often lacks detailed patient information, such as data regarding comorbidities, concomitant medications, and exact dosages, which are crucial for assessing causality and the overall context of AEs. Third, the analysis was restricted to the timeframe from Q1 2020 to Q1 2024; thus, the long-term adverse effects or those emerging beyond this period may not have been captured. Additionally, the Weber effect was evident in FAERS, with AE reports peaking shortly after a drug's release and decreasing over time [38]. Despite these limitations, the

Table 3
The top 50 signal strength of adverse events of enfortumab vedotin ranked by ROR at the PTs level in FAERS database.

System Organ Class (SOC)	Preferred Term (PT)	Case Reports	ROR (95 % CI)	PRR (95 % CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
investigations	kl-6 increased	6	211.7 (93.1, 481.36)	211.43 (92.82, 481.59)	1193.8	7.65 (6.55)	200.91 (101.04)
skin and subcutaneous tissue disorders	toxic erythema of chemotherapy	5	186.18 (75.92, 456.57)	185.98 (75.49, 458.17)	879.24	7.47 (6.29)	177.8 (83.94)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	transitional cell carcinoma	10	100.14 (53.43, 187.67)	99.93 (53.37, 187.1)	955.66	6.61 (5.74)	97.53 (57.66)
nervous system disorders	peripheral motor neuropathy	8	79.48 (39.46, 160.12)	79.35 (39.18, 160.69)	606.94	6.28 (5.33)	77.83 (43.32)
skin and subcutaneous tissue disorders	epidermal necrosis	4	61.85 (23.03, 166.12)	61.8 (23.19, 164.66)	235.66	5.93 (4.65)	60.88 (26.64)
skin and subcutaneous tissue disorders	exfoliative rash	7	45.79 (21.73, 96.51)	45.72 (21.71, 96.29)	302.79	5.5 (4.49)	45.22 (24.23)
skin and subcutaneous tissue disorders	stevens-johnson syndrome	45	43.5 (32.38, 58.43)	43.09 (32.11, 57.82)	1831	5.41 (4.99)	42.65 (33.31)
skin and subcutaneous tissue disorders	skin toxicity	20	42.89 (27.58, 66.7)	42.71 (27.75, 65.74)	806.25	5.4 (4.78)	42.27 (29.22)
skin and subcutaneous tissue disorders	symmetrical drug-related intertriginous and flexural exanthema	4	39.03 (14.57, 104.54)	39 (14.64, 103.91)	146.69	5.27 (4)	38.64 (16.94)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	cancer pain	9	37.04 (19.2, 71.44)	36.97 (19.36, 70.59)	312.1	5.2 (4.3)	36.64 (21.15)
eye disorders	ocular toxicity	3	34.36 (11.02, 107.08)	34.34 (11.02, 107.03)	96.27	5.09 (3.67)	34.05 (13.15)
metabolism and nutrition disorders	hyperglycaemia	78	34.16 (27.29, 42.77)	33.62 (27.1, 41.71)	2449.16	5.06 (4.74)	33.35 (27.63)
skin and subcutaneous tissue disorders	dermatitis exfoliative	3	28.99 (9.31, 90.28)	28.97 (9.29, 90.29)	80.44	4.85 (3.43)	28.77 (11.12)
skin and subcutaneous tissue disorders	toxic epidermal necrolysis	29	28.86 (20.01, 41.64)	28.69 (19.77, 41.64)	769.82	4.83 (4.31)	28.5 (20.97)
skin and subcutaneous tissue disorders	dermatitis bullous	13	28.35 (16.42, 48.95)	28.27 (16.33, 48.94)	339.68	4.81 (4.05)	28.08 (17.78)
skin and subcutaneous tissue disorders	lichenoid keratosis	4	26.89 (10.06, 71.92)	26.87 (10.08, 71.59)	98.97	4.74 (3.47)	26.7 (11.72)
nervous system disorders	taste disorder	75	25.29 (20.12, 31.79)	24.91 (20.08, 30.9)	1711.47	4.63 (4.3)	24.76 (20.44)
gastrointestinal disorders	small intestinal perforation	3	24.51 (7.87, 76.29)	24.5 (7.86, 76.36)	67.2	4.61 (3.19)	24.35 (9.42)
metabolism and nutrition disorders	insulin resistance	4	23.86 (8.93, 63.79)	23.84 (8.95, 63.52)	87.02	4.57 (3.3)	23.71 (10.41)
skin and subcutaneous tissue disorders	skin disorder	66	23.59 (18.49, 30.1)	23.28 (18.4, 29.45)	1400.05	4.53 (4.18)	23.15 (18.88)
nervous system disorders	neuropathy peripheral	176	22.99 (19.77, 26.73)	22.17 (19.33, 25.43)	3544.57	4.46 (4.25)	22.06 (19.44)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to lymph nodes	12	22.48 (12.73, 39.67)	22.42 (12.7, 39.58)	244.26	4.48 (3.69)	22.3 (13.86)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	malignant neoplasm progression	179	21.29 (18.33, 24.73)	20.53 (17.9, 23.55)	3314.58	4.35 (4.14)	20.43 (18.02)

(*continued on next page*)

Table 3 (*continued*)

System Organ Class (SOC)	Preferred Term (PT)	Case Reports	ROR (95 % CI)	PRR (95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
investigations	eastern cooperative oncology group performance status worsened	3	20.13 (6.47, 62.62)	20.12 (6.46, 62.71)	54.24	4.32 (2.9)	20.02 (7.75)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to peritoneum	4	20.05 (7.5, 53.58)	20.04 (7.52, 53.4)	71.99	4.32 (3.05)	19.94 (8.76)
skin and subcutaneous tissue disorders	skin reaction	17	19.48 (12.09, 31.4)	19.42 (12.13, 31.08)	295.61	4.27 (3.6)	19.33 (12.96)
nervous system disorders	peripheral sensory neuropathy	8	19.32 (9.64, 38.72)	19.29 (9.71, 38.31)	138.09	4.26 (3.32)	19.2 (10.73)
skin and subcutaneous tissue disorders	pigmentation disorder	9	18.16 (9.43, 34.98)	18.13 (9.5, 34.62)	145.04	4.17 (3.28)	18.05 (10.43)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to liver	24	17.59 (11.77, 26.29)	17.51 (11.83, 25.91)	372.04	4.12 (3.56)	17.44 (12.46)
hepatobiliary disorders	cholangitis	8	17.48 (8.73, 35.04)	17.46 (8.79, 34.67)	123.59	4.12 (3.17)	17.39 (9.72)
respiratory, thoracic and mediastinal disorders	pulmonary toxicity	11	17.05 (9.43, 30.85)	17.02 (9.45, 30.64)	165.14	4.08 (3.26)	16.95 (10.32)
gastrointestinal disorders	ileus	11	16.18 (8.94, 29.27)	16.15 (8.97, 29.08)	155.68	4.01 (3.19)	16.08 (9.79)
injury, poisoning and procedural complications	compression fracture	4	15.8 (5.92, 42.19)	15.78 (5.92, 42.05)	55.18	3.98 (2.71)	15.73 (6.91)
blood and lymphatic system disorders	myelosuppression	61	15.69 (12.18, 20.21)	15.5 (12.01, 20)	825.1	3.95 (3.59)	15.45 (12.5)
renal and urinary disorders	hydronephrosis	8	15.39 (7.68, 30.83)	15.36 (7.74, 30.5)	107.02	3.94 (2.99)	15.31 (8.56)
skin and subcutaneous tissue disorders	rash vesicular	5	15.28 (6.35, 36.78)	15.26 (6.32, 36.86)	66.39	3.93 (2.77)	15.21 (7.29)
general disorders and administration site conditions	performance status decreased	4	15.27 (5.72, 40.78)	15.26 (5.73, 40.66)	53.1	3.93 (2.66)	15.21 (6.68)
skin and subcutaneous tissue disorders	skin erosion	4	14.97 (5.61, 39.99)	14.96 (5.61, 39.86)	51.92	3.9 (2.63)	14.91 (6.55)
general disorders and administration site conditions	extravasation	3	14.34 (4.61, 44.56)	14.33 (4.6, 44.66)	37.07	3.84 (2.42)	14.28 (5.53)
skin and subcutaneous tissue disorders	drug eruption	18	13.73 (8.64, 21.83)	13.68 (8.55, 21.9)	210.98	3.77 (3.12)	13.64 (9.26)
eye disorders	keratitis	3	13.56 (4.36, 42.15)	13.56 (4.35, 42.26)	34.77	3.76 (2.34)	13.51 (5.23)
gastrointestinal disorders	immune-mediated enterocolitis	6	13.31 (5.97, 29.68)	13.29 (5.95, 29.68)	68	3.73 (2.66)	13.25 (6.78)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to central nervous system	13	12.9 (7.48, 22.26)	12.87 (7.43, 22.28)	141.89	3.68 (2.92)	12.83 (8.13)
infections and infestations	pyelonephritis	8	12.54 (6.26, 25.12)	12.52 (6.3, 24.86)	84.58	3.64 (2.7)	12.49 (6.98)
gastrointestinal disorders	ileus paralytic	3	12.51 (4.03, 38.87)	12.5 (4.01, 38.96)	31.65	3.64 (2.22)	12.47 (4.83)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to lung	11	12.2 (6.75, 22.07)	12.18 (6.77, 21.93)	112.53	3.6 (2.78)	12.14 (7.4)
renal and urinary disorders	nephritis	3	11.8 (3.8, 36.66)	11.79 (3.78, 36.75)	29.55	3.56 (2.14)	11.76 (4.55)
investigations	amylase increased	3	11.16 (3.59, 34.65)	11.15 (3.58, 34.75)	27.64	3.48 (2.06)	11.12 (4.31)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to bone	15	10.63 (6.4, 17.66)	10.6 (6.37, 17.65)	130.13	3.4 (2.69)	10.58 (6.92)
gastrointestinal disorders	gastric ulcer hemorrhage	3	10.19 (3.28, 31.66)	10.19 (3.27, 31.76)	24.8	3.35 (1.93)	10.16 (3.94)

*Indicating statistical significance. Abbreviations: PTs: preferred terms; FAERS, FDA Adverse Event Reporting System; SOC, system organ classe; ROR, Reporting Odds Ratio; PRR, Proportional Reporting Ratio; EBGME, mpirical Bayesian Geometric Mean; CI, confidence interval; IC, information component; IC025, the lower limit of 95 % CI of the IC; EBGM05, the lower limit of 95 % CI of EBGM; χ2,chi-squared.

present study provides valuable insights for the development of precise and targeted policies to prevent adverse reactions caused by EV in real-world settings.

5. Conclusion

Our pharmacovigilance study of EV revealed both known and novel ADEs, including lichenoid keratosis and small intestinal perforation. These findings are essential for improving patient safety through the establishment of enhanced monitoring and preventive measures.

Consent for publication

Not applicable.

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Ethics approval

Review and approval by an ethics committee were not needed for this study because all data were obtained from public databases, and the research did not involve human or animal experiments or the collection of personal privacy information.

Data availability statement

The dataset generated and analyzed in the current study is available from the corresponding author upon reasonable request. The data are included in the article/supplementary material referenced in this article.

CRediT authorship contribution statement

Fuchun Zheng: Formal analysis, Data curation, Conceptualization. **Yuanzhuo Du:** Methodology, Investigation. **Yuyang Yuan:** Resources, Project administration, Methodology. **Zhipeng Wang:** Supervision, Software, Resources. **Sheng Li:** Writing – original draft, Supervision. **Situ Xiong:** Writing – original draft, Visualization, Supervision. **Jin Zeng:** Writing – review & editing, Writing – original draft, Validation. **Yifan Tan:** Validation, Resources, Investigation. **Xiaoqiang Liu:** Validation, Resources, Investigation. **Songhui Xu:** Writing – original draft, Software, Resources. **Bin Fu:** Validation, Supervision, Software. **Wei Liu:** Software, Project administration, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was conducted using the FAERS database provided by the FDA. The information, results, and interpretations of the current study do not represent the opinions of the FDA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37544.

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