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# **BMJ Open**

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

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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 $\geq 65$ 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.<sup>1</sup> <sup>2</sup> The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.<sup>3</sup> The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.<sup>4</sup> Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.<sup>5</sup> Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.<sup>4 6</sup> 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.<sup>47</sup> 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),<sup>8</sup> anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),<sup>9</sup> decongestants (pseudoephedrine),<sup>10</sup> cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,<sup>11</sup> laxatives (lactulose, bisacodyl),<sup>12</sup> nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),<sup>13</sup> and serotonin agonists/antagonists.<sup>14</sup><sup>15</sup> 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

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signal mining studies.<sup>16</sup> 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 druginduced 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 

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relationship between the suspect drug and suspect AE.

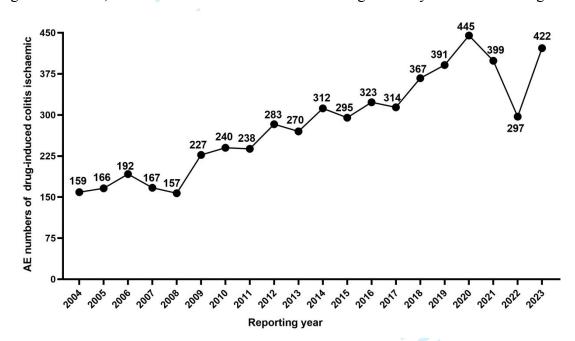
89 Patient and public involvement

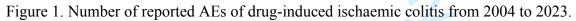
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### **3. RESULTS**

### 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 1. Ischaemic colitis was more prevalent in females (60.12%) than in males (31.02%). Ischaemic colitis was more likely to occur in  $\geq$  65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and  $\leq$  103  $\leq$  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

Table 1. Clinical characteristics of repo	orted drug-induced ischaemic con
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	
	2505 (11.20)
Physician	2507 (44.26)
Consumer	968 (17.09)
Other health-professional	939 (16.58)
-	<i>yyy</i> (10.58)
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)

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57	129
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Required intervention	to	Prevent	43 (0.49)
Permanent Impairment/Damage			נד (יד) נד
Congenital anomaly			4 (0.05)
other serious			3014 (34.60)
<b>Reported countries</b>			
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

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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. 

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Table 2. Top 3(	0 drugs fo	or signal strength.				bmjopen-2024-088512 ( J by copyright, includin	
Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	بت م for 21 Pharmacologic a Stimes s ع ع ع	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 (5-2000) 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 (5-44 g 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 a const	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 channef 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 colonic acidifier	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 laxativer	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 laxativer Lune 13, 2025	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 a	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-HT $\overrightarrow{g}$ B/1D ) receptor agonist $\overrightarrow{g}$	acute treatment of migraine with or without aura

 $\begin{array}{c} 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40 \end{array}$ 

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rizatriptan*	21	33.15	32.86	5.03	32.74	a serotonin (5-HT 1B/11 receptor agonist	e
I		(21.55, 50.98)	(21.35, 50.57)	(4.43)	(22.84)	receptor agonist a serotonin (SHT) 1B/11	or without aura
zolmitriptan*	10	16.96	16.89	4.08	16.86	a serotonin (55HT) 1B/11	• acute treatment of migraine with
· · · ·		(9.11, 31.59)	(9.02, 31.62)	(3.22)	(10.02)	receptor agonist of N	or without aura
sumatriptan*	92	14.51	14.45	3.83	14.23	a serotonin 😹 T1B/1D	) acute treatment of migraine wi
5 annuar i p tani		(11.8, 17.83)	(11.88, 17.58)	(3.54)	(11.98)	receptor agonist	or without aura
benztropine	4	32.37	32.09	5	32.07	an anticholinergic an edication	parkinsonism and extrapyramid
mesylate*		(12.09, 86.64)	(12.04, 85.5)	(3.73)	(14.07)		disorders
		19.07	18.98	4.24	18.92	a serotonin <b>Serotonin</b> a serotonin <b>Serotonin</b> an anticholinergic <b>Consection</b> a central nert <b>Seroto</b> stimulant a sympathomina <b>Bent</b>	attention deficit hyperactivi
dexamfetamine	* 19	(12.14, 29.96)	(12.09, 29.79)	(3.61)	(12.96)	stimulant	disorder; moderate to seve
					(12.90)	dina di tr	binge eating disorder
phentermine*	22	14.28	14.23	3.83	14.17	a sympathomin a sympathomin a sympathomic a amine	e a short-term adjunct in a regime
P		(9.39, 21.72)	(9.43, 21.48)	(3.23)	(9.98)	anorectic	of weight reduction
desogestrel a	19	33.91	33.61	5.07	33.5		contraception
ethinyl estradio	ol	(21.57, 53.32)	(21.41, 52.75)	(4.43)	(22.94)	estrogen and progestine	-
baloxavir	24	44.95	44.42	5.47	44.23	a polymera	influenza
marboxi*	21	(30.03, 67.28)	(30.01, 65.74)	(4.9)	(31.56)	endonuclease inhigitor	mmuonzu
peramivir*	3	35.47	35.14	5.13	35.12	an inhibiter of influenza viru	s influenza
perannvn	5	(11.37, 110.61)	(11.5, 107.4)	(3.71)	(13.56)	neuraminidase o	
oseltamivir*	41	8.97	8.95	3.15	8.89	an inhibiter of influenza viru	s influenza
oseitainivii	71	(6.59, 12.2)	(6.54, 12.25)	(2.71)	(6.87)	neuraminidase la Lune	mnuenza
		18.62	18.53	4.21	18.51	a nonsteroidal ante inflammatory	rheumatoid arthrit
ketoprofen*	7	(8.85, 39.14)	(8.8, 39.02)	(3.21)	(9.94)	<u>0</u> N	osteoarthritis; pain; prima
		(0.05, 5).14)	(0.0, 57.02)	(3.21)	().)4)	drug O25	dysmenorrhea
piroxicam*	6	15.26	15.2	3.92	15.18	a nonsteroidal anti-infummator	rheumatoid arthrit
phoxicali	0	(6.84, 34.03)	(6.81, 33.95)	(2.85)	(7.76)	drug gen	osteoarthritis
daprodustat*	3	16.94	16.87	4.08	16.86	a hypoxia-inducible factor proly	l anemia due to chronic kidne
daprodustat	5	(5.45, 52.68)	(5.41, 52.58)	(2.66)	(6.52)	hydroxylase inhibitor <b>b</b>	disease
ferrlecit*	4	11.75	11.71	3.55	11.71	a iron supplement	iron-deficiency anemia
lemeent	4	(4.4, 31.36)	(4.39, 31.2)	(2.28)	(5.15)		fion-deficiency allerina

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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 bindez	24-088512	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 inhigito	.0	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		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 agonist	receptor	secondary hyperparathyroidism
kayexalate	10	96.57	94.11	6.55	93.95	an antiplatelet s medication a calcium-sensition agonist t a potassium bindee	ownload	hyperkalemia
						a potassium bilidex (ADE2) . Al training, Al training, and similar technologies.	1.bmj.com/ on June 1	

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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 148 149 ischaemic colitis showed that 73% were >65 years old, and the incidence increased with age.<sup>17</sup> Another study showed that the prevalence of ischaemic colitis was 1.1/100,000 in individuals under 40 years 150 old, while in those over 80.3 years old, the incidence was 107/100,000,<sup>18</sup> which suggests that the risk 151 23 <sub>152</sub> of ischaemic colitis increases with age and may be related to the presence of more cardiovascular and 25 <sub>153</sub> cerebrovascular risk factors in the elderly population. In our study, we also found that drug-induced 27 154 ischaemic colitis was more common in people  $\geq 65$  years of age. Although ischaemic colitis usually 29 155 occurs in the elderly, reports were suggesting an increasing prevalence of the disease in younger age groups.<sup>19</sup> which may be associated with factors such as hypercoagulability, vascular disease, long-31 156 distance running, smoking, constipation, and contraceptives.<sup>20-22</sup> With the exception of gender 33 157 unknown (8.86%), the percentage of female ischaemic colitis cases identified was 60.12% in our study. 35 158 In population-based studies, women were more likely than men to suffer ischaemic colitis, with female 37 159 accounting for 61 to 67% of all cases,<sup>23 24</sup> which was consistent with our study. 39 160

Serotonin receptor antagonists, including 5-HT3, 5-HT4, and 5-HT 1B/1D, should be given 41 161 43 162 enough attention in drug-induced ischaemic colitis. 5-HT(3) antagonists are effective in treating 45 <sup>163</sup> chemotherapy-induced vomiting and diarrhea, as well as urgency and pain associated with IBS.<sup>15</sup> 47 <sup>164</sup> Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating diarrhea, urgency, and pain in IBS.<sup>25 26</sup> However, it was regrettable that alosetron was withdrawn from 165 the market after 446,000 prescriptions were issued following reports of 49 cases of ischaemic colitis.<sup>27</sup> 166 This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron 167 does not alter colonic blood flow in experimental animals.<sup>28</sup> Tegaserod is a serotonin-4 (5-HT4) 168 56 169 receptor partial antagonist, with the most common adverse reactions being diarrhea, headache, and **58** 170 abdominal pain. Given that patients with IBS have a higher risk of ischaemic colitis than the general 60 <sub>171</sub> population, no cases of ischaemic colitis associated with tegaserod were reported in over 11,600

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patients enrolled in phase III or post-marketing randomized controlled trials.<sup>29</sup> 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.<sup>29 30</sup> 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.<sup>31</sup> Two studies reported the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptaninduced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic ischaemic colitis.<sup>32 33</sup> Nguyen TQ et al. found 19 cases of zolmitriptan-induced ischaemic colitis in the FAERS database up to May 2013,<sup>34</sup> 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 <sup>35</sup> or vigorous physical activity following zolmitriptan.<sup>36</sup> 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%).<sup>37</sup> In March 2017, the FDA issued a warning regarding an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a gallbladder.<sup>38</sup> Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological 195 examination revealing colonic ischemia involving the entire length of colon.<sup>39</sup> Our study found the 196 197 risk of ischaemic colitis associated with eluxadoline to be ROR=19.46. Both lubiprostone and lactulose 198 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 <sup>58</sup> 200 colitis was reported in 2013, and symptoms improved upon discontinuation of lubiprostone.<sup>40</sup> Our 60 <sub>201</sub> study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However, Page 15 of 20

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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.<sup>41</sup> 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.<sup>42</sup> 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.<sup>43</sup> Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.<sup>44</sup> 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.<sup>45</sup> Regarding oseltamivir, several studies have reported hemorrhagic colitis induced by it rather than ischaemic colitis.<sup>46 47</sup> 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.<sup>48</sup> 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.<sup>49 50</sup> 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.

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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

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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.

#### 238 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.

### 27 244 **Conflict of interest statement**

29 245 All the authors of this study declare that there is no conflict of interest.

#### **31 246 Author contributions**

33 247 XS-D conceived the study. J-A edited the paper conducted the data analysis, wrote all sections of paper.

35 248 T-W, PY-X, CL-Y, YH-F, and QQ-L edited the manuscript.

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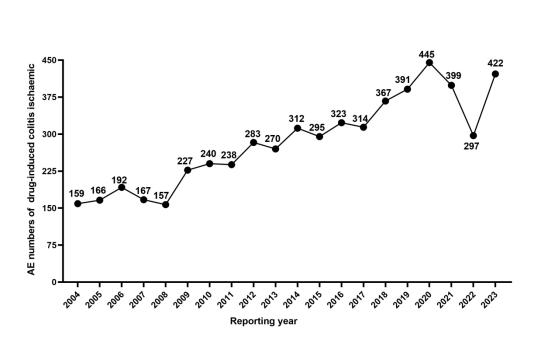
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219x129mm (300 x 300 DPI)

#### 2×2 contingency table

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

Method	Formula	Threshold
ROR	$ROR = \frac{a / c}{b / d}$ $SE(lnROR) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$ $95\%CI = e^{\ln (ROR) \pm 1.96se}$	$a \ge 3$ ROR \ge 3 95%CI (lower limit) > 1
PRR	$PRR = \frac{a / (a + b)}{c / (c + d)}$ $SE(lnPRR) = \sqrt{\frac{1}{a} - \frac{1}{a + b} + \frac{1}{c} - \frac{1}{c + d}}$ $95\%CI = e^{\ln(PRR) \pm 1.96se}$	a ≥ 3 PRR ≥ 2 95%CI (lower limit) > 1
BCPNN	$IC = \log_2 \frac{p(x, y)}{p(x)p(y)} = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC)$ $= \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$ $V(IC) = \frac{1}{(ln2)^2} [\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}$ $+ \frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}$ $+ \frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}]$ $\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$ $IC - 2SD = E(IC) - 2\sqrt{V(IC)}$	IC025>0
EBGM	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $SE(lnEBGM) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$ $95\%CI = e^{\ln{(EBGM) \pm 1.96se}}$	EBGM05>2

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

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Keywords:	Adverse events < THERAPEUTICS, Drug Utilization, Gastroduodenal disease < GASTROENTEROLOGY





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Assessing the association between drug use and ischaemic colitis: a retrospective pharmacovigilance study using FDA Adverse Event data Jie An<sup>a</sup>, Kaiqi Wu<sup>b</sup>, Teng Wu<sup>b</sup>, Pengyang Xu<sup>b</sup>, Chuanli Yang<sup>acd</sup>, Yunhe Fan<sup>a</sup>, Qingqing Li<sup>e</sup>, Xiushan Dong<sup>a</sup>\* <sup>a</sup>Department of General Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China <sup>b</sup>Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, China <sup>c</sup>Key Laboratory of Environmental Medical Engineering and Education Ministry, School of Public Health, Southeast University, Nanjing, Jiangsu, China <sup>d</sup>Department of Preventive Medicine, School of Public Health, Southeast University, Nanjing, China <sup>e</sup>Department of pharmacy, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China om \*Corresponding Author: Xiushan Dong, Email: dongxiushan2012@163.com 

1 2		
- 3 4	17	ABSTRACT
5 6	18	<b>Objective</b> : Drug-induced ischaemic colitis is a significant adverse event (AE) in clinical practice. This
7 8	19	study aimed to recognize the top drugs associated with the risk of ischaemic colitis based on the FDA
9 10	20	Adverse Event Reporting System (FAERS) database.
11 12	21	Design: A cross-sectional design.
13 14	22	Setting: All data retrieved from the FAERS database from the first quarter of 2004 to the fourth quarter
15 16	23	of 2023.
17 18	24	Participants: A total of 5664 drug-induced ischaemic colitis AEs eligible for screening.
	25	Primary and secondary outcome measures: The Medical Dictionary for Regulatory Activities
20 21 22	26	(MedDRA) was used to identify ischaemic colitis (code: 10009895) cases. Disproportionality analysis
23	27	for drug-associated ischaemic colitis signals
	28	<b>Results</b> : Drug-induced ischaemic colitis AEs were more prevalent in females (60.12%) and individuals
26 27	29	aged $\geq 65$ years (34.25%). The common outcomes were hospitalization (46.85%) and death (9.73%).
	30	Disproportionality analysis identified 91 ischaemic colitis signals and the top 30 drugs mainly involved
30 31	31	in the gastrointestinal and nervous systems. The top 5 drugs with the highest reported odds ratio (ROR),
32 33	32	proportional reporting ratio (PRR), information component (IC), and the empirical Bayesian geometric
	33	mean (EBGM), were alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Additionally, 20 of
36 37	34	the top 30 drugs did not have ischaemic colitis risk indicated in the package insert.
38 39	35	Conclusion: Based on the FAERS database analysis, we listed drugs with strong ischaemic colitis
40 41	36	signals. The potential risk of ischaemic colitis is important, and further research is necessary to
42 43	37	understand the mechanisms and enhance drug safety measures.
44 45	38	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.

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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.<sup>1</sup><sup>2</sup> The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.<sup>3</sup> The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.<sup>4</sup> Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.<sup>5</sup> Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.<sup>46</sup> 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.<sup>47</sup> 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),<sup>8</sup> anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),<sup>9</sup> decongestants (pseudoephedrine),<sup>10</sup> cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,<sup>11</sup> laxatives (lactulose, bisacodyl),<sup>12</sup> nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),<sup>13</sup> and serotonin agonists/antagonists.<sup>14</sup> <sup>15</sup> 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

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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.<sup>16</sup> 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** 

#### 84 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**

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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	с	d	c + d	
Total	a + c	b + d	N = a + b + c + d	

Reported odds ratio (ROR) Formula: ROR =  $\frac{a/c}{b/d}$ , 95%*CI* =  $e^{\ln(ROR) \pm 1.96se}$ Signal criteria: ROR  $\ge$  3, a  $\ge$  3 and the lower limit of the 95% confidence interval (CI) > 1. 36 119 Proportional reporting ratio (PRR) Formula:  $PRR = \frac{a/(a+b)}{c/(c+d)}$ ,  $95\% CI = e^{\ln(PRR) \pm 1.96se}$ 38 120 

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

Bayesian confidence propagation neural network (BCPNN) Formula:

<sup>44</sup><sub>45</sub> 123 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. 47 124

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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).

56 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 59 <sub>130</sub> detection process: ROR corrects for biases caused by a small number of reports for specific events. 

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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  $\geq$  65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and  $\leq$ 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 druginduced 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  $\geq 60$  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%).

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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)	
$\leq 18$	77 (1.36)
19-40	596 (10.52)
41-64	1783 (31.48)
$\geq$ 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)
Dutcomes	
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)

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7-28	361 (10.53)
28-60	223 (6.50)
$\geq 60$	998 (29.10)
Unknow	1309 (38.17)

#### **3.2.** Disproportionality analysis 160

A total of 91 ischaemic colitis signals were identified according to the ROR > 3 criteria. The top 161 30 (ranked by ROR) drugs associated with the highest signal intensity in drug-induced ischaemic 162 colitis were listed in Table 3. The top 30 highest drugs used PRR, IC, and EBGM methods consistent 163 164 with the results of RORs. The most common of the top 30 drugs were gastrointestinal and nervous 165 system drugs. These include alosetron (ROR = 339.26, 95% CI: 263.31-437.11, a serotonin-3 receptor 22 <sub>166</sub> 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  $\mu$ -opioid receptor agonist) for the treatment of 24 167 26 168 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: 27.99-28 169 (69.26), lactulose (ROR = 15.34, 95% CI: 5.74-40.96), bisacodyl (ROR = 33.49, 95% CI: 20.46-54.82), 30 170 suprep bowel prep (ROR = 10.63, 95% CI: 5.88-19.23), osmoprep (ROR = 51.87, 95% CI: 30.59-32 171 87.97), and prepopik (ROR = 16.63, 95% CI: 7.45-37.10). Furthermore, serotonin antagonists should 34 172 be given more attention in drug-induced ischaemic colitis, including 5-HT3 and 5-HT 1B/1D receptor 36 173 antagonists. Among them, signal strength were granisetron ROR = 17.05 (95% CI: 9.43-30.86), 38 174 naratriptan ROR = 64.15 (95% CI: 34.31-119.94), rizatriptan ROR = 33.15 (95% CI: 21.55-50.98), 40 175 zolmitriptan ROR = 16.96 (95% CI: 9.11-31.59), sumatriptan ROR = 14.51 (95% CI: 11.8-17.83), 176 44 <sup>177</sup> respectively. Other neurologic drugs that cause drug-induced ischaemic colitis include benztropine mesylate, dexamfetamine, phentermine, and desogestrel and ethinyl estradiol. Moreover, using 178 179 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 180 disease ischemic colitis should be a concern. Other drugs related to drug-induced ischemic colitis 181 182 include daprodustat, ferrlecit, sevelamer carbonate, miglitol, pletal, etelcalcetide, and kayexalate. 55 <sub>183</sub> Among the top 30 drugs in drug-induced ischaemic colitis, there were 20 drugs whose instructions do 57 <sub>184</sub> not indicate the risk of ischaemic colitis.

Table 3. Top 30	) drugs fo	r signal strength.				'bmjopen-2024-088 J by copyright, inc	
Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)	Pharmacologic agtion	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 receptor antagonist	irritable bowel syndrome w 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 a Serota (14) receptor partial antageneration of the seron	irritable bowel syndrome w constipation and chronic idiopat 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 agoint special	irritable bowel syndrome w 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 activetor	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 min.	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)	a stimulant laxative an osmotic laxative a serotonin-3 (5-6TT3) )	cleansing of the colon in preparation 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 and	cleansing of the colon as a preparat 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 <b>Similar</b>	cleansing of the colon as a preparat for colonoscopy
granisetron*	11	17.05 (9.43, 30.86)	16.98 (9.43, 30.57)	4.08 (3.26)	16.95 (10.32)	receptor antagonist $\Xi$	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-HT <b>B</b> /1 <b>b</b> ) receptor agonist	acute treatment of migraine with 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) IBAID receptor agonist	acute treatment of migraine with 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) 11 millor receptor agonist	acute treatment of migraine with 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 <b>g</b> D) receptor agonist	acute treatment of migraine with 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 metrical	parkinsonism and extrapy disorders
dexamfetamine*	19	19.07 (12.14, 29.96)	18.98 (12.09, 29.79)	4.24 (3.61)	18.92 (12.96)	an anticholinergic metalication a central nervous g system stimulant of 21	attention deficit hyperactivity dis moderate to severe binge 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	a short-term adjunct in a regiveright 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)	anorectic a combination of estrogen and progestic	contraception
baloxavir marboxi*	24	44.95 (30.03, 67.28)	44.42 (30.01, 65.74)	5.47 (4.9)	44.23 (31.56)	estrogen and progestitien a polymerase endonuclease inhibitor base	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 influer and an inhibiter of influer and a state of the second	influenza
oseltamivir*	41	8.97 (6.59, 12.2)	8.95 (6.54, 12.25)	3.15 (2.71)	8.89 (6.87)	neuraminidase an inhibiter of influence an inhibiter of influence and a second	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 🗹 🖬 ti-	rheumatoid arthritis; osteoa 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)	inflammatory drug a nonsteroidal anti- inflammatory drug a hypoxia-inducibles fortor	rheumatoid arthritis; osteoarthri
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 in bibigr	anemia due to chronic kidney di
ferrlecit*	4	11.75 (4.4, 31.36)	11.71 (4.39, 31.2)	3.55 (2.28)	11.71 (5.15)		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 reconstruction	secondary hyperparathyroidism
kayexalate	10	96.57 (51.51, 181.03)	94.11 (51.26, 172.79)	6.55 (5.69)	93.95 (55.53)	agonist bioder grad	hyperkalemia

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#### 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.<sup>17</sup> 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,<sup>18</sup> 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  $\geq$  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,<sup>19</sup> which may be associated with factors such as hypercoagulability, vascular disease, longdistance running, smoking, constipation, and contraceptives.<sup>20-22</sup> 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,<sup>23 24</sup> 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.<sup>15</sup> Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating diarrhea, urgency, and pain in IBS.<sup>25 26</sup> 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.<sup>27</sup> This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron does not alter colonic blood flow in experimental animals.<sup>28</sup> 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 Page 13 of 20

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patients enrolled in phase III or post-marketing randomized controlled trials.<sup>29</sup> This may be because 217 the incidence of ischaemic colitis is low that it is unlikely to be detected in phase III trials. However, 218 there were also studies indicating that the increased incidence of ischaemic colitis caused by tegaserod 219 10 220 should be of particular concern.<sup>29 30</sup> 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 221 222 needs to be verified, clinical use of tegaserod should be attentive to the risk of ischaemic colitis. In our 223 study, we identified four 5-HT1B/1D receptor agonists that increase the risk of ischaemic colitis: 224 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 225 21 226 naratriptan-induced ischaemic colitis and concomitant use of contraceptives.<sup>31</sup> Two studies reported 23 <sub>227</sub> the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptan-25 228 induced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic 27 229 ischaemic colitis.<sup>32 33</sup> Nguyen TQ et al. found 19 cases of zolmitriptan-induced ischaemic colitis in the 29 230 FAERS database up to May 2013,<sup>34</sup> whereas, in our study, conducted until December 2023, this number increased to 92 cases. Additionally, other studies suggest that zolmitriptan-induced ischaemic 31 231 colitis may be associated with its overuse <sup>35</sup> or vigorous physical activity following zolmitriptan.<sup>36</sup> In 33 232 summary, although we found an increased risk of ischaemic colitis associated with 5-HT1B/1D 35 233 receptor agonists based on the FAERS database and received support from some case reports, the true 37 234 incidence of ischaemic colitis induced by 5-HT1B/1D receptor agonists still needs to be accurately 39 235 41 236 determined.

43 237 In phase III clinical trials, the most frequent AEs related with eluxadoline were abdominal pain 45 <sup>238</sup> (6.5%), nausea (7.7%), and constipation (8%).<sup>37</sup> In March 2017, the FDA issued a warning regarding 47 <sup>239</sup> an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a 48 49 <sup>240</sup> gallbladder.<sup>38</sup> Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological 50 51 <sup>241</sup> examination revealing colonic ischemia involving the entire length of colon.<sup>39</sup> Our study found the 52 53 242 risk of ischaemic colitis associated with eluxadoline to be ROR=19.46. Both lubiprostone and lactulose 54 55 243 are medications used to treat constipation. Although they have different mechanisms of action, both 56 <sub>244</sub> 57 are associated with drug-induced ischaemic colitis. The first case of lubiprostone-induced ischaemic <sup>58</sup> 245 colitis was reported in 2013, and symptoms improved upon discontinuation of lubiprostone.<sup>40</sup> Our <sup>60</sup> 246 study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However,

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other studies have reported that lubiprostone can protect intestinal mucosal barrier function in colitis 247 animal models and improve intestinal barrier function in patients with Crohn's disease.<sup>41</sup> Regarding 248 lactulose, to our knowledge, only two cases of lactulose-induced ischaemic colitis have been reported. 249 Researchers speculate that this may be due to lactulose causing gaseous distension through fermentation by colonic bacteria.<sup>42</sup> Bowel cleansers are utilized for various indications, with the most 252 common being preparation for colonoscopy. Prior to colonoscopy, it is imperative to clear fecal matter 253 from intestine to effectively visualize abnormalities under the endoscope.<sup>43</sup> Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.<sup>44</sup> We found that bisacodyl, 255 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.<sup>4647</sup> 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.<sup>48 49</sup> 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.<sup>45</sup> This chelation process can alter local osmotic balance, thereby increasing the risk of ischemic colitis.<sup>50</sup> These findings highlight the importance of considering the potential vascular 60 <sub>276</sub> 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.<sup>51</sup> 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.<sup>52</sup> <sup>53</sup> 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.

#### 97 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.

## <sup>54</sup>/<sub>55</sub> 303 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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3 4 307	this manuscript.
5 6 <sup>308</sup>	Author contributions
7 8 <sup>309</sup>	J-A, T-W, PY-X, CL-Y, YH-F, QQ-L, and XS-D conceived the study. J-A conducted the data analysis,
9 10 <sup>310</sup>	wrote all sections of manuscript, and edited the paper. T-W, KQ-W, YH-F, and CL-Y provided
11 12 <sup>311</sup>	technical support for the analysis. KQ-W, T-W, CL-Y, PY-X, QQ-L, YH-F, and XS-D were involved
13 14 <sup>312</sup>	data acquisition. All authors reviewed and contributed to the final version of the manuscript. XS-D is
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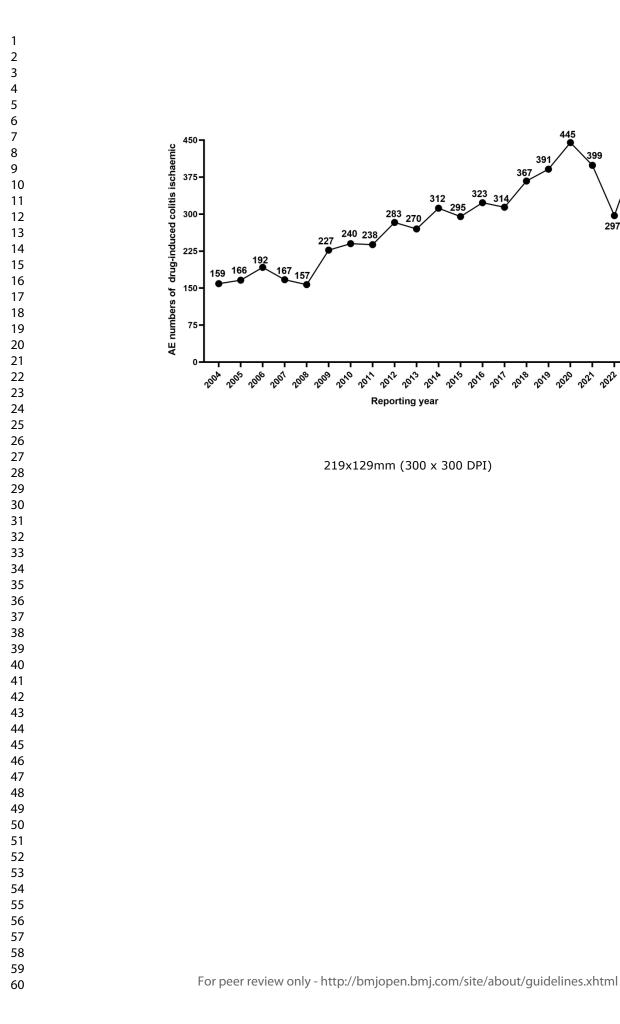
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### Figure legend

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 Jie An<sup>a</sup>, Kaiqi Wu<sup>b</sup>, Teng Wu<sup>b</sup>, Pengyang Xu<sup>b</sup>, Chuanli Yang<sup>acd</sup>, Yunhe Fan<sup>a</sup>, Qingqing Li<sup>e</sup>, Xiushan Dong<sup>a</sup>\* <sup>a</sup>Department of General Surgery, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China <sup>b</sup>Third Hospital of Shanxi Medical University, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Taiyuan, China <sup>c</sup>Key Laboratory of Environmental Medical Engineering and Education Ministry, School of Public Health, Southeast University, Nanjing, Jiangsu, China <sup>d</sup>Department of Preventive Medicine, School of Public Health, Southeast University, Nanjing, China <sup>e</sup>Department of pharmacy, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, China om \*Corresponding Author: Xiushan Dong, Email: dongxiushan2012@163.com 

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2 3 4	17	ABSTRACT
5 6	18	<b>Objective</b> : Drug-induced ischaemic colitis is a significant adverse event (AE) in clinical practice. This
7 8	19	study aimed to recognize the top drugs associated with the risk of ischaemic colitis based on the FDA
9 10	20	Adverse Event Reporting System (FAERS) database.
11 12	21	Design: A cross-sectional design.
13 14	22	Setting: All data retrieved from the FAERS database from the first quarter of 2004 to the fourth quarter
15 16	23	of 2023.
17 17 18	24	Participants: A total of 5664 drug-induced ischaemic colitis AEs eligible for screening.
10 19 20	25	Primary and secondary outcome measures: The Medical Dictionary for Regulatory Activities
20 21 22	26	(MedDRA) was used to identify ischaemic colitis (code: 10009895) cases. Disproportionality analysis
22 23 24	27	for drug-associated ischaemic colitis signals.
25	28	<b>Results</b> : Drug-induced ischaemic colitis AEs were more prevalent in females (60.12%) and individuals
26 27	29	aged $\geq 65$ years (34.25%). The common outcomes were hospitalization (46.85%) and death (9.73%).
28 29	30	Disproportionality analysis identified 91 ischaemic colitis signals and the top 30 drugs mainly involved
30 31	31	in the gastrointestinal and nervous systems. The top 5 drugs with the highest reported odds ratio (ROR),
32 33	32	proportional reporting ratio (PRR), information component (IC), and the empirical Bayesian geometric
34 35	33	mean (EBGM), were alosetron, tegaserod, osmoprep, naratriptan, and kayexalate. Additionally, 20 of
36 37	34	the top 30 drugs did not have ischaemic colitis risk indicated in the package insert.
38 39	35	Conclusion: This study identified key drugs associated with ischaemic colitis, particularly alosetron,
40 41	36	tegaserod, osmoprep, naratriptan, and kayexalate. Notably, two-thirds of these drugs lacked ischaemic
42 43	37	colitis warnings in their package inserts. These findings underscore the need for greater clinical
44 45	38	vigilance, improved regulatory oversight, and further research to clarify underlying mechanisms and
46 47	39	support safer medication use.
48 49	40	STRENGTHS AND LIMITATIONS OF THIS STUDY
50 51	41	• 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

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Ischaemic colitis is the most frequent type of colonic vascular injury, accounting for approximately 50-60% of ischaemic disorders of the gastrointestinal tract.<sup>1</sup><sup>2</sup> The incidence of ischaemic colitis increases with the aging population, primarily affecting the elderly.<sup>3</sup> The etiology of ischaemic colitis is either physiological, including hypotension, secondary to embolism/thrombosis, or iatrogenic, involving secondary to drugs and surgery.<sup>4</sup> Clinically, ischaemic colitis mainly presents with abdominal pain, diarrhea, and rectal bleeding.<sup>5</sup> Decreased blood flow in ischaemic colitis can lead to a spectrum of lesions, ranging from focal ischaemia to severe segmental intestinal infarction.<sup>46</sup> 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.<sup>47</sup> 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),<sup>8</sup> anorectic agents (fenfluramine), chemotherapeutic agents, constipation-inducing drugs (loperamide),<sup>9</sup> decongestants (pseudoephedrine),<sup>10</sup> cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, tumor necrosis factor-alpha inhibitors,<sup>11</sup> laxatives (lactulose, bisacodyl),<sup>12</sup> nonsteroidal anti-inflammatory drugs, psychotropic medications (amphetamine, quetiapine),<sup>13</sup> and serotonin agonists/antagonists.<sup>14</sup> <sup>15</sup> 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.<sup>16</sup> 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. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

#### 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 60 <sub>106</sub> 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 25 <sub>118</sub> each ISR considered an AE report. To identify potential associations between drugs and ischaemic 27 119 colitis, disproportionality analysis was employed as a hypothesis-generating approach. The top 30 29 120 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-31 121 AE signals. All algorithms rely on a 2×2 contingency table (Table 1). Specific formulas and cut-off 33 122 thresholds were detailed as follows, and statistical analyses were performed using R software. A higher 35 123 value indicates a stronger statistical relationship between the suspect drug and suspect AE. 37 124

Table	1.	Four	grid	table.
			0	

	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

7	Signal criteria: ROR	$\geq$	3, a =	/	3 and the lower limit of the 95% confidence interval $(CI) > I$	•

53 54 128	Proportional reporting ratio (PRR) Formula: $PRR = \frac{a/(a+b)}{c/(c+d)}$ , $95\% CI = e^{\ln(PRR) \pm 1.96se}$
55	

56 129 Signal criteria: PRR  $\geq 2$ , a  $\geq 3$  and the lower limit of the 95% CI > 1. 

Bayesian confidence propagation neural network (BCPNN) Formula: 58 130

 a/(a+b)

1 2	
3 4 131 5	$IC = \log_2 \frac{p(x, y)}{p(x)p(y)} = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}, \ IC - 2SD = E(IC) - 2\sqrt{V(IC)}$
6 132 7	Signal criteria: the lower bound of the 95% CI (IC025) $> 0$ .
8 9 133	Empirical Bayesian geometric mean (EBGM) Formula: $EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ , $95\%CI =$
10 11 134	$e^{\ln(EBGM) \pm 1.96se}$
12 13 135	Signal criteria: EBGM05 $>$ 2 (EBGM05 denotes the lower bound of the 95% CI).
14 15 136	In this study, we employed ROR, PRR, BCPNN, and EBGM to detect drug-adverse event signals,
16 17 <sup>137</sup>	considering the unique strengths of each method to ensure a more comprehensive and reliable signal
18 19 <sup>138</sup>	detection process: ROR corrects for biases caused by a small number of reports for specific events.
20 21 <sup>139</sup>	PRR offers higher specificity then ROR, reducing the likelihood of false positives. BCPNN integrates
22 23 <sup>140</sup>	multi-source data and performs cross-validation, enhancing robustness. EBGM adjusts for variability
24 25 <sup>141</sup>	through Bayesian modeling, making it particularly effective for detecting rare adverse events. By
26 27 <sup>142</sup>	combining these methods, we leveraged their respective advantages to broaden the detection scope,
28 29 <sup>143</sup>	validate findings from multiple perspectives, and improve the accuracy and reliability of safety signal
30 <sub>144</sub> 31	detection. The joint application of multiple algorithms allows for cross-validation, reducing false
32 <sub>145</sub> 33	positives and improving the detection of rare adverse reactions.
34 <sub>146</sub> 35	Patient and public involvement
36 <sub>147</sub> 37	None
38 <sub>148</sub> 39	
40 149 41	3. RESULTS
42 150 43	3. RESULTS     3.1. Descriptive analysis
44 151 45	A total of 5664 drug-induced ischaemic colitis AEs were reported in the FAERS database from
46 152 47	the first quarter of 2004 to the fourth quarter of 2023. As shown in Figure 1, the number of reported
48 153	AEs of drug-induced ischaemic colitis peaked in 2020 at 445 cases. Beginning in 2021, the number of
49 50 154	AEs begins to decline, but the overall trend exhibits increasing volatility from 2004 through 2023.
51 52 155	The clinical characteristics of these 5664 AE reports were listed in Table 2. Ischaemic colitis was
53 54 156	more prevalent in females (60.12%) than in males (31.02%). Ischaemic colitis was more likely to occur
55 56 <sup>157</sup>	in $\geq$ 65 years (34.25%), followed by 41-64 years of age (31.48%), 19-40 years of age (10.52%), and
57 58 <sup>158</sup>	$\leq$ 18 years (1.36%). These AE reports from physician reporters had the highest percentage (44.26%),
59 60 <sup>159</sup>	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 druginduced 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  $\geq$  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%).

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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)
$\geq 65$	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)
<b>Reported countries</b>	
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)
$\geq 60$	998 (29.10)
Unknow	1309 (38.17)

#### 29 169 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 31 170 colitis were listed in Table 3. The top 30 highest drugs used PRR, IC, and EBGM methods consistent 33 171 35 172 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 37 173 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 $\mu$ -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), 56 <sub>183</sub> naratriptan ROR = 64.15 (95% CI: 34.31-119.94), rizatriptan ROR = 33.15 (95% CI: 21.55-50.98), 58 <sub>184</sub> zolmitriptan ROR = 16.96 (95% CI: 9.11-31.59), sumatriptan ROR = 14.51 (95% CI: 11.8-17.83), 60 185 respectively. Other neurologic drugs that cause drug-induced ischaemic colitis include benztropine

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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. to beet terien only

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193	Table 3.	Top 30	drugs for	<sup>.</sup> signal	strength.
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	T 11 2 T 20		· · · ·				omjopen-2024- by copyright,	
_	Table 3. Top 30	drugs fo	r signal strength.				-088	
	Drug name	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (IC025)	EBGM (EBGM05)		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-IHT3) receptor antagonist	irritable bowel syndrome wi 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 receptor partial antageneta to partial antageneta	irritable bowel syndrome wi constipation and chronic idiopath 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 agoing to a spinoid receptor agoing the	irritable bowel syndrome wi 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 activetor	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)	a colonic acidifier a stimulant laxative an osmotic laxative an osmotic laxative an osmotic laxative	cleansing of the colon in preparation f 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 and com	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)		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- <b>a</b> T $3$ ) 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-HT <b>B</b> /125 ) receptor agonist	acute treatment of migraine with 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), 11, 10 receptor agonist	acute treatment of migraine with 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) 11 and 10 receptor agonist	acute treatment of migraine with 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 <b>g</b> D) receptor agonist	acute treatment of migraine with without aura

				В	MJ Open	'bmjopen-202 1 by copyrigh	
benztropine mesylate*	4	32.37 (12.09, 86.64)	32.09 (12.04, 85.5)	5 (3.73)	32.07 (14.07)	an anticholinergic me	parkinsonism and extrapyran 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 $\ddot{B}$ system stimulant of 2	attention deficit hyperactivity disor moderate to severe binge e
phentermine*	22	14.28 (9.39, 21.72)	14.23 (9.43, 21.48)	3.83 (3.23)	14.17 (9.98)	a sympathomimetic	a short-term adjunct in a regime 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)	anorectic a combination of a combination	contraception
baloxavir marboxi*	24	44.95 (30.03, 67.28)	44.42 (30.01, 65.74)	5.47 (4.9)	44.23 (31.56)	estrogen and progestition of the strongen and progestition of the strongent and progestition of the strongen	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 or for 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 influence of the second seco	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 $\mathbf{\overline{\omega}} \cdot \mathbf{\overline{m}}$ ti-	rheumatoid arthritis; osteoarth 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 a nonsteroidal a hypoxia-inducible a hypoxia-inducible a factor	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 in biter	anemia due to chronic kidney dise
ferrlecit*	4	11.75 (4.4, 31.36)	11.71 (4.39, 31.2)	3.55 (2.28)	11.71 (5.15)		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 iron supplement a phosphate binder 13, 2	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	t indica	ates ischaemic colit	is risk.			medication a calcium-sensing record agonist a potassium binder re/about/guidelines.xhtml	

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To the best of our knowledge, this study is the first and largest assessment of drug-induced 196 ischaemic colitis in real-world based on the FAERS database. In this study, we outlined the clinical 197 10 <sup>198</sup> features of these AEs and identified the drugs with the highest associations with drug-induced 199 ischaemic colitis. Many of these drugs are not labeled with ischaemic colitis in the package insert and 200 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 201 202 ischaemic colitis showed that 73% were >65 years old, and the incidence increased with age.<sup>17</sup> Another study showed that the prevalence of ischaemic colitis was 1.1/100,000 in individuals under 40 years 203 <sup>21</sup> 204 old, while in those over 80.3 years old, the incidence was 107/100,000,<sup>18</sup> which suggests that the risk 23 <sub>205</sub> of ischaemic colitis increases with age and may be related to the presence of more cardiovascular and 25 <sub>206</sub> cerebrovascular risk factors in the elderly population. In our study, we also found that drug-induced 27 207 ischaemic colitis was more common in people  $\geq 65$  years of age. Although ischaemic colitis usually 29 208 occurs in the elderly, reports were suggesting an increasing prevalence of the disease in younger age groups.<sup>19</sup> which may be associated with factors such as hypercoagulability, vascular disease, long-31 209 distance running, smoking, constipation, and contraceptives.<sup>20-22</sup> With the exception of gender 33 210 unknown (8.86%), the percentage of female ischaemic colitis cases identified was 60.12% in our study. 35 211 In population-based studies, women were more likely than men to suffer ischaemic colitis, with female 37 212 accounting for 61 to 67% of all cases,<sup>23 24</sup> which was consistent with our study. 39 213

40 41 214 Serotonin receptor antagonists, including 5-HT3, 5-HT4, and 5-HT 1B/1D, should be given 42 43 215 enough attention in drug-induced ischaemic colitis. 5-HT(3) antagonists are effective in treating 44 45 216 chemotherapy-induced vomiting and diarrhea, as well as urgency and pain associated with IBS.<sup>15</sup> 46 47<sup>217</sup> Studies have shown that alosetron, a serotonin-3 (5-HT3) receptor antagonist, was effective in treating 48 49 <sup>218</sup> diarrhea, urgency, and pain in IBS.<sup>25 26</sup> However, it was regrettable that alosetron was withdrawn from 50 51 219 the market after 446,000 prescriptions were issued following reports of 49 cases of ischaemic colitis.<sup>27</sup> 52 53 220 This was an unexpected pharmacological outcome. The mechanism behind this is unclear, as alosetron 54 55 221 does not alter colonic blood flow in experimental animals.<sup>28</sup> Tegaserod is a serotonin-4 (5-HT4) 56 <sub>222</sub> receptor partial antagonist, with the most common adverse reactions being diarrhea, headache, and 57 <sup>58</sup> 223 abdominal pain. Given that patients with IBS have a higher risk of ischaemic colitis than the general 59 60 <sub>224</sub> population, no cases of ischaemic colitis associated with tegaserod were reported in over 11,600

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patients enrolled in phase III or post-marketing randomized controlled trials.<sup>29</sup> 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.<sup>29 30</sup> 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.<sup>31</sup> Two studies reported the relationship between rizatriptan and ischaemic colitis, with one case report indicating rizatriptaninduced ischaemic colitis and another suggesting that rizatriptan can trigger acute on top of chronic ischaemic colitis.<sup>32 33</sup> Nguyen TQ et al. found 19 cases of zolmitriptan-induced ischaemic colitis in the FAERS database up to May 2013,<sup>34</sup> 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 <sup>35</sup> or vigorous physical activity following zolmitriptan.<sup>36</sup> 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%).<sup>37</sup> In March 2017, the FDA issued a warning regarding an increased risk of severe pancreatitis in patients receiving eluxadoline treatment without a gallbladder.<sup>38</sup> Additionally, a case of ischaemic colitis was reported, with colonoscopy and histological examination revealing colonic ischemia involving the entire length of colon.<sup>39</sup> 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.<sup>40</sup> Our study also found that lubiprostone may increase the risk of ischaemic colitis (ROR = 44.03). However, Page 15 of 21

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other studies have reported that lubiprostone can protect intestinal mucosal barrier function in colitis 255 animal models and improve intestinal barrier function in patients with Crohn's disease.<sup>41</sup> Regarding 256 lactulose, to our knowledge, only two cases of lactulose-induced ischaemic colitis have been reported. 257 10 258 Researchers speculate that this may be due to lactulose causing gaseous distension through 259 fermentation by colonic bacteria.<sup>42</sup> Bowel cleansers are utilized for various indications, with the most 260 common being preparation for colonoscopy. Prior to colonoscopy, it is imperative to clear fecal matter 261 from intestine to effectively visualize abnormalities under the endoscope.<sup>43</sup> Bowel cleansing agents constitute a class of medications closely associated with ischaemic colitis.<sup>44</sup> We found that bisacodyl, 262 suprep bowel prep (contains sodium sulfate, potassium sulfate, and magnesium sulfate), osmoprep 263 <sup>21</sup> 264 (contains sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous. Inert 23 <sub>265</sub> ingredients include polyethylene glycol and magnesium stearate), and prepopik (contains sodium 25 266 picosulfate, magnesium oxide, and anhydrous citric acid) all increase the risk of ischaemic colitis, as 27 267 documented in their respective package inserts. Therefore, selecting the appropriate bowel cleansers 29 268 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 31 269 33 270 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 35 271 a case of acute ischaemic colitis in a 62-year-old Japanese woman after taking baloxavir marboxil for 37 272 the treatment of influenza A.45 Regarding oseltamivir, several studies have reported hemorrhagic 39 273 41 274 colitis and ischaemic colitis.<sup>4647</sup> There have been no reports of colitis associated with the anti-influenza 43 275 drug peramivir. Recent studies suggested that baloxavir marboxil and oseltamivir may induce ischemic 45 <sup>276</sup> colitis through a shared mechanism, as both drugs exhibit the ability to chelate metal ions in the 47 <sup>277</sup> gastrointestinal tract.<sup>48 49</sup> Metal ion homeostasis is crucial for vascular stability, and its disruption may 48 49 <sup>278</sup> compromise normal blood flow, potentially leading to intestinal ischemia. Furthermore, drugs that 50 51 <sup>279</sup> induce constipation represent an additional risk factor for ischemic colitis, as they can reduce colonic 52 53 280 blood flow and increase intraluminal pressure, thereby exacerbating ischemic conditions. Specifically, 54 55 281 unmetabolized baloxavir and its active metabolite have been reported to chelate dietary metal ions 56 <sub>282</sub> 57 <sup>282</sup> within the intestine.<sup>45</sup> This chelation process can alter local osmotic balance, thereby increasing the <sup>58</sup> 283 risk of ischemic colitis.<sup>50</sup> These findings highlight the importance of considering the potential vascular 60 <sub>284</sub> effects of metal ion-chelating drugs, particularly in patients receiving antiviral treatment for influenza.

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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.<sup>51</sup> 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.<sup>52</sup> <sup>53</sup> 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.

#### 05 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  $\geq 65$  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.

59 313 Conflict of interest statement

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1 2	
3 4 314	All the authors of this study declare that there is no conflict of interest. They have no relevant financial
5 6 <sup>315</sup>	or non-financial interests, including but not limited to employment, consultancies, stock ownership,
7 8 316	honoraria, expert testimony, research funding, patents, or royalties, that could influence the content of
9 10 <sup>317</sup>	this manuscript.
11 12 <sup>318</sup>	Author contributions
13 14 <sup>319</sup>	J-A, T-W, PY-X, CL-Y, YH-F, QQ-L, and XS-D conceived the study. J-A conducted the data analysis,
15 <sub>320</sub> 16	wrote all sections of manuscript, and edited the paper. T-W, KQ-W, YH-F, and CL-Y provided
17 <sub>321</sub> 18	technical support for the analysis. KQ-W, T-W, CL-Y, PY-X, QQ-L, YH-F, and XS-D were involved
19 <sub>322</sub> 20	data acquisition. All authors reviewed and contributed to the final version of the manuscript. XS-D is
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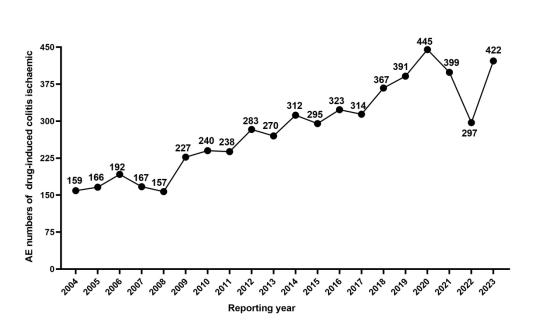
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I	Figure legend
	Figure 1. Number of reported AEs of drug-induced ischaemic colitis from 2004 to 2023.
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