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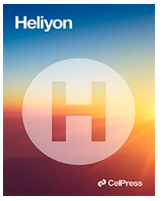

Research article

Safety assessment of dapagliflozin: Real-world adverse event analysis based on the FAERS database from 2012 to 2023

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ABSTRACT

Background: Dapagliflozin possesses the capacity to cure a wide range of diseases, however, there are many adverse events (AEs) that have not yet been acknowledged or recorded.
Aim: Safety assessment of dapagliflozin based on the Food and Drug Administration Adverse Event Reporting System (FAERS) database, to explore differences between the reported AEs to provide a overview of the safety profile of dapagliflozin.
Methods: We extracted data from the United States FAERS database, including from the fourth quarter of 2012 to the third quarter of 2023. Reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric average (EBGM) were used to evaluate the relationship between dapagliflozin and its associated AEs.
Results: A total of 13,593,946 case reports were gathered from the Food and Drug Administration Adverse Event Reporting System database for this investigation. Among these, there were 44,506 episodes of adverse events that were associated with dapagliflozin. Included in the analysis were 341 preferred words and 2 system organ classes that showed statistical significance according to all four methods simultaneously. The system organ classes encompassed illnesses related to metabolism and nutrition, as well as problems affecting the renal and urinary systems. PT levels were screened for adverse drug reaction signals including scrotal gangrene, scrotal cellulitis, perineal cellulitis, diabetic ketoacidosis, and pancreatitis.
Conclusion: The majority of our findings aligned with the specification, however, certain novel indicators of AEs such as acute pancreatitis were not accounted for. The analysis of the AE signals may provide support for clinical monitoring and risk identification of dapagliflozin. Due to the inherent limitations of FAERS data, well-designed studies are required to demonstrate the safety of dapagliflozin.

1. Introduction

Dapagliflozin, as a sodium-glucose cotransporter-2 inhibitor (SGLT-2i), inhibits the reabsorption of sodium and glucose in the proximal renal tubules [1], resulting in the loss of glucose and decreased serum levels in the urine. Clinically, dapagliflozin was

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originally developed as a hypoglycemic agent for the treatment of type 2 diabetes (T2D) [2], but this is only one of its potential indications. Several large clinical studies have shown that dapagliflozin reduces the risk of chronic kidney disease (CKD) [3,4], heart failure [5,6] and end-stage renal disease [7], reduces cardiovascular complications and mortality [8,9], and has potential therapeutic and safety advantages. The latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines advocate for the primary use of dapagliflozin as first line treatment for patients with CKD [10]. Dapagliflozin has shown promising therapeutic and safety benefits in many clinical trials. Nevertheless, with the introduction of dapagliflozin, there are some drug-related adverse events that require our thoughtful evaluation.

Previous study of AEs associated with dapagliflozin have identified several risks. A study reviewed the safety of the SGLT-2i and reported that the most common AEs including euglycemic diabetic ketoacidosis (euDKA) and diabetic ketoacidosis (DKA) [11]. Another study compared the use of SGLT-2i with urinary tract infections (UTIs) and genital mycotic infections (GMIs) [12]. However, these studies focused on common AEs of SGLT-2i [13] and did not fully explore new or rare ae for dapagliflozin. Therefore, there remains a dearth of research on the adverse responses associated with dapagliflozin, particularly in relation to real-world data and large-scale datasets. The US FAERS provides a platform for collecting and analysing adverse drug events associated with substance use [14]. This data is a crucial asset for evaluating the safety and effectiveness of drugs. This research aims to conduct an in-depth analysis of the actual adverse reaction signal data related to dapagliflozin in the FAERS database, using various signal quantification methodologies to assess the data from diverse angles and produce more comprehensive and dependable findings, which could help identify emerging safety issues, assess the risk-benefit profiles, and optimize treatment strategies to minimize patient harm, so as to comprehensively evaluate the potential risks in clinical use and provide safety reference for clinical practice.

2. Methods

2.1. Data sources

The AE data used in this investigation was obtained from the FAERS database. The FAERS database, which has been accessible to the public since 2004, is a platform where healthcare professionals, pharmaceutical makers, patients, and other individuals can upload reports of adverse events. The data is updated every three months and the reporting system is generally acknowledged worldwide for its extensive data and consistency. Data on adverse events linked to dapagliflozin were collected from the FAERS database throughout

Table 1
Four grid table.

	Drug-related AEs	Non-drug-related AEs	Total
Drug	a	b	a + b
Non-drug	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

Method	Formula	Threshold
ROR	$\mathrm{ROR} = \frac{a/c}{b/d}$	a ≥3 ROR ≥3 95%CI (lower limit) > 1
	$SE(lnROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	
	$95\%CI = e^{\ln(ROR)\pm 1.96se}$	
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$	a ≥3 PRR ≥2 ,95%CI (lower limit) > 1
	$SE(lnPRR) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$	
	$95\%CI = e^{\ln(PRR)\pm 1.96se}$	
BCPNN	$\mathrm{IC} = \log_2\frac{p(x,y)}{p(x)p(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025>0
	$\mathrm{E(IC)} = \log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$\mathrm{V(IC)} = \frac{1}{(ln\,2)^2}\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}+\frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}+\frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}\right]$	
	$\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$\mathrm{IC}-2\mathrm{SD} = \mathrm{E(IC)}-2\sqrt{\mathrm{V(IC)}}$	
EBGM	$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05>2
	$SE(lnEBGM) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	
	$95\%CI = e^{\ln(EBGM)\pm 1.96se}$	

AE: adverse effect; SOC: system organ class; ROR: reporting odds ratios; CI: confidence interval.
PRR: proportional reporting ratios; IC: information component; EBGM: empirical Bayesian geometric mean.

Table 2
Clinical features of dapagliflozin reports from the FAERS database (2012 Q4–2023 Q3).

variable	Case number	Case proportion
Year		
2013	8	0.04 %
2014	1056	5.67 %
2015	1788	9.59 %
2016	1470	7.89 %
2017	1428	7.66 %
2018	1724	9.25 %
2019	1418	7.61 %
2020	1619	8.69 %
2021	2037	10.93 %
2022	2778	14.91 %
2023	3310	17.76 %
sex		
female	8010	42.98 %
male	8171	43.85 %
unkown	2455	13.17 %
age		
<18	25	0.13 %
18~45	1074	5.76 %
45~65	4452	23.89 %
65~75	2740	14.70 %
≥75	1987	10.66 %
unknow	8358	44.85 %
Reporter		
Physician	7624	40.91 %
Consumer	6640	35.63 %
Pharmacist	1952	10.47 %
unkown	1756	9.42 %
Other health-professional	604	3.24 %
Lawyer	59	0.32 %
Registered Nurse	1	0.01 %
Reported countries		
United States	10194	54.70 %
Japan	1256	6.74 %
United Kingdom	1249	6.70 %
China	732	3.93 %
Germany	679	3.64 %
other	663	3.56 %
Russia	631	3.39 %
France	409	2.19 %
Canada	395	2.12 %
Australia	373	2.00 %
Brazil	346	1.86 %
South Africa	208	1.12 %
Spain	201	1.08 %
Sweden	114	0.61 %
Denmark	107	0.57 %
Mexico	92	0.49 %
Italy	88	0.47 %
Israel	79	0.42 %
Portugal	79	0.42 %
Turkey	78	0.42 %
Poland	77	0.41 %
Netherlands	74	0.40 %
Greece	72	0.39 %
Romania	68	0.36 %
Belgium	66	0.35 %
Norway	65	0.35 %
Korea, South	63	0.34 %
Ireland	62	0.33 %
Austria	58	0.31 %
Switzerland	58	0.31 %
Outcomes		
other serious	6875	42.29 %
hospitalization	5379	33.09 %
death	2191	13.48 %
life threatening	1365	8.40 %
disability	394	2.42 %
required intervention to Prevent Permanent Impairment/Damage	37	0.23 %
congenital anomaly	17	0.10 %

the period of October 1, 2012, to September 31, 2023, in accordance with the drug's market launch timeline.

2.2. Standardization of drug names and adverse reactions

In this research, dapagliflozin was selected as the suspected drug category, and its name was encoded using RxNorm. Drug names were standardized using the Medex_UIMA_1.8.3 system to ensure consistency across all reports. This step is essential for accurately identifying all reports related to dapagliflozin. Repeat reports were identified and removed to avoid overestimation of AEs. Furthermore, the Medical Dictionary of Regulatory Activities (MedDRA 25.0) was utilized to align the preferred terms (PTs) for adverse reactions associated with dapagliflozin, along with the corresponding system organ classes (SOCs). Various clinical characteristics, such as gender, age, reporting region, reporter identity, reporting timeframe, and patient outcomes related to dapagliflozin-induced adverse events, were gathered. Severe adverse patient outcomes were specifically defined as instances of hospitalization, disability, life-threatening situations, or fatalities.

2.3. Data analysis algorithms

To assess the correlation between pharmaceuticals and AEs, this metric compares the frequency ratios observed in populations that were exposed and those that were not exposed using a four-grid scale (Table 1). To assess the intensity of the correlation between drugs and AEs, the research utilized disproportional analysis (DA) [15], a recognized approach for early signal detection, such as the PRR, ROR, BCPNN, and EBGM. DA is still irreplaceable in the detection of unpredictable adverse events of drugs. ROR provides the benefit of mitigating bias introduced by a limited number of event reports, whereas PRR is recognized for its improved specificity in comparison to ROR. The BCPNN algorithm demonstrates exceptional performance in cross-validation and data integration from various sources, owing to its heavy reliance on the information component (IC) and its corresponding confidence interval (CI). By integrating the ROR, PRR, BCPNN, and EBGM algorithms, the research was able to generate a more comprehensive and reliable safety signal by validating outcomes from multiple perspectives. By modifying thresholds and variances, the combined use of these algorithms enabled the detection of potentially rare adverse reactions and facilitated cross-validation to reduce false positives. Each algorithm utilized a 2×2 concatenated table (Table 1) as its foundation; the formulas and thresholds for each algorithm were specified in Table 2. The statistical analyses were performed utilizing the R software. An increase in the values of these metrics signifies a more pronounced signal strength. At the same time, the analysis shows more secure correlation when multiple algorithms are consistent. The comprehensive approach of the research is depicted in the flowchart (Fig. 1).

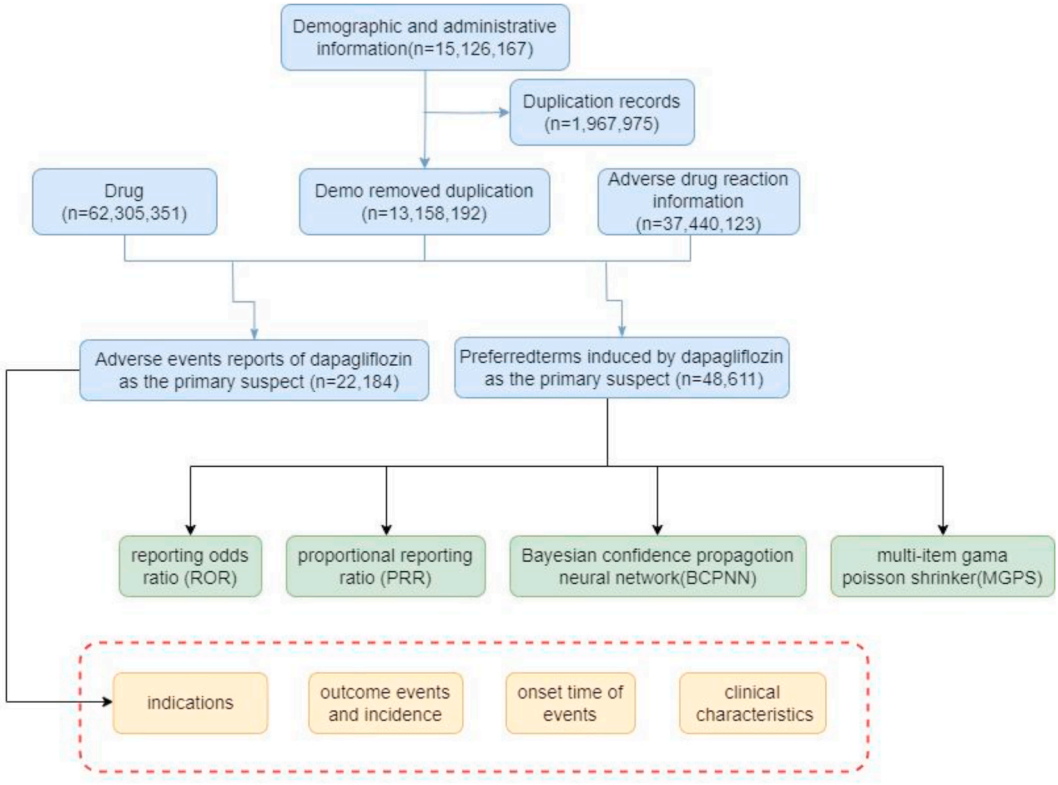

Fig. 1. The flow diagram of selecting dapagliflozin-related AEs from FAES database.

3. Results

3.1. Basic characteristics of dapagliflozin-related AEs

From the 2012 Q4 to the 2023 Q3, a total of 13,593,946 adverse event reports were screened. Out of these, 44,506 were related to dapagliflozin and included 1313 PT and 24 SOC. Regarding AEs (Table 2), the disparity between males and females is minimal (43.85 % vs. 42.98 %). A proportion of the data (44.5 %) lacked age-related information, thereby constraining our comprehensive comprehension of the correlation between age and AE. Based on the available age data, the age grouping of 65–75 years appeared most frequently in reports (25.36 %). The greatest proportion of AE reports are attributed to physicians (40.91 %). Furthermore, the highest number of reports was received by the United States (54.7 %), which was followed by Japan (6.74 %), the United Kingdom (6.7 %), China (3.93 %), Germany (3.64 %), and Russia (3.39 %). Based on the FAERS database analysis, the most prevalent serious adverse events associated with dapagliflozin were as follows: hospitalization, disability, mortality, intervention required to prevent permanent

Table 3
AEs signal intensity of dapagliflozin at the SOC level in the FAERS database.

System organ class	Case Reports	ROR(95 % CI)	PRR(95 % CI)	chisq	IC(IC025)	EBGM (EBGM05)
metabolism and nutrition disorders	5643	6.77(6.58, 6.96)	6.02(5.9, 6.14)	23972.7	2.58(2.54)	5.98(5.85)
renal and urinary disorders	3154	3.81(3.67, 3.95)	3.6(3.46, 3.74)	6025.61	1.84(1.79)	3.59(3.48)
reproductive system and breast disorders	1058	2.98(2.81, 3.17)	2.93(2.76, 3.11)	1355.15	1.55(1.46)	2.93(2.78)
infections and infestations	5183	2.29(2.22, 2.36)	2.13(2.09, 2.17)	3302.21	1.09(1.05)	2.13(2.08)
investigations	4884	1.95(1.89, 2.01)	1.84(1.8, 1.88)	1996.9	0.88(0.84)	1.84(1.79)
cardiac disorders	1431	1.38(1.31, 1.45)	1.36(1.28, 1.44)	142.83	0.45(0.37)	1.36(1.31)
gastrointestinal disorders	3377	0.87(0.84, 0.9)	0.88(0.85, 0.92)	59.27	−0.18 (-0.23)	0.88(0.86)
congenital, familial and genetic disorders	115	0.87(0.72, 1.04)	0.87(0.73, 1.04)	2.27	−0.2(-0.47)	0.87(0.75)
vascular disorders	792	0.85(0.79, 0.91)	0.85(0.79, 0.92)	20.48	−0.23 (-0.33)	0.85(0.8)
hepatobiliary disorders	303	0.81(0.72, 0.91)	0.81(0.72, 0.91)	13.5	−0.3(-0.47)	0.81(0.74)
nervous system disorders	3018	0.8(0.78, 0.83)	0.82(0.79, 0.85)	133.57	−0.29 (-0.34)	0.82(0.79)
ear and labyrinth disorders	150	0.76(0.64, 0.89)	0.76(0.65, 0.89)	11.67	−0.4(-0.63)	0.76(0.66)
skin and subcutaneous tissue disorders	1896	0.74(0.7, 0.77)	0.75(0.72, 0.78)	169.23	−0.42 (-0.48)	0.75(0.72)
general disorders and administration site conditions	5825	0.67(0.65, 0.69)	0.71(0.7, 0.72)	814.48	−0.48 (-0.52)	0.72(0.7)
endocrine disorders	76	0.66(0.53, 0.83)	0.67(0.54, 0.83)	12.82	−0.59 (-0.91)	0.67(0.55)
eye disorders	513	0.57(0.52, 0.62)	0.57(0.53, 0.62)	167.42	−0.8(-0.93)	0.57(0.53)
respiratory, thoracic and mediastinal disorders	1116	0.51(0.48, 0.54)	0.52(0.49, 0.55)	504.45	−0.93 (-1.02)	0.53(0.5)
musculoskeletal and connective tissue disorders	1241	0.5(0.47, 0.53)	0.51(0.48, 0.54)	610.7	−0.96 (-1.05)	0.51(0.49)
immune system disorders	237	0.44(0.39, 0.5)	0.44(0.39, 0.49)	167.32	−1.17 (-1.36)	0.44(0.4)
injury, poisoning and procedural complications	1974	0.4(0.38, 0.42)	0.43(0.41, 0.45)	1684.27	−1.22 (-1.29)	0.43(0.41)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	548	0.4(0.36, 0.43)	0.4(0.37, 0.43)	495.2	−1.3(-1.43)	0.4(0.38)
psychiatric disorders	870	0.34(0.32, 0.36)	0.35(0.33, 0.37)	1109.67	−1.51 (-1.61)	0.35(0.33)
blood and lymphatic system disorders	197	0.26(0.23, 0.3)	0.27(0.24, 0.31)	408.43	−1.91 (-2.12)	0.27(0.24)
pregnancy, puerperium and perinatal conditions	6	0.03(0.01, 0.07)	0.03(0.01, 0.07)	173.74	−4.94 (-6.01)	0.03(0.02)

* Red numbers were statistically significant, $p < 0.05$.
PT: preferred term; SOC: system organ class; ROR: reporting odds ratios; CI: confidence interval.
PRR: proportional reporting ratios; IC: information component; EBGM: empirical Bayesian geometric mean.

Table 4
The top 30 signal strengths of adverse events associated with dapagliflozin ranked by ROR at the PTs level in the FAERS database.

SOC	PTs	Case Reports	ROR(95 % CI)	PRR(95 % CI)	chisq	IC (IC025)	EBGM (EBGM05)
infections and infestations	scrotal gangrene	8	403.62(174.18, 935.31)	403.55(173.73, 937.39)	2184.45	8.1 (7.01)	274.73 (135.99)
infections and infestations	scrotal cellulitis	8	343.08(151.11, 778.95)	343.02(150.59, 781.32)	1948.69	7.94 (6.86)	245.3 (123.52)
infections and infestations	perineal cellulitis	12	311.92(161.09, 603.97)	311.83(160.14, 607.2)	2726.57	7.84 (6.95)	228.95 (131.71)
infections and infestations	scrotal abscess	55	245.96(182.23, 331.98)	245.65(183.08, 329.61)	10417.05	7.58 (7.16)	191.17 (148.75)
infections and infestations	urogenital infection fungal	3	233.89(65.25, 838.42)	233.88(65.42, 836.15)	546.57	7.52 (5.93)	183.97 (63.22)
infections and infestations	genital infection male	7	187.62(82.81, 425.09)	187.59(82.36, 427.29)	1065.97	7.27 (6.17)	154.1(77.73)
infections and infestations	necrotising soft tissue infection	28	179.3(119.31, 269.47)	179.19(118.73, 270.44)	4103.92	7.21 (6.64)	148.39 (105.53)
infections and infestations	fournier's gangrene	267	170.14(149.16, 194.06)	169.1(147.42, 193.97)	37270.33	7.14 (6.96)	141.41 (126.67)
infections and infestations	cellulitis of male external genital organ	14	158.02(89.35, 279.45)	157.97(89.48, 278.89)	1843.98	7.06 (6.27)	133.55 (82.88)
infections and infestations	vulval cellulitis	5	147.87(57.24, 382.02)	147.85(57.71, 378.8)	622.05	6.98 (5.73)	126.26 (57.06)
infections and infestations	perineal abscess	42	134.02(96.8, 185.55)	133.89(95.95, 186.83)	4791.67	6.86 (6.4)	115.94 (88.31)
infections and infestations	genital abscess	31	105.57(72.69, 153.32)	105.49(72.69, 153.09)	2857.09	6.56 (6.03)	94.05(68.82)
infections and infestations	genital infection	23	93.08(60.53, 143.15)	93.04(60.45, 143.2)	1889.12	6.39 (5.79)	84.03(58.62)
infections and infestations	genital infection female	11	92.5(49.66, 172.32)	92.48(49.39, 173.16)	898.51	6.39 (5.53)	83.58(49.66)
infections and infestations	urogenital infection bacterial	3	88.72(27.02, 291.25)	88.71(26.84, 293.23)	235.78	6.33 (4.83)	80.49(29.77)
metabolism and nutrition disorders	ketosis	123	250.06(204.53, 305.73)	249.36(204.98, 303.35)	23571.67	7.6 (7.31)	193.41 (163.47)
metabolism and nutrition disorders	diabetic ketosis	47	231.88(167.99, 320.08)	231.64(169.29, 316.96)	8497.77	7.51 (7.06)	182.59 (139.42)
metabolism and nutrition disorders	euglycaemic diabetic ketoacidosis	443	188.4(169.93, 208.88)	186.5(169.09, 205.7)	67138.45	7.26 (7.11)	153.36 (140.68)
metabolism and nutrition disorders	ketoacidosis	652	145.94(134.25, 158.64)	143.77(132.93, 155.5)	79175.43	6.95 (6.83)	123.27 (114.95)
metabolism and nutrition disorders	diabetic ketoacidosis	1886	116.51(110.95, 122.36)	111.52(107.23, 115.98)	182874.77	6.63 (6.56)	98.8(94.84)
investigations	insulin c-peptide decreased	7	117.72(53.42, 259.4)	117.7(53.74, 257.79)	712.22	6.7 (5.63)	103.62(53.5)
investigations	blood ketone body increased	60	117.36(89.6, 153.73)	117.2(89.08, 154.2)	6081.65	6.69 (6.31)	103.23 (82.36)
investigations	glucose urine present	63	90.93(70.12, 117.91)	90.8(70.38, 117.15)	5059.42	6.36 (5.99)	82.2(66.14)
investigations	urine ketone body	12	90.29(49.81, 163.69)	90.27(50.14, 162.52)	958.46	6.35 (5.53)	81.77(49.7)
investigations	human epidermal growth factor receptor decreased	3	82.99(25.37, 271.48)	82.99(25.6, 269)	221.56	6.24 (4.75)	75.75(28.1)
reproductive system and breast disorders	acquired phimosis	19	243.29(146.16, 404.96)	243.18(146.09, 404.8)	3570.16	7.57 (6.87)	189.68 (123.84)
reproductive system and breast disorders	perineal necrosis	4	127.06(44.46, 363.13)	127.04(44.08, 366.1)	435.66	6.79 (5.43)	110.78 (46.01)
reproductive system and breast disorders	balanoposthitis	63	107.56(82.76, 139.79)	107.41(83.25, 138.58)	5902.05	6.58 (6.21)	95.56(76.74)
renal and urinary disorders	ketonuria	88	182.21(144.74, 229.37)	181.84(143.73, 230.06)	13057.8	7.23 (6.91)	150.2 (123.89)
congenital, familial and genetic disorders	phimosis	72	159.39(123.93, 205.01)	159.13(123.34, 205.31)	9543.19	7.07 (6.71)	134.38 (108.86)

* Red numbers were statistically significant, $p < 0.05$.
PT: preferred term; SOC: system organ class; ROR: reporting odds ratios; CI: confidence interval.
PRR: proportional reporting ratios; IC: information component; EBGM: empirical Bayesian geometric mean.

injury or damage, congenital anomalies, and unknown. In addition to unidentified serious medical events (42.29 %), the most prevalent significant adverse outcome was hospitalization (33.09 %) in 5379 cases; death and life-threatening conditions accounted for 2191 (13.48 %) and 1365 (8.4 %) cases, respectively.

3.2. Detection of dapagliflozin signals

3.2.1. Signals detection according to system organ class levels

The statistical findings indicate that the prevalence of AEs induced by dapagliflozin was predominantly concentrated in 24 SOCs (Table 3). Metabolic and nutrition disorders (n = 5643, ROR 6.77, PRR 6.02, IC 2.58, EBGM 5.98) and renal and urinary disorders (n = 3154, ROR 3.81, PRR 3.6, IC 1.84, EBGM 3.59) were rated as strongly positive in all four algorithms, consistent with the characteristics of dapagliflozin as a drug for diabetes and nephrology. Certain outcomes aligned with the SOCs associated with prevalent adverse reactions as listed in the drug inserts, suggesting a substantial level of trustworthiness in the data. Significantly, the SOCs implicated in several noteworthy adverse reactions were as follows: reproductive system and breast disorders (n = 1058, PRR 2.93, IC 1.55, EBGM 2.93), infections and infestations (n = 5183, PRR 2.13, IC 1.09, EBGM 2.13). The remaining SOCs has no obvious significance in the four algorithms.

3.2.2. Signals detection based on preferred term levels

We ranked the 1313 PTs that satisfied the criteria of the four techniques based on their signal intensity (ROR value) in descending order (Table 4). The aforementioned method resulted in the identification of the top 30 PTs, which were subsequently categorised as SOCs. The results show that the PT exhibits a high level of signal intensity, such as scrotal gangrene (n = 8, ROR 403.62, PRR 403.55, IC 8.1, EBGM 274.73), scrotal cellulitis (n = 8, ROR 343.08, PRR 343.02, IC 7.94, EBGM 245.3) and perineal cellulitis (n = 12, ROR 311.92, PRR 311.83, IC 7.84, EBGM 228.95). The most common PT are diabetic ketoacidosis, death, and fungal infection. In addition to the adverse events already mentioned in the instructions, this study found acute pancreatitis. While the occurrence of adverse effect was infrequent, the signal of pancreatitis intensity was significantly high.

4. Discussion

Dapagliflozin, classified as a SGLT2i, functions by blocking the reabsorption of sodium and glucose in the proximal renal tubules [1], leading to the loss of glucose in the urine and decreased serum levels. Clinically, dapagliflozin was used to treat T2DM [2], CKD [3], cardiovascular disease [7] (CVD), reduce the risk of heart failure [6] and end-stage renal disease development [8], and decrease cardiovascular complications and mortality [7,9], with potential treatment and safety advantages. Nevertheless, it is crucial to closely observe the real-world utilization and negative occurrences of newly introduced medications in order to guarantee their safety and efficacy. This study systematically evaluated the adverse events of dapagliflozin through in-depth analysis of the FAERS database from the 2012 Q4 to the 2023 Q3. Through this process, this study not only confirmed some existing safety information, but also revealed new potential risks. This provides more comprehensively evaluate the potential risks in clinical use and provide safety reference for clinical practice. The following is an in-depth discussion of the study results.

4.1. Demographic characteristics of adverse events to dapagliflozin

It is worth mentioning that a large proportion of the data lacks precise age information, thereby constraining our comprehension of the prevalence of adverse events across various age cohorts. Further studies require accurate age data and explore differences in drug response in different age groups. It is noteworthy to mention that the majority of adverse event reports are submitted by physicians (40.91 %) and consumers (35.63 %). In terms of age composition, the patients with dapagliflozin adverse events were mainly aged over 45 years, accounting for about 49.25 %. This may be related to the higher prevalence of chronic kidney disease, T2DM, and cardiovascular disease in the middle-aged and elderly population, and also consistent with the gradual development of the disease. The top five countries reported cases, including the United States, Japan, the United Kingdom, China and Germany, with the United States accounting for 54.7 %. This suggests that the remaining countries may lack the emphasis on drug safety and also warns other countries to strengthen monitoring and reporting of adverse reactions.

4.2. Diabetic ketoacidosis

DKA is a severe complication of hyperglycemia, and in cases of dapagliflozin-related DKA, patients may exhibit within normal range or slightly elevated blood glucose levels, thus being described as euDKA [11,16]. Previous studies have shown that the use of dapagliflozin is closely correlated with the occurrence of DKA and euDKA [17,18]. In our study, the number of DKA reports was higher than euDKA (1886 vs 443). The mechanism by which dapagliflozin induced DKA and euDKA remains unclear and may be related to the following mechanisms. dapagliflozin reduces blood glucose levels via enhancing urinary glucose excretion, diminishing insulin secretion, and elevating the glucagon/insulin ratio. This results in heightened free fatty acid production, which may be converted into ketones. If the cumulative ketone body levels surpass the body's tolerance threshold, ketoacidosis may occur [16,19]. On the other hand, dapagliflozin can increase urinary glucose excretion, and blood glucose levels will approach normal when excretion is greater than endogenous glucose production [20]. As euDKA is difficult to diagnose, it may occur in relatively normoglycemic conditions and is essential for the identification of this life-threatening diabetic complication. Nausea, vomiting, and tachypnea are important clinical features of patients treated with dapagliflozin and their urine and/or plasma ketones even when blood glucose levels are near normal.

4.3. Urinary tract infections and genital mycotic infections

Common AEs in dapagliflozin include UTIs and GMIs [21], with a higher risk of GMIs rather than UTI than other antidiabetic drugs [22]. Infection can be attributed to the mechanism of action of dapagliflozin. Increased urinary sugar promotes the proliferation of bacteria or fungi in the genitourinary tract. Only higher doses (10 mg of mg) slightly increased risk of urinary tract infection (RR 1.21; 95%CI 1.021.43) [23]. Prior research has indicated that female individuals with diabetes are more susceptible to urinary tract infections [24]. The variation in the occurrence of urinary tract infections between males and females can be attributed to anatomical disparities in the urinary system. Urinary tract infections in female patients can be caused by certain conditions in the urogenital tract, such as the absence of lactobacillus, a low acidic PH on the vaginal surface, and the form of the urethra [25]. However, a meta-study shown that dapagliflozin-associated urinary tract infections can occur in adults of any gender and age [12]. Patients taking dapagliflozin should prioritise personal genital cleanliness, increase water intake, promote frequent urination, and then minimize the risk of infection.

4.4. Acute renal failure (ARF)

In 2016, the Food and Drug Administration (FDA) issued stronger warnings regarding the increased risk of acute kidney injury linked to dapagliflozin, following an assessment of the documented adverse events. dapagliflozin can promote diuresis, leading to a reduction in vascular volume, by decreasing transglomerular pressure and thus lowering the glomerular filtration rate. dapagliflozin increases oxygen consumption in the medulla and elevates the likelihood of hypoxic damage [26]. Previous study has demonstrated that the use of dapagliflozin in patients can lead to elevated levels of plasma erythropoietin and reticulocytosis [27]. These findings may indicate an increase in hypoxia in the renal cortex and medulla [28]. A meta-analysis published in 2013, consisting of 13 randomised controlled studies, revealed that the utilization of dacaglizzine was linked to a higher occurrence of kidney-related adverse events in patients with moderate renal impairment [29]. Research has demonstrated that individuals who develop ARF while using dapagliflozin are predominantly male, tend to be overweight, and are more likely to use diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin II receptor blocker (ARB) medications simultaneously [30]. Thus, those receiving dapagliflozin require more thorough monitoring of blood creatinine levels and should refrain from using diuretics, ACEI, or ARB simultaneously.

4.5. Pancreatitis

The instructions of dapagliflozin highlight significant adverse events such as UTIs, GMIs, and DKA. Severe pancreatitis is not specifically mentioned, but it is important to remain vigilant throughout clinical use. The US FDA [31] and Health Canada [32] have independently released risk assessments on pancreatitis induced by dapagliflozin, suggesting a potential association between dapagliflozin and acute pancreatitis. Dapagliflozin has the potential to heighten the likelihood of developing acute pancreatitis, particularly during the initial phases of medication [33]. Research has demonstrated that the concurrent use of dapagliflozin with dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA), or ACEI elevates the likelihood of developing acute pancreatitis [34]. The precise mechanism by which dapagliflozin causes pancreatitis remains unknown. This could be a medication-induced reaction that is specifically triggered by the immune system or the harmful effects of the drug or its byproducts on the body [35,36]. Some case reports suggest that dapagliflozin leads to acute pancreatitis [37]. The diagnosis of pancreatitis can be based on physical examination, blood amylase or lipase levels, and CT or MRI abdomen imaging. If pancreatitis is suspected, the drug should be stopped immediately.

Our study has several strengths. Firstly, it utilizes the FAERS database to provide a comprehensive dataset for the analysis of AEs associated with dapagliflozin. Secondly, the study benefits from the large sample size, which enhances the statistical power and reliability of the study results. Moreover, this study used four different signal detection algorithms, which improved the confidence of the results. The study also identified a number of new events not previously documented in the medication package insert, such as pancreatitis, psychiatric disorders, highlighting the importance of ongoing pharmacovigilance. Previous studies have focused on one and two common AEs of SGLT-2i and have not fully explored new or rare AEs of dapagliflozin. Additionally, we use the Medex_UIMA_1.8.3 system, remove duplicate reports, combine different combinations and changes of dapagliflozin into a standardized term, and perform consistency checks to verify the accuracy of critical data fields to ensure that each AE is calculated only once. At the same time, drugs, effective components similar to dapagliflozin, were excluded, thus reducing the effect of other drugs on the results. This study enhances the external validity of the findings and its applicability by using real data in the FAERS database to reflect the daily clinical practice.

4.6. Limitation

It is well-known that pharmacovigilance studies have intrinsic limitations based on spontaneous reporting system databases. Thus, there were some intrinsic limitations in utilizing FAERS data for research purposes in our study.Firstly, the incidence of adverse events is susceptible to numerous influences, due to the fact that the data are primarily derived from self-reporting, such as drug properties, individual variations, and underlying medical conditions. For instance, medical professionals should continue to closely monitor the occurrence of adverse events in clinical practice and implement timely interventions; sampling bias may exist in countries and regions with high reporting numbers; and consumer reporting may be less reliable and comprehensive than that of medical professionals. Due to DAs cannot serve as an independent method for evaluating drug-related risks or substituting the clinical judgment of individual

patients, there remains a necessity for more rigorous prospective studies that integrate clinical trials with epidemiological investigations. This approach will provide a more accurate evaluation of the safety risks associated with dapagliflozin.

5. Conclusion

Overall, this research explores the actual adverse reaction signal data related to dapagliflozin in the FAERS database from the epidemiological, pharmacology and safety aspects, so as to comprehensively evaluate the potential risks in clinical use and provide safety reference for clinical practice. This study examines the prevalent negative consequences of dapagliflozin, including ketoacidosis, infection, and acute renal injury. This analysis also uncovered the presence of pancreatitis, a condition that was not expressly stated in the prescription insert. These findings indicate that medical personnel should exercise greater caution when administering dapagliflozin as a medication, and patients should be informed about the possible negative consequences. Due to the inherent limitations of FAERS data, prospective studies are still needed. However, these initial findings undeniably serve as a helpful point of reference for future study and safety oversight. Specifically, the medical community and regulatory bodies should place significant importance on newly identified potential hazards.

Ethics approval and consent to participate

Datasets were extracted from the publicly available FAERS database and ethical approval and consent for participation were not applicable.

Consent for publication

Not applicable.

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Data availability statement

We used original data from the United States Food and Drug Administration Adverse Event Reporting System database. Raw data can be obtained by contacting the corresponding author.

CRediT authorship contribution statement

Zhengxi Zhou: Formal analysis. **Xiaotian Yao:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation.

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.

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This study was performed using the FAERS source that was provided by the FDA. The information, results, or interpretation of the current study do not represent any opinion of the FDA.

Abbreviations

AEs	adverse events
FAERS	the Food and Drug Administration Adverse Event Reporting System
ROR	reporting odds ratio
PRR	proportional reporting ratio
BCPNN	Bayesian confidence propagation neural network
EBGM	empirical Bayesian geometric average
SGLT-2i	sodium-glucose cotransporter-2 inhibitor
T2D	type 2 diabetes
CKD	chronic kidney disease
KDIGO	Kidney Disease: Improving Global Outcomes
euDKA	euglycemic diabetic ketoacidosis

DKA	diabetic ketoacidosis
UTIs	urinary tract infections
GMIs	genital mycotic infections
MedDRA	25.0 the Medical Dictionary of Regulatory Activities
PTs	preferred terms
SOCs	system organ classes
IC	information component
CI	confidence interval
CVD	cardiovascular disease
FDA	the Food and Drug Administration
ACEI	angiotensin-converting enzyme inhibitors
ARB	angiotensin II receptor blocker
DPP-4i	dipeptidyl peptidase-4 inhibitors
GLP-1RA	glucagon-like peptide-1 receptor agonists
ARF	acute renal failure
DA	disproportional analysis

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33306.

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Here are the references formatted in the style of "Duro J.A., Lauk C., Kastner T., Erb K.H., Haberl H. Global inequalities in food consumption, cropland demand and land-use efficiency: a decomposition analysis. Global Environ. Change. 2020; 64 doi: 10.1016/J.GLOENVCHA.2020.102124":

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