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Research Article

Digestive Tract Cancer-Related Adverse Events Correlated with Proton Pump Inhibitors Use: A Pharmacovigilance Study of the FDA Adverse Event Reporting System

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Background. Proton pump inhibitors (PPIs) are widely used to treat digestive system diseases. Previous studies have suggested conflicting results between PPI treatment and the risk for digestive tract cancers (DTCs). This study aimed to assess the effect of PPI use on DTCs by data mining of the FDA Adverse Event Reporting System (FAERS) database. *Method*. This study examined the correlations between six PPI agents and DTCs by mining the FAERS database from January 2004 to September 2021 by using OpenVigil 2.1. The reporting odds ratio (ROR) defined as the ratio between the odds of reporting a specific adverse event for one drug divided by the corresponding odds for all other drugs, with 95% confidence intervals (CIs), was used to detect statistically significant correlations between PPIs and DTCs. High-level terms (HLTs) and preferred terms (PTs) were defined by the Medical Dictionary for Regulatory Activities 24.0 (MedDRA24.0). *Result*. A total of 2553 DTC adverse event reports were screened, with positive signals obtained from gastric neoplasms malignant (GNM) (ROR: 1.09, 95% CI: 1.01–1.18) and bile duct neoplasms malignant (BDNM) (ROR: 1.80, 95% CI: 1.44–2.25). Esomeprazole showed the strongest signal (ROR: 1.85, 95% CI: 1.66–2.06) for GNM, while rabeprazole for BDNM (ROR: 2.94, 95% CI: 1.32–6.56), and female PPI users had a higher risk of BDNM (ROR: 2.44, 95% CI: 1.77–3.35). Among subordinate PTs, adenocarcinoma gastric and the combination of "bile duct cancer" and "chol-angiocarcinoma" were highly correlated with PPI use. *Conclusion*. By mining the FAERS database, we provided important clues for the correlation between PPI use and DTC risk.

1. Introduction

Since omeprazole was developed by AstraZeneca and approved to enter the market in 1987, proton pump inhibitors (PPIs) have been widely used to treat acid-related diseases, including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and upper gastrointestinal bleeding (GIB) [1]. Due to their relatively good clinical efficacy and safety, PPIs have been recognized as a milestone in the treatment of digestive system diseases in the 20th century [2]. However, in recent years, more new or serious adverse drug reactions (ADRs) have been reported with long-term PPI use [3].

Evidence from epidemiological and mechanistic studies is accumulating that supports a possible relationship between PPI use and digestive tract cancers (DTCs) [4–6]. The risk of DTCs was first noticed for hypoacidity and hypergastrinemia as a consequence of long-term PPI use [7]. In addition, the microbiota composition has been shown to be disrupted with a reduction of gastric acid secretion, causing microbiota "dysbiosis" [8], and the enrichment of specific bacterial communities has been shown to be accompanied by the production of oncogenic metabolites [8, 9].

The present results indicated that long-term use of PPIs may lead to the initiation and progression of different

tumour types arising from many sites in the digestive tract, including oesophageal, gastric, colorectal, pancreatic, liver, and biliary tract cancers [10, 11]. The result of a meta-analysis showed that the use of PPIs may increase the risk of overall DTCs (relative risk (RR): 1.63, 95% confidence interval (CI): 1.33–2.00), among which the risk of gastric cancer was the greatest (RR: 1.78, 95% CI: 1.38–2.31), followed by pancreatic cancer (RR: 1.72, 95% CI: 1.05–2.82) and liver cancer (RR: 1.62, 95% CI: 1.04–2.52) [12]. In addition, several clinical studies confirmed that the use of PPI was correlated with increased risk of gallbladder cancer (odds ratio (OR): 1.56, 95% CI: 1.07–2.19) [13], colorectal cancer (<2 years, hazard ratio (HR): 0.93, 95% CI: 0.83–1.04; 2–4 years, HR: 1.45, 95% CI: 1.28–1.60; ≥4 years, HR: 1.60, 95% CI: 1.42–1.80) [14], and oesophageal adenocarcinoma (standardized incidence ratios (SIRs): 3.93, 95% CI: 3.63–4.24) [15]. In turn, opposing voices were raised, disapproving of research and statistical methods in epidemiology and highlighting the complexity of the real-world data [16, 17]. In addition, the incipient symptoms of gastric, pancreatic, and liver cancer, such as heartburn, bloating, abdominal pain, nausea, and vomiting, are similar to those of acid-related peptic diseases, so patients have been treated with PPIs empirically before being diagnosed with DTCs [12].

The FDA Adverse Event Reporting System (FAERS) as the world's largest spontaneous reporting database has been publicly available online and updated quarterly since 2004, submitted by healthcare professionals from medical institutions, pharmaceutical companies, patients, and other members [18]. In the past few years, data mining of adverse events (AEs) maintained in the FAERS has been performed to investigate drug utilization in clinical practice and has been recognized as an essential tool for identifying drug-related AEs [19]. For the voluntary submission nature of FAERS as a spontaneous reporting system, FAERS data have several limitations, such as the possibilities of under-reporting, overreporting, or missing data on patient demographics, clinical outcomes, drug doses, and concomitant drug use [20, 21]. However, the limitations are compensated by the strength, lying principally in the large data set which can avoid the potential bias and reflect the real-world clinical settings [22]. Thus, in this study, we aimed to identify DTC-related AEs correlated with PPI use by performing a FAERS analysis to provide new insights into this issue.

2. Methods

2.1. Data Source.
To identify DTC-related AEs reported to be correlated with PPI use, we retrieved relevant datasets from the public release of the FAERS database from the first quarter (Q1) of 2004 to the third quarter (Q3) of 2021. Data were retrieved in January, 2022. All data in the FAERS database have been fully anonymized by the regulatory authorities.

OpenVigil 2.1 has been used in many pharmacovigilance studies as a pharmacovigilance data extraction, cleaning, mining, and analysis tool of the FAERS database [18, 23, 24]. OpenVigil 2.1 is designed for complete case analyses and is stable and superior for analyses of disproportionality [25]. After data cleaning by OpenVigil 2.1, 9,217,181 reports from 2004 Q1 to 2021 Q3 were identified for data analysis.

2.2. Data Processing.
This study included all FDA-approved PPIs as targeted agents, including omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole. H2-receptor antagonists (H2RAs) were also included in the study, including cimetidine, famotidine, and roxatidine, for the same acid-suppressive effect but without the potential carcinogenic effect, referring to previous clinical studies [26, 27]. Ilaprazole and dexrabeprazole were excluded because both have not yet been marketed in the United States, while ranitidine and nizatidine were excluded because these two drugs had been recalled due to carcinogenesis of impurities.

FAERS data are publicly available and consist of seven report forms containing demographic, drug information, patient outcomes, and reporting sources. The information about age, sex, drug name, and outcome from retrieved AE reports were collected, and categorical variables were reported as numbers of cases and the corresponding percentage. Suspect cases of PPIs-related DTCs were searched using high-level terms (HLTs) coded from the Medical Dictionary for Regulatory Activities 24.0 (MedDRA 24.0), as shown in Table 1. Preferred terms (PTs), grouped into different HLTs, were further retrieved. Fourteen PTs subordinate to the HLT "GNM," combined with thirteen PTs subordinate to the HLT "BDNM" (Table 1), were added as search terms, to get the related ADRs reported through publicly available FAERS data.

2.3. Data Mining Algorithm.
In pharmacovigilance studies, disproportionality analysis is the most common statistical approach used to mine data from spontaneous reporting systems through detecting the signals of disproportionate reporting (SDR), which refers to statistical correlations between the use of the study drug and ADRs [28]. In this study, SDRs were generated by calculating the reporting odds ratio (ROR) along with a 95% CI by using the following formulas. ROR was calculated as the ratio of the odds of reporting DTCs versus all other ADRs for a given drug, compared with this reporting odd for all other drugs present in the FAERS database over the same time period.

$$\mathrm{ROR} = \frac{a/c}{b/d},$$

$$95\%\,\mathrm{CI} = e^{\ln(\mathrm{ROR}) \pm 1.96\sqrt{(1/a)+(1/b)+(1/c)+(1/d)}}, \quad (1)$$

where a is the number of reports of target AEs for target drugs, b is the number of reports of other AEs for target drugs, c is the number of reports of target AEs for other drugs, and d is the number of reports of other AEs for other drugs.

Basically, a higher ROR suggested a stronger signal strength [29]. The signal was considered positive if the lower limit of the 95% CI was greater than 1, and at least

TABLE 1: HLTs and PTs according to MedDRA 24.0.

HLT subordinate to the HLGT "gastrointestinal neoplasms malignant and unspecified"			
HLT	Abbreviations	HLT	Abbreviations
Gastric neoplasms malignant	GNM	Colorectal neoplasms malignant	CNM
Pancreatic neoplasms malignant	PNM	Anal canal neoplasms malignant	ACNM
Bile duct neoplasms malignant	BDNM	Gallbladder neoplasms malignant	GBNM
Small intestinal neoplasms malignant	SINM	Hepatic neoplasms malignant	HNM
Oesophageal neoplasms malignant	ONM		
PT subordinate to the HLT "gastric neoplasms malignant"			
PT	Adenocarcinoma gastric	Gastric cancer	Gastric cancer recurrent
	Gastric cancer stage 0	Gastric cancer stage I	Gastric cancer stage II
	Gastric cancer stage III	Gastric cancer stage IV	Gastric sarcoma
	Gastroesophageal cancer	Gastroesophageal cancer recurrent	HER2-positive gastric cancer
	Linitis plastica	Metastatic gastric cancer	
PT subordinate to the HLT "bile duct neoplasms malignant"			
PT	Bile duct adenocarcinoma	Bile duct adenosquamous carcinoma	Bile duct cancer
	Bile duct cancer recurrent	Bile duct cancer stage 0	Bile duct cancer stage I
	Bile duct cancer stage II	Bile duct cancer stage III	Bile duct cancer stage IV
	Bile duct squamous cell carcinoma	Biliary cancer metastatic	Cholangiocarcinoma
	Cholangiosarcoma		

HLGT, high-level group term; HLTs, high-level terms; PTs, preferred terms.

three cases were reported [30]. All analyses were performed using Microsoft Excel 2010 and GraphPad Prism 7.

3. Results

3.1. Correlation between PPI Use and DTCs. Overall, 387,929 AE reports related to PPIs and 109,724 AE reports related to DTCs were reported to FAERS from January 2004 to September 2021. The systematic research progress from the FAERS database is shown in Figure 1. We screened 2,553 DTC AE reports correlated with the use of PPIs from the FAERS database, the characteristics of which are described in Table 2. The numbers of reports for GNM, CNM, PNM, HNM, ONM, BDNM, SINM, GBNM, and ACNM were 687 (26.9%), 586 (23.0%), 456 (17.9%), 405 (15.9%), 327 (12.8%), 83 (3.3%), 38 (1.5%), 33 (1.3%), and 20 (0.8%), respectively. Serious outcomes of AE-related HLTs focused on hospitalization (948, 37.1%) and death (826, 32.4%).

Signal detection was conducted first based on all PPIs and H2RAs. Positive signals were obtained for all PPIs correlated with the GNM (ROR: 1.09, 95% CI: 1.01–1.18) and BDNM (ROR: 1.80, 95% CI: 1.44–2.25), while the H2RA cohort ($n = 153$) had no positive signal as shown in Figure 2(a).

Three subset analyses were performed to further demonstrate whether gender, age, and individual PPI molecules influenced the reporting of DTCs.

A previous study had demonstrated that the correlations between DTCs and PPI use differed by sex [14]. According to Table 2, PPI reports correlated with DTCs were higher in males than females (46.3% versus 38.9%, respectively). Same variation trends were observed in ONM (64.2% in males versus 29.7% in females), GNM (30.9% in males versus 26.2% in females), and HNM (59.3% in males versus 34.8% in females), whereas cases of SINM (44.7% in males versus 52.6% in females), CNM (45.7% in males versus 50.7% in females), ACNM (45.0% in males versus 55.0% in females), PNM (47.6% in males versus 48.5% in
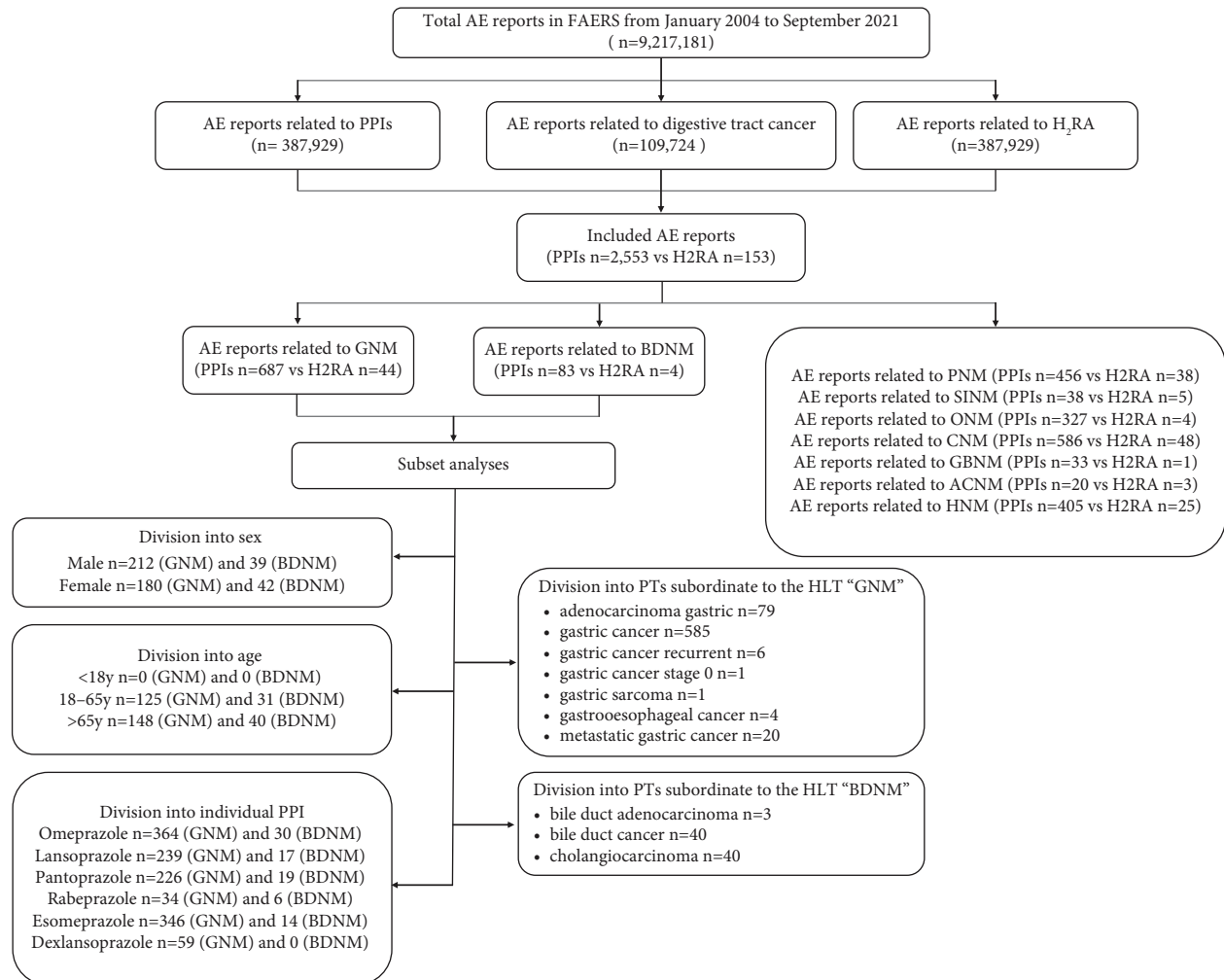
Figure 1: Flowchart for studying the correlation between PPIs and digestive tract cancer risk.

females), GBNM (30.3% in males versus 60.6% in females), and BDNM (47.0% in males versus 50.6% in females) had an opposite trend. The gender subset analysis showed that a further increase in signal was obtained in the female group for PPIs correlated with BDNM with a ROR of 2.44 (95% CI: 1.77–3.35) as shown in Figure 2(b). Although the GNM cohort had the largest number of AE reports for the cancer category, accounting for 26.9%, the signal was negative after stratifying by sex, which might be caused by the removal of unknown or missing groups.

When stratified by age, most AE reports were distributed in the middle age group (18–65 years) and old age group (>65 years), regardless of whether DTCs were considered as a whole or split into subcategories as shown in Table 2. The young people group (<18 years old) was not included in the disproportionality analysis due to the small number of AE reports. Statistically significant RORs of assessed AEs for BDNM were found in both the middle group (ROR: 2.00, 95% CI: 1.38–2.89) and the old group (ROR: 1.72, 95% CI: 1.24–2.39) as shown in Figure 2(c). A negative signal was detected for PPIs in GNM after stratifying by age which is same as the sex stratification analysis.

Furthermore, we conducted a subset analysis stratified by different PPIs. The results are represented in Supplementary Table 1 and visualized using heatmaps, showing the relationship between different DTCs and different PPIs (Figure 3). We found statistically significant GNM signals for the following single agents (Figure 4(a)): omeprazole (ROR: 1.41, 95% CI: 1.27–1.56), lansoprazole (ROR: 1.87, 95% CI: 1.65–2.13), pantoprazole (ROR: 1.32, 95% CI: 1.16–1.51), esomeprazole (ROR: 1.85, 95% CI: 1.66–2.06), and dexlansoprazole (ROR: 1.56, 95% CI: 1.21–2.01). For BDNM detection (Figure 5(a)), rabeprazole had the strongest signal (ROR: 2.94, 95% CI: 1.32–6.56), followed by lansoprazole (ROR: 1.86, 95% CI: 1.15–3.00) and omeprazole (ROR: 1.63, 95% CI: 1.13–2.34).

3.2. Correlation between PPI Use and GNM. Abrahami et al. found that there was a slight difference in hazard rates for the correlation between the use of specific types of PPIs and gastric cancer [27]. Thus, to better understand gastric cancer of different types and individual PPI molecules (esomeprazole, lansoprazole, omeprazole, pantoprazole,

TABLE 2: The characteristics of digestive tract cancer adverse events of proton pump inhibitors.

Characteristics	ONM Case (%)	GNM Case (%)	SINM Case (%)	CNM Case (%)	ACNM Case (%)	PNM Case (%)	HNM Case (%)	GBNM Case (%)	BDNM Case (%)	ALL Case/N
Case	327 (12.8%)	687 (26.9%)	38 (1.5%)	586 (23.0%)	20 (0.8%)	456 (17.9%)	405 (15.9%)	33 (1.3%)	83 (3.3%)	2553
Patient gender										
Male	210 (64.2%)	212 (30.9%)	17 (44.7%)	268 (45.7%)	9 (45.0%)	217 (47.6%)	240 (59.3%)	10 (30.3%)	39 (47.0%)	1183 (46.3%)
Female	97 (29.7%)	180 (26.2%)	20 (52.6%)	297 (50.7%)	11 (55.0%)	221 (48.5%)	141 (34.8%)	20 (60.6%)	42 (50.6%)	993 (38.9%)
Unknown or missing	20 (6.1%)	295 (42.9%)	1 (2.6%)	21 (3.6%)	0 (0.0%)	18 (3.9%)	24 (5.9%)	3 (9.1%)	2 (2.4%)	377 (14.8%)
Patient age group (years)										
<18	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
18–65	118 (36.1%)	125 (18.2%)	18 (47.4%)	203 (34.6%)	12 (60.0%)	171 (37.5%)	155 (38.3%)	14 (42.4%)	31 (37.3%)	816 (32.0%)
>65	86 (26.3%)	148 (21.5%)	14 (36.8%)	254 (43.3%)	0 (0.0%)	178 (39.0%)	154 (38.0%)	11 (33.3%)	40 (48.2%)	862 (33.8%)
Unknown or missing	123 (37.6%)	414 (60.3%)	6 (15.8%)	128 (21.8%)	8 (40.0%)	107 (23.5%)	95 (23.5%)	8 (24.2%)	12 (14.5%)	873 (34.2%)
Serious outcome of adverse events										
Hospitalization	74 (22.6%)	155 (22.6%)	20 (52.6%)	295 (50.3%)	7 (35.0%)	196 (43.0%)	171 (42.2%)	21 (63.6%)	39 (47.0%)	948 (37.1%)
Disability	12 (3.7%)	11 (1.6%)	3 (7.9%)	21 (3.6%)	0 (0.0%)	25 (5.5%)	18 (4.4%)	3 (9.1%)	6 (7.2%)	95 (3.7%)
Life-threatening	38 (11.6%)	27 (3.9%)	3 (7.9%)	61 (10.4%)	0 (0.0%)	62 (13.6%)	33 (8.1%)	8 (24.2%)	11 (13.3%)	239 (9.4%)
Death	96 (29.4%)	177 (25.8%)	7 (18.4%)	157 (26.8%)	1 (5.0%)	238 (52.2%)	141 (34.8%)	9 (27.3%)	31 (37.3%)	826 (32.4%)
PPIs										
Omeprazole	105 (32.1%)	368 (53.6%)	12 (31.6%)	170 (29.0%)	13 (65.0%)	170 (37.3%)	124 (30.6%)	18 (54.5%)	30 (36.1%)	966 (37.8%)
Lansoprazole	64 (19.6%)	240 (34.9%)	8 (21.1%)	121 (20.6%)	1 (5.0%)	57 (12.5%)	60 (14.8%)	5 (15.2%)	17 (20.5%)	560 (21.9%)
Pantoprazole	46 (14.1%)	228 (33.2%)	8 (21.1%)	144 (24.6%)	3 (15.0%)	121 (26.5%)	109 (26.9%)	3 (9.1%)	19 (22.9%)	659 (25.8%)
Rabeprazole	11 (3.4%)	36 (5.2%)	6 (15.8%)	29 (4.9%)	0 (0.0%)	21 (4.6%)	26 (6.4%)	1 (3.0%)	6 (7.2%)	127 (5.0%)
Esomeprazole	162 (49.5%)	346 (50.4%)	10 (26.3%)	166 (28.3%)	5 (25.0%)	121 (26.5%)	98 (24.2%)	7 (21.2%)	14 (16.9%)	893 (35.0%)
Dexlansoprazole	9 (2.8%)	59 (8.6%)	2 (5.3%)	4 (0.7%)	1 (5.0%)	7 (1.5%)	5 (1.2%)	0 (0.0%)	0 (0.0%)	82 (3.2%)

PPIs, proton pump inhibitors; ONM, oesophageal neoplasms malignant; GNM, gastric neoplasms malignant; SINM, small intestinal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal canal neoplasms malignant; PNM, pancreatic neoplasms malignant; HNM, hepatic neoplasms malignant; GBNM, gallbladder neoplasms malignant; BDNM, bile duct neoplasms malignant.
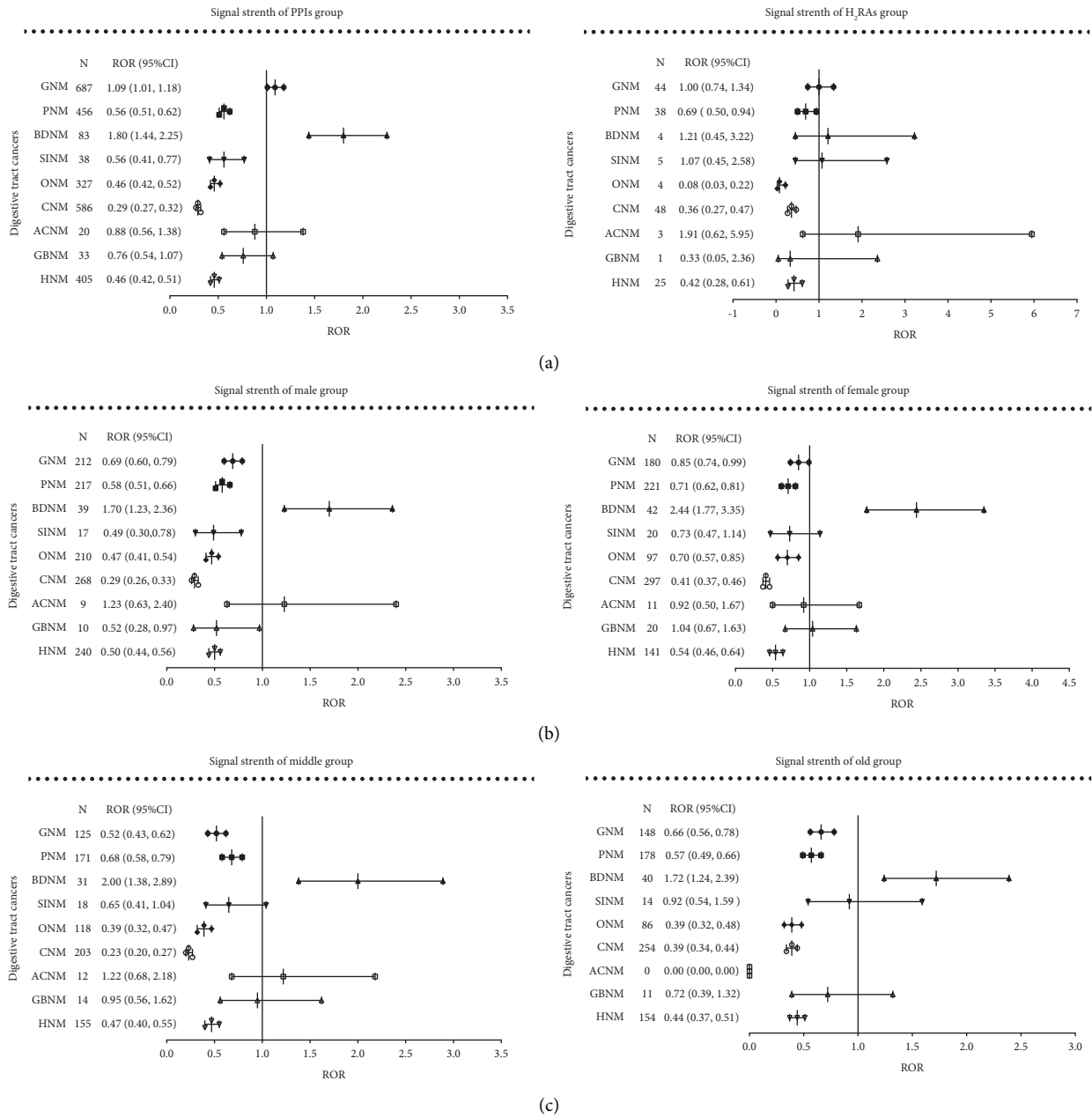
Figure 2: Forest plot of signal detections for PPIs and digestive tract cancers with subgroup analysis stratified by gender and age. (a) Signal strength for PPIs and H2RAs correlated with digestive tract cancers. (b) Subset analysis stratified by gender. (c) Subset analysis stratified by age. PPIs, proton pump inhibitors; H2RA, H2-receptor antagonist; GNM, gastric neoplasms malignant; PNM, pancreatic neoplasms malignant; BDNM, bile duct neoplasms malignant; SINM, small intestinal neoplasms malignant; ONM, oesophageal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal canal neoplasms malignant; GBNM, gallbladder neoplasms malignant; HNM, hepatic neoplasms malignant; ROR, reporting odds ratio; CI, confidence interval.

rabeprazole, dexlansoprazole, or combinations), we additionally assessed a new disproportionality analysis.

The total number of reports for PPIs correlated with GNM was 678 after the removal of related indications to reduce the "indication bias," most of which belonged to gastric cancer (585, 86.3%) and adenocarcinoma gastric (79, 11.7%). Four statistically significant signals were identified, including adenocarcinoma gastric (ROR: 9.99, 95% CI: 7.67–13.02), gastric cancer recurrent (ROR: 3.25, 95% CI: 1.38–7.65), gastroesophageal cancer (ROR: 3.37, 95% CI: 1.18–9.64), and metastatic gastric cancer (ROR: 4.38, 95% CI: 2.71–7.06) as shown in Figure 4(b). In the further stratification analysis, the signals of adenocarcinoma gastric and metastatic gastric cancer were positive regardless of whether they were correlated with any one PPI molecule (Figure 4(c)) or PPIs assessed together as a drug class, while statistically significant gastric cancer recurrent signals were found only for
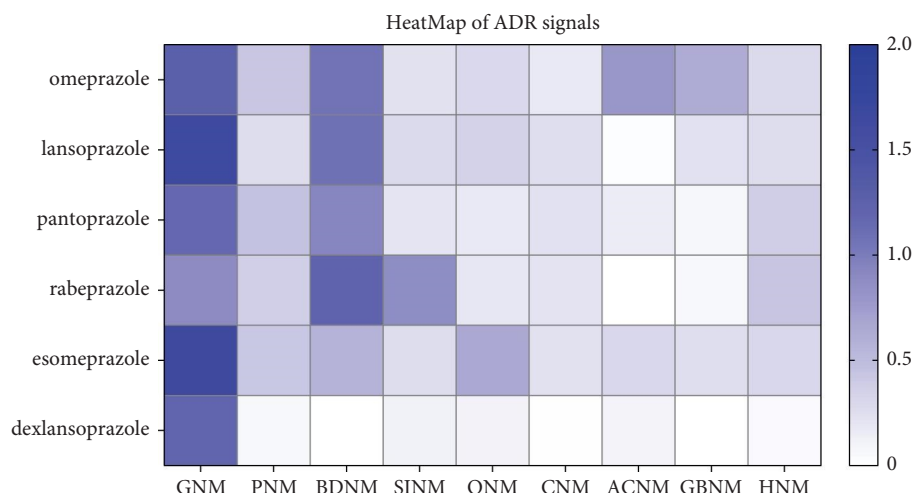
FIGURE 3: Heatmap of signal strength for different PPIs correlated with different digestive tract cancers (ROR lower bound of 95% CI). PPIs, proton pump inhibitors; GNM, gastric neoplasms malignant; PNM, pancreatic neoplasms malignant; BDNM, bile duct neoplasms malignant; SINM, small intestinal neoplasms malignant; ONM, oesophageal neoplasms malignant; CNM, colorectal neoplasms malignant; ACNM, anal canal neoplasms malignant; GBNM, gallbladder neoplasms malignant; HNM, hepatic neoplasms malignant; ROR, reporting odds ratio; CI, confidence interval.

esomeprazole (ROR: 7.04, 95% CI: 2.53–19.59) and omeprazole (ROR: 6.50, 95% CI: 2.56–16.41), with lower case numbers.

The disproportionality analysis between PPIs and gastric cancer revealed interesting results. Cases correlated with GNM were mainly from gastric cancer, but the ROR lower bound of the 95% CI of gastric cancer was detected to be not more than but close to 1 (ROR: 1.07, 95% CI: 0.98–1.16). Surprisingly, when different PPIs were analysed as a single agent, all drugs obtained positive signals except rabeprazole (Figure 4(c) and Supplementary Table 2). Further investigation is needed to prove this possibility instead of simply explaining the lack of gastric cancer risk in patients treated with rabeprazole.

3.3. Correlation between PPI Use and BDNM. Recently, more attention has been given to the risk of biliary tract cancer in persons treated with PPIs, largely due to a nationwide clinical study conducted in Sweden [31]. Therefore, the total number of reports for PPIs correlated with BDNM was low, with only 33 cases after indications were removed. However, the results of the disproportionality analysis between PPIs and BDNM were significant and are presented in Figure 5 and Supplementary Table 3. Overall, based on the criteria for the data mining algorithm, we found statistically significant RORs of assessed AEs for bile duct cancer (ROR: 1.63, 95% CI: 1.18–2.25) and cholangiocarcinoma (ROR: 2.52, 95% CI: 1.82–3.50). Further stratified analysis was conducted, which provided a possibility for a correlation between bile duct cancer and lansoprazole (ROR: 2.14, 95% CI: 1.18–3.88) as well as rabeprazole (ROR: 3.47, 95% CI: 1.30–9.28). In addition, we found statistically significant cholangiocarcinoma signals for the following agents: omeprazole (ROR: 2.32, 95% CI: 1.41–3.83) and pantoprazole (ROR: 2.19, 95% CI: 1.17–4.10). However, these significant results

were unlikely due to the small number of reported cases, which only provided important clues for subsequent studies.

Bile duct cancer is also known as cholangiocarcinoma [32], but bile duct cancer and cholangiocarcinoma are distinguished in MedDRA. We combined bile duct cancer and cholangiocarcinoma as a group for analysis. The results (Supplementary Table 4) showed a total of 80 cases identified corresponding to this new group, and the signals detected with the PT combination (ROR: 2.00, 95% CI: 1.59–2.51) were positive. We also identified sex differences between PPI use and the new group, and the correlation was stronger in females (ROR: 2.63, 95% CI: 1.89–3.66). The data showed that dexlansoprazole listed much later showed no signals for the few data reported, and the signal of esomeprazole did not reach statistical significance, while the other four PPIs did show statistically significant signals, as noted in Supplementary Table 4.

4. Discussion

Ongoing postmarketing surveillance is essential due to the following limitations of clinical trials: population type, group size, duration, and indications. The longer-term safety of drugs and occurrence of rare adverse effects are to a large part evaluated using postmarketing surveillance data, which increases the value of spontaneous reporting systems such as the FAERS to some extent. Therefore, the FAERS database has been widely used to identify passive pharmacovigilance risk signals in a real-world clinical setting.

PPIs, one of the most commonly prescribed drugs worldwide, have been recognized as a relatively safe drug based on the findings of clinical trials. However, with the increasing use of PPIs, more and more novel or even severe PPIs-related ADRs have been reported, especially after long-term and high-dose treatment [27, 33]. The content of the ADR part in drug instructions should be revised according
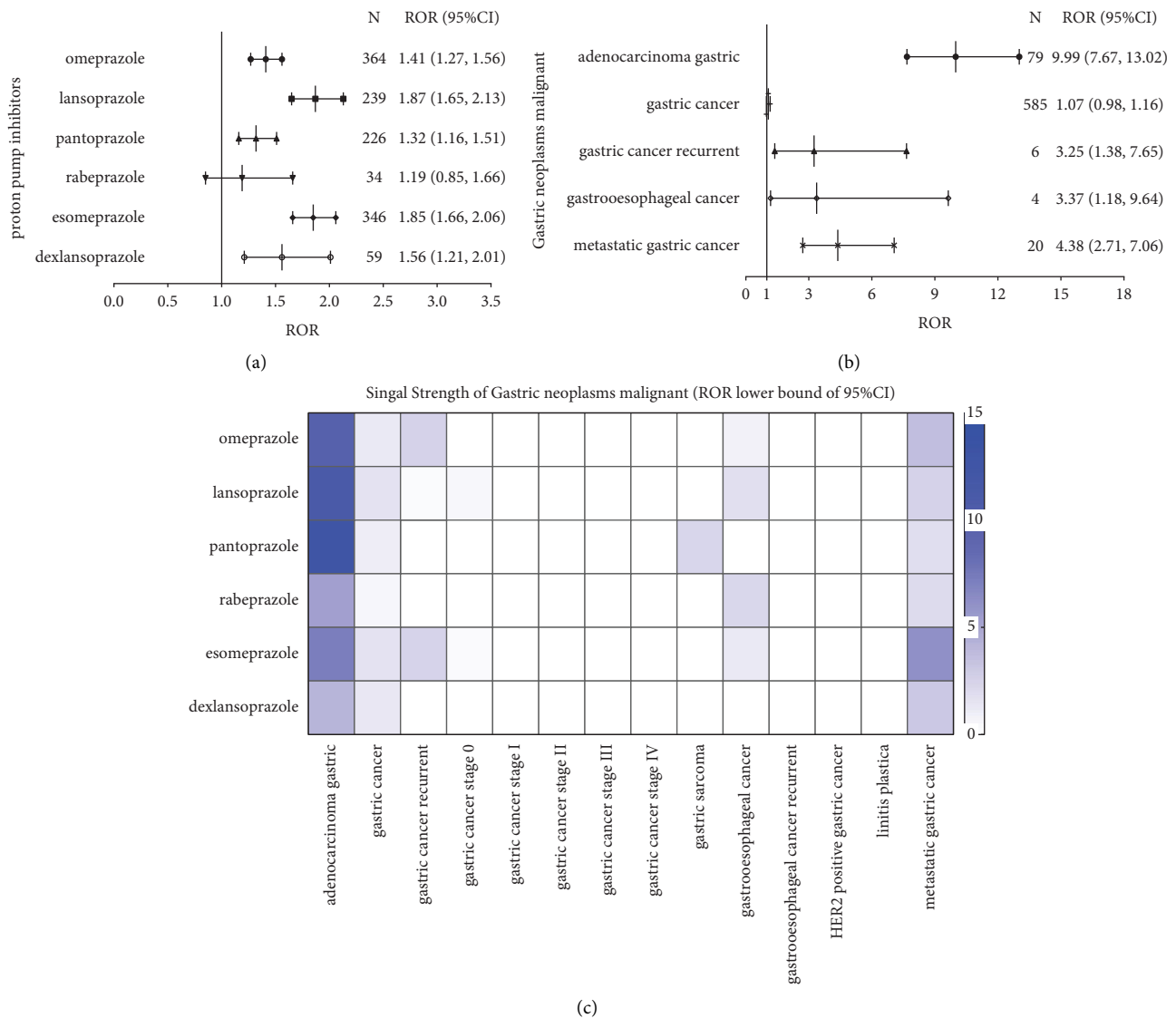
(a)

(b)

(c)

FIGURE 4: Signal strength for different PPIs correlated with GNM at the PTs level. (a) Forest plot of signal detections for different PPIs and GNM. (b) Forest plot of signal detections for PPIs as a whole and PTs subordinated to the HLT "GNM" after removing parts of PTs for the low number of reported cases. (c) Heatmap of signal strength for different PPIs correlated with PTs subordinated to the HLT "GNM" (ROR lower bound of 95% CI). PPIs, proton pump inhibitors; GNM, gastric neoplasms malignant; PTs, preferred terms; HLT, high-level term; ROR, reporting odds ratio; CI, confidence interval.

to the announcement of the National Medical Products Administration of China on February 24, 2022, and was requested additional warning on the risk of severe ADRs due to PPI therapy, such as difficile-associated diarrhea, hypomagnesemia, and fractures. Most surprising is that PPIs as first-line drugs for treating acid-related gastric diseases may induce or be correlated with DTCs [12]. The inconsistent results obtained from emerging clinical trials may initiate more discussion on the correlations between PPI use and DTC risk.

Based on a large-scale ADR dataset, the correlations between PPIs and the risk for fracture [34], dementia [35], hepatotoxicity [36], subacute cutaneous lupus erythematosus [37], kidney injury, and chronic kidney disease [38] were investigated to provide valuable information on potential ADRs.

Therefore, this study was the first to evaluate the correlations between PPI use and DTC risk using the unique resources of FAERS. Using the data mining method, statistically significant signals between PPIs and nine HLT categories of DTCs classed by MedDRA were detected in this study. Two positive signals for the HLTs "GNM" and "BDNM" were identified and were consistent with prior reports of an increased risk for gastric cancer and bile duct cancer with use of PPIs [27, 31, 39, 40]. In contrast, DTCs were not correlated with the use of H2RAs in our study, which was consistent with the results of the meta-analysis and observational studies in the epidemiology group [26, 27].

This observation can be explained by the possible mechanism by which PPIs have a better acid-inhibitory effect than H2RAs, resulting in inhibiting the secretion of

(a)

(b)

Singal Strength of Bile duct neoplasms malignant (ROR lower bound of 95%CI)
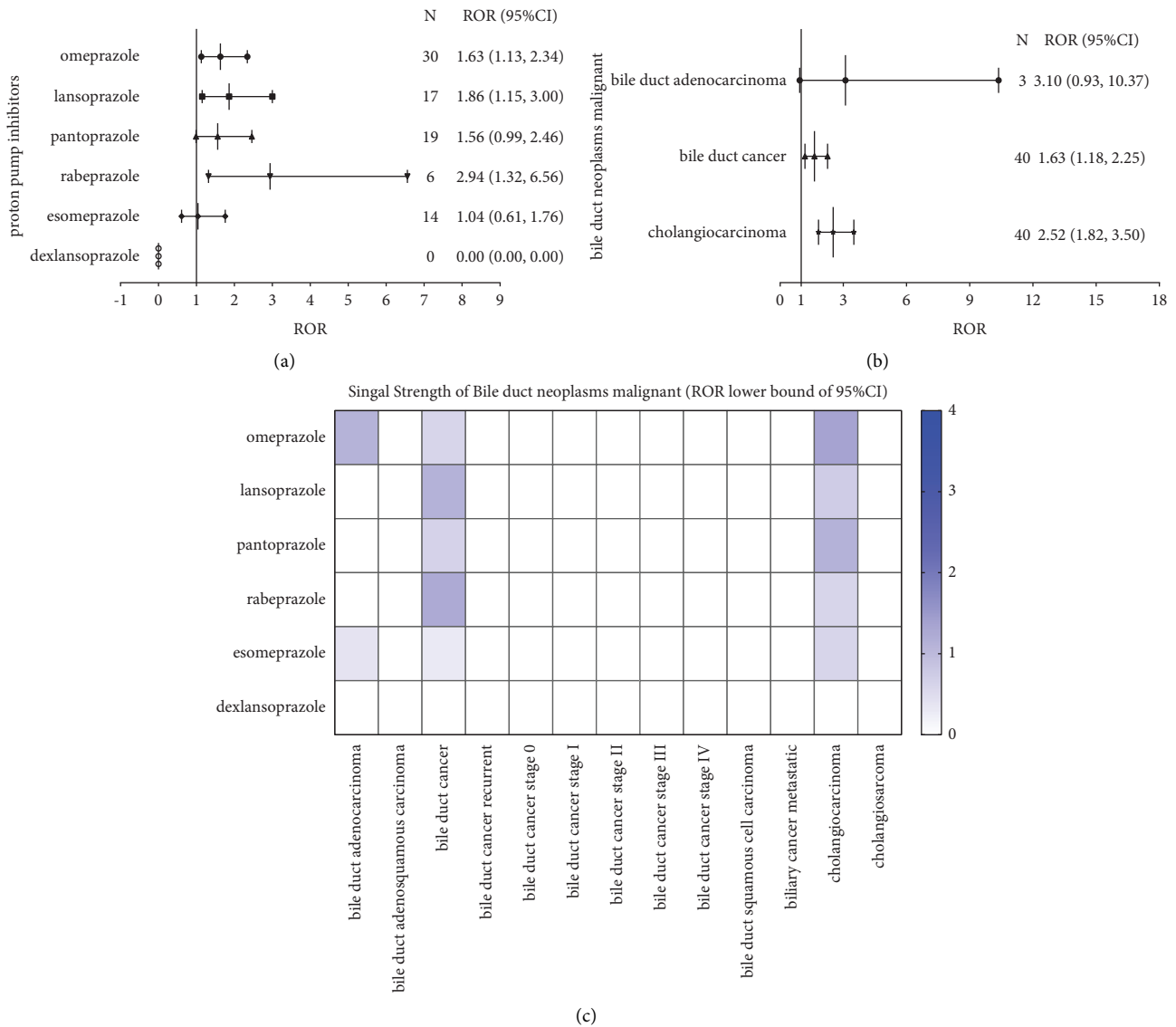
(c)

FIGURE 5: Signal strength of different PPIs correlated with BDNM at the PTs level. (a) Forest plot of signal detections for different PPIs and BDNM. (b) Forest plot of signal detections for PPIs as a whole and PTs subordinated to the HLT "BDNM" after removing parts of PTs for the low number of reported cases. (c) Heatmap of signal strength for different PPIs correlated with PTs subordinated to the HLT "BDNM" (ROR lower bound of 95% CI). PPIs, proton pump inhibitors; BDNM, bile duct neoplasms malignant; PTs, preferred terms; HLT, high-level term; ROR, reporting odds ratio; CI, confidence interval.

gastrointestinal hormones and changing the gastrointestinal microbiome [41, 42]. PPIs were given to inhibit gastric acid secretion by suppressing the parietal cell proton pump and thus induce elevated levels of gastrin as a negative feedback regulation to the raised gastric pH [43]. Gastrin, a peptide hormone produced by G-cells, may cause enterochromaffin-like cell hyperplasia and induce the proliferation of pancreatic, gastric, and colonic epithelial cells, which are correlated with gastrointestinal carcinogenesis [44–46]. Furthermore, an elevated gastric pH will also alter the oral, gastric, duodenum, and gut microbiome [47–49], and alterations in the microbiome can lead to digestive cancer through upregulated cell proliferative signalling pathways and mediated inflammation because of modulation of immune responses and carcinogenic metabolites [50].

When analyses were stratified by age and sex, GNM showed no signals, most likely due to large proportions of missing variable values. This is an inevitable limitation of the spontaneous reporting mechanism of the FAERS database. We also screened the signals of each PPI, indicating no significant signal between rabeprazole and GNM. Lansoprazole and esomeprazole (ROR lower bound of 95% CI: 1.65–1.66) showed stronger signals than omeprazole, pantoprazole, and dexlansoprazole (ROR lower bound of 95% CI: 1.16–1.27), partly differing from the various degrees of risk for gastric cancer reported in one population-based cohort study from England: lansoprazole > omeprazole ≈ rabeprazole > esomeprazole > pantoprazole [27]. Combining this literature and our study, there may be slightly different risks of gastric cancer using different PPIs, while

the highest risk of lansoprazole still needs to be validated further to draw a reliable conclusion after considering the limits of the current analysis.

Adenocarcinoma accounts for over 95% of gastric malignancies, and gastric cancer generally refers to gastric adenocarcinoma [51]. We performed separate analyses for PTs subordinate to the HLT "GNM." There was no doubt that ADR cases correlated with gastric adenocarcinoma showed a statistically significant signal under the HLT "GNM," which is consistent with the findings in the literature that the risk of gastric adenocarcinoma was similar to that of gastric cancer of any type [52]. In the single signal analysis, each kind of PPI showed high ROR values, suggesting that further research on these ADR-related disease signals may be worthwhile. In contrast, the positive signals of gastroesophageal cancer and gastric cancer recurrent were not analysed due to the small data volume, which easily led to a false-positive result.

Two notable findings were observed for the detected signals for the HLT "BDNM" and its stratification analyses. One was that a sex-based difference was observed in this correlation between PPIs and bile duct cancer. There was only one study involving bile duct cancer risk, in which no sex-specific differences were observed. Previous work proved that increased levels of estrogen may play a role in the etiology of biliary tract cancers by stimulating the proliferation of cholangiocytes and decreasing biliary motility [53, 54], while the potential impact of longer-term PPIs use can also affect biliary motility and reduce acid output, thereby increasing the risk of infection and inflammation in the biliary tract [55]. Therefore, sex hormones and PPIs may both be predisposing factors with a synergistic effect on cholangiocarcinogenesis.

The other was the deficiencies in some MedDRA term definitions. Bile duct cancer and cholangiocarcinoma should not be set as two PTs in MedDRA. We combined bile duct cancer and cholangiocarcinoma as a group for analysis, and there is no doubt that the signal was statistically significant between this new PT combination and PPI use (ROR: 2.00, 95% CI: 1.59–2.51), and this correlation was stronger among female patients (ROR: 2.63, 95% CI: 1.89–3.66). Therefore, the results between the new PT combination and PPI use were consistent with prior results that there may be an increased risk for BDNM with PPI use in females, which were worth exploring further.

Although the use of PPIs was reported to be correlated with the subsequent risk of oesophageal cancer, colorectal cancer, pancreatic cancer, and liver cancer [15, 26, 33, 56], the correlations were not confirmed in our study. This finding does not preclude the possible correlations because results obtained from the FAERS should be interpreted with caution for the limitations of the FAERS database.

First, the FAERS database is a passive surveillance system and drug-ADR correlations may be substantially mislabelled, overreported, or underreported [57]. In addition, the large proportions of missing variable values call into question the completeness and accuracy of the data, namely, the overall quality. For example, a large number of FAERS reports of GNM were missing information on patient age

and sex, resulting in the blurring of group differences. Second, due to the absence of total exposed numbers and the presence of confounders, the analysis results from the FAERS database had inevitable and unquantifiable bias and were difficult to interpret [57]. Therefore, a causal relationship between one drug and one ADR cannot be confirmed based on the FAERS data alone, as information bias may occur. Moreover, information were not analysed in this study, such as dose and route of administration, clinical course, concomitant medications, and the combined disorder, because the data presented by OpenVigil do not allow this to be examined further.

Despite these limitations, the ROR values are reliable and credible, and signal strength can partly reflect the extent of the correlation between drugs and specific ADRs from a statistical standpoint. We believe that several potential correlations generated by our extensive analyses from the large database are valuable and can provide several important clues for future in-depth clinical research. Future research could pay more attention to differences among various types of PPIs, rather than just focusing on the dose and course. By considering too few related studies, PPIs-related BDNM merit attention for its relatively strong warning signals, especially epidemiological studies based on a wider study population and the underlying pathogenic mechanisms.

5. Conclusions

This is the first study to assess the correlations between PPI use and DTC risk using the unique resources of FAERS. Through analysis of passive pharmacovigilance data, we found a statistically significant correlation of PPIs with GNM and BDNM risks. The risk was higher in the female group than in the male group for BDNM. Esomeprazole and rabeprazole showed the greatest risk for GNM and BDNM, respectively. The findings of the present study may provide important clues for further clinical research.

Data Availability

The data supporting the findings of this study were derived from the following resources available in the public domain: https://openvigil.sourceforge.net/.

Disclosure

Sheng-ying Gu and Shi-dan Yu are the co-first authors. A preprint has previously been published [58].

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Guo-rong Fan designed the study and supervised the work. Sheng-ying Gu and Shi-dan Yu collected the data, analysed the data, and drafted the manuscript. Shuo-wen Wang,

Supplementary Materials

Supplementary 1: supplementary Table 1 describes the signal strength for PPIs at the HLTs level. Supplementary 2: supplementary Table 2 describes the signal strength for PPIs correlated with GNM at the HLT and PTs level. Supplementary 3: supplementary Table 3 describes the signal strength for PPIs correlated with BDNM at the HLT and PTs level. Supplementary 4: supplementary Table 4 describes the signal strength for PPIs correlated with bile duct cancer and cholangiocarcinoma in combination at the PT level. (*Supplementary Materials*)

References

[1] J. Mossner, "The indications, applications, and risks of proton pump inhibitors," *Deutsches Ärzteblatt International*, vol. 113, no. 27-28, pp. 477–483, 2016.

[2] M. F. Vaezi, Y. X. Yang, and C. W. Howden, "Complications of proton pump inhibitor therapy," *Gastroenterology*, vol. 153, no. 1, pp. 35–48, 2017.

[3] Y. Kinoshita, N. Ishimura, and S. Ishihara, "Advantages and disadvantages of long-term proton pump inhibitor use," *Journal of Neurogastroenterology and Motility*, vol. 24, no. 2, pp. 182–196, 2018.

[4] Y. J. Shao, T. S. Chan, K. Tsai, and S. Y. Wu, "Association between proton pump inhibitors and the risk of hepatocellular carcinoma," *Alimentary Pharmacology & Therapeutics*, vol. 48, no. 4, pp. 460–468, 2018.

[5] T. Sasaki, S. Mori, S. Kishi et al., "Effect of proton pump inhibitors on colorectal cancer," *International Journal of Molecular Sciences*, vol. 21, no. 11, 2020.

[6] S. W. Lai, "Proton pump inhibitors and the risk of pancreatic cancer," *Journal of Gastroenterology*, vol. 56, no. 3, pp. 293-294, 2021.

[7] R. Fossmark, L. Sagatun, I. S. Nordrum, A. K. Sandvik, and H. L. Waldum, "Hypergastrinemia is associated with adenocarcinomas in the gastric corpus and shorter patient survival," *Acta Pathologica, Microbiologica et Immunologica Scandinavica*, vol. 123, no. 6, pp. 509–514, 2015.

[8] R. Berni Canani and G. Terrin, "Gastric acidity inhibitors and the risk of intestinal infections," *Current Opinion in Gastroenterology*, vol. 26, no. 1, pp. 31–35, 2010.

[9] C. Llorente and B. Schnabl, "The gut microbiota and liver disease," *Cellular and Molecular Gastroenterology and Hepatology*, vol. 1, no. 3, pp. 275–284, 2015.

[10] Y. C. Peng, C. L. Lin, W. Y. Hsu et al., "Association between cholangiocarcinoma and proton pump inhibitors use: a nested case-control study," *Frontiers in Pharmacology*, vol. 9, p. 718, 2018.

[11] S. W. Lai, H. C. Lai, C. L. Lin, and K. F. Liao, "Proton pump inhibitors and risk of gastric cancer in a case-control study," *Gut*, vol. 68, no. 4, pp. 765–767, 2019.

[12] R. Zeng, Y. Cheng, D. Luo et al., "Comprehensive analysis of proton pump inhibitors and risk of digestive tract cancers," *European Journal of Cancer*, vol. 156, pp. 190–201, 2021.

[13] J. Xiong, Y. Wang, G. Chen, and L. Jin, "Proton pump inhibitors and the risk of gallbladder cancer: a hospital-based case-control study," *Gut*, vol. 69, no. 12, pp. 2265–2267, 2020.

[14] D. Abrahami, E. G. McDonald, M. E. Schnitzer, A. N. Barkun, S. Suissa, and L. Azoulay, "Proton pump inhibitors and risk of colorectal cancer," *Gut*, vol. 71, no. 1, pp. 111–118, 2022.

[15] N. Brusselaers, L. Engstrand, and J. Lagergren, "Maintenance proton pump inhibition therapy and risk of oesophageal cancer," *Cancer Epidemiology*, vol. 53, pp. 172–177, 2018.

[16] P. Moayyedi, S. J. O. Veldhuyzen van Zanten, L. Hookey, D. Armstrong, N. Jones, and G. I. Leontiadis, "Proton pump inhibitors and gastric cancer: association is not causation," *Gut*, vol. 68, no. 8, pp. 1529.2-1530, 2019.

[17] A. Babic, X. Zhang, V. Morales-Oyarvide et al., "Acid-suppressive medications and risk of colorectal cancer: results from three large prospective cohort studies," *British Journal of Cancer*, vol. 123, no. 5, pp. 844–851, 2020.

[18] J. Huang, L. Meng, B. Yang, S. Sun, Z. Luo, and H. Chen, "Safety profile of epidermal growth factor receptor tyrosine kinase inhibitors: a disproportionality analysis of FDA adverse event reporting system," *Scientific Reports*, vol. 10, no. 1, p. 4803, 2020.

[19] C. Daluwatte, P. Schotland, D. G. Strauss, K. K. Burkhart, and R. Racz, "Predicting potential adverse events using safety data from marketed drugs," *BMC Bioinformatics*, vol. 21, no. 1, p. 163, 2020.

[20] Y. Zhou, M. Chen, L. Liu, and Z. Chen, "Difference in gastrointestinal risk associated with use of GLP-1 receptor agonists: a real-world pharmacovigilance study," *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 15, pp. 155–163, 2022.

[21] K. E. Evoy, C. Teng, V. G. Encarnacion et al., "Comparison of quetiapine abuse and misuse reports to the FDA adverse event reporting system with other second-generation antipsychotics," *Substance Abuse: Research and Treatment*, vol. 13, Article ID 117822181984420, 2019.

[22] C. Zheng and R. Xu, "The Alzheimer's comorbidity phenome: mining from a large patient database and phenome-driven genetics prediction," *JAMIA Open*, vol. 2, no. 1, pp. 131–138, 2019.

[23] R. Bohm, C. Bulin, V. Waetzig, I. Cascorbi, H. J. Klein, and T. Herdegen, "Pharmacovigilance-based drug repurposing: the search for inverse signals via OpenVigil identifies putative drugs against viral respiratory infections," *British Journal of Clinical Pharmacology*, vol. 87, no. 11, pp. 4421–4431, 2021.

[24] X. F. Jiao, H. L. Li, X. Y. Jiao et al., "Ovary and uterus related adverse events associated with statin use: an analysis of the FDA Adverse Event Reporting System," *Scientific Reports*, vol. 10, no. 1, Article ID 11955, 2020.

[25] R. Bohm, L. von Hehn, T. Herdegen et al., "OpenVigil FDA-inspection of U.S. American adverse drug events pharmacovigilance data and novel clinical applications," *PLoS One*, vol. 11, no. 6, Article ID 157753, 2016.

[26] K. T. Tran, U. C. McMenamin, B. Hicks et al., "Proton pump inhibitor and histamine-2 receptor antagonist use and risk of liver cancer in two population-based studies," *Alimentary Pharmacology & Therapeutics*, vol. 48, no. 1, pp. 55–64, 2018.

[27] D. Abrahami, E. G. McDonald, M. E. Schnitzer, A. N. Barkun, S. Suissa, and L. Azoulay, "Proton pump inhibitors and risk of gastric cancer: population-based cohort study," *Gut*, vol. 71, no. 1, pp. 16–24, 2022.

[28] O. Caster, Y. Aoki, L. M. Gattepaille, and B. Grundmark, "Disproportionality analysis for pharmacovigilance signal detection in small databases or subsets: recommendations for limiting false-positive associations," *Drug Safety*, vol. 43, no. 5, pp. 479–487, 2020.

[29] A. Bate, A. Pariente, M. Hauben, and B. Bernard, "Quantitative Signal Detection and Analysis in Pharmacovigilance," *Mann's Pharmacovigilance*, John Wiley & Sons, Hoboken, NJ, USA, 2014.

[30] A. Bate and S. J. Evans, "Quantitative signal detection using spontaneous ADR reporting," *Pharmacoepidemiology and Drug Safety*, vol. 18, no. 6, pp. 427–436, 2009.

[31] H. Kamal, O. Sadr-Azodi, L. Engstrand, and N. Brusselaers, "Association between proton pump inhibitor use and biliary tract cancer risk: a Swedish population-based cohort study," *Hepatology*, vol. 74, no. 4, pp. 2021–2031, 2021.

[32] E. M. Kim, Y. M. Bae, M. H. Choi, and S. T. Hong, "Connexin 43 plays an important role in the transformation of cholangiocytes with Clonochis sinensis excretory-secretory protein and N-nitrosodimethylamine," *PLoS Neglected Tropical Diseases*, vol. 13, no. 4, p. 6843, 2019.

[33] W. Y. Lei, J. H. Wang, C. H. Yi et al., "Association between use of proton pump inhibitors and colorectal cancer: a nationwide population-based study," *Clinics and Research in Hepatology and Gastroenterology*, vol. 45, no. 1, Article ID 101397, 2021.

[34] L. Wang, M. Li, Y. Cao et al., "Proton pump inhibitors and the risk for fracture at specific sites: data mining of the FDA adverse event reporting system," *Scientific Reports*, vol. 7, no. 1, p. 5527, 2017.

[35] B. Wu, Q. Hu, F. Tian, F. Wu, Y. Li, and T. Xu, "A pharmacovigilance study of association between proton pump inhibitor and dementia event based on FDA adverse event reporting system data," *Scientific Reports*, vol. 11, no. 1, Article ID 10709, 2021.

[36] Y. Zeng, Y. Dai, Z. Zhou, X. Yu, and D. Shi, "Hepatotoxicity-related adverse effects of proton pump inhibitors: a cross-sectional study of signal mining and analysis of the FDA adverse event report system database," *Frontiers of Medicine*, vol. 8, Article ID 648164, 2021.

[37] N. Aggarwal, "Drug-Induced subacute cutaneous lupus erythematosus associated with proton pump inhibitors," *Drugs Real World Outcomes*, vol. 3, no. 2, pp. 145–154, 2016.

[38] B. Wu, D. Li, T. Xu, M. Luo, Z. He, and Y. Li, "Proton pump inhibitors associated acute kidney injury and chronic kidney disease: data mining of US FDA adverse event reporting system," *Scientific Reports*, vol. 11, no. 1, p. 3690, 2021.

[39] D. Segna, N. Brusselaers, D. Glaus, N. Krupka, and B. Misselwitz, "Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis," *Therap Adv Gastroenterol*, vol. 14, Article ID 175628482110514, 2021.

[40] J. Xiong, Y. Wang, W. Xu et al., "Proton pump inhibitors and odds of cholangiocarcinoma: a retrospective case-control study," *Liver International*, vol. 40, no. 11, pp. 2848–2857, 2020.

[41] L. Lundell, M. Vieth, F. Gibson, P. Nagy, and P. J. Kahrilas, "Systematic review: the effects of long-term proton pump inhibitor use on serum gastrin levels and gastric histology," *Alimentary Pharmacology & Therapeutics*, vol. 42, no. 6, pp. 649–663, 2015.

[42] F. Imhann, M. J. Bonder, A. Vich Vila et al., "Proton pump inhibitors affect the gut microbiome," *Gut*, vol. 65, no. 5, pp. 740–748, 2016.

[43] M. L. Schubert, "Adverse effects of proton pump inhibitors: fact or fake news?" *Current Opinion in Gastroenterology*, vol. 34, no. 6, pp. 451–457, 2018.

[44] A. Varro, S. Kenny, E. Hemers et al., "Increased gastric expression of MMP-7 in hypergastrinemia and significance for epithelial-mesenchymal signaling," *American Journal of Physiology- Gastrointestinal and Liver Physiology*, vol. 292, no. 4, pp. G1133–G1140, 2007.

[45] Y. X. Yang, S. Hennessy, K. Propert, W. T. Hwang, A. Sedarat, and J. D. Lewis, "Chronic proton pump inhibitor therapy and the risk of colorectal cancer," *Gastroenterology*, vol. 133, no. 3, pp. 748–754, 2007.

[46] Y. Ko, J. Tang, S. Sanagapalli, B. S. Kim, and R. W. Leong, "Safety of proton pump inhibitors and risk of gastric cancers: review of literature and pathophysiological mechanisms," *Expert Opinion on Drug Safety*, vol. 15, no. 1, pp. 53–63, 2016.

[47] N. Kawar, S. G. Park, J. L. Schwartz et al., "Salivary microbiome with gastroesophageal reflux disease and treatment," *Scientific Reports*, vol. 11, no. 1, p. 188, 2021.

[48] J. H. Lim, J. Shin, and J. S. Park, "Effect of a proton pump inhibitor on the duodenum microbiome of gastric ulcer patients," *Life*, vol. 12, no. 10, p. 1505, 2022.

[49] J. H. Oh, D. Kang, W. Kang, E. Guallar, J. Cho, and Y. W. Min, "Proton pump inhibitor use increases pyogenic liver abscess risk: a nationwide cohort study," *J Neurogastroenterol Motil*, vol. 27, no. 4, pp. 555–564, 2021.

[50] S. Kannan, J. Vimal, and I. Himal, "Role of microbial dysbiosis in carcinogenesis & cancer therapies," *Indian Journal of Medical Research*, vol. 152, no. 6, pp. 553–561, 2020.

[51] S. Ai, C. Li, X. Li et al., "A state-of-the-art review for gastric histopathology image analysis approaches and future development," *BioMed Research International*, vol. 2021, Article ID 6671417, 19 pages, 2021.

[52] N. Brusselaers, K. Wahlin, L. Engstrand, and J. Lagergren, "Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden," *BMJ Open*, vol. 7, no. 10, Article ID 17739, 2017.

[53] S. K. Park, G. Andreotti, A. Rashid et al., "Polymorphisms of estrogen receptors and risk of biliary tract cancers and gallstones: a population-based study in Shanghai, China," *Carcinogenesis*, vol. 31, no. 5, pp. 842–846, 2010.

[54] S. K. Park, G. Andreotti, L. C. Sakoda et al., "Variants in hormone-related genes and the risk of biliary tract cancers and stones: a population-based study in China," *Carcinogenesis*, vol. 30, no. 4, pp. 606–614, 2009.

[55] K. Shindo, M. Machida, M. Fukumura, K. Koide, and R. Yamazaki, "Omeprazole induces altered bile acid metabolism," *Gut*, vol. 42, no. 2, pp. 266–271, 1998.

[56] I. C. Hwang, J. Chang, and S. M. Park, "Association between proton pump inhibitor use and the risk of pancreatic cancer: a Korean nationwide cohort study," *PLoS One*, vol. 13, no. 9, Article ID 203918, 2018.

[57] Y. Kan, J. Nagai, and Y. Uesawa, "Evaluation of antibiotic-induced taste and smell disorders using the FDA adverse event reporting system database," *Scientific Reports*, vol. 11, no. 1, p. 9625, 2021.

[58] G. R. Fan, S. Y. Gu, S. D. Yu et al., "Digestive tract cancer related adverse events associated with proton pump inhibitors use: a pharmacovigilance study of the FDA adverse event reporting system," 2023, https://d197for5662m48.cloudfront.net/documents/publicationstatus/126545/preprint_pdf/b6edc293a3f3b4f08f4f41e8006eb566.pdf.