Investigation of Adverse Effects of Oral Voriconazole In The Treatment of Fungal Infection Using The FDA Adverse Event Reporting System (FAERS)

By

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Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Investigation of adverse effects of oral voriconazole in the treatment of fungal infection using the FDA Adverse Event Reporting System (FAERS)" submitted by Kazi Onanna (19346063) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy on July, 2023.

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Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

This investigation examines pharmacovigilance databases to find the most common adverse effects associated with voriconazole. I performed a statistical analysis of voriconazole adverse events using data from the FDA's Adverse Event Reporting System (FAERS). Each adverse event was assigned a frequency and reported odds ratio (ROR). A total of 2511 reports were produced by the FAERS database. While voriconazole remains an important medicine for fungal treatment, the adverse reactions associated with voriconazole should be considered. The Major five adverse effect of voriconazole was highlighted in this study based on the highest number of signals received.

Keywords: Food and Drug Administration Adverse Event Reporting System (FAERS)**;** reported odds ratios (ROR)**;** fungal treatment; adverse reactions**;** pharmacovigilance

Dedication

Dedicated to my faculty members, family and friends

Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with the strength during this whole period; I am indebted and would like to express my sincere gratefulness and gratitude towards Dr. Mesbah Talukder, Professor, School of Pharmacy, Brac University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey.

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List of Acronyms

FAERS	FDA Adverse Event Reporting System
MedDRA	Medical Dictionary for Regulatory Activities
AE	Adverse Events
ROR	Reporting Odds Ratio
CI	Confidence Interval
FDA	Food and Drug Administration

Chapter 1

Introduction

1.1 The class of Drug

A drug known as an antifungal agent kills fungal pathogens from a host in a selective manner while causing little harm to the host. Antifungals may be categorized into three groups based on how they work: Azoles, which stop ergosterol, the primary sterol present in fungus, from being produced, Polyenes, which physically interact with sterols found in fungi's membranes; and 5-fluorocytosine, which prevents the synthesis of large molecules (Johnson & Kauffman, 2003a). Azole drugs are basically sub-divided into two categories. One is Imidazole and another one is Triazole. They are basically classified based on their nitrogen number present in the five-member azole ring (Greer, 2003). Voriconazole is known as a triazole antifungal drug. It is a fluconazole synthetic derivative. When a fluorinated pyrimidine was substituted for one of the triazole rings and a -methyl group was added, the activity was increased in comparison to fluconazole. This expanded antifungal range was a key factor in the creation of voriconazole (Johnson & Kauffman, 2003b). The first triazole antifungal medication with a 1-(1H-1,2,4-triazol-1-yl) butan-2-ol substructure was voriconazole (VCZ) approved by FDA on May 24, 2002 under the trade name of 'Vfend' (Ghobadi et al., 2022) .The Molecular formula of Voriconazole is $C_{16}H_{14}F_3N_5O$. The structure of voriconazole is:

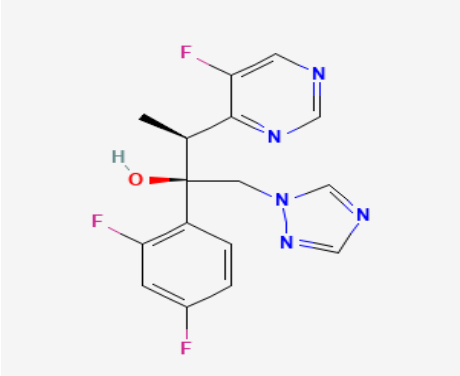

Figure 1: Structure of Voriconazole

1.2 Voriconazole

Now accessible, "voriconazole" is the first of the second-generation triazoles to show significant activity against a wide variety of clinically-relevant fungal infections.. Oral dosing of voriconazole results in rapid absorption with a greater than 90% oral bioavailability, allowing for the use of both oral and intravenous forms when clinically administrated. Because of its capacity-limited elimination, voriconazole has nonlinear pharmacokinetics, and its pharmacokinetics are consequently dose-dependent. The plasma concentration-time curve's (AUC) area under the curve for voriconazole increases super proportionally with dose. Voriconazole pharmacokinetics seem to be linear for doses administered to children (age 12 years). In approximately 5 days following intravenous and oral administration, steady-state plasma concentrations are reached. There is a volume of distribution for voriconazole of 2-4.6 L/kg which indicates widespread dispersion into extracellular and intracellular compartments. In addition to cerebrospinal fluid, in tissue samples taken from the heart, lungs, liver, kidney, and kidneys, voriconazole was examined. A little over 60% of plasma protein binding is unaffected by dose or plasma concentration. CYP2C19, CYP2C9, and CYP3A4 are hepatic cytochrome P450 (CYP) isoenzymes perform N-oxidative hepatic clearance. The half-life of voriconazole's elimination is roughly six hours, and three quarter of the complete dose is recovered in the urine (Theuretzbacher et al., 2006). The drug voriconazole is used to treat a number of severe fungus infections. Invasive aspergillosis is one of them; it begins in the lungs and eventually spreads through the circulation to the other organs. Additionally, the drug can cure esophageal candidiasis, a yeast infection that results in white patches in the mouth and throat. Additionally, Voriconazole can treat yeast infections of the skin, kidney, stomach, bladder, and wounds. Agitation, anxiety, headaches, dry mouth, appetite loss, nausea, and vomiting are a few of the more frequent side effects of voriconazole (Stefan et al., 2022). Patients who receive prolonged therapy are developing new and unusual side effects. Most

worrying is the increased risk of cutaneous malignancies, particularly squamous cell carcinoma (SCC), which is time dependent and has a tendency to be more aggressive and multifocal. Additionally, voriconazole is linked to phototoxicity (which could be a sign of cancer development), periostitis, hallucinations, encephalopathy, peripheral neuropathy, alopecia, changes in the appearance of the nails, hyponatremia, and other side effects (Levine & Chandrasekar, 2016).

Chapter 2

Method

2.1 Data Source

All the data were collected from FDA Adverse Reporting System Database (FAERS). Data from four quartile (Q1-Q4) of 2020-2022 (Q1-Q4) were selected to conduct the analysis. System organ classifications (SOCs) as well as recommended terms (PTs) were taken from the Medical Dictionary for Regulatory Activities (MedDRA-version 24.0) were used to define adverse events (AEs). To calculate the relationship of adverse event between voriconazole and every other medication listed in the database system, reported odds ratio (ROR) was utilized (Jeu et al., 2003).

2.2 Procedure

Data is compiled quarterly that includes information on adverse event reports. All reports of voriconazole were taken from FAERS during 2020 (Q1-Q4) to 2022 (Q1-Q4) for this investigation. All the files were loaded into R studio and same type of file type such as: All Drugs, All Reaction and All Demographics were bind together. Due to the fact that FAERS contains duplicate records, deduplication operation was executed. When the "CASEID" and FDA Date are identical, the FDA advises eliminating duplicate data by selecting the more current FDA Date, as well as based on greater primaryid and dduplication for the same age, weight, and event_DT (Hu et al., 2020). To locate records of target pharmaceuticals, both brand names and generic names were used because drug names are not standardized by FAERS (Purkins et al., 2002). Table S1 in the Supplementary Materials provided an index for the chosen drug. According to MedDRA (version 24.0), each and every "Adverse Event" was tagged as a preferred phrase (PT). These PTs were also accompanied by the principal system organ classes (SOCs), which were analogous to the system categorization in other medical

terminologies. All drug except ‘Voriconazole’, dduplicated demo and reaction were combined so for the drug ‘Voriconazole’, dduplicated demo and reaction files were combined together. AEs were extracted from both files and merge together to perform the reported odds ratio (ROR). Severe outcomes were defined as those that were life-threatening or led to hospitalization, disability, or death. Any severe adverse event that wasn't included in the FDA's medication prescription guidelines was regarded as unexpected.

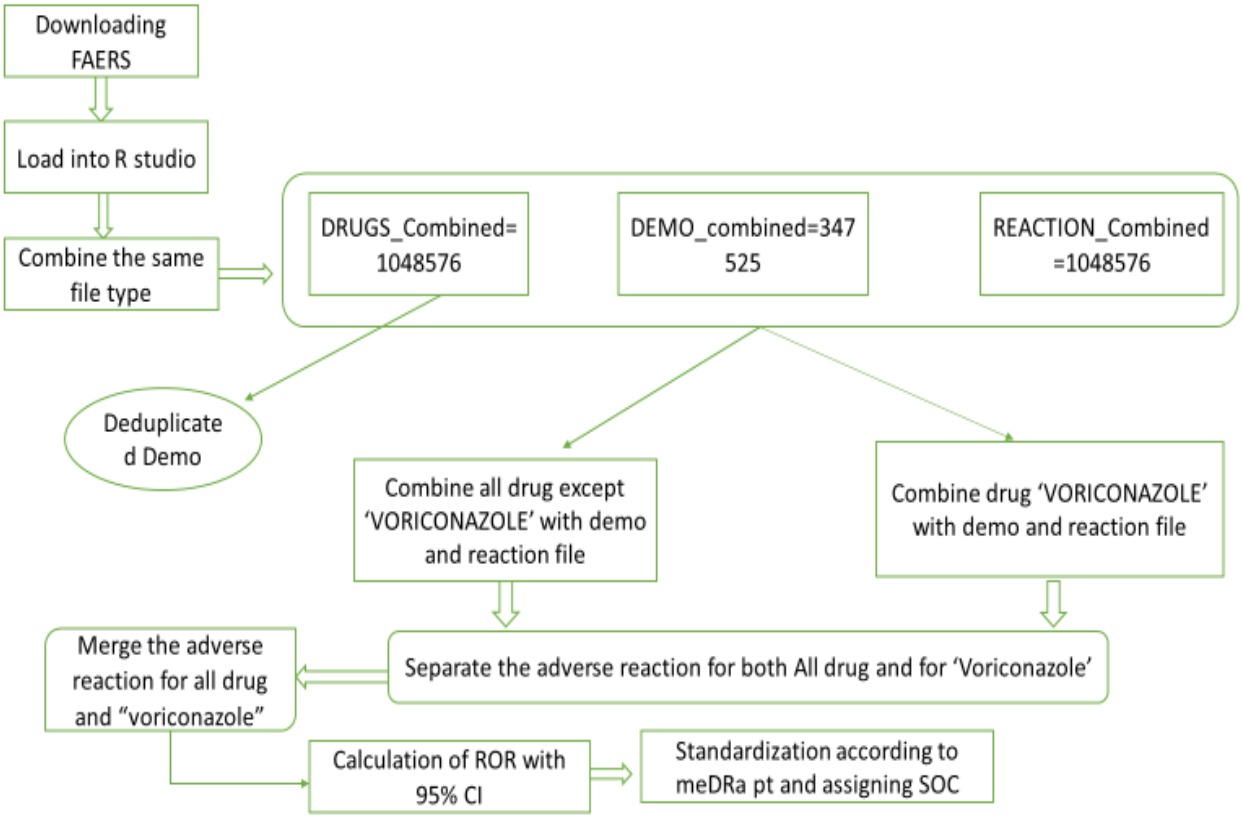

Figure 02: Method used to do the processing

2.3 Statistical Analysis

The study used disproportionality analysis to identify signals of probable elevated risk of harmful adverse events. An abnormally high frequency of drug-event pairings in the database may indicate the presence of a significant signal in quantitative signal identification. To

validate the stability of the identified signals, one disproportional signal identification approach based on frequency - the proportional report odds ratio (ROR) - was applied.

The ROR is calculated as follow:

$$\text{ROR}=\frac{Nobserved+0.5}{Nexpected+0.5}$$

All metrics of disproportionality are calculated using the same methods, utilizing the 2 by 2 table. Nobserved = X, where "X" is the observed quantity of records for the relevant drug-AE pairings. The predicted number of intriguing drug-AE records is Nexpected, the term "N_{drug}" stands for "number of target drug records", The terms N_{event} and N_{total} refer to the total number of target AE records and the total number of records in the whole database, respectively.

Chapter 3

Results

3.1 Descriptive Analysis

From 2020 (q1-q4) to 2022 (q1-q4), the FDA received 10,48,575 AE reports, with 47,670 relating to the use of voriconazole. A total of 29,357 AE was collected for Voriconazole among which 15091 (51%) are male which is the most reported case and 11197 (38%) are female and the rest of the case gender are unknown. The median age was 60 and most of the instances were people under the age of 70. The second highest number of people were under age 40 to 60. Drug ineffective, drug-drug interaction, aspergillus infection and the most common reported results were deaths.

Table 01: AE's on Gender

Gender	Count
Male	15091
Female	11197
NA	3069

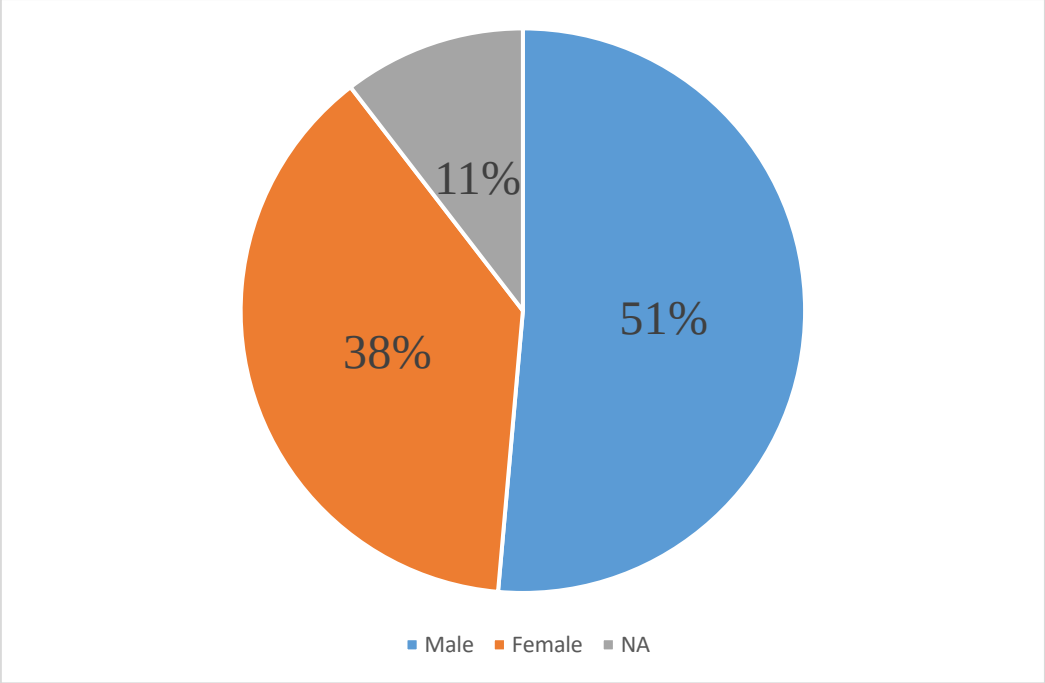

Figure 03: Adverse reaction of VORICONAZOLE on Gender

Table 02: AE's On Age

Age		**Total Count**
0-19		4354
20-39		3729
40-59		6326
60-79		9505
80-99		865
unknown		4578

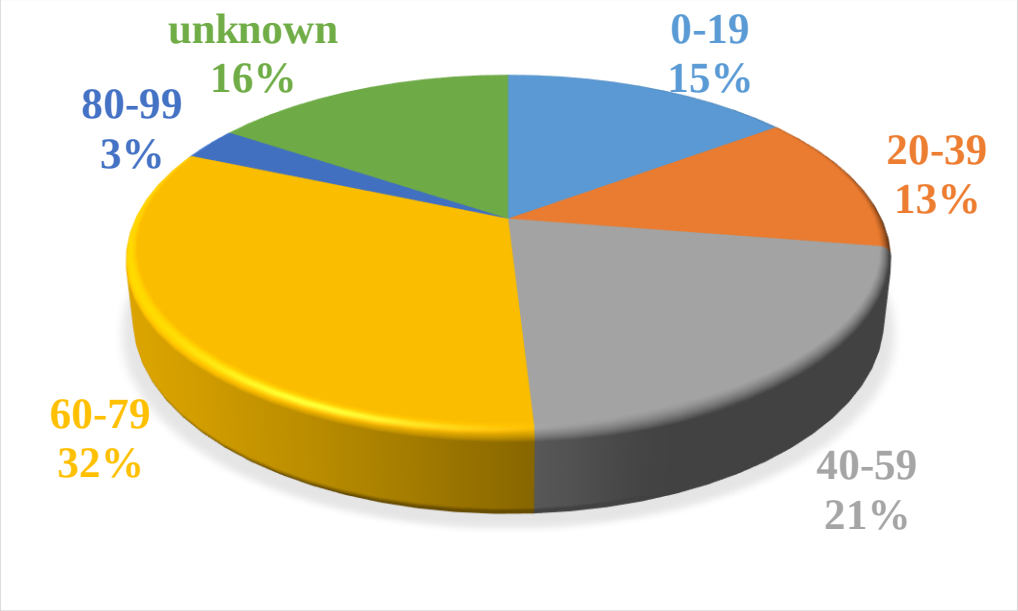

Figure 04: AE's on different age group.

Table 03: Outcome for Voriconazole

Outcome	**value**
Drug ineffective	1882
Off label use	1555
Drug interaction	923
Aspergillus infection	610
Pyrexia	602
Condition aggravated	477
Death	446

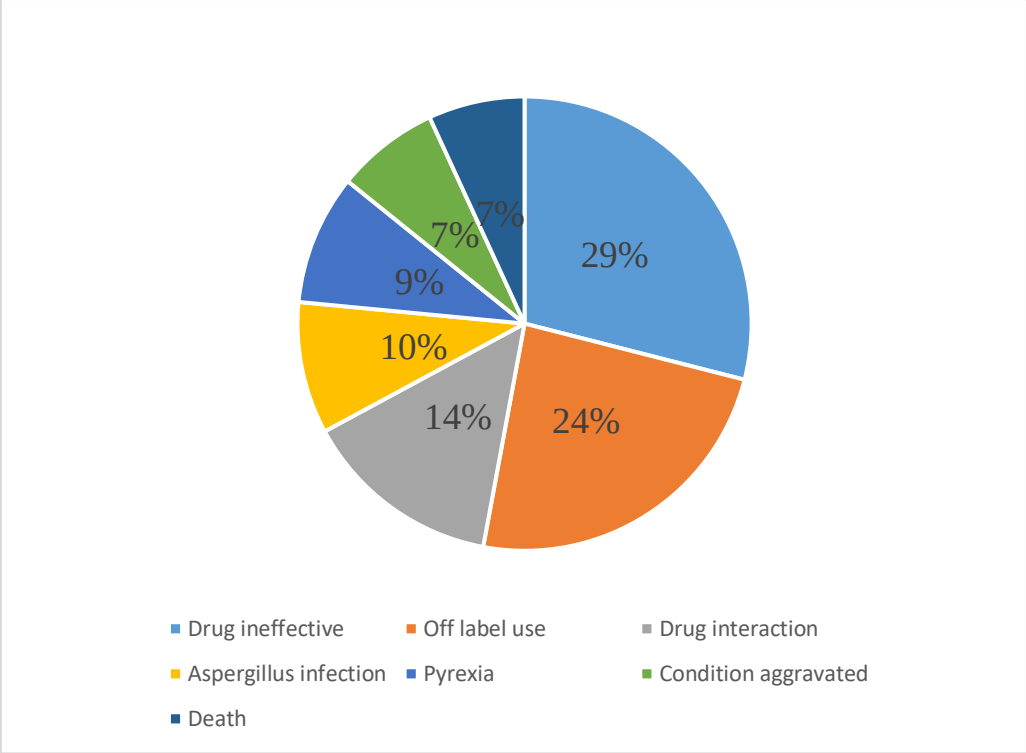

Figure 05: Outcome of AE's on Voriconazole

Table 04: AE's signal for Voriconazole

SOC	Voriconazole	ALL_except_Voriconazole	ROR	Lower -CI	Upper_CI
Blood and lymphatic system disorders	2031	657540	1.82	1.74	1.9
Cardiac disorders	3470	2002304	1.02	0.99	1.06
Congenital, familial and genetic disorders	69	6418	6.34	5	8.03
Ear and labyrinth disorders	134	149836	0.53	0.44	0.62
Endocrine disorders	2486	2821221	0.52	0.5	0.54
Eye disorders	7375	2084901	2.08	2.04	2.13
Gastrointestinal disorders	1485	1178477	0.74	0.71	0.78
General disorders and administration site conditions	7	22368	0.18	0.09	0.39
Hepatobiliary disorders	1927	1551224	0.73	0.7	0.77
Immune system disorders	3739	2346623	0.94	0.91	0.97
Infections and infestations	1333	767622	1.02	0.97	1.08
Injury, poisoning and procedural complications	4083	2150495	1.12	1.08	1.15
Investigations	19	12175	0.92	0.59	1.44

Metabolism and nutrition disorders	1366	219300	3.67	3.48	3.87
Musculoskeletal and connective tissue disorders	850	677547	0.74	0.69	0.79
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	798	410915	1.14	1.07	1.23
Nervous system disorders	1534	294758	3.07	2.92	3.22
Pregnancy, puerperium and perinatal conditions	1101	1052469	0.62	0.58	0.65
Psychiatric disorders	2471	1585928	0.92	0.88	0.96
Renal and urinary disorders	87	106374	0.48	0.39	0.59
Reproductive system and breast disorders	7695	4669459	0.97	0.95	0.99
Respiratory, thoracic and mediastinal disorders	108	87053	0.73	0.61	0.88
Skin and subcutaneous tissue disorders	15	123701	0.07	0.04	0.12
Social circumstances	1746	355126	2.9	2.76	3.04
Surgical and medical procedures	900	2260285	0.23	0.22	0.25

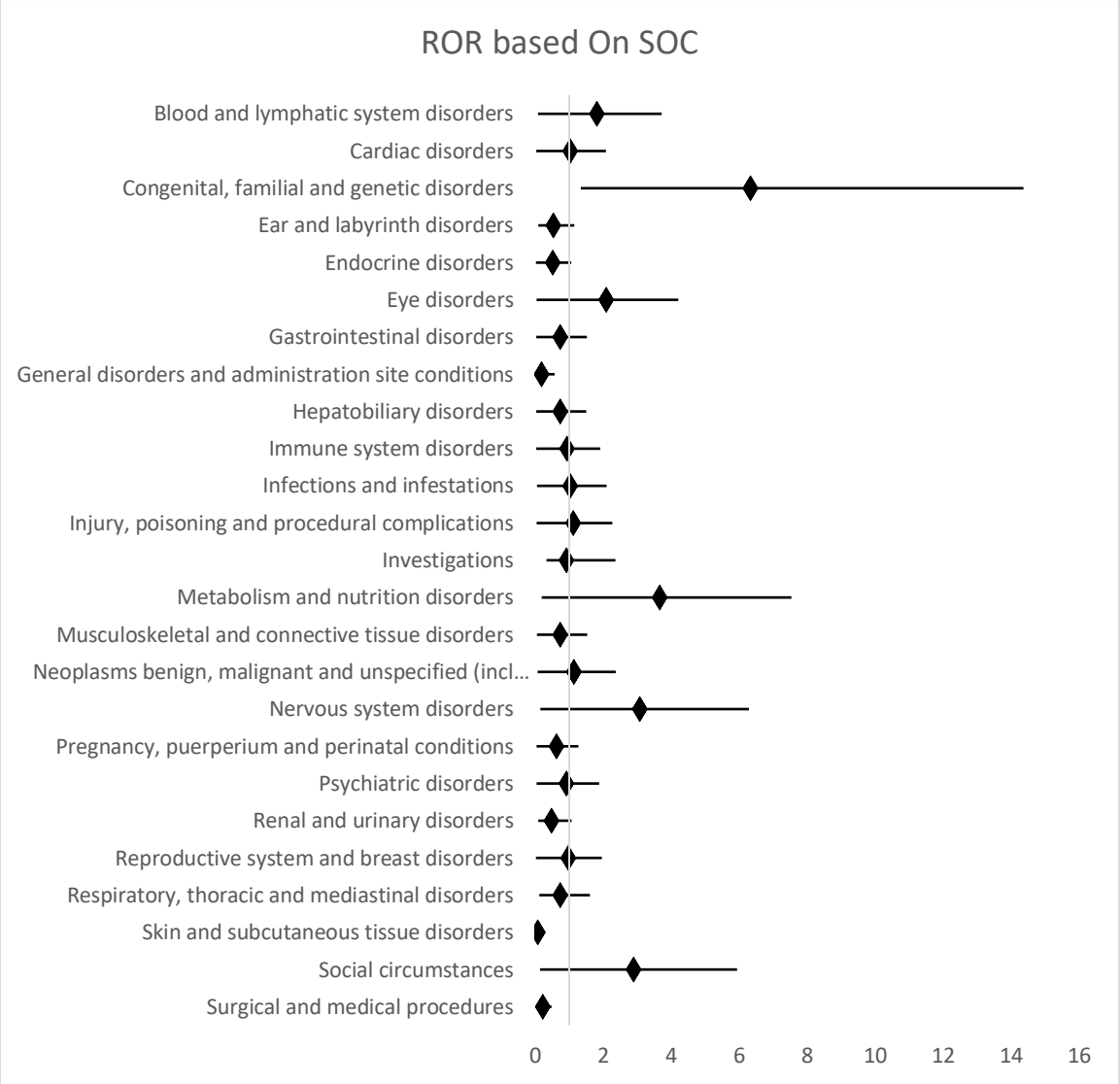

Figure 06: Forest plot based on SOC

Chapter 4

Discussion

ROR, which is based on a statistical idea (it belongs to the frequency approach) and can represent the target drug-AE link in a mutually verified, rapid, and quantified way, was used in this experiment to determine the probable adverse signals of voriconazole (Pfaller et al., 2002). A total of 2511 pt (preferred term) was observed after the analysis. Among them Drug ineffective, Off-level use, Drug-drug interaction and aspergillus infection were most identified signals. An article based on adverse effect associate with long term administration of azole antifungal agents has shown that voriconazole have been associated with peripheral neuropathies. In addition, voriconazole has been associate with periostitis, phototoxic reaction and squama's cell carcinoma (Benitez & Carver, 2019). However, the study which was conducted here has shown a slightly different result compare to the article which is drug ineffective, Off-level use, Drug-drug interaction and aspergillus infection were most common adverse effect which was observed by the report.

Chapter 5

Limitation

The fact that I neglected to use the Bayesian confidence propagation neural network of information components (IC) to confirm the stability of the identified signals is one of the study's drawbacks. The fact that FAERS, an SRS, has inherent flaws such underreporting, duplicate data, uneven information quality, a lack of controls, and the inability to calculate incidence rates is another drawback of this study's execution. Even after manual correction and de-duplication, target drug data that were left out may still exist (Zhou et al., 2021). Although disproportionality analysis in pharmacovigilance is well-established, one drawback of such approaches is the absence of a gold standard for evaluating the validity and scope of suspected safety problems (Almenoff et al., 2007).

Chapter 6

Conclusion

Concerns about voriconazole's safety have arisen due to its widespread clinical use. This study thoroughly investigated the potential AE signs of voriconazole (Fernández-ávila et al., 2021). Here, in this study we observed different AE among different age group of people and the highest potential signals in gender as well. There were around 2511 signals was calculated however among them we also highlighted the most significant 5 signals. Our findings can only point to the AEs that are overreported for voriconazole; Additional information is necessary to establish causation, such as pharmacoepidemiological studies, pharmacokinetic and pharmacodynamic plausibility, or pharmacological traits and etiology (Mangal et al., 2018).

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