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Adverse reactions of immune checkpoint inhibitors combined with Proton pump inhibitors: a pharmacovigilance analysis of drug-drug interactions

Xiayang Ren[1], Lu Li[1], Yiran Chen[2], Xiangli Cui[3], Rui Wan[4*] and Yanfeng Wang[5*]

Abstract

Background Combining immune checkpoint and proton pump inhibitors is widely used in cancer treatment. However, the drug-drug interactions of these substances are currently unknown. This study aimed to explore drug-drug interactions associated with concomitant immune checkpoint and proton pump inhibitors.

Methods Data were obtained from the US Food and Drug Administration Adverse Event Reporting System from 2014 to 2023. Disproportionality analysis was used for data mining by calculating the reporting odds ratios (RORs) with 95% confidence intervals (95%CIs). The adjusted RORs (RORadj) were then analysed using logistic regression analysis, considering age, sex, and reporting year. Drug-drug interactions occur when a combination treatment enhances the frequency of an event. Further confirmation of the robustness of the findings was achieved using additive and multiplicative models, which are the two statistical methodologies for signal detection of DDIs using spontaneous reporting system.

Results The total number of reports on immune checkpoint combined with proton pump inhibitors was 4,276. Median patient age was 66 years (interquartile range [IQR]: 60–74 years). Significant interaction signals were observed for congenital, familial and genetic disorders (RORadj = 2.66, 95%CI, 1.38–5.14, additive models = 0.7322, multiplicative models = 3.5142), hepatobiliary disorders (RORcrude = 6.64, 95%CI, 5.82–7.58, RORadj = 7.10, 95%CI, 6.16–8.18, additive models = 2.0525, multiplicative models = 1.1622), metabolism and nutrition disorders (RORcrude = 3.27, 95%CI, 2.90–3.69, RORadj = 2.66, 95%CI, 2.30–3.08, additive models = 0.6194), and skin and subcutaneous tissue disorders (RORcrude = 1.41, 95%CI, 1.26–1.58, RORadj = 1.53, 95%CI, 1.34–1.75, additive models = 0.6927, multiplicative models = 5.3599). Subset data analysis showed that programmed death-1 combined with proton pump inhibitors was associated with congenital, familial, and genetic disorders; hepatobiliary disorders; and skin and subcutaneous tissue disorders. Programmed death ligand-1 combined with proton pump inhibitors was associated with adverse reactions

*Correspondence:
Rui Wan
wanrui243@163.com
Yanfeng Wang
wangyf@cicams.ac.cn

Full list of author information is available at the end of the article

of metabolism and nutrition disorders. Cytotoxic T-lymphocyte antigen-4 combined with proton pump inhibitors was associated with congenital, familial, and genetic disorders, and skin and subcutaneous tissue disorders.

Conclusions Based on real-world data, four Standardized MedDRA Query System Organ Class toxicities were identified as drug-drug interactions associated with combining immune checkpoint and proton pump inhibitors. Clinicians should be cautious when administering these drugs concomitantly. Preclinical trials and robust clinical studies are required to explore the mechanisms and relationships underlying interactions, thus improving understanding of drug-drug interactions associated with this combination therapy.

Keywords Immune checkpoint inhibitors, Proton pump inhibitors, Drug-drug interaction, Pharmacovigilance, FDA (Food and Drug Administration) adverse event reporting System (FAERS)

Background

In recent years, immune checkpoint inhibitors (ICIs), including programmed death-1 (PD-1) inhibitors, programmed death ligand-1 (PD-L1) inhibitors and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, have revolutionised the strategic therapies for a wide variety of tumours [1]. Multiple clinical trials have demonstrated the effectiveness of ICIs in treating different cancers, and immunotherapy is positively correlated with the rate of complete response to treatment [2–4]. ICI resistance is influenced by cancer and T cell genomics, body composition, tumour microenvironment, and processes that affect the gut microbiota (gut dysbiosis) [5, 6]. Due to the fact that 70–80% of the human immune system is distributed in or around the intestine, the intestinal microbiota is associated with a weakened immune system and immune-mediated toxicity [7]. The enrichment in *Faecalibacterium* was related to colitis treated with ipilimumab in melanoma patients. Low *Bacteroidetes/Firmicutes* ratios could lead to acute pancreatitis related to ICI [8].

Proton pump inhibitors (PPIs), which are often used to treat gastroesophageal reflux and peptic ulcer diseases, are also commonly used as supplemental drugs in cancer treatment [9, 10]. PPIs can alter the gut microbiomeand impact the effectiveness of ICIs [11–13]. Gut microbiota alpha diversity is reduced, and *Actinomycetales*, *Micrococcaceae*, and *Streptococcaceae* are relatively abundant in the gut of patients undergoing PPI treatment compared with those in patients who are not receiving PPIs [14–16]. The diversities of *Bifidobacterium* and *Ruminococcaceae*, which are crucial for immunity, may also be impacted [12, 13, 17]. According to a recent meta-analysis, PPI use has a negative impact on overall and progression free survival in patients with advanced cancer undergoing ICI treatment [18].

Polypharmacy, present in 77.1%, is a common problem in older cancer patients treated with ICIs, with a median of 6 regular medications. Inappropriate prescription practices were observed in patients treated with ICI [19]. The concurrent use of multiple drugs can cause drug-drug interactions (DDIs), resulting in drug toxicities, suboptimal therapy, and treatment failure, all of which negatively impact the full benefit of treatment [20]. DDIs are estimated to cause around 30% of unexpected adverse reactions [21]. The need for enhanced general medical care and attention to enhance medication management in patients treated with ICI is highlighted.The safety profile of ICI has rarely been discussed in published literature [18]. Moreover, the combination of ICIs and PPIs for the treatment of cancer and the potential DDIs remain largely unexplored in research. Moreover, obtaining sufficient information on DDIs from real-world data will enable a better understanding of the general aspects of the concomitant use of ICIs and PPIs.

With increased administration of ICIs and PPIs in patients with cancer, an urgent need arises for oncologists to determine whether ICIs combined with PPIs would result in adverse events associated with DDIs and to carefully consider the necessity of PPIs for patients. Therefore, the aim of this study was to analyse DDIs descriptively and disproportionally to evaluate the potential harmful effects of combining ICIs and PPIs, using the FDA (Food and Drug Administration) Adverse Event Reporting System (FAERS) database. Using big data, we summarised the interaction characteristics, confirmed the intensity and occurrence patterns of adverse reactions, and provided a reference for clinical decision-making.

Methods

Data source

The FAERS database was used for this retrospective pharmacovigilance study [22]. This database is publicly available and comprises adverse event reports from health professionals, patients, and manufacturers worldwide. Data were extracted from the first quarter (Q1) of 2014 (1 January 2014) to the fourth quarter (Q4) of 2023 (31 December 2023).

Procedures

Data were obtained from the REAC (regulatory activity) files according to the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) at the preferred term (PT) level based on all 27 Standardized MedDRA Query

System Organ Class (SOC) [23]. The 27 SOCs are listed in Table S1 in the supplementary material. The DRUG file contains generic name records of all drugs, with the role code as either 'PS' (primary suspect) or 'SS' (secondary suspect). The combined immunotherapy drugs included anti-PD-1 drugs (pembrolizumab, nivolumab, cemiplimab, dostarlimab, prolongolimab, tislelizumab, toripalimab, sintilimab, camrelizumab, penpulimab, zimberelimab, and serplulimab), anti-PDL-1 drugs (atezolizumab, durvalumab, avelumab, envafolimab, and sugemalimab), and anti-CTLA-4 drugs (ipilimumab and tremelimumab). PPIs included omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and dexlansoprazole. To remove duplicate reports, the last FDA_DT (date FDA received Case) was selected when the 'CASE_ID' was identical, and the 'PRIMARY_ID' with the greater value was selected when the CASE_ID and FDA_DT were identical, as directed in the FAERS user instructions [22]. The flowchart for data processing is shown in Fig. 1. The clinical features of patients administered ICIs combined with PPIs were synthesised using descriptive analyses of data collected from the FAERS database.

Data analysis

In spontaneous reporting databases, the detection of possible interactions is based on the demonstration that a suspected adverse event is reported more frequently with a combination of two drugs than when the drugs are administered alone [24–26]. Therefore, the reports were divided into three index groups: (i) reports of patients exposed to ICIs alone, i.e., no concomitant PPIs; (ii) reports of patients exposed to PPIs alone, i.e., no concomitant ICIs; (iii) reports of patients exposed to both ICIs and PPIs at the time of the event. The reference

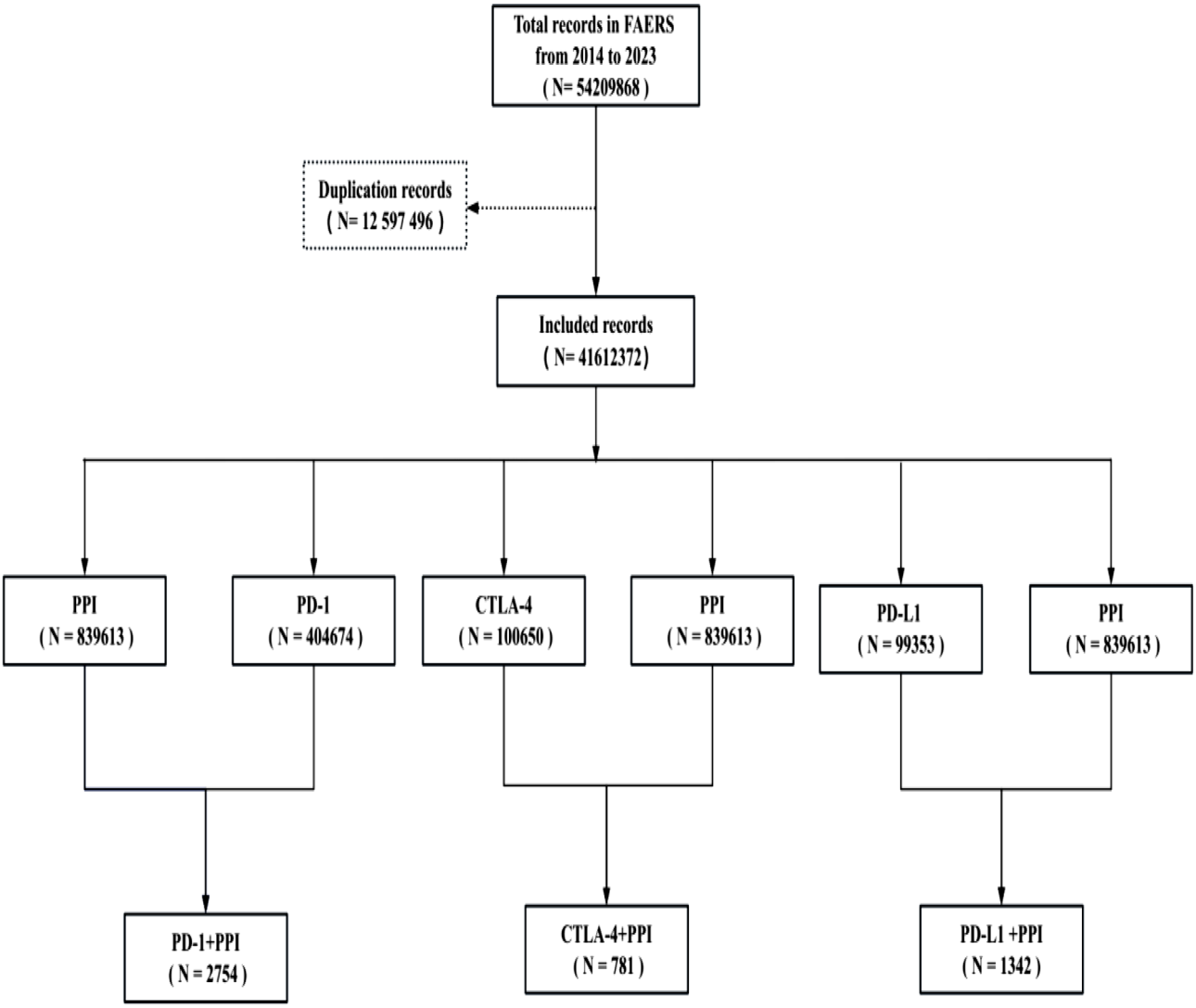

Fig. 1 Flowchart for data processing FAERS, US Food and Drug Administration (FDA) Adverse Event Reporting System; PD-1, programmed death-1; PPI, proton pump inhibitor; PDL-1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4

group comprised patients who were not exposed to ICIs or PPIs.

Disproportionality was calculated using the reporting odds ratio (ROR) with a relevant 95% confidence interval (95% Cl), which was defined as statistically significant when the lower limit of the 95% Cl exceeded 1, with at least three cases of interest reported [27]. In quantitative signal detection, combinations of a drug and a clinical event that are disproportionately highly represented in the database, may represent an important signal based upon a difference from the background frequency. The ROR algorithm is utilized to determine if a drug has a significant relationship with an adverse event or not [28].

To identify potential confounders in the database, crude RORs (RORcrude) were recalculated using unconditional logistic regression analysis based on age, sex, and reporting year [21]. The logistic model was as follows: Log (risk of the event) = $\beta_0+\beta_1$ ICIs$+\beta_2$ PPI$+\beta_3$ ICIs * PPI$+\beta_4$ age$+\beta_5$ sex$+\beta_6$ reporting year. An interaction can be claimed when the combination is linked to an enhanced ROR compared with other index groups [29]. Logistic regression is among the most commonly used multivariate analysis models in epidemiology. Measurements can be made of the association between the occurrence of an event and factors that are susceptible to influence it [30].

To assess the consistency and reliability of drug interactions, we used multiplicative and additive models [21]. The additive model is based on drug-related risks increasing additively, while the multiplicative model is based on drug-related risks increasing synergistically. The analysis provided a measurement of the threshold for detecting DDI signals. In the multiplicative model, the risk associated with a drug is *multiplied* by the background risk, whereas in the additive model, the risk associated with the drug is *added* to the background risk. The risk(drug1*drug2)/((risk(drug1) x risk(drug2))>1 and risk(drug1*drug2) -(risk(drug1)+risk(drug2))>0, respectively, indicates that the multiplicative and additive models generate a drug interaction signal. A positive interaction is indicated if the value (interaction term) reaches beyond 0 or 1 in the additive or multiplicative models [31]. Data management and analyses were performed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA).

Table 1 Characteristics of patients administered ICIs combined with angiogenesis inhibitors from FAERS*

Characteristics	Overall
Total number of cases	1012
Patient's age, years, median (Q1-Q3)	66 (60–74)
<18 years	29 (2.87%)
18–65 years	336 (33.20%)
≥ 65 years	523 (51.68%)
Unknown	124 (12.25%)
Patient's sex [n (%)]	
Male	566 (55.93%)
Female	378 (37.35%)
Unknown	68 (6.72%)
Type of reporter	
Health professional	639 (63.14%)
Non-health professional	64 (6.32%)
Unknown	309 (30.53%)
Outcome	
Hospitalization	425 (42.00%)
Life-threatening	96 (9.49%)
Death	114 (11.26%)
Reported regions	
North America	288 (28.46%)
South America	1 (0.99%)
Europe	518 (51.19%)
Asia	168 (16.60%)
Oceania	8 (7.91%)
Unknown	29 (2.87%)
Reported year	
2014	4 (0.40%)
2015	0 (0.00%)
2016	5 (0.49%)
2017	38 (3.75%)
2018	70 (6.92%)
2019	89 (8.79%)
2020	152 (15.02%)
2021	233 (23.02%)
2022	163 (16.11%)
2023	258 (25.49%)

ICI, immune checkpoint inhibitors; Q, quarter; FAERS, US Food and Drug Administration (FDA) Adverse Event Reporting System

*1 January 2014 to 31 December 2023

Results

Descriptive analysis

From 1 January 2014 to 31 December 2023, a total of 54,209,868 reports were extracted from the FAERS database; 41,612,372 reports were included in the final analysis, of which 4,276 reports on ICIs combined with PPI were identified. The clinical features of the patients are summarised in Table 1. The median patient age was 66 years (interquartile range [IQR], 60–74 years). The proportion of males (55.93%) was higher than that of females (37.35%). The number of reports submitted by health care professionals was relatively high (63.14%). Europe reported the highest adverse drug reactions (51.19%), followed by North America (28.46%), Asia (16.60%), Oceania (7.91%), and South America (0.99%) (Fig. 2A). The number of reports steadily increased over time, from 0.40% in 2014 to 25.49% in 2023 (Fig. 2B).

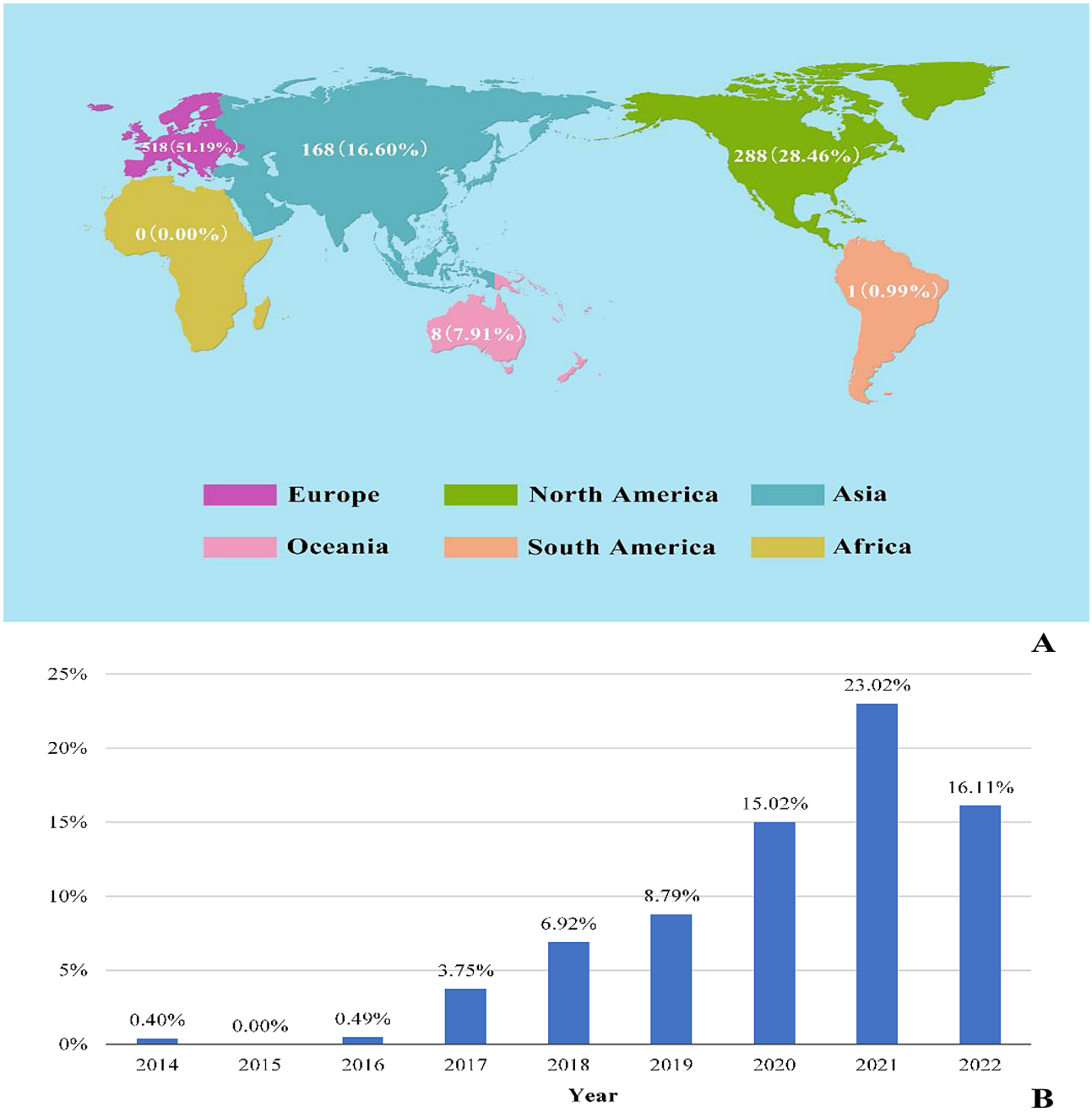

Fig. 2 Concomitant use of immune checkpoint inhibitors and proton pump inhibitors. (**A**) Geographical regions reporting concomitant use of ICIs and PPIs. (**B**) Years of reports of concomitant use of ICIs and PPIs. ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor

Disproportionality analysis

The signal detection results of DDIs with the concomitant use of ICIs and PPIs for all 27 SOCs are shown in Table 2. The crude/adjusted RORs and 95% CIs for all comparisons are presented using the disproportionality method. We estimated the DDIs according to additive/multiplicative models. Positive signals were detected in four SOCs: congenital, familial, and genetic disorders; hepatobiliary disorders; metabolism and nutrition disorders; and skin and subcutaneous tissue disorders (Table 3). For congenital, familial and genetic disorders, the crude/adjusted ROR for the use of PPI alone was 1.00 (95% CI, 0.96–1.05)/1.19 (95% CI, 1.11–1.29), and the crude/adjusted ROR for ICIs alone was 0.29 (95% CI, 0.27–0.32)/0.67 (95% CI, 0.60–0.75). An increase signal for the concomitant use of ICIs and PPIs emerged (RORadj=2.66, 95% CI, 1.38–5.14). The positive interaction signal was supported by additive (0.7322) and multiplicative (3.5142) models. For hepatobiliary disorders, the crude/adjusted ROR for PPIs alone was 1.35

Table 2 Reporting odds ratios and drug interaction approaches for ICIs and PPIs

SOC	Exposure	Cases	Non-cases	RORcrude (95%CI)	RORadj (95%CI)	Additive model	Multiplicative model
Blood and lymphatic system disorders	No ICI, no PPI	629,855	39,584,457	reference	reference	0.0217	0.9573
	PPI, no ICI	14,686	823,405	1.09 (1.08–1.11)	1.06 (1.04–1.09)		
	ICI, no PPI	21,755	534,298	2.44 (2.41–2.48)	2.15 (2.11–2.18)		
	ICI, PPI	176	4100	2.56 (2.20–2.98)	2.23 (1.89–2.64)		
Cardiac disorders	No ICI, no PPI	910,453	39,303,859	reference	reference	-1.2272	0.1.50
	PPI, no ICI	22,189	815,902	1.16 (1.15–1.18)	1.32 (1.30–1.35)		
	ICI, no PPI	15,369	540,684	1.21 (1.19–1.23)	1.15 (1.13–1.17)		
	ICI, PPI	14	4262	0.15 (0.09–0.25)	0.13 (0.07–0.24)		
Congenital, familial and genetic disorders	No ICI, no PPI	110,939	40,103,373	reference	reference	**0.7322**	**3.5142**
	PPI, no ICI	2296	835,795	1.00 (0.96–1.05)	**1.19 (1.11–1.29)**		
	ICI, no PPI	442	555,611	0.29 (0.27–0.32)	**0.67 (0.60–0.75)**		
	ICI, PPI	12	4264	1.03 (0.58–1.81)	**2.66 (1.38–5.14)**		
Ear and labyrinth disorders	No ICI, no PPI	172,466	40,041,846	reference	reference	-0.0327	0.7108
	PPI, no ICI	2931	835,160	0.82 (0.79–0.85)	0.93 (0.89–0.97)		
	ICI, no PPI	1188	554,865	0.50 (0.48–0.53)	0.50 (0.47–0.54)		
	ICI, PPI	5	4271	0.29 (0.12–0.71)	0.27 (0.10–0.73)		
Endocrine disorders	No ICI, no PPI	78,637	40,135,675	reference	reference	-7.0403	0.2352
	PPI, no ICI	4885	833,206	2.40 (2.33–2.47)	2.95 (2.84–3.07)		
	ICI, no PPI	17,490	538,563	12.94 (12.73–13.16)	19.25 (18.86–19.65)		
	ICI, PPI	79	4197	7.30 (5.84–9.12)	10.62 (8.32–13.56)		
Eye disorders	No ICI, no PPI	791,542	39,422,770	reference	reference	-0.1145	0.2758
	PPI, no ICI	10,406	827,685	0.64 (0.63–0.65)	-		
	ICI, no PPI	6230	549,823	0.58 (0.56–0.59)	-		
	ICI, PPI	8	4268	0.10 (0.05–0.20)	-		
Gastrointestinal disorders	No ICI, no PPI	3,272,891	36,941,421	reference	reference	-0.0299	0.9253
	PPI, no ICI	93,797	744,294	1.36 (1.35–1.37)	1.54 (1.53–1.56)		
	ICI, no PPI	58,479	497,574	1.28 (1.27–1.29)	1.43 (1.42–1.45)		
	ICI, PPI	566	3710	1.61 (1.47–1.76)	1.89 (1.72–2.09)		
General disorders and administration site conditions	No ICI, no PPI	7,159,532	33,054,780	reference	reference	0.0277	0.9481
	PPI, no ICI	98,183	739,908	0.66 (0.66–0.67)	0.83 (0.82–0.84)		
	ICI, no PPI	81,617	474,436	0.83 (0.83–0.84)	0.90 (0.89–0.91)		
	ICI, PPI	395	3881	0.52 (0.47–0.58)	0.60 (0.54–0.68)		
Hepatobiliary disorders	No ICI, no PPI	310,037	39,904,275	Reference	reference	**2.0525**	**1.1622**
	PPI, no ICI	9187	828,904	**1.35 (1.32–1.38)**	**1.65 (1.61–1.69)**		
	ICI, no PPI	19,206	536,847	**4.24 (4.18–4.31)**	**4.21 (4.14–4.28)**		
	ICI, PPI	234	4042	**6.64 (5.82–7.58)**	**7.10 (6.16–8.18)**		
Immune system disorders	No ICI, no PPI	463,601	39,750,711	reference	reference	-0.6971	0.2339
	PPI, no ICI	10,059	828,032	1.04 (1.02–1.06)	1.23 (1.20–1.26)		
	ICI, no PPI	5545	550,508	0.87 (0.84–0.89)	0.87 (0.84–0.90)		
	ICI, PPI	10	4266	0.21 (0.11–0.39)	0.57 (0.37–0.88)		
Infections and infestations	No ICI, no PPI	2,136,526	38,077,786	reference	Reference	0.4196	1.6918
	PPI, no ICI	26,691	811,400	0.60 (0.60–0.61)	0.66 (0.65–0.67)		
	ICI, no PPI	32,082	523,971	1.09 (1.08–1.11)	1.09 (1.08–1.11)		
	ICI, PPI	252	4024	1.12 (0.98–1.27)	1.04 (0.90–1.20)		
Injury, poisoning and procedural complications	No ICI, no PPI	4,090,230	36,124,082	reference	reference	-0.0565	0.6434
	PPI, no ICIs	59,824	778,267	0.71 (0.70–0.72)	0.87 (0.86–0.87)		
	ICIs, no PPI	35,702	520,351	0.64 (0.63–0.65)	0.56 (0.55–0.56)		
	ICIs, PPI	125	4151	0.29 (0.24–0.35)	0.24 (0.20–0.30)		

Table 2 (continued)

SOC	Exposure	Cases	Non-cases	RORcrude (95%CI)	RORadj (95%CI)	Additive model	Multiplicative model
Investigations	No ICIs, no PPI	2,309,808	37,904,504	Reference	Reference	0.0044	1.0213
	PPI, no ICIs	43,592	794,499	0.90 (0.90–0.91)	1.17 (1.15–1.18)		
	ICIs, no PPI	38,265	517,788	1.20 (1.18–1.21)	1.11 (1.09–1.12)		
	ICIs, PPI	272	4004	1.11 (0.98–1.25)	1.06 (0.92–1.21)		
Metabolism and nutrition disorders	No ICI, no PPI	795,759	39,418,553	reference	reference	**0.6194**	0.9926
	PPI, no ICI	27,719	810,372	**1.62 (1.61–1.65)**	**1.97 (1.94-2.00)**		
	ICI, no PPI	22,960	533,093	**2.03 (2.00-2.06)**	**2.02 (1.99–2.05)**		
	ICI, PPI	286	3990	**3.27 (2.90–3.69)**	**2.66 (2.30–3.08)**		
Musculoskeletal and connective tissue disorders	No ICI, no PPI	2,098,215	38,116,097	reference	reference	-0.5395	0.3359
	PPI, no ICI	46,976	791,115	1.08 (1.07–1.09)	1.22 (1.20–1.23)		
	ICI, no PPI	20,987	535,066	0.73 (0.72–0.74)	0.74 (0.73–0.75)		
	ICI, PPI	58	4218	0.26 (0.20–0.34)	0.26 (0.20–0.35)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	No ICIs, no PPI	1,153,267	39,061,045	reference	reference	-0.5328	1.2962
	PPI, no ICIs	8260	829,831	0.34 (0.34–0.35)	0.28 (0.27–0.29)		
	ICIs, no PPI	34,232	521,821	2.14 (2.12–2.17)	1.62 (1.60–1.65)		
	ICIs, PPI	117	4159	0.95 (0.79–1.14)	0.66 (0.54–0.82)		
Nervous system disorders	No ICIs, no PPI	3,198,465	37,015,847	Reference	reference	0.2465	1.3327
	PPI, no ICIs	53,260	784,831	0.81 (0.80–0.81)	1.02 (1.01–1.03)		
	ICIs, no PPI	31,026	525,027	0.71 (0.70–0.72)	0.76 (0.75–0.78)		
	ICIs, PPI	256	4020	0.76 (0.67–0.86)	0.68 (0.58–0.79)		
Pregnancy, puerperium and perinatal conditions	No ICIs, no PPI	164,178	40,050,134	reference	reference	-	-
	PPI, no ICIs	2577	835,514	0.77 (0.74–0.80)	-		
	ICIs, no PPI	195	555,858	0.09 (0.08–0.10)	-		
	ICIs, PPI	-	-	-	-		
Product issues	No ICIs, no PPI	702,193	39,512,119	reference	reference	0.7090	0.5312
	PPI, no ICIs	4345	833,746	0.31 (0.30–0.31)	-		
	ICIs, no PPI	447	555,606	0.05 (0.04–0.05)	-		
	ICIs, PPI	4	4272	0.02 (0.01–0.02)	-		
Psychiatric disorders	No ICIs, no PPI	2,200,356	38,013,956	reference	Reference	0.2619	0.0397
	PPI, no ICIs	35,344	802,747	0.78 (0.77–0.79)	1.15 (1.14–1.17)		
	ICIs, no PPI	7434	548,619	0.25 (0.24–0.25)	0.32 (0.31–0.32)		
	ICIs, PPI	67	4209	0.29 (0.23–0.37)	0.29 (0.21–0.40)		
Renal and urinary disorders	No ICIs, no PPI	627,007	39,587,305	reference	Reference	-1.4287	0.5906
	PPI, no ICIs	140,472	697,619	8.90 (8.84–8.95)	3.41 (3.36–3.45)		
	ICIs, no PPI	15,930	540,123	1.52 (1.50–1.54)	1.52 (1.49–1.55)		
	ICIs, PPI	647	3629	7.99 (7.35–8.68)	9.18 (8.36–10.08)		
Reproductive system and breast disorders	No ICIs, no PPI	318,781	39,895,531	reference	reference	0.2946	0.3097
	PPI, no ICIs	3616	834,475	0.56 (0.54–0.57)	-		
	ICIs, no PPI	1098	554,955	0.25 (0.24–0.27)	-		
	ICIs, PPI	3	4273	0.10 (0.03–0.32)	-		
Respiratory, thoracic and mediastinal disorders	No ICIs, no PPI	1,829,710	38,384,602	reference	reference	-0.2167	0.8973
	PPI, no ICIs	45,824	792,267	1.19 (1.18–1.20)	1.41 (1.40–1.43)		
	ICIs, no PPI	38,531	517,522	1.51 (1.49–1.52)	1.54 (1.52–1.56)		
	ICIs, PPI	291	3985	1.48 (1.31–1.66)	1.53 (1.34–1.75)		
Skin and subcutaneous tissue disorders	No ICIs, no PPI	2,201,846	38,012,466	reference	Reference	**0.6927**	**5.3599**
	PPI, no ICIs	33,471	804,620	**0.73 (0.73–0.74)**	**0.96 (0.95–0.97)**		
	ICIs, no PPI	29,851	526,202	**0.99 (0.97-1.00)**	**1.12 (1.10–1.14)**		
	ICIs, PPI	329	3947	**1.41 (1.26–1.58)**	**1.53 (1.34–1.75)**		

Table 2 (continued)

SOC	Exposure	Cases	Non-cases	RORcrude (95%CI)	RORadj (95%CI)	Additive model	Multiplicative model
Social circumstances	No ICIs, no PPI	166,215	40,048,097	Reference	reference	0.1432	0.4354
	PPI, no ICIs	3040	835,051	0.89 (0.86–0.92)	-		
	ICIs, no PPI	495	555,558	0.22 (0.20–0.24)	-		
	ICIs, PPI	4	4272	0.25 (0.09–0.67)	-		
Surgical and medical procedures	No ICIs, no PPI	564,145	39,650,167	reference	reference	0.6347	3.3937
	PPI, no ICIs	5353	832,738	0.46 (0.45–0.48)	0.37 (0.35–0.38)		
	ICIs, no PPI	3565	552,488	0.47 (0.45–0.48)	0.36 (0.35–0.38)		
	ICIs, PPI	33	4243	0.56 (0.40–0.79)	0.53 (0.36–0.78)		
Vascular disorders	No ICIs, no PPI	807,698	39,406,614	reference	reference	-0.6259	0.3225
	PPI, no ICIs	14,814	832,738	0.88 (0.87–0.89)	1.01 (0.99–1.03)		
	ICIs, no PPI	11,591	544,462	1.04 (1.02–1.06)	0.95 (0.93–0.97)		
	ICIs, PPI	25	4251	0.30 (0.20–0.44)	0.23 (0.14–0.37)		

ICI, immune checkpoint inhibitor; PPI, proton pump inhibitor; SOC, Standardized MedDRA Query 'System Organ Class'; ROR, reporting odds ratio; RORadj, adjusted ROR; RORcrude, crude ROR; CI, confidence interval

(95% CI, 1.32–1.38)/1.65 (95% CI, 1.61–1.69), and the crude/adjusted ROR for ICIs alone was 4.24 (95% CI, 4.18–4.31)/4.21 (95% CI, 4.14–4.28). An increase signal for the concomitant use of ICIs and PPIs emerged (RORcrude=6.64, 95% CI, 5.82–7.58, RORadj=7.10, 95% CI, 6.16–8.18). The positive interaction signal was supported by additive (2.0525) and multiplicative (1.1622) models. For metabolism and nutrition disorders, the crude/adjusted ROR for PPIs alone was 1.63 (95% CI, 1.61–1.65)/1.97 (95% CI, 1.94-2.00), and the crude/adjusted ROR for ICIs alone was 2.03 (95% CI, 2.00-2.06)/2.02 (95% CI, 1.99–2.05). An increased signal for concomitant use of ICIs and PPIs emerged (RORcrude=3.27, 95% CI, 2.90–3.69, RORadj=2.66; 95% CI, 2.30–3.08). The positive interaction signal was supported by additive models (0.6194). For skin and subcutaneous tissue disorders, the crude/adjusted ROR for PPIs alone was 0.73 (95% CI, 0.73–0.74)/0.96 (95% CI, 0.95–0.97), and the crude/adjusted ROR for ICIs alone was 0.99 (95%CI, 0.97-1.00)/1.12 (95% CI, 1.10–1.14). An increase signal for the concomitant use of ICIs and PPIs emerged (RORcrude=1.41, 95% CI, 1.26–1.58, RORadj=1.53, 95% CI, 1.34–1.75). The positive interaction signal was supported by additive (0.6927) and multiplicative (5.3599) models.

Subset data analyses

A subset analysis of PPI in combination with PD-1, PDL-1, and CTLA-4, respectively, was conducted for the four positive SOCs (Tables 4 and 5). For **congenital, familial and genetic disorders**, both PD-1 and CTLA-4 in combination with PPI revealed positive DDI signals, which were verified using additive and multiplicative models. In **hepatobiliary disorders**, PD-1 combined with PPI revealed positive DDI signals, which were verified using additive and multiplicative models. For **metabolism and nutrition disorders**, PDL-1 combined with PPI revealed positive DDI signals, which were verified using additive and multiplicative models. For **skin and subcutaneous tissue disorders**, the combination of PD-1 and CTLA-4 with PPI revealed positive DDI signals, which were verified using additive and multiplicative models.

Discussion

To our knowledge, this is the first pharmacovigilance study to assess drug interactions between ICIs and PPIs. Our study provides a comprehensive collection of information on the clinical characteristics and DDIs of ICIs combined with PPIs in a real-world setting. Several notable main findings emerged. (1) DDIs of ICIs combined with PPIs occurred in four SOCs: congenital, familial, and genetic disorders; hepatobiliary disorders; metabolism and nutrition disorders; and skin and subcutaneous tissue disorders. (2) PD-1 combined with PPI was associated with congenital, familial, and genetic disorders, hepatobiliary disorders, and skin and subcutaneous tissue disorders. (3) PDL-1 combined with PPI was associated with adverse reactions of metabolism and nutritional disorders. (4) CTLA-4 combined with PPI was associated with congenital, familial, and genetic disorders, and skin and subcutaneous tissue disorders.

Negative regulatory immune signals are blocked by ICIs, which activate the host immune response against tumours [32, 33]. Up to 30% of patients with cancer are administered PPIs as a supplement for cancer treatment particularly in patients with a history of peptic ulcer disease or for those who have been administered nonsteroidal anti-inflammatory drugs to treat cancer pain [34, 35]. Gut dysbiosis has been found to negatively affect systemic immune responses and ICI efficacy [11, 12, 36]. PPIs are associated with gut dysbiosis, reduced

Table 3 Summary of methods used to analyze drug-drug interactions for all SOCs

SOC	RORcrude	RORadj	Additive model	Multiplicative model
Blood and lymphatic system disorders	-	-	√	-
Cardiac disorders	-	-	-	-
Congenital, familial and genetic disorders	-	√	√	√
Ear and labyrinth disorders	-	-	-	-
Endocrine disorders	-	-	-	-
Eye disorders	-	-	-	-
Gastrointestinal disorders	√	√	-	-
General disorders and administration site conditions	-	-	√	-
Hepatobiliary disorders	√	√	√	√
Immune system disorders	-	-	-	-
Infections and infestations	-	-	√	√
Injury, poisoning and procedural complications	-	-	-	-
Investigations	-	-	√	√
Metabolism and nutrition disorders	√	√	√	-
Musculoskeletal and connective tissue disorders	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	-	-	√
Nervous system disorders	-	-	√	√
Pregnancy, puerperium and perinatal conditions	-	-	-	-
Product issues	-	-	√	-
Psychiatric disorders	-	-	√	-
Renal and urinary disorders	-	√	-	-
Reproductive system and breast disorders	-	-	√	-
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Skin and subcutaneous tissue disorders	√	√	√	√
Social circumstances	-	-	√	-
Surgical and medical procedures	-	-	√	√
Vascular disorders	-	-	-	-

SOC, Standardized MedDRA Query 'System Organ Class'; ROR, reporting odds ratio; RORadj, adjusted ROR; RORcrude, crude ROR

bacterial diversity, and improved T cell tolerance [13]. PPIs can affect the gut microbiota because gastric acid is the main defense system against bacterial influx from food and oral bacterial flora [14]. Evidence suggests that ICI efficacy is negatively affected by PPIs. Patients with metastatic nonsquamous non-small cell lung carcinoma (NSCLC) treated with atezolizumab who were administered PPIs had worse survival outcomes [37]. PPI use was found to be a negative prognostic marker that can impact the effectiveness of ICIs [38].

A study including 159 patients with metastatic melanoma treated by ipilimumab combined with 12 classes of chronic medications (including PPIs) revealed that no medication class was associated with an increased risk of grades 3–5 immune-related adverse events (irAEs) [39]. A retrospective study of 158 patients treated with anti-PD-1/PDL-1 therapy found no statistically significant differences in the proportions of grade 3 or 4 colitis or grade 3 or 4 pneumonitis between PPI users and non-users [40]. In an analysis of advanced urothelial cancer clinical trials (IMvigor210 and IMvigor211), no significant association between PPI use and the first occurrence of atezolizumab-induced grade≥1AE, grade≥3 AE, grade≥1 immune related AE, or grade≥1 diarrhoea were identified [41]. In a retrospective study including 212 patients treated with anti-PD-1 ICIs, 78 (36.8%) experienced AEs; however, antibiotic or PPI use did not result in significant increases in AEs [17]. In a retrospective study of 300 patients, 54.3% of the patients were administered PPIs and nivolumab or pembrolizumab for advanced NSCLC; univariate analysis revealed no significant difference in the incidence of irAEs with respect to concomitant medications [42]. A retrospective analysis of data from the GETUG-AFU 26 NIVOREN (NCT03013335) phase II study (729 patients with metastatic renal cell carcinoma treated with nivolumab) showed that grade 3–5 irAEs were more common among PPI users (25.5% vs. 15.3%). That real-world study revealed that PPIs negatively affected the safety of nivolumab [43].

The two types of drug interactions are pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions can occur when different drugs have mechanisms of action that affect the same physiological processes. Pharmacokinetic interactions occur when a drug affects another drug's absorption, distribution, metabolism, and excretion [44]. DDIs can result in either increased or decreased therapeutic or adverse effects, or a unique response that is not caused by either agent alone [20]. Liver toxicity is prevalent in patients who are administered ICIs, occurring in 2–25% of patients. Toxicity typically manifests as an asymptomatic increase in hepatic enzymes with or without hyperbilirubinemia [45, 46]. ICI-related hepatotoxicity has not yet been fully understood [47]. The proposed explanation involves increased autoimmunity of hepatocytes caused by T-cell activation from ICIs: T cells respond to shared antigens that are present on both tumors and target organs, generate antibodies that bind to target organs, and overexpress immune cells resulting in excessive cytokine secretion [48]. The liver is one of the most commonly involved organs [49]. The vigorous immune response resulting from ICIs causes immune-mediated hepatotoxicity.

Table 4 Disproportionality analyses and drug interaction approaches for the various drug combinations

SOC	Drug-drug interaction of interest	Exposure	Cases	Non-cases	RORcrude (95%CI)	RORadj (95%CI)	Additive model	Multiplicative model
Congenital, familial and genetic disorders	PD-1 + PPI	No PD-1, no PPI	111,096	40,252,287	reference	reference	1.2988	6.0298
		PD-1, no PPI	285	404,389	0.26 (0.23–0.29)	0.62 (0.55–0.71)		
		PPI, no PD-1	2296	837,317	1.00 (0.96–1.04)	1.19 (1.10–1.28)		
		PD-1, PPI	12	2742	1.56 (0.88–2.75)	3.13 (1.62–6.06)		
	PDL-1 + PPI	No PDL-1, no PPI			reference	reference	-	-
		PDL-1, no PPI	93	99,260	0.34 (0.28–0.42)	-		
		PPI, no PDL-1	2308	838,717	1.00 (0.96–1.05)	-		
		PDL-1, PPI	-	-	-	-		
	CTLA-4 + PPI	No CTLA-4, no PPI	111,345	40,556,062	reference	reference	3.4747	27.23
		CTLA-4, no PPI	36	100,614	0.13 (0.10–0.18)	10.32(4.87–21.86)		
		PPI, no CTLA-4	2299	839,287	1.00 (0.96–1.04)	1.18 (1.09–1.27)		
		CTLA-4, PPI	9	772	3.61 (1.87–6.96)	10.32(4.87–21.86)		
Hepatobiliary disorders	PD-1 + PPI	No PD-1, no PPI	315,032	40,041,238	reference	reference	3.7362	1.4418
		PD-1, no PPI	14,211	390,463	4.31 (4.24–4.39)	4.09 (4.02–4.17)		
		PPI, no PD-1	9229	830,384	1.35 (1.32–1.38)	1.62 (1.59–1.66)		
		PD-1, PPI	192	2562	8.40 (7.25–9.73)	8.17 (6.98–9.55)		
	PDL-1 + PPI	No PDL-1, no PPI	325,227	40,336,364	reference	reference	-1.1751	0.6117
		PDL-1, no PPI	4016	95,337	4.96 (4.81–5.12)	4.15 (4.00-4.31)		
		PPI, no PDL-1	9374	831,651	1.37 (1.34–1.40)	1.57 (1.54–1.61)		
		PDL-1, PPI	47	1295	4.16 (3.11–5.56)	3.77 (2.67–5.34)		
	CTLA-4 + PPI	No CTLA-4, no PPI	324,942	40,335,352	reference	reference	-0.2946	0.7403
		CTLA-4, no PPI	4301	96,349	5.25 (5.09–5.41)	4.65 (3.29–6.56)		
		PPI, no CTLA-4	9385	832,201	1.37 (1.34–1.40)	1.58 (1.54–1.61)		
		CTLA-4, PPI	36	745	5.32 (3.81–7.44)	4.65 (3.29–6.56)		
Metabolism and nutrition disorders	PD-1 + PPI	No PD-1, no PPI	801,795	39,535,891	reference	reference	-0.9465	0.5189
		PD-1, no PPI	16,924	387,750	2.06 (2.02–2.09)	2.16 (2.12–2.20)		
		PPI, no PD-1	27,907	811,706	1.63 (1.61–1.65)	1.94 (1.91–1.97)		
		PD-1, PPI	98	2656	1.74 (1.42–2.13)	2.68 (3.16–3.73)		
	PDL-1 + PPI	No PDL-1, no PPI	814,795	39,828,212	reference	reference	2.6998	1.6675
		PDL-1, no PPI	3924	95,429	1.94 (1.88-2.00)	1.85 (1.78–1.92)		
		PPI, no PDL-1	27,859	813,166	1.63 (1.61–1.65)	1.90 (1.88–1.93)		
		PDL-1, PPI	146	1196	5.27 (4.44–6.26)	5.43 (4.47–6.61)		
	CTLA-4 + PPI	No CTLA-4, no PPI	813,805	39,827,905	reference	reference	-1.8437	0.3034
		CTLA-4, no PPI	4914	95,736	2.40 (2.33–2.47)	0.97 (0.60–1.57)		
		PPI, no CTLA-4	27,986	813,600	1.63 (1.61–1.65)	1.91 (1.89–1.94)		
		CTLA-4, PPI	19	762	1.19 (0.75–1.88)	0.97 (0.60–1.57)		
Skin and subcutaneous tissue disorders	PD-1 + PPI	No PD-1, no PPI	2,208,811	38,123,080	reference	reference	1.1392	2.5094
		PD-1, no PPI	22,886	381,788	1.04 (1.02–1.05)	1.19 (1.17–1.20)		
		PPI, no PD-1	33,513	806,100	0.73 (0.73–0.74)	0.96 (0.95–0.97)		
		PD-1, PPI	287	2467	1.91 (1.69–2.16)	2.14 (1.86–2.45)		
	PDL-1 + PPI	No PDL-1, no PPI	2,227,593	38,409,619	reference	reference	-0.0272	0.8382
		PDL-1, no PPI	4104	95,249	0.76 (0.74–0.78)	0.80 (0.77–0.83)		
		PPI, no PDL-1	33,766	807,259	0.74 (0.73–0.75)	0.95 (0.94–0.96)		
		PDL-1, PPI	34	1308	0.47 (0.33–0.66)	0.45 (0.30–0.69)		
	CTLA-4 + PPI	No CTLA-4, no PPI	2,225,784	38,410,131	reference	reference	0.4978	1.6526
		CTLA-4, no PPI	5913	94,737	1.08 (1.05–1.11)	1.45 (1.08–1.95)		
		PPI, no CTLA-4	33,744	807,842	0.74 (0.73–0.74)	0.95 (0.94–0.96)		
		CTLA-4, PPI	56	725	1.31 (1.00-1.72)	1.46 (1.09–1.95)		

SOC, Standardized MedDRA Query 'System Organ Class'; reporting odds ratio; RORadj, adjusted ROR; RORcrude, crude ROR; PPI, proton pump inhibitor; PD-1, programmed death-1; PPI, proton pump inhibitor; PDL-1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4; CI, confidence interval

Table 5 Summary of methods used to analyse drug-drug interactions in four SOCs

SOC	Exposure	RORcrude	RORadj	Additive model	Multiplicative model
Congenital, familial and genetic disorders	PD-1 + PPI	-	√	√	√
	PDL-1 + PPI	-	-	-	-
	CTLA-4 + PPI	√	√	√	√
Hepatobiliary disorders	PD-1 + PPI	√	√	√	√
	PDL-1 + PPI	-	-	-	-
	CTLA-4 + PPI	-	-	-	-
Metabolism and nutrition disorders	PD-1 + PPI	-	√	-	-
	PDL-1 + PPI	√	√	√	√
	CTLA-4 + PPI	-	-	-	-
Skin and subcutaneous tissue disorders	PD-1 + PPI	√	√	√	√
	PDL-1 + PPI	-	-	-	-
	CTLA-4 + PPI	-	√	√	√

SOC, Standardized MedDRA Query 'System Organ Class'; ROR, reporting odds ratio; RORadj, adjusted ROR; RORcrude, crude ROR; PD-1, programmed death-1; PPI, proton pump inhibitor; PDL-1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4

Conversely, conventional drug-induced liver injury occurs from either direct or idiosyncratic effects [50]. The onset of immuno-related hepatitis typically occurs 8–12 weeks after the initiation of ICI therapy [51]. According to the manufacturers' drug labels, hepatic disorders occur in less than 1% of patients and are not clearly associated with PPIs [52]. Drug-induced liver injury is believed to cause PPI-induced hepatic dysfunction; however, few case studies have reported this adverse effect [53, 54]. In this study, only PD-1 interacted with PPI to generate liver toxicity signals. During clinical trials, CTLA-4 inhibitors are known to produce the most hepatoxicity, with rates generally between 0 and 30%. While PD-1 inhibitors result in the lowest rate of hepatoxicity with rates between 0 and 3% [47]. Hepatotoxicity is more likely to occur when ICI are used in combination with chemotherapy drugs such as dacarbazine, paclitaxel, carboplatin and bevacizumab. A detailed medication history should be conducted. The combination medication should be thoroughly evaluated and a risk assessment should be carried out.

In this study, PDL-1 combined with PPI revealed positive DDI signals for metabolism and nutrition disorders. Impaired absorption of nutrients is one of the adverse reactions caused by long-term use of PPIs [55]. Acid secretion in the stomach plays a significant role in the absorption of several nutrients. Long-term use of PPIs reduces the acidity in the stomach, causing a reduction in the absorption and digestion of various minerals and vitamins, leading to related metabolism and nutrition disorders [56]. The gastrointestinal tract contains many microbes living symbiotically. A weak immune response is necessary to ensure the survival of the microbiota. The commensal microbiota may become target antigens due to immune overactivation after ICI treatment. *Bacteroides* and *Burkholderia* rapidly decreased in the small intestinal mucosa after anti-CTLA-4 treatment and the amount of *Clostridium* in feces increased [7]. The cross-regulation and entrainment between nutrients and the gut microbiota has the potential to affect host health and immune-mediated diseases [57].

For skin and subcutaneous tissue disorders, PD-1 and CTLA-4 combined with PPI revealed positive DDI signals. Cutaneous toxicities have been reported for 30–50% of all side effects of ICI therapies [58]. Anti-CTLA-4 monotherapy is associated with higher rates of cutaneous adverse events (44–59%) than anti-PD-1 (34–42%) or anti-PD-L1 (20%). Besides T cell activation after ICI treatment, cross-reaction of antigens on the target tumor cells and self-antigens on cutaneous tissues is another mechanism. Vitiligo is associated with a cross-reaction between melanoma-associated antigens and melanocytes [59]. PPI-induced adverse skin reactions are mostly immunological and include both immediate and delayed-type hypersensitivity reactions. These reactions are sometimes life-threatening. All PPIs can induce immediate IgE-mediated reactions [60].

Dermatological toxicity is the most commonly reported irAE [61]. Dermatological toxicity of all grades reportedly occurs in 30–40% of patients who are administered PD-1/PD-L1 blockade and in 50% of patients who are administered ipilimumab; most of these reactions are grade 1 or 2 [62, 63]. Skin toxicity associated with PPIs is uncommon, and less than 1% of patients who are administered omeprazole experience rashes [52]. PPIs are not closely linked to severe skin reactions, including toxic epidermal necrolysis, and to date only five cases have been documented in the literature [64–66]. In a study of 47 patients who were administered anti-PD-1 ICIs and PPIs, 4.3% ($n=2$) developed cutaneous eruption [17]. A study of patients who were administered nivolumab or pembrolizumab for advanced NSCLC found that 54.3% were administered PPIs and 45.7% had irAEs ($n=137$). Rash, pruritus, and erythema multiforme were the most commonly reported skin toxicities ($n=63$). Mirura et al.'s retrospective study found five reports of hepatitis cases of all-grades, with one case ≥ grade 3 [42].

Our study had some limitations which must be considered when interpreting the results. First, FAERS is a spontaneous reporting system (SRS). The quantification of adverse reaction signals based on the total number of adverse reactions was not possible using the collected data. The purpose of this study was to provide a qualitative indicator using the signal intensity between the drugs and the reactions alone. Second, compared with clinical trials and cohort studies, SRS data are generally less

reliable. The identification and reporting of AEs within SRSs are subject to less stringent controls. Third, identifying significant risk factors between disorders and drugs is difficult because of deficiencies in preexisting disorders and comorbidities that may affect the disease. Furthermore, this study was not restricted to a particular disease, which is significantly different from the approach of clinical trials. Fourth, this study used SOCs as the target reactions to encompass all adverse reactions; however, the scope of the SOC is broad, and subgroup analysis was not performed. Fifth, calculation, justification, and power analyses for the selected sample size in this study were not conducted as the intention was to include all eligible adverse drug reactions.Sixth, data mining revealed imperfect reporting, with inaccuracies and incomplete entries, which is caused by the FAERS database itself and could potentially lead to analytical bias. Seventh, adverse events are underreported in spontaneous reporting systems, with an average of 6% [67]. While, the ranking order of adverse event rates in the FAERS database was consistent with the results of published studies [68]. Finally, Signal scores can be suppressed by a significant number of reports that link the same adverse event to other drugs.

Nevertheless, our findings, although limited by FAERS, highlighted that DDIs are associated with concomitant administration of ICIs and PPIs. The results will provide a framework for rigorous research to further elucidate and validate the findings.

Conclusion

Our study identified four types of DDIs associated with concomitant use of ICIs and PPIs using real-world FAERS data. Therefore, clinicians should be cautious when administering these two classes of drugs together. Preclinical trials are required to explore the mechanisms underlying these interactions. Further robust clinical studies are necessary to elucidate these relationships, promote understanding of the risk of DDIs associated with this combination therapy, and to provide more granular details.

Abbreviations

CI	confidence interval
IQR	interquartile range
ROR	reporting odds ratio
RORadj	adjusted ROR
RORcrude	crude ROR
ICI	immune checkpoint inhibitors
PD-1	programmed death 1
PDL-1	programmed death ligand 1
CTLA-4	cytotoxic T-lymphocyte antigen-4
PPI	proton pump inhibitor
DDI	drug-drug interaction
FAERS	Food and Drug Administration (FDA) Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
REAC	regulatory activity
SOC	Standardized MedDRA Query 'System Organ Class'
PS	primary suspect
SS	secondary suspect
FDA_DT	Food and Drug Administration/date FDA received Case
irAE	immune-related adverse event
NSCLC	non-small lung cell carcinoma
SRS	spontaneous reporting system

Supplementary Information

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Supplementary Material 1

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Author contributions

XR drafted the manuscript. Lu Li and Yiran Chen participated in data analysis and interpretation. Xiangli Cui prepared the figures. Rui Wan and Yanfeng Wang contributed to the topic selection of the article. All authors have read and approved the manuscript.

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Data availability

The data that support the findings of this study are available upon from the corresponding author, Yanfeng Wang, on reasonable request. The raw data can be obtained from the FAERS database at the following link: FAERS Quarterly Data Extract Files (fda.gov).

Declarations

Ethics approval and consent to participate

Not applicable. Ethical approval was not required for this study because we used the FAERS database, which is a free open-access database.

Consent for publication

Not applicable. This study did not include data from any individual person.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pharmacy, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[2]Department of Gynecologic Oncology, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[3]Department of pharmacy, Beijing Friendship hospital, Capital Medical University, Bejing, China
[4]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China
[5]Department of Comprehensive Oncology, National Cancer Center, National Clinical Research Center for Cancer, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China

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