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Drug-induced ischaemic colitis: a disproportionality analysis of the FAERS database

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ABSTRACT

Objective: Drug-induced ischaemic colitis is a significant adverse event (AE) in clinical practice. This study aimed to recognize the top drugs associated with the risk of ischaemic colitis based on the FDA Adverse Event Reporting System (FAERS) database.

Design: A cross-sectional design.

Setting: All data retrieved from the FAERS database from the first quarter of 2004 to the fourth quarter of 2023.

Participants: A total of 5664 drug-induced ischaemic colitis AEs eligible for screening.

Primary and secondary outcome measures: The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify ischaemic colitis (code: 10009895) cases. Disproportionality analysis for drug-associated ischaemic colitis signals

Results: Drug-induced ischaemic colitis AEs were more prevalent in females (60.12%) and individuals aged ≥65 years (34.25%). The common outcomes were hospitalization (46.85%) and death (9.73%). Disproportionality analysis identified 91 ischaemic colitis signals and the top 30 drugs mainly involved in the gastrointestinal and nervous systems. The top 5 drugs with the highest ROR, PRR, IC, and EBGM were alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Additionally, 20 of the top 30 drugs did not have ischaemic colitis risk indicated in the package insert.

Conclusion: Based on the FAERS database analysis, we listed drugs with strong ischaemic colitis signals. The potential risk of ischaemic colitis is important, and further research is necessary to understand the mechanisms and enhance drug safety measures.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Our current real-world drug surveillance study provides valuable insights for identifying drugs that may induce ischaemic colitis.
- Our study provides valuable clues for clinical drug analysis in ischaemic colitis..
- Our study could not directly prove a causal relationship between drugs and ischaemic colitis.

1. INTRODUCTION

Ischaemic colitis is the most frequent type of colonic vascular injury, accounting for approximately 50-60% of ischaemic disorders of the gastrointestinal tract.[1 2] The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.[3] The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.[4] Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.[5] Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.[4 6] In addition, ischaemic colitis can cause complications, including obstruction, necrosis, and perforation. Therefore, identification of patients with ischaemic colitis is recommended, with colonoscopic evaluation ideally performed within 48 hours of symptom onset.[4 7] Colonoscopy can differentiate cases amenable to conservative treatment from those requiring urgent resection.

Ischaemic colitis can occur secondary to various conditions such as mesenteric artery embolism, thrombosis, or trauma, which may lead to occlusive vascular diseases and compromised colon perfusion, as well as hypoperfusion states resulting from congestive heart failure. Additionally, a myriad of drugs predispose to ischaemic colitis, including antibiotics (amoxicillin-clavulanate),[8] anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),[9] decongestants (pseudoephedrine),[10] cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,[11] laxatives (lactulose, bisacodyl),[12] nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),[13] and serotonin agonists/antagonists.[14 15] Currently, information on ischaemic colitis risks is primarily documented in package inserts, depending on the results of clinical trials. Due to constraints in sample size and follow-up duration, clinical trials may not precisely reflect the occurrence of drug-induced ischaemic colitis in real-world situations. The ischaemic colitis risk of certain drugs may not be readily recognized in clinical trials. In addition, the majority of drug-induced ischaemic colitis in the clinical setting was reported in the form of case reports, and data from large-scale real-world studies are not available. Therefore, the correlation between drugs and ischaemic colitis still needs to be completed.

Post-marketing surveillance is a vital method to determine the association between drugs and adverse events (AEs). FAERS is a self-reporting system for collecting post-marketing AEs for drugs. FAERS, owing to its extensive data repository and open accessibility, is commonly utilized in drug

signal mining studies.[16] This study aimed to investigate the risk of drug-induced ischaemic colitis by FAERS database thoroughly and to identify drugs with a potential risk of ischaemic colitis that are not described in the drug inserts.

2. METHODS

2.1. Data sources

American Standard Code for Information Interchange (ASCII) report files from the FAERS database spanning the 1st quarter of 2004 to the 4th quarter of 2023 were downloaded for this study. The data were imported into MySQL 15.0 and managed using Navicat Premium 15 software.

2.2. Definition of AEs and drugs

AEs extracted from the FAERS database underwent coding according to nomenclature using the Preferred Term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA). The term "colitis ischaemic" (MedDRA code: 10009895) was employed in the PT column to identify drugs associated with colitis ischaemic. Subsequently, all reports concerning ischemic colitis were retrieved. The generic name served as the unique drug identifier for statistical analysis. However, numerous reports in the FAERS database utilized drug brand names, necessitating conversion into generic names via the DrugBank database. Additionally, any drug names that could not be retrieved from the DrugBank database were considered incorrect reports and were subjected to manual elimination.

2.3. Statistical analysis

Descriptive analysis was conducted to describe the clinical characteristics of patients with drug-induced ischaemic colitis, including age, gender, reporter, outcome, and reported country. Individual safety reports (ISR) were enumerated, with each ISR considered an AE report. The top 30 drugs associated with ischaemic colitis were screened. Disproportionate analysis was employed to generate hypotheses regarding potential associations between drugs and ischaemic colitis.

In our study, four disproportionality methods, the reported odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the empirical Bayesian geometric mean (EBGM), were used to detect drug AE signals. The calculation equation and criteria were provided in Supplementary Table 1. All algorithms rely on a 2×2 contingency table. Specific formulas and cut-off thresholds were detailed in Supplementary Table 1, and statistical analyses were performed using R software. A higher value indicates a stronger statistical

relationship between the suspect drug and suspect AE.

Patient and public involvement

None

3. RESULTS

3.1. Descriptive analysis

A total of 5664 drug-induced ischaemic colitis AEs were reported in the FAERS database from the first quarter of 2004 to the fourth quarter of 2023. As shown in Figure 1, the number of reported AEs of drug-induced ischaemic colitis peaked in 2020 at 445 cases. Beginning in 2021, the number of AEs begins to decline, but the overall trend exhibits increasing volatility from 2004 through 2023.

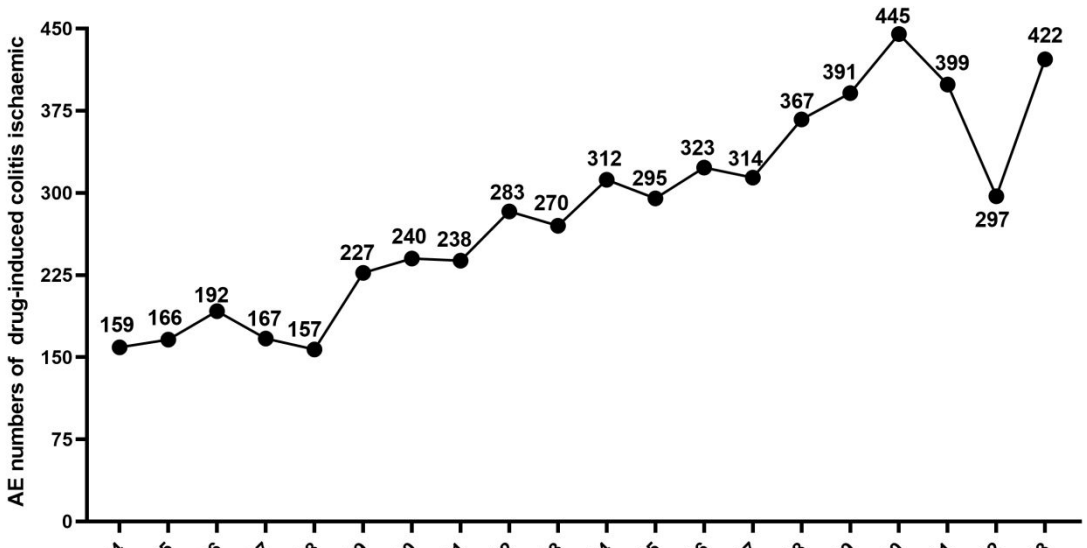

Figure 1. Number of reported AEs of drug-induced ischaemic colitis from 2004 to 2023.

The clinical characteristics of these 5664 AE reports were listed in Table 1. Ischaemic colitis was more prevalent in females (60.12%) than in males (31.02%). Ischaemic colitis was more likely to occur in ≥ 65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and ≤18 years (1.36%). These AE reports from physician reporters had the highest percentage (44.26%), thus increasing the credibility of this study. The top 5 most frequently reported outcomes were hospitalization (46.85%), followed by death (9.73%), life-threatening (6.28%), disability (2.00%), and required intervention to prevent permanent impairment (0.49%). Notably, the most number of drug-

induced ischaemic colitis reports were from the United States (n = 1534, 27.08%), followed by Japan (n = 657, 11.60%), France (n = 464, 8.19%), and the United Kingdom (n = 210, 3.71%).

Table 1. Clinical characteristics of reported drug-induced ischaemic colitis

Characteristics	Reports, n (%)
Sex	
Female	3405 (60.12)
Male	1757 (31.02)
unknown	502 (8.86)
Age (year)	
≤ 18	77 (1.36)
19-40	596 (10.52)
41-64	1783 (31.48)
≥ 65	1940 (34.25)
unknown	1268 (22.39)
Reporter	
Physician	2507 (44.26)
Consumer	968 (17.09)
Other health-professional	939 (16.58)
Pharmacist	868 (15.32)
Lawyer	65 (1.15)
Sales	1 (0.02)
unknown	316 (5.58)
Outcomes	
Hospitalization	4081 (46.85)
Death	848 (9.73)
Life threatening	547 (6.28)
Disability	174 (2.00)

Required intervention to Prevent Permanent Impairment/Damage	43 (0.49)
Congenital anomaly	4 (0.05)
other serious	3014 (34.60)
Reported countries	
United States	1534(27.08)
Japan	657(11.60)
France	464(8.19)
United Kingdom	210(3.71)
other	2799(49.42)

3.2. Disproportionality analysis

A total of 91 ischaemic colitis signals were identified according to the ROR > 3 criteria. The top 30 (ranked by ROR) drugs associated with the highest signal intensity in drug-induced ischaemic colitis were listed in Table 2. The top 30 highest drugs used PRR, IC, and EBGM methods consistent with the results of RORs. The most common of the top 30 drugs were gastrointestinal and nervous system drugs. These include alosetron (ROR = 339.26, 95% CI: 263.31-437.11, a serotonin-3 receptor antagonist), tegaserod (ROR = 67.52, 95% CI: 55.47-82.19, a serotonin-4 receptor antagonist), and eluxadoline (ROR = 19.46, 95% CI: 11.28-33.59, a μ-opioid receptor agonist) for the treatment of irritable bowel syndrome (IBS). Additionally, drugs for the treatment of constipation and cleansing of the colon in preparation for colonoscopy were included: lubiprostone (ROR = 44.03, 95% CI: 27.99-69.26), lactulose (ROR = 15.34, 95% CI: 5.74-40.96), bisacodyl (ROR = 33.49, 95% CI: 20.46-54.82), suprep bowel prep (ROR = 10.63, 95% CI: 5.88-19.23), osmoprep (ROR = 51.87, 95% CI: 30.59-87.97), and prepopik (ROR = 16.63, 95% CI: 7.45-37.10). Furthermore, serotonin antagonists should be given more attention in drug-induced ischaemic colitis, including 5-HT3 and 5-HT 1B/1D receptor antagonists. Among them, signal strength were granisetron ROR = 17.05 (95% CI: 9.43-30.86), naratriptan ROR = 64.15 (95% CI: 34.31-119.94), rizatriptan ROR = 33.15 (95% CI: 21.55-50.98), zolmitriptan ROR = 16.96 (95% CI: 9.11-31.59), sumatriptan ROR = 14.51 (95% CI: 11.8-17.83), respectively. Other neurologic drugs that cause drug-induced ischaemic colitis include benztropine

mesylate, dexamfetamine, phentermine, and desogestrel and ethinyl estradiol. Moreover, using baloxavir marboxi (ROR = 44.95), peramivir (ROR = 35.47), osteoarthritis (ROR = 8.97), ketoprofen (ROR = 18.62), and piroxicam (ROR = 15.26) for the treatment of influenza and rheumatoid arthritis disease ischemic colitis should be a concern. Other drugs related to drug-induced ischemic colitis include daprodustat, ferrlecit, sevelamer carbonate, miglitol, pletal, etelcalcetide, and kayexalate. Among the top 30 drugs in drug-induced ischaemic colitis, there were 20 drugs whose instructions do not indicate the risk of ischaemic colitis.

Table 2. Top 30 drugs for signal strength.

Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	Pharmacologic action	Indications
alosetron	66	339.26 (263.31, 437.11)	310.89 (245.73, 393.33)	8.26 (7.9)	307.28 (248.57)	a serotonin-3 (5-HT3) receptor antagonist	irritable bowel syndrome with diarrhoea
tegaserod*	103	67.52 (55.47, 82.19)	66.34 (54.53, 80.7)	6.03 (5.74)	65.15 (55.26)	a serotonin-4 (5-HT4) receptor partial antagonista	irritable bowel syndrome with constipation and chronic idiopathic constipation
eluxadoline*	13	19.46 (11.28, 33.59)	19.37 (11.19, 33.53)	4.27 (3.51)	19.32 (12.24)	a opioid receptor agonist	irritable bowel syndrome with diarrhoea
lubiprostone*	19	44.03 (27.99, 69.26)	43.52 (27.73, 68.31)	5.44 (4.8)	43.38 (29.69)	a chloride channel activator	constipation
lactulose	4	15.34 (5.74, 40.96)	15.28 (5.73, 40.71)	3.93 (2.66)	15.27 (6.71)	a colonic acidifier	constipation
bisacodyl	16	33.49 (20.46, 54.82)	33.19 (20.33, 54.18)	5.05 (4.36)	33.1 (21.92)	a stimulant laxative	constipation and empty the bowel
suprep bowel prep	11	10.63 (5.88, 19.23)	10.61 (5.89, 19.1)	3.4 (2.59)	10.59 (6.45)	an osmotic laxative	cleansing of the colon in preparation for colonoscopy
osmoprep	14	51.87 (30.59, 87.97)	51.17 (30.14, 86.86)	5.67 (4.94)	51.04 (32.81)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
prepopik	6	16.63 (7.45, 37.10)	16.56 (7.41, 36.99)	4.05 (2.98)	16.54 (8.45)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
granisetron*	11	17.05 (9.43, 30.86)	16.98 (9.43, 30.57)	4.08 (3.26)	16.95 (10.32)	a serotonin-3 (5-HT3) receptor antagonist	nausea and vomiting
naratriptan*	10	64.15 (34.31, 119.94)	63.07 (34.35, 115.8)	5.98 (5.11)	62.96 (37.3)	a serotonin (5-HT1B/1D) receptor agonist	acute treatment of migraine with or without aura

rizatriptan*	21	33.15 (21.55, 50.98)	32.86 (21.35, 50.57)	5.03 (4.43)	32.74 (22.84)	a serotonin (5HT1B/1D receptor agonist	acute treatment of migraine with or without aura
zolmitriptan*	10	16.96 (9.11, 31.59)	16.89 (9.02, 31.62)	4.08 (3.22)	16.86 (10.02)	a serotonin (5HT1B/1D receptor agonist	acute treatment of migraine with or without aura
sumatriptan*	92	14.51 (11.8, 17.83)	14.45 (11.88, 17.58)	3.83 (3.54)	14.23 (11.98)	a serotonin (5HT1B/1D) receptor agonist	acute treatment of migraine with or without aura
benztropine mesylate*	4	32.37 (12.09, 86.64)	32.09 (12.04, 85.5)	5 (3.73)	32.07 (14.07)	an anticholinergic medication	parkinsonism and extrapyramidal disorders
dexamfetamine*	19	19.07 (12.14, 29.96)	18.98 (12.09, 29.79)	4.24 (3.61)	18.92 (12.96)	a central nervous system stimulant	attention deficit hyperactivity disorder ; moderate to severe binge eating disorder
phentermine*	22	14.28 (9.39, 21.72)	14.23 (9.43, 21.48)	3.83 (3.23)	14.17 (9.98)	a sympathomimetic amine anorectic	a short-term adjunct in a regimen of weight reduction
desogestrel and ethinyl estradiol	19	33.91 (21.57, 53.32)	33.61 (21.41, 52.75)	5.07 (4.43)	33.5 (22.94)	a combination of synthetic estrogen and progestin	contraception
baloxavir marboxi*	24	44.95 (30.03, 67.28)	44.42 (30.01, 65.74)	5.47 (4.9)	44.23 (31.56)	a polymerase acidic endonuclease inhibitor	influenza
peramivir*	3	35.47 (11.37, 110.61)	35.14 (11.5, 107.4)	5.13 (3.71)	35.12 (13.56)	an inhibiter of influenza virus neuraminidase	influenza
oseltamivir*	41	8.97 (6.59, 12.2)	8.95 (6.54, 12.25)	3.15 (2.71)	8.89 (6.87)	an inhibiter of influenza virus neuraminidase	influenza
ketoprofen*	7	18.62 (8.85, 39.14)	18.53 (8.8, 39.02)	4.21 (3.21)	18.51 (9.94)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis; pain; primary dysmenorrhea
piroxicam*	6	15.26 (6.84, 34.03)	15.2 (6.81, 33.95)	3.92 (2.85)	15.18 (7.76)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis
daprodustat*	3	16.94 (5.45, 52.68)	16.87 (5.41, 52.58)	4.08 (2.66)	16.86 (6.52)	a hypoxia-inducible factor prolyl hydroxylase inhibitor	anemia due to chronic kidney disease
ferrlecit*	4	11.75 (4.4, 31.36)	11.71 (4.39, 31.2)	3.55 (2.28)	11.71 (5.15)	a iron supplement	iron-deficiency anemia

sevelamer carbonate*	34	16.69 (11.9, 23.4)	16.62 (11.91, 23.19)	4.05 (3.57)	16.52 (12.45)	a phosphate binder	control of serum phosphorus
miglitol	3	14.32 (4.61, 44.5)	14.26 (4.58, 44.45)	3.83 (2.42)	14.26 (5.52)	a glucosidase inhibitor	type 2 diabetes mellitus
pletal	8	8.82 (4.4, 17.65)	8.8 (4.43, 17.47)	3.14 (2.19)	8.79 (4.92)	an antiplatelet aggregation medication	peripheral arterial disease
etelcalcetide*	4	24.4 (9.12, 65.24)	24.24 (9.1, 64.59)	4.6 (3.33)	24.23 (10.64)	a calcium-sensing receptor agonist	secondary hyperparathyroidism
kayexalate	10	96.57 (51.51, 181.03)	94.11 (51.26, 172.79)	6.55 (5.69)	93.95 (55.53)	a potassium binder	hyperkalemia

*Package insert indicates ischaemic colitis risk.

4. DISCUSSION

To the best of our knowledge, this study is the first and largest assessment of drug-induced ischaemic colitis in real-world based on the FAERS database. In this study, we outlined the clinical features of these AEs and identified the drugs with the highest associations with drug-induced ischaemic colitis. Many of these drugs are not labeled with ischaemic colitis in the package insert and are not known to present an ischaemic colitis risk.

Age is considered a significant risk factor for ischaemic colitis. A study of 1,560 patients with ischaemic colitis showed that 73% were >65 years old, and the incidence increased with age.[17] Another study showed that the prevalence of ischaemic colitis was 1.1/100,000 in individuals under 40 years old, while in those over 80.3 years old, the incidence was 107/100,000,[18] which suggests that the risk of ischaemic colitis increases with age and may be related to the presence of more cardiovascular and cerebrovascular risk factors in the elderly population. In our study, we also found that drug-induced ischaemic colitis was more common in people ≥ 65 years of age. Although ischaemic colitis usually occurs in the elderly, reports were suggesting an increasing prevalence of the disease in younger age groups,[19] which may be associated with factors such as hypercoagulability, vascular disease, long-distance running, smoking, constipation, and contraceptives.[20-22] With the exception of gender unknown (8.86%), the percentage of female ischaemic colitis cases identified was 60.12% in our study. In population-based studies, women were more likely than men to suffer ischaemic colitis, with female accounting for 61 to 67% of all cases,[23 24] which was consistent with our study.

Serotonin receptor antagonists, including 5-HT3, 5-HT4, and 5-HT 1B/1D, should be given enough attention in drug-induced ischaemic colitis. 5-HT(3) antagonists are effective in treating chemotherapy-induced vomiting and diarrhea, as well as urgency and pain associated with IBS.[15] Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating diarrhea, urgency, and pain in IBS.[25 26] However, it was regrettable that alosetron was withdrawn from the market after 446,000 prescriptions were issued following reports of 49 cases of ischaemic colitis.[27] This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron does not alter colonic blood flow in experimental animals.[28] Tegaserod is a serotonin-4 (5-HT4) receptor partial antagonist, with the most common adverse reactions being diarrhea, headache, and abdominal pain. Given that patients with IBS have a higher risk of ischaemic colitis than the general population, no cases of ischaemic colitis associated with tegaserod were reported in over 11,600

patients enrolled in phase III or post-marketing randomized controlled trials.[29] This may be because the incidence of ischaemic colitis is low that it is unlikely to be detected in phase III trials. However, there were also studies indicating that the increased incidence of ischaemic colitis caused by tegaserod should be of particular concern.[29 30] In the current study, we found the highest number of cases of tegaserod-induced ischaemic colitis (n=103) and a higher risk (ROR=67.52). Although the mechanism needs to be verified, clinical use of tegaserod should be attentive to the risk of ischaemic colitis. In our study, we identified four 5-HT1B/1D receptor agonists that increase the risk of ischaemic colitis: naratriptan, rizatriptan, zolmitriptan, and sumatriptan. To our knowledge, there are six reported cases of naratriptan-induced ischaemic colitis, with two cases suggesting a possible association between naratriptan-induced ischaemic colitis and concomitant use of contraceptives.[31] Two studies reported the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptan-induced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic ischaemic colitis.[32 33] Nguyen TQ *et al*. found 19 cases of zolmitriptan-induced ischaemic colitis in the FAERS database up to May 2013,[34] whereas, in our study, conducted until December 2023, this number increased to 92 cases. Additionally, other studies suggest that zolmitriptan-induced ischaemic colitis may be associated with its overuse [35] or vigorous physical activity following zolmitriptan.[36] In summary, although we found an increased risk of ischaemic colitis associated with 5-HT1B/1D receptor agonists based on the FAERS database and received support from some case reports, the true incidence of ischaemic colitis induced by 5-HT1B/1D receptor agonists still needs to be accurately determined.

In phase III clinical trials, the most frequent AEs related with eluxadoline were abdominal pain (6.5%), nausea (7.7%), and constipation (8%).[37] In March 2017, the FDA issued a warning regarding an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a gallbladder.[38] Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological examination revealing colonic ischemia involving the entire length of colon.[39] Our study found the risk of ischaemic colitis associated with eluxadoline to be ROR=19.46. Both lubiprostone and lactulose are medications used to treat constipation. Although they have different mechanisms of action, both are associated with drug-induced ischaemic colitis. The first case of lubiprostone-induced ischaemic colitis was reported in 2013, and symptoms improved upon discontinuation of lubiprostone.[40] Our study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However,

other studies have reported that lubiprostone can protect intestinal mucosal barrier function in colitis animal models and improve intestinal barrier function in patients with Crohn's disease.[41] Regarding lactulose, to our knowledge, only two cases of lactulose-induced ischaemic colitis have been reported. Researchers speculate that this may be due to lactulose causing gaseous distension through fermentation by colonic bacteria.[42] Bowel cleansers are utilized for various indications, with the most common being preparation for colonoscopy. Prior to colonoscopy, it is imperative to clear fecal matter from intestine to effectively visualize abnormalities under the endoscope.[43] Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.[44] We found that bisacodyl, suprep bowel prep, osmoprep, and prepopik all increase the risk of ischaemic colitis, as documented in their respective package inserts. Therefore, selecting the appropriate bowel cleansers becomes especially crucial in patients with different comorbidities. In addition, in our study, three antiviral drugs and two non-steroidal anti-inflammatory drugs (NSAIDs) were found to increase the risk of drug-induced ischaemic colitis. Since influenza A infection itself can induce ischaemic colitis, reports of ischaemic colitis caused by anti-influenza drugs are relatively rare. Kanai N *et al*. reported a case of acute ischaemic colitis in a 62-year-old Japanese woman after taking baloxavir marboxil for the treatment of influenza A.[45] Regarding oseltamivir, several studies have reported hemorrhagic colitis induced by it rather than ischaemic colitis.[46 47] There have been no reports of colitis associated with the anti-influenza drug peramivir. Ketoprofen and piroxicam are two common NSAIDs that exert their effects by inhibiting cyclooxygenase-2. NSAIDs are considered to be important triggers for the activation of inflammatory bowel diseases. Yen EF *et al*. found that long-term use of NSAIDs was independently associated with the development of microscopic colitis.[48] Another study indicated that ketoprofen can reduce inflammation and colonic mucosal injury in a rat colitis model, but it was associated with visible gastric bleeding and increased methane output.[49 50] The risk of gastrointestinal adverse events, including bleeding, ulceration, and gastric or intestinal perforation, is reflected in the labels of NSAID drugs, but ischaemic colitis is not mentioned. This should attract more attention in clinical practice.

Our current real-world drug surveillance study provides valuable insights for identifying drugs that may induce ischaemic colitis. However, it should be noted that there are inevitable limitations. Firstly, the lack of detailed case counts for each drug the calculation and comparison of the true incidence rates of ischaemic colitis induced by each drug. Furthermore, the spontaneous reporting

nature of FAERS database means that biases like underreporting, incomplete reporting, and false reporting might affect the conclusions. Thirdly, it is challenging to determine the risk factors for ischaemic colitis among patients due to the lack of baseline indicators of gut health and information on concomitant medications. Nonetheless, the FAERS database persists as a critical resource for conducting drug surveillance analyses, offering valuable leads for upcoming prospective clinical studies.

Conclusion

In this study, we used the FAERS database to comprehensively evaluate drugs associated with ischaemic colitis risk. Two-thirds of the high-risk drugs were not listed in the package insert. It is worth noting that the potential ischaemic colitis risk is important and should be given close attention in medical practice. Further research is also needed to clarify the molecular mechanisms underlying the association between these drugs and ischaemic colitis.

Conflict of interest statement

All the authors of this study declare that there is no conflict of interest.

Author contributions

XS-D conceived the study. J-A edited the paper conducted the data analysis, wrote all sections of paper. T-W, PY-X, CL-Y, YH-F, and QQ-L edited the manuscript.

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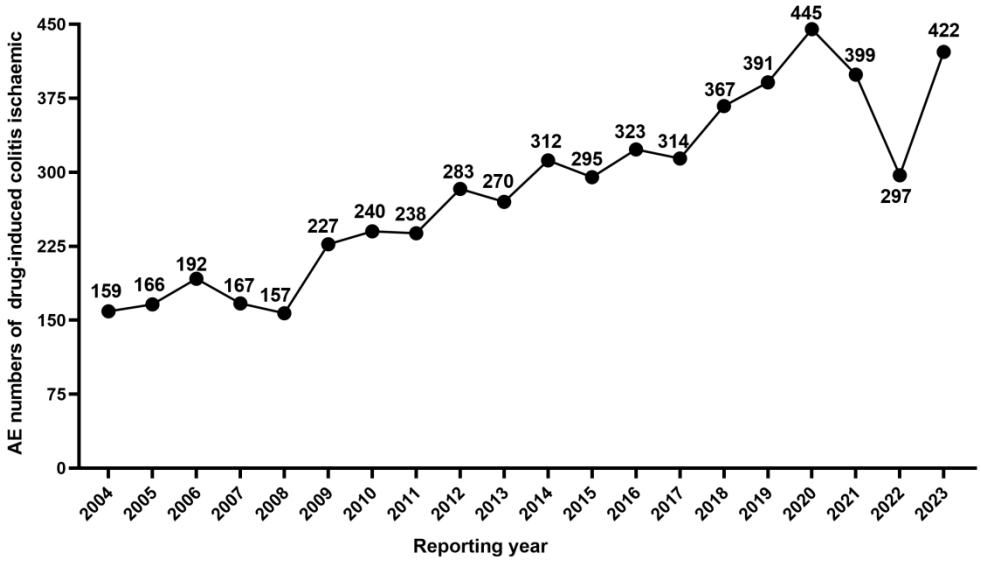

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2×2 contingency table

	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
	$\mathrm{E(IC)} = \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$\mathrm{V(IC)} = \frac{1}{(ln2)^2}[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)} + \frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)} + \frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}]$	
	$\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$\mathrm{IC} - 2\mathrm{SD} = \mathrm{E(IC)} - 2\sqrt{\mathrm{V(IC)}}$	
EBGM	$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05>2
	$SE(lnEBGM) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$	
	$95\%CI = e^{\ln(EBGM)\pm 1.96se}$	

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Assessing the association between drug use and ischaemic colitis: a retrospective pharmacovigilance study using FDA Adverse Event data

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ABSTRACT

Objective: Drug-induced ischaemic colitis is a significant adverse event (AE) in clinical practice. This study aimed to recognize the top drugs associated with the risk of ischaemic colitis based on the FDA Adverse Event Reporting System (FAERS) database.

Design: A cross-sectional design.

Setting: All data retrieved from the FAERS database from the first quarter of 2004 to the fourth quarter of 2023.

Participants: A total of 5664 drug-induced ischaemic colitis AEs eligible for screening.

Primary and secondary outcome measures: The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify ischaemic colitis (code: 10009895) cases. Disproportionality analysis for drug-associated ischaemic colitis signals

Results: Drug-induced ischaemic colitis AEs were more prevalent in females (60.12%) and individuals aged ≥65 years (34.25%). The common outcomes were hospitalization (46.85%) and death (9.73%). Disproportionality analysis identified 91 ischaemic colitis signals and the top 30 drugs mainly involved in the gastrointestinal and nervous systems. The top 5 drugs with the highest reported odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and the empirical Bayesian geometric mean (EBGM), were alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Additionally, 20 of the top 30 drugs did not have ischaemic colitis risk indicated in the package insert.

Conclusion: Based on the FAERS database analysis, we listed drugs with strong ischaemic colitis signals. The potential risk of ischaemic colitis is important, and further research is necessary to understand the mechanisms and enhance drug safety measures.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study utilized the FDA Adverse Event Reporting System (FAERS), a large and real-world pharmacovigilance database, to investigate drug-induced ischaemic colitis.
- Disproportionality analysis methods, including reported odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric mean (EBGM), were used to evaluate the associations between drugs and adverse events.
- The use of a cross-sectional design limits the ability to infer causality between drug use and ischaemic colitis.

- FAERS is a self-reporting system, which may introduce biases such as under-reporting, incomplete information, and variability in data quality.

1. INTRODUCTION

Ischaemic colitis is the most frequent type of colonic vascular injury, accounting for approximately 50-60% of ischaemic disorders of the gastrointestinal tract.[1 2] The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.[3] The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.[4] Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.[5] Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.[4 6] In addition, ischaemic colitis can cause complications, including obstruction, necrosis, and perforation. Therefore, identification of patients with ischaemic colitis is recommended, with colonoscopic evaluation ideally performed within 48 hours of symptom onset.[4 7] Colonoscopy can differentiate cases amenable to conservative treatment from those requiring urgent resection.

Ischaemic colitis can occur secondary to various conditions such as mesenteric artery embolism, thrombosis, or trauma, which may lead to occlusive vascular diseases and compromised colon perfusion, as well as hypoperfusion states resulting from congestive heart failure. Additionally, a myriad of drugs predispose to ischaemic colitis, including antibiotics (amoxicillin-clavulanate),[8] anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),[9] decongestants (pseudoephedrine),[10] cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,[11] laxatives (lactulose, bisacodyl),[12] nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),[13] and serotonin agonists/antagonists.[14 15] Currently, information on ischaemic colitis risks is primarily documented in package inserts, depending on the results of clinical trials. Due to constraints in sample size and follow-up duration, clinical trials may not precisely reflect the occurrence of drug-induced ischaemic colitis in real-world situations. The ischaemic colitis risk of certain drugs may not be readily recognized in clinical trials. In addition, the majority of drug-induced ischaemic colitis in the clinical setting was reported in the form of case reports, and data from large-scale real-world studies are not available. Therefore, the correlation between drugs and ischaemic colitis still needs to be completed.

Post-marketing surveillance is a vital method to determine the association between drugs and

adverse events (AEs). FAERS is a self-reporting system for collecting post-marketing AEs for drugs. FAERS, owing to its extensive data repository and open accessibility, is commonly utilized in drug signal mining studies.[16] This study aimed to investigate the risk of drug-induced ischaemic colitis by FAERS database thoroughly and to identify drugs with a potential risk of ischaemic colitis that are not described in the drug inserts.

2. METHODS

2.1. Data sources

The data for this study were obtained from the FAERS, covering the period from the 1st quarter of 2004 to the 4th quarter of 2023. The American Standard Code for Information Interchange (ASCII) report files were downloaded directly from the FAERS Public Dashboard. They included the following datasets: DEMO (demographic information), DRUG (drug information), REAC (reaction information), and OUTC (outcome information). The data were imported into MySQL 15.0 for structured storage and efficient query management. Navicat Premium 15 software was employed for database management and data retrieval. Before analysis, data cleaning and standardization were performed to ensure consistency and accuracy.

2.2. Definition of AEs and drugs

AEs extracted from the FAERS database were coded using the Preferred Term (PT) system in the Medical Dictionary for Regulatory Activities (MedDRA) to standardize nomenclature. To identify cases of drug-induced colitis ischaemic, reports containing the PT "colitis ischaemic" (MedDRA code: 10009895) in the REAC dataset were retrieved. Once these reports were identified, all associated drug records were extracted for further analysis. Since FAERS reports may include both generic drug names and brand names, standardizing drug nomenclature was essential to maintain consistency in analysis. Drug names were first matched to their corresponding generic names using the DrugBank database, which serves as a comprehensive reference for drug classification. Any drug names that could not be retrieved from the DrugBank database were considered incorrect reports and were subjected to manual elimination. This standardization process helped ensure data accuracy and reliability for statistical evaluation.

2.3. Statistical analysis

Descriptive analysis was conducted to describe the clinical characteristics of patients with drug-

induced ischaemic colitis, including age, gender, reporter, outcome (Hospitalization, Death, Life threatening, Disability, Required intervention to Prevent Permanent Impairment/Damage, Congenital anomaly, other serious), and reported country. Individual safety reports (ISR) were enumerated, with each ISR considered an AE report. To identify potential associations between drugs and ischaemic colitis, disproportionality analysis was employed as a hypothesis-generating approach. The top 30 drugs most strongly associated with ischaemic colitis were identified based on their disproportionality metrics. Four widely used disproportionality analysis methods were applied to detect potential drug-AE signals. All algorithms rely on a 2×2 contingency table (Table 1). Specific formulas and cut-off thresholds were detailed as follows, and statistical analyses were performed using R software. A higher value indicates a stronger statistical relationship between the suspect drug and suspect AE.

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

Reported odds ratio (ROR) Formula: $\mathrm{ROR} = \frac{a/c}{b/d}$, $95\%CI = e^{\ln(ROR) \pm 1.96se}$

Signal criteria: ROR $\geqslant$ 3, a $\geqslant$ 3 and the lower limit of the 95% confidence interval (CI) > 1.

Proportional reporting ratio (PRR) Formula: $\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$, $95\%CI = e^{\ln(PRR) \pm 1.96se}$

Signal criteria: PRR ≥ 2, a ≥ 3 and the lower limit of the 95% CI > 1.

Bayesian confidence propagation neural network (BCPNN) Formula:

$$\mathrm{IC} = \log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)},\ \mathrm{IC}-2\mathrm{SD} = \mathrm{E(IC)} - 2\sqrt{\mathrm{V(IC)}}$$

Signal criteria: the lower bound of the 95% CI (IC025) > 0.

Empirical Bayesian geometric mean (EBGM) Formula: $\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$, $95\%CI = e^{\ln(EBGM) \pm 1.96se}$

Signal criteria: EBGM05 > 2 (EBGM05 denotes the lower bound of the 95% CI).

In this study, we employed ROR, PRR, BCPNN, and EBGM to detect drug-adverse event signals, considering the unique strengths of each method to ensure a more comprehensive and reliable signal detection process: ROR corrects for biases caused by a small number of reports for specific events.

PRR offers higher specificity then ROR, reducing the likelihood of false positives. BCPNN integrates multi-source data and performs cross-validation, enhancing robustness. EBGM adjusts for variability through Bayesian modeling, making it particularly effective for detecting rare adverse events. By combining these methods, we leveraged their respective advantages to broaden the detection scope, validate findings from multiple perspectives, and improve the accuracy and reliability of safety signal detection. The joint application of multiple algorithms allows for cross-validation, reducing false positives and improving the detection of rare adverse reactions.

Patient and public involvement

None

3. RESULTS

3.1. Descriptive analysis

A total of 5664 drug-induced ischaemic colitis AEs were reported in the FAERS database from the first quarter of 2004 to the fourth quarter of 2023. As shown in Figure 1, the number of reported AEs of drug-induced ischaemic colitis peaked in 2020 at 445 cases. Beginning in 2021, the number of AEs begins to decline, but the overall trend exhibits increasing volatility from 2004 through 2023.

The clinical characteristics of these 5664 AE reports were listed in Table 2. Ischaemic colitis was more prevalent in females (60.12%) than in males (31.02%). Ischaemic colitis was more likely to occur in ≥ 65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and ≤18 years (1.36%). These AE reports from physician reporters had the highest percentage (44.26%), thus increasing the credibility of this study. The top 5 most frequently reported outcomes were hospitalization (46.85%), followed by death (9.73%), life-threatening (6.28%), disability (2.00%), and required intervention to prevent permanent impairment (0.49%). Notably, the most number of drug-induced ischaemic colitis reports were from the United States (n = 1534, 27.08%), followed by Japan (n = 657, 11.60%), France (n = 464, 8.19%), and the United Kingdom (n = 210, 3.71%). Additionally, the most frequently reported time-to-onset of drug-induced ischemic colitis was ⩾ 60 days (n = 998, 29.10%), followed by < 7 days (n = 538, 15.69%), 7-28 days (n = 361, 10.53%), and 28-60 days (n = 223, 6.50%).

Table 2. Clinical characteristics of reported drug-induced ischaemic colitis

Characteristics	Reports, n (%)
Sex	
Female	3405 (60.12)
Male	1757 (31.02)
unknown	502 (8.86)
Age (year)	
≤ 18	77 (1.36)
19-40	596 (10.52)
41-64	1783 (31.48)
≥ 65	1940 (34.25)
unknown	1268 (22.39)
Reporter	
Physician	2507 (44.26)
Consumer	968 (17.09)
Other health-professional	939 (16.58)
Pharmacist	868 (15.32)
Lawyer	65 (1.15)
Sales	1 (0.02)
unknown	316 (5.58)
Outcomes	
Hospitalization	4081 (46.85)
Death	848 (9.73)
Life threatening	547 (6.28)
Disability	174 (2.00)
Required intervention to Prevent	43 (0.49)
Congenital anomaly	4 (0.05)
other serious	3014 (34.60)
Reported countries	
United States	1534(27.08)
Japan	657(11.60)
France	464(8.19)
United Kingdom	210(3.71)
other	2799(49.42)
Time-to-onset ischemic colitis (days)	
<7	538 (15.69)

7-28	361 (10.53)
28-60	223 (6.50)
⩾ 60	998 (29.10)
Unknow	1309 (38.17)

3.2. Disproportionality analysis

A total of 91 ischaemic colitis signals were identified according to the ROR > 3 criteria. The top 30 (ranked by ROR) drugs associated with the highest signal intensity in drug-induced ischaemic colitis were listed in Table 3. The top 30 highest drugs used PRR, IC, and EBGM methods consistent with the results of RORs. The most common of the top 30 drugs were gastrointestinal and nervous system drugs. These include alosetron (ROR = 339.26, 95% CI: 263.31-437.11, a serotonin-3 receptor antagonist), tegaserod (ROR = 67.52, 95% CI: 55.47-82.19, a serotonin-4 receptor antagonist), and eluxadoline (ROR = 19.46, 95% CI: 11.28-33.59, a μ-opioid receptor agonist) for the treatment of irritable bowel syndrome (IBS). Additionally, drugs for the treatment of constipation and cleansing of the colon in preparation for colonoscopy were included: lubiprostone (ROR = 44.03, 95% CI: 27.99-69.26), lactulose (ROR = 15.34, 95% CI: 5.74-40.96), bisacodyl (ROR = 33.49, 95% CI: 20.46-54.82), suprep bowel prep (ROR = 10.63, 95% CI: 5.88-19.23), osmoprep (ROR = 51.87, 95% CI: 30.59-87.97), and prepopik (ROR = 16.63, 95% CI: 7.45-37.10). Furthermore, serotonin antagonists should be given more attention in drug-induced ischaemic colitis, including 5-HT3 and 5-HT 1B/1D receptor antagonists. Among them, signal strength were granisetron ROR = 17.05 (95% CI: 9.43-30.86), naratriptan ROR = 64.15 (95% CI: 34.31-119.94), rizatriptan ROR = 33.15 (95% CI: 21.55-50.98), zolmitriptan ROR = 16.96 (95% CI: 9.11-31.59), sumatriptan ROR = 14.51 (95% CI: 11.8-17.83), respectively. Other neurologic drugs that cause drug-induced ischaemic colitis include benztropine mesylate, dexamfetamine, phentermine, and desogestrel and ethinyl estradiol. Moreover, using baloxavir marboxi (ROR = 44.95), peramivir (ROR = 35.47), oseltamivir (ROR = 8.97), ketoprofen (ROR = 18.62), and piroxicam (ROR = 15.26) for the treatment of influenza and rheumatoid arthritis disease ischemic colitis should be a concern. Other drugs related to drug-induced ischemic colitis include daprodustat, ferrlecit, sevelamer carbonate, miglitol, pletal, etelcalcetide, and kayexalate. Among the top 30 drugs in drug-induced ischaemic colitis, there were 20 drugs whose instructions do not indicate the risk of ischaemic colitis.

185 Table 3. Top 30 drugs for signal strength.

Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	Pharmacologic action	Indications
alosetron	66	339.26 (263.31, 437.11)	310.89 (245.73, 393.33)	8.26 (7.9)	307.28 (248.57)	a serotonin-3 (5-HT3) receptor antagonist	irritable bowel syndrome with diarrhoea
tegaserod*	103	67.52 (55.47, 82.19)	66.34 (54.53, 80.7)	6.03 (5.74)	65.15 (55.26)	a serotonin-4 (5-HT4) receptor partial antagonist	irritable bowel syndrome with constipation and chronic idiopathic constipation
eluxadoline*	13	19.46 (11.28, 33.59)	19.37 (11.19, 33.53)	4.27 (3.51)	19.32 (12.24)	a opioid receptor agonist	irritable bowel syndrome with diarrhoea
lubiprostone*	19	44.03 (27.99, 69.26)	43.52 (27.73, 68.31)	5.44 (4.8)	43.38 (29.69)	a chloride channel activator	constipation
lactulose	4	15.34 (5.74, 40.96)	15.28 (5.73, 40.71)	3.93 (2.66)	15.27 (6.71)	a colonic acidifier	constipation
bisacodyl	16	33.49 (20.46, 54.82)	33.19 (20.33, 54.18)	5.05 (4.36)	33.1 (21.92)	a stimulant laxative	constipation and empty the bowel
suprep bowel prep	11	10.63 (5.88, 19.23)	10.61 (5.89, 19.1)	3.4 (2.59)	10.59 (6.45)	an osmotic laxative	cleansing of the colon in preparation for colonoscopy
osmoprep	14	51.87 (30.59, 87.97)	51.17 (30.14, 86.86)	5.67 (4.94)	51.04 (32.81)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
prepopik	6	16.63 (7.45, 37.10)	16.56 (7.41, 36.99)	4.05 (2.98)	16.54 (8.45)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
granisetron*	11	17.05 (9.43, 30.86)	16.98 (9.43, 30.57)	4.08 (3.26)	16.95 (10.32)	a serotonin-3 (5-HT3) receptor antagonist	nausea and vomiting
naratriptan*	10	64.15 (34.31, 119.94)	63.07 (34.35, 115.8)	5.98 (5.11)	62.96 (37.3)	a serotonin (5-HT1B/1D) receptor agonist	acute treatment of migraine with or without aura
rizatriptan*	21	33.15 (21.55, 50.98)	32.86 (21.35, 50.57)	5.03 (4.43)	32.74 (22.84)	a serotonin (5-HT) 1B/1D receptor agonist	acute treatment of migraine with or without aura
zolmitriptan*	10	16.96 (9.11, 31.59)	16.89 (9.02, 31.62)	4.08 (3.22)	16.86 (10.02)	a serotonin (5-HT) 1B/1D receptor agonist	acute treatment of migraine with or without aura
sumatriptan*	92	14.51 (11.8, 17.83)	14.45 (11.88, 17.58)	3.83 (3.54)	14.23 (11.98)	a serotonin (5-HT1B/1D) receptor agonist	acute treatment of migraine with or without aura

benztropine mesylate*	4	32.37 (12.09, 86.64)	32.09 (12.04, 85.5)	5 (3.73)	32.07 (14.07)	an anticholinergic medication	parkinsonism and extrapyramidal disorders
dexamfetamine*	19	19.07 (12.14, 29.96)	18.98 (12.09, 29.79)	4.24 (3.61)	18.92 (12.96)	a central nervous system stimulant	attention deficit hyperactivity disorder; moderate to severe binge eating disorder
phentermine*	22	14.28 (9.39, 21.72)	14.23 (9.43, 21.48)	3.83 (3.23)	14.17 (9.98)	a sympathomimetic amine anorectic	a short-term adjunct in a regimen of weight reduction
desogestrel and ethinyl estradiol	19	33.91 (21.57, 53.32)	33.61 (21.41, 52.75)	5.07 (4.43)	33.5 (22.94)	a combination of synthetic estrogen and progestin	contraception
baloxavir marboxi*	24	44.95 (30.03, 67.28)	44.42 (30.01, 65.74)	5.47 (4.9)	44.23 (31.56)	a polymerase acidic endonuclease inhibitor	influenza
peramivir*	3	35.47 (11.37, 110.61)	35.14 (11.5, 107.4)	5.13 (3.71)	35.12 (13.56)	an inhibiter of influenza virus neuraminidase	influenza
oseltamivir*	41	8.97 (6.59, 12.2)	8.95 (6.54, 12.25)	3.15 (2.71)	8.89 (6.87)	an inhibiter of influenza virus neuraminidase	influenza
ketoprofen*	7	18.62 (8.85, 39.14)	18.53 (8.8, 39.02)	4.21 (3.21)	18.51 (9.94)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis; pain; primary dysmenorrhea
piroxicam*	6	15.26 (6.84, 34.03)	15.2 (6.81, 33.95)	3.92 (2.85)	15.18 (7.76)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis
daprodustat*	3	16.94 (5.45, 52.68)	16.87 (5.41, 52.58)	4.08 (2.66)	16.86 (6.52)	a hypoxia-inducible factor prolyl hydroxylase inhibitor	anemia due to chronic kidney disease
ferrlecit*	4	11.75 (4.4, 31.36)	11.71 (4.39, 31.2)	3.55 (2.28)	11.71 (5.15)	a iron supplement	iron-deficiency anemia
sevelamer carbonate*	34	16.69 (11.9, 23.4)	16.62 (11.91, 23.19)	4.05 (3.57)	16.52 (12.45)	a phosphate binder	control of serum phosphorus
miglitol	3	14.32 (4.61, 44.5)	14.26 (4.58, 44.45)	3.83 (2.42)	14.26 (5.52)	a glucosidase inhibitor	type 2 diabetes mellitus
pletal	8	8.82 (4.4, 17.65)	8.8 (4.43, 17.47)	3.14 (2.19)	8.79 (4.92)	an antiplatelet aggregation medication	peripheral arterial disease
etelcalcetide*	4	24.4 (9.12, 65.24)	24.24 (9.1, 64.59)	4.6 (3.33)	24.23 (10.64)	a calcium-sensing receptor agonist	secondary hyperparathyroidism
kayexalate	10	96.57 (51.51, 181.03)	94.11 (51.26, 172.79)	6.55 (5.69)	93.95 (55.53)	a potassium binder	hyperkalemia

*Package insert indicates ischaemic colitis risk.

4. DISCUSSION

To the best of our knowledge, this study is the first and largest assessment of drug-induced ischaemic colitis in real-world based on the FAERS database. In this study, we outlined the clinical features of these AEs and identified the drugs with the highest associations with drug-induced ischaemic colitis. Many of these drugs are not labeled with ischaemic colitis in the package insert and are not known to present an ischaemic colitis risk.

Age is considered a significant risk factor for ischaemic colitis. A study of 1,560 patients with ischaemic colitis showed that 73% were >65 years old, and the incidence increased with age.[17] Another study showed that the prevalence of ischaemic colitis was 1.1/100,000 in individuals under 40 years old, while in those over 80.3 years old, the incidence was 107/100,000,[18] which suggests that the risk of ischaemic colitis increases with age and may be related to the presence of more cardiovascular and cerebrovascular risk factors in the elderly population. In our study, we also found that drug-induced ischaemic colitis was more common in people ≥ 65 years of age. Although ischaemic colitis usually occurs in the elderly, reports were suggesting an increasing prevalence of the disease in younger age groups,[19] which may be associated with factors such as hypercoagulability, vascular disease, long-distance running, smoking, constipation, and contraceptives.[20-22] With the exception of gender unknown (8.86%), the percentage of female ischaemic colitis cases identified was 60.12% in our study. In population-based studies, women were more likely than men to suffer ischaemic colitis, with female accounting for 61 to 67% of all cases,[23 24] which was consistent with our study.

Serotonin receptor antagonists, including 5-HT3, 5-HT4, and 5-HT 1B/1D, should be given enough attention in drug-induced ischaemic colitis. 5-HT(3) antagonists are effective in treating chemotherapy-induced vomiting and diarrhea, as well as urgency and pain associated with IBS.[15] Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating diarrhea, urgency, and pain in IBS.[25 26] However, it was regrettable that alosetron was withdrawn from the market after 446,000 prescriptions were issued following reports of 49 cases of ischaemic colitis.[27] This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron does not alter colonic blood flow in experimental animals.[28] Tegaserod is a serotonin-4 (5-HT4) receptor partial antagonist, with the most common adverse reactions being diarrhea, headache, and abdominal pain. Given that patients with IBS have a higher risk of ischaemic colitis than the general population, no cases of ischaemic colitis associated with tegaserod were reported in over 11,600

patients enrolled in phase III or post-marketing randomized controlled trials.[29] This may be because the incidence of ischaemic colitis is low that it is unlikely to be detected in phase III trials. However, there were also studies indicating that the increased incidence of ischaemic colitis caused by tegaserod should be of particular concern.[29 30] In the current study, we found the highest number of cases of tegaserod-induced ischaemic colitis (n=103) and a higher risk (ROR=67.52). Although the mechanism needs to be verified, clinical use of tegaserod should be attentive to the risk of ischaemic colitis. In our study, we identified four 5-HT1B/1D receptor agonists that increase the risk of ischaemic colitis: naratriptan, rizatriptan, zolmitriptan, and sumatriptan. To our knowledge, there are six reported cases of naratriptan-induced ischaemic colitis, with two cases suggesting a possible association between naratriptan-induced ischaemic colitis and concomitant use of contraceptives.[31] Two studies reported the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptan-induced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic ischaemic colitis.[32 33] Nguyen TQ *et al*. found 19 cases of zolmitriptan-induced ischaemic colitis in the FAERS database up to May 2013,[34] whereas, in our study, conducted until December 2023, this number increased to 92 cases. Additionally, other studies suggest that zolmitriptan-induced ischaemic colitis may be associated with its overuse [35] or vigorous physical activity following zolmitriptan.[36] In summary, although we found an increased risk of ischaemic colitis associated with 5-HT1B/1D receptor agonists based on the FAERS database and received support from some case reports, the true incidence of ischaemic colitis induced by 5-HT1B/1D receptor agonists still needs to be accurately determined.

In phase III clinical trials, the most frequent AEs related with eluxadoline were abdominal pain (6.5%), nausea (7.7%), and constipation (8%).[37] In March 2017, the FDA issued a warning regarding an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a gallbladder.[38] Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological examination revealing colonic ischemia involving the entire length of colon.[39] Our study found the risk of ischaemic colitis associated with eluxadoline to be ROR=19.46. Both lubiprostone and lactulose are medications used to treat constipation. Although they have different mechanisms of action, both are associated with drug-induced ischaemic colitis. The first case of lubiprostone-induced ischaemic colitis was reported in 2013, and symptoms improved upon discontinuation of lubiprostone.[40] Our study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However,

other studies have reported that lubiprostone can protect intestinal mucosal barrier function in colitis animal models and improve intestinal barrier function in patients with Crohn's disease.[41] Regarding lactulose, to our knowledge, only two cases of lactulose-induced ischaemic colitis have been reported. Researchers speculate that this may be due to lactulose causing gaseous distension through fermentation by colonic bacteria.[42] Bowel cleansers are utilized for various indications, with the most common being preparation for colonoscopy. Prior to colonoscopy, it is imperative to clear fecal matter from intestine to effectively visualize abnormalities under the endoscope.[43] Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.[44] We found that bisacodyl, suprep bowel prep (contains sodium sulfate, potassium sulfate, and magnesium sulfate), osmoprep (contains sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous. Inert ingredients include polyethylene glycol and magnesium stearate), and prepopik (contains sodium picosulfate, magnesium oxide, and anhydrous citric acid) all increase the risk of ischaemic colitis, as documented in their respective package inserts. Therefore, selecting the appropriate bowel cleansers becomes especially crucial in patients with different comorbidities. In addition, in our study, three antiviral drugs and two non-steroidal anti-inflammatory drugs (NSAIDs) were found to increase the risk of drug-induced ischaemic colitis. Since influenza A infection itself can induce ischaemic colitis, reports of ischaemic colitis caused by anti-influenza drugs are relatively rare. Kanai N *et al*. reported a case of acute ischaemic colitis in a 62-year-old Japanese woman after taking baloxavir marboxil for the treatment of influenza A.[45] Regarding oseltamivir, several studies have reported hemorrhagic colitis and ischaemic colitis.[46 47] There have been no reports of colitis associated with the anti-influenza drug peramivir. Recent studies suggested that baloxavir marboxil and oseltamivir may induce ischemic colitis through a shared mechanism, as both drugs exhibit the ability to chelate metal ions in the gastrointestinal tract.[48 49] Metal ion homeostasis is crucial for vascular stability, and its disruption may compromise normal blood flow, potentially leading to intestinal ischemia. Furthermore, drugs that induce constipation represent an additional risk factor for ischemic colitis, as they can reduce colonic blood flow and increase intraluminal pressure, thereby exacerbating ischemic conditions. Specifically, unmetabolized baloxavir and its active metabolite have been reported to chelate dietary metal ions within the intestine.[45] This chelation process can alter local osmotic balance, thereby increasing the risk of ischemic colitis.[50] These findings highlight the importance of considering the potential vascular effects of metal ion-chelating drugs, particularly in patients receiving antiviral treatment for influenza.

Further studies are warranted to elucidate the exact mechanisms underlying these drug-induced vascular alterations and their clinical implications.

Ketoprofen and piroxicam are two common NSAIDs that exert their effects by inhibiting cyclooxygenase-2. NSAIDs are considered to be important triggers for the activation of inflammatory bowel diseases. Yen EF *et al*. found that long-term use of NSAIDs was independently associated with the development of microscopic colitis.[51] Another study indicated that ketoprofen can reduce inflammation and colonic mucosal injury in a rat colitis model, but it was associated with visible gastric bleeding and increased methane output.[52 53] The risk of gastrointestinal adverse events, including bleeding, ulceration, and gastric or intestinal perforation, is reflected in the labels of NSAID drugs, but ischaemic colitis is not mentioned. This should attract more attention in clinical practice.

Our current real-world drug surveillance study provides valuable insights for identifying drugs that may induce ischaemic colitis. However, it should be noted that there are inevitable limitations. Firstly, the lack of detailed case counts for each drug the calculation and comparison of the true incidence rates of ischaemic colitis induced by each drug. Furthermore, the spontaneous reporting nature of FAERS database means that biases like underreporting, incomplete reporting, and false reporting might affect the conclusions. Thirdly, it is challenging to determine the risk factors for ischaemic colitis among patients due to the lack of baseline indicators of gut health and information on concomitant medications. Nonetheless, the FAERS database persists as a critical resource for conducting drug surveillance analyses, offering valuable leads for upcoming prospective clinical studies.

Conclusion

In this study, we used the FAERS database to comprehensively evaluate drugs associated with ischaemic colitis risk. Two-thirds of the high-risk drugs were not listed in the package insert. It is worth noting that the potential ischaemic colitis risk is important and should be given close attention in medical practice. Further research is also needed to clarify the molecular mechanisms underlying the association between these drugs and ischaemic colitis.

Conflict of interest statement

All the authors of this study declare that there is no conflict of interest. They have no relevant financial or non-financial interests, including but not limited to employment, consultancies, stock ownership, honoraria, expert testimony, research funding, patents, or royalties, that could influence the content of

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Author contributions

J-A, T-W, PY-X, CL-Y, YH-F, QQ-L, and XS-D conceived the study. J-A conducted the data analysis, wrote all sections of manuscript, and edited the paper. T-W, KQ-W, YH-F, and CL-Y provided technical support for the analysis. KQ-W, T-W, CL-Y, PY-X, QQ-L, YH-F, and XS-D were involved data acquisition. All authors reviewed and contributed to the final version of the manuscript. XS-D is the guarantor.

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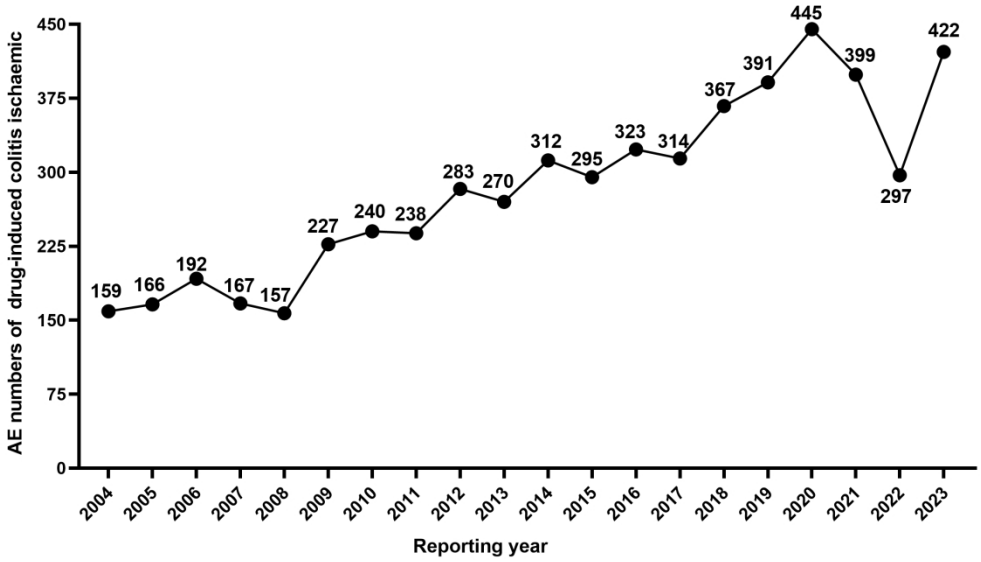
Figure legend

Figure 1. Number of reported AEs of drug-induced ischaemic colitis from 2004 to 2023.



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Assessing the association between drug use and ischaemic colitis: a retrospective pharmacovigilance study using FDA Adverse Event data

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Assessing the association between drug use and ischaemic colitis: a retrospective pharmacovigilance study using FDA Adverse Event data

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ABSTRACT

Objective: Drug-induced ischaemic colitis is a significant adverse event (AE) in clinical practice. This study aimed to recognize the top drugs associated with the risk of ischaemic colitis based on the FDA Adverse Event Reporting System (FAERS) database.

Design: A cross-sectional design.

Setting: All data retrieved from the FAERS database from the first quarter of 2004 to the fourth quarter of 2023.

Participants: A total of 5664 drug-induced ischaemic colitis AEs eligible for screening.

Primary and secondary outcome measures: The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify ischaemic colitis (code: 10009895) cases. Disproportionality analysis for drug-associated ischaemic colitis signals.

Results: Drug-induced ischaemic colitis AEs were more prevalent in females (60.12%) and individuals aged ≥65 years (34.25%). The common outcomes were hospitalization (46.85%) and death (9.73%). Disproportionality analysis identified 91 ischaemic colitis signals and the top 30 drugs mainly involved in the gastrointestinal and nervous systems. The top 5 drugs with the highest reported odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and the empirical Bayesian geometric mean (EBGM), were alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Additionally, 20 of the top 30 drugs did not have ischaemic colitis risk indicated in the package insert.

Conclusion: This study identified key drugs associated with ischaemic colitis, particularly alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Notably, two-thirds of these drugs lacked ischaemic colitis warnings in their package inserts. These findings underscore the need for greater clinical vigilance, improved regulatory oversight, and further research to clarify underlying mechanisms and support safer medication use.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study utilized the FDA Adverse Event Reporting System (FAERS), a large and real-world pharmacovigilance database, to investigate drug-induced ischaemic colitis.
- Disproportionality analysis methods, including reported odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and empirical Bayesian geometric mean (EBGM), were used to evaluate the associations between drugs and adverse events.

- The use of a cross-sectional design limits the ability to infer causality between drug use and ischaemic colitis.
- FAERS is a self-reporting system, which may introduce biases such as under-reporting, incomplete information, and variability in data quality.

1. INTRODUCTION

Ischaemic colitis is the most frequent type of colonic vascular injury, accounting for approximately 50-60% of ischaemic disorders of the gastrointestinal tract.[1 2] The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.[3] The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.[4] Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.[5] Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.[4 6] In addition, ischaemic colitis can cause complications, including obstruction, necrosis, and perforation. Therefore, identification of patients with ischaemic colitis is recommended, with colonoscopic evaluation ideally performed within 48 hours of symptom onset.[4 7] Colonoscopy can differentiate cases amenable to conservative treatment from those requiring urgent resection.

Ischaemic colitis can occur secondary to various conditions such as mesenteric artery embolism, thrombosis, or trauma, which may lead to occlusive vascular diseases and compromised colon perfusion, as well as hypoperfusion states resulting from congestive heart failure. Additionally, a myriad of drugs predispose to ischaemic colitis, including antibiotics (amoxicillin-clavulanate),[8] anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),[9] decongestants (pseudoephedrine),[10] cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,[11] laxatives (lactulose, bisacodyl),[12] nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),[13] and serotonin agonists/antagonists.[14 15] Currently, information on ischaemic colitis risks is primarily documented in package inserts, depending on the results of clinical trials. Due to constraints in sample size and follow-up duration, clinical trials may not precisely reflect the occurrence of drug-induced ischaemic colitis in real-world situations. The ischaemic colitis risk of certain drugs may not be readily recognized in clinical trials. In addition, the majority of drug-induced ischaemic colitis in the clinical setting was reported in the form of case reports, and data from large-scale real-world studies are not

available. Therefore, the correlation between drugs and ischaemic colitis still needs to be completed.

Post-marketing surveillance is a vital method to determine the association between drugs and adverse events (AEs). FAERS is a self-reporting system for collecting post-marketing AEs for drugs. FAERS, owing to its extensive data repository and open accessibility, is commonly utilized in drug signal mining studies.[16] This study aimed to investigate the risk of drug-induced ischaemic colitis by FAERS database thoroughly and to identify drugs with a potential risk of ischaemic colitis that are not described in the drug inserts.

2. METHODS

2.1. Data sources

The data for this study were obtained from the FAERS, covering the period from the 1st quarter of 2004 to the 4th quarter of 2023. The American Standard Code for Information Interchange (ASCII) report files were downloaded directly from the FAERS Public Dashboard. They included the following datasets: DEMO (demographic information), DRUG (drug information), REAC (reaction information), and OUTC (outcome information). The data were imported into MySQL 15.0 for structured storage and efficient query management. Navicat Premium 15 software was employed for database management and data retrieval. Before analysis, data cleaning and standardization were performed to ensure consistency and accuracy.

2.2. Definition of AEs, drugs, and outcomes

AEs extracted from the FAERS database were coded using the Preferred Term (PT) system in the Medical Dictionary for Regulatory Activities (MedDRA) to standardize nomenclature. To identify cases of drug-induced colitis ischaemic, reports containing the PT “colitis ischaemic” (MedDRA code: 10009895) in the REAC dataset were retrieved. Once these reports were identified, all associated drug records were extracted for further analysis. Since FAERS reports may include both generic drug names and brand names, standardizing drug nomenclature was essential to maintain consistency in analysis. Drug names were first matched to their corresponding generic names using the DrugBank database, which serves as a comprehensive reference for drug classification. Any drug names that could not be retrieved from the DrugBank database were considered incorrect reports and were subjected to manual elimination. This standardization process helped ensure data accuracy and reliability for statistical evaluation. In this study, outcomes are categorised into seven types. Disability refers to cases in which

the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions. Required intervention to prevent permanent impairment/damage refers to cases where medical or surgical intervention was deemed necessary to preclude permanent impairment of body function or prevent permanent damage to body structure. Life-threatening refers to cases where the patient was at substantial risk of dying at the time of the adverse event or where continued use of the medical product might have resulted in death.

2.3. Statistical analysis

Descriptive analysis was conducted to describe the clinical characteristics of patients with drug-induced ischaemic colitis, including age, gender, reporter, outcome (Hospitalization, Death, Life threatening, Disability, Required intervention to Prevent Permanent Impairment/Damage, Congenital anomaly, other serious), and reported country. Individual safety reports (ISR) were enumerated, with each ISR considered an AE report. To identify potential associations between drugs and ischaemic colitis, disproportionality analysis was employed as a hypothesis-generating approach. The top 30 drugs most strongly associated with ischaemic colitis were identified based on their disproportionality metrics. Four widely used disproportionality analysis methods were applied to detect potential drug-AE signals. All algorithms rely on a 2×2 contingency table (Table 1). Specific formulas and cut-off thresholds were detailed as follows, and statistical analyses were performed using R software. A higher value indicates a stronger statistical relationship between the suspect drug and suspect AE.

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

Reported odds ratio (ROR) Formula: $\mathrm{ROR} = \frac{a/c}{b/d}$, $95\%CI = e^{\ln(ROR) \pm 1.96se}$

Signal criteria: ROR $\geqslant$ 3, a $\geqslant$ 3 and the lower limit of the 95% confidence interval (CI) > 1.

Proportional reporting ratio (PRR) Formula: $\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$, $95\%CI = e^{\ln(PRR) \pm 1.96se}$

Signal criteria: PRR ≥ 2, a ≥ 3 and the lower limit of the 95% CI > 1.

Bayesian confidence propagation neural network (BCPNN) Formula:

$$IC = \log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)},\ IC-2SD = E(IC)-2\sqrt{V(IC)}$$

Signal criteria: the lower bound of the 95% CI (IC025) > 0.

Empirical Bayesian geometric mean (EBGM) Formula: $EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$, $95\%CI = e^{\ln(EBGM) \pm 1.96se}$

Signal criteria: EBGM05 > 2 (EBGM05 denotes the lower bound of the 95% CI).

In this study, we employed ROR, PRR, BCPNN, and EBGM to detect drug-adverse event signals, considering the unique strengths of each method to ensure a more comprehensive and reliable signal detection process: ROR corrects for biases caused by a small number of reports for specific events. PRR offers higher specificity then ROR, reducing the likelihood of false positives. BCPNN integrates multi-source data and performs cross-validation, enhancing robustness. EBGM adjusts for variability through Bayesian modeling, making it particularly effective for detecting rare adverse events. By combining these methods, we leveraged their respective advantages to broaden the detection scope, validate findings from multiple perspectives, and improve the accuracy and reliability of safety signal detection. The joint application of multiple algorithms allows for cross-validation, reducing false positives and improving the detection of rare adverse reactions.

Patient and public involvement

None

3. RESULTS

3.1. Descriptive analysis

A total of 5664 drug-induced ischaemic colitis AEs were reported in the FAERS database from the first quarter of 2004 to the fourth quarter of 2023. As shown in Figure 1, the number of reported AEs of drug-induced ischaemic colitis peaked in 2020 at 445 cases. Beginning in 2021, the number of AEs begins to decline, but the overall trend exhibits increasing volatility from 2004 through 2023.

The clinical characteristics of these 5664 AE reports were listed in Table 2. Ischaemic colitis was more prevalent in females (60.12%) than in males (31.02%). Ischaemic colitis was more likely to occur in ≥ 65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and ≤18 years (1.36%). These AE reports from physician reporters had the highest percentage (44.26%), thus increasing the credibility of this study. The top 5 most frequently reported outcomes were

hospitalization (46.85%), followed by death (9.73%), life-threatening (6.28%), disability (2.00%), and required intervention to prevent permanent impairment (0.49%). Notably, the most number of drug-induced ischaemic colitis reports were from the United States (n = 1534, 27.08%), followed by Japan (n = 657, 11.60%), France (n = 464, 8.19%), and the United Kingdom (n = 210, 3.71%). Additionally, the most frequently reported time-to-onset of drug-induced ischemic colitis was ⩾ 60 days (n = 998, 29.10%), followed by < 7 days (n = 538, 15.69%), 7-28 days (n = 361, 10.53%), and 28-60 days (n = 223, 6.50%).

Table 2. Clinical characteristics of reported drug-induced ischaemic colitis

Characteristics	Reports, n (%)
Sex	
Female	3405 (60.12)
Male	1757 (31.02)
unknown	502 (8.86)
Age (year)	
≤ 18	77 (1.36)
19-40	596 (10.52)
41-64	1783 (31.48)
≥ 65	1940 (34.25)
unknown	1268 (22.39)
Reporter	
Physician	2507 (44.26)
Consumer	968 (17.09)
Other health-professional	939 (16.58)
Pharmacist	868 (15.32)
Lawyer	65 (1.15)
Sales	1 (0.02)
unknown	316 (5.58)
Outcomes	
Hospitalization	4081 (46.85)
Death	848 (9.73)
Life threatening	547 (6.28)
Disability	174 (2.00)
Required intervention to Prevent	43 (0.49)

Congenital anomaly	4 (0.05)
other serious	3014 (34.60)
Reported countries	
United States	1534(27.08)
Japan	657(11.60)
France	464(8.19)
United Kingdom	210(3.71)
other	2799(49.42)
Time-to-onset ischemic colitis (days)	
<7	538 (15.69)
7-28	361 (10.53)
28-60	223 (6.50)
⩾ 60	998 (29.10)
Unknow	1309 (38.17)

3.2. Disproportionality analysis

A total of 91 ischaemic colitis signals were identified according to the ROR > 3 criteria. The top 30 (ranked by ROR) drugs associated with the highest signal intensity in drug-induced ischaemic colitis were listed in Table 3. The top 30 highest drugs used PRR, IC, and EBGM methods consistent with the results of RORs. The most common of the top 30 drugs were gastrointestinal and nervous system drugs. These include alosetron (ROR = 339.26, 95% CI: 263.31-437.11, a serotonin-3 receptor antagonist), tegaserod (ROR = 67.52, 95% CI: 55.47-82.19, a serotonin-4 receptor antagonist), and eluxadoline (ROR = 19.46, 95% CI: 11.28-33.59, a μ-opioid receptor agonist) for the treatment of irritable bowel syndrome (IBS). Additionally, drugs for the treatment of constipation and cleansing of the colon in preparation for colonoscopy were included: lubiprostone (ROR = 44.03, 95% CI: 27.99-69.26), lactulose (ROR = 15.34, 95% CI: 5.74-40.96), bisacodyl (ROR = 33.49, 95% CI: 20.46-54.82), suprep bowel prep (ROR = 10.63, 95% CI: 5.88-19.23), osmoprep (ROR = 51.87, 95% CI: 30.59-87.97), and prepopik (ROR = 16.63, 95% CI: 7.45-37.10). Furthermore, serotonin antagonists should be given more attention in drug-induced ischaemic colitis, including 5-HT3 and 5-HT 1B/1D receptor antagonists. Among them, signal strength were granisetron ROR = 17.05 (95% CI: 9.43-30.86), naratriptan ROR = 64.15 (95% CI: 34.31-119.94), rizatriptan ROR = 33.15 (95% CI: 21.55-50.98), zolmitriptan ROR = 16.96 (95% CI: 9.11-31.59), sumatriptan ROR = 14.51 (95% CI: 11.8-17.83), respectively. Other neurologic drugs that cause drug-induced ischaemic colitis include benztropine

mesylate, dexamfetamine, phentermine, and desogestrel and ethinyl estradiol. Moreover, using baloxavir marboxi (ROR = 44.95), peramivir (ROR = 35.47), oseltamivir (ROR = 8.97), ketoprofen (ROR = 18.62), and piroxicam (ROR = 15.26) for the treatment of influenza and rheumatoid arthritis disease ischemic colitis should be a concern. Other drugs related to drug-induced ischemic colitis include daprodustat, ferrlecit, sevelamer carbonate, miglitol, pletal, etelcalcetide, and kayexalate. Among the top 30 drugs in drug-induced ischaemic colitis, there were 20 drugs whose instructions do not indicate the risk of ischaemic colitis.

193 Table 3. Top 30 drugs for signal strength.

Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	Pharmacologic action	Indications
alosetron	66	339.26 (263.31, 437.11)	310.89 (245.73, 393.33)	8.26 (7.9)	307.28 (248.57)	a serotonin-3 (5-HT3) receptor antagonist	irritable bowel syndrome with diarrhoea
tegaserod*	103	67.52 (55.47, 82.19)	66.34 (54.53, 80.7)	6.03 (5.74)	65.15 (55.26)	a serotonin-4 (5-HT4) receptor partial antagonist	irritable bowel syndrome with constipation and chronic idiopathic constipation
eluxadoline*	13	19.46 (11.28, 33.59)	19.37 (11.19, 33.53)	4.27 (3.51)	19.32 (12.24)	a opioid receptor agonist	irritable bowel syndrome with diarrhoea
lubiprostone*	19	44.03 (27.99, 69.26)	43.52 (27.73, 68.31)	5.44 (4.8)	43.38 (29.69)	a chloride channel activator	constipation
lactulose	4	15.34 (5.74, 40.96)	15.28 (5.73, 40.71)	3.93 (2.66)	15.27 (6.71)	a colonic acidifier	constipation
bisacodyl	16	33.49 (20.46, 54.82)	33.19 (20.33, 54.18)	5.05 (4.36)	33.1 (21.92)	a stimulant laxative	constipation and empty the bowel
suprep bowel prep	11	10.63 (5.88, 19.23)	10.61 (5.89, 19.1)	3.4 (2.59)	10.59 (6.45)	an osmotic laxative	cleansing of the colon in preparation for colonoscopy
osmoprep	14	51.87 (30.59, 87.97)	51.17 (30.14, 86.86)	5.67 (4.94)	51.04 (32.81)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
prepopik	6	16.63 (7.45, 37.10)	16.56 (7.41, 36.99)	4.05 (2.98)	16.54 (8.45)	an osmotic laxative	cleansing of the colon as a preparation for colonoscopy
granisetron*	11	17.05 (9.43, 30.86)	16.98 (9.43, 30.57)	4.08 (3.26)	16.95 (10.32)	a serotonin-3 (5-HT3) receptor antagonist	nausea and vomiting
naratriptan*	10	64.15 (34.31, 119.94)	63.07 (34.35, 115.8)	5.98 (5.11)	62.96 (37.3)	a serotonin (5-HT1B/1D) receptor agonist	acute treatment of migraine with or without aura
rizatriptan*	21	33.15 (21.55, 50.98)	32.86 (21.35, 50.57)	5.03 (4.43)	32.74 (22.84)	a serotonin (5-HT) 1B/1D receptor agonist	acute treatment of migraine with or without aura
zolmitriptan*	10	16.96 (9.11, 31.59)	16.89 (9.02, 31.62)	4.08 (3.22)	16.86 (10.02)	a serotonin (5-HT) 1B/1D receptor agonist	acute treatment of migraine with or without aura
sumatriptan*	92	14.51 (11.8, 17.83)	14.45 (11.88, 17.58)	3.83 (3.54)	14.23 (11.98)	a serotonin (5-HT1B/1D) receptor agonist	acute treatment of migraine with or without aura

benztropine mesylate*	4	32.37 (12.09, 86.64)	32.09 (12.04, 85.5)	5 (3.73)	32.07 (14.07)	an anticholinergic medication	parkinsonism and extrapyramidal disorders
dexamfetamine*	19	19.07 (12.14, 29.96)	18.98 (12.09, 29.79)	4.24 (3.61)	18.92 (12.96)	a central nervous system stimulant	attention deficit hyperactivity disorder; moderate to severe binge eating disorder
phentermine*	22	14.28 (9.39, 21.72)	14.23 (9.43, 21.48)	3.83 (3.23)	14.17 (9.98)	a sympathomimetic amine anorectic	a short-term adjunct in a regimen of weight reduction
desogestrel and ethinyl estradiol	19	33.91 (21.57, 53.32)	33.61 (21.41, 52.75)	5.07 (4.43)	33.5 (22.94)	a combination of synthetic estrogen and progestin	contraception
baloxavir marboxi*	24	44.95 (30.03, 67.28)	44.42 (30.01, 65.74)	5.47 (4.9)	44.23 (31.56)	a polymerase acidic endonuclease inhibitor	influenza
peramivir*	3	35.47 (11.37, 110.61)	35.14 (11.5, 107.4)	5.13 (3.71)	35.12 (13.56)	an inhibiter of influenza virus neuraminidase	influenza
oseltamivir*	41	8.97 (6.59, 12.2)	8.95 (6.54, 12.25)	3.15 (2.71)	8.89 (6.87)	an inhibiter of influenza virus neuraminidase	influenza
ketoprofen*	7	18.62 (8.85, 39.14)	18.53 (8.8, 39.02)	4.21 (3.21)	18.51 (9.94)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis; pain; primary dysmenorrhea
piroxicam*	6	15.26 (6.84, 34.03)	15.2 (6.81, 33.95)	3.92 (2.85)	15.18 (7.76)	a nonsteroidal anti-inflammatory drug	rheumatoid arthritis; osteoarthritis
daprodustat*	3	16.94 (5.45, 52.68)	16.87 (5.41, 52.58)	4.08 (2.66)	16.86 (6.52)	a hypoxia-inducible factor prolyl hydroxylase inhibitor	anemia due to chronic kidney disease
ferrlecit*	4	11.75 (4.4, 31.36)	11.71 (4.39, 31.2)	3.55 (2.28)	11.71 (5.15)	a iron supplement	iron-deficiency anemia
sevelamer carbonate*	34	16.69 (11.9, 23.4)	16.62 (11.91, 23.19)	4.05 (3.57)	16.52 (12.45)	a phosphate binder	control of serum phosphorus
miglitol	3	14.32 (4.61, 44.5)	14.26 (4.58, 44.45)	3.83 (2.42)	14.26 (5.52)	a glucosidase inhibitor	type 2 diabetes mellitus
pletal	8	8.82 (4.4, 17.65)	8.8 (4.43, 17.47)	3.14 (2.19)	8.79 (4.92)	an antiplatelet aggregation medication	peripheral arterial disease
etelcalcetide*	4	24.4 (9.12, 65.24)	24.24 (9.1, 64.59)	4.6 (3.33)	24.23 (10.64)	a calcium-sensing receptor agonist	secondary hyperparathyroidism
kayexalate	10	96.57 (51.51, 181.03)	94.11 (51.26, 172.79)	6.55 (5.69)	93.95 (55.53)	a potassium binder	hyperkalemia

*Package insert indicates ischaemic colitis risk.

4. DISCUSSION

To the best of our knowledge, this study is the first and largest assessment of drug-induced ischaemic colitis in real-world based on the FAERS database. In this study, we outlined the clinical features of these AEs and identified the drugs with the highest associations with drug-induced ischaemic colitis. Many of these drugs are not labeled with ischaemic colitis in the package insert and are not known to present an ischaemic colitis risk.

Age is considered a significant risk factor for ischaemic colitis. A study of 1,560 patients with ischaemic colitis showed that 73% were >65 years old, and the incidence increased with age.[17] Another study showed that the prevalence of ischaemic colitis was 1.1/100,000 in individuals under 40 years old, while in those over 80.3 years old, the incidence was 107/100,000,[18] which suggests that the risk of ischaemic colitis increases with age and may be related to the presence of more cardiovascular and cerebrovascular risk factors in the elderly population. In our study, we also found that drug-induced ischaemic colitis was more common in people ≥ 65 years of age. Although ischaemic colitis usually occurs in the elderly, reports were suggesting an increasing prevalence of the disease in younger age groups,[19] which may be associated with factors such as hypercoagulability, vascular disease, long-distance running, smoking, constipation, and contraceptives.[20-22] With the exception of gender unknown (8.86%), the percentage of female ischaemic colitis cases identified was 60.12% in our study. In population-based studies, women were more likely than men to suffer ischaemic colitis, with female accounting for 61 to 67% of all cases,[23 24] which was consistent with our study.

Serotonin receptor antagonists, including 5-HT3, 5-HT4, and 5-HT 1B/1D, should be given enough attention in drug-induced ischaemic colitis. 5-HT(3) antagonists are effective in treating chemotherapy-induced vomiting and diarrhea, as well as urgency and pain associated with IBS.[15] Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating diarrhea, urgency, and pain in IBS.[25 26] However, it was regrettable that alosetron was withdrawn from the market after 446,000 prescriptions were issued following reports of 49 cases of ischaemic colitis.[27] This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron does not alter colonic blood flow in experimental animals.[28] Tegaserod is a serotonin-4 (5-HT4) receptor partial antagonist, with the most common adverse reactions being diarrhea, headache, and abdominal pain. Given that patients with IBS have a higher risk of ischaemic colitis than the general population, no cases of ischaemic colitis associated with tegaserod were reported in over 11,600

patients enrolled in phase III or post-marketing randomized controlled trials.[29] This may be because the incidence of ischaemic colitis is low that it is unlikely to be detected in phase III trials. However, there were also studies indicating that the increased incidence of ischaemic colitis caused by tegaserod should be of particular concern.[29 30] In the current study, we found the highest number of cases of tegaserod-induced ischaemic colitis (n=103) and a higher risk (ROR=67.52). Although the mechanism needs to be verified, clinical use of tegaserod should be attentive to the risk of ischaemic colitis. In our study, we identified four 5-HT1B/1D receptor agonists that increase the risk of ischaemic colitis: naratriptan, rizatriptan, zolmitriptan, and sumatriptan. To our knowledge, there are six reported cases of naratriptan-induced ischaemic colitis, with two cases suggesting a possible association between naratriptan-induced ischaemic colitis and concomitant use of contraceptives.[31] Two studies reported the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptan-induced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic ischaemic colitis.[32 33] Nguyen TQ *et al*. found 19 cases of zolmitriptan-induced ischaemic colitis in the FAERS database up to May 2013,[34] whereas, in our study, conducted until December 2023, this number increased to 92 cases. Additionally, other studies suggest that zolmitriptan-induced ischaemic colitis may be associated with its overuse [35] or vigorous physical activity following zolmitriptan.[36] In summary, although we found an increased risk of ischaemic colitis associated with 5-HT1B/1D receptor agonists based on the FAERS database and received support from some case reports, the true incidence of ischaemic colitis induced by 5-HT1B/1D receptor agonists still needs to be accurately determined.

In phase III clinical trials, the most frequent AEs related with eluxadoline were abdominal pain (6.5%), nausea (7.7%), and constipation (8%).[37] In March 2017, the FDA issued a warning regarding an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a gallbladder.[38] Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological examination revealing colonic ischemia involving the entire length of colon.[39] Our study found the risk of ischaemic colitis associated with eluxadoline to be ROR=19.46. Both lubiprostone and lactulose are medications used to treat constipation. Although they have different mechanisms of action, both are associated with drug-induced ischaemic colitis. The first case of lubiprostone-induced ischaemic colitis was reported in 2013, and symptoms improved upon discontinuation of lubiprostone.[40] Our study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However,

other studies have reported that lubiprostone can protect intestinal mucosal barrier function in colitis animal models and improve intestinal barrier function in patients with Crohn's disease.[41] Regarding lactulose, to our knowledge, only two cases of lactulose-induced ischaemic colitis have been reported. Researchers speculate that this may be due to lactulose causing gaseous distension through fermentation by colonic bacteria.[42] Bowel cleansers are utilized for various indications, with the most common being preparation for colonoscopy. Prior to colonoscopy, it is imperative to clear fecal matter from intestine to effectively visualize abnormalities under the endoscope.[43] Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.[44] We found that bisacodyl, suprep bowel prep (contains sodium sulfate, potassium sulfate, and magnesium sulfate), osmoprep (contains sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous. Inert ingredients include polyethylene glycol and magnesium stearate), and prepopik (contains sodium picosulfate, magnesium oxide, and anhydrous citric acid) all increase the risk of ischaemic colitis, as documented in their respective package inserts. Therefore, selecting the appropriate bowel cleansers becomes especially crucial in patients with different comorbidities. In addition, in our study, three antiviral drugs and two non-steroidal anti-inflammatory drugs (NSAIDs) were found to increase the risk of drug-induced ischaemic colitis. Since influenza A infection itself can induce ischaemic colitis, reports of ischaemic colitis caused by anti-influenza drugs are relatively rare. Kanai N *et al*. reported a case of acute ischaemic colitis in a 62-year-old Japanese woman after taking baloxavir marboxil for the treatment of influenza A.[45] Regarding oseltamivir, several studies have reported hemorrhagic colitis and ischaemic colitis.[46 47] There have been no reports of colitis associated with the anti-influenza drug peramivir. Recent studies suggested that baloxavir marboxil and oseltamivir may induce ischemic colitis through a shared mechanism, as both drugs exhibit the ability to chelate metal ions in the gastrointestinal tract.[48 49] Metal ion homeostasis is crucial for vascular stability, and its disruption may compromise normal blood flow, potentially leading to intestinal ischemia. Furthermore, drugs that induce constipation represent an additional risk factor for ischemic colitis, as they can reduce colonic blood flow and increase intraluminal pressure, thereby exacerbating ischemic conditions. Specifically, unmetabolized baloxavir and its active metabolite have been reported to chelate dietary metal ions within the intestine.[45] This chelation process can alter local osmotic balance, thereby increasing the risk of ischemic colitis.[50] These findings highlight the importance of considering the potential vascular effects of metal ion-chelating drugs, particularly in patients receiving antiviral treatment for influenza.

Further studies are warranted to elucidate the exact mechanisms underlying these drug-induced vascular alterations and their clinical implications.

Ketoprofen and piroxicam are two common NSAIDs that exert their effects by inhibiting cyclooxygenase-2. NSAIDs are considered to be important triggers for the activation of inflammatory bowel diseases. Yen EF *et al*. found that long-term use of NSAIDs was independently associated with the development of microscopic colitis.[51] Another study indicated that ketoprofen can reduce inflammation and colonic mucosal injury in a rat colitis model, but it was associated with visible gastric bleeding and increased methane output.[52 53] The risk of gastrointestinal adverse events, including bleeding, ulceration, and gastric or intestinal perforation, is reflected in the labels of NSAID drugs, but ischaemic colitis is not mentioned. This should attract more attention in clinical practice.

Our current real-world drug surveillance study provides valuable insights for identifying drugs that may induce ischaemic colitis. However, it should be noted that there are inevitable limitations. Firstly, the lack of detailed case counts for each drug the calculation and comparison of the true incidence rates of ischaemic colitis induced by each drug. Furthermore, the spontaneous reporting nature of FAERS database means that biases like underreporting, incomplete reporting, and false reporting might affect the conclusions. Thirdly, it is challenging to determine the risk factors for ischaemic colitis among patients due to the lack of baseline indicators of gut health and information on concomitant medications. Nonetheless, the FAERS database persists as a critical resource for conducting drug surveillance analyses, offering valuable leads for upcoming prospective clinical studies.

Conclusion

This study identified 91 drugs associated with ischaemic colitis using the FAERS database, with the strongest signals observed for alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Cases were more common in females and individuals aged ≥65 years, suggesting higher susceptibility in these groups. Two-thirds of the top 30 drugs lacked relevant warnings in their package inserts, indicating potential gaps in safety labeling. Many implicated drugs act on the gastrointestinal or nervous systems. These findings highlight the need for greater clinical vigilance and further research into the underlying mechanisms of the association between these drugs and ischaemic colitis.

Conflict of interest statement

All the authors of this study declare that there is no conflict of interest. They have no relevant financial or non-financial interests, including but not limited to employment, consultancies, stock ownership, honoraria, expert testimony, research funding, patents, or royalties, that could influence the content of this manuscript.

Author contributions

J-A, T-W, PY-X, CL-Y, YH-F, QQ-L, and XS-D conceived the study. J-A conducted the data analysis, wrote all sections of manuscript, and edited the paper. T-W, KQ-W, YH-F, and CL-Y provided technical support for the analysis. KQ-W, T-W, CL-Y, PY-X, QQ-L, YH-F, and XS-D were involved data acquisition. All authors reviewed and contributed to the final version of the manuscript. XS-D is the guarantor.

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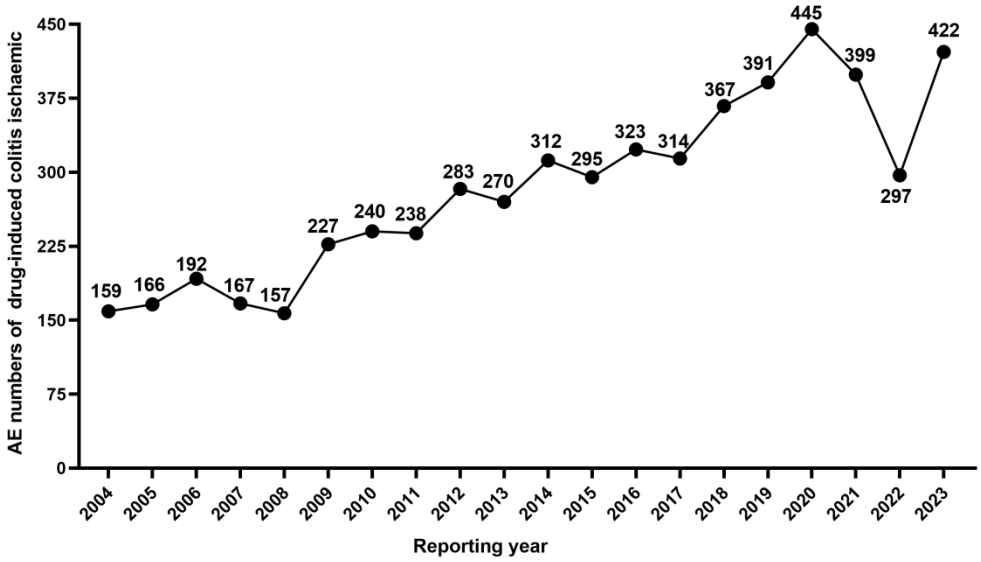
Figure legend

Figure 1. Number of reported AEs of drug-induced ischaemic colitis from 2004 to 2023.



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