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SHORT COMMUNICATION

Relationship Between Clozapine and Non-Hematological Malignant Tumors: A Pharmacovigilance Analysis Using the FDA Adverse Event Reporting System Database

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Abstract

Background and Objectives Clozapine shows higher efficacy against treatment-resistant schizophrenia than other antipsychotics. This study aimed to investigate whether clozapine is associated with the risk of non-hematological malignant tumors, utilizing the US Food and Drug Administration (FDA) Adverse Event Report System (FAERS) database.

Methods The records from the first quarter of 2004 to the third quarter of 2012 were used for disproportionality analysis, and patients who developed non-hematological malignant tumors were identified by the Standardized Medical Dictionary for Regulatory Activities Queries (SMQ).

Results Of the 3,641,281 patients with 12,401,586 reports of adverse drug events, 151,904 reports belonged to non-hematological malignant tumors (SMQ). We identified 1668 reports of non-hematological malignant tumors (SMQ) in clozapine users, and the reporting odds ratio (ROR) was calculated to be 1.28 (95% confidence interval (CI): 1.22–1.34). ROR (95% CI) for the relationship between clozapine and the risk of testis cancer was calculated as 10.94 (6.99–17.12), 9.87 (7.42–13.15) for gastrointestinal carcinoma, 7.48 (5.57–10.05) for metastatic lung cancer, 6.71 (4.52–9.97) for throat cancer, 6.12 (4.56–8.21) for metastases to the spine, 5.97 (5.30–6.72) for lung malignant neoplasm, 5.07 (3.69–6.95) for esophageal carcinoma, 1.88 (1.43–2.47) for colon cancer, and 1.65 (1.24–2.21) for metastases to the liver. Colon cancer, esophageal carcinoma, and throat cancer were predominantly reported in males, and metastases to the spine and liver were in females.

Conclusion This study detected signals indicating a relationship between clozapine and certain non-hematological malignant tumors, utilizing the FAERS database. Despite the database relying on spontaneous reporting, the current results justify further investigation.

1 Introduction

Schizophrenia is a psychiatric disorder that is characterized by positive symptoms, including hallucinations and delusions, negative symptoms, such as reduced motivation and decreased emotional expression, and cognitive impairment. Schizophrenia affects approximately 1% of the population. These symptoms are attenuated by antipsychotics, on which drug therapy for schizophrenia is based. "Guideline for Pharmacological Therapy of Schizophrenia 2022" published by the Japanese Society of Neuropsychopharmacology and the Japanese Society of Clinical Neuropsychopharmacology strongly recommends the

Key Points

The relationship between clozapine use and risks for non-hematological malignant tumors was examined using the FAERS database.

Clozapine was associated with increased risks of the reporting of some non-hematological malignant tumors including lung malignant neoplasm, colon cancer, esophageal carcinoma, throat cancer, and metastases to spine.

Colon cancer, esophageal carcinoma, and throat cancer were more common in male clozapine users, and metastases to liver and spine were in female users.

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continued administration of antipsychotics to patients with stable schizophrenia. The administration of atypical antipsychotics does not ameliorate symptoms in some patients with schizophrenia or they cannot continue taking them due to side effects. The percentage of patients with treatment-resistant schizophrenia was previously reported to be 30% [1]. Clozapine is currently the most effective and only antipsychotic indicated for treatment-resistant schizophrenia [1]. However, patients receiving clozapine are at risk of bowel obstruction, glucose intolerance, weight gain, seizure, myocarditis, pneumonia, and agranulocytosis [2].

Some drugs have been reported to increase the risk of cancer. A cohort study previously demonstrated that the use of pioglitazone for more than 2 years was associated with a higher risk of bladder cancer [3]. Another study reported a relationship between the use of antihypertensive drugs and an increased incidence of colorectal and renal cancers [4]. A population-based inception cohort study showed that thiazide was linked to an increased risk of skin cancer [5]. Additionally, the administration of antipsychotics may be associated with tumor development. The analysis of adverse drug event reporting systems is valuable for detecting signals between drug administration and adverse events. Two pharmacovigilance studies using the US Food and Drug Administration (FDA) Adverse Event Report System (FAERS) database and the European pharmacovigilance database detected safety signals for pituitary tumors with antipsychotics including risperidone, by applying the Multi-item Gamma Poisson Shrinker data mining algorithm with a Bayesian model and by calculating the reporting odds ratio (ROR), respectively [6, 7]. Another study using Vigibase, the World Health Organization's adverse drug events dataset, identified a signal associating clozapine use with higher reported frequencies of hematological malignancies [8]. This finding was confirmed by a nationwide case-control and cohort study [9]. However, the relationship between clozapine and non-hematological malignant tumors remains unknown.

The purpose of the present study was to investigate the association between clozapine use and reported frequencies of non-hematological malignant tumors using the FAERS database through disproportionality analysis. The study analyzed reports in the FAERS database from the first quarter of 2004 to the third quarter of 2012.

2 Materials and Methods

2.1 The US Food and Drug Administration (FDA) Adverse Event Report System (FAERS) Database

We downloaded data recorded in the FAERS database between January 2004 and September 2012 via the FDA website (http://www.fda.gov). It contains reports on adverse drug events submitted by physicians, pharmacists, other healthcare professionals, manufacturers, and consumers from the US and other countries. All data from the FAERS database were fully anonymized by the relevant regulatory authority before we accessed them. Accordingly, ethical approval was not required for the present study. We integrated the information obtained into a relational database using JMP Pro 17.0 (SAS Institute, Cary, NC, USA) and FileMaker Pro 20.1 (Claris, Cupertino, CA, USA). According to the FDA's recommended method (the downloadable file 'Asc_nts.doc' from the FAERS database website), we identified duplicate cases. Among reports with the same CASE number, those with lower Individual Safety Report (ISR) numbers were excluded from the analysis. Starting from the fourth quarter in 2012, there is no longer any description of how to delete duplicate reports. Therefore, we conducted our analysis using data up to the third quarter of 2012.

2.2 Definitions of Drugs and Adverse Drug Events

In this study, records of patients receiving four atypical antipsychotics, clozapine, aripiprazole, quetiapine, and risperidone, were analyzed. The FAERS database permits contributors to register drugs under any name, including a trade name and an abbreviation. We used generic and trade names for drug definitions. We searched trade names using the DrugBank Online (https://go.drugbank.com) and Drugs.com (https://www.drugs.com). The trade names used for the analysis are listed in Table 1.

Drugs in the FAERS were classified into four categories: Primary Suspected drug (PS), Secondary Suspected drug (SS), Concomitant (C), and Interacting (I), according to their anticipated degree of involvement in adverse events. All reports were analyzed regardless of categories of the medicines.

Adverse drug events in the FAERS database are coded using the preferred term (PT) derived from the Medical Dictionary for Regulatory Activities (MedDRA, https://www.meddra.org). The standardized MedDRA Queries (SMQ) index, a comprehensive search formula, involves groupings of MedDRA terms, ordinarily at the PT level that relate to a defined medical condition or area of interest, and is widely accepted and used in analyses of the FAERS database. We used SMQ version 26.0 to extract case reports related to non-hematological malignant tumors (SMQ code: 20000228, containing 1102 related PT).

2.3 Reporting Odds Ratio

We compiled a cross-tabulation based on two classifications: the presence or absence of non-hematological malignant tumors, and the suspected medicine. Then, ROR

Table 1 Trade names of clozapine, aripiprazole, quetiapine, and risperidone used in the present study

Generic name	Trade name
Clozapine	Azaleptine, Clopine, Clozaril, Clozapin, Denzapine, Elcrit, FazaClo, Froidir, Klozapol, Lanolept, Leponex, Lozapine, Sensipin, Zaponex
Aripiprazole	Abilify, Ariprazole, Arpizol
Quetiapine	Cacepin, Etiasel, Ketilept, Ketipinor, Kventiax, Quetiapina, Quetidin, Quetipin, Qutipin, Seroquel
Risperidone	Belivon, Respidon, Riatul, Ridal, Riscon, Risdone, Rispedral, Rispelen, Rispen, Risperat, Risperdal, Risperidona, Risperin, Risperlet, Risperoprol, Rispolept, Rispolux, Rispond, Risset, Rixadone, Sizodon, Zargus

Two-by two contingency table

	NHMT	Other AEs
Suspected medicine	a	b
All other medicines	c	d

$$ROR = (a/b)/(c/d)$$

$$95\%\ CI = \exp\left\{\log(ROR) \pm 1.96 \times \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}\right\}$$

Figure 1 Equations for reporting odds ratio and 95% confidence interval. *NHMT* non-hematological malignant tumor, *AEs* adverse events, *ROR* reporting odds ratio, *CI* confidence interval

and its the 95% confidence interval (CI) were calculated, according to the formula shown in Fig. 1. The ROR is the ratio of one reporting specific adverse effect versus all other adverse effects for a given drug to this reporting odds for all other drugs present in the database. The ROR is frequently used with the spontaneous reporting database as an index of the relative risk of drug-associated adverse events. A signal was considered to be detected when the lower limit of the 95% CI was > 1.

3 Results

3.1 Relationship Between Atypical Antipsychotics and Non-hematological Malignant Tumors (SMQ)

After exclusion of duplicates from the FAERS database following the FDA recommendation, 12,401,586 reports for adverse drug events in 3,641,281 ISRs were analyzed. The FAERS database contained 107,305 reports of adverse drug events in 28,591 ISRs with clozapine. The numbers of ISRs with aripiprazole, quetiapine, and risperidone were 24,982, 66,012, and 33,823, respectively. Their report numbers of adverse drug events were 84,376, 281,364, and 147,857, respectively.

Six hundred and thirty types of PT related to non-hematological malignant tumors (SMQ) were identified in the FAERS database, and their report number was 151,904. Breast cancer (PT code: 10006187) was the most frequently reported, with 30,791 reports. This was followed by female breast cancer (PT code: 10057654) with 15,453 reports, malignant neoplasm (PT code: 10028997) with 11,993, lung malignant neoplasm (PT code: 10058467) with 5,889, metastatic breast cancer (PT code: 10055113) with 4,970, and prostate cancer (PT code: 10060862) with 4,210.

Table 2 represents the RORs for the relationship between the use of the atypical antipsychotics and the risk of the reporting of non-hematological malignant tumors (SMQ). Among ISRs with clozapine, there were 1,668 reports of non-hematological malignant tumors. The ROR (95% CI) was calculated as 1.28 (1.22–1.34), resulting in the signal detection. The RORs including 95% CI were less than 0.30 for aripiprazole, quetiapine, and risperidone, indicating that no signal was detected.

3.2 Relationship Between Clozapine and Non-Hematological Malignant Tumors

In ISRs with clozapine, 133 types of non-hematological malignant tumors were reported. The RORs of non-hematological malignant tumors reported in 20 or more ISRs were shown in Table 3. Lung malignant neoplasm was reported in 291 ISRs with clozapine, and this was the highest number of non-hematological malignant tumors reported in ISRs with clozapine. The ROR (95% CI) was 5.97 (5.30–6.72), suggesting the association of the use of clozapine with an increase in reported frequency of lung malignant neoplasm. Signals were also detected in malignant neoplasm, colon cancer, gastrointestinal carcinoma, metastatic lung cancer, metastases to liver, metastases to spine, esophageal

Table 2 Report numbers of non-hematological malignant tumors (SMQ) in patients receiving atypical antipsychotics, and reporting odds ratios for their relationship

	Report no.		ROR	95% CI
	NHMT (SMQ)	Other AEs		
Total	151,904	12,249,682		
Clozapine	1668	105,637	1.28	1.22–1.34
Aripiprazole	241	84,135	0.23	0.20–0.26
Quetiapine	892	280,472	0.25	0.24–0.27
Risperidone	466	147,391	0.25	0.23–0.28

NHMT non-malignant hematological tumors, *SMQ* Standardized Medical Dictionary for Regulatory Activities queries, *AEs* adverse events, *ROR* reporting odds ratio, *CI* confidence interval

carcinoma, metastatic neoplasm, metastases to central nerve system, metastasis, throat cancer, and testis cancer.

Regarding ISRs with aripiprazole, malignant neoplasm, breast cancer, and metastases to the bone were reported in 35, 27, and 21 ISRs, respectively. There were no malignant tumors for which a signal was detected among these tumors. No signal was detected for quetiapine and risperidone in non-hematological malignant tumors registered in more than 20 reports.

3.3 Reporting Odds Ratio for the Relationship Between Clozapine and Non-hematological Malignant Tumors After Stratification by Sex

We examined the relationship between clozapine and reported frequencies of malignant tumors with the names of organs, after stratification by sex (Table 4). Relationships between clozapine and increases in the reported frequencies of colon cancer, esophageal carcinoma, metastases to the central nerve system, and throat cancer were recognized in males, but not in females. Clozapine was related to metastases to the liver and to spine in females, but not in males.

Breast cancer and male breast cancer were reported in 139 and 115 ISRs for males, respectively, who were not administered clozapine.

3.4 Reporting Odds Ratio for the Relationship Between Clozapine and Non-hematological Malignant Tumors After Stratification by the Role of Clozapine

Among the 28,591 ISRs in which the administration of clozapine was recorded, there were 23,108 in which clozapine was registered as the primary suspected drug. The numbers of adverse drug events classified into non-hematological

Table 3 Report numbers of non-hematological malignant tumors in patients receiving clozapine, and reporting odds ratio for their relationship

Preferred term (code)	Report no.			
	Clozapine use	No use	ROR	95% CI
Lung malignant neoplasm (10058467)	291	5598	5.97	5.30–6.72
Malignant neoplasm (10028997)	242	11,751	2.36	2.08–2.68
Breast cancer (10006187)	171	30,620	0.64	0.55–0.74
Colon cancer (10009944)	53	3230	1.88	1.43–2.47
Gastrointestinal carcinoma (10017940)	51	592	9.87	7.42–13.15
Metastatic lung cancer (10050017)	47	720	7.48	5.57–10.05
Metastases to the liver (10027457)	47	3257	1.65	1.24–2.21
Metastases to the spine (10027468)	47	880	6.12	4.56–8.21
Esophageal carcinoma (10030155)	40	905	5.07	3.69–6.95
Metastatic neoplasm (10061289)	35	1256	3.19	2.28–4.47
Metastases to the CNS (10059282)	32	2081	1.76	1.24–2.50
Metastasis (10062194)	29	1314	2.53	1.75–3.65
Metastases to bone (10027452)	28	3263	0.98	0.68–1.43
Throat cancer (10043515)	26	444	6.71	4.52–9.97
Pancreatic carcinoma (10033609)	25	2255	1.27	0.86–1.88
Prostate cancer (10060862)	23	4187	0.63	0.42–0.95
Female breast cancer (10057654)	22	15,431	0.16	0.11–0.25
Testis cancer (10057644)	21	220	10.94	6.99–17.12
Metastases to the lung (10027458)	20	1990	1.15	0.74–1.79
Ovarian cancer (10033128)	20	2565	0.89	0.58–1.39

ROR reporting odds ratio, *CI* confidence interval, *CNS* central nervous system

Table 4 Reporting odds ratio for the relationship between clozapine and non-hematological malignant tumors after stratification by sex

SMQ or preferred term	Sex	Report no.		ROR	95% CI
		Clozapine use	No use		
NHMT (SMQ)	Male	857	43,421	1.38	1.28–1.47
	Female	786	101,578	1.36	1.27–1.46
Lung malignant neoplasm	Male	190	2542	5.20	4.49–6.03
	Female	98	2771	6.20	5.07–7.59
Breast cancer	Male	0	0		
	Female	164	29,895	0.96	0.82–1.12
Colon cancer	Male	39	1290	2.10	1.53–2.89
	Female	13	1784	1.28	0.74–2.20
Gastrointestinal carcinoma	Male	39	213	12.72	9.04–17.89
	Female	11	327	5.89	3.23–10.74
Metastatic lung cancer	Male	22	352	4.34	2.82–6.68
	Female	24	341	12.33	8.15–18.65
Metastases to the liver	Male	14	1344	0.72	0.43–1.22
	Female	33	1849	3.13	2.22–4.41
Metastases to the spine	Male	5	294	1.18	0.49–2.86
	Female	41	567	12.67	9.23–17.40
Esophageal carcinoma	Male	39	570	4.75	3.44–6.57
	Female	1	286	0.61	0.09–4.36
Metastases to the CNS	Male	20	798	1.74	1.12–2.71
	Female	12	1196	1.76	0.99–3.10
Metastases to bone	Male	14	1324	0.73	0.43–1.24
	Female	13	1887	1.21	0.70–2.08
Throatcancer	Male	24	244	6.83	4.49–10.39
	Female	2	185	1.89	0.47–7.63
Pancreatic carcinoma	Male	12	1050	0.79	0.45–1.40
	Female	13	1065	2.14	1.24–3.69
Prostate cancer	Male	23	4047	0.39	0.26–0.59
	Female		Not applicable		
Female breast cancer	Male		Not applicable		
	Female	22	15,304	0.25	0.17–0.38
Testis cancer	Male	21	219	6.66	4.25–10.42
	Female		Not applicable		
Metastases to the lung	Male	9	883	0.71	0.37–1.36
	Female	11	1069	1.80	0.99–3.26
Ovarian cancer	Male		Not applicable		
	Female	20	2506	1.40	0.90–2.17

SMQ standardized medical dictionary for regulatory activities queries, *ROR* reporting odds ratio, *CI* confidence interval, *NHMT* non-hematological malignant tumors, *CNS* central nerve system

malignant tumors (SMQ) were 1,482 and 186 in ISRs in which the role of clozapine was registered as the primary suspected drug and others, respectively. RORs are shown in Table 5. The majority of non-hematological malignant tumors in patients treated with clozapine were suspected to be primarily caused by clozapine.

4 Discussion

In the analysis of 12,401,586 reports of adverse drug events, we identified 151,904 reports of non-hematological malignant tumors, equating to a ratio of 1.22%. Among

patients treated with clozapine, this ratio rose to 1.55%. In comparison, the ratios were 0.29% for aripiprazole and 0.32% for quetiapine and risperidone. Table 2 illustrates that only clozapine was associated with an increased reported frequency of non-hematological malignant tumors (SMQ). Notably, a recent analysis of Australian spontaneous adverse drug event reports indicated the development of breast cancer, colon cancer, and lung cancer in clozapine-treated patients [10]. In the present study, among 28,591 clozapine-treated patients, there were 171 cases of breast cancer and 22 cases of female breast cancer, but no significant signal was detected (Table 3). Even in an analysis of data exclusively from females, no signal was found (Table 4). Colon cancer was reported in 53 clozapine users, and a correlation was detected. Additionally, lung malignant neoplasm was the most prevalent among patients receiving clozapine, with 291 reported cases. A signal indicating their relationship was also identified. Regarding lung cancers, an association between clozapine and metastatic lung cancer was evident. Although not

Table 5 Reporting odds ratio for the relationship between clozapine and non-hematological malignant tumors after stratification by role of clozapine

SMQ or preferred term	Clozapine role	Report no.		ROR	95% CI
		Clozapine use	No use		
NHMT (SMQ)	Primary Suspected	1482	150,422	1.50	1.42–1.58
	Others	186	151,718	0.59	0.51–0.68
Lung malignant neoplasm	Primary Suspected	287	5602	7.76	6.89–8.74
	Others	4	5885	0.33	0.12–0.87
Breast cancer	Primary Suspected	133	30,658	0.65	0.55–0.78
	Others	38	30,753	0.59	0.43–0.82
Colon cancer	Primary Suspected	53	3230	2.48	1.89–3.25
	Others	0	3283	–	
Gastrointestinal carcinoma	Primary Suspected	50	593	12.74	9.54–17.00
	Others	1	642	0.75	0.11–5.33
Metastatic lung cancer	Primary Suspected	41	726	8.53	6.23–11.69
	Others	6	761	3.80	1.70–8.48
Metastases to the liver	Primary Suspected	42	3262	1.94	1.43–2.64
	Others	5	3299	0.73	0.30–1.75
Metastases to the spine	Primary Suspected	14	913	2.32	1.37–3.93
	Others	33	894	17.79	12.57–25.18
Esophageal carcinoma	Primary Suspected	33	912	5.47	3.86–7.74
	Others	7	938	3.59	1.71–7.56
Metastases to the CNS	Primary Suspected	25	2088	1.81	1.22–2.68
	Others	7	2106	1.60	0.76–3.36
Metastases to bone	Primary Suspected	28	3,263	1.30	0.89–1.88
	Others	0	3291	–	
Throat cancer	Primary Suspected	26	444	8.84	5.96–13.14
	Others	0	470	–	
Pancreatic carcinoma	Primary Suspected	25	2255	1.67	1.13–2.48
	Others	0	2280	–	
Prostate cancer	Primary Suspected	19	4191	0.68	0.44–1.07
	Others	4	4206	0.46	0.17–1.22
Female breast cancer	Primary Suspected	9	15,444	0.09	0.05–0.17
	Others	13	15,440	0.40	0.24–0.70
Testis cancer	Primary Suspected	18	223	12.19	7.54–19.71
	Others	3	238	6.07	1.94–18.95
Metastases to the lung	Primary Suspected	20	1990	1.52	0.98–2.36
	Others	0	2010	–	
Ovarian cancer	Primary Suspected	20	2565	1.18	0.76–1.83
	Others	0	2585	–	

SMQ standardized medical dictionary for regulatory activities queries, *ROR* reporting odds ratio, *CI* confidence interval, *NHMT* non-hematological malignant tumors, *CNS* central nervous system

included in the table, 19 reports concerning non-small-cell lung cancer (code: 10061873) in clozapine patients were identified, yielding a calculated ROR of 2.83 (95% CI 1.79–4.46). Therefore, monitoring the lungs in patients receiving clozapine might be advisable. To our knowledge, this study represents the first report detailing the relationship between clozapine and certain non-hematological malignant tumors through a disproportionality analysis.

Since smoking, alcohol, substance abuse, obesity, and a lack of exercise are prevalent among schizophrenic patients [11], schizophrenia may be a risk factor for cancer. However, a meta-analysis of seven cohort studies showed that the overall risk of cancer was not significantly higher in patients with schizophrenia than in the general population [12]. On the contrary, the incidence of malignant melanoma and prostate cancer was lower in patients with schizophrenia [12]. In a meta-analysis of 12 cohort studies, the relationship between schizophrenia and the incidence of lung cancer was unclear [13]. It has been hypothesized that genetic factors linked to schizophrenia may protect against cancer [14]. On the other hand, a population-based cohort study showed that schizophrenia was associated with a higher risk of female breast cancer, lung cancer, esophageal cancer, and pancreatic cancer [15]. Therefore, the relationship between schizophrenia and the incidence of cancer is controversial. In addition, it has not yet been clarified whether alcohol and tobacco consumption is higher in patients with treatment-resistant schizophrenia. Therefore, the involvement of confounding factors by indication in the present study cannot be ruled out. Furthermore, this study did not take into account the effects of age.

Swildens et al. [16] showed that the utilization of specialist somatic healthcare was lower for patients with non-affective psychotic disorders, including schizophrenia, than for matched controls. This may delay cancer detection and lead to metastases to the spine.

The 95% CI of the RORs of aripiprazole, quetiapine, and risperidone for non-hematological malignant tumors (SMQ) was less than 1 (Table 2). An inverse signal in a disproportionality analysis may become a trigger for drug development through drug repurposing. An inverse signal is obtained by under-reporting in a disproportionality analysis using a spontaneous reporting system database. An inverse signal must be carefully interpreted when analyzing the spontaneous reporting system database of adverse events [17].

Clozapine is oxidized in neutrophils and in the heart to a chemically reactive nitrenium ion [18–20]. This bioactivation of clozapine is postulated to be involved in the pathogenesis of agranulocytosis, myocarditis, and cardiomyopathy. Chrétien et al. [8] discussed the relationship between nitrenium ion of clozapine and hematologic malignant tumors. However, there is limited information available to support a link between clozapine and the occurrence of non-hematological malignant tumors. Further research is necessary to confirm the relationship between clozapine and the risk of non-hematological malignant tumors.

The current study, utilizing a clinical spontaneous reporting system for adverse drug events, revealed a relationship between clozapine and metastases (Tables 3 and 4). To the best of our knowledge, there are no reports detailing the molecular mechanisms through which clozapine promotes cancer metastasis. Additionally, the relationship between drugs and cancer metastasis has not been extensively investigated in clinical settings. Further research is essential to understand these mechanisms and potential clinical implications fully.

There are several limitations that need to be addressed. The FAERS database is based on a spontaneous reporting system. Therefore, a reporting bias, such as over- or under-reporting, may be inevitable. Furthermore, deduplication is never perfect [21]. Because clozapine induces agranulocytosis, convulsions, gastrointestinal obstruction, myocarditis, and diabetes, clozapine-treated patients need to be monitored more closely. In the present study, we were unable to rule out the possibility of over-reporting on the development of non-hematological malignant tumors in patients taking clozapine. Since the FAERS database only contains information on patients who developed adverse drug events, the onset of an adverse drug event may affect the results. ROR is not a robust indicator of signal strength and may not correspond to the risk of adverse drug events; it also indicates an increased risk of adverse drug event reporting. The 95% CI is appropriate when no two observations in a dataset are related to each other or affect each other in any way. Since individual PTs were not independent in the present study, this is clearly not a valid assumption for the individual PT analysis reported herein. In addition, unknown confounding factors may have affected the results of logistic regression analyses. Therefore, the present results need to be interpreted in consideration of these limitations.

5 Conclusion

Our disproportionality analysis detected signals associating clozapine use with higher reported frequencies of non-hematological malignant tumors, encompassing lung malignant neoplasm, gastrointestinal carcinoma, esophageal carcinoma, throat cancer, and metastases to the spine, using the FAERS database. The results obtained suggest that sex differences play a role in the development of specific tumors and metastases among clozapine users. Since the FAERS database relies on spontaneous reporting, further

pharmacoepidemiological studies are essential to validate these results.

Declarations

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Conflicts of Interest YU and TN declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Ethics Approval Institutional Review Board approval was not required as this research was conducted using publicly available, fully anonymized, retrospective data from the FAERS database.

Consent to Participate Not applicable.

Consent to Participate Not applicable.

Data Availability Statement The datasets generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Author Contributions YU contributed to the study conception, design, analysis, and interpretation, drafted the manuscript, and revised the manuscript. TN reviewed the manuscript. All authors have approved the final version of the article.

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