# LEVERAGING PHARMACOVIGILANCE DATA MINING WITH "THE PATIENT" IN MIND

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# LEVERAGING PHARMACOVIGILANCE DATA MINING WITH "THE PATIENT" IN MIND

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# Editorial: Leveraging pharmacovigilance data mining with "the patient" in mind

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Editorial on the Research Topic
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Despite the emergence of new technologies, the use of individual case safety report (ICSR) is a central activity in the advance of pharmacovigilance. Revisions in causality assessment continue to be a topic of interest, such as the recently reported vigiGroup clustering system (Norén et al., 2021). Furthermore, some groups are working on the data integration through artificial intelligence, particularly machine learning (Kreimeyer et al., 2021; Ball and Dal Pan, 2022). However, while the objectives of these advances is fundamental to improve the signal detection process, the eleven papers in this Research Topic serve as reminders that the multifactorial nature of "the patient" must remain at the forefront of any pharmacovigilance-related activities, including detection, understanding, assessing, preventing, managing and communicating adverse drug events.

As part of pharmacovigilance activities, data mining of adverse events related to pharmaceuticals is critical for early identification of potential safety signals, validation of safety signals, risk assessment and establishment of risk minimization activities. Databases to support the collection of ICSR may be used in early identification monitoring systems for specific adverse events, such as the National Tuberculosis Program in Pakistan which Massud et al. reported as minimizing the risk of adverse events among drug-resistant *tuberculosis* patients. However, most adverse event patterns for signal detection are gained through wider scope systems, such as those utilized by five articles appearing in this Research Topic (Guo et al.; Ji et al.; Liu et al.; Khan et al.; Cai et al.).

The importance of ICSR databases for previously undescribed safety concerns was highlighted by Khan et al., where ICSR from the pharmacovigilance center of the Balcali Hospital in Turkey were used to explore differences in adverse event profiles across pediatric age groups; a population which the authors reported have limited available data in that country. Guo et al. using the Henan Adverse Drug Reaction Monitoring Center in China determined signals for adverse events not previously described for antipsychotic drugs. Liu et al. used the US Food and Drug Administration Adverse Event Reporting System, one of the largest national safety databases, to examine known cardiotoxic adverse events of anaplastic lymphoma kinase tyrosine inhibitors and identified difference across the drug class.

The incongruence between frequentist and Bayesian disproportionality methodologies of signal detection was discussed by Liu et al. and has been supported by other authors (Faich and Morris, 2012; Lee et al., 2020; Khouri et al., 2021). Ji et al. explored an analytical modeling that integrates pharmacology information, such as known drug adverse event associations and other intrinsic drug properties with Bayesian disproportionality analytics. The modeling advanced by these authors is likely to stimulate conversations on a hopeful transformational improvement.

The relevance of phenotypic and genetic information in the adverse events process is gaining attention (Mahmoudpour et al., 2022); however, consideration of these patient specific factors as part of ICSRs remains under-explored. Crutchley and Keuler examined the impact of differences in the Cytochrome (CYP) enzymes, specifically CYP2D6, on the efficacy of psychotropic drugs and remission rates with comparison among Black, Latinos and Whites and thus provided good support to the addition of genetic information in guiding therapeutic interventions that may minimize risk. Similarly, the articles of Koomdee et al. and Tiwattanon et al. both reported on benefits of the integrating Human Leukocyte Antigen genotyping to reduce possible drug–induced severe cutaneous adverse drug reactions.

The use of machine learning in the pharmacovigilance data mining processes has attracted the interest of many stakeholders (Kreimeyer et al., 2021; Trifirò and Crisafulli, 2022). However, as we advance the use of "*computer algorithms*" to define the patient, we need to remain mindful of ICSR guidelines provided by the International Council on Harmonization, which encourages the inclusion of reporter narratives of cases. Although the unstructured nature of narratives is challenging for aggregated data analysis, such information is crucial for causality assessment. Cai et al. highlighted absence of patient hypersensitivity history in the analysis of cephalosporin induced adverse events in children. The article by Lee et al. reports on a direct relationship between poor medication adherence and adverse events among patients on multiple pharmaceuticals for long-term. Furthermore, the willingness of this patient group to adhere to medication is highly dependent on behavioural factors; which is the focus of the perspective article of Brown et al. and posits for the revision of the ICSR guidelines to support inclusion of such information. These three articles in this special topic serve as a reminder that there is a need for efforts to be made to integrate reported narratives into the signal detection processes.

In conclusion, as recent advances made in pharmacovigilance are poised to improve the science, the contributed articles of this special topic emphasize the need to ensure "the patient" is adequately represented in ICSR. The evidence presented herein add to a topic dearth of information and justify further exploration into the inclusion of more patient related factors in signal detection processes, in order to appropriately attribute blame.

## Authors contribution

MG-W drafted the editorial and MS revised the first draft. Both authors contributed to the revisions and approved the submitted version.

## Conflict of interest

Author MS is employed by Daiichi Sankyo, Inc.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

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ORIGINAL RESEARCH
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# Status and Safety Signals of Cephalosporins in Children: A Spontaneous Reporting Database Study

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**Introduction:** Cephalosporins are widely used in clinical treatment of children, but it is difficult to carry out clinical trials and there is no strong evidence of their safety. Therefore, adverse drug reactions (ADR) of cephalosporins can be a public health problem that deserves attention.

**Methods:** ADR reports collected by the Hubei Adverse Drug Reaction Monitoring Center from 2014 to 2019 were analysed. The safety of Cephalosporins was described by descriptive analysis and three signal mining methods, including the reporting odd ratio (ROR), proportional reporting ratio (PRR), and comprehensive standard method (MHRA).

**Results:** The findings indicated that the age groups of 0–1 and 2–3 years had the highest rates of reporting ADRs. Children aged 0–4 years reported more ADRs, while the proportion of severe ADRs was lower than the average (6.63%). Among the 37 cephalosporins, the severe ADRs of ceftezole, ceftazidime, cefoperazone/sulbactam, cefotaxime, ceftriaxone were reported more and the proportion of severe ADRs was higher. The proportion of severe ADRs of most cephalosporin compound preparations was higher than that of corresponding single components. A total of 99.18% of the cases improved after treatment. There were four deaths whose ADRs were mainly anaphylactic shock, dyspnoea, and anaphylactoid reaction. In signal mining, the three methods produced 206 signals that were the same, and 73 of them were off-label ADRs.

**Conclusion:** ADRs were common but not serious in children aged 0–4 years. And the reported rate of serious ADRs in children aged over 4 years increased with age. ADR reports of ceftezole, ceftazidime, cefoperazone/sulbactam, cefotaxime, ceftriaxone were numerous and serious, and the safety of cephalosporin compound preparations in children was doubtful. Ceftezole may cause off-label ADRs including tremor, face oedema, cyanosis, pallor, rigors, and palpitation. The labeling of ADRs in children in cephalosporin instructions and the record of allergic history need to be improved.

**Keywords: cephalosporin, children, spontaneous reporting system, signal detection, measures of disproportionality**

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# INTRODUCTION

Cephalosporins belong to β-lactam class of antibiotics and have been developed to the fifth generation at present. Cephalosporins are widely used in the world for their broad antibacterial spectrum, low toxicity, penicillinase resistance and rich varieties. The subsequent adverse drug reactions (ADRs) have also become the focus of public concern. In China, an ADR is defined as the harmful reaction of qualified drugs under normal usage and dosage, which has nothing to do with the purpose of drug use (2011). The annual reports of national ADR monitoring in China from 2017 to 2019 all showed that ADR reports of cephalosporins were the most in the reports of anti-infective drugs, which also had the most reports of serious ADRs (Administration, N.M.P, 2018; Administration, N.M.P, 2019; Administration, N.M.P, 2020).

With the implementation of the two-child policy in 2015 and the three-child policy in 2021, the number of children (0–14) in China has increased rapidly, and the safety of children's medication has become a key point to improve the health of children. G. M. Park found that antibiotics were the most common ADR causing drugs in children, among which the third cephalosporin was the most common (Park et al., 2012). Jung also believed that antibiotics were the most common drugs that might cause ADRs in children ($n$ = 5,159), among which cephalosporins were the most common drugs ($n$ = 5,101). Gastrointestinal tract and skin clinical features were the most frequently reported ADR (Jung et al., 2017). In 2015, the National Medical Products Administration warned that cefathiamidine could cause severe ADRs like anaphylactic shock, and a high proportion of ADRs of cefathiamidine have been reported in the ADR reports of children (Administration, S.F.a.D, 2015). Children, as a special medication population, are prone to ADR due to their underdevelopment of liver, kidney and central nervous system and poor ability of metabolism, excretion and tolerance of drugs.

Cephalosporin ADRs in children is a public health problem that deserves attention. It is difficult to carry out clinical trials in children, and there is no strong evidence of safety. And the use of cephalosporins is mostly based on long-term clinical practice. Therefore, it is necessary to re-evaluate the safety of cephalosporins in children after marketing. The purpose of this study was to analyze the provincial spontaneous reporting system (SRS) database to investigate the safety of cephalosporins in children from all aspects of ADRs.

# MATERIALS AND METHODS

## Data Source and Preprocessing

The data of the ADR reports collected by Adverse Drug Reaction Monitoring Center of Hubei Province from January 2014 to December 2019 were classified and analysed.

The data were cleaned and preprocessed to ensure that they were clean and complete. The ADR database includes all reported ADR reports. Reports of cephalosporin in children aged 0–14 were selected for inclusion. The analysis only included reports with certain, probable, and possible relationships of drugs and ADR evaluated by the reporting unit, and excluded reports that were unlikely or impossible to evaluate. Since there was no unified standard for the entry of drug names and ADRs in the report, the names of active pharmaceutical ingredients (APIs) registered in the National Center For Drug Evaluation were used as the standard to unify the generic names and the ADRs and clinical manifestations were organized according to the World Health Organization Adverse Reaction Terms (WHO-ART).

For the death cases, relevant information was detailed and carefully analysed to find other key points that had contributed.

From January 2014 to December 2019, the ADR Monitoring Center collected a total of 420,114 reports, containing 60,433 reports from children aged 0–14. There were 15,857 reports meeting the inclusion criteria. Since there might be two or more ADRs in a report or case, and the occurrence of an ADR in the use of a certain drug was considered an event, 20,681 events were included in the statistics.

**TABLE 1 |** The fourfold table used in measures of disproportionality.

| Category of drugs | Target ADR N | Other ADRs N | Sum |
|---|---|---|---|
| Target drug | a | b | a+b |
| Other drugs | c | d | c + d |
| Sum | a+c | b + d | N = a+b + c + d |

## Data Analysis

A descriptive analysis of sex, age, allergic history, drug, severity, types, and results of ADRs in the reports was carried out.

The amount of each ADR of each cephalosporin was sorted for ADR signal mining, which quantifies the qualitative nature of the relationship between drugs and ADRs (Hauben et al., 2005). In ADR signal mining, the reporting odds ratio (ROR), proportional reporting ratio (PRR), and comprehensive standard method (MHRA) as measures of disproportionality were adopted, which is generally used in this area to detect the imbalance of target events compared with other events in the database (Hauben et al., 2005; Moore et al., 2005). When the frequency of the target drug event combination (DEC) is significantly higher and reaches the threshold compared to the background frequency, a signal is considered to be generated (van Puijenbroek et al., 2002). The strength of the association between drugs and ADRs was expressed as the ROR and PRR with 95% confidence intervals (CIs). The fourfold table used in the measures of disproportionality is shown in **Table 1**. The calculation formulas and the threshold for generating a signal with these three methods are presented in **Table 2**. In this study, signal mining of a single drug and a single ADR was conducted without considering the combination of drug use and drug interaction.

**TABLE 2 |** Formulas and criteria for generating signals of ROR, PRR, and MHRA.

| Method | Formula | Criteria and threshold |
|---|---|---|
| ROR | $ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$ | a ≥ 3 and lower limit of 95%CI > 1 |
| | $SE(\ln ROR) = \sqrt{(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d})}$ | |
| | $95\%CI = e^{\ln(ROR) \pm 1.96SE(\ln ROR)}$ | |
| PRR | $PRR = \frac{a/(a+b)}{c/(c+d)}$ | a ≥ 3 and lower limit of 95%CI > 1 |
| | $SE(\ln PRR) = \sqrt{(\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d})}$ | |
| | $95\%CI = e^{\ln(ROR) \pm 1.96SE(\ln PRR)}$ | |
| MHRA | $PRR = \frac{a/(a+b)}{c/(c+d)}$ | a ≥ 3, PRR ≥ 2, and $\chi 2 \geq 4$ |
| | $\chi^2 = \frac{n(\lvert ad-bc\rvert - \frac{n}{2})^2}{(a+b)(a+c)(b+c)(c+d)}$ | |

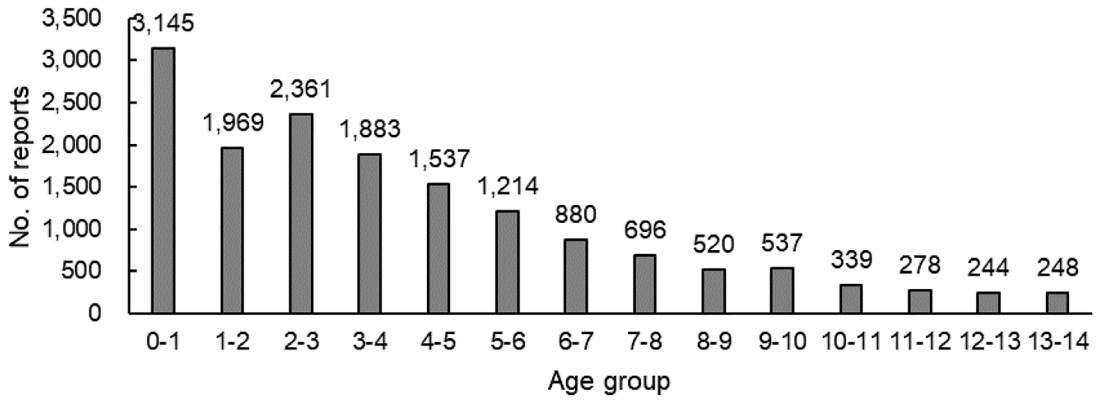


**FIGURE 1 |** Number of reports in each age group (*n*=15,851).

**TABLE 3 |** Number of reports of cephalosporins (*n* = 15,857).

| Generation | Cephalosporins | N | Generation | Cephalosporins | N |
|---|---|---|---|---|---|
| 1st | Ceftezole | 2,325 | 3rd | Ceftazidime | 1,692 |
| | Cefathiamidine | 815 | | Cefoperazone/Sulbactam | 1,565 |
| | Cefazolin pentahydrate | 240 | | Cefotaxime | 1,328 |
| | Cefazolin | 169 | | Ceftriaxone | 1,128 |
| | Cefazedone | 65 | | Cefoperazone/Tazobactam | 924 |
| | Cefadroxil | 37 | | Ceftizoxime | 700 |
| | Cefalexin | 17 | | Ceftriaxone/Tazobactam | 425 |
| | Cefradine | 16 | | Cefotaxime/Sulbactam | 314 |
| | Cefalotin | 2 | | Cefixime | 253 |
| | Cefalexin/Trimethoprim | 1 | | Cefmenoxime | 97 |
| 2nd | Cefamandole nafate | 1,589 | | Cefodizime | 93 |
| | Cefuroxime | 1,394 | | Cefoperazone | 56 |
| | Cefotiam | 231 | | Cefpiramide | 56 |
| | Cefaclor | 150 | | Cefdinir | 55 |
| | Cefprozil | 23 | | Cefpodoxime proxetil | 6 |
| | Cefuroxime axetil | 14 | | Ceftazidime/Tazobactam | 4 |
| | Cefonicid | 3 | | Ceftriaxone/Sulbactam | 1 |
| 4th | Cefepime | 64 | | Ceftizoxime/Sulbactam | 1 |
| | Cefoselis | 1 | Unknown | Unknown | 3 |

# RESULTS

## Basic Information for ADR Reports

Among the 15,857 reports related to cephalosporins in children, except for 14 cases in which the sex was unknown, the number of men (9,740) who had ADRs was significantly greater than that of women (6,103), and the male-female ratio was 1.60:1 with a big discrepancy. Excluding six reports of unknown age, the age groups with higher reporting rates were concentrated in 0-1-year-olds (3,145) and 2-3-year-olds (2,361) (see **Figure 1**).

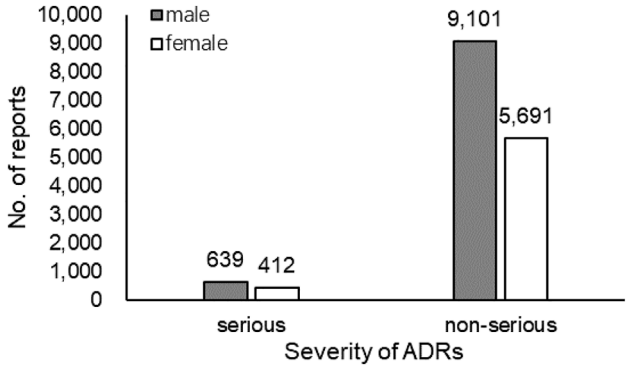


**FIGURE 2 |** Number of serious and non-serious reports by sex (*n*=15,843).

That is, newborns, infants, and young children were the most common.

According to the data that had been recorded, 38 reports were allergic to cephalosporin; 45 reports were allergic to penicillin; 10 reports were allergic to both of them; and 10 reports had a history of alcohol consumption.

## Frequently Reported Cephalosporins

A total of 15,857 cases of cephalosporins in children were reported, which involved 37 kinds of cephalosporins except three cases of unknown cephalosporins. The third cephalosporin was the most reported. Ceftezole, ceftazidime, cefamandole nafate, and cefoperazone/sulbactam were reported in large numbers (see **Table 3**).

The main route of administration was injection (15,271, 96.30%), followed by oral administration (581, 3.66%).

## Severity of the Reported ADRs

The Administrative Measures on Reporting and Monitoring of ADRs states that according to the severity of ADRs, ADRs were divided into serious and non-serious ADRs. Serious ADRs result in death, life-threatening effects, cancer, a congenital anomaly, birth defects, significant or permanent human disability, damage to organ function, hospitalization or prolonged hospitalization or events that require intervention and treatment to avoid the above results. New and known ADRs are also subdivided according to whether the ADRs are recorded in the drug insert. In addition, ADRs whose types are known but whose severity is greater than that described in the drug insert are also regarded as new ADRs (Administration, 2011) Serious and new ADRs have always been the focus of ADR research, as they pose a greater threat to the life and health of patients.

Among the 15,857 reports related to cephalosporins in children, there were 1,052 reports of serious ADRs, accounting for 6.63% of the total reports, of which 154 were new and serious reports. There were 14,805 non-serious reports containing 1,573 new and non-serious reports, accounting for 93.37% of the total. The severity of ADRs in males and females was presented in **Figure 2**. The severity of ADRs was not significantly different by sex ($\chi2 = 0.219$, $p = 0.640 > 0.05$). **Figure 3** described serious and non-serious reports in different age groups and the proportion of serious reports, excluding six cases with age unknown. It could be found that the proportion of severe ADRs in children aged 0–4 years was lower than the average (6.63%) although there were more reported ADRs, while the proportion of severe ADRs in children older than 4 years was higher than the average ($\chi2 = 31.691$, $p = 0.000 < 0.05$).

**Table 4** shows the number and proportion of serious reports of cephalosporin in children (ordered by the number of reports). Ceftezole, ceftazidime, cefoperazone/sulbactam, cefotaxime, and ceftriaxone had the most severe reports with a higher proportion of severe ADRs. It is worth mentioning that the proportion of severe ADRs of compound preparations was higher than that of corresponding single components except for compound preparations with a small number of reports, such as cefoperazone/sulbactam (9.14% > 7.14%), ceftriaxone/tazobactam (7.76% > 7.27%), and cefotaxime/sulbactam (8.60% > 7.83%).

## Frequently Reported ADRs

A total of 20,681 events involved a total of 21 system-organ damage, mainly including skin and appendage disorders, body as a whole-general disorders and gastro-intestinal system disorders. The detailed number and proportion of events were shown in **Table 5**.

According to the statistics, a total of 153 ADRs were identified, which were concentrated in rash, pruritus, urticaria, maculo-papular rash, allergic reaction, nausea, and vomiting. **Table 6** shows the distribution of the number of ADRs in the top 95%. Allergic reaction were the most concerned ADRs, accounting for 15.92%.

## Outcome of ADRs

The vast majority of children (99.18%) improved or recovered after treatment and intervention after the occurrence of ADRs. Among the four deaths, two were males and two were females. The children mainly suffered from respiratory and urologic diseases. The main ADRs were anaphylactic shock (2), dyspnoea (1) and anaphylactoid reaction (1) (see **Table 7**).

## Signal Mining Results

According to the calculation formulas and thresholds, DEC signals that do not meet the criteria were excluded. The ROR generated 211 signals, the PRR generated 207 signals, and the MHRA generated 376 signals. The three signal mining methods produced a total of 206 signals of the same DECs, and some of the signals are shown in **Table 8**. The larger the ROR and PRR values, the stronger is the correlation between the drug and ADR. All positive signals were sorted into **Table 9**, and off-label ADRs were marked.

# DISCUSSION

According to statistics, in recent 6 years, the ADR reports of cephalosporins in children aged 0–14 reported by SRS were mainly concentrated in children aged 0–3. Jiang found that

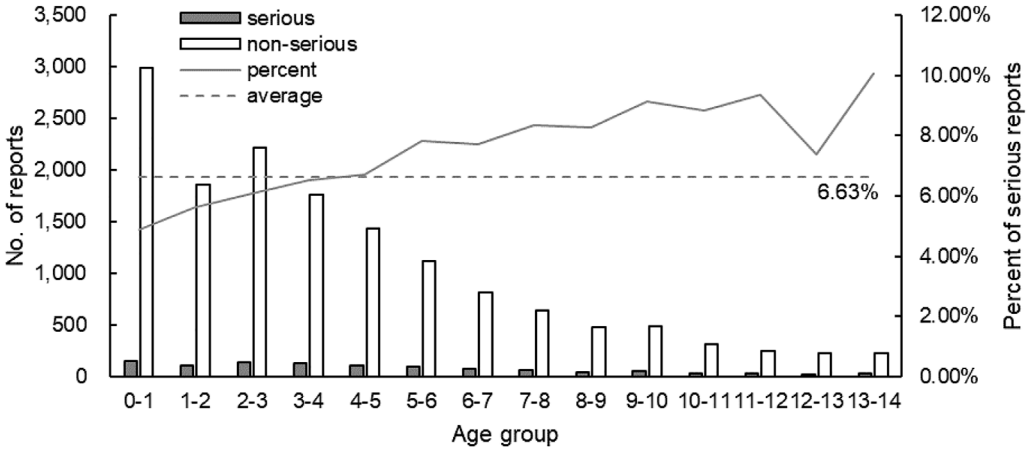


**FIGURE 3 |** Number of reports and the proportion of serious reports in each age group (*n*=15,851).

**TABLE 4 |** Number and proportion of serious reports by cephalosporin in children (*n* = 15,857).

| Cephalosporins | Serious N (%) | Total | Cephalosporins | Serious N (%) | Total |
|---|---|---|---|---|---|
| Ceftezole | 168 (7.23) | 2,325 | Cefazedone | 2 (3.08) | 65 |
| Ceftazidime | 126 (7.45) | 1,692 | Cefepime | 2 (3.13) | 64 |
| Cefamandole nafate | 73 (4.59) | 1,589 | Cefoperazone | 4 (7.14) | 56 |
| Cefoperazone/Sulbactam | 143 (9.14) | 1,565 | Cefpiramide | 0 (0.00) | 56 |
| Cefuroxime | 77 (5.52) | 1,394 | Cefdinir | 2 (3.64) | 55 |
| Cefotaxime | 104 (7.83) | 1,328 | Cefadroxil | 2 (5.41) | 37 |
| Ceftriaxone | 82 (7.27) | 1,128 | Cefprozil | 0 (0.00) | 23 |
| Cefoperazone/Tazobactam | 60 (6.49) | 924 | Cefalexin | 0 (0.00) | 17 |
| Cefathiamidine | 44 (5.40) | 815 | Cefradine | 1 (6.25) | 16 |
| Ceftizoxime | 35 (5.00) | 700 | Cefuroxime axetil | 1 (7.14) | 14 |
| Ceftriaxone/Tazobactam | 33 (7.76) | 425 | Cefpodoxime proxetil | 0 (0.00) | 6 |
| Cefotaxime/Sulbactam | 27 (8.60) | 314 | Ceftazidime/Tazobactam | 1 (25.00) | 4 |
| Cefixime | 12 (4.74) | 253 | Cefonicid | 0 (0.00) | 3 |
| Cefazolin pentahydrate | 13 (5.42) | 240 | Cefalotin | 0 (0.00) | 2 |
| Cefotiam | 9 (3.90) | 231 | Cefalexin/Trimethoprim | 0 (0.00) | 1 |
| Cefazolin | 16 (9.47) | 169 | Ceftriaxone/Sulbactam | 0 (0.00) | 1 |
| Cefaclor | 7 (4.67) | 150 | Cefoselis | 0 (0.00) | 1 |
| Cefmenoxime | 1 (1.03) | 97 | Ceftizoxime/Sulbactam | 0 (0.00) | 1 |
| Cefodizime | 6 (6.45) | 93 | Unknown | 1 (33.33) | 3 |

**TABLE 5 |** Number and percentage of ADR events related to system-organ damage (top 10, *n* = 20,681).

| Rank | System-organ damage | N | Percentage (%) |
|---|---|---|---|
| 1 | skin and appendages disorders | 13,295 | 64.29 |
| 2 | body as a whole-general disorders | 3,886 | 18.79 |
| 3 | gastro-intestinal system disorders | 1,703 | 8.23 |
| 4 | respiratory system disorders | 536 | 2.59 |
| 5 | autonomic nervous system disorders | 515 | 2.49 |
| 6 | central and peripheral nervous system disorders | 257 | 1.24 |
| 7 | urinary system disorders | 151 | 0.73 |
| 8 | psychiatric disorders | 105 | 0.51 |
| 9 | metabolic and nutritional disorders | 90 | 0.44 |
| 10 | vision disorders | 53 | 0.26 |

among the people who had ADRs after taking cephalosporins, young children were the most prominent (Jiang et al., 2021). Zheng's investigation on a hospital found that the number of children with ADRs to cephalosporins was mainly 0–3 years old (Zheng et al., 2018). The above results were consistent with the results of this study, which suggested that the

**TABLE 6 |** Number and proportion of ADRs ($n$ = 23,377).

| ADR | N | Percentage (%) | Cumulative percentage (%) | ADR | N | Percentage (%) | Cumulative percentage (%) |
|---|---|---|---|---|---|---|---|
| rash | 7,482 | 36.18 | 36.18 | coughing | 182 | 0.88 | 89.73 |
| pruritus | 3,919 | 18.95 | 55.13 | erythematous rash | 171 | 0.83 | 90.56 |
| allergic reaction | 3,293 | 15.92 | 71.05 | face oedema | 142 | 0.69 | 91.24 |
| urticaria | 1,160 | 5.61 | 76.66 | fever | 142 | 0.69 | 91.93 |
| vomiting | 703 | 3.40 | 80.06 | rigors | 109 | 0.53 | 92.46 |
| nausea | 390 | 1.89 | 81.94 | anaphylactoid reaction | 108 | 0.52 | 92.98 |
| flushing | 333 | 1.61 | 83.55 | cyanosis | 108 | 0.52 | 93.50 |
| maculo-papular rash | 329 | 1.59 | 85.15 | dizziness | 103 | 0.50 | 94.00 |
| abdominal pain | 287 | 1.39 | 86.53 | palpitation | 101 | 0.49 | 94.49 |
| diarrhoea | 284 | 1.37 | 87.91 | dermatitis | 101 | 0.49 | 94.98 |
| dyspnoea | 195 | 0.94 | 88.85 | agitation | 86 | 0.42 | 95.39 |

**TABLE 7 |** Detailed information of the 4 deaths.

| case | Sex | Age | Suspected drug | Diseases | Dosage (g) | ADR |
|---|---|---|---|---|---|---|
| 1 | male | 1 | Ceftriaxone | upper respiratory tract infection | 1 | Anaphylactic shock |
| 2 | female | 5 | Ceftriaxone | Urinary tract infection | 2 | anaphylactoid reaction |
| 3 | male | 5 | Ceftriaxone | acute bronchitis | 2 | Anaphylactic shock |
| 4 | female | 14 | Ceftazidime | upper respiratory tract infection | 2 | dyspnoea |

**TABLE 8 |** Some of the signals of ADRs (3 methods).

| Cephalosporins | ADR | ROR | 95% CI lower limit | PRR | 95% CI lower limit | $\chi^2$ |
|---|---|---|---|---|---|---|
| Cefadroxil | nausea | 51.28 | 3.2 | 40.99 | 3.12 | 306.65 |
| Cefoperazone/Tazobactam | pneumonia | 100.03 | 3.17 | 99.64 | 3.17 | 147.43 |
| Cefixime | diarrhoea | 32.34 | 3.08 | 29.28 | 3.02 | 710.24 |
| Cefradine | nausea | 54.83 | 3.01 | 43.13 | 2.98 | 164.49 |
| Cefathiamidine | skin disorder | 52.41 | 2.97 | 52.09 | 2.97 | 169.26 |
| Cefazolin | vesicular rash | 53.55 | 2.77 | 52.75 | 2.77 | 92.29 |
| Cefoperazone/Tazobactam | eye pain | 89.89 | 2.71 | 89.67 | 2.71 | 72.25 |
| Cefaclor | diarrhoea | 25.58 | 2.68 | 23.53 | 2.64 | 267.05 |
| Cefprozil | diarrhoea | 40.26 | 2.64 | 35.19 | 2.64 | 99.84 |
| Cefoperazone/Sulbactam | back pain | 112.29 | 2.46 | 112.12 | 2.46 | 56.54 |
| Cefradine | vomiting | 30.12 | 2.41 | 23.79 | 2.39 | 87.73 |
| Cefamandole nafate | abdomen enlarged | 106.04 | 2.4 | 105.89 | 2.4 | 53.29 |
| Cefoperazone/Sulbactam | urticaria acute | 18.85 | 2.37 | 18.69 | 2.36 | 189.1 |
| Ceftriaxone/Tazobactam | eye abnormality | 25.44 | 2.35 | 25.21 | 2.35 | 96.28 |
| Cefalexin | nausea | 31.01 | 2.21 | 26.91 | 2.24 | 51.04 |
| Ceftriaxone | allergic reaction | 10.21 | 2.2 | 7.54 | 1.93 | 2,158.99 |
| Cefuroxime | injection site pruritus | 43.63 | 2.17 | 43.55 | 2.17 | 42.5 |
| Cefoperazone/Sulbactam | anaphylactic shock | 14.51 | 2.16 | 14.37 | 2.15 | 170.13 |
| Cefamandole nafate | rash | 9.28 | 2.14 | 5.38 | 1.63 | 3,394.92 |
| Cefathiamidine | rash | 8.97 | 2.07 | 5.17 | 1.58 | 1,850.75 |
| Cefotaxime | larynx oedema | 20.69 | 2.06 | 20.62 | 2.06 | 63.53 |
| Ceftriaxone/Tazobactam | rash | 9.08 | 2.05 | 5.14 | 1.55 | 1,071.36 |
| Ceftizoxime | diarrhoea | 11.31 | 2.05 | 10.93 | 2.02 | 241.18 |
| Cefuroxime axetil | vomiting | 22.79 | 2.05 | 19 | 2.05 | 51.59 |
| Cefazolin | allergic reaction | 10.38 | 2.04 | 7.43 | 1.8 | 346.89 |
| Cefotaxime/Sulbactam | rash | 8.82 | 1.99 | 5.05 | 1.52 | 767.47 |
| Ceftriaxone | local anaesthesia | 18.38 | 1.98 | 18.31 | 1.98 | 60.13 |
| Cefixime | rash erythematous | 14.16 | 1.97 | 13.77 | 1.96 | 89.4 |
| Cefmenoxime | allergic reaction | 10.38 | 1.95 | 7.41 | 1.73 | 205.47 |
| Cefaclor | dermatitis | 19.14 | 1.94 | 18.71 | 1.94 | 48.55 |

physiological function of children, especially newborns and infants, was not fully mature; drug metabolism was slow; and drug accumulation was easy to occur, resulting in a high incidence of ADR. Due to the limitations of data collection, it was not possible to know the frequency of cephalosporin use by age group.

**TABLE 9 |** All positive ADR signals.

| Generation | Cephalosporins | Signal N | ADR |
|---|---|---|---|
| 1st | Ceftezole | 23 | tremor[a], cyanosis[a], pallor[a], rigors[a], palpitation[a], dizziness[a], face oedema[a], agitation[a], rash, pruritus, erythematous rash, urticaria, urticaria acute, nausea, vomiting, abdominal pain, flushing, sweating increased, fever, hyperpyrexia, coughing, allergic reaction, dyspnoea |
| | Cefathiamidine | 11 | dermatitis[a], coughing[a], lip disorder[a], rash, pruritus, urticaria, skin disorder, hyperpyrexia, rigors, oedema, anaphylactoid reaction |
| | Cefazolin | 5 | vesicular rash[a], abdominal pain[a], nausea, vomiting, allergic reaction |
| | Cefazolin pentahydrate | 5 | rash maculo-papular[a], dermatitis[a], urticaria[a], rash, pruritus |
| | Cefazedone | 3 | coughing[a], pruritus[a], rash |
| | Cefadroxil | 2 | nausea, allergic reaction |
| | Cefradine | 2 | nausea, vomiting |
| | Cefalexin | 2 | nausea, vomiting |
| 2nd | Cefuroxime | 16 | tremor[a], injection site pruritus[a], rash, pruritus, nausea, vomiting, abdominal pain, rigors, fever, hyperpyrexia, dizziness, palpitation, anaphylactoid reaction, allergic reaction, dyspnoea, injection site reaction |
| | Cefamandole nafate | 12 | pruritus[a], coughing[a], abdomen enlarged[a], chest pain[a], face oedema[a], agitation[a], rash, urticaria, skin disorder, fever, hyperpyrexia, injection site reaction |
| | Cefaclor | 7 | dermatitis[a], abdominal pain[a], flushing[a], vomiting, nausea, diarrhoea, allergic reaction |
| | Cefotiam | 6 | face oedema[a], rash, rash erythematous, urticaria, flushing, fever |
| | Cefprozil | 3 | nausea, vomiting, diarrhoea |
| | Cefuroxime axetil | 1 | vomiting |
| 3rd | Cefoperazone/Sulbactam | 17 | flushing[a], dyspnoea[a], agitation[a], dermatitis[a], dizziness[a], palpitation[a], back pain[a], cyanosis[a], rash, pruritus, rash maculo-papular, urticaria acute, nausea, vomiting, abdominal pain, allergic reaction, anaphylactic shock |
| | Ceftazidime | 15 | pallor[a], flushing[a], cyanosis[a], rigors[a], increased stool frequency[a], rash, pruritus, rash maculo-papular, rash erythematous, urticaria, urticaria acute, nausea, vomiting, abdominal pain, allergic reaction |
| | Cefotaxime | 14 | rash maculo-papular[a], dermatitis[a], vesicular rash[a], palpitation[a], larynx oedema[a], lip disorder[a], rash, pruritus, nausea, vomiting, headache, allergic reaction, anaphylactic shock, dyspnoea |
| | Cefoperazone/ Tazobactam | 10 | vesicular rash[a], coughing[a], pneumonia[a], face oedema[a], eye pain[a], eye abnormality[a], agitation[a], rash, pruritus, urticaria |
| | Ceftriaxone | 9 | dyspnoea[a], anaesthesia local[a], pain[a], pruritus, rash erythematous, abdominal pain, anaphylactoid reaction, allergic reaction, anaphylactic shock |
| | Ceftizoxime | 9 | rash maculo-papular[a], flushing[a], pallor[a], rigors[a], cyanosis[a], oedema periorbital[a], rash, diarrhoea, allergic reaction |
| | Cefixime | 7 | rash, rash erythematous, urticaria, nausea, diarrhoea, flushing, sweating increased |
| | Cefotaxime/Sulbactam | 6 | anaphylactoid reaction[a], face oedema[a], oedema[a], eye abnormality[a], rash, pruritus |
| | Ceftriaxone/Tazobactam | 5 | coughing[a], eye abnormality[a], rash, pruritus, urticaria |
| | Cefodizime | 4 | rash, pruritus, rash maculo-papular, allergic reaction |
| | Cefmenoxime | 3 | rash maculo-papular[a], rash erythematous, allergic reaction |
| | Cefoperazone | 3 | rash, rash erythematous[a], diarrhoea |
| | Cefpiramide | 2 | rash, allergic reaction |
| | Cefdinir | 2 | rash, diarrhoea |
| 4th | Cefepime | 2 | diarrhoea, allergic reaction |
| | Total | 206 | — |

[a]*Off-label ADRs.*

The patient's allergy history may be incomplete, making it difficult to make a meaningful analysis. However, a study involving 13,153 cases of cefazolin skin testing in South Korea found that 15% of patients with a history of β-lactam allergy were positive for the skin test; 1.35% of the patients without a history of β-lactam antibiotic allergy were positive, indicating that the history of β-lactam allergy may be associated with the occurrence of cephalosporin allergic reactions (Kwon et al., 2019). In addition, there may also be cross-reactivity in cephalosporin allergy (Li et al., 2019). Perfecting the records of allergic history will be helpful to the prediction of allergic reactions.

Combined with the severity of ADRs, the results showed that there was no significant difference in the distribution of the severity of ADRs between different sexes. Notably, although there were many ADR reports in children aged 0–4 years, the proportion of severe ADRs is the lowest. The likely reason was that doctors were more cautious in using cephalosporins when treating newborns and infants, prioritizing safety over efficacy (Lu et al., 2018). The reported rate of severe ADRs generally increased with age. Children at this age were in a period of rapid growth and development, and their physical conditions fluctuated greatly, so it was difficult to determine the appropriate dose. This may have something to do with the difficulty in accurately estimating the appropriate dose from experience and the increasing confidence of doctors in medication as children age. It was suggested that doctors strictly followed the drug instructions and antibiotic medication guidelines, comprehensively analyzed the state of the children, strictly controlled the dosage and prevented the inducing of drug resistance.

This study found that the use of cephalosporin compound preparations in children was more prominent in severe ADRs, and the proportion of severe ADRs in most cephalosporin compound preparations was higher than the average. At present, there were few studies on ADRs of cephalosporin compound preparations, among which the research of cefoperazone/sulbactam was the most abundant. In China, a number of retrospective studies on efficacy and ADRs reported that the efficacy of cefoperazone/sulbactam was significantly higher than that of ceftazidime in the control group, and the incidence of ADRs was considered lower than that of the control group (Zhu, 2019; Wang et al., 2020). The subjects in these studies were all older than 20 years. The noninferiority trial conducted by Liu on pneumonia patients over 18 years old showed no significant difference in the mortality rate and proportion of severe ADRs in the cefoperazone/sulbactam group compared with the cefepime group, suggesting that the two groups had the same efficacy and safety (Liu et al., 2019). In adults, ADRs and severe ADRs caused by cephalosporin compound preparations appeared to be no different or better than those caused by other conventional cephalosporins. Few studies have been conducted on ADRs of cephalosporin compound preparations in children. But the only studies that have been done on children seem to come to a different conclusion than adults, Pareek et al. compared the efficacy and safety of cefotaxime/sulbactam with amoxicillin clavulanate (conventional treatment) and found that one patient in the cefotaxime/sulbactam group reported a severe ADR to convulsion, except that both drugs were safe and well tolerated in the study population (Pareek et al., 2008). A clinical study involving 986 patients treated with cefotaxime/sulbactam found a higher incidence of ADRs in children than adults (12.73 vs. 6.46%, $p < 0.05$) (Chen et al., 2017). The ADRs of cephalosporin compound preparations in children may have different characteristics from that of adults. In addition, the pharmacokinetic trials of cephalosporin compound preparations in human volunteers were conducted in healthy adults, and the results showed no pharmacokinetic interaction between the two components, but it was not clear whether the it was consistent in children (Ma et al., 2003; Mingjie et al., 2008; Yang et al., 2011). ADRs, severe ADRs, factors and other aspects related to the safety of cephalosporin compound preparations in children may need more and in-depth studies.

In this study, it was found that the proportion of severe ADRs of most cephalosporin compound preparations was higher than that of the corresponding single formulations. Cephalosporins in compound preparation can effectively prevent bacteria from synthesizing cell wall and inhibit bacterial division, but is easily hydrolyzed by β-lactamase. Sulbactam and tazobactam are β-lactamase inhibitors, which can inhibit the activity of hydrolase but have weak antibacterial effect. Combined use of the two can increase the stability of cephalosporins and enhance the antibacterial effect. Many *in vitro* and *in vivo* experiments at earlier times have confirmed that cephalosporin compound preparations have better antibacterial effect than the corresponding single preparations (Crosby and Gump, 1982; Knapp et al., 1990; Fu et al., 2002; You et al., 2003; Prakash et al., 2005; Yong et al., 2006; Li et al., 2010). However, no comparative studies on safety between compound preparations and single preparations have been found, and only comparative studies on toxicity reactions were identified. Li investigated the difference of toxicity reaction between cefoperazone/tazobactam and single component. Acute toxicity test showed no abnormal reaction and no death in the tested animals; The long-term toxicity test showed no significant differences in hematology, blood biochemistry, coefficient of vital organs and pathology between the cefoperazone/tazobactam group and the single component group (Li et al., 2003). This study suggested that the use of cephalosporin compound preparations in children may increase the efficacy as well as ADR compared with the single preparations, probably because the impurity profile of compound preparations is not the simple summation of impurity profile of single formulations, but there are more new impurities and change quickly, indicating more allergic reactions.

ADRs of Cephalosporins in children mainly involved skin and accessory damage, systemic damage and gastrointestinal system damage, including rash, pruritus, urticaria, allergic reaction, vomiting, and nausea. There were only a few ADRs such as liver function damage, hematuria, and leucopenia. Misreporting was a common problem in SRS. Reactions of skin, gastrointestinal tract and the whole body were easy to detect, while ADRs related to liver, kidney, and blood may need to be reflected by biochemical indicators. And it was possible that medical institutions and doctors may choose not to report serious ADRs out of self-interest.

After treatment and intervention, ADRs of most patients have been improved or cured, but a few patients still left sequelae or died. Anaphylactoid reaction and anaphylactic shock accounted for the majority of the death reports, among which three cases of death reports used ceftriaxone from the same manufacturer. So it cannot be ruled out that ADRs may be caused by product quality problems. Besides, the safety of ceftriaxone has been a prominent problem. In the pharmacovigilance database of Iran from 1998 to 2009, ceftriaxone had the highest number of deaths (49 cases) (Shalviri et al., 2012); Ceftriaxone was the main drug in 112 cases of anaphylactic shock reported by SRS of Republic of Crimea from 2010 to 2018. Some literature analysis on severe ADRs of ceftriaxone showed that there were more cases of severe allergic reaction and anaphylactic shock, and anaphylactic shock was the main cause of death (Zhang et al., 2010; Lu et al., 2011). The safety of ceftriaxone still needs extra attention. Doctors should strictly follow the medication indications, strengthen the monitoring and treatment of allergic reactions, and actively carry out anti-allergy treatment.

In this study, ADR signals obtained from signal mining in the background of medication use in children may have child specificity. Combined with the drug instructions, 73 off-label ADRs were found. The off-label ADR signals of ceftezole with the largest number of reported cases were analyzed one by one.

De-Sarro reported that ceftezole was characterized by the presence of a tetrazole nucleus similar to pententytetrazole at position seven, and thus has convulsion activity. Tremor, convulsion and limb spasm occurred in both rats and dogs after intravenous administration (De Sarro et al., 1995). No cases of tremor after using ceftezole have been found in children, but a documented case of tremor and convulsion after intravenous ceftezole in an adult woman with uremia has been reported (Jin, 2009). Due to uremia, drug excretion was slowed down; plasma half-life was prolonged; the blood-brain barrier was damaged; and drugs accumulated in the central nervous system. Patients with uremia were more likely to develop antibiotic encephalopathy, or in severe cases of grand mal epilepsy. Given the six cases reported in this study

and the fact that renal function and blood-brain barrier were not fully developed in children, tremor may be associated with the drug.

The occurrence of dizziness appeared to be a rare ADR of ceftezole, and few cases have been identified in related studies. When Geng evaluated the efficacy of a drug in children with ceftezole as the control group, dizziness occurred in three out of 40 cases (Geng, 2017). In the drug efficacy studies without age limits, Wang found dizziness in four cases ($n = 40$) and Yang found dizziness in three cases ($n = 136$) (Yang et al., 2010; Wang and Zeng, 2021). However, the specific mechanism of ceftezole induced dizziness remained unclear and more research was needed.

No facial edema has been reported with ceftezole. In this study, facial edema was mainly presented as facial and eyelid edema. Given the positive signals and description of the reported data, more studies were needed.

Anxiety with ceftezole was not common. Ma used the SF-36 score to evaluate the mental state of patients (without age limit) after the use of ceftezole. The higher the score, the better the state. The study obtained a low mental state score of 61.29 (Ma, 2018). It was difficult to judge whether the anxiety and restlessness was caused by the drug, because it seemed understandable that the child was anxious in an unfamiliar environment and in a state of physical discomfort.

Reports of ADRs such as cyanosis, pallor, chill, and palpitation with ceftezole have occasionally been seen. Wei analyzed 113 cases of ADRs of ceftezole in a hospital, and found two cases of chill (Jiao et al., 2010). Guo reported a case of elderly patients with sudden palpitations, pallor, and cold extremities after the injection of ceftezole (Guo and Sun, 2005). Since there were few studies related to children, there were no reported cases of these ADRs in children, and the relevant mechanism studies were even less.

In cephalosporin instructions, ADRs are well documented, most of which include the data of clinical trial and passive monitoring. In the process of examining the instructions, it was found that the ADR items of each cephalosporin were approximately consistent with the statistics for the number of ADRs in the study. However, there are few ADR annotations and clinical trial reports of ADRs related to medication in children in cephalosporin instructions. Due to economic and ethical issues, clinical trials of medicines for children are limited, resulting in a lack of efficacy and safety data for children. Some European countries have introduced relevant policies and regulations that allow manufacturers to enrich clinical trials of drugs with children as research subjects when conditions permit (Marinovic et al., 2016; Ciato et al., 2017). In addition, ADR signals of cephalosporins with children's particularity could be obtained by data mining, which could be used as data support of ADRs in the instructions to enrich the label of ADRs related to medication in children.

The statistical results and ADR signals obtained in this study are helpful in guiding the safe use of cephalosporins for children in the clinic, and might be clues for ADR mechanism research, even providing advice for modifying drug labels based on results that may be special to children and the detection of off-label ADRs. In addition, this study has potential limitations. The effect estimated in the study is based on the data of a single province. Although the data are considerable, the external validity of the conclusion still needs to be improved. Due to the limitation of the selected signal mining method, the combination of drugs is not considered, and the conclusions may be biased.

## CONCLUSION

ADRs were common but not serious in children aged 0–4 years. And the reported rate of serious ADRs in children aged over 4 years increased with age, possibly because the body fluctuated greatly at this stage and it was difficult to determine the appropriate dose with empirical medication. ADR reports of ceftezole, ceftazidime, cefoperazone/sulbactam, cefotaxime, ceftriaxone were numerous, and serious, which deserved attention. Studies on the safety of cephalosporin compound preparations in children were few, and the safety of cephalosporin compound preparations in children was doubtful. ADR signal mining was helpful to identify off-label ADRs. Ceftezole may cause off-label ADRs including tremor, face oedema, cyanosis, pallor, rigors, and palpitation. It was also found that the labeling of ADRs in children in cephalosporin instructions and the record of allergic history need to be improved.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data is provided by Adverse Drug Reaction Monitoring Center of Hubei Province and the data is not publicly available due to institutional confidentiality requirements. Requests to access these datasets should be directed to RH, hys19810612@163.com.

## AUTHOR CONTRIBUTIONS

Conceptualization: RH. Methodology: YC. Formal analysis: LY. Investigation: XS. Resources: RH. Data curation: YC and LY. Writing original draft preparation: YC. Review and editing: YC and XS. Visualization: YZ. Supervision: RH. Project administration: RH. funding acquisition: RH. All authors listed have sufficiently made contributions to the entire content of the article and have given their consent for publication.

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# Evaluation of Adverse Drug Reactions in Paediatric Patients: A Retrospective Study in Turkish Hospital

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Drug safety in paediatric patients is a serious public health concern around the world. The paediatric patients are more prone to adverse drug reactions (ADRs) than adults. Moreover, there is a scarcity of information about ADRs in paediatric patients. This study was conducted to determine the frequency, causality, severity, preventability of paediatric patients' ADRs reported in a tertiary care hospital in Adana, Turkey. A retrospective study was conducted on all spontaneously reported ADRs between January 01, 2020, to July 30, 2021, in paediatric patients. The ADRs reports were evaluated in terms of gender, age, ADR characteristics, suspected drugs and reporting source. All included ADRs reports were characterized according to the Naranjo Algorithm/World Health Organization (WHO) causality scales, Hartwig/Siegel and Common Terminology Criteria for Adverse Events (CTCAE) severity scales, the modified Schoumock and Thornton preventability scale and hospital pharmacovigilance center criteria for seriousness. Therapeutic groups were also coded using the WHO-Anatomical Therapeutic and Chemical (ATC) classification. During the study period, 8,912 paediatric patients who were admitted had 16 ADRs with 1.7 ADRs/1,000 admissions. The majority of ADRs were found in infants (31.2%) and children (56.2%) as compared to adolescents (12.5%). ADRs were observed more in females (81.2%) than males. Skin (62.5%) was the most affected organ due to the ADRs, and maculopapular rash and erythema multiforme were the most commonly reported symptoms. Most ADRs were probable/likely (93.7%), severe (50%), preventable or probably preventable (43.7%) and serious (37.5%). Antibiotics (93.7%) were found to be the most common cause of ADRs in paediatric patients. The majority of ADRs were associated with vancomycin (68.7%). Most of the ADRs were reported by a medical doctor in this study. This small sample size study highlights significant problems of ADRs in paediatric patients, mainly caused by antibiotics and with a majority of ADRs manifest as skin reactions. Furthermore, a high proportion of the identified ADRs were found to be preventable. More focused efforts are needed at the national level to avoid preventable ADRs in hospitals. Monitoring and management of ADRs and future studies would be beneficial for better patient care and safety.

**Keywords: adverse drug reactions, children, paediatric, antibiotics, patient safety, Turkey**

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## INTRODUCTION

Adverse drug reactions (ADRs) are a leading cause of illness and mortality worldwide (Giardina et al., 2018). Spontaneous reporting of ADRs is critical for effective post-marketing drug surveillance and patient safety (Noda et al., 2020). ADRs are also related to more serious cases of liver injury due to drugs as presented in different databases (Noda et al., 2020; Teschke and Danan, 2021), but many of these liver injury cases were poorly documented and used a global introspection method for causality (Teschke and Danan, 2021). The limitations of these approaches include case selection based solely on published case numbers rather than a strong causality assessment method. Changes in the method of causality assessment of ADRs are required to improve data quality and database reliability. Therefore, an objective approach like Roussel Uclaf Causality Assessment method (RUCAM) should be used to assess causality of ADRs cases for the better outcomes in future studies (Danan and Teschke, 2016; Danan and Teschke, 2019; Teschke and Danan, 2021. Drug safety is an important part of health care and understanding ADRs is crucial for avoiding harmful effects (Dittrich et al., 2020). The safety of drugs in paediatric patients is a serious public health problem (Rosli et al., 2017; Khan et al., 2020a). ADRs in paediatric patients have been shown to cause not only hospital admissions or lengthy hospitalization, but also chronic disability or even death (Le et al., 2006).

The medication mistakes in paediatric patients were found to be three times higher than in adults, mostly due to considerable variation in body mass, which necessitates individual dose measurements depending on patient age, weight, or body surface as well as the clinical situation (Khan et al., 2020a). The development of renal functions and enzyme systems, pharmacokinetic and pharmacodynamic parameters in paediatric patients also alter throughout time (Rosli et al., 2017). Paediatric patients are provided a wide range of medications, with an elevated risk of ADRs linked with off-label prescribing (Bellis et al., 2014). ADRs are responsible for an increased morbidity level in paediatric patients (Priyadharsini et al., 2011; Angamo et al., 2016; Venkatasubbaiah et al., 2018).

Paediatric patients are one of the most vulnerable populations to ADRs. It is reported that ADRs account for nearly 5% of all hospital admissions in paediatric patients (Angamo et al., 2016). A previous study revealed that ADRs affects around one out of every ten children in the hospital, with 12% of them were serious (Clavenna and Bonati, 2009). According to systematic reviews, the overall average incidence of ADRs in paediatric patients was 9.52–9.53% (Impicciatore et al., 2001; Khan et al., 2020a). ADRs also imposed a higher financial cost on patients. It is reported that the average cost of treating an ADR per patient was estimated to be United States dollars (USD) 9,491, with hospitalization or room expenditures accounting for 50% of the total cost (Ayani et al., 1999; Oshikoya et al., 2011). Another study calculated a total cost to a hospital of USD 27,358 for the hospitalization of patients with ADRs in an emergency room over 6 weeks (Patel et al., 2007).

Children rarely articulate their personal medication therapy experiences; they are more susceptible to ADRs. As a result, inappropriate drugs usage in paediatric patients has a significant chance of causing a variety of ADRs (Khan et al., 2020a; Nasso et al., 2020). The paediatric patients are considered susceptible populations and are frequently underrepresented in randomized controlled trials (RCTs). Therefore, there is scarce data about detecting ADRs which provides limited safety information in paediatric patients (Nor-Aripin et al., 2012). To compensate for the limitations of RCTs, spontaneous ADR reporting is an important source of medication safety data in paediatric patients that aren't often studied in RCTs (Rosli et al., 2017; Gentili et al., 2018).

A statewide, volunteer pharmacovigilance (PV) system exists in Turkey, as in many other nations. Its primary goal is to alert the public about previously unknown risks associated with the use of medications in everyday life (Turkey pharmacovigilance center TÜFAM, 2005). Additional research is usually required to confirm these safety signals. All Health care professionals (HCPs; doctors, nurses, pharmacists, etc.), patients and caregivers are the primary source of voluntary ADRs reporting (Ergün et al., 2019; Khan et al., 2020b; Haines et al., 2020). Under-reporting of ADRs continues to be a widespread issue (Ergün et al., 2019; Güner and Ekmekci, 2019; Khan et al., 2020a). According to a recent report, Turkey submitted only 89 ADR reports per million population to the World Health Organization (WHO) Vigiflow database in 2020 (Turkey Pharmaceuticals and Medical Devices Agency TPMDA, 2020). However, the WHO recommended that ADR reports should be produced at a rate of 200 per million population per year (World health organization WHO, 2021a).

Underreporting is a well-known issue in voluntary ADRs reporting schemes (Hazell and Shakir, 2006; Khan et al., 2020b). Underreporting of ADRs in paediatric patients is also due to a lack of knowledge about adverse reactions to prescribed drugs (Rosli et al., 2017; Khan et al., 2020b; Dittrich et al., 2020). Timely reporting of ADRs and periodic monitoring are useful for improved care and safety in paediatric patients (Dittrich et al., 2020). Moreover, there is a scarcity of information about ADRs in paediatric patients in our healthcare setting and as well in Turkey. Therefore, this study aimed to determine the frequency, causality, severity, preventability of paediatric patients' ADRs recorded in a tertiary care hospital in Adana, Turkey.

## MATERIALS AND METHODS

A retrospective study was conducted in a pharmacovigilance center of Balcalı Hospital in Adana, Turkey, to evaluate paediatric patients' (0–17 years old) ADR reporting forms. Balcalı Hospital is a tertiary care teaching hospital with 1,171 beds that provides both in-patient and out-patient care. It offers health care facilities to the rural and urban population of Adana, (Turkey's fifth-largest city). This research was carried out per the Helsinki Declaration's principles. Due to the retrospective nature of the study, involvement of official member of pharmacovigilance center and examination of ADRs reporting

forms, the hospital's institutional ethics committee waived ethical approval. All paediatric patients' ADRs reported to pharmacovigilance officer by HCPs from January 1, 2020, to July 30, 2021, were included. ADR forms with missing information with unclear causality were omitted from the analysis.

A clinical pharmacologist working at the pharmacovigilance center and researchers analyzed all individual recognized ADR reports. The ADRs reports were evaluated in terms of gender, age, ADR characteristics, suspected drugs, reporting source and outcomes were extracted. The Naranjo algorithm (the total scores range from −4 to 13, the reaction is considered Definite if score >8, probable 5–8, possible 1–4 and doubtful = 0) and WHO-Uppsala Monitoring Centre (the suspected ADR is assessed as certain, probable, possible, unlikely and unclassified/unclassifiable) criteria were used to determine the causality of each suspected ADR (Naranjo et al., 1981; World health organization and Uppsala Monitoring Centre WH/UMC, 2013). These validated tools have been used in several studies (Dittrich et al., 2020; Nasso et al., 2020; Trubiano et al., 2016). Hartwig's Severity Assessment Scale was used to evaluate the ADRs' severity. ADRs were classified as mild, moderate, or severe (Hartwig et al., 1992). The severity of the ADRs was also determined by using the Common Terminology Criteria for Adverse Events (CTCAE) scale. For each ADR, the CTCAE displays grades 1 through 5 along with a specific clinical description of severity (Common Terminology Criteria for Adverse Events CTCAE, 2017; Dittrich et al., 2020). The modified Schoumock and Thornton scale was used to assess preventability (ADRs are divided into three categories: definitely preventable, probably preventable and not preventable) (Schumock and Thornton, 1992; Al-Damen and Basheti, 2019). Hospital pharmacovigilance center criteria were used to determine the seriousness of ADR. Our hospital pharmacovigilance criteria is designed according to the Turkish pharmacovigilance center (TUFAM) recommendations. The hospital pharmacovigilance officer assessed the nature and outcome of ADR after follow-up and classify the cases as "death, life-threatening, caused hospitalization/prolonged hospitalization, caused permanent disability, Other (any other adverse effect due to a drug) and then forward the form to TUFAM and also discussed with HCPs. This form shows the outcome of ADRs experienced by patients. Therapeutic groups and drugs were also coded using the WHO-Anatomical Therapeutic and Chemical (ATC) classification (World Health organization (WHO), 2020b).

SPSS Statistics version 25 (IBM Corp., SPSS Statistics) was used to perform a descriptive analysis of the data for frequency, mean, and percentage. All of the information is presented in tabular and graphical formats.

**TABLE 1 |** Characteristics and assessment of paediatric patients ADR reports.

| | – |
|---|---|
| Gender | n (%) |
| Male | 3 (18.75) |
| Female | 13 (81.25) |
| Age groups | |
| Neonates (birth to 1 month) | 0 (0) |
| Infants (>1 month to 2 years) | 5 (31.25) |
| Children (>2–12 years) | 9 (56.25) |
| Adolescents (>12–17 years) | 2 (12.5) |
| Year of reporting | |
| 2020 | 11 (68.75) |
| 2021 | 5 (31.25) |
| Causality | |
| Naranjo algorithm | – |
| Probable | 15 (93.75) |
| Definite | 1 (6.25) |
| WHO/UMC | – |
| Likely | 15 (93.75) |
| Certain | 1 (6.25) |
| Severity | |
| Modified Hartwig/Siegel scale | – |
| Level 2 (mild) | 3 (18.75) |
| Level 4 (moderate) | 5 (31.25) |
| Level 5 (severe) | 8 (50) |
| CTCAE scale | – |
| Grade 2 (moderate) | 5 (31.25) |
| Grade 3 (severe) | 4 (25) |
| Grade 4 (life-threatening) | 7 (43.75) |
| Preventability | |
| Definitely preventable/Probably preventable | 7 (43.75) |
| Not preventable | 9 (56.25) |
| Seriousness criteria (Hospital criteria) | |
| Death | 0 (0) |
| Life-threatening | 6 (37.5) |
| Caused hospitalization/prolonged hospitalization | 9 (56.25) |
| Caused permanent disability | 0 (0) |
| Other | 1 (6.25) |
| System organ class | |
| Skin | 10 (62.5) |
| Renal and urinary disorders | 4 (25) |
| Circulatory system | 2 (12.5) |
| Management | |
| The medication was stopped | 9 (56.25) |
| Another medication was substituted | 1 (6.25) |
| Dose was reduced | 2 (12.5) |
| Another medication was added to combat adverse effect | 4 (25) |
| Outcomes | |
| Recovered | 14 (87.5) |
| Recovering | 2 (12.5) |
| Fatal | 0 (0) |

*Abbreviation ADRs = Adverse drug reactions, n = frequency, % = percentage, WHO/UMC = World health organization-Uppsala monitoring centre, CTCAE = Common terminology criteria for adverse events.*

## RESULTS

A total of 29 ADRs were submitted to the hospital pharmacovigilance center during 2020–2021. Of these 17 (58.6%) were related to paediatric patients. One ADR form was excluded due to the missing information. Finally, 16 eligible ADRs forms (11 reports during 2020 and 5 in 2021)

**TABLE 2 |** Drugs associated with ADRs.

| Drug class | WHO/ATC code | n (%) | Reaction details (no of patients) |
|---|---|---|---|
| Antibiotic | | | |
| Vancomycin | J01XA01 | 11 (68.75) | Maculopapular rash (5) |
| — | — | — | Anaphylaxis (2) |
| — | — | — | Erythema multiforme/Redness on the whole body (2) |
| — | — | — | Acute kidney injury (1) |
| — | — | — | Increase creatinine level (1) |
| Clindamycin | J01FF01 | 1 (6.25) | Maculopapular rash (1) |
| Colistin-Linezolid | J01XB01-J01XX08 | 1 (6.25) | Increase creatinine level (1) |
| Ceftriaxone | J01DD04 | 1 (6.25) | Rashes and urticaria (1) |
| Amphotericin B | J02AA01 | 1 (6.25) | Maculopapular rash (1) |
| Antiviral | | | |
| Aciclovir | J05AB01 | 1 (6.25) | Acute kidney injury (1) |

*Abbreviation ADRs = Adverse drug reactions, n = frequency, % = percentage, WHO/ATC = World health organization/Anatomical therapeutic and chemical classification.*

were analyzed in this study. According to the hospital data, a total of 8,912 (4,701 in 2020 and 4,211 in 2021) paediatric patients were admitted during the study period with 1.7 ADRs/1,000 admissions. These ADRs were observed during hospital admission and reported to the hospital pharmacovigilance center. The majority of ADRs were found in infants (31.2%) and children (56.2%) as compared to adolescents (12.5%). ADRs were observed more in females (81.2%) than males. The median age of the patients was 6.5 years (2 months–13.5 years).

According to the Naranjo algorithm/WHO-UMC scales, 15 of the ADRs were probable/likely (93.75%) and 1 was definite/certain (15.8%). Hartwig's Severity Assessment Scale shows that 3 of the ADRs were mild (18.75%), 5 were moderate (31.25%) and 8 were severe (50%) requiring an intensive medical intervention. The CTCAE criteria showed that five ADRs were grade 2, four ADRs were grade 3, and seven ADRs were grade 4. According to the modified Schumock and Thornton scale, 7 ADRs were measured as preventable (43.5%) and among them, four were "definitely preventable" (25%) and three were "probably preventable" (18.75%). The remaining ($n$ = 9; 56.25%) were "non-preventable". Moreover, according to the hospital pharmacovigilance center criteria, 9 (56.25%) of the ADRs caused hospitalization/prolonged hospitalization and 6 (37.5%) were life-threatening (**Table 1**).

Skin (62.5%) and renal system (25%) were the most affected organs due to the ADRs. The suspected medication was discontinued in 10 (62.5%) of the patients and replaced with another medication for the same indication. The dose of suspected medication was reduced in 2 (12.5%) patients to alleviate symptoms, while another drug was given to overcome adverse effects in 4 (25%) cases. The results of ADR management revealed that 87.5% had been recovered and 12.5% were in the process of recovering. No fatal case due to ADR was reported in the current study (**Table 1**).

In our study, ADRs were mostly associated with antibiotics (15; 93.75%) followed by antiviral ($n$ = 1, 6.25%). Vancomycin ($n$ = 11, 68.75%) was associated with the highest number of ADRs. The most common reported ADRs with vancomycin use were maculopapular rash ($n$ = 5, 31.25%) and anaphylaxis ($n$ = 2, 12.5%). Antiviral drug (Aciclovir) is associated with acute kidney failure. The most common drugs that cause ADRs, as well as associated reactions, are listed in **Table 2**.

These ADRs were first time reported in the hospital pharmacovigilance center. All of the ADRs were reported by doctors ($n$ = 15, 93.75%) and nurses ($n$ = 1; 6.25%). We did not observe any ADR reported by a pharmacist and other paramedical staff in this study.

## DISCUSSION

Periodic evaluation of ADRs in paediatric patients is very important. This study explored the causality, preventability, severity of ADRs as well as therapeutic groups and reactions related to ADRs. The current retrospective study is the first attempt that has been conducted to analyze the paediatric patients' ADRs in our healthcare setting. As a result, it could serve as a baseline for future study, as well as provide critical evidence for healthcare stakeholders and government decision-makers to take the necessary steps to reduce the burden of ADRs in paediatric patients.

In our study, out of the total reported ADRs in hospital pharmacovigilance centers, 58.6% were related to paediatric patients. Similar studies conducted in Netherlands (Dittrich et al., 2020) and Malaysia (Rosli et al., 2017) observed that 26 and 14% of admitted paediatric patients had ADRs, respectively. Moreover, the observed rate of ADR related to paediatric patients was 1.7 ADRs per 1,000 admissions. Nasso et al. also reported similar findings (1.6 ADRs/1,000 admissions) in paediatric patients (Nasso et al., 2020). However, another study conducted by Lombardi et al., observed 2.2 ADRs per 1,000 paediatric admissions, which was higher as compared to our study (Lombardi et al., 2018). These differences in ADR rates among studies may be due to variation in data collection methods, sample size, methodology, and healthcare setting.

Causality analysis is necessary to understand the factors that contribute to the occurrence of ADRs (Venkatasubbaiah et al., 2018). In the current study, the Naranjo algorithm and WHO-UMC scales of causality assessment observed that most of the ADRs were probable/likely categories. Similar findings were also reported by Nasso et al., 2020, Al-Damen and Basheti, 2019, and Saqib et al., 2018). Because of their simplicity, the Naranjo algorithm and WHO-UMC scales are also used to evaluate the causality score in paediatric patients. We used Naranjo and the WHO method because these are

suitable for non-hepatic ADRs, but not for hepatic ADRs (García-Cortés et al., 2011; Teschke et al., 2013; Danan and Teschke, 2016; Lin et al., 2019). Therefore, in future studies showing paediatric patients with suspected drug-induced liver injury (DILI) or herb-induced liver injury (HILI), all cases should be assessed for causality using the updated RUCAM published in 2016 (Danan and Teschke, 2016; Danan and Teschke, 2019).

In the current study, according to the severity assessment of ADRs using the Modified Hartwig and Siegel scale, the majority of ADRs fell into the severe followed by moderate and mild categories. However, these findings deviated from the studies conducted in Malaysia (Rosli et al., 2017) and India (Sundaran et al., 2018) which disclosed a higher ADRs proportion as mild and moderate while a small number were severe. In addition, CTCAE criteria showed that the majority of ADRs were grade 3 (severe) and 4 (life-threatening) categories in this study. Similar findings were also reported in the Netherlands study (Dittrich et al., 2020). The severity of ADRs must be assessed to take serious steps against the drug's continued use. Severe ADRs have been linked to a longer stay in the hospital and a higher financial cost due to the need for more intensive medical care. (Walter et al., 2017; Fasipe et al., 2019).

In this study, preventability assessment using Modified Schumock and Thornton scale showed 43.7% of ADRs were definitely and probably preventable. Supported findings were also reported in the Jordan study and reported that 44.7% of ADRs were definitely and probably preventable (Al-Damen and Basheti, 2019). Another study conducted among paediatric patients observed that 20% of ADRs were preventable or probably preventable (Nasso et al., 2020). In the current study, most of the identified ADRs were found to be preventable. The establishment of active ADR surveillance and raise awareness is important to encourage safer drug use. Periodic ADR reporting programs are required to educate and enhance awareness among all HCPs. More focused efforts are needed at the national level to avoid preventable ADRs in hospitals. Therefore, ADRs should be monitored carefully to avert hazardous effects.

In the present study, antibiotics were the most common drug class followed by antiviral reported for ADRs in paediatric patients. Similar results were detected by previously published studies (Rashed et al., 2012; Rosli et al., 2017). The most frequently involved antibiotics associated with ADRs were Vancomycin followed by Ceftriaxone, Clindamycin and Colistin-Linezolid in our study. A study conducted among paediatric patients reported Amoxicillin and beta-lactamase inhibitors as frequently contributed to ADRs (Nasso et al., 2020). A large number of antibiotics were prescribed in the general paediatric patients, and a higher number of ADRs were reported for drugs in this treatment group (Gallo et al., 2012; Nasso et al., 2020; Priyadharsini et al., 2011). Due to the problem of antibiotic resistance, paediatric patients infections were frequently treated with a combination and broad-spectrum of antibiotics at high doses (Manan et al., 2016).

The skin was the most affected organ by ADRs in this study. Similar findings were also reported by previously published studies (Priyadharsini et al., 2011; Rosli et al., 2017; Nasso et al., 2020). However, a study conducted by Dittrich and colleagues observed that gastrointestinal disorders were more frequently seen in paediatric patients (Dittrich et al., 2020). The reason for increased cutaneous involvement of ADRs in paedriatric patients can be attributed to this age group's unique physiology; in fact, they have a partially matured epidermis that is not fully developed (Rashed et al., 2012; Rosli et al., 2017). As a result, the skin becomes more porous and vulnerable to chemical and microbial attacks (Stamatas et al., 2011).

In this study, the majority of the antibiotics were linked to ADRs related to skin reactions, which is consistent with the findings of other studies (Priyadharsini et al., 2011; Rosli et al., 2017). Maculopapular rashes followed by anaphylaxis and redness on the whole body (erythema multiforme), acute kidney injury were the main ADRs of Vancomycin observed in our study. Al-Damen and Basheti were also reported acute kidney injury with Vancomycin use (Al-Damen and Basheti, 2019). In addition, erythema multiforme has been linked to a variety of antibiotics, including b-lactams, macrolides, aminoglycosides, glycopeptides, and others (Diaz and Ciurea, 2012). According to the previously published study, the main Vancomycin-related ADRs were skin rashes and elevated serum creatinine (An et al., 2011). Another study also reported anaphylaxis to intravenous Vancomycin in paediatric patients (Xie et al., 2021). Close monitoring of laboratory testing, including complete blood counts with differential analysis, is recommended for the early and precise diagnosis of ADRs associated with Vancomycin use (An et al., 2011; Xie et al., 2021).

Antifungal antibiotic drug (Amphotericin B) caused rashes in one paediatric patient in this study. A study conducted in India observed renal failure and diarrhea as ADRs due to Amphotericin-B use (Sundaran et al., 2018). It is reported that prolonged Amphotericin-B treatment can be associated with maculopapular rash, eosinophilia and also systemic symptoms (Cesaro et al., 1999; Hagihara et al., 2015). Careful monitoring of the patient being treated for the first time is warranted in the case of Amphotericin B. Antiviral drug (Aciclovir) was responsible for Acute kidney injury-related ADR in our study. Acyclovir is an antiviral medicine that is commonly prescribed to paediatric patients, and it can cause acute kidney injury (Fleischer and Johnson, 2010). A recent study also reported that an acute renal injury occurred in 13% of parenteral Aciclovir treatment episodes (Ryan et al., 2018). Therefore, dosage adjustments for baseline renal function and optimal body weight are crucial to prevent ADRs (Yildiz et al., 2013).

In the current retrospective study, no DILI case was reported. A previously published study conducted by Zhu et al. observed serious conditions of DILI in children and antibiotics were the most commonly reported drug class with risk of liver injury (Zhu et al., 2015). Limited data is available regarding DILI cases in paediatric patients. It is reported by Shi et al. that DILI in children accounts for about 1% of all reported ADRs throughout all age groups, less than 10% of all clinical DILI cases, and around 20% of all acute liver failure cases in children. (Shi et al., 2017). DILI is one of the most serious ADRs and accounts for 13% of all cases of acute liver failure in the United States (Ostapowicz et al., 2002). Moreover, HILI also accounts for 24.2% of the study cohort consisting of both, DILI and HILI cases in China (Li et al., 2007), 11% in Spain (Andrade et al., 2005) and 0.60% in Korea (Cho et al., 2017). Various studies also reported DILI and HILI cases in adults (Mitchell and Hilmer,

2010; Cho et al., 2017; Teschke and Danan, 2017; Amadi and Orisakwe, 2018; Becker et al., 2019).

Many of the used drugs in our study also may cause DILI such as previously reported with antibiotics and other therapeutic drugs (Danan and Teschke, 2016; Teschke, 2018; Zhang et al., 2019; Teschke and Danan, 2020), confirming previous data of various RUCAM based DILI cases caused by multiple drugs as published in worldwide cases (Teschke and Danan, 2017; Teschke, 2018; Teschke and Danan, 2020). The underline reasons for lack of DILI and HILI in our study may be that the reporting rate of ADRs to the pharmacovigilance center was very low. We observed all reported ADRs during the study period however no ADR case was reported due to DILI and HILI. Low reporting rate of ADRs is the main reason as indicated in previous studies (Ghabril et al., 2010; Cho et al., 2017; Teschke and Danan, 2017). The risk of liver injury due to medication in children should be taken seriously, and particular emphasis should be placed on the risk of liver injury caused by drugs (Zhang et al., 2019). Therapeutic monitoring of drugs and assessment of liver tests indicators are necessary for timely and correct diagnosis of liver injury (Lee and Senior, 2005; Avigan et al., 2014). However, liver tests were mentioned in only 3 cases of vancomycin in the reported ADR form in our study and none of the patients did have increased Aspartate transaminase (AST) and Alanine transaminase (ALT) levels. Therefore, more active surveillance training on ADRs for all healthcare professionals (HCPs) is crucial for proper monitoring of ADRs in children to avoid the risk of liver injure and better patient safety.

Most of the ADRs were reported by a medical doctor in this study. Nurses reported only one ADR and reporting from the pharmacist was not observed. The accurate spontaneous ADRs reporting mechanisms used by prescribers, nurses, pharmacists, and other paramedical workers are critical for the detection of serious ADRs in hospitals (Giardina et al., 2018; Güner and Ekmekci, 2019). ADR underreporting is a global issue that has been documented in previous international studies (AlShammari and Almoslem, 2018; Alwhaibi and AlAloola, 2020). One of the Turkish government's major priorities is to monitor and report ADRs (Turkey Pharmaceuticals and Medical Devices Agency TPMDA, 2014). In 2005, Turkey established the "Turkish Pharmacovigilance Center (Turkish: Türkiye Farmakovijilans Merkezine)" to coordinate PV activities across the country. In Turkey, all HCPs are expected to be vigilant in identifying and reporting ADRs to the hospital pharmacovigilance center or directly to TUFAM (Ergün et al., 2019; Khan et al., 2020b). However, despite the potential hazards of ADRs and the implementation of WHO standard pharmacovigilance in Turkey, the under-reporting of ADRs continues to be a widespread issue (Ergün et al., 2019; Güner and Ekmekci, 2019; Khan et al., 2020b; Turkey Pharmaceuticals and Medical Devices Agency TPMDA, 2020). Previously published studies in Turkey as well as at a global level reported that HCPs have insufficient knowledge about pharmacovigilance systems and ADRs reporting (Ergün et al., 2019; Güner and Ekmekci, 2019; Alwhaibi and AlAloola, 2020; Nadew et al., 2020). Lack of knowledge about adverse reactions to prescribed drugs in paediatric patients is also responsible for underreporting of ADRs (Rosli et al., 2017; Khan et al., 2020b; Dittrich et al., 2020). Therefore, the creation of a mandatory unified periodic education intervention on ADRs of drugs is crucial for better paediatric patients care. Turkish health policymakers should also emphasize the importance of adequate cooperation between international, local health authorities and manufacturers to stimulate and support regular joint training programs for all HCPs to increase ADR knowledge and reporting.

Our research contains both limitations and strengths. This is a single-center study involving only paediatric patients; therefore, it cannot be generalized to other healthcare settings across the country. Moreover, a small number of identified ADRs ($n$ = 16) were evaluated due to a low reporting rate in hospital pharmacovigilance centers. Lack of training, inaccessibility to ADR reporting forms, poor skills, time restrictions, and a lack of incentives are all plausible reasons for HCPs underreporting (Venkatasubbaiah et al., 2018; Khan et al., 2020b). There may be also a chance of unreported mild ADRs due to the voluntarily reported system in the hospital which may pose some underestimation of ADRs. Therefore, a multicenter study and active surveillance of ADRs with a large sample size are required to further verify the current study's findings. The retrospective nature of the study may have been limited data accuracy and information. However, almost all of the information was obtained from registered ADR reports available in a hard form in the hospital pharmacovigilance center. We did not observe any DILI cases in this study. The possible reason may be a small number of reported ADRs and a lack of information regarding liver tests on ADRs forms. However, it is confirmed that three patients had liver tests reports but none of the patients did have increased liver tests such as AST and ALT. There is a need for continuous periodic training on ADRs surveillance to monitor medication in children to avoid the risk of liver injury. Moreover, our findings on the most commonly reported drug and clinical symptoms may be divergent from other populations with different prescribing patterns, disease epidemiology, and ethnicities. On the other hand, our study highlights the importance of a pharmacovigilance monitoring system to improve quality reporting. Periodic monitoring of ADRs is useful for paediatric patients' safety and also for additional literature data, which is currently rare. Moreover, this is the first study of ADRs among paediatric patients in our hospital. As a result, it could serve as a starting point for future research and give essential evidence for healthcare stakeholders and government decision-makers to take the required actions to lessen the burden of ADRs in paediatric patients.

## CONCLUSION

This small-scale retrospective study revealed the current ADRs pattern in paediatric patients. Antibiotics were the leading cause of ADRs, which may reflect the widespread use of antibiotics in this population. The majority of ADRs were related to skin reactions, and a considerable proportion was preventable types. More focused efforts are needed at the national level to avoid preventable ADRs in hospitals. Monitoring and management of ADRs and future studies would be valuable for improved patient care and safety. Moreover, a large sample

size and multi-central studies are needed to validate the current study results and highlight the area for further improvement in different healthcare settings.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

Study concept and design—ZK and YK; literature search—ZK and YK; analysis and interpretation of data—ZK, YK, and OK; drafting of the manuscript—ZK; critical revision of the manuscript for important intellectual content—YK and OK. All authors approved the version to be submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# Combining a Pharmacological Network Model with a Bayesian Signal Detection Algorithm to Improve the Detection of Adverse Drug Events

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**Introduction:** Improving adverse drug event (ADE) detection is important for post-marketing drug safety surveillance. Existing statistical approaches can be further optimized owing to their high efficiency and low cost.

**Objective:** The objective of this study was to evaluate the proposed approach for use in pharmacovigilance, the early detection of potential ADEs, and the improvement of drug safety.

**Methods:** We developed a novel integrated approach, the Bayesian signal detection algorithm, based on the pharmacological network model ($IC_{PNM}$) using the FDA Adverse Event Reporting System (FAERS) data published from 2004 to 2009 and from 2014 to 2019Q2, PubChem, and DrugBank database. First, we used a pharmacological network model to generate the probabilities for drug-ADE associations, which comprised the proper prior information component (IC). We then defined the probability of the propensity score adjustment based on a logistic regression model to control for the confounding bias. Finally, we chose the Side Effect Resource (SIDER) and the Observational Medical Outcomes Partnership (OMOP) data to evaluate the detection performance and robustness of the $IC_{PNM}$ compared with the statistical approaches [disproportionality analysis (DPA)] by using the area under the receiver operator characteristics curve (AUC) and Youden's index.

**Results:** Of the statistical approaches implemented, the $IC_{PNM}$ showed the best performance (AUC, 0.8291; Youden's index, 0.5836). Meanwhile, the AUCs of the IC, EBGM, ROR, and PRR were 0.7343, 0.7231, 0.6828, and 0.6721, respectively.

**Conclusion:** The proposed $IC_{PNM}$ combined the strengths of the pharmacological network model and the Bayesian signal detection algorithm and performed better in detecting true drug-ADE associations. It also detected newer ADE signals than a DPA and may be complementary to the existing statistical approaches.

**Keywords: adverse drug events, pharmacological network model, signal detection algorithm, FDA adverse event reporting system, pharmacovigilance**

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## INTRODUCTION

Adverse drug events (ADEs), which are unresolved and major issues in the medical field, pose a serious threat to public health. ADEs have resulted in high morbidity, mortality, and medical costs. In the United States, ADEs are the fourth leading cause of death after cancer and heart disease (Lazarou, et al., 1998) and cause more than 100,000 deaths per year (Giacomini, et al., 2007). Therefore, the early and accurate detection of potential ADEs can reduce health risks and improve drug safety. However, traditional toxicity testing and clinical trials are limited by issues such as sample sizes and the type of data collected in the pre-market stages, and risk management is continued in the post-market stages.

Improving the detection mechanism for ADEs is key to strengthening post-marketing drug safety surveillance (Harpaz, et al., 2017). Pharmacovigilance has been employed in the early detection of rare or unknown ADEs that were not found in the pre-market stages. Various computational methods have been developed and implemented using different databases that contain ADE information during the post-market stages. Among these databases, the US Food and Drug Administration's Adverse Event Reporting System (FAERS) is one of the well-known spontaneous reporting systems (SRSs). A disproportionality analysis (DPA), also called a signal detection algorithm, is an important statistical approach used in the SRS analysis and is also used frequently to detect ADEs during pharmacovigilance. The proportional reporting ratio (PRR) and reporting odds ratio (ROR) are notable in frequentist DPAs (Evans et al., 2001; Van Puijenbroek, et al., 2002). The empirical Bayesian geometric mean (EBGM) and information component (IC) belong to the widely used Bayesian DPAs (Bate, et al., 1998; DuMouchel, 1999). Additionally, the three-component mixture model (3CMM) has been proposed based on the use of the EBGM, and the likelihood ratio test (LRT) as the frequentist method for the assessment of drug-ADE associations (Huang, et al., 2011; Zhang, et al., 2018). According to a recent study, among ten methods, IC achieved the best area under the receiver operator characteristics curve (AUC) (IC:0.6939) when OMOP is selected as the true ground for testing (Pham, et al., 2019). Another study showed that PRR and ROR had similar performances and that the EBGM outperformed the others (Harpaz, et al., 2013a). These findings were similar to those reported by Pham et al. Recently, a label propagation frame based on four popular signal detection algorithms (PRR, ROR, EBGM, IC) has emerged, which constructs a drug similarity network using chemical structures and combines pre-clinical drug chemical structures with the post-market database FAERS (Liu and Zhang, 2019). The different pharmacovigilance methods have been evaluated using a variety of performance metrics (Ding, et al., 2020).

However, DPA ignores the influence of a confounding bias in the analysis, which may lead to false positives and an under-detection of ADEs (DuMouchel, et al., 2013; Candore, et al., 2015). To overcome these limitations, machine learning algorithms and other methods have been used to detect ADEs using SRSs; some network-based methods and machine learning algorithms have been developed to predict ADEs using different public databases (Cami, et al., 2011; Liu, et al., 2012; Cheng, et al., 2013; Lin, et al., 2013; Davazdahemami and Delen, 2018; Jamal, et al., 2019). For example, a pharmacological network model (PNM) was developed to predict new and unknown drug-ADE associations (Cami, et al., 2011). The PNM integrated various types of data, including information from the Lexicomp, PubChem, and DrugBank databases. Phenotypic and chemical features based on the drug-ADE bipartite network were defined. Liu et al. integrated the phenotypic characteristics of drugs (i.e., indications and known adverse drug reactions), chemical structures, and biological properties of protein targets and pathway information, and used five machine learning methods to predict ADEs (Liu, et al., 2012). Moreover, Jamal et al. integrated the biological, chemical, and phenotypic features of drugs and used machine learning methods (random forest and sequential minimum optimization) to predict cardiovascular adverse reactions (Jamal, et al., 2019). Their results showed that the phenotypic data showed the best prediction effect and that drugs with similar chemical structures were more likely to exhibit similar ADEs. Furthermore, incorporating chemical and database information after marketing, which had the potential to detect clinically important ADEs.

Due to the rich value of DPAs in SRS analyses, we aimed to further optimize the use of DPAs and to improve ADE detection by combining the advantages of the Bayesian method and the pharmacological network model. In addition, the signal detection performances and properties of the top-ranked drug-ADE pairs generated by different DPAs were also investigated.

## MATERIALS AND METHODS

### Study Scheme

The overall framework of this study is shown in **Figure 1**. First, we constructed the drug-ADE network and trained the PNM using the FAERS, PubChem, and DrugBank databases. Second, the probabilities of drug-ADE associations (that not in the training data) were generated using the PNM. Third, IC was transformed using Bayes' rule, and then the probability was predicted using the PNM as the prior probability in the IC algorithm after the Bayesian transformation. Finally, a Bayesian signal detection algorithm based on a pharmacological network model ($IC_{PNM}$) was developed through data mining and the control of confounding biases based on a PS-adjusted logistic regression according to the data set.

### Data Sources

#### FAERS Database

As the largest SRS, the FAERS database collects ADE reports from physicians, manufacturers, nurses, and patients, and is updated quarterly (US Food and Drug Administration, 2020). We adopted a curated and standardized method to obtain FAERS data between 2004 and 2019Q2 (Banda, et al., 2016). For duplicated reports that shared the same primary IDs, the latest reports were used in our dataset. Drug names were mapped to

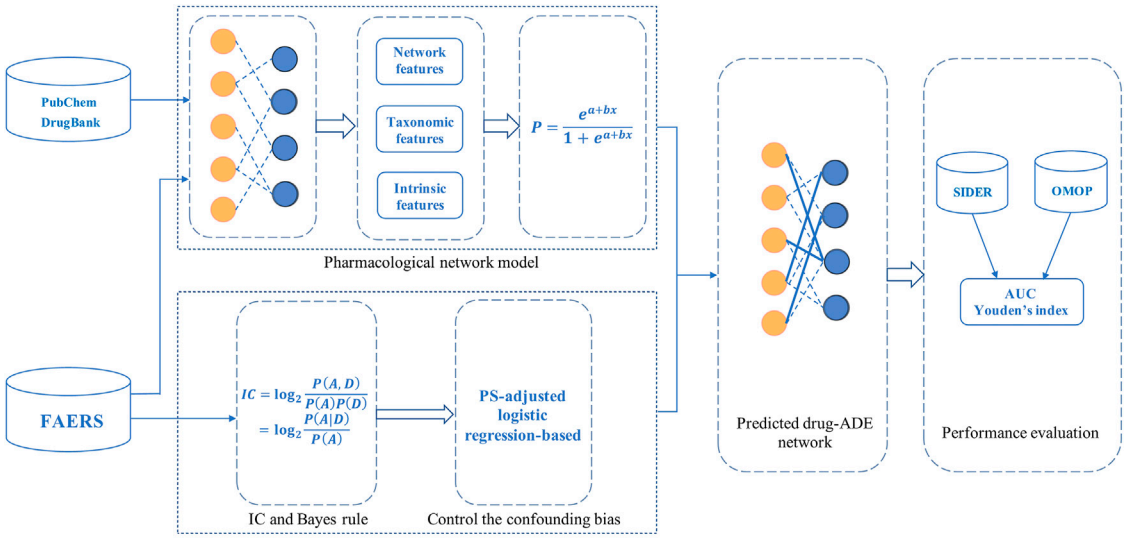


**FIGURE 1 |** Overall framework, performance evaluation, and thus generating enhanced drug-ADE signals using a Bayesian signal detection algorithm based on pharmacological network model ($IC_{PNM}$).

RxNorm concepts, and the ADEs annotated in the Medical Dictionary for Regulatory Activities (MedDRA) were mapped to the preferred terms (PTs) (MedDRA, 2020). Herein, we selected two datasets as our sources to fully evaluate the performance and robustness, which included the FAERS data from 2004 to 2009 and the FAERS data from 2014 to 2019Q2.

FAERS 2004 data for the first 120 days were selected for the training set for the early detection of ADEs in the FAERS data between 2004 and 2009; the remaining FAERS data until 2009 were included in the testing set. All the drugs were extracted during this period and standardized according to the Drug Bank IDs (DrugBank, 2020). A total of 97 ADEs included the most concerning ADEs in the field of clinical medicine and the four ADEs from OMOP (these ADEs are listed in **Supplementary Table S1**). We then obtained 1,177 distinctive drugs, 107 to 97 ADEs, and 10,307 drug-ADE associations for the training set. The testing set included 22,358 new drug-ADE pairs (not in the training set) between 1,177 drugs and 97 ADEs. On the other hand, the FAERS data from 2014 to 2019Q2 were selected to further evaluate the performance and robustness of the proposed novel approach, in which FAERS 2014 data were chosen as the training set (3,500 drugs, 97 ADEs, and 27,821 drug-ADE associations) and the FAERS data from 2015 to 2019Q2 were chosen as the testing set (3,500 drugs and 97 ADEs, 24,300 drug-ADE associations that were not in the training set).

### SIDER Database

The Side Effect Resource (SIDER) database contains marketed drugs and their recorded adverse drug reactions (ADRs), which are extracted from package inserts and public documents (Side Effect Resource, 2020). The current version 4.1 uses the MedDRA dictionary preferred terms; this dictionary contains 1,430 drugs, 5,868 ADRs, and 139,756 drug-ADE associations. We used the drug-ADE associations extracted from the SIDER 4.1 database as the true data for the analyses and evaluations. Among 22,358 drug-ADE pairs in the testing set, the intersection with the SIDER database revealed 1,148 pairs. Furthermore, among the 24,300 drug-ADE pairs in the testing set, the intersection with the SIDER database revealed 655 pairs.

### OMOP Benchmark

The Observational Medical Outcomes Partnership (OMOP) established the gold standard for pharmacovigilance research (Ryan, et al., 2013). It contains 398 drug-ADE pairs composed of 181 drugs and four ADEs (acute myocardial infarction, acute renal failure, liver injury, and gastrointestinal bleeding), which were divided into 164 positive controls and 234 negative controls. We also used the OMOP gold standard to further evaluate the performance of the signal detection algorithms. Among the 22,358 drug-ADE pairs in the testing set, the intersection with the OMOP benchmark contained 158 pairs (80 positive controls and 78 negative controls). Moreover, among the 24,300 drug-ADE pairs in the testing set, the intersection with the OMOP benchmark contained 63 pairs (27 positive controls and 36 negative controls).

## Pharmacological Network Model

A pharmacological network model, also called a predictive pharmaco-safety network, was developed to predict new and unknown drug-ADE associations based on the drug-ADE bipartite network using FAERS, PubChem, and DrugBank database. The overview of PNM is shown in **Supplementary Figure S1**. The PNM generated three types of features, namely, network, taxonomic, and intrinsic features (14 of these features are listed in **Supplementary Table S2**). Based on these features, we trained a logistic regression (LR) model using the training data. In the LR model, the probabilities for drug-ADE associations being true were defined as follows:

**TABLE 1 |** Association strength equation and threshold of signal detection algorithms.

| | Method | Equation | Threshold |
|---|---|---|---|
| Frequentist statistical methods | PRR | $PRR = \frac{c_{ij}/c_{i+}}{(c_{+j}-c_{ij})/(c_{++}-c_{i+})}$ | $PRR\_025 > 1$ |
| | ROR | $ROR = \frac{c_{ij}/(c_{+j}-c_{ij})}{(c_{i+}-c_{ij})/(c_{++}-c_{i+}-c_{+j}+c_{ij})}$ | $ROR\_025 > 1$ |
| Bayesian statistical methods | IC | $IC \sim \log_2 \frac{p_{ij}}{p_{i+}\times p_{+j}}$ | $IC\_05 > 0$ |
| | EBGM | $EBGM_{ij} = 2^{E[\log(\lambda)\|C=c_{ij}]/\log(2)}$ | $EB\_05 \geq 2$ |

$$p_{ij} = \frac{exp\left(\sum_s q_s x_s(i,j)\right)}{\left[1 + exp\left(\sum_s q_s x_s(i,j)\right)\right]} \quad (1)$$

Here, $i$ denoted the number of drugs, $j$ the number of ADEs, $q_s$ the regression parameter, $x_s$ the PNM features. We used the training data to fit the model through a 10-fold cross validation, and the optimal parameters were obtained using the optimal model that had the lowest Akaike Information Criterion (AIC).

Once we obtained a fully trained LR model, we could predict the probability of each drug-ADE association in the testing data using **Eq. 2** as follows:

$$pro_{ij} = \frac{1}{\left[1 + exp\left(-\sum_s q_s x_s(i,j)\right)\right]} \quad (2)$$

## Signal Detection Algorithms

Our research covered four classic signal detection algorithms: PRR, ROR, IC, and EBGM. Under the assumption that there was no association between the drug and the ADE, the DPAs assessed the drug-ADE associations by comparing the reported frequencies to the expected frequencies. We used the lower bound of the 95% confidence interval as the criterion for signal detection, and the main information of each algorithm is listed in **Table 1**. We defined $c_{ij}$ as the number of reports containing a drug-ADE pair. Furthermore, $c_{i+}$ and $c_{+j}$ were the number of reports containing the drug $i$ and ADE $j$ respectively, and $c_{++}$ was the total number of reports in the database.

## Bayesian Signal Detection Algorithm Based on the Pharmacological Network Model ($IC_{PNM}$)

The IC is a measure of disproportionality in the Bayesian confidence propagation neural network (BCPNN). The IC assumes that the parameters follow the beta distribution to estimate the prior probability and assumes that the hyperparameter values are all 1. However, the PNM can generate probabilities for the drug-ADE associations, and these probabilities have different interpretations from the population the drug-ADE frequencies estimated using the SRS databases. To further improve ADE detection and optimize the statistical approach for pharmacovigilance, we developed a novel integrated method, namely, the Bayesian signal detection algorithm based on the pharmacological network model ($IC_{PNM}$).

In our method, the Bayes rule gave the following transformation, and the IC was expressed as:

$$IC = \log_2 \frac{P(A,D)}{P(A)P(D)} = \log_2 \frac{P(A|D)}{P(A)} \quad (3)$$

In this equation, (D) denoted the prior probability of a drug, which represented the probability of a drug appearing in the data set (A) the prior probability of an ADE, which represented the probability of an ADE appearing in the data set (A,D) the joint probability of the appearance of a drug and an ADE in the same report in the data set; and $P(A|D)$ the conditional probability, which represented the probability of drug D inducing an ADE A.

As mentioned in **Section 2.2**, a PNM can generate probabilities for any drug-ADE association. Furthermore, the small sample size drug-ADE pairs contain more negative and positive data than large sample size drug-ADE pairs. In training of the PNM model, the training model should include both positive and negative data when selecting the training data (Ji, et al., 2021). Therefore, the PNM can control the influence of any confounding bias. The probability generated by the PNM was expressed as:

$$\text{logit}\left[P\left(A_j|D_i\right)\right] = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \cdots \alpha_{14} x_{14} \quad (4)$$

Where, in **Eq. 4**, $\alpha_0$, $\alpha_1 \cdots \alpha_{14}$ denoted the regression parameters, and $x_1, x_2 \cdots x_{14}$ the 14 the features of the PNM.

Based on **Eqs 3**, **4**, we combined the PNM and Bayesian methods and proposed an improved signal detection algorithm, called the Bayesian signal detection algorithm using the pharmacological network model ($IC_{PNM}$), which was defined as follows:

$$IC_{PNM}(i,j) = \log_2 \frac{P\left(A_j, D_i\right)}{P\left(A_j\right)P(D_i)} = \log_2 \frac{P\left(A_j|D_i\right)}{P\left(A_j\right)} \quad (5)$$

Then, we calculated the probabilities of the ADEs in the dataset. When the data contained sufficient independent and identically distributed samples, the probability of an ADE $A_j$ was obtained using the frequency value $Pr(A) = c_{+j}/c_{++}$ from the data set according to Bernoulli's law of large numbers. $Pr(A)$ was also rewritten according to **Eq. 6**. However, this probability did not consider the influence of any confounding bias.

$$Pr\left(A_j\right) = \frac{\exp(\beta)}{1 + \exp(\beta)} \quad (6)$$

Where, in **Equation 6**, $\beta = \ln \frac{C_{+j}/C_{++}}{1-C_{+j}/C_{++}}$.

When using FAERS data to detect ADE signals, the confounding factors in the data may affect the results and cause signal masking or result in false positive signals. The common confounding factors in FAERS include the patient demographics (such as age, gender, etc., as these data contribute greatly to missing data), combined medication information, etc., among which combined medication is a common phenomenon in the data. To eliminate the influence of combined medication on the results and correct for the confounding bias caused due to it, we calculated the propensity score (PS) to address the confounding bias in the data set. The confounding bias caused by combined medication is the propensity score of drugs, which represented the probability of drug exposure in each report. In other words, the probability of drug selection (that is, the propensity score of each drug) was computed using **Eq. 7**. Subsequently, for each drug-ADE pair, we estimated the drug effect with an adjustment of PS through the logistic regression model (8).

$$\text{Logit}\left[\boldsymbol{P}\left(\boldsymbol{Drug}=1\right)\right] = \boldsymbol{\gamma}_0 + \sum_{i=1}^{n} \boldsymbol{\gamma}_i \boldsymbol{PC}_i \tag{7}$$

$$\text{Logit}\left[\boldsymbol{P}\left(\text{ADE}=1\right)\right] = \boldsymbol{\beta}_0 + \boldsymbol{\beta}_1 \times \text{Drug} + \boldsymbol{\beta}_2 \times \text{PS} \tag{8}$$

In **Equation 7**, $n$ denoted the number of principle components (PCs). From **Eq. 8**, we proposed and defined the probability $P(A_j)$ of ADE according to the PS-adjusted logistic regression. Assuming the estimated value of the regression coefficient in **Eq. 8** as $(\tilde{\beta}_0, \tilde{\beta}_1, \tilde{\beta}_2)$, for K reports, $P(A_j)$ was expressed as follows with an adjustment for PS value:

$$\boldsymbol{P}\left(\boldsymbol{A}_j\right) = \sum_{k=1}^{k} \frac{\exp\left(\tilde{\boldsymbol{\beta}} + \tilde{\boldsymbol{\beta}}_0 + \tilde{\boldsymbol{\beta}}_1 + \tilde{\boldsymbol{\beta}}_2 \boldsymbol{PS}_k\right)}{1 + \exp\left(\tilde{\boldsymbol{\beta}} + \tilde{\boldsymbol{\beta}}_0 + \tilde{\boldsymbol{\beta}}_1 + \tilde{\boldsymbol{\beta}}_2 \boldsymbol{PS}_k\right)} \tag{9}$$

According to **Eqs 4**, **5**, **9**, the lower bound of the 95% confidence interval ($IC_{PNM}\_05$) for $IC_{PNM}$ was defined as follows, and the criterion for signal detection was an $IC_{PNM}\_05$ of $\geq 2$. This criterion ensured with a high degree of confidence that, regardless of the count size, the frequency of reporting drug-ADE association was at least twice that when there was no association between the drug and ADE.

$$\boldsymbol{IC}_{\boldsymbol{PNM}}\_05 = \log_2 \frac{\boldsymbol{P}\left(\boldsymbol{A}_j|\boldsymbol{D}_i\right)}{\boldsymbol{P}\left(\boldsymbol{A}_j\right)} \cdot \exp\left(\frac{-2}{\sqrt{\boldsymbol{c}_{\text{ij}}+1}}\right) \tag{10}$$

In **Equation 10**, $P(A_j|D_i)$ is generated by PNM, and $P(A_j)$ is obtained from **Eq. 9**.

# RESULTS

## Evaluation and Comparison With Other Signal Detection Algorithms

We compared the proposed $IC_{PNM}$ method with the Bayesian statistical methods (IC and EBGM) using 1,148 pairs that intersected with the SIDER database and 158 pairs that intersected with the OMOP benchmark, respectively, as the testing set from FAERS between 2004 and 2009. The detection performance is presented in **Figure 2**. The $IC_{PNM}$ performed better than the IC and EBGM in terms of AUC scores when 1,148 SIDER drug-ADE pairs were used as the testing set (AUC scores: 0.7098, 0.6737, and 0.6619 for $IC_{PNM}$, IC, and EBGM, respectively). Furthermore, $IC_{PNM}$ still achieved better performance when 158 OMOP drug-ADE pairs were the testing set (AUC scores: 0.6271, 0.6154, and 0.6024 for $IC_{PNM}$, IC, and EBGM, respectively). EBGM showed a generally worse performance compared with the other two methods. On the other hand, from the ROC for three Bayesian statistical methods plotted in **Figure 2A**, $IC_{PNM}$ had higher sensitivity at high specificity points (>0.6 specificity), whereas IC had higher sensitivity at low specificity points (0.3<specificity<0.6), followed by $IC_{PNM}$. In contrast, we performed quantitative bias analysis when $IC_{PNM}$ did not control the confounding bias, and the confusion matrices were listed in **Supplementary Tables S3A, S4A**. In summary, the above results presented that the $IC_{PNM}$ can enhance drug safety because it combined the strengths of both the PNM and the Bayesian methods and it controlled the confounding bias.

We also evaluated the performance of the $IC_{PNM}$ compared with the frequentist statistical methods (ROR and PRR) using the FAERS data between 2004 and 2009. As shown in **Figure 3**, $IC_{PNM}$ still performed better than ROR and PRR in terms of AUC scores when 1,148 drug-ADE pairs and 158 drug-ADE pairs were the testing set, respectively. In general, the Bayesian statistical methods were superior to the frequentist methods, and among them, the ROR performed better than the PRR.

Overall, AUCs, Youden's sensitivities and Youden's specificities and Youden's indices for our $IC_{PNM}$ and other four statistical methods are shown in **Table 2**, which were calculated using the FAERS data between 2004 and 2009 based on SIDER and OMOP. The maximum of sensitivity and specificity values are Youden's index, and the position of the Youden index indicates the optimal cut-off point of an algorithm's decision threshold. When SIDER data was used as the testing set, the $IC_{PNM}$ had the highest AUC and Youden's index, and the IC had the second highest. When the OMOP data was used as the testing set, the $IC_{PNM}$ still had the highest AUC and Youden's index, and IC the second-highest AUC and third-highest Youden's index. Moreover, EBGM had the third-highest AUC and second-highest Youden's index. The confusion matrices for the results of **Table 2** are presented in **Supplementary Tables S3, S4**.

## Evaluating the Performance and Robustness of $IC_{PNM}$

To verify the performance and robustness of the proposed method, we selected the FAERS data from 2014 to 2019Q2 and the SIDER data for additional analyses. The detection performance is shown in **Figure 4**, and the experimental results are summarized in **Table 3**. Among the five signal detection algorithms, the $IC_{PNM}$ had the highest performance (AUC score,0.8291; Youden's index, 0.5836) for these statistical

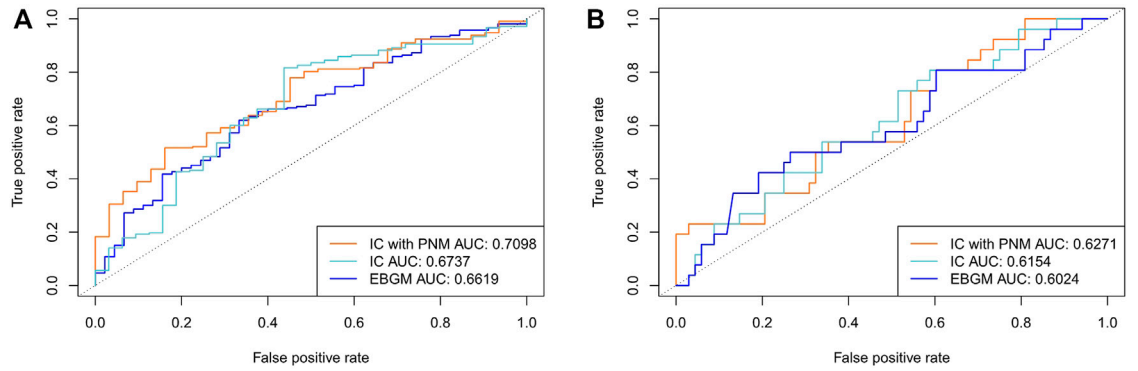


**FIGURE 2 | (A)** Comparison of performances of $IC_{PNM}$, IC, and EBGM with SIDER data as the testing set using FAERS 2004–2009 data **(B)** Comparison of performances of $IC_{PNM}$, IC, and EBGM with OMOP data as the testing set using FAERS 2004–2009 data.

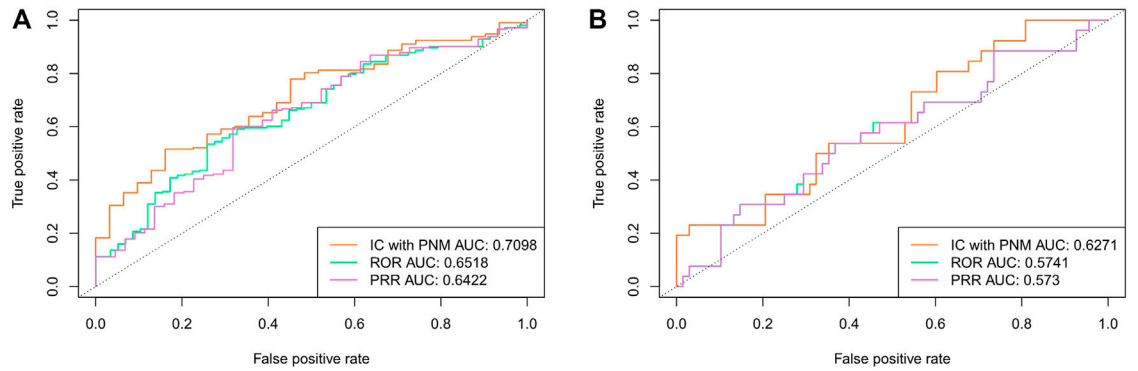


**FIGURE 3 | (A)** Comparison of performances of $IC_{PNM}$, ROR, and PRR with SIDER data as the testing set using FAERS 2004–2009 data **(B)** Comparison of performances of $IC_{PNM}$, ROR, and PRR with OMOP data as the testing set using FAERS 2004–2009 data.

**TABLE 2 |** Results of performance of different signal detection algorithms using FAERS 2004–2009 data.

| Testing set | Method | AUC | Youden's sensitivity | Youden's specificity | Youden's index |
|---|---|---|---|---|---|
| SIDER | $IC_{PNM}$ | **0.7098** | 0.5264 | 0.8547 | **0.3811** |
| | IC | 0.6737 | 0.8169 | 0.5625 | 0.3794 |
| | EBGM | 0.6619 | 0.6297 | 0.6667 | 0.2964 |
| | ROR | 0.6518 | 0.5352 | 0.7414 | 0.2766 |
| | PRR | 0.6422 | 0.5963 | 0.6818 | 0.2781 |
| OMOP | $IC_{PNM}$ | **0.6271** | 0.5284 | 0.7251 | **0.2535** |
| | IC | 0.6154 | 0.8077 | 0.4118 | 0.2195 |
| | EBGM | 0.6024 | 0.5012 | 0.7353 | 0.2365 |
| | ROR | 0.5741 | 0.5385 | 0.6324 | 0.1709 |
| | PRR | 0.5730 | 0.5385 | 0.6324 | 0.1709 |

*The bold values are to highlight the performance of the method, and have no specific meaning.*

methods. On the other hand, from the ROC for Bayesian methods and frequentist methods plotted in **Figure 4**, $IC_{PNM}$ still had higher sensitivity at high specificity points (>0.6 specificity), whereas $IC_{PNM}$'s sensitivity was close to the sensitivity of IC at low specificity points (specificity<0.6), and higher than that of EBGM. It is further confirmed that Bayesian DPAs were superior to frequentist DPAs. Our experiments also showed that the signals generated using our cut-off have high enough specificity to deserve further investigation. In contrast, we also performed quantitative bias analysis when $IC_{PNM}$ did not control the confounding bias, and the confusion matrices were listed in **Supplementary Table S5A**. The result showed that controlling the confounding bias could improve the

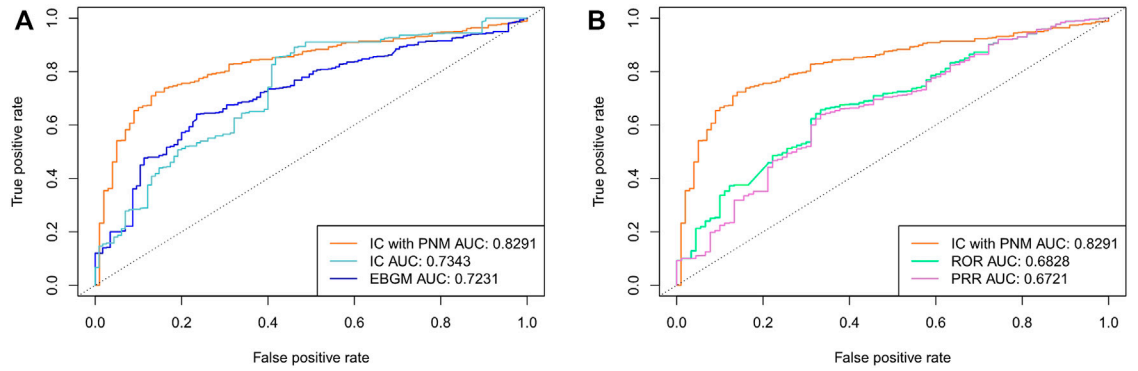


**FIGURE 4 | (A)** Comparison of performances of $IC_{PNM}$, IC, and EBGM with SIDER data as the testing set using FAERS 2014-2019Q2 data **(B)** Comparison of performances of $IC_{PNM}$, ROR, and PRR with SIDER data as the testing set using FAERS 2014-2019Q2 data.

**TABLE 3 |** Results of performance of different signal detection algorithms using FAERS 2014–2019Q2 data.

| Testing set | Method | AUC | Youden's sensitivity | Youden's specificity | Youden's index |
|---|---|---|---|---|---|
| SIDER | $IC_{PNM}$ | **0.8291** | 0.7236 | 0.8600 | **0.5836** |
| | IC | 0.7343 | 0.8537 | 0.5826 | 0.4363 |
| | EBGM | 0.7231 | 0.6407 | 0.7652 | 0.4059 |
| | ROR | 0.6828 | 0.6561 | 0.6667 | 0.3228 |
| | PRR | 0.6721 | 0.6381 | 0.6667 | 0.3048 |

*The bold values are to highlight the performance of the method, and have no specific meaning.*

**TABLE 4 |** Results of performance of different signal detection algorithms using cross validation and FAERS 2014–2019Q2 data.

| Testing set | Method | AUC | Youden's sensitivity | Youden's specificity | Youden's index |
|---|---|---|---|---|---|
| SIDER | $IC_{PNM}$ | **0.7486** | 0.5909 | 0.8083 | **0.3992** |
| | IC | 0.7227 | 0.7983 | 0.3233 | 0.1216 |
| | EBGM | 0.6939 | 0.6222 | 0.7233 | 0.3455 |
| | ROR | 0.5352 | 0.7999 | 0.3010 | 0.1009 |
| | PRR | 0.5217 | 0.7171 | 0.3733 | 0.0904 |

*The bold values are to highlight the performance of the method, and have no specific meaning.*

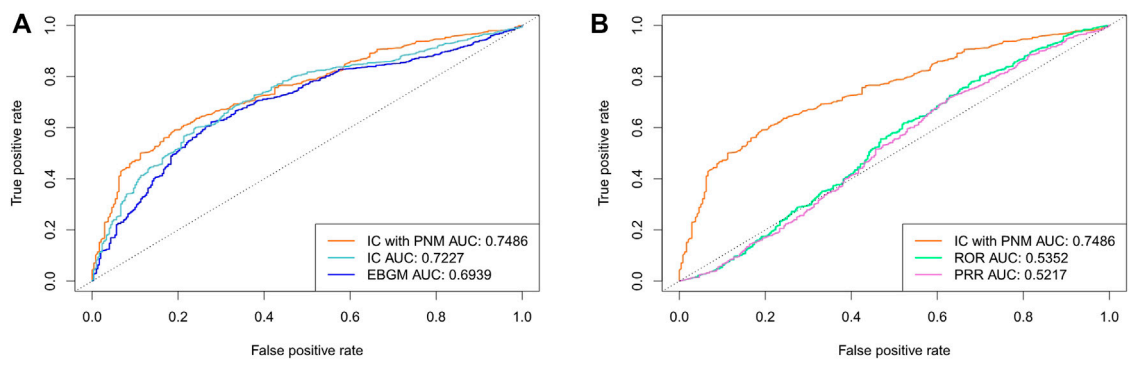


**FIGURE 5 | (A)** Comparison of performances of $IC_{PNM}$, IC, and EBGM using cross validation based on the FAERS 2014-2019Q2 data and SIDER **(B)** Comparison of performances of $IC_{PNM}$, ROR, and PRR using cross validation based on the FAERS 2014-2019Q2 data and SIDER.

**TABLE 5 |** Performance metrics of $IC_{PNM}$ based on the different threshold values, sensitivity, specificity and PPV using FAERS 2014–2019Q2 data.

| Threshold | $IC_{PNM}$ | | |
|---|---|---|---|
| | Sensitivity | Specificity | PPV |
| 1 | 0.9642 | 0.1333 | 0.8202 |
| 1.5 | 0.9138 | 0.36 | 0.8541 |
| 2 | 0.8617 | 0.54 | 0.8848 |
| 2.5 | 0.756 | 0.8 | 0.9394 |
| 3 | 0.6325 | 0.91 | 0.9773 |

*PPV, positive predictive value.*

performance of the algorithm. Moreover, the confusion matrices for the results of **Table 3** are presented in **Supplementary Table S5**.

We further evaluated the performance using cross validation and the training set composed of 10% of the data from each year (2014-2019Q2). The detection performance is shown in **Table 4** and **Figure 5**. Among the five signal detection algorithms, $IC_{PNM}$ had the highest performance (AUC score, 0.7486; Youden's index, 0.3993) for these methods. Furthermore, from the ROC for Bayesian methods and frequentist methods plotted in **Figure 5**, $IC_{PNM}$ still had higher sensitivity at high specificity points (>0.6 specificity), whereas $IC_{PNM}$'s sensitivity was higher than the sensitivity of IC at low specificity points (specificity<0.6), and higher than that of EBGM.

For the $IC_{PNM}$, we further performed analysis using different thresholds and compared the results. **Table 5** provided performance metrics for sensitivity, specificity, and different threshold values. When the threshold decreased, sensitivity increased, specificity decreased and PPV also decreased. For example, when the threshold was decreased to 1, the sensitivity increased to 0.9642 at the expense of dropping specificity to 0.1333. In contrast, when the threshold increased to 3, sensitivity decreased to 0.6325, specificity increased to 0.91, and the PPV was 0.9773.

We analyzed the correlation between the proposed $IC_{PNM}$ algorithm and the other statistical methods (IC, EBGM, ROR, and PRR). The correlation coefficients of the $IC_{PNM}$ with the EBGM and IC were 0.6619 and 0.5039, respectively, and the correlation coefficients with the ROR and the PRR were 0.1606 and 0.1602, respectively (Detailed information is presented in **Supplementary Table S6**). According to these results, $IC_{PNM}$ not only had a superior performance but also complemented the existing statistical approaches.

## Properties of the Top-Ranked Signals

We observed the top 50 signals generated using different statistical approaches. The Top-50 drug-ADE signals were further investigated using the SIDER data. First, the FAERS data between 2004 and 2009 were selected as the testing data. For the frequentist statistical methods, none of the top 50-ranked signals identified by ROR and PRR were validated using the SIDER data. For the Bayesian statistical methods, 13 of the top 50-ranked signals identified by the EBGM were validated using the SIDER data, and the $IC_{PNM}$ and the IC had 10 and 9 drug-ADE pairs, respectively. Among the 13 signals of the EBGM and the nine signals of the IC, the four signals were the same. Ten $IC_{PNM}$ signals were completely different from those of the EBGM and the IC. Next, the FAERS data between 2014 and 2019Q2 were selected as the testing data. For the frequentist statistical methods, one of the top 50-ranked signals identified by the ROR were validated using the SIDER data, and one using the PRR, with the overlapping signal being the same. For the Bayesian statistical methods, the $IC_{PNM}$, IC, and EBGM had 12, 9, and 12 overlapping drug-ADE signals using the SIDER data, respectively. Among the 12 signals of the EBGM and the nine signals of the IC, seven signals were the same. Among the 12 signals of the EBGM and the 12 signals of the $IC_{PNM}$, four signals were the same. There were two overlapping signals between the $IC_{PNM}$ and the IC (Signals identified by each approach using the SIDER data are shown in **Supplementary Tables S7, S8**).

# DISCUSSION

This study was designed to evaluate the performance of statistical methods in detecting unknown and new drug safety signals early and accurately. The performance of our proposed approach $IC_{PNM}$ was superior to that of a DPA using AUC and Youden's index. Furthermore, $IC_{PNM}$ performed well on the high and low ends of specificity and had the highest sensitivity among the DPAs when specificity was >0.6, here using 1,177 drugs and 97 ADEs in FAERS 2004-2009 as the experimental data. This also meant that $IC_{PNM}$ had good performance in detecting true-positive signals and false-positive signals. Then $IC_{PNM}$ had a higher sensitivity and specificity using 3,500 drugs and 97 ADEs in FAERS 2014-2019Q2 data. We believe that the increase in the number of drugs in the training data can improve the performance of the algorithm. In some cases, the traditional DPA performed well and was simple to calculate. However, the lack of accuracy in the signal detection, which may have been influenced by noise, may have caused important signals to be missed and the inclusion of some false-positive signals. These limitations may be attributed to the characteristics of these methods. At the same time, although SRSs also suffered from some limitations due to their own attributes, such as the overreporting and misattribution of causality, SRSs still have the advantage of being irreplaceable in drug safety surveillance (Harpaz, et al., 2012).

To improve ADE detection and overcome the limitations with the use of traditional DPAs, the signal detection algorithm $IC_{PNM}$ was developed based on different types of databases. Meanwhile, several other related studies confirmed that the utilization and combination of multiple databases could improve the detection of ADEs (Harpaz, et al., 2012; Xu and Wang, 2014; Li, et al., 2015; Harpaz, et al., 2017; Li, et al., 2020). However, the publicly available FAERS database required data curation before it could be used correctly, and different data cleaning and standardization strategies may have had a significant impact on the analysis results. Therefore, the first step was to process the FARES data. We used a curated and standardized method to

obtain the data (Banda, et al., 2016). Then, using the FAERS, PubChem, and DrugBank databases, we extracted various types of information. The $IC_{PNM}$ calculated the probabilities for the drug-ADE associations using the network, taxonomic, and intrinsic features based on the PNM. Among the algorithms tested, the $IC_{PNM}$ achieved the best performance in detecting true signals while controlling for any confounding bias. The $IC_{PNM}$ performed well in ADE detection, and the AUCs of previous similar studies using the OMOP Benchmark 398 drug-ADE pairs was less than 0.75 (Zhang, et al., 2018; Pham, et al., 2019; Harpaz, et al., 2013b).

The performance of the proposed algorithm can be explained by several important strengths. First, the $IC_{PNM}$ used the chemical and phenotypic characteristics and logistical regression models to calculate the probability of drug-ADE pairs. The $IC_{PNM}$ combined pre-clinical drug information with post-marketing safety reports. Furthermore, while the drug-ADE pairs with small sample sizes had more negative data than the drug-ADE pairs with large sample sizes, they also contained positive data. As stated in our previous research, in training a PNM model, the training model should include both large and small sample size drug-ADE pairs when selecting the training data (Ji, et al., 2021). Therefore, the probabilities calculated by PNM were not influenced by any confounders. Second, the $IC_{PNM}$ calculated the defined feature effects based on a drug-ADE bipartite network, which effectively reflected the properties of the drugs and made use of a powerful network function compared to the DPA. Finally, we proposed and defined a PS-adjusted logistic regression based on the control of the confounding bias from the FAERS data. In contrast, the influence of the confounding bias was ignored in the DPA analysis, which may have led to a signal bias and hence, inaccuracy. The $IC_{PNM}$ generated enhanced safety signals through the probability generated by PNM as the prior probability and PS-adjusted logistic regression.

Our proposed $IC_{PNM}$ detected potential ADE signals that were not detected by the traditional DPAs. It was challenging to identify the different ADEs using limited data. Hence, it is important to be able to detect potential ADEs using a post-market database. The traditional DPAs (IC, EBGM, ROR and PRR) showed insufficient sensitivities or specificities, resulting in false-negative or false-positive results, and their advantages and disadvantages were discussed in the recent scientific literature (Ding, et al., 2020). An important finding of our study was that the top signals of the different signal detection algorithms had different patterns. For instance, the top-50 signals generated by the $IC_{PNM}$ and the DPAs, the IC and the EBGM had the most overlapped signals while the $IC_{PNM}$ had fewer signals due to its powerfully different patterns. These results demonstrated that the signals generated by $IC_{PNM}$ were complementary to the existing statistical methods. This study also showed that the use of a combination of different signal detection algorithms in quantitative detection research achieved higher accuracy compared with the use of a signal detection algorithm alone.

Our study had some limitations. First, the performance of the proposed $IC_{PNM}$ relied heavily on the features of the PNM and the training data. Among them, the network features of the PNM had obvious advantages; the taxonomic and intrinsic features improved the prediction performance; however, they also increased the complexity of the data. To improve the practicability of the $IC_{PNM}$ to SRS alone, the use of network features only can also generate probabilities for the drug-ADE associations. Second, while the variety of the confounding variables can be controlled using multiple regression or propensity score analyses (Caster, et al., 2010; Tatonetti, et al., 2012; Tatonetti, et al., 2011), it was not easy to integrate the confounding variables into Bayesian DPA methods (especially, patient demographic information such as age, gender, etc., which have a large number of missing data in FAERS database), and the development of an appropriate methodology was required (Goldstein, et al., 2017). Currently, there is no signal detection algorithm that can overcome all such data quality problems. Third, as discussed in the literature by Ding et al., other limitations of these DPAs include relying on subjective thresholds. Youden index can be used as a comprehensive index to evaluate the ability of methods. In the future, further research is needed on how to select the optimal threshold without affecting the sensitivity. Lastly, we used the SIDER database and OMOP benchmarks as the gold standards against which to evaluate the performance of the $IC_{PNM}$ and DPAs. Using different databases and reference sets might lead to different performance characteristics.

In conclusion, our novel Bayesian signal detection algorithm, the $IC_{PNM}$, which combined a pharmacological network model with the Bayesian method, achieved superior performance and detected newer ADE signals compared with that achieved with the use of traditional DPAs. The use of the $IC_{PNM}$ generated drug safety signals using data from the post-market database FAERS and pre-clinical drug information, and it controlled the confounding bias using a PS-adjusted logistic regression. Additionally, an increase in the number of drugs in the training set can improve the performance of the algorithm, that is, $IC_{PNM}$ can obtain superior AUC, specificity, and sensitivity. Moreover, the signals generated using different methods had different patterns, and they complemented each other. Thus, the $IC_{PNM}$ not only had a better performance but also complemented the existing statistical approaches.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

## AUTHOR CONTRIBUTIONS

XJ conceived the study. XJ, GC, CX, and YR contributed to the study design. Data analysis was curated by XJ, YR, and JH. The first draft of the manuscript was written by XJ. GC, CX, JH, and YZ critically revised the manuscript. All authors read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.773135/full#supplementary-material

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# Safety Profile of Antipsychotic Drugs: Analysis Based on a Provincial Spontaneous Reporting Systems Database

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**Introduction:** Antipsychotic drugs are the main therapy for schizophrenia and have been widely used in mental disorder fields. However, the research on the safety of antipsychotic drugs in the real-world is rare. The purpose of this research is to evaluate the safety of antipsychotic drugs based on real-world data.

**Methods:** ADR reports collected by the Henan Adverse Drug Reaction Monitoring Center from 2016 to 2020 were analyzed. We described the safety of antipsychotic drugs by descriptive analysis and four signal mining methods. Meanwhile, the risk factors for serious adverse reactions of antipsychotics were identified.

**Results:** A total of 3363 ADR reports related to antipsychotics were included. We found that the number of adverse drug reaction reports and the proportion of serious adverse reactions have increased year by year from 2016 to 2020. Most adverse drug reactions occurred within 3 months after taking the medicine. The symptoms caused by typical antipsychotics and atypical antipsychotics were different and dyskinesia was more common in typical antipsychotics. Most patients improved or recovered after treatment or intervention while only one patient had sequelae. Low-level hospitals, psychiatric hospitals, youth, and old age could increase the risk of serious adverse reactions. Four off-label signals were found through signal mining, including amisulpride-pollakiuria, ziprasidone-dyspnoea, quetiapine-urinary incontinence, olanzapine-hepatic function abnormal.

**Conclusion:** We found that most ADRs occurred within 3 months after taking the medicine, so close observation was required for patients during the first 3 months of treatment. The ADRs of antipsychotics involved multiple organ-system damages but were not serious. It might be recommended to take alternative drugs after a serious ADR occurred. The symptoms caused by typical APDs and atypical APDs were different. For patients with typical APDs, dyskinesia was more common and should be given special attention. Statistics showed that low-level hospitals, psychiatric hospitals, youth, and old age were risk factors for serious ADRs. The four off-label signals obtained by signal mining

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should be paid special attention, including amisulpride-pollakiuria, ziprasidone-dyspnoea, quetiapine-urinary incontinence, and olanzapine-hepatic function abnormal.

**Keywords: antipsychotics, adverse drug reaction, spontaneous reporting system, signal mining, risk factor, pharmacovigilance, schizophrenia**

## INTRODUCTION

Schizophrenia is a severe emotional disorder marked by delusions and hallucinations, cognitive impairment, and blunted affect, which threatens health and causes a heavy economic burden for the patients. The Global Burden of disease Study 2016 showed that the economic burden of schizophrenia ranked 12th among 310 diseases and injuries in the world (Vos et al., 2017). In China, the lifetime prevalence of schizophrenia is 6‰ with approximately 8.4 million (Huang et al., 2019). Antipsychotic drugs (APDs) are the main therapy for schizophrenia, which maintain the stability of disease remission, improves patients' social function, attain the purpose of recovery and return to society (Gaebel et al., 2011; Sampson et al., 2013; De Hert et al., 2015). However, long-term APDs treatment is associated with many adverse reactions, such as weight gain, sexual dysfunction, akathisia, extrapyramidal disorder, orthostatic hypotension, hyperprolactinemia, etc (Muench and Hamer, 2010; Young et al., 2015; Ames et al., 2016). According to World Health Organization (WHO), adverse drug reactions (ADRs) refer to a response to a drug that is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (Edwards and Aronson, 2000). It has been reported the ADRs of APDs will negatively affect the patient s' medication compliance, aggravate the patient s' condition, and even increase the risk of certain diseases (Manu et al., 2015; Mouton et al., 2016). Hert reported that weight gain, cardiovascular and metabolic abnormalities caused by APDs might increase the risk of obesity, diabetes, and related cardiovascular diseases in schizophrenia patients (De Hert et al., 2012).

Currently, studies on the safety of APDs mainly focused on clinical trials. But the research based on real-world ADRs data is rare. Clinical trials have strict eligibility criteria, which may prohibit the inclusion of patients with multiple morbidities, and certain patient profiles may not have been represented, which might further limit the generalizability of these trials (Harpaz et al., 2012). Researches based on real-world data could sufficiently appreciate the risks and benefits of the medication, which might improve treatment decisions made by patients and their providers and support regulatory decision-making (Franklin et al., 2019). In this context, a safety evaluation of antipsychotics based on real-world data is warranted. Previous researches based on the real-world spontaneous reporting system database has focused on certain side effects or a few kinds of antipsychotics. Kato evaluated the relationship between antipsychotic drugs and adverse hyperglycemic events by using the FDA Adverse Event Reporting System database (Kato et al., 2015). McLean found that quetiapine treatment was related to alopecia based on the analysis of case reports from the New Zealand Intensive Medicines Monitoring Programme (McLean and Harrison-Woolrych, 2007). Sakai conducted a disproportionality analysis of second-generation antipsychotic exposure during pregnancy using the Japanese Adverse Drug Event Report database and found a potential signal for miscarriage for aripiprazole (Sakai et al., 2017). Although some studies have been carried out on antipsychotics based on the spontaneous reporting system database, the overall safety assessment of antipsychotics is still lacking. We performed a overall safety evaluation of APDs based on the spontaneous reporting system (SRS) of Henan Province in China. The purpose of this research was to study the safety of APDs from different perspectives of ADRs.

## MATERIALS AND METHODS

### Data Source and Preprocessing

ADR reports come from the SRS in Henan Province, China, which includes basic information of patients, drug usage, symptoms, severity, and outcome of ADRs. In the reports, suspected drugs refer to drugs related to the occurrence of ADRs. In addition to suspected drugs, other drugs used by patients are concomitant drugs. The relationship between drugs and ADR was evaluated as certain, probable, possible, unlikely, or impossible.

The inclusion criteria are as follows:1) Reports were reported and entered into the system between 2016 and 2020; 2) Reports in which APDs were considered as suspected drugs; 3) Reports in which the relationship between APDs and ADRs was evaluated as certain, probable, or possible.

The exclusion criteria are as follows: 1) Reports were reported and entered into the system before 2016 or after 2020; 2) Reports didn't involve APDs or in which APDs were considered as concomitant drugs; 3) Reports in which the relationship between APDs and ADRs was evaluated as unlikely or impossible.

The data were cleaned and preprocessed to ensure that they were clean and complete. In this research, APDs were defined as any drug of the N05A Anatomical-Therapeutic-Chemical (ATC) code group, which is a drug classification system developed by World Health Organization Collaborating Centre (WHO Collaborating Centre for Drug Statistics Methodology, 2021). Since there was no unified standard for drug names and ADR names in the reports, the drug names in the ATC classification system were used as the standard to unify the generic names, and the ADRs and clinical manifestations were unified based on Medical Dictionary for Regulatory Activities (MedDRA). According to The Administrative Measures on Reporting and Monitoring of ADRs, ADRs were divided into serious and non-

**TABLE 1 |** The fourfold table used in data mining.

| Category of drugs | Target ADR N | Other ADRs N | Sum |
|---|---|---|---|
| Target drug | a | b | a+b |
| Other drugs | c | d | c + d |
| Sum | a+c | b + d | n = a+b + c + d |

serious ADRs. Serious ADRs result in death, life-threatening effects, cancer, a congenital anomaly, birth defects, significant or permanent human disability, damage to organ function, hospitalization or prolonged hospitalization or events that require intervention and treatment to avoid the above results (China, N.H.C.o.t.P.s.R.o., 2021). The hospital levels were classified into three levels according to the Measures for the Administration of the Hospital Grade. The level 1 hospital are primary healthcare institutions that directly provide comprehensive services of medical treatment, prevention, rehabilitation, and healthcare to the community. The level 2 hospital are regional hospitals that provide medical and health services across several communities and are technical centers for regional medical prevention. The level 3 hospital is a medical prevention technology center with comprehensive medical, teaching, and scientific research capabilities providing across provinces and cities medical and health services to the whole country (China, N.H.C.o.t.P.s.R.o., 2016). Antipsychotic drugs were divided into two types, typical and atypical (Meltzer, 2013). The definition for polypharmacy included the use of three or more medications. Since there may be more than one ADR in a report, each report was divided into multiple drug-ADR combinations before signal mining.

## Data Analysis

A descriptive analysis of gender, age, reporting year, drug, severity, and outcome of ADRs in the reports was performed. Logistic regression analysis was used to calculate the adjusted odds ratio. All data analyses were performed using SPSS 24.0 (IBM Corp. Armonk, NY). The level of significance was set at $p < 0.05$ (two-tailed).

In this paper, We used four signal mining methods for generating potential safety signals, including reporting odds ratio (ROR) (van Puijenbroek et al., 1999; van Puijenbroek et al., 2000), proportional reporting ratio (PRR) (van Puijenbroek et al., 2002), the method employed by the United Kingdom Medicines and Healthcare products Regulatory Agency using the PRR and chi-squared (abbreviated as 'MHRA' in this study) (Evans et al., 2001), and Bayesian Confidence Propagation Neural Network (BCPNN) (Bate et al., 1998; Orre et al., 2000). **Table 1** shows how to calculate the counts of each drug-ADR combination. Then, signal mining was performed according to the formulas and criteria in **Table 2**.

# RESULTS

## Basic Information of the Reports

According to the inclusion and exclusion criteria, 3,363 reports were finally included from 570,000 ADR reports, with a male/female ratio of 1.10 and an average age of 33.29 ± 16.651 years. Most patients suffered from schizophrenia. In particular, we found that the number of reports and proportion of serious ADRs increased year by year from 2016 to 2020. This trend can be found in **Figure 1**.

## Characteristics of ADR

**Figure 2** shows the occurrence time of ADRs after starting the medication. Most ADRs occurred within 3 months after taking the medicine. Only a small amount of ADR occurred on the day.

3,363 reports related to 15 antipsychotic drugs, which were divided into two categories: typical and atypical. There were seven typical and eight atypical antipsychotics. Atypical APDs reported more reports of ADRs (2,970) and a higher proportion of severe ADRs (9.26%). In particular, we found that risperidone has the largest number of reports and chlorpromazine has the highest proportion of severe ADRs. See **Table 3** for details.

Since there may be more than one ADR in a report, 3,363 reports were divided into 3,953 drug-ADR combinations. The symptoms and system-organ damages related to ADRs of antipsychotics were counted. The symptoms were unified based on Preferred Term (PT) in MedDRA and system-organ damages were unified based on primary system organ class

**TABLE 2 |** Formulas and criteria for signal mining.

| Method | Formula | Criteria |
|---|---|---|
| ROR | $ROR = \frac{a/c}{b/d}$<br>$SE(lnROR) = \sqrt{(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d})}$<br>$95\%CI = e^{lnROR \pm 1.96SE(lnROR)}$ | a≥3 and lower limit 95%CI > 1 |
| PRR | $PRR = \frac{a/(a+b)}{c/(c+d)}$ $SE(lnPRR) = \sqrt{(\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d})}$ $95\%CI = e^{lnPRR \pm 1.96SE(lnPRR)}$ | a≥3 and lower limit 95%CI > 1 |
| MHRA | $PRR = \frac{a/(a+b)}{c/(c+d)}$<br>$\chi^2 = \frac{(\lvert ad-bc\rvert - n/2)^2 n}{(a+b)(c+d)(a+c)(b+d)}$<br>OR $\chi^2 = \frac{(ad-bc)^2 n}{(a+b)(c+d)(a+c)(b+d)}$ | a≥3,PRR≥2 and $\chi 2 \geq 4$ |
| BCPNN | $E(IC) = \log_2(\frac{(a+1)(n+2)^2}{(n+4)(a+b+1)(a+c+1)})$<br>$V(IC) = (\ln 2)^{-2}(\frac{n-a+3}{(a+1)(n+5)} + \frac{n-(a+b)+1}{(a+b+1)(n+3)} + \frac{n-(a+c)+1}{(a+c+1)(n+3)})$ $95\%CI = E(IC) \pm 2\sqrt{V(IC)}$ | lower limit 95%CI > 0 |

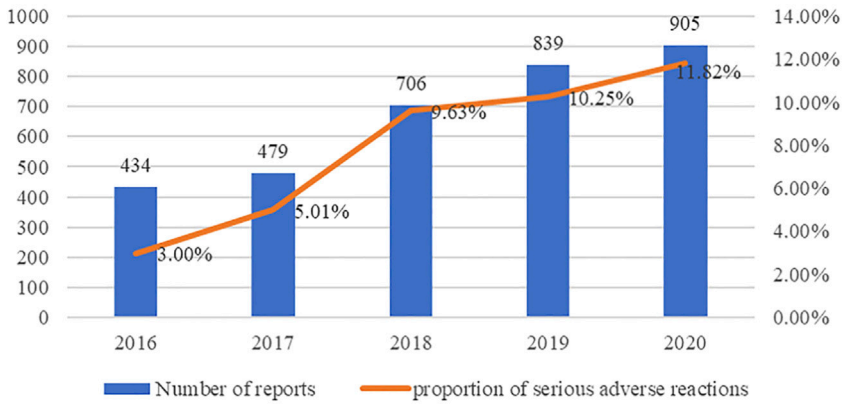


**FIGURE 1 |** number of reports and proportion of serious ADRs in each year.

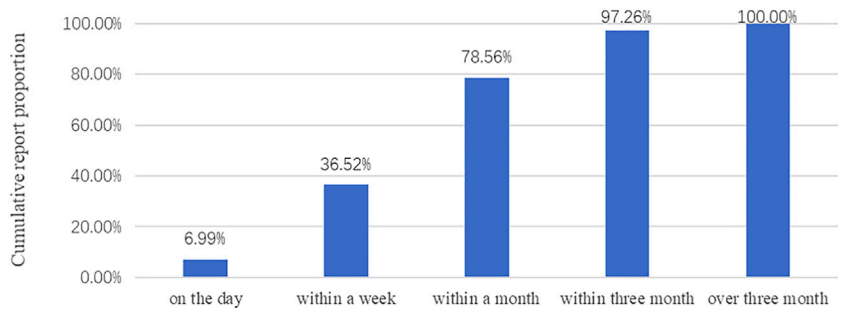


**FIGURE 2 |** Occurrence time of ADRs.

**TABLE 3 |** Drugs of the reports.

| Drug type | Drug | Non-serious | Serious | Sum |
|---|---|---|---|---|
| atypical | | 2,695 (90.74%) | 275 (9.26%) | 2,970 |
| | risperidone | 984 (90.86%) | 99 (9.14%) | 1,083 |
| | clozapine | 497 (89.71%) | 57 (10.29%) | 554 |
| | olanzapine | 321 (91.71%) | 29 (8.29%) | 350 |
| | Aripiprazole | 220 (93.22%) | 16 (6.78%) | 236 |
| | quetiapine | 189 (88.32%) | 25 (11.68%) | 214 |
| | amisulpride | 191 (92.27%) | 16 (7.73%) | 207 |
| | ziprasidone | 180 (87.38%) | 26 (12.62%) | 206 |
| | perospirone | 113 (94.17%) | 7 (5.83%) | 120 |
| typical | | 370 (94.15%) | 23 (5.85%) | 393 |
| | haloperidol | 211 (97.69%) | 5 (2.31%) | 216 |
| | perphenazine | 57 (89.06%) | 7 (10.94%) | 64 |
| | sulpiride | 57 (93.44%) | 4 (6.56%) | 61 |
| | chlorpromazine | 36 (83.72%) | 7 (16.28%) | 43 |
| | penfluridol | 5 (100.00%) | | 5 |
| | chlorprothixene | 3 (100.00%) | | 3 |
| | droperidol | 1 (100.00%) | | 1 |

(primary SOC). Statistics showed that 3,953 drug-ADR combinations involved a total of 20 system-organ damage, which mainly includes nervous system disorders (47.43%), gastrointestinal disorders (11.99%), and cardiac disorders (7.24%). Investigations (11.38%) indicate that various inspections are abnormal, but there is no clear system organ damage. **Table 4** listed top 10 primary SOC.

A total of 238 ADRs were identified. Extrapyramidal disorder (23.96%) was the most common symptom, followed by akathisia (5.94%) and constipation (5.01%). The ADR symptoms of typical and atypical APDs were different. Dystonia, abnormal sensation in eye, hypertonia, dry mouth, orthostatic hypotension, and insomnia were common ADR symptoms in typical APDs. Constipation, white blood cell count decreased, hepatic function abnormal, dizziness, and tachycardia were more common in atypical APDs. **Table 5** listed top 10 symptoms. In this paper, we differentiated akathisia from extrapyramidal disorder based on the original description of the reports. Patients described as extrapyramidal disorder by the reporting agency experienced multiple extrapyramidal symptoms at the same time, such as dystonia, restlessness, and akathisia. Patients described as akathisia usually experienced only one symptom. Based on the above differences, we separate statistics for the two adverse reactions.

Except for 109 cases in which the outcomes were unknown, most patients (94.56%) improved or recovered after treatment or intervention while only one patient had sequelae. See **Table 6** for details.

**TABLE 4 |** Number and percentage of ADRs related to primary SOC(TOP10).

| SOC | Frequency | Percentage (%) |
|---|---|---|
| Nervous system disorders | 1875 | 47.43 |
| Gastrointestinal disorders | 474 | 11.99 |
| Investigations | 450 | 11.38 |
| Cardiac disorders | 286 | 7.24 |
| Psychiatric disorders | 149 | 3.77 |
| General disorders and administration site conditions | 108 | 2.73 |
| Skin and subcutaneous tissue disorders | 97 | 2.45 |
| Hepatobiliary disorders | 94 | 2.38 |
| Eye disorders | 92 | 2.33 |
| Metabolism and nutrition disorders | 87 | 2.20 |

**TABLE 5 |** Frequently reported ADRs (TOP10).

| Typical | | | Atypical | | | Total | | |
|---|---|---|---|---|---|---|---|---|
| ADR | Frequency | Percentage | ADR | Frequency | Percentage | ADR | Frequency | Percentage |
| Extrapyramidal disorder | 181 | 40.58% | Extrapyramidal disorder | 766 | 21.84% | Extrapyramidal disorder | 947 | 23.96% |
| Dystonia | 29 | 6.50% | Akathisia | 220 | 6.27% | Akathisia | 235 | 5.94% |
| Tremor | 26 | 5.83% | Constipation | 194 | 5.53% | Constipation | 198 | 5.01% |
| Akathisia | 15 | 3.36% | White blood cell count decreased | 147 | 4.19% | Drooling | 156 | 3.95% |
| Abnormal sensation in eye | 14 | 3.14% | Drooling | 147 | 4.19% | White blood cell count decreased | 152 | 3.85% |
| Drooling | 9 | 2.02% | Tremor | 98 | 2.79% | Tremor | 124 | 3.14% |
| Hypertonia | 9 | 2.02% | Hepatic function abnormal | 78 | 2.22% | Somnolence | 83 | 2.10% |
| Dry mouth | 7 | 1.57% | Somnolence | 77 | 2.20% | Hepatic function abnormal | 80 | 2.02% |
| Somnolence | 6 | 1.35% | Dizziness | 74 | 2.11% | Dizziness | 79 | 2.00% |
| Orthostatic hypotension | 6 | 1.35% | Tachycardia | 71 | 2.02% | Tachycardia | 75 | 1.90% |
| Insomnia | 6 | 1.35% | \ | \ | \ | \ | \ | \ |

**TABLE 6 |** Outcomes of the reported ADRs.

| Variable | Frequency | Percentage (%) |
|---|---|---|
| Relieved | 587 | 17.45 |
| Cured | 2,593 | 77.10 |
| Not relieved | 73 | 2.17 |
| Left with sequelae | 1 | 0.03 |
| Missing | 109 | 3.24 |

## Risk Factors of Serious ADRs

In this study, there were 298 (8.86%) reports of serious ADRs. The logistic regression analysis showed that the high-grade hospitals have a lower proportion of serious ADRs than low-grade hospitals (grade 2 adjusted OR 0.41, $p = 0.002$ and grade 3 adjusted OR 0.37, $p = 0.002$), and psychiatric hospitals reported a higher percentage of serious ADRs (adjusted OR 2.61, $p < 0.001$). Besides, compared with people aged 18 to 35, people younger than 18 years (adjusted OR 1.59, $p = 0.008$) and older than 64 years (adjusted OR 2.17, $p = 0.011$) were at higher risk of serious ADRs. Detailed results are shown in **Table 7**.

## Signal Mining Results

Through signal mining, the four methods obtained common 44 positive signals. Larger PRR values stand for the stronger association between the drug and ADR. Four off-label positive signals were found by comparing with the drug instructions. Sorted by PRR value, the top 10 positive signals and off-label positive signals were listed in **Table 8**. ROR (LI95), PRR (LI95), and IC(LI95) represent the lower limit of 95% confidence interval of ROR, PRR, and IC and superscript a represents off-label ADR.

# DISCUSSION

Statistics showed that the number of ADR reports and the proportion of serious ADRs increased year by year from 2016 to 2020. One reason may be that the prevalence of mental disorders has been rising, leading to an increase in the use of APDs (Charlson et al., 2018; Huang et al., 2019). The other reason may be that the under-reporting and false-reporting problems in SRS had been improved, which is due to the application of CHPS and the improvement of the education level of medical staff (Lirong, 2021). In 2016, the National Center for ADR Monitoring

**TABLE 7 |** Risk factors of serious ADRs.

| Variable | | P | Adjusted OR | 95%CI |
|---|---|---|---|---|
| Female (refer to Male) | | 0.073 | 1.25 | (0.980,1.589) |
| Age | 18–35 | 0.002 | | |
| | 18< | 0.008 | 1.59 | (1.128,2.247) |
| | 35–65 | 0.869 | 0.98 | (0.739,1.292) |
| | ≥65 | 0.011 | 2.17 | (1.189,3.942) |
| Season | spring | 0.196 | | |
| | summer | 0.788 | 0.95 | (0.655,1.379) |
| | autumn | 0.171 | 1.26 | (0.905,1.748) |
| | winter | 0.182 | 1.31 | (0.882,1.937) |
| Atypical (refer to Typical) | | 0.056 | 1.55 | (0.989,2.441) |
| Hospital level | 1 | 0.006 | | |
| | 2 | 0.002 | 0.41 | (0.236,0.716) |
| | 3 | 0.002 | 0.37 | (0.198,0.705) |
| Psychiatric hospital (refer to General hospital) | | <0.001 | 2.61 | (1.684,4.043) |
| Multiple disease (refer to Single disease) | | 0.299 | 1.67 | (0.634,4.410) |
| Polypharmacy (refer to Non-polypharmacy) | | 0.611 | 0.92 | (0.677,1.258) |

**TABLE 8 |** The signals of ADRs (4 methods, TOP10 and off-label).

| Drug | ADR | ROR (LI95) | PRR | PRR (LI95) | $\chi 2$ | IC(LI95) |
|---|---|---|---|---|---|---|
| perphenazine | Tongue induration | 4.34 | 15.51 | 4.36 | 21.05 | 2.23 |
| sulpiride | Insomnia | 5.70 | 13.29 | 5.60 | 45.33 | 2.34 |
| chlorpromazine | Blood pressure decreased | 3.55 | 11.81 | 3.58 | 17.01 | 2.07 |
| chlorpromazine | Orthostatic hypotension | 4.79 | 10.63 | 4.70 | 37.87 | 2.17 |
| chlorpromazine | Pruritus | 3.38 | 11.19 | 3.41 | 16.04 | 2.01 |
| haloperidol | Dystonia | 6.66 | 9.54 | 6.14 | 136.25 | 2.05 |
| olanzapine | Obesity | 2.13 | 8.48 | 2.13 | 9.36 | 0.78 |
| amisulpride | Pollakiuria[a] | 2.00 | 7.95 | 2.00 | 7.74 | 1.03 |
| chlorpromazine | Rash | 2.74 | 7.46 | 2.76 | 14.91 | 1.62 |
| haloperidol | Nuchal rigidity | 2.57 | 7.32 | 2.57 | 14.50 | 1.21 |
| ziprasidone | Dyspnoea[a] | 1.64 | 5.07 | 1.65 | 7.27 | 0.77 |
| quetiapine | Urinary incontinence[a] | 1.41 | 5.28 | 1.41 | 4.62 | 0.65 |
| olanzapine | Hepatic function abnormal[a] | 2.17 | 3.18 | 2.12 | 33.54 | 0.80 |

*The superscript a represents off-label adverse reactions.*

established the Chinese Hospital Pharmacovigilance System (CHPS), which had been gradually promoted in China. By docking with hospital information systems and laboratory information systems, CHPS can detect ADR reports promptly, and realize the generation, review, report, feedback, and analysis of ADR information online, which improved the problem of under-reporting and false reporting and increase the number of reports. Under the influence of the Covid-19 epidemic, it is foreseeable that the incidence of mental disorders will further increase, and with the improvement of the adverse drug reaction monitoring system, the number of ADR reports of antipsychotic drugs will continue to increase, but the proportion of serious adverse reaction reports may decline.

In terms of the occurrence time, most ADRs occurred within 3 months after taking the medicine, which means patients and family members should take more responsibility for identifying ADRs. Close observation is required for the first 3 months after taking the medicine. The ADRs of antipsychotics mainly involved nervous system disorders, gastrointestinal disorders, and Cardiac disorders. The most common symptom of APDs was extrapyramidal disorder. Some scholars classified APDs as typical or atypical based on their liability to cause the extrapyramidal disorder (Meltzer, 2000). Compared with typical APDs, atypical APDs had a lower incidence of extrapyramidal side effects at conventional clinical doses (Meltzer, 2013). In this research, atypical APDs reported more reports and a higher proportion of serious ADRs. The reason may be that more patients use atypical APDs, and only patients in good condition use typical APDs. The symptoms caused by typical APDs and atypical APDs were different. Dyskinesia was more common in typical APDs, such as dystonia and hypertonia. Some research shows that the incidence of tardive dyskinesia was twenty percent in patients using typical APDs, and only one or two percent in patients using atypical APDs (Al Hattab et al., 2018). For patients with typical APDs, tardive dyskinesia should be given special attention, because it is not easy to detect, usually insensitive to treatment, and may be permanent.

Most patients were improved or cured after treatment and intervention while only one patient had sequelae. This patient was diagnosed with schizophrenia and developed sinus bradycardia after taking sulpiride tablets. The doctor believed that continuing to take this drug would benefit the patient more than harm, so this patient continued to use it until leading to long-term sinus

bradycardia. We suggested that it might be wiser to replace the drug after a serious ADR occurred.

Our research showed that low-level hospitals, psychiatric hospitals, youth, and old age were risk factors for serious ADRs. Many studies had shown that adolescents have a higher risk of ADRs while using APDs (Safer, 2004; Correll, 2008; Sikich et al., 2008). Sikich found that weight gain and extrapyramidal effects were more common and severe in adolescents treated with risperidone and olanzapine (Sikich et al., 2004). The elderly should be extra careful when using APDs as well. Research performed by Daniel showed that older age is a risk factor for death from the neuroleptic malignant syndrome, which is a potentially fatal idiosyncratic reaction caused by APDs (Guinart et al., 2021). There may be two reasons for the lower proportion of severe ADR in high-level hospitals. On the one hand, high-level hospitals have more experienced doctors and nurses who will pay close attention to patients so they could find ADR early and avoid the occurrence of severe ADR. On the other hand, the strict ADR monitoring and reporting system makes high-level hospitals rarely underreport. On the contrary, lack of staff and imperfect systems in low-level hospitals are the main reasons for the high proportion of serious ADRs. Psychiatric hospitals have reported a higher proportion of severe ADRs, which may be due to the fact that they have more severe psychiatric patients. In China, the general hospital psychiatric units and psychiatric hospitals are the main provider of mental health services, and psychiatric hospitals usually provide intensive services for severe psychiatric disorders (Chen et al., 2013). As patients with severe illness often require high-dose medications, they are more likely to develop severe ADR.

44 Drug-ADR combinations were identified as positive signals by all four signal mining methods. A positive signal indicates that this combination is significantly higher and reaches the threshold compared to the background frequency. If the signal included an off-label ADR, it is necessary to do further analysis to prevent potential drug safety incidence. By comparing with drug instructions, we found four off-label signals, including amisulpride-pollakiuria, ziprasidone-dyspnoea, quetiapine-urinary incontinence, olanzapine-hepatic function abnormal. We have not found any reports of amisulpride-related pollakiuria in medical literature, but Mendhekar and Lohia (2009) and Niranjan et al. (2017) respectively reported a case of amisulpride causing urinary incontinence (Mendhekar and Lohia, 2009; Niranjan et al., 2017). Considering that pollakiuria could cause urge urinary incontinence, we suspected that pollakiuria might be an early symptom of urinary incontinence caused by amisulpride. Further research on amisulpride-related pollakiuria or urinary incontinence requests more case reports. Tsai and Harada separately reported one case of dyspnoea after ziprasidone administration (Tsai et al., 2008; Harada et al., 2018). This study found four cases of dyspnoea caused by ziprasidone and considered ziprasidone-dyspnoea as a positive signal. The mechanism of ziprasidone inducing dyspnea is to cause respiratory muscle or laryngeal dystonia, and timely withdrawal and treatment with anticholinergic agents can help alleviate the symptoms (Tsai et al., 2008). Elyasi reported two cases of urinary incontinence caused by quetiapine in patients with bipolar disorder (Elyasi and Darzi, 2017). Between July 2011 to July 2018, The National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI)received six reports of quetiapine-induced urinary incontinence. Experts at the NCC-PVPI analyzed six reports and found that there was a strong causal relationship between quetiapine and urinary incontinence. Thus they recommended that the instructions of quetiapine should be modified to treat urinary incontinence as a clinically significant ADR (World Health Organization, 2019). Urinary incontinence is a serious and embarrassing side effect, which adversely affects the patients' quality of life and compliance. Therefore, we think the doctors and patients should be warned about the risk of quetiapine-related urinary incontinence. There were many reports of olanzapine-related hepatic function abnormality (Farooque, 2003; Kahn, 2014; Katagiri et al., 2018). It is generally believed that olanzapine could cause an isolated asymptomatic increase in the aminotransferase levels, but Lam reported a case of a 17-year-old man with first-episode schizophrenia who developed olanzapine-induced hepatitis, cholestasis, and splenomegaly, indicating that olanzapine could cause much liver damage (Lui et al., 2009). The mechanism of olanzapine-induced liver dysfunction remains unclear. A study by TingJiang showed that up-regulation of FATP2/FABP1 and down-regulation of hepatic OCTN2 probably contribute to olanzapine-induced liver steatosis (Jiang et al., 2019).

In general, we performed a safety evaluation of antipsychotic drugs by analyzing a database of the provincial spontaneous reporting system. As clinical trials were carried out under specific conditions and usually couldn't include adequate people, our research plays an important role in evaluating the safety of antipsychotic drugs. The statistical results and ADR signals obtained in this study are helpful in guiding the safe use of antipsychotics, and might be clues for ADR mechanism research, even providing advice for modifying drug labels based on the detection of off-label ADRs.

This study has potential limitations. Firstly, the results were biased due to the inevitable under-reporting and false-reporting in SRS. Secondly, the signal detection method is based on the reported quantitative correlation rather than biological correlation, and cannot represent the inevitable causal relationship between drugs and adverse reactions. However, based on the following considerations, our research still was important. The development of CHPS had greatly reduced the under-reporting and false-reporting, so the bias caused by data has been reduced as much as possible. Although we couldn't prove the causal relationship between drugs and ADRs, the positive signals could provide clues for further research. At the same time, we provide relevant literature to support the off-label signals. Overall, this study has a positive impact on promoting the rational use of APDs.

## CONCLUSION

In this research, we found that most ADRs occurred within 3 months after taking the medicine, so close observation was

required for the first 3 months. The ADRs of antipsychotics involved multiple organ-system damages but were not severe, most patients were improved or cured after treatment and intervention while only one patient had sequelae. But it might be wiser to replace the drug after a serious ADR occurred. The symptoms caused by typical APDs and atypical APDs were different. For patients with typical APDs, dyskinesia was more common and should be given special attention. Statistics showed that low-level hospitals, psychiatric hospitals, youth, and old age were risk factors for serious ADRs. The four off-label signals obtained by signal mining should be paid special attention, including amisulpride-pollakiuria, ziprasidone-dyspnoea, quetiapine-urinary incontinence, and olanzapine-hepatic function abnormal.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data may be obtained from a third party and are not publicly available. Requests to access these datasets should be directed to fengda@hust.edu.cn.

## ETHICS STATEMENT

This ethical approval was obtained from the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (2020S204). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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# Influence of Jamaican Cultural and Religious Beliefs on Adherence to Pharmacotherapy for Non-Communicable Diseases: A Pharmacovigilance Perspective

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Worldwide, socio-cultural determinants have been shown to influence the beliefs of patients about their health and decision making for treatment. This is consistent with the evidence that cultural and religious beliefs affect illness conceptualization and behaviors of Jamaican patients living with non-communicable diseases, such as diabetes mellitus and hypertension. Despite these known socio-cultural influences, an acknowledgment of relevance of adherence to pharmacotherapy has been grossly understudied. Furthermore, while poor adherence to pharmacotherapy, especially in the management of patients living with non-communicable diseases is associated with adverse drug reactions; reporting of such information in the pharmacovigilance process is inadequate. We review previous studies on the cultural and religious beliefs within the Jamaican context that may contribute to poor adherence to pharmacotherapy, especially among those patients living with non-communicable diseases. We support the ongoing perspective that current pharmacovigilance processes need retooling with the inclusion of socio-cultural influences on adherence to pharmacotherapy.

**Keywords: adherence, pharmacotherapy beliefs, cultural, religious, pharmacovigilance**

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## INTRODUCTION

Non-communicable diseases (NCDs) represent a significant portion of the global disease burden and are managed by lifelong pharmacotherapy. According to the World Health Organization (WHO), NCDs disproportionally affect developing countries and among these patients, adherence to pharmacotherapy rates is less than fifty percent (Sabaté, 2003). These challenges coupled with the limited resources to care for the health needs of its population increases the morbidity and mortality rates of NCDs in developing countries (Rose et al., 2016). Developing countries, such as Jamaica, encounter unique challenges at the various levels of the healthcare system (Figueroa et al., 1999; Wilks et al., 2001; Gossell-Williams et al., 2014; Hartzler et al., 2014; Mitchell-Fearon et al., 2015; Wilson et al., 2018). However, arguably and more important in impacting public health is having a health-conscious populace that is motivated to leverage the health system to the betterment of their overall well-being.

**TABLE 1 |** Overview of the studies presenting measures of non-adherences among Jamaicans living with NCDs. For all studies the measure of adherence.

| References | Chronic disorder of patients (sample size) | Non-adherence rate (based on self-report) | Theme identified by patients as reasons for non-adherence |
|---|---|---|---|
| Adeniyi et al. (2021) | DM and HTN (85) | 40% for patients with only DM<br>31.2% for patients with only HTN<br>30.8% for both conditions | Financial difficulty, Insurance problems, medication non-availability at local pharmacy and difficulty collecting medication |
| Barrett-Brown et al. (2021) | DM (101) | 53.5% | High pill burden—"tired of taking medications" |
| Bridgelal-Nagassar et al. (2016) | DM (260) | 33% overall; 28.5% amongst those with health-insurance | Not reported |
| Chambers et al. (2008) | Systemic lupus erythematosus (75) | 44% | Financial difficulty, medication non-availability in local pharmacy, fear of side effects, preference for herbal therapies, perception of mild disease, religious beliefs |
| Duff et al. (2006) | DM (133) | 55% | Not reported |
| Gossell-Williams et al. (2014) | 52 HTN (52) | Range from 9.6 to 40.4% | Adverse drug reactions, prefer not to take medication in the absence of symptoms, general inconvenience and pill burden |
| Mowatt (2013) | DM (104) | 34% | Not specified |
| Pusey-Murray et al. (2010) | Mental disorders (344) | 55.3% | Side-effects, running out of medication, forgetting to take medication, medication makes things worse |
| Watson and Ferrillo, (2021) | DM and HTN (116) | 19.2% for patients with DM<br>32.1% for patients with HTN | Did not recognize the importance of taking medication consistently to manage chronic illness |
| Welsh et al. (2015) | HTN (48) | 56.3% | Adverse drug reactions, pill burden, difficulty obtaining medication at the pharmacy, preference for herbal therapies |
| Wilson et al. (2018) | HTN (307) | 17.5% for patients with uncontrolled HTN<br>21.4% for patients with controlled HTN | Not reported |

*DM, diabetes mellitus; HTN, hypertension.*

According to terminology agreed by European consensus, adherence to pharmacotherapy is defined as the process by which patients take their medications as prescribed (Vrijens et al., 2012). A major contributor to adherence to pharmacotherapy is culture which is defined as a decision-making heuristic that can be found in values, beliefs, or social norms (Nunn, 2012). More specifically, various sociocultural factors have been found to affect patient health behaviours, decision-making and health outcomes (Oates et al., 2020), of which multidimensional factors, such as cultural and religious beliefs are among the most recognized (Leporini et al., 2014). Hordern (2016) emphasized the need for physicians to understand and respect the significance of cultural and religious beliefs of patients, as they inform the manner of their engagement with recommended treatment.

The goal of this paper is to explore how these socio-cultural factors impact adherence to pharmacotherapy for common NCDs in Jamaica, as well as to highlight their potential role in the pharmacovigilance process. We highlight peer reviewed publications reporting adherence to pharmacotherapy in Jamaican patients with NCDs after 2003, the year of implementation of the National Health Fund, which subsidizes the cost of drugs to Jamaicans (https://www.nhf.org.jm/images/pdfs/nhf_act_merged.pdf). The available studies involving Jamaican patients with NCDs suggest their adherence to pharmacotherapy is poor, with concerns about adverse drug reactions, having to take the drugs consistently even when no symptoms are being experienced and the general inconvenience featuring prominently. (**Table 1**) (Duff et al., 2006; Chambers et al., 2008; Pusey-Murray et al., 2010; Mowatt, 2013; Gossell-Williams et al., 2014; Welsh et al., 2015; Bridgelal-Nagassar et al., 2016; Wilson et al., 2018; Adeniyi et al., 2021; Barrett-Brown et al., 2021).

## Beliefs About Illness

Beliefs as defined by Macionis (2015, p. 95) are "specific thoughts or ideas that people hold to be true". Understanding patients' health beliefs is imperative as research has consistently shown that this predicts their health behaviors, including adherence to pharmacotherapy (Street and Haidet, 2011). Cultural beliefs relate to what is internalized to inform thinking and actions, while religious beliefs relate to beliefs in a social institution based on recognizing the sacred (Macionis, 2015). These terms are not mutually exclusive, as religion may be considered a cultural system (Bonney, 2004).

The way illness is conceptualized through a particular cultural lens has a direct impact on the kinds of actions taken in its management. Considering the diversity implicit within the Jamaican experience, it is difficult to define a cultural attitude towards pharmacological intervention which is all encompassing. However, insights have been offered to explain relevant ethnographic factors. Mitchell (1983) gave a comprehensive description of the ethnomedical landscape in Jamaica during the 1980s which is still relevant nearly 40 years later. The way in which Jamaicans conceptualize and treat diseases involve an emphasis on symptomatology and bodily-feeling; there is a need to feel a "cure" working in the body to counteract a particular ill-effect and the elimination of symptoms through treatment signifies the elimination of the disease, regardless of whether it is chronic and incurable (Mitchell, 1983). These perceptions have been corroborated in survey studies done amongst patients in Jamaica and the Jamaican diaspora living

in the United Kingdom and the United States of America where poor adherence to pharmacotherapy was related to the practice of "leaving-off" pills, which was justified by the idea that illness exists only in the presence of symptoms (Myfanwy and Watkins, 1988; Brown et al., 2007; Alhomoud et al., 2013; Smith, 2012; Gossell-Williams et al., 2014; Welsh et al., 2015).

## Beliefs About Alternative Treatments

The desire to feel a cure working is one potential explanation for the cultural beliefs in herbal preparations observed throughout Jamaican society. Many herbal preparations, especially in the form of teas, elicit instantaneous bodily sensations, such as "warmth" or "bitterness." For example, Cerasee tea (made from the plant *Momordica charantia*) is viewed as an effective treatment for diabetes mellitus because of the perceived counteracting or balancing effect of the bitter taste (Mitchell, 1983; Smith, 2012). It is important to explore not only whether herbal preparations are efficacious, but also the cultural cognitions that lead Jamaican's to combat illness in a particular way. Sobo (1993) examined the health perspectives of impoverished rural Jamaicans and how they approach well-being. There was an emphasis on natural, easily accessible options with attention being paid most carefully to the balancing of the system through "washouts" and "purification" rather than taking prescription drugs.

Considering Jamaica's extensive history of traditional knowledge systems (Payne-Jackson and Alleyne, 2004; Seaga, 2005; Delgoda et al., 2010; Picking et al., 2019; Adeniyi et al., 2021; Bateman James, 2021), it is not surprising that Jamaicans from various backgrounds turn regularly to alternative treatments. Records of the 1866 Commission investigating the Morant Bay Rebellion highlight the long history of Jamaicans consulting physicians on current medicine, but then relying on alternative treatments (Barima, 2016). Payne-Jackson and Alleyne (2004) in their 1991–1992 questionnaire-based survey of rural communities in Jamaica highlighted the involvement of physicians and alternative practitioners (e.g., bush-doctors, spiritual mothers and occult healers) in the treatment of illness, which inevitably leads to several treatment recommendations being used sequentially and simultaneously. This approach towards managing illness remains popular and thus the prescribed pharmacotherapy is often replaced or supplemented with alternative treatment options, popularly believed to be effective (Mitchell, 1983; Gardner et al., 2000; Delgoda et al., 2004; Gossell-Williams et al., 2008; Delgoda et al., 2010; Picking et al., 2011; Welsh et al., 2015; Foster et al., 2017; Owusu et al., 2020; Adeniyi et al., 2021). Patient testimonials about the anti-cancer benefits of herbal preparations travel by word of mouth, reaffirming their perceived efficacy and swaying others towards their utilization. Owusu et al. (2020) found in a western Jamaican sample of patients with hypertension and type two diabetes mellitus that the motivation for an alternative treatment plan included the belief that it is the more natural choice, and the belief that it is beneficial to utilize pharmacological and herbal preparations concurrently.

In exploring the factors which contribute to the popularity of herbal preparations in Jamaica, especially for the treatment of cancer, Foster et al. (2017) found that 80% of patients surveyed used them, often without the knowledge of their oncologist. In a survey canvasing the level of herbal preparation use concomitantly with pharmacological interventions amongst Jamaicans in both urban and rural settings, Picking et al. (2011) found that 72.6% of respondents had used herbal preparations in the last 12 months. Additionally, of those who were using both forms of treatment simultaneously, only 19.4% shared this information with their physician (Picking et al., 2011) corroborating the findings of Foster et al. (2017). One reason cited for withholding the self-administering of herbal preparations is that the physician simply did not ask (Picking et al., 2011; Smith 2012; Owusu et al., 2020). This presents a major concern about the risk of adverse drug reactions to concomitant users and reasons for this gap in patient-physician communication need to be explored.

## Religious Beliefs About Illness and Pharmacotherapy

Several religions are practiced in Jamaica and although the influence of religious beliefs on illness and healing perception have been reviewed (Sutherland et al., 2014), the relationship between religious beliefs and adherence to pharmacotherapy has been minimally explored. At an individual level, the influence of religion is highly subjective with some patients interpreting their healthcare provider's recommendations as God's way of helping them to help themselves, while others take a more fatalistic approach believing that their illness is God's will and therefore how it unfolds is out of their hands (Brown et al., 2007; Shahin et al., 2019; Smith, 2012; Hope et al., 2020). Taking this line of reasoning one step further, some highly religious patients may believe that their illness is a punishment from God for improper religious adherence and although they may respect their physician's diagnosis and recommendations, their ultimate concern rests with the judgement of their higher power (Rumun, 2014).

Chambers et al. (2008) explored the influence of Christianity among Jamaicans living with systemic lupus erythematosus; they found that several of the patients held a "strong belief in the possibility that they could be healed of lupus at any time" p.767. Amongst this cohort however these beliefs did not appear to hinder their adherence to pharmacotherapy. Anecdotal reports included the belief that healing was obtained at a crusade, leading to a patient ceasing to take their medication and their eventual death. Another patient reported finding prayer to be an effective way for them to relieve some of their pain and discomfort until they were able to replenish their medication (Chambers et al., 2008).

## A Role for Cultural and Religious Beliefs in the Pharmacovigilance Process

Jamaica, as a full member of the World Health Organization global database since 2012, collects individual case safety reports of adverse drug reactions following guidelines established by the International Conference on Harmonization (E2B (R3) Individual

case Safety Report Specification and Related Files; https://www.ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files). This global pharmacovigilance database facilitates detection of possible adverse drug reactions; however, the processes of data analysis and whether there is adequate focus on patient safety has been questioned (Edwards, 2017; Streefland, 2018; Ibrahim et al., 2021). According to Edwards (2017, p. 365) "We must develop a more holistic evaluation of suboptimal therapeutic outcomes, and do this without apportioning unnecessary blame".

Recent systematic reviews and observational studies highlight the relevance of socio-cultural determinants on adherence to pharmacotherapy among patients living with NCDs (Dhar et al., 2017; Niriayo et al., 2018; Swihart et al., 2018; Shahin et al., 2019; Al-Ganmi et al., 2020; Park et al., 2020; Raza et al., 2020; Świątoniowska-Lonc et al., 2021); however, the dearth of published literature suggests such awareness in pharmacovigilance processes is yet to be realized. Although poor adherence to pharmacotherapy is a common predictor of adverse drug reactions; the converse is also true (Gellad et al., 2011; Adem et al., 2021; Elangwe et al., 2020) and therefore enriching pharmacovigilance processes with what is referred to as 'the patient's voice' may facilitate causality analysis of adverse drug reactions (Simon et al., 2020).

## CONCLUSION

Cultural and religious beliefs have been shown to negatively impact adherence to pharmacotherapy in patients living with NCDs; despite this, current pharmacovigilance processes fail to give these beliefs much consideration in understanding poor adherence to pharmacotherapy, a known contributor to adverse drug reaction occurrences. Elaborating on the possible relationship between these factors and poor adherence to pharmacotherapy in the Jamaican context was the goal of this article, with several notable themes emerging. Among these were the cultural perception of illness as existing only in the presence of symptoms, and the importance of combating illness by targeting symptoms with treatments that one can feel acting in the body. Also featured were religious influences on the way patients make meaning of their experience of illness, along with the role they ascribe to physicians in facilitating their treatment.

Based on the empirical articles reviewed, the cultural and religious beliefs of Jamaicans about pharmacotherapy may be a significant contributor to poor adherence rates among patients living with NCDs. Adding this information is important in a comprehensive pharmacovigilance process, and future research should explore the optimization of adverse drug reaction reporting with patient data in these domains.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

MG-W and RB conceived the study. RB led the sourcing of the relevant literature and worked with MG-W to analyse the literature. MG-W and RB worked together to complete the first draft of the article. CB reviewed the draft and made substantial intellectual contributions, including addition of personal work done on the topic. All subsequent drafts were reviewed by all authors, including the submitted version.

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# Adverse Drug Reactions of Antihypertensives and *CYP3A5*3* Polymorphism Among Chronic Kidney Disease Patients

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Chronic kidney disease (CKD) patients may be more susceptible to adverse drug reactions (ADRs), given their complex medication regimen and altered physiological state driven by a decline in kidney function. This study aimed to describe the relationship between *CYP3A5*3* polymorphism and the ADR of antihypertensive drugs in CKD patients. This retrospective, multi-center, observational cohort study was performed among adult CKD patients with a follow-up period of up to 3 years. ADRs were detected through medical records. *CYP3A5*3* genotyping was performed using the direct sequencing method. From the 200 patients recruited in this study, 33 (16.5%) were found to have ADRs related to antihypertensive drugs, with 40 ADRs reported. The most frequent ADR recorded was hyperkalemia (n = 8, 20.0%), followed by bradycardia, hypotension, and dizziness, with 6 cases (15.0%) each. The most common suspected agents were angiotensin II receptor blockers (n = 11, 27.5%), followed by angiotensin-converting enzyme inhibitors (n = 9, 22.5%). The *CYP3A5*3* polymorphism was not found to be associated with antihypertensive-related ADR across the genetic models tested, despite adjustment for other possible factors through multiple logistic regression ($p > 0.05$). After adjusting for possible confounding factors, the factors associated with antihypertensive-related ADR were anemia (adjusted odds ratio [aOR] 5.438, 95% confidence interval [CI]: 2.002, 14.288) and poor medication adherence (aOR 3.512, 95% CI: 1.470, 8.388). In conclusion, the *CYP3A5*3* polymorphism was not found to be associated with ADRs related to antihypertensives in CKD patients, which requires further verification by larger studies.

**Keywords: adverse drug reaction, chronic kidney disease, pharmacogenetics, CYP3A5, antihypertensive drugs**

## INTRODUCTION

An adverse drug reaction (ADR) is defined as a noxious and unintended reaction to a drug at doses normally used in humans (World Health Organization, 2002). ADRs are a burden to the healthcare system, as patients with ADRs are found to have a longer duration of hospitalization and higher hospitalization costs (Suh et al., 2000). However, studies related to ADRs are mainly conducted among hospitalized patients rather than patients seen in outpatient settings (Laville et al., 2020). Among patients with chronic illness, chronic kidney disease (CKD) patients frequently report ADR. CKD patients might be more susceptible to ADRs given the need for multiple therapeutic agents to manage the various comorbidities of CKD (Laville et al., 2020).

ADRs could be potentially difficult to be predicted, given the multifactorial nature of ADRs, especially among CKD patients. Due to different physiological factors as a result of kidney function decline, it is difficult to extrapolate findings on the propensity of ADRs from existing studies among the general population to CKD patients. In addition, the unpredictable interindividual drug responses in the form of ADR might be driven by genetic polymorphisms that affect drug metabolism pathways and drug metabolism activity (Zanger and Schwab, 2013). Genetic polymorphisms that affect the drug metabolism pathways, such as the cytochrome P (CYP) 450 system, are of clinical prominence, as CYP450 metabolizes more than 80% of drugs (Zanger and Schwab, 2013). Therefore, CYP450 pharmacogenomics might be a promising approach to mitigate ADRs, especially in CKD patients.

The CYP3A family is the most abundantly expressed isoform of CYP450 enzymes, especially the CYP3A4 and CYP3A5 enzymes (Dorji et al., 2019). The presence of single-nucleotide polymorphism (SNP) in genes encoding these enzymes may result in variations in expression and activity of these enzymes (Lolodi et al., 2017). The consequential change in CYP enzyme activity causes alterations to the pharmacokinetic properties of the affected drugs, which then causes variation in the drug effects (Dorji et al., 2019). While SNPs to genes-encoding CYP3A4 enzyme are rare in East Asians, SNPs of the *CYP3A5* gene, especially *CYP3A5*3* (rs776746), are more common in Asian populations with an estimate of 65.7–71.3% (Dorji et al., 2019; Liang et al., 2021). The *CYP3A5*3* polymorphism, in which guanine (G) replaces adenine (A) at position 6,986 of the gene, causes alternative splicing that affects the quantity of the functioning CYP3A5 enzyme, which reduces the metabolic capacities of CYP3A5-substrate drugs (Kuehl et al., 2001; Zhang et al., 2014). The wild-type allele of the *CYP3A5* gene is *CYP3A5*1*, in which individuals with this allele express the CYP3A5 protein (Kuehl et al., 2001).

*CYP3A5* polymorphism is potentially associated with hypertension and blood pressure regulation (Zhang et al., 2014). Furthermore, drug responses might differ according to the status of *CYP3A5*3* polymorphism. The blood pressure response to the angiotensin-converting enzyme inhibitor (ACEI) was previously found to be significantly blunted in *CYP3A5*1* carriers, which might be contributed by sodium-retaining effects and/or elevated activity of the renin-angiotensin-aldosterone system (RAAS) (Eap et al., 2007). The opposite might occur in the absence of the *CYP3A5*1* allele, in which the adverse effect of hyperkalemia commonly seen with RAAS blockade by angiotensin-converting enzyme inhibitor (ACEI), angiotensin II blocker (ARB), or spironolactone might be potentiated. However, there is limited evidence linking *CYP3A5* polymorphism with these agents. In addition, CKD patients with RAAS blockers might be more predisposed to clinically significant hyperkalemia, especially those with advanced CKD (Weir and Rolfe, 2010).

*CYP3A5*3* polymorphism was previously reported to be associated with peripheral edema associated with amlodipine in general population (Liang et al., 2021). However, the generalizability of ADR studies among the general population to the CKD population might be limited, given the possibility of CKD influencing drug disposition (Yeung et al., 2014). In addition to reduction of renal clearance, CKD might attenuate a number of CYP-mediated metabolic pathways through several possible mechanisms, ranging from direct competitive inhibition by uremic constituents to alterations in gene transcription and translation (Yeung et al., 2014).

Hypertension is closely associated with CKD as a decline in kidney function precipitates the increase in blood pressure, but hypertension accelerates the progression of CKD (Judd and Calhoun, 2015). Optimization of antihypertensive therapy is therefore important for CKD patients. However, antihypertensive agents were found to be commonly related to ADRs (Laville et al., 2020). The identification of the potential contributing factors to ADRs related to antihypertensive agents is therefore important for preventive measures to minimize the suboptimal effects associated with antihypertensive agents in CKD patients. This study aimed to describe the relationship between *CYP3A5*3* polymorphism and ADR to antihypertensive drugs in CKD patients.

## MATERIALS AND METHODS

### Study Design and Study Population

This retrospective, multi-center, observational cohort study was performed among adult CKD patients aged 18 years and above with routine care for at least 5 years in nephrology specialist clinics in three Malaysian tertiary hospitals. Patients who were pregnant, lactating, had dementia, had incomplete medication records, or kidney transplant recipients were excluded. Written informed consent was obtained from all patients included in this study.

The study protocol was approved by the Medical Research Ethics Committee, Malaysia (KKM.NIHSEC.P19-2320 (11)) and the Universiti Kebangsaan Malaysia Research Ethic Committee (UKM PPI/111/8/JEP-2020-048). This study was conducted in compliance with the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines.

### Data Collection

Each participant who provided informed consent was assigned a unique subject identification number linked to a password-

protected database. Information about all medications used, use of traditional/complementary medicine (TCM), and adherence to medications was retrieved from the medical records. The name, dosage form, dose, frequency, timing of administration, and duration of administration of each medication were recorded. Medications used were categorized in accordance with the World Health Organization Anatomical Therapeutic Classification system classification (WHO Collaborating Centre for Drug Statistics Methodology, 2019). Consumption of traditional/complementary medicine was defined as the use of herbs (or botanicals) or over-the-counter nutritional/dietary supplements which were not prescribed by hospitals or health clinics, based on patient recall (Lee et al., 2021b).

Patients' medical records were then accessed to obtain sociodemographic characteristics, clinical information, laboratory data, medication records, as well as ADRs related to antihypertensives that were reported and occurred during the study period. ADRs were then assessed using the Naranjo scale, whereby ADRs with a causality probability category score equivalent to the "possible" category of at least a score of 1 and above were included (Naranjo et al., 1981; Laville et al., 2020). For reproducibility, the causality assessment for each ADR was performed by two pharmacists independently. The assessment also included a review of all concurrent drugs and TCM during the ADRs to detect any potential drug–drug or TCM–drug interactions. In view of the various herbal concoctions used in TCM, the identification of the active ingredients of each TCM was performed using the QUEST3+ System of the National Pharmaceutical Regulatory Agency, a centralized online system for product registration and licensing in Malaysia. The ADRs were grouped according to the Medical Dictionary for Regulatory Activities (MedDRA).

The kidney function of patients was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Stages of CKD and proteinuria status of the patients were categorized as per Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines (KDIGO, 2012).

Medication adherence was assessed through medical records. Medication adherence was considered poor if discrepancies from prescribers' orders for drug, dose, frequency, and duration in any of the three medication adherence phases were recorded (Vrijens et al., 2012; Lee et al., 2021b).

## Sample Size Calculation

Calculation of sample size was performed using G*Power 3.1.9.7 for logistic regression, with $\alpha = 0.05$, $1\text{-}\beta = 0.8$, Pr(Y = 1|X = 1) H0 of 0.211 based on 21.1% of ADRs reported among those without *CYP3A5*3/*3* genotype (Liang et al., 2021); Pr(Y = 1|X = 1) H1 of 0.317 based on 31.7% of ADRs reported in those with *CYP3A5*3/*3* genotype (Liang et al., 2021); and hence the effect size based on the odds ratio of 1.74 derived from the software. Based on the calculation, 166 patients were required.

## Detection of *CYP3A5*3* Gene Polymorphism

Venous blood was collected from patients and DNA was extracted using the DNeasy® Blood and Tissue extraction kit (Qiagen, Hilden, Germany). A polymerase chain reaction of the region encompassing the *CYP3A5*3* gene polymorphism was performed using the TopTaq Mastermix Kit (Qiagen, Hilden, Germany), followed by direct sequencing using the BigDye® Terminator version 3.1 cycle sequencing kit, which was run on a 96-capillary 3730xl DNA Analyzer (developed by Applied Biosystem, United States and produced by Thermo Fisher Scientific) (Boutin et al., 2000; Lee et al., 2021a). Other gene polymorphisms of the *CYP3A5* gene were not assessed, given the low prevalence of other polymorphisms in South East and East Asian populations (Dorji et al., 2019).

## Statistical Analysis

The results are presented as frequencies and percentages for categorical data. Numerical data are presented as median (interquartile range, IQR), as the numerical data were found to be non-normally distributed upon inspection of histograms. Pearson's Chi-square test for independence was used to study the association between categorical data, but if the assumptions of the test were not met, Fisher's exact test was used instead. The Mann–Whitney test was used for the non-normally distributed numerical data. A $p$-value < 0.05 was considered statistically significant.

Adherence to the Hardy–Weinberg equilibrium assumption was examined using a Chi-square test which compared the study results with the predicted allele and genotype distribution derived from the Hardy–Weinberg equation. A $p$-value > 0.05 indicated that the observed genotype distribution was consistent with the assumptions of Hardy–Weinberg Equilibrium (Tahir et al., 2020). The association of genetic polymorphism with ADRs related to antihypertensives was then assessed using logistic regression on the genetic models of dominant [0 = *CYP3A5*1/*1* (TT), 1 = *CYP3A5*1/*3* (TC) + *CYP3A5*3/*3* (CC)], recessive [0 = *CYP3A5*1/*1* (TT) + *CYP3A5*1/*3* (TC), 1 = *CYP3A5*3/*3* (CC)], additive [0 = *CYP3A5*1/*1* (TT), 1 = *CYP3A5*1/*3* (TC); 2 = *CYP3A5*3/*3* (CC)], and allele models [0 = *CYP3A5*1* (T), 1 = *CYP3A5*3* (C)] (Yoshida et al., 2009).

Simple and multiple stepwise logistic regression were performed on all variables, with variables of $p$-value < 0.25 found from the simple logistic regression included in the multiple logistic regression (Hosmer et al., 2013). Factors with a $p$-value < 0.05 in the multiple logistic regression were considered significant. The possibility of multicollinearity among variables was examined (Meyers et al., 2006; Hosmer et al., 2013). The resulting model was also checked for interaction terms to be adjusted if any were found. The Hosmer–Lemeshow goodness-of-fit test, classification tables, and area under the receiver operating characteristic curve were used to investigate any misrepresentation of data (Hosmer et al., 2013). All statistics were performed using the IBM Statistical Package for Social Science for Windows version 23 (IBM Corp, Armonk, NY, United States).

**TABLE 1 |** Demographic characteristics and factors associated with antihypertensive-related ADR (simple logistic regression).

| Variable | Number of patients without ADR, *n* (%) (*n* = 167) | Number of patients with ADR, *n* (%) (*n* = 33) | *p*-value[a] | Odds Ratio (95% CI) | *p*-value |
|---|---|---|---|---|---|
| Female gender | 77 (46.1) | 23 (69.7) | 0.021 | 2.688 (1.205, 5.997) | 0.016 |
| Ethnicity | | | | | |
| Malay | 83 (49.7) | 20 (60.6) | | 1.000 | |
| Chinese | 67 (40.1) | 9 (27.3) | 0.383[c] | 0.557 (0.238, 1.304) | 0.178 |
| Others | 17 (10.2) | 4 (12.1) | | 0.976 (0.296, 3.221) | 0.969 |
| Age, median (IQR) | 59.0 (25.0) | 55.0 (33.3) | 0.215[b] | 0.982 (0.959, 1.005) | 0.118 |
| Baseline eGFR <30 | 62 (37.1) | 16 (48.5) | 0.245 | 1.594 (0.752, 3.379) | 0.224 |
| A3 Albuminuria | 65 (43.0) | 16 (48.5) | 0.215 | 1.764 (0.781, 3.985) | 0.172 |
| Cause of CKD | | | | | |
| Glomerulonephritis | 25 (15.0) | 4 (12.1) | | 1.000 | |
| Hypertension | 17 (10.2) | 3 (9.1) | | 1.103 (0.219, 5.567) | 0.906 |
| Diabetes mellitus | 51 (30.5) | 8 (24.2) | 0.646 | 0.980 (0.269, 3.569) | 0.976 |
| Lupus nephritis | 30 (18.0) | 10 (30.3) | | 2.083 (0.582, 7.457) | 0.259 |
| Others | 44 (26.3) | 8 (24.2) | | 1.136 (0.311, 4.156) | 0.847 |
| Smoking | 8 (4.8) | 2 (6.1) | 0.671[c] | 1.282 (0.260, 6.329) | 0.760 |
| Presence of obesity | 46 (13.8) | 8 (24.2) | 0.845 | 0.864 (0.278, 2.685) | 0.800 |
| Presence of anaemia | 80 (47.9) | 27 (81.8) | <0.001 | 4.894 (1.921, 12.469) | 0.001 |
| Absence of diabetes mellitus | 89 (53.3) | 23 (69.7) | 0.088 | 2.016 (0.904, 4.496) | 0.087 |
| Presence of hypertension | 136 (81.4) | 23 (69.7) | 0.156 | 0.524 (0.227, 1.213) | 0.131 |
| Presence of dyslipidemia | 122 (73.1) | 20 (60.6) | 0.207 | 0.567 (0.261, 1.235) | 0.153 |
| Presence of congestive cardiac failure | 13 (7.8) | 2 (6.1) | 1.000[c] | 0.764 (0.164, 3.557) | 0.732 |
| Presence of gout | 36 (21.6) | 8 (24.2) | 0.818 | 1.164 (0.484, 2.800) | 0.734 |
| Number of medications at baseline, median (IQR) | 7 (4) | 6 (5) | 0.876 | 1.028 (0.891, 1.185) | 0.707 |
| Traditional/complementary medicine use | 21 (12.6) | 3 (9.1) | 0.772[c] | 0.695 (0.195, 2.480) | 0.575 |
| Poor medication adherence | 51 (30.5) | 18 (54.5) | 0.010 | 2.729 (1.276, 5.838) | 0.010 |
| ACEI/ARB use | 124 (74.3) | 23 (69.7) | 0.666 | 0.798 (0.351, 1.810) | 0.589 |
| Beta blocker use | 76 (45.5) | 16 (48.5) | 0.849 | 1.127 (0.534, 2.380) | 0.754 |
| Calcium channel blocker use | 112 (67.1) | 25 (75.8) | 0.414 | 1.535 (0.650, 3.623) | 0.329 |
| Diuretic use | 55 (32.9) | 12 (36.4) | 0.840 | 1.164 (0.534, 2.536) | 0.703 |
| Spironolactone use | 17 (10.2) | 7 (21.2) | 0.074[c] | 2.376 (0.897, 6.290) | 0.082 |
| Alpha-blocker use | 26 (15.6) | 7 (21.2) | 0.444 | 1.460 (0.574, 3.714) | 0.427 |
| Additive model | | | | | |
| *CYP3A5*1/*1* | 36 (21.6) | 6 (18.2) | | 1.000 | |
| *CYP3A5*1/*3* | 85 (50.9) | 14 (42.4) | 0.431 | 0.988 (0.352, 2.776) | 0.982 |
| *CYP3A5*3/*3* | 46 (27.5) | 13 (39.4) | | 1.696 (0.587, 4.900) | 0.329 |
| Recessive model | | | | | |
| *CYP3A5*1/*1+CYP3A5*1/*3* | 121 (72.5) | 20 (60.6) | 0.210 | 1.000 | 0.176 |
| *CYP3A5*3/*3* | 46 (27.5) | 13 (39.4) | | 1.710 (0.787, 3.717) | |
| Dominant model | | | | | |
| *CYP3A5*1/*1* | 36 (21.6) | 6 (18.2) | 0.816 | 1.000 | 0.664 |
| *CYP3A5*1/*3+ CYP3A5*3/*3* | 131 (78.4) | 27 (81.8) | | 1.237 (0.474, 3.225) | |
| Allele model | | | | | |
| *CYP3A5*1* | 157 (47.0) | 26 (39.4) | 0.281 | 1.000 | 0.258 |
| *CYP3A5*3* | 177 (53.0) | 40 (60.6) | | 1.365 (0.796, 2.338) | |

[a]*Chi-square tests were carried out unless specified.*
[b]*Mann–Whitney test was performed.*
[c]*Fisher's exact test was performed.*
*ACEI, angiotensin-converting enzyme inhibitor; ADR, adverse drug reaction; ARB, angiotensin II receptor blocker; CI, confidence interval; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; IQR, interquartile range.*

# RESULTS

## Study Population

Two hundred patients were recruited in this study, with half of them (n = 100, 50.0%) being females, and a median age of 58.5 years (IQR 26.0 years). The study patients had a median of 6 medications (range: 2–15) at baseline. Out of the 200 patients, 33 (16.5%) were found to have ADRs related to antihypertensive drugs, in which most of them were female (n = 23, 69.7%) and approximately half (n = 16, 48.5%) had a baseline eGFR of less than 30 ml/min/1.73 $m^2$. The *CYP3A5*3* allele frequency was found to be 54.3% (n = 217 out of 400, as one person had two *CYP3A5* alleles). The distribution of the genotypes fulfilled the Hardy–Weinberg equilibrium assumptions ($p$ = 0.968). The *CYP3A5*1/*1* genotype was found in 42 (21.0%) patients, while the *CYP3A5*1/*3* genotype was found in 99 (49.5%) patients, and

**TABLE 2 |** Details of antihypertensive-related ADRs reported.

| Type of ADR | Number of ADR, n (%) | Suspected agents (n) | Genotype (n) | | | Allele (n) | |
|---|---|---|---|---|---|---|---|
| | | | *CYP3A5 *1/*1* | *CYP3A5 *1/*3* | *CYP3A5 *3/*3* | *CYP3A5*1* | *CYP3A5*3* |
| Hyperkalemia | 8 (20.0) | Perindopril (5), valsartan (1), telmisartan (1), spironolactone (1) | 2 | 3 | 3 | 7 | 9 |
| Bradycardia | 6 (15.0) | Atenolol (4), metoprolol (2) | 2 | 2 | 2 | 6 | 6 |
| Hypotension | 6 (15.0) | Amlodipine (2), felodipine (1), bisoprolol (1), valsartan (1), telmisartan/amlodipine/metoprolol (1) | 1 | 1 | 4 | 3 | 9 |
| Dizziness | 6 (15.0) | Amlodipine (3), losartan (1), telmisartan (1), prazosin (1) | 0 | 4 | 2 | 4 | 8 |
| Acute kidney injury | 4 (10.0) | Telmisartan (2), losartan (1), perindopril (1) | 1 | 3 | 0 | 5 | 3 |
| Drug intolerance | 4 (10.0) | Prazosin (2), losartan (1), spironolactone (1) | 0 | 2 | 2 | 2 | 6 |
| Blood creatinine increased | 3 (7.5) | Perindopril (1), hydrochlorothiazide (1), losartan (1) | 1 | 2 | 0 | 4 | 2 |
| Dry cough | 2 (5.0) | Perindopril (2) | 0 | 1 | 1 | 1 | 3 |
| Pedal edema | 1 (2.5) | Minoxidil (1) | 0 | 0 | 1 | 0 | 2 |
| Total | 40 | | 7 | 18 | 15 | 32 | 48 |

*ACEI, angiotensin-converting enzyme inhibitor; ADR, adverse drug reaction; ARB, angiotensin II receptor blocker.*

the *CYP3A5*3/*3* genotype was found in 59 (29.5%) patients (**Table 1**).

## Description of ADRs Related to Antihypertensives

Forty ADRs related to antihypertensives were reported among the 33 patients, with 7 (21.2%) patients reporting more than one ADR during the study period. The most frequent ADR recorded was hyperkalemia (n = 8, 20.0%), followed by bradycardia, hypotension, and dizziness with 6 cases (15.0%) each (**Table 2**).

The most common suspected agents were ARBs (n = 11, 27.5%), followed by ACEI (n = 9, 22.5%) and calcium channel blockers (n = 7, 17.5%). Most ADRs had one suspected agent implicated per ADR, with only 1 (2.4%) ADR recorded with three suspected agents (**Table 2**). The number of ADRs by drug class (**Table 2**) reflected the frequency of prescribed drug classes (ACEI/ARB followed by calcium channel blockers, **Table 1**). However, the proportion of patients with ADRs varied by pharmacological classes. Most patients were prescribed ACEI/ARB during the study period (n = 147, 73.5%), with 8.2–16.1% ADRs reported among the patients prescribed with the agents, respectively (**Supplementary Material**). In contrast, among the patients prescribed with calcium channel blockers (n = 137, 68.5%), less ADRs (3.1–6.3%) were reported (**Supplementary Material**).

As for the causality of the ADRs, most ADRs were classified as "possible" (n = 38, 95.0%), while 2 (5.0%) were categorized as "probable," respectively. Three (7.5%) ADRs were related with hospitalizations, with no fatality recorded.

One-third of the patients who reported the use of TCM did not specify the name of the TCM used (n = 8). No drug–drug interactions or drug–TCM interactions were detected pertaining to the use of CYP3A5 inducers/inhibitors in the ADRs reported.

About half of the ADRs were managed by discontinuation of the suspected agents (n = 23, 57.5%). Meanwhile, 11 (27.5%) ADRs were addressed by substitution with another agent, and 1 (2.5%) was given correction therapy on top of drug discontinuation. On the other hand, 2 (5.0%) ADRs were managed by dose reduction, while the remaining 1 (2.5%) ADR was managed by reduction in frequency.

**TABLE 3 |** Factors associated with antihypertensive-related ADR (multiple logistic regression).

| Variable | b | Adjusted odds ratio (95%CI) | *p*-value |
|---|---|---|---|
| Anemia | 1.677 | 5.348 (2.002, 14.288) | 0.001 |
| Poor medication adherence | 1.256 | 3.512 (1.470, 8.388) | 0.005 |

*Multiple stepwise logistic regression was performed with adjustment of gender, ethnicity, age, baseline eGFR, albuminuria, diabetes mellitus, hypertension, dyslipidemia, spironolactone use, and recessive model of* CYP3A5*3 *polymorphism. Multicollinearity and interaction term were not found. Model fit was examined using the Hosmer–Lemeshow test (p = 0.995), classification table (84.4%), and area under receiver operating characteristic curve (73.5%).*
*ADR, adverse drug reaction; CI, confidence interval; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate.*

## *CYP3A5*3* Polymorphism Status and Association With Antihypertensive-Related ADRs

A simple (**Table 1**) and multiple logistic regression (**Table 3**) model were performed on variables to identify factors of antihypertensive-related ADRs. From the simple logistic regression, female, anemia, and poor medication adherence were found to be associated with ADRs related with antihypertensives in the study population (**Table 1**). Variables from the simple logistic regression with a *p*-value of <0.25 were then included into the multiple logistic regression model (gender, ethnicity, age, baseline eGFR, anemia, diabetes mellitus, hypertension, dyslipidemia, poor medication adherence, use of spironolactone, and the recessive model). After adjusting for possible confounding factors, the factors associated with antihypertensive-related ADR were anemia (adjusted odds ratio [aOR] 5.348, 95% confidence interval [CI]: 2.002, 14.288) and poor medication adherence (aOR 3.512, 95% CI: 1.470, 8.388) (**Table 3**).

Additional analysis was performed to determine the relationship between ADRs potentially related to CYP3A5 pharmacokinetics/drug level and *CYP3A5*3* polymorphism status, but no significant association was found ($p = 0.955$).

## DISCUSSION

This study provides a novel, pharmacogenomics-driven approach to assess ADRs related to antihypertensives in CKD. CKD patients might be more susceptible to ADRs given the need for multiple medications, in addition to physiological differences contributed by kidney function decline. In addition, the possibility of genetic susceptibility to ADRs has to be taken into consideration. The study findings improved the understanding of the relationship between genetic polymorphism and the development of ADRs related to antihypertensive agents in CKD patients.

In view of the common occurrence of *CYP3A5*3* polymorphism among Southeast Asian populations, it is important to understand the association of the gene polymorphism with antihypertensives, which are commonly used in CKD populations and play an important role in managing CKD (KDIGO, 2012). Furthermore, CKD patients have different physiological states given the changes to their excretory functions in contrast with healthy patients, which might affect the propensity of ADRs among these patients. The differences between the general population and CKD patients reflected the limited applicability of the current literature to CKD patients.

ADRs with antihypertensives were found in 16.5% of patients, which was similar to the findings from previous studies of hospitalized cohorts of 10–20% (Danial et al., 2018; Laville et al., 2020). From our study findings, RAAS blockers were found to be the most common suspected agents, which was also similar to that previously reported (Laville et al., 2020). The study findings corresponded with the prescribing pattern of the antihypertensives in the study population, with more than half reported to use ACEI or ARB, corresponding to the RAAS blockade as an important foundation of pharmacotherapy in CKD (KDIGO, 2012). Of note, calcium channel blockers, another frequently implicated agent, were also commonly used among the study cohort. Contrary to the findings of Laville et al. in which acute kidney injury was most commonly reported across several antihypertensive classes (Laville et al., 2020), the present study recorded hyperkalemia as the most common ADR.

The current work demonstrated that anemia was a factor of antihypertensive-related ADR, which concurred with previous reports in CKD patients (Laville et al., 2020). While causality could not be established from this study, the mechanism linking anemia and antihypertensive-related ADR could be explored in future studies. Blood pressure control is likely suboptimal in CKD patients with fluid overload, requiring the use of antihypertensives. A potential mechanism to be examined is pharmacokinetic changes driven by increased fluid status in CKD patients that may have led to a diluted hemoglobin concentration due to volume overload, as supported by the findings that more than half of anemic CKD patients were found to have volume overload (Hung et al., 2015), which led to dilutional anemia (Hildegard Stancu et al., 2018). Nevertheless, the findings improved the understanding of the potential presentation of CKD patients possibly affected by ADRs, in which these patients might have other underlying concurrent medical issues that need to be corrected.

Poor medication adherence was found to be associated with antihypertensive-related ADR in CKD patients, which corroborates the outcomes from previous studies (Laville et al., 2020; Seng et al., 2020). While poor adherence might be multifactorial, the association between poor medication adherence and antihypertensive-related ADR might reflect underlying issues with medication use (Laville et al., 2020). Of these, the most obvious link between ADR and adherence has been reported in studies that document poor adherence to medications that were suspected to be associated with previous ADR episodes (McKillop and Joy, 2013). It is quite possible that the uncomfortable nature of certain ADRs may lead patients to forgo their medication. Given the dynamic nature of medication adherence that might change over time (Unni et al., 2015), this study highlighted the importance of assessing medication adherence regularly among CKD patients through optimization of pharmaceutical care. In addition, current findings that many antihypertensive regimens were adjusted post-ADRs also reflect the need for closer monitoring among these patients, given the close association of antihypertensive drug adjustments with poorer disease outcomes (Lee et al., 2021b).

Although there was a lack of association between *CYP3A5*3* and ADR occurrence, further work is recommended. A challenge of studying *CYP3A5*3* polymorphism is the potential compensatory functions by CYP3A4 enzyme, owing to the structural similarity with the CYP3A5 enzyme (Lolodi et al., 2017). The low activity of the CYP3A5 enzyme, as a result of *CYP3A5*3* polymorphism, might be compensated by the CYP3A4 enzyme, which conceals the phenotype normally expected of the *CYP3A5*3* polymorphism. Hence, future work should take CYP3A4 activity into account to evaluate the relationship between *CYP3A5*3* polymorphism and susceptibility to ADRs related to antihypertensives in CKD.

Another challenge in utilizing pharmacogenetics in clinical practice is the potential confounding factor of TCM use. TCM may affect the drugs' metabolism and the propensity of ADRs. An example of this is the use of CYP3A4/5 inhibitors, such as *Allium sativum*, which could potentially inhibit CYP3A5 activity, regardless of the polymorphism status. Of note, TCM use was not found to be a factor of ADRs from our findings. While TCM use is in an increasing trend in this country (Siti et al., 2009; Abdullah et al., 2018), the low number of TCM reported among our study population may reflect underreporting, which limits the ability to detect an association between TCM use and antihypertensive-associated ADRs.

This study's major strength is the ascertainment of ADR cases from intensive medical record review, which addressed the possible limitation of underreporting found in many ADR studies using data from spontaneous pharmacovigilance reporting systems. In addition, *CYP3A5*3* genotyping was performed using the gold standard direct sequencing method. However, a few limitations were noted due to the retrospective study design, which could not imply causality. As such, some ADRs, such as dizziness, might be caused by anemia rather than the implied drugs. On the other hand, there is a possibility of underestimation in the ADRs related to antihypertensives, as some ADRs might not be recorded in the medical records. The small sample size of the study cohort is another limitation in which the study might be underpowered to detect the association between *CYP3A5*3* polymorphism and specific antihypertensives or specific doses. In addition, the retrospective nature of the study renders limitations in detailed analysis pertaining to drug–TCM interactions. It was challenging to verify the detailed composition of each TCM, not only due to incomplete data but also due to the fact that many TCMs are not registered with the Ministry of Health, which renders the complete contents of unregistered TCMs unknown (Lee et al., 2020).

In conclusion, the findings of the study indicate that ADRs related with antihypertensives among CKD patients were not associated with *CYP3A5*3* polymorphism alone among our study cohort, which requires verification through further studies with greater sample size. These ADRs might be propagated by pathways other than CYP3A5-related metabolism. Additional prospective studies with multiple genetic polymorphisms, and assessments of fluid status could be conducted to verify the findings.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions: The authors do not have permission to share the data. The data underlying the results presented in the study are available upon request from the corresponding author for researchers who meet the criteria for accessing confidential data. Requests to access these datasets should be directed to faridaislahudin@ukm.edu.my.

## ETHICS STATEMENT

The study protocol was approved by the Medical Research Ethics Committee, Malaysia (KKM.NIHSEC.P19-2320 (11)) and the Universiti Kebangsaan Malaysia Research Ethic Committee (UKM PPI/111/8/JEP-2020-048). This study was conducted in compliance with the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

Conceptualization: FL and FI; methodology: FL and FI, software: FL; validation: FI; formal analysis: FL and FI; investigation: FL; resources: AA, H-SW, and SB; data curation: FL and FI; writing—original draft preparation: FL and FI; writing—review and editing: FL, FI, AA, H-SW, SB, SS, AR, and MM-B; supervision: FI, AA, H-SW, SB, and MM-B; project administration: FI; funding acquisition: FI, MM-B, AR, and SS. All authors have read and agreed to the published version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.848804/full#supplementary-material

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# Anaplastic Lymphoma Kinase Tyrosine Kinase Inhibitor-Associated Cardiotoxicity: A Recent Five-Year Pharmacovigilance Study

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**Background:** Clinical trials frequently reported anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs) associated with cardiac adverse drug events (AEs) but minimal postmarketing data. We aimed to research real-world cardiac disorders associated with ALK-TKIs based on the Food and Drug Administration Adverse Event Reporting System (FAERS).

**Methods:** Extract reports from the FAERS from the first quarter of 2016 to the second quarter of 2021 were obtained. Data mining of cardiac disorders associated with ALK-TKIs was carried out using disproportionality analysis to determine the clinical characteristics of AEs.

**Results:** In total, 605 cases were screened out. These events were found to be more prevalent in patients ≥45 years (50.74%) and women (50.74%). The onset time of cardiac disorders was variable and concentrated within 2 months, with a median time of 33 days. The outcomes tended to be poor, with 20.93% fatality proportion. Cardiac arrhythmia was a common adverse event of ALK-TKIs, especially bradycardia. Crizotinib and lorlatinib showed positive signals in cardiac disorders, especially in heart failure, and brigatinib presented no signals. The study also found that myocarditis caused by ceritinib and cardiomyopathy caused by lorlatinib may be potential new adverse drug reactions.

**Conclusion:** ALK-TKIs were reported more frequently in cardiotoxicity than other drugs and could often manifest earlier. We also found potential new AE signals in specific drugs and need more clinical studies to confirm. Our study helps fill the safety information of ALK-TKIs in the heart and provides directions for further research.

**Keywords: anaplastic lymphoma kinase tyrosine kinase inhibitors, cardiotoxicity, FAERS, real-world study, disproportionality analysis**

## INTRODUCTION

Anaplastic lymphoma kinase (ALK) is a highly conserved receptor protein tyrosine kinase (RPTK) that belongs to the insulin receptor (IR) superfamily (Du et al., 2018). Most of the time, the ALK gene remains dormant, but it could cause cancers by genetic rearrangement, gene fusion, or gene overexpression once it is activated (Hallberg and Palmer, 2013). Lung cancer is the leading cause of cancer-associated deaths worldwide, and non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer patients (Sung et al., 2021). Many scholars in this field found that most patients have alterations in certain driver genes, which could encode specific proteins to accelerate the proliferation of tumors. The primary ALK mutant gene in NSCLC was the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene, which was found by Soda et al. (2007) and could encode EML4-ALK fusion proteins. These proteins could correspond with convoluted signals by activating multiple downstream pathways, such as PLC-γ, RAS, mTOR, and MAPK, driving aberrant proliferation and survival (Itchins et al., 2017; Lin et al., 2017). This has realized an excellent extensive perspective in NSCLC. After many years of research, ALK-TKIs have been used to treat NSCLC patients with the ALK mutant gene, which could inhibit the growth of tumor cells by inhibiting tyrosine kinase and thereby destroying the signaling pathway (Lin et al., 2017). Further research into ALK-TKIs revealed mutations of the ALK gene in other types of tumors, and the use of ALK inhibitors may produce good efficacy, for example, in anaplastic large-cell lymphoma (Mossé et al., 2013) and inflammatory myofibroblastic tumors (Butrynski et al., 2010).

Over the past dozen years, anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs) have been developed and have achieved ideal clinical outcomes via copious clinical trials (Kwak et al., 2010; Iragavarapu et al., 2015; Wu et al., 2018). Crizotinib was a multi-targeted TKI with activity against MET, ALK, and ROS1 and was the first ALK-TKI approved by the FDA for metastatic NSCLC positive for ALK rearrangements (Du et al., 2018). Because of many reasons, such as secondary mutations, tumor heterogeneity, and driving gene conversion, which may cause drug resistance (Doebele et al., 2012), second- and third-generation ALK-TKIs have been researched and developed. The U.S. Food and Drug Administration (FDA) has approved five ALK-TKIs, namely, crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib. The three generations of ALK-TKIs greatly enriched the therapeutic regimens of ALK-positive cancer patients, but drug selection needs to consider many factors, among which the toxicity profile was one of the critical considerations.

With further studies of ALK-TKIs in clinical trials and increasing use in clinical practice (Costa et al., 2018; Kassem et al., 2019; Breadner et al., 2020), despite the benefits of ALK-TKIs, many adverse events (AEs) have been described, which mainly involve the gut, lung, liver, heart, nerve, and skin and have a potential effect on any other tissues (Hou et al., 2019; Wang and Wang, 2021). As an essential organ that provides sufficient blood flow to other organs and tissues, supplies oxygen and various nutrients, and maintains the normal metabolism and function of cells, the heart plays a significant role in the human body, especially in cancer patients. In several clinical trials of ALK-TKIs (Solomon et al., 2014; Camidge et al., 2018; Solomon et al., 2018; Cho et al., 2019; Zhou et al., 2019), cardiotoxicity associated with these drugs concentrated on bradycardia and QT prolongation, with an incidence of approximately 9–15%, and the severity was usually less than grade 2, with a probability of grades 3 to 4 of roughly 1–4% (Costa et al., 2018).

In clinical trials of ALK inhibitors, the cardiotoxicity associated with these drugs had mainly focused on bradycardia and QT prolongation, with a low incidence and severity usually less than grade 2. However, due to the small sample size and short observation time, clinical trials were often unable to reveal the complete safety information of drugs. Within a few years after the marketing of these drugs, several pieces of literature in clinical practice showed that cardiotoxicity associated with ALK-TKIs had a more comprehensive range, with different incidences and severities, and sometimes it could even lead to severe heart failure (Fukuizumi et al., 2015).

With the increasing variety and indication of ALK-TKIs, it was necessary to update the understanding promptly and provide an overview of the risk and characteristics of cardiac AEs for further prevention and management. However, most evidence of ALK-TKI-associated cardiotoxicity stemmed from case reports and clinical trials. We mainly needed real-world data to complement or verify clinical trial information and fully assess the cardiac safety of these drugs.

The FDA Adverse Event Reporting System (FAERS), a postmarketing database, is used to store AE reports associated with FDA-approved therapy reported spontaneously in the real world by healthcare professionals or patients and lawyers. The pharmacovigilance system of FAERS was critical for continuous monitoring of the relationship between AEs and drugs (Kamitaki et al., 2021). Therefore, this study was based on the FAERS database. We conducted disproportionality analysis (van Puijenbroek et al., 2002) to dissect the cardiac AE signals submitted to the FAERS to identify potential cardiotoxicities and assess the correlations between different ALK-TKIs and cardiac AEs. From the perspective of the real world, this study's purpose was to assess ALK-TKIs in a more realistic environment.

## MATERIALS AND METHODS

### Data Source

The data of this retrospective pharmacovigilance study were retrieved from the FAERS, and the time horizon was from the first quarter of 2016 to the second quarter of 2021. The reporters could be healthcare providers (physician, pharmacist, health professional), and non-healthcare providers (lawyer, consumer). Much helpful data files were offered to us: report source (PRSR), demographic and administrative information (DEMO), drug information (DRUG), preferred terms (PTs) coded for the adverse event (REAC), therapy start dates, and

end dates for reported drugs (THER), patient outcomes (OUTC), and indications for drug administration (INDI).

According to the recommendation of the FDA, when the PRIMARYID (the number for identifying a FAERS case) was the same as the FDA_DT (date FDA received case) in the FAERS data files, we removed the datum that occurred repeatedly and selected the latest one. Then, we obtained 7,621,815 cases that used the keywords associated with the target drugs. The keywords included generic names and brand names of the ALK-TKIs, which were registered in the FDA. Through ROLE_COD (code for drug's reported role event) in DRUG files, we chose the cases that the target drug that was considered the primary suspected drug (PS). In addition, to prevent the situation in which irregular and diverse terms of AEs would interfere with our study, we transformed the submitted AE names to the standard preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Finally, 29,964 cases were retained for subsequent research. MedDRA is a standard set of terms covering a wide range of AE terms and is the most widely used AE coding dictionary in international studies. MedDRA was attributed and associated through five layers, from top to bottom: system organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest level term (LLT). The higher the level, the smaller the number of terms and the wider the range. To reduce confusion and deviation and better assess the association between ALK-TKIs and cardiotoxicity, our study was mainly based on cardiac disorder SOC and the level of HLGT contained in it, and all PTs were also included in the study.

## Definition of Cardiac Adverse Events

Based on MedDRA, the SOC we researched was "cardiac disorders (10007541)." The associated HLGT was as follows: "heart failures (10019280)," "coronary artery disorders (10011082)," "pericardial disorders (10034468)," "myocardial disorders (10028593)," "cardiac arrhythmias (10007521)," "cardiac valve disorders (10046973)," "cardiac disorders, signs, and symptoms NEC (10082206)." The associated PT was as follows: "cardiac failure acute [10007556)," "cardiopulmonary failure (10051093)," "left ventricular failure (10024119)," "pericardial effusion (10034474)," "cardiac tamponade (10007610)," "pericarditis (10034484)," "cardiomyopathy (10007636)," "bradycardia (10006093)," "sinus node dysfunction (10075889)," and "sinus bradycardia (10040741)."

## Data Mining

On account of the principle of disproportionality analysis, we used the reporting odds ratio (ROR) method (Bate and Evans, 2009) to compare the whole drug-associated AEs with the reported AEs of the target drug and intend to recognize the valid connections between the investigated drugs and the reported AEs. We also performed a sensitivity analysis, which only included cases from healthcare professionals. It was regarded as a detected signal only if an AE met the algorithm's criteria before and after sensitivity analysis simultaneously.

## Statistical Analysis

Descriptive analyses were utilized to summarize the clinical characteristics of the patients with ALK-TKI-associated cardiac AEs collected from the FAERS database, and the continuous variable was represented by mean ± standard deviation (SD). The nonparametric test (Kruskal–Wallis test) was used to compare the onset time of ALK-TKI-associated cardiac AEs and the contingency table Chi-square test or Fisher's test was used to assess whether the fatality proportions of patients with ALK-TKI-associated cardiac AEs were different. All statistical analyses were conducted by IBM® SPSS® Statistics (version 26). Differences with $p$ values <0.05 were considered statistically significant.

# RESULTS

## Descriptive Analysis

The FAERS database has recorded 7,621,815 cases from the first quarter of 2016 to the second quarter of 2021, including 605 cases of cardiac disorders associated with ALK-TKIs. We summarize the characteristics of patients in these 605 cases, which are summarized in the form of charts (**Table 1**). The chart shows little difference in patient characteristics between each ALK-TKI. Most of the cases came from North America (32.07%), Asia (33.39%), and Europe (28.93%) and were mainly reported by healthcare professionals (78.35%). The patients affected were more often female (50.74%) than male (39.67%), with 9.59% of the events gender unknown or missing. Moreover, except for 23.47% of the age data not available, the age of patients with cardiac disorders remained consistent across all drugs, which tended to be approximately 45–74 years (50.74%), with an average of 62.96 ± 14.48 years.

## Signal Detection

The signal detection of ALK-TKIs associated with cardiac disorders (SOCs) is shown in **Table 2**. According to the aforementioned criteria for signal occurrence, both crizotinib and lorlatinib generated signals before and after sensitivity analysis. We summarized the HLGT of these drugs involved in cardiac disorders, and the calculation results of the disproportionality analysis are listed in **Table 3**. The four kinds of HLGT presented a significant association with ALK-TKIs for heart failures, pericardial disorders, myocardial disorders, and cardiac arrhythmias. From the total data of all ALK-TKIs, only heart failure and pericardial disorders had positive signals. In terms of individual ALK-TKIs, the drugs associated with heart failure were lorlatinib and crizotinib, of which lorlatinib had a stronger association than crizotinib. Except for brigatinib, the other four drugs could cause pericardial disease, of which ceritinib appeared to have the strongest relevance, and alectinib was the last. In addition, the drugs involved in cardiac arrhythmias include crizotinib and alectinib, among which crizotinib had a stronger relevance. We should also note that only lorlatinib could cause myocardial disorders.

We also selected PT, which had positive signals in the aforementioned HLGT, and the calculation results of the disproportionality analysis are listed in **Table 4**. Judging

**TABLE 1 |** Characteristics in ALK-TKI-associated cardiac disorders cases[a].

| Characteristic | Cases, N (%) | | | | | |
|---|---|---|---|---|---|---|
| | Total | Crizotinib | Alectinib | Ceritinib | Brigatinib | Lorlatinib |
| Sex of patient | | | | | | |
| Female | 307 (50.74%) | 134 (49.08%) | 86 (53.75%) | 33 (51.56%) | 15 (45.45%) | 39 (52.00%) |
| Male | 240 (39.67%) | 107 (39.19%) | 64 (40.00%) | 27 (42.19%) | 15 (45.45%) | 27 (36.00%) |
| Unknown | 58 (9.59%) | 32 (11.72%) | 10 (6.25%) | 4 (6.25%) | 3 (9.09%) | 9 (12.00%) |
| Age group (years) | | | | | | |
| <18 | 2 (0.33%) | 2 (0.73%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 18–44 | 47 (7.77%) | 14 (5.13%) | 12 (7.50%) | 10 (15.63%) | 4 (12.12%) | 7 (9.33%) |
| 45–64 | 182 (30.08%) | 83 (30.40%) | 43 (26.88%) | 26 (40.63%) | 6 (18.18%) | 24 (32.00%) |
| 65–74 | 125 (20.66%) | 60 (21.98%) | 25 (15.63%) | 12 (18.75%) | 9 (27.27%) | 19 (25.33%) |
| >74 | 107 (17.69%) | 61 (22.34%) | 30 (18.75%) | 2 (3.13%) | 3 (9.09%) | 11 (14.67%) |
| Unknown | 142 (23.47%) | 53 (19.41%) | 50 (31.25%) | 14 (21.88%) | 11 (33.33%) | 14 (18.67%) |
| Age (years) | | | | | | |
| Mean ± SD | 62.96 ± 14.48 | 64.92 ± 14.31 | 63.46 ± 14.81 | 56.20 ± 12.53 | 60.27 ± 14.51 | 61.51 ± 14.48 |
| Reporters | | | | | | |
| Healthcare professionals | 474 (78.35%) | 224 (82.05%) | 122 (76.25%) | 46 (71.88%) | 21 (63.64%) | 61 (81.33%) |
| Non-healthcare professionals | 120 (19.83%) | 46 (16.85%) | 38 (23.75%) | 10 (15.63%) | 12 (36.36%) | 14 (18.67%) |
| Unknown | 11 (1.82%) | 3 (1.10%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Reporting region | | | | | | |
| Asia | 202 (33.39%) | 83 (30.40%) | 56 (35.00%) | 28 (43.75%) | 1 (3.03%) | 34 (45.33%) |
| North America | 194 (32.07%) | 87 (31.87%) | 61 (38.13%) | 7 (10.94%) | 15 (45.45%) | 24 (32.00%) |
| Europe | 175 (28.93%) | 89 (32.60%) | 39 (24.38%) | 19 (29.69%) | 13 (39.39%) | 15 (20.00%) |
| South America | 14 (2.31%) | 10 (3.66%) | 1 (0.63%) | 2 (3.13%) | 1 (3.03%) | 0 (0.00%) |
| Oceania | 9 (1.49%) | 2 (0.73%) | 1 (0.63%) | 1 (1.56%) | 3 (9.09%) | 2 (2.67%) |
| Africa | 2 (0.33%) | 1 (0.37%) | 1 (0.63%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Unspecified | 9 (1.49%) | 1 (0.37%) | 1 (0.63%) | 7 (10.94%) | 0 (0.00%) | 0 (0.00%) |

[a]*N: the number of cases; SD: standard deviation.*

from the 11 types of PT, pericardial effusion occurred in all four ALK-TKIs, and the correlation of these AEs was stronger than that of other types of PT associated with cardiac AEs according to ROR ranking. There were many PT types involved in ceritinib, including pericardial effusion, cardiac tamponade, and pericarditis, and the strong ROR signals indicated that it might cause a variety of pericardial disorders. The relevance of pericarditis was the strongest, which suggested that it may be a specific AE of ceritinib. We also found that in terms of cardiac arrhythmias, ALK-TKIs mainly caused bradycardia-associated AEs.

**TABLE 2 |** Signal detection of cardiac disorders[a].

| Regimen | [b]Without sensitive analysis | | [c]With sensitive analysis | |
|---|---|---|---|---|
| | N | ROR (95% CI) | N | ROR (95% CI) |
| ALK-TKIs | 605 | 1.14 (1.05, 1.24) | 475 | 1.75 (1.60, 1.92) |
| Crizotinib | 273 | 1.24 (1.10, 1.40) | 224 | 2.89 (2.53, 3.31) |
| Alectinib | 160 | 1.12 (0.95, 1.31) | 122 | 3.08 (2.56, 3.71) |
| Ceritinib | 64 | 1.10 (0.86, 1.42) | 47 | 2.66 (1.98, 3.58) |
| Brigatinib | 33 | 0.63 (0.44, 0.89) | 21 | 1.41 (0.91, 2.17) |
| Lorlatinib | 75 | 1.34 (1.06, 1.70) | 61 | 2.97 (2.29, 3.86) |

[a]CI*: confidence interval;* N*: the number of cases;* ROR*: reporting odds ratio.*
[b]*AE reporters were not limited, including healthcare providers and non-healthcare providers.*
[c]*AE reporters were limited in healthcare providers.*

## Time to Onset of ALK-TKI-Associated Cardiac Adverse Effects

According to all ALK-TKIs, the median onset time is 33 days, and the interquartile range is 10.0–105.5 days. The distribution of onset time of all ALK-TKIs is shown in **Figure 1**, which was concentrated in approximately 0–30 days. Due to the difference in the time-to-market and the discrepancy in the clinical use of ALK-TKIs, only considering the number of reports may not be able to accurately compare the occurrence of AEs among the five drugs, so we not only reported the number of reports (bar chart), the proportion of onset time was also shown as a supplement (line graph). We used the Kruskal–Wallis test to describe the onset time of cardiac disorders statistically and showed a significant difference ($p$ = 0.006). Interestingly, after removing the data of brigatinib, there was no significant difference in the onset time of the other ALK-TKIs (Kruskal–Wallis test, $p$ = 0.083), which could be supposed that brigatinib had a longer onset time of cardiac AEs. The median (M) and interquartile range (IQR) of onset time were crizotinib (M: 40 days, IQR: 9.0–166.0 days), alectinib (M: 28 days, IQR: 10.5–96.5 days), ceritinib (M: 25 days, IQR: 7.0–60.0 days), brigatinib (M: 168 days, IQR: 19.0–365.0 days), and lorlatinib (M: 42 days, IQR: 14.0–92.25 days). Overall, 47.89% of cardiac AEs occurred within 30 days after medication, and 61.13% occurred within 60 days, but 9.30% still occurred after 365 days, so the long-term cardiotoxicity of ALK-TKIs is still worthy of our attention.

**TABLE 3 |** Signal detection of HLGT for ALK-TKI-associated cardiac disorders[a].

| Regimen | HLGT | Heart failures | Coronary artery disorders | Pericardial disorders | Myocardial disorders | Cardiac arrhythmias | Cardiac valve disorders | Cardiac disorders, signs, and symptoms NEC |
|---|---|---|---|---|---|---|---|---|
| ALK-TKIs | N | 137 | 67 | 125 | 28 | 267 | 3 | 50 |
| | ROR (95% CI) | 1.64 (1.38, 1.94) | 0.65 (0.51, 0.82) | 6.66 (5.58, 7.95) | 0.80 (0.55, 1.16) | 1.13 (1.00, 1.28) | 0.21 (0.07, 0.67) | 0.41 (0.31, 0.55) |
| Crizotinib | N | 72 | 28 | 48 | 8 | 126 | 2 | 22 |
| | ROR (95% CI) | 2.07 (1.64, 2.61) | 0.65 (0.45, 0.94) | 6.09 (4.58, 8.10) | 0.55 (0.27, 1.10) | 1.28 (1.08, 1.53) | 0.34 (0.09, 1.37) | 0.44 (0.29, 0.67) |
| Alectinib | N | 31 | 15 | 30 | 6 | 83 | 1 | 9 |
| | ROR (95% CI) | 1.37 (0.96, 1.95) | 0.54 (0.32, 0.89) | 5.87 (4.09, 8.41) | 0.64 (0.29, 1.42) | 1.31 (1.05, 1.63) | 0.26 (0.04, 1.88) | 0.28 (0.14, 0.53) |
| Ceritinib | N | 5 | 8 | 29 | 1 | 24 | 0 | 6 |
| | ROR (95% CI) | 0.54 (0.22, 1.30) | 0.71 (0.35, 1.41) | 14.19 (9.81, 20.51) | 0.26 (0.04, 1.86) | 0.92 (0.62, 1.38) | - | 0.45 (0.20, 1.01) |
| Brigatinib | N | 5 | 7 | 3 | 2 | 16 | 0 | 4 |
| | ROR (95% CI) | 0.61 (0.25, 1.48) | 0.7 (0.33, 1.47) | 1.63 (0.52, 5.05) | 0.59 (0.15, 2.38) | 0.70 (0.42, 1.14) | - | 0.34 (0.13, 0.92) |
| Lorlatinib | N | 24 | 9 | 15 | 11 | 18 | 0 | 9 |
| | ROR (95% CI) | 2.72 (1.81, 4.07) | 0.82 (0.42, 1.58) | 7.47 (4.49, 12.42) | 2.99 (1.65, 5.41) | 0.71 (0.45, 1.13) | - | 0.7 (0.37, 1.36) |

[a]*CI: confidence interval; N: the number of cases, ROR: reporting odds ratio.*

**TABLE 4 |** Positive signals of PT for ALK-TKI-associated cardiac disorders[a].

| HLGT/PT | Crizotinib | | Alectinib | | Ceritinib | | Lorlatinib | |
|---|---|---|---|---|---|---|---|---|
| | N | ROR (95% CI) | N | ROR (95% CI) | N | ROR (95% CI) | N | ROR (95% CI) |
| Heart failures | | | | | | | | |
| Cardiac failure | 52 | 3.08 (2.33, 4.05) | - | - | - | - | 15 | 3.40 (2.04, 5.81) |
| Cardiac failure acute | 4 | 2.78 (1.04, 7.43) | - | - | - | - | - | - |
| Cardiopulmonary failure | 3 | 4.38 (1.41, 13.60) | - | - | - | - | - | - |
| Left ventricular failure | - | - | 3 | 6.66 (2.14, 20.70) | - | - | - | - |
| Pericardial disorders | | | | | | | | |
| Pericardial effusion | 41 | 9.06 (6.66, 12.34) | 23 | 7.83 (5.19, 11.81) | 19 | 16.06 (10.20, 25.29) | 13 | 10.83 (6.26, 19.47) |
| Cardiac tamponade | - | - | 5 | 7.41 (3.08, 17.84) | 6 | 22.00 (9.85, 49.14) | 3 | 10.78 (3.47, 35.11) |
| Pericarditis | - | - | - | - | 15 | 26.49 (15.90, 44.12) | - | - |
| Myocardial disorders | | | | | | | | |
| Cardiomyopathy | - | - | - | - | - | - | 3 | 4.39 (1.41, 13.95) |
| Cardiac arrhythmias | | | | | | | | |
| Bradycardia | 56 | 4.89 (3.75, 6.36) | 42 | 5.67 (4.18, 7.69) | - | - | - | - |
| Sinus node dysfunction | - | - | 4 | 11.39 (4.26, 30.43) | - | - | - | - |
| Sinus bradycardia | 12 | 6.38 (3.62, 11.26) | 9 | 7.39 (3.84, 14.23) | 3 | 6.06 (1.95, 18.82) | - | - |

[a]*CI: confidence interval; N: the number of cases, ROR: reporting odds ratio.*

## Fatality Proportion Due To ALK-TKI-Associated Cardiac Disorders

To analyze the patient prognosis after cardiac AEs, we performed a statistical analysis of the outcomes recorded in the DEMO file. We chose DE (death) due to cardiac disorders regarding inpatient outcomes. We calculated the proportions of deaths and have displayed the results in **Figure 2**.

The study showed 20.93% fatality proportion in total, indicating that the outcome of cardiac AEs was relatively unsatisfactory. The contingency table chi-square test for frequency of death indicates a moderate correlation between different ALK-TKIs and the fatality proportion ($p < 0.001$, Cramer's V = 0.191). The pairwise comparison results showed that the fatality proportion in the alectinib group was considerably lower than that in the other therapy groups. Except for the difference between alectinib therapy and the other four drugs, there was no significant difference between the other two groups. The fatality proportion and $p$-value between alectinib and others were as follows: alectinib and crizotinib (9.03 vs. 25.00%, $p < 0.001$), alectinib and ceritinib (9.03 vs. 20.97%, $p = 0.016$), alectinib and brigatinib (9.03 vs. 36.36%, $p < 0.001$), and alectinib and lorlatinib (9.03 vs. 24.64%, $p = 0.002$).

## DISCUSSIONS

The occurrence of drug-induced cardiac disorders significantly impacts patients and is one of the leading causes of death in drug-induced diseases (Lopez-Gonzalez et al., 2009). Currently, some scholars in the international community have conducted research

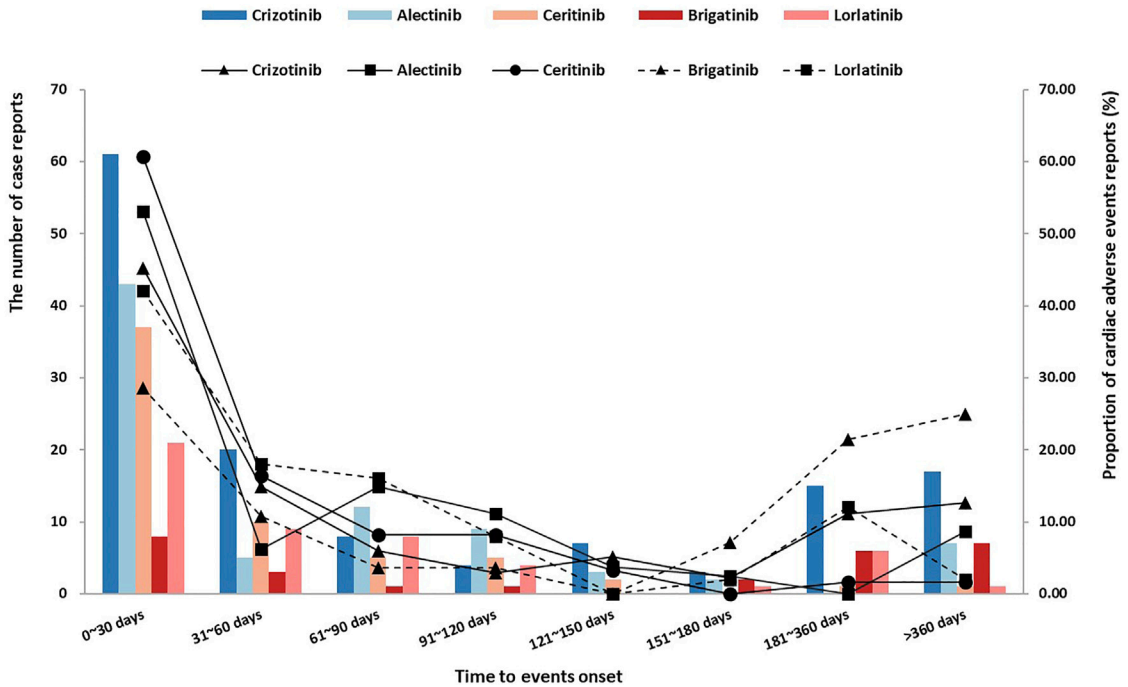
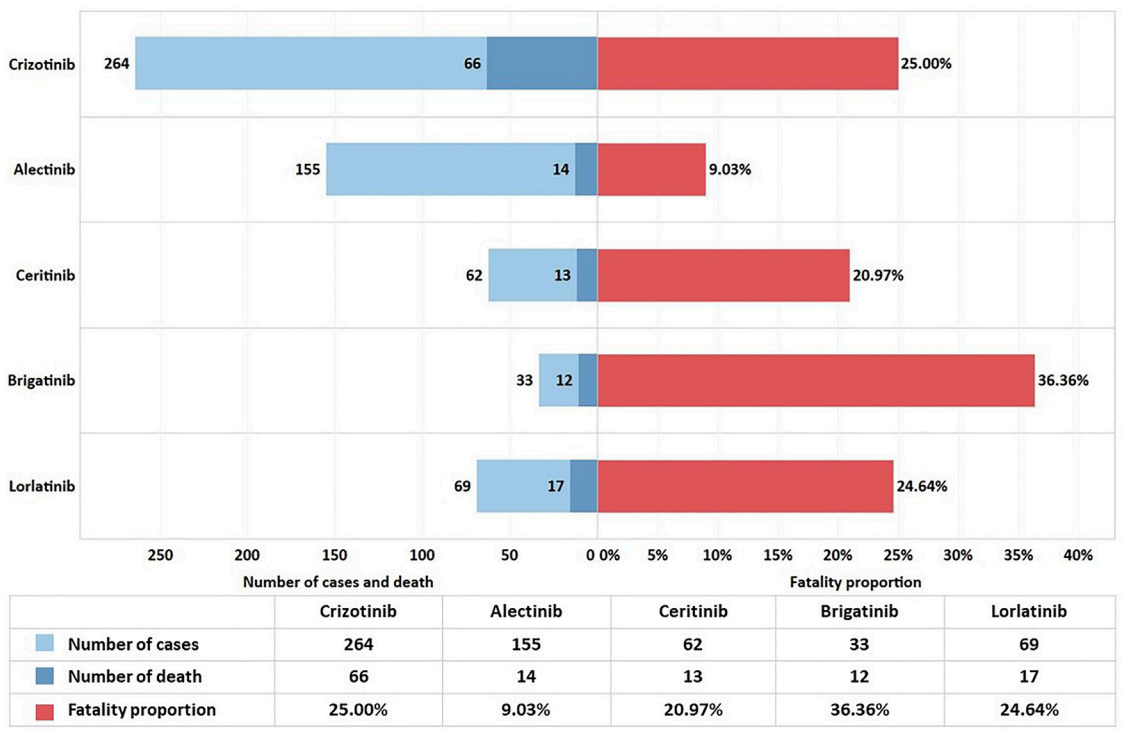



**FIGURE 1 |** Time to ALK-TKI-associated cardiac disorder onset.




| | Crizotinib | Alectinib | Ceritinib | Brigatinib | Lorlatinib |
|---|---|---|---|---|---|
| Number of cases | 264 | 155 | 62 | 33 | 69 |
| Number of death | 66 | 14 | 13 | 12 | 17 |
| Fatality proportion | 25.00% | 9.03% | 20.97% | 36.36% | 24.64% |

**FIGURE 2 |** Fatality proportion from ALK-TKI-associated cardiac disorders.

and assessments on the cardiotoxicity of ALK-TKIs. However, due to the limitations of clinical trials, we needed more real-world studies after marketing to improve the safety information of drugs. Therefore, this study uses disproportionality analysis to detect the ALK-TKI-associated cardiac AEs reported in the FAERS database. Among all cases of ALK-TKI-associated cardiotoxicity in this study, patients were mainly female (50.75%) and old (38.25% ≥ 65 years old, median = 65 years old). The results of data mining showed that among 5 ALK-TKIs, crizotinib and lorlatinib presented a higher risk of cardiotoxicity, with HLGT involved mainly in heart failure, pericardial disorders, myocardial disorders, and arrhythmia. Other drugs had no signal at the SOC but presented some cardiotoxicity risk at specific HLGT and PT. Ceritinib was associated with a higher risk of pericardial disorders, while alectinib was associated with a higher risk of pericardial disorders and arrhythmias. It was interesting that no signals were mined in brigatinib. We also studied the onset time and the fatality proportion, which showed ALK-TKI-associated cardiotoxicity may have the earlier time of onset and higher fatality proportion.

From the current studies, it can be perceived that old age is a risk factor for various cancers and decreases cardiac function (Shaw et al., 2011; Ou et al., 2013), but no clinical study has shown sex differences in cardiac disorders caused by ALK-TKIs (Ou et al., 2013; Ou et al., 2016). Patients aged 45–64 years (30.08%) also accounted for a high proportion, which may be associated with the high frequency that patients with NSCLC harboring the EML4-ALK fusion gene were observed in relatively younger patients (Baldi et al., 2014; Toyokawa and Seto, 2014).

According to our analysis of FAERS data, there were few types of cardiac AEs caused by these drugs, but the characteristics of cardiac AEs of the five ALK-TKIs were different. Among all ALK-TKIs, crizotinib and lorlatinib presented stronger cardiotoxic signals, and the type of cardiotoxicity involved in them was synchronous. In terms of HLGT, these two drugs had significant signals in heart failure and pericardial disorders. For serious cardiac AEs such as HLGT of heart failure (HF), fewer studies have reported HF induced by these drugs, just a few cases have been reported, and some studies have shown that there is nothing to do with the treatment of ALK-TKIs. Nevertheless, this may be associated with the physiological status of the patients. If the patient had risk factors such as older age and heart disease before therapy, it should be noted that ALK-TKIs may lead to HF in clinical practice (Fukuizumi et al., 2015). From the perspective of pericardial disorders, in addition to crizotinib and lorlatinib, alectinib and ceritinib also showed strong signals in this HLGT, and it mainly involved pericardial effusion and cardiac tamponade. Existing clinical studies have shown pericardial effusion and cardiac tamponade be life-threatening complications of NSCLC, and severe pericardial effusion was indicative of advanced cancer (Atar et al., 1999; Wang et al., 2000; Mufti et al., 2018). At present, there was one case report on pericardial effusion caused by alectinib (Ulhoi et al., 2021), but more case reports have shown that the symptoms of pericardial effusion can be effectively improved using ALK-TKIs (Gadgeel et al., 2014; Hao et al., 2015; Matsuo et al., 2016; Kasai et al., 2018). Our analysis indicated a relationship between ALK-TKIs and the aforementioned pericardial disorders, which was most likely a false-positive result caused by complications of the original disease. In addition to these common signals, crizotinib was associated with a higher risk of arrhythmia, and lorlatinib was associated with a higher frequency of myocardial disorders. Arrhythmia was a common adverse drug reaction of ALK-TKIs in recent studies, mainly including bradycardia, QT prolongation, and atrioventricular (AV) block, and most of them were assessed as less than or equal to grade 2, but rare serious AEs still possibly exist (Atar et al., 1999; Fukuizumi et al., 2015; Bauer et al., 2019; Gaillard et al., 2019). It has been reported that the decrease in the heart rate (HR) was a pharmacodynamic phenomenon of crizotinib, and every 100 ng/ml increase in plasma crizotinib concentration reduced the HR by an average of 2.5 bpm, which could be explained by the antagonist effect of the drug on L-type calcium channels, a chronotropic effect on a sinoatrial node, or an anti-mesenchymal epithelial transition effect of crizotinib (Nickens et al., 2011; Ou et al., 2013). A global, randomized, phase 3 clinical trial (Shaw et al., 2020) showed a significant difference in the incidence of bradycardia arrhythmia with crizotinib and lorlatinib (12 vs. 1%). Another ongoing phase I/II study involved 295 healthy volunteers with therapeutic of lorlatinib (ClinicalTrials.gov identifier: NCT01970865) (Bauer et al., 2019), two patients (0.7%) were reported to have asymptomatic first-degree AV block (grade 1 in severity), one patient (0.3%) was reported to have grade 3 that led to temporary discontinuation from treatment, and it should be noted that this patient had pre-existing second-degree AV block. QT prolongation was reported in 19 patients (6.4%), most of which were less than grade 2, although one event was grade 3 in severity and required temporary discontinuation. None of these events resulted in permanent treatment discontinuation. All the aforementioned studies showed a low risk of arrhythmia caused by lorlatinib, which was consistent with the results of our study. No positive signals of QT prolongation or atrioventricular block were detected in this study, and only alectinib and crizotinib produced positive signals of cardiac arrhythmia. The reason may be that QT prolongation here does not belong to cardiac disorders (SOCs), but some cardiac and vascular investigations (excluding enzyme tests) or cardiac arrhythmias caused by other drugs were milder and hard to be identified as drug-induced AEs. Lorlatinib-caused cardiomyopathy is not shown in the FDA package inserts. There was no description in the literature of cardiomyopathy associated with lorlatinib, and the results of our study suggested that it was necessary to verify it through further standard tests.

Although no signal was detected at SOC for the other three drugs, except for brigatinib, alectinib and ceritinib had certain signals at specific HLGT and PT. It is worth noting that the signals of ceritinib-caused pericarditis were also not included in the FDA package inserts. Remarkably, the high ROR value of pericarditis presents a strong correlation with ceritinib, suggesting that this might be a specific adverse drug reaction of ceritinib. A case report reported that after 2 months of ceritinib, a female patient developed acute respiratory distress with pericarditis and pleurisy, resulting in delayed hypersensitivity reaction, which was confirmed to be an adverse drug reaction caused by ceritinib (Gaillard et al.,

2019). The result of our study and fewer case reports suggested that pericarditis may be a potentially rare, specific adverse drug reaction to ceritinib, and more studies are needed to confirm the association.

The onset time of these drugs was variable. Except for brigatinib, there was no significant difference in the distribution of onset time of the other four drugs, and it was mainly within 2 months after the medication, with a median time of 33 days. It was suggested that cardiac AEs might occur shortly after the first administration of these drugs. The median time of brigatinib was 168 days which was different from others. However, few studies have examined the onset time of ALK-TKI-associated cardiotoxicity. Our study showed that brigatinib had a longer onset time of cardiotoxicity than others, so the reason why we did not detect any signals of brigatinib might be that it has long-term cardiotoxicity, and our observation was relatively short. Indeed, we need more cases and studies to confirm this. Our study also indicated that patients with cardiac AEs associated with ALK-TKIs usually had a poor prognosis, with a death proportion of 20.92%. However, it should be noted that the death proportion of alectinib (9.03%) was the lowest, which was significantly different from others, suggesting that alectinib may cause a relatively small risk of death after cardiac AEs. At present, clinical studies have also shown that alectinib therapy is well tolerated and does not prolong the QT interval or cause clinically relevant changes in cardiac function (Morcos et al., 2017). It is worth noting that the results of data mining showed that brigatinib did not detect any signal at any level, but the fatality proportion was significantly higher than other drugs. We think it might be because of its less toxicity to the heart and the AEs were not monitored during medication, resulting in underreporting, which made the number of reports in the denominator part low. In addition, according to the instructions, clinical treatment guidelines, and actual clinical medication, brigatinib is mainly used to treat ALK rearrangement in NSCLC. Although it is listed as first-line therapy in the NCCN guideline, it belongs to "other recommendations." Clinically, brigatinib also showed significant advantages after the failure of alectinib, crizotinib, and other ineffective or poor treatments (Hochmair et al., 2019). Therefore, the cardiotoxicity of brigatinib we researched was likely the AEs occurred in the subsequent therapy. The patients themself were in the later stage of the disease course, and it was very reasonable that the patients would die due to the progression or complications of the disease itself. By this token, it was not surprising that the fatality proportion of patients treated with brigatinib was significantly higher.

Since FAERS did not report on patients' treatment lines, we could not separate treatment lines for analysis. However, for a report, the reporters could fill in multiple drugs related to AEs and classify the drugs into primary suspect drug (PS), secondary suspect drug (SS), concomitant (C), and interacting (I), which were marked in the ROLE_COD column in the drug file. To minimize the deviation caused by the treatment line, we tried to exclude the reports involving other ALK-TKIs in the drug-related to the target AEs with the target drug as PS. For patients, the occurrence of the target AEs was associated with only one ALK-TKI. We found that such reports were only 6, and the resulting signal generation results were not different from those before culling. The signal detection is shown in **Supplementary Tables S1–S3**. Nevertheless, this approach did not fully address the various treatment stages of patients, which remains a limitation of our study.

We noted that a more extensive FAERS study of ALK-TKIs (Omar et al., 2021) was recently published where the authors analyzed all AEs of ALK-TKIs primarily at the SOC, but they did not report any cardiac AEs. The reason might be that the data mining methods we used were different. Data mining methods are mainly divided into frequency analysis and Bayesian analysis. We only used frequency analysis for research, and this study used a combination of the two methods. However, the sensitivity of Bayesian analysis is lower (Faich and Morris, 2012), especially for less-reported potential AEs that do not generate a signal, which may allow investigators to miss some rarer AEs of concern. From the perspective of clinical trials, compared with other common AEs, the number of reports and types of cardiotoxicity of ALK-TKIs is low, and the current literature often only repeated the cardiac AEs reported in clinical trials. Cardiotoxicity of ALK-TKIs is not well understood or concerned, but there are still severe and new cardiotoxicities noticed by case reports. From this point of view, if Bayesian analysis was used, there might still be no signal for these AEs, and we still ignored them. Therefore, we only use frequency analysis which has higher sensitivity, hoping to find possible overlooked significant cardiotoxicity and making up for the lack of current research. Moreover, besides SOC, we also conducted signal mining in HLGT and PT, which were discussed as secondary outcomes, to enable our research to be more detailed and provide readers with more possible research directions.

In general, according to the results of this signal detection, crizotinib and lorlatinib generated more and stronger signals, while brigatinib did not generate signals at any level. Compared with other ALK-TKIs, crizotinib and lorlatinib had poor cardiac safety, and brigatinib had a better safety profile.

## Limitations

Although data mining improved the drug safety content through real-world data, it still had some limitations: A) The FARES database was a spontaneous reporting system, and due to the different standardizations and habits of different reporters, omissions and misstatements were inevitable, which may impact the results of sensitivity analysis. B) The disproportionality method has high sensitivity but cannot confirm the causal relationship but only the statistical association between AEs and drugs. There may be the risk of reverse causality. For example, the signals of pericardial effusion and cardiac tamponade detected in this study are most likely caused by the disease progression. C) There have been many studies on data mining based on SOC classification, but SOC is not classified by specific

diseases, so it may not be able to assess the safety risk of drugs in specific diseases. In addition, some cardiac-related PTs, such as electrocardiogram QT interval abnormal, belong to the SOC of investigations, rather than the SOC of cardiac disorders, which may prevent these PTs from being included in the study. D) The limitation of the reported outcome: there was no certainty between death and ALK-TKIs use, and death may be more related to disease progression. E) Clinical information such as the severity of the patient's cancer and other treatment measures were lacking (Chen et al., 2021).

## CONCLUSION

Based on the FAERS database, we assessed the cardiotoxicity of five ALK-TKIs and their potential association with the characteristics involved in pathogenesis. ALK-TKIs were reported more frequently than other drugs in cardiotoxicity, suggesting potential cardiotoxicity risks which could often manifest earlier. In general, we should focus on ALK-TKI-associated HLGT, including heart failures, pericardial disorders, and cardiac arrhythmias. In all drugs, crizotinib and lorlatinib had a higher frequency of cardiotoxicity reporting, and brigatinib presented no signals. Myocarditis to ceritinib and cardiomyopathy to lorlatinib may be potential specific adverse drug reactions. We should pay close attention to patients with old age or poor cardiac function in clinical practice. Moreover, drug combinations for patients with high cardiotoxicity or reduced cardiac function should be avoided as much as possible.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. These data can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

## AUTHOR CONTRIBUTIONS

Conceptualization: YL; methodology: LC and CC; software and validation: XH; formal analysis and investigation: YL and CR; writing—original: YL and CC; writing—review and editing: CC and LC; visualization: YL; supervision: LC; project administration: LC; and funding acquisition: LC. All the authors critically reviewed the manuscript and interpreted the results. The final manuscript was read, checked, and approved by all authors.

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## SUPPLEMENTARY MATERIAL

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# Evolution of *HLA-B* Pharmacogenomics and the Importance of PGx Data Integration in Health Care System: A 10 Years Retrospective Study in Thailand

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**Background:** The *HLA-B* is the most polymorphic gene, play a crucial role in drug-induced hypersensitivity reactions. There is a lot of evidence associating several risk alleles to life-threatening adverse drug reactions, and a few of them have been approved as valid biomarkers for predicting life-threatening hypersensitivity reactions.

**Objectives:** The objective of this present study is to present the progression of *HLA-B* pharmacogenomics (PGx) testing in the Thai population during a 10-year period, from 2011 to 2020.

**Methods:** This was a retrospective observational cohort study conducted at the Faculty of Medicine Ramathibodi Hospital. Overall, 13,985 eligible patients who were tested for *HLA-B* risk alleles between periods of 2011–2020 at the study site were included in this study.

**Results:** The *HLA* PGx testing has been increasing year by year tremendously, 94 *HLA-B* testing was done in 2011; this has been raised to 2,880 in 2020. Carbamazepine ($n$ = 4,069, 33%), allopurinol ($n$ = 4,675, 38%), and abacavir ($n$ = 3,246, 26%) were the most common drugs for which the *HLA-B* genotyping was performed. *HLA-B*13:01, HLA-B*15:02* and *HLA-B*58:01* are highly frequent, *HLA-B*51:01* and *HLA-B*57:01* are moderately frequent alleles that are being associated with drug induced hypersensitivity. *HLA-B*59:01* and *HLA-B*38:01* theses alleles are rare but has been reported with drug induced toxicity. Most of the samples were from state hospital (50%), 36% from private clinical laboratories and 14% from private hospitals.

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**Conclusion:** According to this study, *HLA-B* PGx testing is increasing substantially in Thailand year after year. The advancement of research in this field, increased physician awareness of PGx, and government and insurance scheme reimbursement assistance could all be factors. Incorporating PGx data, along with other clinical and non-clinical data, into clinical decision support systems (CDS) and national formularies, on the other hand, would assist prescribers in prioritizing therapy for their patients. This will also aid in the prediction and prevention of serious adverse drug reactions.

**Keywords: HLA-B, PGx, pharmacogenetics, thailand, adverse drug reactions, incorporating PGx data**

## INTRODUCTION

ADRs are any unrelated or unexpected reactions to drugs that have been approved for normal use in normal dosage (Cameron and Ramsay, 1984). When it becomes serious, unpredictable, and life threatening, it becomes a public concern. Another significant problem with ADRs are the financial burden and longer hospital stays. According to data from the United States (1966–1996), 6.7 people out of every 100 patients have severe ADRs (Lazarou et al., 1998; Chyka, 2000), whereas in China, severe ADRs account for 10% of the 1.676 million ADRs complaints (CDR-ADR, 2021). In the case of Thailand, ThaiVigibase received around 600,000 reports between 1984 and 2014, with over half of them reported in the last 6 years and significant ADRs accounting for 20% of all reports (Genome, 2012).

Pharmacovigilance is the science of detecting, assessing, and comprehending ADRs signals in order to prevent ADRs or other drug-related problems in the future (DRPs) (Edwards and Aronson, 2000). Throughout the drug development process, a variety of approaches are used to predict and assess ADRs. Safety pharmacology profiling (*in vitro* biochemical and cellular assays) and computational methods, such as protein target-based and chemical structure-based approaches, were used in the preclinical stage (Whitebread et al., 2005). In different stages of clinical trial, the safety is monitored only in few people. Only during post-marketing surveillance, through spontaneous ADRs reporting, observational case-control, and cohort studies, can meaningful ADRs data be collected.

PGx is an important data source for customizing treatment and predicting and preventing ADRs. In the last 10 years, ADRs-pharmacogenetics has moved beyond just identifying risk alleles to developing different guidelines in different nations based on the clinical relevance of those risk genes. The comprehensive integration of this genetic data into clinical practice, however, has remained a considerable challenge. The reason could be a lacuna in the integration of various biological data with clinical efficacy and ADRs. However, integrative approaches to ADRs prediction have recently gained popularity. A new computational framework was developed to predict ADRs by Huang et al., in which the biological data such as protein-target interaction, protein-protein interaction, gene ontology, annotation, and reported ADRs were integrated (Huang et al., 2011). Recently, studies have shown the integration of phenotypic information with chemical and biological properties of drugs to predict ADRs (Liu et al., 2012a).

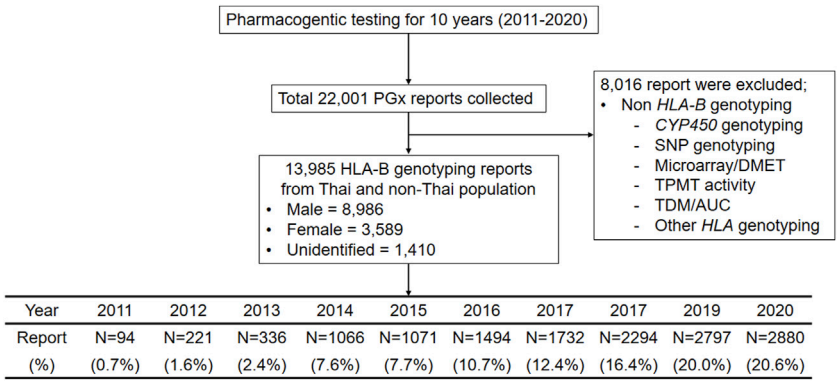
However, integration of preclinical study data with ADRs may not be that effective because it is well known that the pharmacodynamics of a drug is a complex phenomenon, especially with regard to its on-target and off-target interactions. Hence, it is important to develop one framework to understand the ADRs by integrating various types of data into it (Liu et al., 2012b). The various types of data include biological, genetic, pharmacokinetic, and other clinical and non-clinical data.

Human leukocyte antigen (*HLA*) variations and their relationship to drug-induced severe hypersentivity reactions are intensively investigated in ADRspharmacogenetics in various countries, especially in Thailand. Carbamazepine (Phillips et al., 2018), oxcarbazepine (Leckband et al., 2013), phenytoin (Karnes et al., 2020), allopurinol (Hershfield et al., 2013), and abacavir (Martin et al., 2012a) are the five medications for which *Clinical Pharmacogenetics Implementation Consortium* (CPIC) PGx implementation recommendations are now available. Despite the fact that Thailand is the first country in East Asia and the fourth in Asia to publish a large number of PGx research papers (Ang et al., 2017), this is the first cohort study in Thailand to use more than 10,000 data to report the evolution of *HLA-B* PGx testing for various drugs. The goal of this study is to present the 10 years *HLA-B* data and to recommend the importance of incorporating PGx data into clinical decision support systems (CDS), particularly in the prevention of severe cutaneous adverse drug reactions (SCARs).

## MATERIALS AND METHODS

### Study Design/Setting

This was a cohort study that was conducted retrospectively. All PGx data was obtained from the Pharmacogenomics and Personalized Medicine laboratory (PPM) at the Somdech Phra Debaratana Medical Center (SDMC), Faculty of Medicine Ramathibodi Hospital, Bangkok Thailand (N = 22,001). A descriptive, observational, cross-sectional, retrospective study was conducted with 13, 985 *HLA-B* genotyping reports during 2011–2020 (**Figure 1**). This study was approved by the Ethical Review Committee on Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (ID 04-56-42). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting




| Year | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2017 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|
| Report | N=94 | N=221 | N=336 | N=1066 | N=1071 | N=1494 | N=1732 | N=2294 | N=2797 | N=2880 |
| (%) | (0.7%) | (1.6%) | (2.4%) | (7.6%) | (7.7%) | (10.7%) | (12.4%) | (16.4%) | (20.0%) | (20.6%) |

**FIGURE 1 |** Flow chart of Clinical pharmacogenomics study designed, inclusion and exclusion criteria for 10 years during 2011–2020. This flow diagram illustrates the pharmacogenetic reports collected in this study, the number of reports (N = 22,001) and inclusion and exclusion criteria.

guideline was followed for cohort studies in this study (Von Elm et al., 2008).

## Data Selection

The *HLA-B* PGx testing approach to prescribing medications was represented by this cohort. The PPM provided a total of 22,001 PGx testing results. This study includes 13,985 eligible patients who were treated with drugs such as allopurinol, abacavir and carbamazepine etcfrom all Out-Patient Department (OPD)/In-Patient Department (IPD) and screened for *HLA-B* gene or risk alleles. Patients or samples who had their *HLA-B* gene or alleles tested only at our lab were included, but no restriction was kept from including the samples from different sources in Thailand. For example, the samples came from throughout the country, from private and public hospitals. The samples received from lab centers that serve many hospitals and clinical sectors in Thailand were also included. We have included all the *HLA-B* genetic biomarkers regardless of the availability of the CPIC recommendations. Patients tested for genetic variants of *CYP450,* other genes, and therapeutics drug monitoring (TDM), on the other hand, were not included in the study (N = 8,016).

## *HLA-B* Genotyping

The polymerase chain reaction-sequence-specific Oligonucleotide probe (PCR-SSOP) test and LuminexTM Multiplex Technology were used to analyze *HLA-B* alleles according to well-established protocols. Briefly, the PCR products were hybridized against a panel of oligonucleotide probes coated on polystyrene microspheres. The probe sequences were complementary to polymorphic sequence stretches within the target *HLA-B* alleles. A colorimetric reaction and fluorescence detection technology were used to visualize the amplicon-probe complex. *HLA* fusion™2.0 software was used to analyze data from the *HLA-B* assays. The discovered alleles can be accurately reported at the 2-field or 4-digit level using the common intermediate well document (CIWD; version 3.0.0: common, intermediate, and well-documented *HLA* alleles in world populations) 2020. A recommended CIWD list is made up of the most prevalent category in the total or any of the seven geographic/ancestral/ethnic groups.

## Variables and Data Analysis

This study examines the progress of *HLA-B* PGx testing in the Thai population during a 10 years period, from 2011 to 2020. Based on this 10 years data, the number of *HLA-B* tests performed each year, the most prevalent drugs for which *HLA-B* genotyping was requested, the *HLA-B* allele and carrier frequency were reported. In addition, the paper analyzed the sources of samples and the frequency of common PGx biomarkers that have a strong correlation with various ADRs.

Descriptive statistics were employed to summarize the collected data and applied to analyze the genotyping data. The *HLA-B* allele frequencies of the samples were assayed by direct counting and, subsequently, by dividing the total number of occurrences of that allele by the total number of alleles at that locus in the population.

# RESULTS

## Pharmacogenomics(PGx) Testing in Thailand

A total of 13,985 patients were found to be eligible from the 22,001 data reviewed, including 8,986 males and 3,589 females (**Figure 1**). The reports were excluded from this analysis if there were non-*HLA-B* genotyping such as *CYP450* genotyping, microarray for drug metabolism enzyme and transpoter genes (DMET), Thiopurine S-methyltransferase (TPMT) activity and therapeutic drug monitoring/area under the curve (TDM/AUC).

**Figure 2** illustrates the trend of PGx testing from 2011 to 2020 in Thailand. Totally, 22,001 PGx testing were performed in the last 10 years. Interestingly, only 220 samples were requested by clinicain, but the number of PGx testing was escalated to 3,450 in the 2020. This demonstrates that PGx testing has been utilized in clinical practice of Thailand routinely.

The similar trend was found in *HLA-B* PGx testing; it started with 94 tests in 2011 and has gradually risen every year, with the greatest number of tests reported in 2020 with 2,880 tests. The

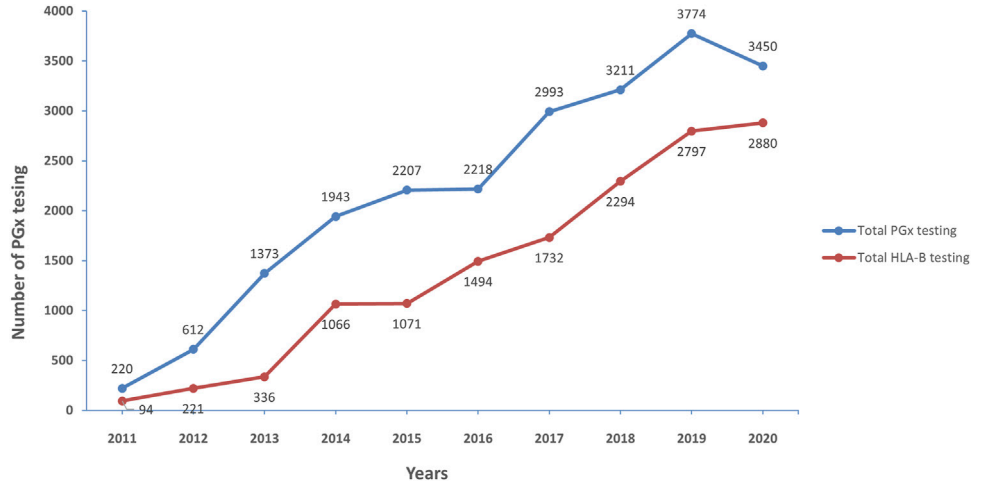



**FIGURE 2 |** Number of pharmacogenetic testing for 10 years (2011–2020), the increase of pharmacogenetic testing (blue line) and *HLA-B*-pharmacogenetic testing (red line) over 10 years during 2011–2020.

**TABLE 1 |** The *HLA-B* alleles associated with cutaneous adverse drug reactions (CADRs) and carrier frequency of Thai population (N = 12,425).

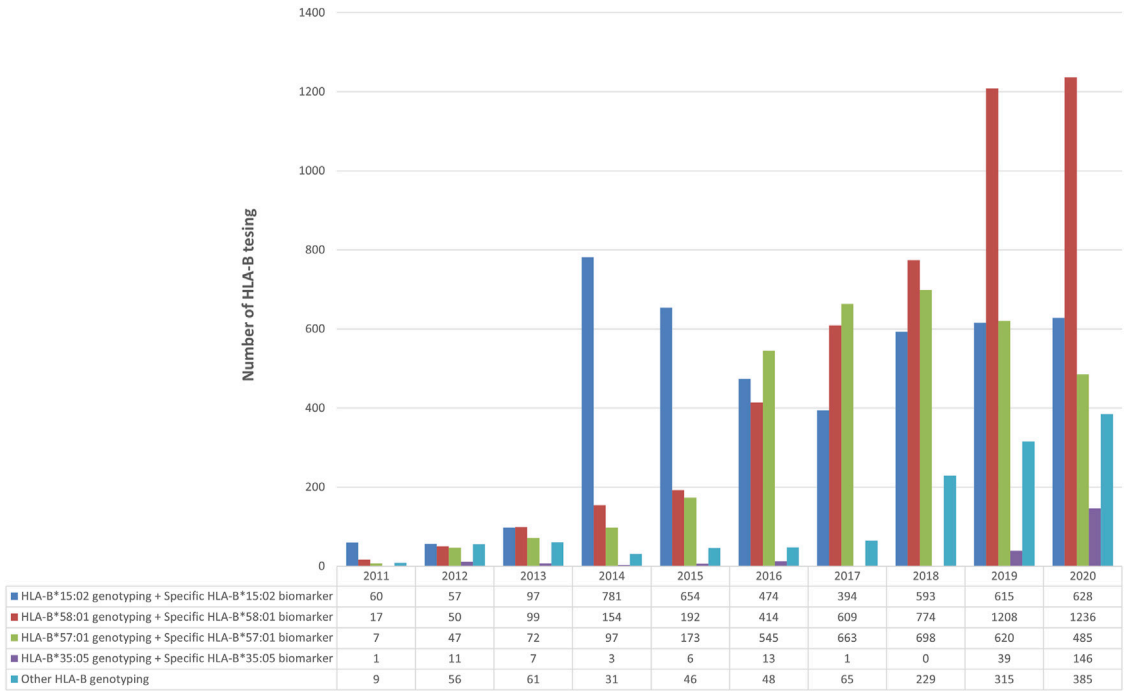
| ***HLA*pharmacogenetics Marker** | **Drug** | **ADR Type** | **Carrier Frequencies (%)** |
|---|---|---|---|
| *HLA-B*13:01* | Phenytoin | SCARs | 12.91 |
| | Phenobarbital | DRESS | |
| | Dapsone | SCARs | |
| | Co-trimoxazole | DRESS | |
| | Salazosulfa-pyridine | DRESS | |
| *HLA-B*15:02* | Carbamazepine | SJS/TEN | 14.96 |
| | Oxcarbazepine | SJS/TEN | |
| | Co-trimoxazole | SJS/TEN | |
| *HLA-B*15:08* | Carbamazepine | SJS/TEN | 0.13 |
| | Phenytoin | SJS/TEN | |
| | Co-trimoxazole | SJS/TEN | |
| *HLA-B*15:11* | Carbamazepine | SJS/TEN | 0.60 |
| *HLA-B*15:13* | Phenytoin | SJS/TEN, DRESS | 1.66 |
| *HLA-B*15:21* | Carbamazepine | SJS/TEN | 1.09 |
| *HLA-B Serotype 75 (HLA-B*15:02, HLA-B*15:08,HLA-B*15:11, HLA-B*15:21)* | Carbamazepine | SJS/TEN | 16.78 |
| *HLA-B*35:05* | Nevirapine | SJS/TEN, DRESS | 3.72 |
| *HLA-B*38:01* | Co-trimoxazole | SJS/TEN | 0.22 |
| *HLA-B*38:02* | Oxcarbazepine | MPE | 6.94 |
| | Co-trimoxazole | SJS/TEN | |
| *HLA-B*51:01* | Phenobarbital | SJS/TEN | 7.18 |
| *HLA-B*56:02* | Phenytoin | DRESS | 1.01 |
| *HLA-B*57:01* | Abacavir | AHS | 3.33 |
| | Flucloxacillin | DILI | |
| *HLA-B*58:01* | Allopurinol | CADRs, SCARs, MPE | 16.03 |
| *HLA-B*59:01* | Methazolamide | SJS/TEN | 0.00 |

*MPE, maculopapular exanthema; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; AGEP, Acute Generalized ExanthematousPustulosis; CF, carrier frequency;* HLA, human leukocyte antigen.

most common *HLA-B* genotyping was requested before prescription of allopurinol, abacavir, and carbamazepine.

## *HLA-B* Allele and Carrier Frequency in Thai Population

Among the total of 13,985 *HLA-B* genotyped data, 1,560 report were identified as non-Thai. Therefore, the allele and carrier frequencies of *HLA-B* alleles in the 12,425 Thai population are presented in supplement table 1S.This information is based on 10 years of PGx testing at the PPM laboratory. Among all the listed alleles, five *HLA-B* alleles are commonly distributed among Thai population and those are *HLA-B*46:01* (24.56%), *HLA-B*40:01* (17.87%), *HLA-B*58:01* (16.03%), *HLA-B*15:02* (14.96%), *HLA-B*13:01* (12.91%). Among these common alleles, *HLA-B*13:01* (dapsone and co-trimoxazole), *HLA-B*15:*




| | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|---|---|---|---|---|---|
| HLA-B*15:02 genotyping + Specific HLA-B*15:02 biomarker | 60 | 57 | 97 | 781 | 654 | 474 | 394 | 593 | 615 | 628 |
| HLA-B*58:01 genotyping + Specific HLA-B*58:01 biomarker | 17 | 50 | 99 | 154 | 192 | 414 | 609 | 774 | 1208 | 1236 |
| HLA-B*57:01 genotyping + Specific HLA-B*57:01 biomarker | 7 | 47 | 72 | 97 | 173 | 545 | 663 | 698 | 620 | 485 |
| HLA-B*35:05 genotyping + Specific HLA-B*35:05 biomarker | 1 | 11 | 7 | 3 | 6 | 13 | 1 | 0 | 39 | 146 |
| Other HLA-B genotyping | 9 | 56 | 61 | 31 | 46 | 48 | 65 | 229 | 315 | 385 |

**FIGURE 3 |** Number of *HLA-B*-pharmacogenetic testing for (1) carbamazepine (2) allopurinol (3) abacavir (4) Nevirapine and (5) other drugs over 10 years during 2011–2020.

*02* (carbamazepine and oxcarbazapine), and *HLA-B*58:01* (allopurinol) have been found to be substantially related with drug-induced toxicity in the Thai population.

The frequency of following alleles *HLA-B*51:01, HLA-B*52:01, HLA-B*55:02, HLA-B*57:01, HLA-B*07:05, HLA-B*15:01* and *HLA-B*44:03* was found to be in the range of 3.00-9.00%. Out of those, *HLA-B*57:01* were found to be substantially linked to abacavir-induced hypersensitivity reactions. Some alleles are not presented in higher frequencies among Thai people, but they have been associated to a number of significant drug-related disorders such as *HLA-B*15:08, HLA-B*38:01*, and *HLA-B*59:01*.

The distribution of PGx markers associated with various drug induced cutaneous reactions among Thai patients is shown in **Table 1**. Another high-frequency allele revealed in this study was *HLA-B*58:01*, this frequency rate in our study is greater rate than other Thai studies. *HLA-B*13:01* has been associated with SCARs induced by phenytoin, phenobarbital, dapsone, cotrimoxazole, and salazosulfa-pyridine. Carbamazepine, oxcarbazepine, and cotrimoxazole-induced Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN) were found to be associated with *HLA-B*15:02*. Other *HLA-B* alleles in serotype 75, including *HLA-B*15:08, HLA-B*15:11, and HLA-B*15:21*, have been associated with SJS/TEN caused by carbamazepine. Some genotypes have a lesser incidence, yet they have a strong link to medication toxicity. *HLA-B*59:01 and HLA-B*38:01*, for example, have been associated with SJS/TEN caused by methazolamide and co-trimoxazole respectively. Since 2011, the *HLA-B* gene has been the most frequently genotyped gene, with a particularly notable increase after 2015. This constitutes 63% of the total PGx testing in our lab.

## *HLA-B* Genotyping

*HLA-B* genotyping was done either a specific allele or the entire gene for drugs to determine their association with toxicity. Among all the *HLA-B* genotyping, the number of specific *HLA-B*15:02* alleles or the whole *HLA-B* genetic testing for carbamazepine was higher since the beginning. However, the maximum number of tests was done in 2014; later the rate was slightly reduced but still held the second place in *HLA-B* PGx testing. The allopurinol-induced SCARs has been linked to *HLA-B*58:01*. The number of tests for the past 10 years has been increasing upward. Since 2017, the rate has surpassed the *HLA-B*15:02* testing. In 2020, this was the most tested *HLA-B* allele in our lab ($n$ = 1,236). *HLA-B* and specific *HLA-B*57:01* were tested for abacavir-induced hypersensitivity reactions. In 2017 and 2018, its testing rate was higher than *HLA-B*15:02*. Other than these alleles, recently the number of nevirapine and *HLA-B*35:05* association tests was higher than in any other year (**Figure 3**).

**Figure 4** shows the number of *HLA-B* pharmacogenetic testing requested for Thai patients to prevent SCARs over 10 years during 2011–2020. Specific *HLA-B*15:02* allele was genotyped less frequently than the entire *HLA-B* geneto prevent carbamazepine induced SCARs. For example, out of the 4,069 total carbamazepine samples analyzed, 75% requested the *HLA-B* gene tested, whereas the remaining 25% requested the *HLA-B*15:02* variant tested alone. Similarly, 29% of

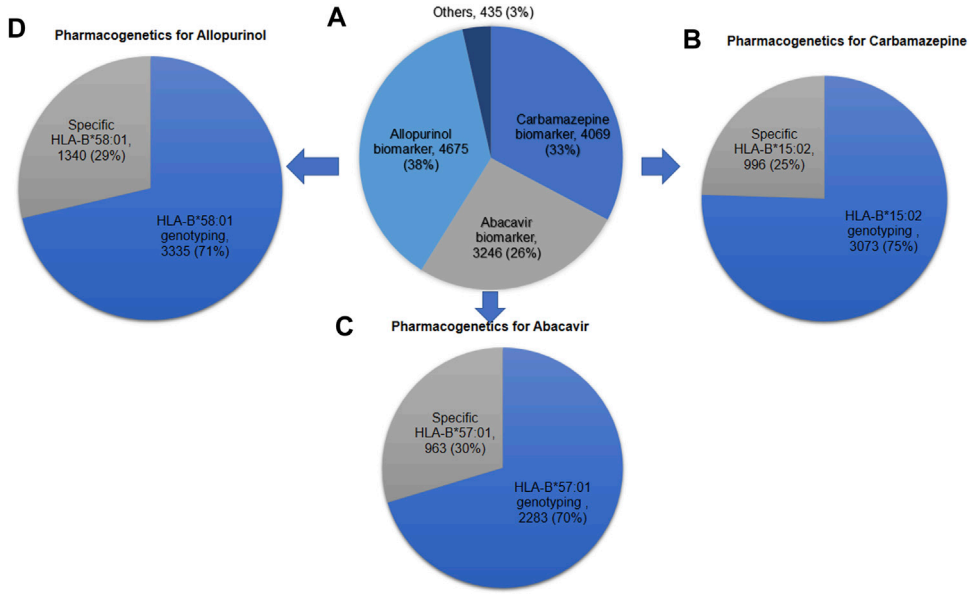



**FIGURE 4 |** Number of *HLA-B* pharmacogenetic testing requested for Thai patients to prevent severe cutaneous adverse drug reactions over 10 years during 2011–2020 **(A)** *HLA-B* pharmacogenetic testing for all drugs (N = 12,425); **(B)** Pharmacogenetic testing for carbamazepine (N = 4,069); **(C)** Pharmacogenetic testing for abacavir (N = 3,246); **(D)** Pharmacogenetic testing for allopurinol (N = 4,675).

the 4,675 samples asked for the *HLAB*58:01* alleleto be tested. In abacavir, the particular allele, *HLA-B*57:01*, was tested in 30% of the samples.

## DISCUSSION

### *HLA-B* Variants and Their Association With SCARs

This cohort study showed the PGx data of *HLA* gene and its association with various drug induced ADRs. In our investigation, the *HLA-B*46:01* allele was shown to be more prevalent (24.56%) but its association with any ADRs not significant. However, this allele was identified as a risk factor for cutaneous adverse drug reactions (CADRs) in a recent study conducted among Han Chinese (Deng et al., 2017). Another high-frequent allele revealed in our study was *HLA-B*58:01,* which has a greater rate than (16.33%) other Thai studies (Tassaneeyakul et al., 2009). This could be because our results are based solely on PGx testing done in our facility. This allele distribution is higher among central Africans (10–15%), and it ranges from 5 to 15% in India (Hughes et al., 2004). In the present study, we found that 16.33% of Thai people carry the *HLA-B*58:01* allele, which is associated with allopurinol hypersensitivity in gout treatment (Saokaew et al., 2014; Ueta et al., 2014). For example, the strength of the association was higher in the Han Chinese (100%) (Hung et al., 2005), Thai (100%) (Tassaneeyakul et al., 2009), and Korean populations (80%) (Kang et al., 2011) than in the Japanese (55%) (Kaniwa et al., 2008), and European populations (56%) (Lonjou et al., 2008).

*HLA-B*15:02* was the next most prevalent allele which considered to be the known valid pharmacogenetic biomarker for carbamazepine induced SJS/TEN. Chung W H et al. was first reported its association with carbamazepine-SJS/TEN in Taiwanese Han Chinese (Chung et al., 2004). This association was later confirmed in several other populations, including Chinese (Wang et al., 2019), Thai (Tassaneeyakul et al., 2010), Malaysians (Chang et al., 2011), Indians (Mehta et al., 2009), Vietnamese (Nguyen et al., 2015), and Indonesians (Yuliwulandari et al., 2017). A recent meta-analysis study which included 11 studies of Chinese, Korean and Thai populations revealed a strong association between *HLA-B*15:02* and lamotrigine induced SJS/TEN in the Chinese population (OR = 2.4) (Deng et al., 2018). The association between *HLA-B*15:02* and oxcarbazepine-induced SJS/TEN has also been demonstrated by Hung S I et al., 2010. In the same serotype B 75, *HLA-B*15:21* has shown positive association with carbamazepine induced SJS, this has been confirmed many other Asian population such as Thai (Jaruthamsophon et al., 2017) Indonesian (Khor et al., 2014; Yuliwulandari et al., 2017) and in Filipinos (Capule et al., 2020). Other than these alleles, in *HLA-B* 15 family, *HLA-B 15:11, HLA-B*15:13, HLA-B*15:08* were found to be the risk factors for drug induced hypersensitivity reactions in various populations (Kaniwa et al., 2010; Chang et al., 2017).

Our study reveals that 13% of the population carry *HLA-B*13:01.* In Chinese, the frequency of *HLA-B*13:01* ranges between 3 and 8% across North and South China, but the people of Papua New Guinea and Melanesians and Australian Aboriginals who are evolutionarily related to Papuans, to have the highest reported allele frequency in the world (28%) (Gonzalez-Galarza et al.,

2011). This allele was initially discovered as a risk factor and predictor of drug hypersensitivity syndrome (DHS) in the Chinese population (Zhang et al., 2013). *HLA-B*13:01* has been shown in multiple other studies in Asia as being a strong predictor of the dapsone induced DHS (Chen et al., 2018; Tangamornsuksan and Lohitnavy, 2018). However, few studies reported its association with Aromatic antiepileptic drugs (AEDs) induced hypersensitivity reactions (Shi et al., 2011; Min et al., 2019).

Abacavir is a prodrug, and a nucleoside reverse transcriptase inhibitor (NRTI) used for the treatment of HIV. It elicits DHR in up to 8% of the population, with drug hypersensitivity reactions (DHR) attributed to the prodrug itself. Fever, malaise, nausea, vomiting, rashes are the clinical features of abacavir-induced DHR. In 2002, *HLA-B*57:01* was found to be associated with abacavir induced DHR in the North American population, and later on, this association was confirmed in the Australian and United Kingdom populations (Hetherington et al., 2002; Mallal et al., 2002; Hughes et al., 2004). However, this association was not noticeable among black people. The reason could be the lesser prevalence of this allele in this population (2.5%) (Saag et al., 2008) European population (6–7%). This allele frequency among Asians is found to be around 12.6% (Martin et al., 2012b). However, in this study, the prevalence was found to be around 3.3%. The reason could be the frequency data is based the data from our lab. This association has been well validated and is a good example of a pharmacogenetic test used widely in the clinic before drug prescription, with abacavir not now being prescribed for individuals positive for *HLA-B*57:01* (Pavlos et al., 2017).

The *HLA-B*51:01* allele has consistently been associated with AEDs-induced CADRs in various Asian ethnicities. Its frequency in our study was found to be 7%. In a Han-Chinese population, a relationship between carbamazepine-induced Maculopapular exanthema (MPE)/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and *HLA-B*51:01* (OR 4.56, 95 percent CI 2.0–10.5, $p = 0.01$) was discovered (Hsiao et al., 2014). This allele association with AEDs-induced CADRs has been confirmed in North and South India (Ihtisham et al., 2019; John et al., 2021), Japan (Kaniwa et al., 2013), Thailand (Tassaneeyakul et al., 2016; Manuyakorn et al., 2020), and among Koreans (Kim. et al., 2016). As a result, in some populations where *HLA-B*51:01* is more common, *HLA-B*51:01* could be a phenotype-specific genetic marker for carbamazepine-phenytoin/SCARs or phenytoin-DRESS.

## Recommendations for Integration of PGx in CDS and Other National Guidelines

Because the majority of pharmaceuticals are discovered in western countries (United States, Europe, Australia, New Zealand, and Canada), therapy selection is successful in only half of the world population in most cases (Howard, 2002). Only little thought has been given about how these drugs will be used throughout the world. Individualized treatment is regarded to be the greatest choice for therapy selection, and good level therapy selection is based on geographical/ethnicity/racial population. The worst method of treatment selection is based on a common population estimate. Integrating PGx data with other clinical and non-clinical data can assist clinical practitioner in selecting the best and most appropriate treatment for their patients.

To achieve a positive therapeutic outcome, rational prescribing is critical. Incorporating PGx data into drug formularies can aid clinical decision-making in public health. Amadioquine is an anti-malarial drug whose usage has been restricted due to its hepatotoxicity. However, there is a considerable demand for this drug in Africa and Southeast Asia, where malaria is still a serious problem. However, it was only after 2005 that it was shown that patients with the *CYP2C8*3* allele were linked to Amadioquine-induced hepatotoxicity (Cavaco et al., 2005). Combining PGx data with national drug formularies, particularly for drugs on the essential drug list, can aid in public health decision-making (Roederer and McLeod, 2010). It has the potential to increase physician and other health-care professionals' awareness of PGx, as well as their confidence in using it in medical practice. It can assist clinicians in prioritizing treatment for each patient based on PGx data. This may assist the researcher in obtaining funding and infrastructural support for future PGx experiments.

However, because clinical practice differs widely between nations, discrepancies in PGx implementation guidelines is another significant issue in integrating PGx data with the Essential Drug List. When the same drug has distinct genotyping and dose recommendations, for example, this disparity causes confusion among health care providers when using clinical PGx guidelines (Guo et al., 2019). Better guidelines could be developed based on ethnic and geographic preferences.

Another step in individualized treatment and preventing severe adverse drug responses is to combine PGx data in a CDS. Every year in the United States, over 10,000 people die as a result of ADRs, despite the fact that drugs are properly prescribed and provided. According to Phillips et al., 60% of the 27 ADRs involved medications had a PGx connection (Lazarou et al., 1998; Phillips et al., 2001). Hence, every ethnic/geographical community requires a PGx clinical decision support tool. A previous study revealed the establishment of a disease-drug search engine data base, which was subsequently combined with the genomic prescribing system. The study recommended PGx in CDS would make drug prioritization easier.

Our study shows that *HLA-B* PGx testing has been increasing tremendously for the past 10 years in our lab. The general reasons could be the emerging sequencing technologies which shrinking the cost of sequencing (Schwarze et al., 2018), the better understanding or awareness about PGx application among health care professional especially among physician, and availability of standard international and national guideline on the clinical utility of PGx testing (Guo et al., 2021).

The first south East Asian country which had record breaking research and publications in this field, and scientific bodies that funding many genomic research projects such as Thailand center of excellence for life sciences (TCELS), Genomic Thailand initiatives (GTI) gives the opportunity for researcher to produce clinically valid data for each PGx biomarkers in Thai population. Since 2011, the

**TABLE 2 |** The HLA alleles associated with SCARs and carrier frequency of Thai population (N = 470) from published article (Satapornpong et al., 2020).

| HLA Allele | Drugs | Type of SCARs | Thailand CF (%) | Ethnic Group | Ref |
|---|---|---|---|---|---|
| *HLA-A*01:01* | Phenobarbital | SCARs | 4.468 | Thai | Manuyakorn et al. (2016) |
| *HLA-A*02:06* | Cold medicine | SJS,TEN | 4.468 | Japanese | Ueta et al. (2014) |
| *HLA-A*24:02* | Carbamazepine<br>Lamotrigine<br>phenytoin | SJS,TEN,MPE | 20.213 | Han Chinese, Korean | (Moon et al., 2015; Shi et al., 2017) |
| *HLA-A*31:01* | Carbamazepine | SJS/TEN, AGEP | 1.489 | Caucasian, Japanese, Korean, Chinese, and patients of mixed origin | Amstutz et al. (2014) |
| *HLA-A*32:01* | Vancomycin | AGEP, DRESS,SJS/TEN | 0.426 | Europeans | (Cristallo et al., 2011; Konvinse et al., 2019) |
| *HLA-A*33:03* | Allopurinol | SJS,TEN | 21.064 | Caucasian, Asian populations | (Cristallo et al., 2011; Li et al., 2017) |
| *HLA-A*68:01* | Lamotrigine | SCARs | 1.915 | Europeans | Kazeem et al. (2009) |
| *HLA-C*03:02* | Allopurinol | SJS,TEN | 14.68 | Caucasian, Asian populations | Li et al. (2017) |
| *HLA-C*04:01* | Nevirapine | SJS,TEN | 9.36 | Malawian | (Carr et al., 2013; Carr et al., 2017) |
| *HLA-C*06:02* | Co-trimoxazole | SJS,TEN | 8.51 | Thai | Kongpan et al. (2015) |
| *HLA-C*08:01* | Carbamazepine | SJS,TEN | 19.15 | Han Chinese | Shi et al. (2017) |
| | Phenytoin | | | | Hung et al. (2010) |
| | Allopurinol | | | Caucasian | Cristallo et al. (2011) |
| | Co-trimoxazole | | | Thai | Kongpan et al. (2015) |
| *HLA-C*14:02* | Phenytoin | DRESS | 5.74 | Thai | Manuyakorn et al. (2020) |
| *HLA-DRB1*12:02* | Carbamazepine | SJS,TEN | 28.51 | Han Chinese | Shi et al. (2017) |
| *HLA-DRB1*13:02* | Allopurinol | SJS,TEN | 2.77 | Caucasian | Cristallo et al. (2011) |
| *HLA-DRB1*15:02* | Allopurinol | SJS,TEN | 26.38 | Caucasian | Cristallo et al. (2011) |
| *HLA-DRB1*16:02* | Phenytoin | SJS,TEN | 0.0 | Han Chinese | Hung et al. (2010) |

*MPE, maculopapular exanthema; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; AGEP, Acute Generalized ExanthematousPustulosis; CF, carrier frequency; HLA, human leukocyte antigen.*

*HLA-B* has been the most frequently genotyped gene, with a particularly notable increase after 2015. This constitutes 63% of the total PGx testing in our lab. The *CYP450* gene was the next common gene for genotyping. The maximum number of *HLA-B* tests was done in 2020 (n = 2,880). The reason could be that the Thai population that comes under the Universal Coverage Scheme (UCS) has coverage for *HLA-B*15:02* screening with a reimbursement of 28 dollars per person. Our study also shows that 50% of the samples were from state hospital, this could be due to establishment of a policy that require *HLA-B*15:02* pharmacogenetic testing prior to the start of carbamazepine medication by the Thai Department of Medical Sciences and the National Health Security Office (NHSO) in 2013 and 2018 respectively (Kaniwa et al., 2008).

However, there is currently no PGx alert system connected with the electronic health records (EHR) in Thailand. Failure to integrate PGx alert into the EHR system could result in major clinical consequences. For example, in Thailand, an inpatient with the *HLA-B*15:02* allele was initially administered phenytoin but was later switched to carbamazepine due to a lack of a PGx alert system in the EHR, and the patient died as a result of carbamazepine-induced TEN (Sukasem et al., 2021).

Lastly, other *HLA* was reported to be associated with drug-induced SCARs, including DRESS, SJS/TEN, and AGEP (**Table 2**). When determined the carrier frequency from the previous study (Satapornpong et al., 2020), the frequencies of these biomarkers were common in Thai population. Especially, pharmacogenetic markers associated with different ethnic groups such as *HLA-A*24:02* and *HLA-A*31:01* for carbamazepine, *HLA-A*33:03* and *HLA-C*03:02* for allopurinol etc. Further case-control study with large sample size need to be warranted to confirm these findings in Thai population.

## CONCLUSION

For the past 10 years, our PPM lab has seen an increase in *HLA-B* genotyping, particularly for medications like carbamazepine, allopurinol, abacavir, and nevirapine. *HLA-B*15:02, HLA-B*58:01, HLA-B*57:01, HLA-B*13:01, HLA-B*15:21, HLA-B*35:05* alleles are found to be associated with drug-induced hypersensitivity reactions. This study shows that in the future, Thailand will have even more PGx data available for numerous medications. However, it will be hard to predict and avoid serious ADRs if we do not take full advantage of PGx, pharmacovigilance, as well as other biological, clinical, and non-clinical data. As a result, it is critical to create a single framework that incorporates all data in order to provide tailored treatment. It is crucial in countries like Thailand, where there's already a lot of PGx data.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Ramathibodi Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

NK, CK, SJ, and CS: wrote the manuscript; CS: designed and conceptualization the research; All authors performed the research; NK and CK: Analyzed and curation the data. The final manuscript was revised by all authors, and this version was approved to be published.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.866903/full#supplementary-material

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# Sub-Analysis of CYP-GUIDES Data: Assessing the Prevalence and Impact of Drug-Gene Interactions in an Ethnically Diverse Cohort of Depressed Individuals

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**Introduction:** Minority groups are underrepresented in pharmacogenomics (PGx) research. Recent sub-analysis of CYP-GUIDES showed reduced length of stay (LOS) in depressed patients with CYP2D6 sub-functional status. Our primary objective was to determine whether PGx guided (G) versus standard treatment (S) influenced LOS among different race/ethnic groups. Secondary objectives included prevalence of drug-gene interactions (DGIs) and readmission rates (RAR).

**Methods:** Retrospective sub-analysis of CYP-GUIDES data comprising CYP2D6 phenotypes was reclassified using standardized CYP2D6 genotype to phenotype recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG). The Mann-Whitney test was used to determine differences in LOS between groups G and S and Kruskal Wallis test to compare LOS among different race/ethnic groups. Logistic regression was used to determine covariates associated with RAR.

**Results:** This study included 1,459 patients with 67.3% in G group ($n$ = 982). The majority of patients were White (57.5%), followed by Latinos (25.6%) and Blacks (12.3%). Although there were no differences in LOS between G and S groups, Latinos had significant shorter LOS than Whites ($p$ = 0.002). LOS was significantly reduced by 5.6 days in poor metabolizers in group G compared to S ($p$ = 0.002). The proportion of supra functional and ultra-rapid metabolizers (UMs) were 6 and 20.3% using CYP-GUIDES and CPIC/DPWG definitions, respectively. Prevalence of DGIs was 40% with significantly fewer DGIs in Blacks ($p$ < 0.001). Race/ethnicity was significantly associated with RAR (aOR 1.30; $p$ = 0.003).

**Conclusion:** A greater number of patients were classified as CYP2D6 UMs using CPIC/DPWG definitions as compared to CYP-GUIDES definitions. This finding may have clinical implications for using psychotropics metabolized by CYP2D6.

**Keywords: ethnicity, race, length of stay, drug-gene interactions, depression, CYP2D6 phenotype**

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## INTRODUCTION

Depression is the leading cause of disability worldwide with 16 million Americans suffering from moderate or severe depression and costs exceeding $210 billion annually (Vos et al., 2012; Bradley et al., 2018). Antidepressants are commonly prescribed in the United States (US) with approximately 10% of adults reporting recent use in the past month (Bradley et al., 2018). Despite common antidepressant use, only one-third of newly diagnosed depressed individuals achieve remission during their first treatment course (Trivedi et al., 2006; Gaynes et al., 2009). Reasons for treatment failure include baseline severity/duration of depression, underlying neuropathology, concurrent medical conditions, and poor tolerability. This is significant because consequences of ineffective treatment of depression lead to a worsening disease course, higher suicidal risk, and greater societal and economic burden.

Current treatment approaches for depression are insufficient relying on a trial-and-error approach. Drug-gene interactions (DGIs) play a contributory role in inter-patient variability in treatment response to antidepressants. These can manifest as different drug metabolizer status phenotypes [i.e., poor metabolizer (PM)/ultra-rapid metabolizer (UM)] and/or ineffective drug target signaling involving serotonin transporters and receptors (Hicks et al., 2015; Caudle et al., 2017). Integration of pharmacogenomics (PGx) into healthcare practices (i.e., clinical practice, clinical trials and pharmacovigilance programs) (Sosa-Macías et al., 2016), can lead to a personalized medicine approach, ultimately improving patient response and assisting patients to reach targeted treatment outcomes promptly. The latter is significant since early response to therapy in depressed individuals is a predictor of treatment outcome (Beard and Delgadillo, 2019). Knowledge of PGx for a patient can help guide the prescriber in identifying the most appropriate medication before initiating therapy, reduce adverse events (Zhou et al., 2015) and hospital admission, and promote medication safety (Panza et al., 2016). Recent clinical studies involving treatment resistant depressed patients have reported significantly improved remission rates for those whose DGIs were taken into consideration versus those receiving treatment as usual (Hall-Flavin et al., 2012, 2013; Winner et al., 2013; Singh, 2015; Pérez et al., 2017; Bradley et al., 2018; Greden et al., 2019; Thase et al., 2019).

Although combinatorial panel-based PGx testing has improved medication selection and cost effectiveness for those with underlying DGIs, the generalizability of these findings to different race/ethnic populations remains unknown because of their large under-representation in clinical studies (Rush et al., 2006; Lesser et al., 2007; Claudio-Campos et al., 2015). For example, according to the genome-wide association study (GWAS) catalog, although individuals of European descent comprise only 16% of the world population, almost 80% are included as all GWAS participants (Martin et al., 2019). In 2020, White non-Hispanics were the most prevalent ethnic group (57.8%) in the United States followed by Latinos accounting for the second largest group (18.7%) and then by Blacks/African Americans (12.1%) (Jensen et al., 2021). Race/ethnicity is an important consideration since the prevalence of genetic variants in drug metabolism may vary across different race/ethnic groups and could ultimately influence therapeutic recommendations (Shah and Gaedigk, 2018). Although it is unclear what threshold constitutes race/ethnic diversity, Federal agencies such as the National Human Genomic Research Institute encourage inclusion and recruitment of under-represented minorities into genomics-related research (Bonham and Green, 2021).

Length of stay (LOS) during hospitalization can be influenced by CYP2D6 phenotype. Impaired functional status in CYP2D6 has been associated with prolonged LOS while UM CYP2D6 phenotype has been associated with increased risk for readmission rates (RAR) (Laika et al., 2009; Ruaño et al., 2013; Takahashi et al., 2017). Both LOS and RAR (Takahashi et al., 2017) influence the financial cost of patients living with major depressive disorder (MDD) and increase the disease burden (Jencks et al., 2009).

The CYP-GUIDES (Cytochrome Psychotropic Genotyping Under Investigation for Decision Support) randomized clinical trial included patients with MDD admitted to one location at the Institute of Living at Hartford Hospital (Ruaño et al., 2020). A total of 1,500 depressed individuals were randomized (2:1) to Genetically guided therapy (Group G, $n = 982$) and Standard Care (Group S, $n = 477$). This original, prospective, randomized controlled trial reported no differences in 1,459 depressed, hospitalized patients for LOS and RAR between the CYP2D6 genetically-guided and standard therapy groups (Ruaño et al., 2020). One of the strengths of this study is that it included a racially and ethnically diverse population as it included Blacks and Latinos. In this study, Latinos had a significantly shorter LOS than Whites. Authors of this study suggested that potential confounders such as these could have obscured the results of using PGx guidance for treatment of depression. A recent subgroup analysis of this study concluded that PGx guided therapy reduced the LOS in depressed patients with sub-functional CYP2D6 status who were prescribed CYP2D6 major psychotropic medications (Ruaño et al., 2021). This sub-analysis specifically addressed three potential confounders such as a single electronic medical record, a minimum 3-day LOS, and stratification of patients by CYP2D6 phenotype.

Data analyses from both the CYP-GUIDES trial and the subsequent sub-analysis excluded patients who were supra-functional CYP2D6 metabolizers because of their lower representation (6.2 and 6.7%, respectively) of the total cohort that could lead to underpowered data comparisons, especially, with respect to treatment outcomes involving LOS and RAR. As noted by the authors in these studies, functional categories for CYP2D6 were implemented in 2014. However, recent consensus recommendations from Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) were published regarding standardization of CYP2D6 genotype to phenotype (Caudle et al., 2020). These recommendations support a UM in CYP2D6 as having a total activity score of greater than 2.25.

Given the need for including underrepresented groups in clinical PGx studies and the recent updated standardization of CYP2D6 phenotypes, the primary objective of our analysis was to determine whether pharmacogenetics-guided (Group G) versus standard therapy (Group S) influenced LOS among different race/ethnicities in the CYP-GUIDES trial. Secondary objectives included determination of the prevalence of DGIs and RAR among different race/ethnic groups.

## METHODS

A retrospective sub-analysis was performed using the publicly available CYP-GUIDES dataset (Tortora et al., 2020). Detailed methodology for the trial including eligibility criteria has been described previously (Ruaño et al., 2020). The dataset included anonymized data from 1,500 patients; randomized (2:1) to Genetically guided therapy (Group G, $n$ = 982) and Standard Care (Group S, $n$ = 477).

Two electronic medical records (EMRs) were used during the study period: the Clinical Evaluation and Monitoring System (CEMS) and Epic EMR. Study patients with no genomic information were excluded from our sub-analysis ($n$ = 41). In terms of CYP2D6 genotyping, 21 common allelic variants comprising of either null, deficient or rapid function were interrogated in the CYP-GUIDES trial (Ruaño et al., 2020). The metabolic reserve (MR) index incorporated in the CYP-GUIDES trial was used to quantify CYP450 functional phenotypes (Ruaño et al., 2011; Villagra et al., 2011). The MR index equivalent to a total activity score is calculated by adding the activity score of each of the two CYP2D6 alleles for each patient (Tortora et al., 2020). These phenotypes included the following categories: sub-functional (activity score (AS ≤ 1.0) or MR of 0.0, 0.5 or 1.0, functional (1.5 ≤ AS<2.5) or MR of 1.5, 2.0 or 2.5, and supra-functional (AS ≥ 3.0) or MR of 3.0 or 3.5. In our sub-analysis, phenotypes for patients were reclassified using updated standardization of CYP2D6 genotype to phenotype translation from consensus recommendations from CPIC and the DPWG (Caudle et al., 2020). These latter phenotypes included the following: PMs with AS = 0; intermediate metabolizers (IMs) ranging 0 < AS < 1.25; normal metabolizers (NMs) ranging 1.25 ≤ AS ≤ 2.25; and UMs with an AS > 2.25.

LOS was defined as the duration of inpatient care; time from admission till discharge (Segen's Medical Dictionary, 2002). RAR was defined as hospitalization within 30 days of discharge of the current admission (Ruaño et al., 2020). Diagnosis was stratified by six categories: depression, MDD without psychotic features, MDD with psychotic features, MDD recurrent, MDD recurrent with psychotic features and other. In our sub-analysis, a DGI was defined as follows: a patient who is either a PM (AS of zero), IM (AS of 0.5 and 1), or UM (AS of 2.5, 3 and 3.5) and is administered a major CYP2D6 substrate psychotropic medication at least once during hospitalization.

We restricted some of our data analyses to patients who had a LOS >3 days to account for the turn-around time necessary for physicians to obtain CYP2D6 genotyping results for therapeutic guidance. Additional data analyses were conducted where necessary by including only CEMS, since this was the more familiar EMR health care providers had been using before transitioning to the Epic EMR during the clinical trial.

The Mann-Whitney test was used to determine differences in LOS between groups G and S. The Kruskal Wallis test was used to determine differences in LOS among different race/ethnic groups with the Dunn test with Bonferroni adjustment as a post hoc test (adjusted alpha = 0.013). Analysis of variance (ANOVA) was used to determine differences in LOS between race/ethnicities in groups G and S. Logistic regression was used to determine potential covariates or confounders associated with RAR and DGIs. All data analyses were conducted with Stata 17 (Stata Corp LCC, College Station, TX).

## RESULTS

### Demographics and Prevalence of Drug-Gene Interactions (DGIs)

This study included 1,459 patients with 67.3% in group G ($n$ = 982). Majority of patients were White (57.5%), followed by Latinos (25.6%) and Blacks (12.3%). MDD with recurrence was the most prevalent reported diagnosis (42.2%), with a higher prevalence in group G (43.3%) compared to S (39.8%). Whites reported more MDD with recurrence ($n$ = 399, 47.6%) compared to Blacks ($n$ = 71, 40%) and Latinos ($n$ = 113, 30.3%). MDD with recurrence with psychotic features was more prevalent among Latinos ($n$ = 42, 11.3%) compared to Blacks ($n$ = 9, 5%) and Whites ($n$ = 28, 3.3%). Similarly, MDD with psychotic features was most prevalent among Latinos ($n$ = 61, 16.4%) compared to Blacks ($n$ = 17, 9.5%) and Whites ($n$ = 29, 3.5%).

DGIs were comparable between Groups G (39.5%) and S (40%) with an overall prevalence of 39.7% in the study. Significantly fewer DGIs were present among Blacks compared to Latinos (24 versus 42.9%, respectively; OR = 2.3 95% CI 1.6-3.5, $p$ < 0.001) and Whites (24 versus 42.2%, respectively; OR 2.2 95% CI 1.5-3.2, $p$ < 0.001). However no significant differences were observed between DGIs in group G and S ($p$ = 0.7) as well as between other demographic variables in groups G and S. Refer to **Table 1** for baseline demographics of the study population.

### Prevalence of CYP2D6 Phenotypes in Study Population

Most patients were CYP2D6 NMs (40.2%), followed by IMs (34.3%), UMs (20.3%), and PMs (5.1%). Refer to **Figure 1A**. There were no significant differences in prevalence of CYP2D6 phenotypes between groups G and S ($p$ = 0.6). PMs and IMs in CYP2D6 were more prevalent among Whites (6.8 and 36.8%) compared to Latinos (3.5 and 32.1%) and Blacks (0.6 and 33%), respectively. However, UMs were more prevalent among Latinos (24.4%) compared to Whites (19.5%) and Blacks (11.7%). Refer to **Figure 1B**.

### Length of Stay (LOS)

The median LOS was 6.6 and 6.1 days when restricting LOS to >3 days and LOS to >3 days and using CEMS only, respectively. LOS was not significantly different between groups G and S for

**TABLE 1 |** Demographics of study population.

| | Group G *n* (%) | Group S *n* (%) | Total *n* (%) |
|---|---|---|---|
| Total study population N (%) | 982 (67.31) | 477 (32.69) | 1,459 (100) |
| Female (%) | 504 (51.3) | 240 (50.3) | 744 (51.0%) |
| Age, median [IQR] | 37 [24–51] | 37 [25–51] | 37 [38.7] |
| Race/ethnicity | | | |
| Latino | 249 (25.4) | 124 (26.0) | 373 (25.6) |
| Black | 111 (11.3) | 68 (14.3) | 179 (12.3) |
| White | 578 (58.9) | 260 (54.5) | 838 (57.4) |
| Unknown | 44 (4.5) | 25 (5.2) | 69 (4.7) |
| Electronic record | | | |
| Clinical Evaluation and Monitoring (CEMS) | 549 (55.9) | 277 (58.1) | 826 (56.6) |
| Epic | 433 (44.1) | 200 (41.9) | 633 (43.4) |
| Diagnosis at admission | | | |
| Depression | 172 (17.5) | 97 (20.3) | 269 (18.4) |
| MDD without psychotic features | 252 (25.7) | 123 (25.8) | 375 (25.7) |
| MDD with psychotic features | 77 (7.8) | 35 (7.3) | 112 (7.7) |
| MDD recurrent | 426 (43.4) | 190 (39.8) | 616 (42.2) |
| MDD recurrent with psychotic features | 52 (5.3) | 30 (6.3) | 82 (5.62) |
| Other | 3 (0.3) | 2 (0.4) | 5 (0.3) |
| Number of patients prescribed a major substrate CYP2D6 psychotropic medication | 633 (64.5) | 321 (67.3) | 954 (65.4) |
| Latino | 167 (67.0) | 92 (74.2) | 259 (69.4) |
| Black | 60 (54.1) | 42 (61.8) | 102 (57.0) |
| White | 381 (65.9) | 172 (66.2) | 553 (66.0) |
| Drug-gene interactions (DGIs)[a] | 388 (39.5) | 191 (40.0) | 579 (39.7) |
| Latino | 105 (42.2) | 55 (44.4) | 160 (42.9) |
| Black | 24 (21.6) | 19 (27.9) | 43 (24.0)[b] |
| White | 245 (42.4) | 109 (41.9) | 354 (42.2) |
| Total number of psychotropics prescribed, median [IQR] | 2 [2–4] | 3 [2–3] | 3 [2–4] |
| Latino | 3 [2–4] | 3 [2–3] | 3 [2–4] |
| Black | 2 [1–3] | 2 [2–3] | 2 [2–3] |
| White | 2 [2–4] | 3 [2–4] | 3 [2–4] |

[a]*In our sub-analysis, definition of a drug-gene interaction (DGI) was defined as a patient who is either a PM (AS, of zero), IM (AS, including 0.5 and 1), or UM (includes AS, of 2.5, 3 and 3.5) and is administered a major CYP2D6 substrate psychotropic medication at least once during hospitalization.*

[b]*Overall, Blacks experienced significantly less DGIs, compared to Whites (*p *< 0.001) and Latinos (*p *< 0.001).*

patients admitted for >3 days ($p$ = 0.6) or admitted for >3 days using CEMS only ($p$ = 0.4). Further stratification of data analysis for LOS was restricted to LOS to >3 days and using CEMS EMR only when comparing LOS between groups G and S with regards to CYP2D6 phenotype and race/ethnicity. CYP2D6 phenotype was associated with LOS ($p$ = 0.03); however, only PMs in group G had a significantly shorter LOS compared to group S (median 5.8 days versus median 11.4 days; $p$ = 0.002). Race/ethnicity was significantly associated with LOS ($p$ = 0.004). However, no significant differences were detected in LOS between groups G and S among different race/ethnic groups including Blacks ($p$ = 0.06). Overall, Latinos had a significantly shorter LOS compared to Whites (total median 5.8 versus 6.6 days, respectively; $p$ = 0.002). Refer to **Table 2**.

## Readmission Rates (RAR)

A total of 142 patients (9.7%) were re-admitted within 30 days post discharge, with slightly more in group G ($n$ = 99, 10.1%) compared to group S ($n$ = 43, 9%). There were no differences in RAR for groups G and S after adjusting for confounders including age, sex, treatment group, CYP2D6 phenotype, diagnosis at admission (aOR = 0.9; $p$ = 0.6). However, race/ethnicity was significantly associated with RAR (aOR = 1.3, $p$ = 0.003). RAR was lower among Latinos in group G ($n$ = 16, 6.4%) compared to group S ($n$ = 8, 8.1%). However, for Blacks ($n$ = 8, 7.2% versus $n$ = 3, 4.4%) and Whites ($n$ = 73, 12.6% versus $n$ = 28, 10.8%), RAR was greater in group G versus group S, respectively. Overall, RAR was highest in Whites ($n$ = 101, 12.1%) compared to Blacks ($n$ = 11, 6.2%) and Latinos ($n$ = 26, 7.0%).

## Number of Psychotropic Medication Administrations

Data analysis for the number of psychotropic medication administrations was restricted to patients with a LOS >3 days and who were treated with major CYP2D6 substrates. The following psychotropic major CYP2D6 substrate medications were administered during this study: haloperidol, mirtazapine, aripiprazole, fluoxetine, risperidone, venlafaxine, duloxetine, clonidine, chlorpromazine, amitriptyline, fluphenazine,

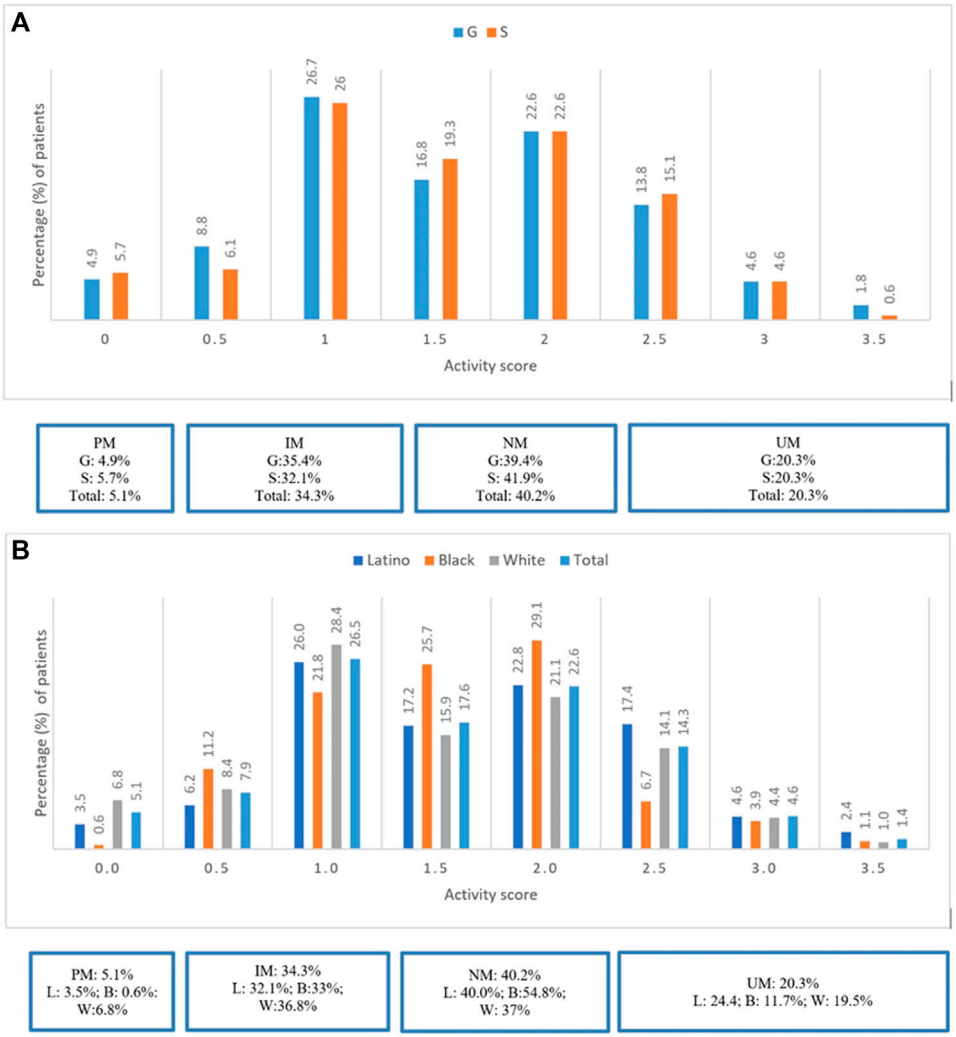


**FIGURE 1 | (A)** Prevalence of CYP2D6 Phenotypes stratified by groups G and S. **(B)** Prevalence of CYP2D6 Phenotypes stratified by ethinicity for the total study population.

perphenazine, doxepin, nortriptyline, fluvoxamine, clomipramine and imipramine. Overall, fewer patients were administered major CYP2D6 substrates in group G (68.1%) compared to S (71.6%). Overall, PMs in group G received less CYP2D6 major substrates compared to group S. No differences were observed for UMs regarding administration of major CYP2D6 substrates between groups G and S. Refer to **Figures 2A–D**. Overall, Blacks were prescribed less psychotropics compared to Whites and Latinos. Refer to **Table 1**.

## DISCUSSION

In our evaluation of the CYP-GUIDES data, we discuss the importance of including race/ethnicity in PGx studies and the need for using updated standardized reporting of CYP2D6 phenotypes. These are important pharmacovigilant factors underrepresented in pharmacogenomic clinical studies which can impact therapeutic recommendations and ultimately treatment outcomes in managing MDD.

### Prevalence of CYP2D6 Phenotypes and Drug-Gene Interactions

Patient population from the CYP-GUIDES trial was racially/ethnically diverse with Whites (57.5%), Latinos (25.6%) and Blacks (12.3%). Reported diagnoses varied by race/ethnicity with MDD with recurrence commonly representative as the primary diagnosis.

Most patients were CYP2D6 NMs (40.2%), followed by IMs (34.3%), UMs (20.3%), and PMs (5.1%). PMs were more commonly representative among Whites (6.8%) and UMs among Latinos (24.4%). Overall, prevalence of DGIs for the total study population was approximately 40%. Notably

**TABLE 2 |** Length of Stay stratified by Groups G and S according to CYP2D6 phenotype and race/ethnicity.

| | Group G Median [IQR] *n* (%) | Group S Median [IQR] *n* (%) | Total Median [IQR] *n* (%) |
|---|---|---|---|
| LOS >3 days | 6.7 [5.0–8.8], 798 (67.3) | 6.5 [4.7–9.5], 387 (32.7) | 6.6 [4.9–8.9], 1,185 (100.0) |
| LOS >3 days and CEMS | 6.1 [4.8–8.0], 428 (66.5) | 6.0 [4.3–8.3], 216 (33.5) | 6.1 [4.7–8.1], 644 (100.0) |
| CYP2D6 phenotype* | | | |
| Poor metabolizer | 5.8 [4.8–7.5]**, 21 (4.9) | 11.4 [6.2–21.1], 13 (6.0) | 6.1 [5.0–9.0], 34 (5.3) |
| Intermediate metabolizer | 6.8 [5.0–8.2], 159 (37.2) | 6.0 [4.2–9.6], 75 (34.7) | 6.8 [4.8–8.6], 234 (36.3) |
| Normal metabolizer | 5.8 [4.6–7.8], 147 (34.4) | 5.9 [4.0–7.5], 86 (39.8) | 5.8 [4.5–7.7], 233 (36.2) |
| Ultra-rapid metabolizer | 6.4 [5.1–8.9], 101 (23.6) | 5.8 [4.4–8.0], 42 (19.4) | 6.2 [4.8–8.9], 143 (22.2) |
| Race/ethnicity*** | | | |
| Latino | 5.8 [4.4–7.7], 116 (27.1) | 5.6 [4.3–7.9], 60 (27.8) | 5.8 [4.4–7.7], 176 (27.3) |
| Black | 6.6 [5.1–8.9], 43 (10.1) | 5.1 [4.1–6.8], 33 (15.3) | 5.8 [4.5–7.8], 76 (11.8) |
| White | 6.6 [5.0–8.5], 254 (59.4) | 7.0 [4.5–11.4], 118 (54.6) | 6.6 [4.9–8.8], 372 (57.8) |

*p = *0.03; CYP2D6 phenotype was associated with LOS.*

**p = *0.002; poor metabolizers in group G had a significantly shorter LOS, compared to group S.*

***p = *0.004; race/ethnicity was significantly associated with LOS, with Latinos having a significantly shorter LOS, compared to Whites (*p = *0.002).*

significantly fewer DGIs (24%) occurred in Blacks; this could be secondary to the lower prevalence of PMs and UMs in CYP2D6 in this race and greater prevalence of NM status (54.8%) compared to Whites and Latinos. Furthermore, Blacks also used less CYP2D6 major substrate psychotropic medications (57%) compared to Whites (66%) and Latinos (69.4%).

In our sub-analysis, using a reclassified definition of activity scores of CYP2D6 phenotypes, we observed greater representation of UMs than previously reported in the CYP-GUIDES trial (20.3 versus 6%, respectively) (Tortora et al., 2020). This step of pharmacovigilance demonstrates the importance of using standardized reporting to guide therapeutic recommendations regarding utility of CYP2D6 substrate medications because these can potentially impact treatment outcomes such as LOS and RAR.

## Length of Stay (LOS)

In our sub-analysis we did not observe significant differences in LOS between groups G and S for patients admitted for >3 days using both CEMS and Epic or admitted for >3 days using CEMS only. It is possible that the overall LOS appeared to be longer with regards to the former since physicians were more familiar with CEMS than with Epic introduced later in the study. Furthermore, when stratifying data analyses for >3 days and using CEMS only by CYP2D6 phenotype, PMs in group G had significantly shorter LOS compared to group S (median 5.8 days versus median 11.4 days; $p = 0.002$). Similar trends were noted by a recent sub-analysis by Ruaño et al. (2021), in which they observed LOS to be significantly shorter (mean difference of 2 days) among sub-functional patients in group G compared to S. These findings suggest that using PGx clinical decision support to manage depression can help to reduce overall healthcare expenditures associated with LOS, particularly for CYP2D6 PMs who are at increased risk for adverse effects when receiving treatment with medications metabolized predominantly by CYP2D6 (Maciel et al., 2018; Martin et al., 2019).

On the other hand, both IMs and UMs appeared to have a greater LOS in group G versus S in our sub-analysis. One potential explanation for this finding with UMs was that the original CYP-GUIDES trial did not use the updated standardized classification of CYP2D6 phenotype, accounted for in our sub-analysis. Consequently, it is possible that patients who were categorized as NMs in the original trial were in fact UMs missing out on potential opportunities for therapeutic interventions that could have resulted in a shorter LOS in the group G versus S.

Latinos and Blacks had greater LOS in group G versus S, but the contrary was observed among Whites. Given that there was a greater prevalence of PMs in Whites compared to Blacks and Latinos, it is possible that Whites in group G benefitted the most from PGx guidance administration of psychotropics resulting in a shorter LOS than those in group S. Overall Latinos had a shorter LOS compared to Whites (median difference = 0.8 days). Latinos experience various challenges when seeking care for depression. Some of these challenges include communication barriers, stigma, lack of insurance (Camacho et al., 2015; Sanchez et al., 2019; American Psychiatric Association, 2021) which might explain the shorter overall LOS experienced by Latinos in our sub-analysis.

## Readmission Rates (RAR)

In our sub-analysis, race/ethnicity was significantly associated with RAR. In particular, lower RAR was evident among Latinos in group G versus S, but reportedly greater among Blacks and Whites in group G versus S. This could be due to a greater percentage of patients with MDD recurrence diagnosis in group G in Blacks (41.5%) and Whites (48.4%) compared to Latinos (32.5%). Takahasi et al. (2017) reported that patients with supra CYP2D6 functional status were more likely to be readmitted. This finding is in contrast to our sub-analysis which showed lower RAR among Latinos, even though a significant proportion of these individuals were categorized as UMs. However, patients

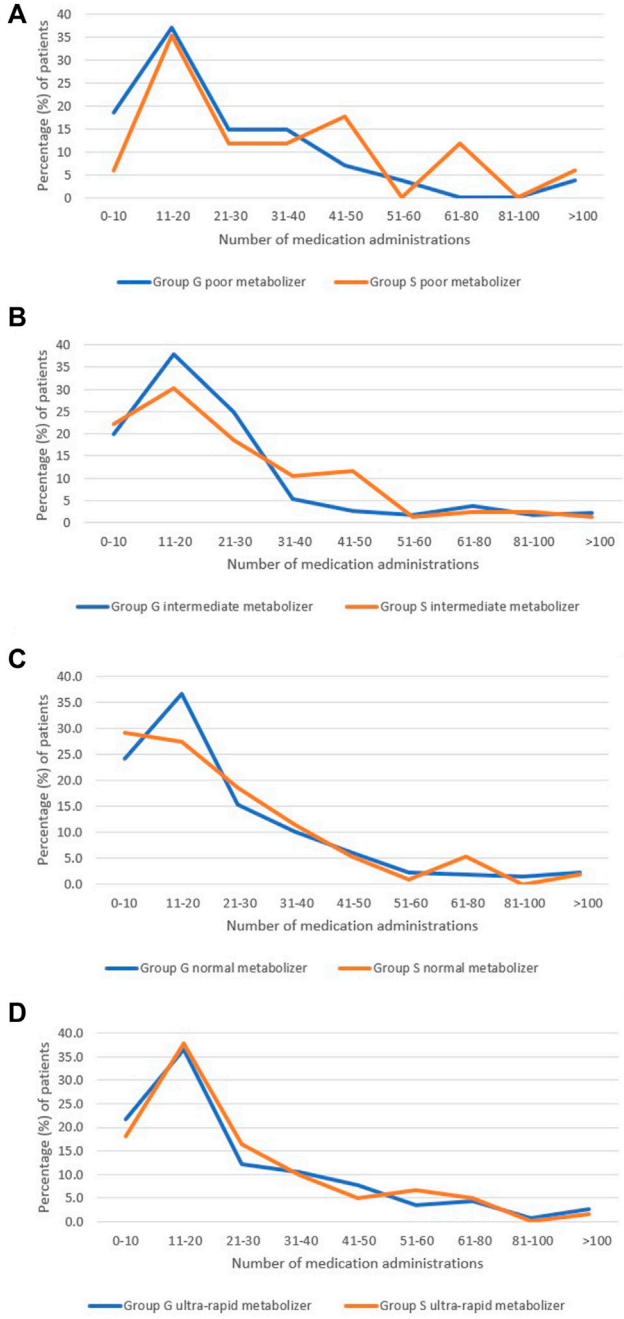


**FIGURE 2 |** Summary of number of psychotropic medication administrations among Groups G and S stratified by CYP2D6 functional status. **(A)**: Number of psychotropic medication among Groups G and S in poor metabolizers. **(B)**: Number of psychotropic medication among Groups G and S in intermediate metabolizers. **(C)**: Number of psychotropic medication among Groups G and S in normal metabolizers. **(D)**: Number of psychotropic medication among Groups G and S in ultra-rapid metabolizers.

in the Takahasi study were older (median age: 49 years) and followed over a period of 9 years. In another study, Berges. (2015) found that older patients with greater severity of depressive symptoms were at higher risk for re-admission. Kompella et al. (2021) reported that older age, race (Caucasians versus Blacks and Latinos), and medication non-adherence increased the risk of readmission. Our sub-analysis supports similar findings of higher RAR among Whites who were older. Furthermore, a greater proportion of White patients compared to Blacks and Latinos in our sub-analysis had a diagnosis of MDD recurrence at admission, potentially contributing to the higher RAR and LOS observed among Whites.

## Number of Psychotropic Medication Administrations

Majority of the medications used for treatment of depression are metabolized by CYP450 enzymes, specifically, CYP2D6 and CYP2C19 (Brøsen, 2004). CYP2D6 is a highly polymorphic enzyme metabolizing approximately 25% of commonly used medications (Whirl-Carrillo et al., 2021) and up to 80% of psychotropic medications (Panza et al., 2016). A patient's CYP2D6 phenotype can influence response to treatment with medications which are major CYP2D6 substrates. Our sub-analysis included patients with a LOS >3 days and who were treated with major CYP2D6 substrates. Overall, fewer patients were administered major CYP2D6 substrates in group G compared to group S with this finding particularly reflective of PMs. This is consistent with Ruaño et al. (2021) reporting PGx guided therapy to reduce the use of major CYP2D6 substrates in patients with MDD, especially, for patients who had CYP2D6 sub-functional status. Unlike Ruaño study 2021, our sub-analysis accounted for UMs and used the standardized genotype to phenotype classification for CYP2D6. In our sub-analysis, no differences were observed for UMs related to administration of major CYP2D6 substrates between groups G and S. It is possible that therapeutic guidance, interventions made by prescribers, and treatment outcomes including LOS and RAR may have appeared differently had reclassification of UM status been used previously in the original CYP-GUIDES trial. Latinos and Whites appeared to use more psychotropics compared to Blacks. This may be attributed to potentially greater severity of diagnoses requiring treatment augmentation in these former race/ethnic populations.

## Limitations

Our sub-analysis is not without limitations. The original CYP-GUIDES dataset did not include patient comorbid conditions, other concurrent non-psychotropic medications and socio-economic status (for example-insurance coverage) which could be considered confounding factors influencing treatment outcomes (Tortora et al., 2020; Ghosh et al., 2021). The study was also conducted at only one facility. Although majority of antidepressants are metabolized by CYP2C19 and CYP2D6 (Budhwani et al., 2015), only CYP2D6 genotyping was conducted during the CYP-GUIDES trial. Broader PGx testing information involving CYP2C19 or panel-based testing including additional pharmacokinetic and pharmacodynamic markers from patients in the CYP-GUIDES trial could have provided even more targeted therapeutic guidance to ensure rationale

prescribing of psychotropics for management of MDD. Therefore, our analyses cannot be generalized to all patients with depression. Both diagnosis and race/ethnicity were also self-reported by patients. Self-reporting of ethnicity may be a limitation as it may not be a true reflection of the true genetic composition of individuals (Mersha and Abebe, 2015). One potential confounder that we did not account for was phenoconversion. This potential confounder involving drug-drug interactions can ultimately influence the prevalence of DGIs and treatment response. For example, concomitant administration of medications such as bupropion, fluoxetine and paroxetine which are CYP2D6 inhibitors could result in an adjusted CYP2D6 phenotype that is different to genotype-based prediction of drug metabolism (Owen et al., 2009; Cicali et al., 2021; Hahn and Roll, 2021). Another limitation in our sub-analysis includes the small number of patients restricting additional data analyses related to RAR and race/ethnicity (Ruaño et al., 2020). The reader is encouraged to review other operational limitations suggested in the original CYP-GUIDES trial that could be considered for evaluation in future study.

## CONCLUSION

Using a reclassified definition of AS of CYP2D6 phenotype from genotype, we observed greater representation of UMs than previously reported in the CYP-GUIDES trial, especially, in Latinos. Given the dynamic, budding field of PGx, this step of pharmacovigilance demonstrates the importance of using standardized reporting to guide therapeutic interventions involving psychotropic medications metabolized by CYP2D6. Therapeutic guidance, interventions made by prescribers, and treatment outcomes including LOS and RAR may have reflected differently had a standardized reclassification of UM status been used in the original CYP-GUIDES trial. Future evaluation of the CYP-GUIDES data related to the impact of phenoconversion is warranted.

## DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://data.mendeley.com/datasets/25yjwbphn4/1.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

Writing of original manuscript draft and data analyses was completed by NK, and writing, editing and review of manuscript was completed by RDC.

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# Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study

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Drug-resistant tuberculosis (DR-TB) management is often linked with a higher rate of adverse drug reactions (ADRs) needing effective and timely management of these ADRs, which, if left untreated, may result in a higher rate of loss to follow-up of drug-resistant patients.

**Study objective:** The study was aimed at prospectively identifying the nature, frequency, suspected drugs, and management approaches for ADRs along with risk factors of ADRs occurrence among DR-TB patients at Nishtar Medical University, Hospital, Multan, Pakistan.

**Materials and Methods:** The prospective study included all the DR-TB patients enrolled for treatment from January 2016 to May 2017 at the study site**.** Patients were evaluated for the treatment-induced ADRs as per standard criteria of the National Tuberculosis Program, Pakistan. Multivariate logistic regression was used to assess the independent variables associated with the occurrence of ADRs.

**Results:** Out of 271 DR-TB patients included in the final analysis, it was observed that 55 patients (20.3%) experienced at least three ADRs. A total of 50 (18.5%) patients experienced zero adverse effects, while 15 (5.5%), 33 (12.2%), and 53 (19.6%) patients experienced one, two, and four ADRs, respectively. Gastrointestinal disturbances (66.7%), nervous system disorders (59.4%), and electrolyte disturbances (55.7%) remained the highest reported ADRs during therapy, followed by arthralgia (49.1%), ototoxicity (24%), pruritic reactions/rash (12.9%), dyspnoea (12.5%), and tinnitus (8.8%). Pulmonary cavitation at the baseline visit (*p*-value 0.001, OR 3.419; 95% CI (1.694–6.902) was significantly associated with the occurrence of ADRs among DR-TB patients.

**Conclusion:** The frequency of ADRs was high among the study cohort; however, these were managed effectively. Patients with recognized risk factors for ADRs occurrence need continuous clinical management efforts.

**Keywords: adverse drug reactions, frequency, management, drug-resistance tuberculosis, Pakistan**

## INTRODUCTION

Tuberculosis (TB), an infectious malaise, has been considered the 13th leading cause of mortality and the second leading infectious killer after COVID-19 around the globe (Cohen, 2021; WHO, 2021). TB is a curable and preventable disease, but the inability to diagnose, delayed diagnosis, malpractices, and irrational use of anti-TB drugs lead to the emergence of drug-resistant tuberculosis (DR-TB) (Pritchard et al., 2003; WHO, 2015). According to the WHO global tuberculosis report in 2021, based on the estimated incidence of TB and DR-TB cases per year, Pakistan stands fifth in terms of drug-susceptible tuberculosis (DS-TB) and fourth in terms of DR-TB (WHO, 2020; WHO, 2021). The emergence of resistant strains of *Mycobacterium tuberculosis* (the causative pathogen for TB) against isoniazid and rifampicin is the main cause of DR-TB over the past decade (Günther, 2014). DS-TB can be effectively treated with first-line anti-TB drugs (FLDs), including isoniazid, rifampicin, ethambutol, and pyrazinamide, while DR-TB treatment requires a broader combination of second-line anti-TB drugs (SLDs), which include fluoroquinolones (levofloxacin and moxifloxacin) and aminoglycosides (amikacin, kanamycin, and capreomycin). Other core SLDs include ethionamide, prothionamide, cycloserine, linezolid, and clofazimine. Add-on drugs include bedaquiline and delamanid. FLDs which retain sensitivity against TB microbe may also be included in the therapeutic regimen (Falzon et al., 2017).

Compliance with treatment guidelines and good microbial diagnosis are considered the main factors for successful treatment outcomes among DR-TB patients. Anti-TB SLDs are not only less effective, more noxious, and costly as compared to FLDs (Basit et al., 2014) but are also linked to more frequent and incurable ADRs. An ADR is defined as "a response to a drug which is noxious and unintended, which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or modification of physiological functions" (WHO, 1972). The nature and frequency of ADRs vary among patients when treated with anti-TB drugs which may result in morbidity and mortality if not detected earlier during treatment (Forget and Menzies, 2006; Gülbay et al., 2006; Tan et al., 2007).

Most of the ADRs that occur are minor and mild in nature and can be managed without the modification or termination of the regimen. Few may pose a serious threat to life, requiring hospitalization or even mortality risk, compelling for modification or termination of drug regimen. Factors that may contribute to the occurrence of ADRs range from socio-demographic background to the clinical status of the patients (Edwards and Aronson, 2000). The most common ADRs on SLDs used in published literature include drug-induced hepatitis, psychotic and gastrointestinal disturbances, homeostasis fluctuations, nephrotic disorders, neuropathy, arthralgia, skin allergies, and ototoxicity (WHO, 2012; Avong et al., 2015; Falzon et al., 2017). In this context, the National Tuberculosis Program (NTP), Pakistan, and WHO recommend early identification and management of ADRs among DR-TB patients (NTP, 2017; WHO, 2019).

Programmatic management of drug-resistant tuberculosis (PMDT) was initiated in Pakistan in 2010, with 33 PMDT sites currently functional throughout the country. Few studies, to date, have reported the frequency and nature of ADRs among DR-TB patients in Pakistan (Ahmad et al., 2018; Javaid et al., 2018; Atif et al., 2022). This is the first prospective study about the frequency, management, and evaluation of risk factors for ADRs occurrence at the present site, Nishtar Medical University (NMU) Hospital, Multan, Pakistan.

## METHODOLOGY

### Study Setting

The study was conducted at the PMDT unit of NTP, Pakistan, established at the pulmonology ward, NMU, Multan, Pakistan. The pulmonology ward provides free of cost health care to DS-TB and DR-TB patients under the supervision of medical specialists (pulmonologists), pharmacists, psychologists, treatment coordinators, nurses, and other support staff. A fully equipped pathology referral laboratory at NMU provides all the necessary diagnostic services, such as smear microscopy and Xpert-MTB/RIF. The radiology and pathology department of NMU provides services to DR-TB patients on a daily basis. Drug susceptibility testing (DST) samples are referred to the national referral laboratory in Islamabad, Pakistan.

### Study Design

This was a prospective observational study of all the DR-TB confirmed patients enrolled at the study site from January 2016 to May 2017. Patients enrolled for treatment from September 2016 and onwards were followed prospectively from the baseline visit till the treatment outcome was met, while patients enrolled before September 2016 were followed retrospectively till august 2016 and then prospectively. Resistance to rifampicin is also considered multidrug resistance (MDR) and is the pre-requisite for the 18-month DR-TB treatment post sputum culture conversion with SLDs (NTP, 2014a; Ullah et al., 2016; WHO, 2019). Exclusion criteria of the study were age less than 18 years, pregnancy, and patients with intellectual disability. Participants' marital status was categorized into married and unmarried groups as cohabitation is not in line with the cultural norms of the current study population. Baseline weight was categorized as less than 40 kg and equal to or more than 40 kg. A weight equal to or more than 40 kg has been associated with the occurrence of ADRs among DR-TB patients (Ahmad et al., 2018; Atif et al., 2022). Baseline age was categorized into three age categories (18–35, 36–50, and more than 50 years). It has been reported that age more than 50 years in Pakistan is more prone to disability or disease (Qureshi, 2017). Ethical approval was granted by the institutional ethical review board (IRB) at NMU, Multan, after the evaluation of the research study. Patients' consent (written

or oral) to the use of anonymous clinical information was obtained at the initiation of the study.

## Treatment Protocol

Patients were treated as per national and WHO guidelines. The conventional treatment therapy for DR-TB, recommended by WHO in 2011, termed a long treatment regimen, was applicable during the study period. It was comprised of at least 8-month treatment of one injectable aminoglycoside (amikacin/kanamycin/capreomycin) +levofloxacin or moxifloxacin + ethionamide + cycloserine + pyrazinamide and 12-month treatment with levofloxacin + ethionamide + cycloserine + pyrazinamide. For any patients who had a previous history of SLD use or resistance, it was recommended to add Vit B6 and para-aminosalicylic acid to the already described regimen (Falzon et al., 2011; NTP, 2014b). In 2016, WHO recommended a shorter treatment regimen (STR) for 9–11-month treatment. However, transition to STR or all oral bedaquiline based treatment regimen was yet to start at the time of initiation of the study.

Sputum samples collected from the study cohort were evaluated by direct sputum smear microscopy (Zielh-Neelson stain) and Gene Xpert/Rif (Cepheid, Sunnyvale, CA, United States). With positive smear microscopy and rapid rifampicin resistance results, patients were directed for DR-TB treatment initiation with an empirical regimen, except for those with a previous history of fluoroquinolones, as recommended by the national guidelines for DR-TB (NTP, 2014b). After the availability of sputum culture and DST results against both FLDs and SLDs, study participants were switched to an individualized regimen based on a patient-specific resistance pattern. The aim was to have at least four likely effective SLDs with a maximum recommended daily dose. Complete blood count (CBC), serum electrolytes, liver function tests (LFTs), renal function tests (RFTs), random blood glucose tests, and uric acid tests were conducted on a monthly basis. Thyroid tests, hepatitis, and HIV screening were conducted at the initiation of therapy. Visual and audiometry tests were conducted on the recommendation of the clinician for some patients and were repeated when deemed necessary on the physician's judgment. All patients were treated free of cost on an ambulatory basis with a monthly support allowance and transportation charges.

ADRs were identified, recorded, and managed as recommended by NTP, Pakistan, criteria for PMDT sites (NTP, 2017). Patients were screened for any pre-existing symptoms before the initiation of therapy. As per PMDT protocol, the physician is required to closely monitor ADRs on a monthly basis. These may be patient-reported (subjective complaint of the sufferer), physician-observed (objective indication of disease by a health professional), or laboratory-confirmed. These were documented on the ADRs reporting form. National guidelines for PMDT were followed for the management of ADRs with medical judgement by the physician (NTP, 2014b). All patients were provided necessary education concerning drug use, compliance, possible ADRs, treatment regimen, and length of treatment. During each follow-up visit, patients were inquired about their symptoms and medication adherence. WHO operational definitions were followed regarding patient identification and diagnosis as given in **Table 1** (WHO, 2013).

## Data Collection

A standardized form was formulated for data incorporation about patients' demographics (age, gender, marital and residential status, and smoking), clinical history (previous TB history, length of disease, previous SLDs use, co-morbidities, lung cavitation, DST result, and resistance pattern), and baseline laboratory parameters (sputum grading and BMI) on a regular monthly basis. Patients, partially followed retrospectively, were examined from the complete patient record, including detailed laboratory parameters and ADRs reporting form with management. On each monthly visit, patients were closely monitored and evaluated for any anti-TB drug-induced ADRs by the physician and were recorded in the patients' pharmacovigilance form purposely formulated for DR-TB therapy induced ADRs documentation. ADRs that can be verified by any laboratory value or judged by the physician based on clinical criteria, self-observed or patient-reported, the occurrence of at least one abnormal laboratory value or episode/event was considered sufficient for defining ADR (WHO, 2014a). Symptomatic management with or without regimen modification was recorded. A detailed description of the ADRs definition is provided in **Table 2**.

## Statistical Analysis

Clinical data obtained were analyzed using SPSS 26, IBM Corp. for Windows™. Descriptive analysis was performed to describe study enrolled participants. For a continuous variable, mean and standard deviation were used, while frequencies and percentages were used for categorical variables. Regression analysis was used to evaluate the relationship between study participants and the occurrence of ADRs (dependent variable). Variables having $p < 0.05$ in univariate analysis were considered for multivariate binary logistic regression analysis to establish a possible link between the occurrence of ADRs and any affecting variable. Statistical significance was set to be $p < 0.05$.

# RESULTS

## Demographic Data

As per sample size calculation, 246 patients were calculated based on the DR-TB incidence rate in Pakistan in 2016. After including the 20% dropout criteria, the sample size was calculated to be 308 (USM, 2017). Excluded patients included five pregnant women at the start of the study, 31 patients less than 18 years old, and one patient with an intellectual disability, thus making the total sum of 37 participants. The remaining 271 patients, who had met their final treatment outcome, whether successful (cured and completed) or unsuccessful (died, failed, or defaulted), were included in the study.

**TABLE 1 |** Operational definitions.

| Terms | Operational definitions |
|---|---|
| Mono-drug resistant TB | TB patients are non-responsive to a single anti-TB drug other than H and R in FLDs |
| Poly-drug resistant (PDR) TB | TB patients are non-responsive to more than one FLDs, not including H and R |
| Rifampicin resistant (RR) TB | TB patient non-responsive to R only |
| Multidrug resistant TB (MDR-TB | TB patient non-responsive to both H and R |
| Extensive drug-resistant TB (XDR-TB) | TB patient non-responsive to any FQs and any of the injectable SLDs (Am, Km, and Cm) in addition to H and R |
| Cured | DR-TB patient completes the TB treatment without any sign of therapy failure and obtains at least five consecutive negative sputum cultures in the final treatment year taken a month apart |
| Treatment completed | DR-TB patient completes the TB treatment with inadequate bacteriological results (less than five negative cultures in the final year of treatment) but without any sign of therapy failure |
| Died | DR-TB patient expires during the period of TB treatment |
| Treatment failed | DR-TB patient obtains two or even more positive cultures out of the five cultures during the last year of therapy or if there is a lack of improvement in therapeutic response |
| Defaulted | A gap of two or more consecutive months in the treatment of a DR-TB patient due to non-medical reasons |
| Successful outcomes | Cured or treatment completed |
| Unsuccessful outcomes | Died or treatment failed or defaulted |
| Married | Legally recognized union between people called spouses |
| Unmarried | Without any legally recognized union |

*TB, tuberculosis; FLDs, first-line anti TB drugs; SLDs, second-line anti TB drugs; H, isoniazid; R, rifampicin; FQs, fluoroquinolones; Am, amikacin; Km, kanamycin; Cm, capreomycin.*

**TABLE 2 |** Adverse drug reactions.

| Adverse drug reactions (ADRs) | Definition |
|---|---|
| Allergic skin reaction | Any skin change characterized by pruritis, rash, acne, or photosensitivity reported by the patients and cross-examined by the physician for possible anti-TB drugs effects |
| Anemia | At least 1 serum hemoglobin value <13 g/dl (male) or <11.5 g/dl (female)* |
| Arthralgia | Joint pain reported by the patients and recorded by the physician with or without arthritis |
| Body pain and headache | As reported by the patients |
| Dyspnoea | Any difficulty in breathing as reported by the patients and evaluated by the physician |
| Gastrointestinal disturbances | Any case of gastritis, nausea, vomiting, abdominal pain, or diarrhea reported by the patients or documented by the physician |
| Gynecomastia | Consistent and painful enlargement of breast documented by the physician for possible anti-TB drug effects |
| Hemoptysis | Spitting of blood with cough as reported by the patients and documented by the physician |
| Hepatotoxicity | In the absence of symptoms, at least 1 elevated serum value of transaminase or bilirubin five times higher than the upper normal value or three times higher in case of symptoms |
| Hypothyroidism | At least 1 increased serum TSH value >10 IU/ml* |
| Hypokalemia | 1 serum potassium value <3 mmol/L* |
| Hyperuricemia | At least 1 serum increased value of uric acid >9 mg/dl* |
| Nephrotoxicity | At least 1 serum creatinine value >130 μmol/L* |
| Ototoxicity | Hearing loss or tinnitus as reported by the patients and confirmed by audiometry or clinician examination |
| Peripheral neuropathy | Symptoms linked with numbness or burning sensation of extremities as reported by the patients and evaluated by the physician |
| Psychiatric disturbances | Any cases of depression or psychosis evaluated by a psychologist or psychiatrist |
| Sleep disturbances | As reported by the patients and documented by the physician |
| Swelling | Evaluated by the physician by physical examination |
| Vertigo and dizziness | As reported by the patients and evaluated by the physician |
| Visual disturbances | DIFFICULTY in vision as reported by the patients |

*Normal Ranges: Alanine aminotransferases (ALT) = up to 41 U/L; Bilirubin total = Up to 1.2 mg/dl; serum creatinine = 0.74–1.35 mg/dl; Hemoglobin (Hb) Male (13–18) g/dl Female (11.5–16.5) g/dl.*

## Patients' Characteristics and Frequency of Adverse Drug Reactions

Males ($n$ = 139) and females ($n$ = 132) were nearly in an equal proportion in the study. The mean age of all the participants was 36.75 (SD = 15.69) years. The mean baseline body weight was 45.44 (SD = 11.61) kg. Non-smoker patients ($n$ = 248, 88.6%) constituted the major proportion of the study. Most of the participants were married ($n$ = 195, 72%). Rural and urban participants were 131 (48.3%) and 140 (51.7%), respectively. The illness duration for nearly half of the study participants (53.5%) before DR-TB diagnosis was between 6–12 months. Most of the patients weighed less than 40 Kg. Half of the patients (56.8%) had bilateral lung cavitation at the baseline visit. None of the patients had positive HIV status. DR-TB cases, in the current study, used an average of 5 (4–9) most likely effective drugs in the intensive phase of treatment, while an average of 6.38 (5–12) anti-TB drugs throughout the treatment. The median

**TABLE 3 |** Patients' characteristics and frequency of ADRs.

| Characteristics | | Adverse drug reactions *n* (%) | |
|---|---|---|---|
| | ***n* (%)** | **Yes (*n* = 220)** | **No (*n* = 51)** |
| Gender | | 221 (81.2) | 51 (18.8) |
| Male | 139 (51.3) | 111 (79.9) | 28 (20.1) |
| Female | 132 (48.7) | 109 (82.6) | 23 (17.4) |
| Age (years) (Mean ± SD = 36.75 ± 15.69) | | | |
| 18–35 years | 139 (51.3) | 122 (87.8) | 17 (12.2) |
| 36–50 years | 80 (29.5) | 62 (77.5) | 18 (22.5) |
| >50 years | 52 (19.2) | 36 (69.2) | 16 (30.8) |
| Patient weight at baseline (kg) (Mean ± SD = 45.44 ± 11.61) | | | |
| <40 kg | 188 (69.4) | 153 (81.4) | 35 (18.6) |
| ≥40 kg | 83 (30.6) | 67 (80.7) | 16 (19.3) |
| Marital Status | | | |
| Unmarried | 76 (28) | 70 (92.1) | 6 (7.9) |
| Married | 195 (72) | 150 (76.9) | 45 (23.1) |
| Residence | | | |
| Rural | 131 (48.3) | 108 (82.4) | 23 (17.6) |
| Urban | 140 (51.7) | 112 (80) | 28 (20) |
| Smoking history | | | |
| Non-smoker | 240 (88.6) | 194 (80.8) | 46 (19.2) |
| Active and ex-smoker | 31 (11.4) | 25 (80.6) | 5 (19.4) |
| Duration of illness prior to DR-TB diagnosis | | | |
| Less than 6 months | 74 (27.3) | 64 (86.5) | 10 (13.5) |
| 6–12 months | 145 (53.5) | 117 (80.7) | 28 (19.3) |
| 1–2 years | 37 (13.7) | 27 (73) | 10 (27) |
| More than 2 years | 15 (5.5) | 12 (80) | 3 (20) |
| Treatment category | | | |
| New | 38 )14 | 32 (84.2) | 6 (15.8) |
| Relapse | 6 (2.2) | 3 (50) | 3 (50) |
| Treatment after failure | 198 (73.1) | 161 (81.3) | 37 (18.7) |
| Treatment after loss to follow-up | 26 (9.6) | 22 (84.6) | 4 (15.4) |
| Others | 3 (1.1) | 2 (66.7) | 1 (33.3) |
| Previous TB treatment | | | |
| Yes | 233 (86.3) | 188 (80.7) | 45 (19.3) |
| No | 37 (13.7) | 31 (83.8) | 6 (16.2) |
| Resistance to All FLDs | | | |
| Yes | 14 (5.2) | 12 (85.7) | 2 (14.3) |
| No | 257 (94.8) | 208 (80.9) | 49 (19.1) |
| Previous use of SLDs | | | |
| Yes | 17 (6.5) | 12 (70.6) | 5 (29.4) |
| No | 244 (93.5) | 198 (81.1) | 46 (18.9) |
| Resistance to any SLDs | | | |
| Yes | 71 (26.2) | 57 (80.3) | 14 (19.7) |
| No | 200 (73.8) | 163 (81.5) | 37 (18.5) |
| Co-morbidity | | | |
| Yes | 45 (16.6) | 38 (84.4) | 7 (15.6) |
| No | 226 (83.4) | 182 (80.5) | 44 (19.5) |
| Patients' family TB history/status | | | |
| No TB | 251 (92.6) | 206 (82.1) | 45 (17.9) |
| DS-TB | 14 (5.2) | 11 (78.6) | 3 (21.4) |
| DR-TB | 6 (2.2) | 3 (50) | 3 (50) |
| Hemoglobin level at baseline | | | |
| Normal | 64 (27) | 56 (87.5) | 8 (12.5) |
| Less than normal | 173 (73) | 150 (86.7) | 23 (13.3) |
| Baseline sputum grading | | | |
| Negative | 22 (8.1) | 18 (81.8) | 4 (18.2) |
| Scanty[a], +1[b] | 134 (49.4) | 107 (79.9) | 27 (20.1) |
| +2[c], +3[d] | 115 (42.4) | 95 (82.6) | 20 (17.4) |
| Lung cavitation at baseline | | | |
| No cavitation | 50 (18.5) | 30 (60) | 20 (40) |
| Unilateral cavitation | 67 (24.7) | 62 (92.5) | 5 (7.5) |
| Bilateral cavitation | 154 (56.8) | 128 (83.1) | 26 (16.9) |
| Body mass index (BMI) | | | |
| Underweight | 41 (15.1) | 31 (75.6) | 10 (24.4) |
| Normal | 77 (28.4) | 66 (85.7) | 11 (14.3) |

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**TABLE 3 |** (*Continued*) Patients' characteristics and frequency of ADRs.

| Characteristics | | Adverse drug reactions *n* (%) | |
|---|---|---|---|
| | ***n* (%)** | **Yes (*n* = 220)** | **No (*n* = 51)** |
| Overweight | 153 (56.5) | 123 (80.4) | 30 (19.6) |
| Patient resistance category | | | |
| RR only | 134 (49.4) | 110 (82.1) | 24 (17.9) |
| PDR | 1 (0.4) | 1 (100) | 0 |
| MDR | 128 (47.2) | 104 (81.3) | 24 (18.8) |
| XDR | 8 (3) | 5 (62.5) | 3 (37.5) |
| Treatment outcome category | | | |
| Cured | 187 (69) | 182 (82.7) | 5 (9.8) |
| Died | 48 (17.7) | 29 (60.4) | 19 (39.6) |
| Failed | 2 (0.7) | 2 (100) | 0 |
| Loss to follow-up (defaulted) | 34 (12.5) | 7 (20.6) | 27 (79.4) |

*FLDs, first-line anti-TB drugs; SLDs, second-line anti-TB drugs; DS-TB, drug-susceptible TB; DR-TB, drug-resistant TB; kg, kilogram; SD, standard deviation.*
[a]*1–9 Acid-fast bacilli (AFB)/100 high power field (HPF).*
[b]*10–99 AFB/100HPF.*
[c]*1–9 AFB/HPF.*
[d]*>9 AFB/HPF.*

**TABLE 4 |** Drugs used along with daily dose and frequency of patients receiving each drug.

| Group | Drugs | Recommended dose (mg/kg of body weight) | Frequency of patients receiving each drug *n* (%) |
|---|---|---|---|
| Group 1 FLDs | H | 16–20 once daily (Max dose 1,500 mg) | 0 |
| | E | 25 once daily (Max dose 2,000 mg) | 73 (26.9) |
| | Z | 30 to 40 | 269 (99.3) |
| Group 2 injectable anti-TB drugs | Am | 15 to 20 | 249 (91.9) |
| | Cm | 15 to 20 | 35 (12.9) |
| | Km | 15 to 20 | 0 |
| | S | 12–18 once daily (Max dose 1,000 mg) | 1 (0.4) |
| Group 3 fluoroquinolones | Lfx | 7.5 to 10 | 241 (88.9) |
| | Mfx | 7.5 to 10 | 33 (12.2) |
| Group 4 oral bacteriostatic SLDs | Eto | 15 to 20 | 271 (100) |
| | Pto | 15 to 20 | 0 |
| | Cs | 15 to 20 | 271 (100) |
| | PAS | 150 (Max dose 8–12 g) | 236 (87.1) |
| | Cfz | 100 mg once daily | 19 (7) |
| | Lzd | 600 my once daily | 19 (7) |
| | Bdq | 400 mg once daily for 2 weeks and then 200 mg three times per week | 1 (0.4) |
| Group 5 anti-TB drugs with limited data available on the efficacy | Amx/Clv | 1,500/375 mg daily | 12 (4.4) |
| | Clr | 1,000 mg once daily | 8 (3) |

*H, isoniazid; E, ethambutol; Z, pyrazinamide; Cs, cycloserine; Eto, ethionamide; PAS, para-amino salicylic acid; Am, amikacin; Cm, capreomycin; Km, kanamycin; S, streptomycin; Lfx, levofloxacin; Mfx, moxifloxacin; Pto, prothionamide; Cfz, clofazimine; Bdq, bedaquiline; Amx, Amoxicillin; Clv, Clavolonate; Lzd, linezolid; Clr, clarithromycin.*

length of injectable administration was nine months (range 4–14), and the median length of DR-TB treatment was 20 months (range 1–32). Successful treatment outcome (cured and completed) was noted for 187 (69%), while unsuccessful treatment outcome was observed for 48 (17.7%) died, 34 (12.5%) defaulted, and 2 (0.7%) treatment failure. A detailed description of the patient's socio-demographic characteristics and clinical history has been provided in **Table 3**.

## Patients' Treatment Regimen

Most of the patients were administered at least four or more likely effective drugs in the intensive phase. Patients were kept on empirical therapy until the availability of DST results. After the availability of DST results, an individualized regimen was started. The detail of drugs used, along with daily doses and frequency of patients using each drug, has been described in **Table 4**.

**TABLE 5 |** Identification of suspected drugs, frequency, and management of ADRs among DR-TB patients (*n* = 271).

| Adverse drug reaction | Suspected drugs | ADR frequency (%) | Action taken | Modified RR/MDR-TB regiment | Type of Action taken | | |
|---|---|---|---|---|---|---|---|
| | | | | | Dose reduction | Temporary withdrawal | Permanent withdrawal |
| Gastrointestinal Disturbances | | 181 (66.7) | | | | | |
| Gastrointestinal upset | H, PAS, Cs, Eto | 146 (53.8) | Counselled and reassured. Patients were prescribed *PPI* along with *prokinetics* drugs. Medication was modified for one patient and was replaced with *Lzd* | PAS (1) | | | PAS (1) |
| Nausea and Vomiting | PAS | 29 (10.7) | Counselled and reassured. All patients were prescribed d*omperidone* along with *prokinetics* drugs. PAS dose was reduced in one patient | | PAS (1) | | |
| Diarrhea | PAS, H | 4 (1.47) | Patients were prescribed *diosmectite* powder | | | | |
| Hiccups | — | 1 (0.36) | The patient was prescribed *Baclofen* along with *PPI* | | | | — |
| Oral Ulcer | — | 1 (0.36) | The patient was prescribed *Lignocaine* gel and advised for use of mouthwash | | | | |
| Nervous System Disorders | Cs | 161 (59.4) | | — | — | — | — |
| Depression | Cs | 75 (27.6) | Counselled and prescribed *SSRI* antidepressants. The dose of *Vit B6* was also increased. The offending agent was withheld temporarily in one patient and dose was reduced in another patient | Cs (2) | Cs (1) | Cs (1) | — |
| Sleep disturbances | Cs | 48 (17.7) | All patients were counselled and prescribed *Benzodiazepines* | None | — | — | — |
| Psychosis | Cs | 27 (10) | All the patients were prescribed antipsychotic medication after referral to the psychiatry ward. 27 patients were prescribed *risperidon*e. The offending drug was temporarily and permanently stopped in two and one patient, respectively, and dose was reduced in one patient | Cs (5) | Cs (2) | Cs (2) | Cs (1) |
| Aggression | Cs | 5 (1.84) | Counselled and referred to the psychiatry ward. All patients were prescribed *Fluphenazine HCl* and *nortriptyline* | None | — | — | — |
| Visual disturbances | — | 4 (1.47) | Patients were counselled and were referred to an ophthalmologist. *Vit B6* dose was increased in all patients | None | | | |
| Memory loss | Cs | 2 (0.7) | The patients were prescribed a higher dose of *Vit B6* | None | — | — | — |
| Electrolyte disturbances | Am | 151 (55.7) | Patients were monitored and two patients were advised for potassium-rich food and a *potassium* supplement was added to two patients' treatment regimen due to Hypokalemia | None | | | |
| Arthralgia/ Hyperuricemia | Z, Cs, H | 137 (49.1) | Patients were prescribed *NSAIDs* for symptomatic relief. One patient was prescribed *Allopurinol* and dose of Z was reduced in another patient | Z (1) | Z (1) | | |

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**TABLE 5 |** (*Continued*) Identification of suspected drugs, frequency, and management of ADRs among DR-TB patients (*n* = 271).

| Adverse drug reaction | Suspected drugs | ADR frequency (%) | Action taken | Modified RR/MDR-TB regiment | Type of Action taken | | |
|---|---|---|---|---|---|---|---|
| | | | | | Dose reduction | Temporary withdrawal | Permanent withdrawal |
| Ototoxicity | Am, S | 65 (24) | Counselled. Am was replaced to Cm in 33 patients and dose was reduced in nine patients while use was withheld temporarily and permanently in one and three patients, respectively. Nine patients were kept without management as they had completed their injectable treatment and this ADR was subsided | Am (45) S (1) | Am (9) | Am (1) | Am (3) |
| Pruritis/Rash/ Acne | Am | 35 (12.9) | Counselling was provided to patients. *Antihistamine* and *hydrocortisone* therapy was prescribed along with the use of r | Skin emollients. *Fusidic acid* was prescribed for one patient. Two patients were prescribed *anti-acne* therapy | None | | |
| Dyspnoea | | 34 (12.5) | All patients were counselled and prescribed a *bronchodilator* | None | | | |
| Body Pain and Headache | | 27 (10) | All patients were counselled and prescribed *NSAIDs* | None | | | |
| Tinnitus | Am, Cm, Eto | 24 (8.8) | All patients were counselled and prescribed *Betahistine*. The Injection was stopped temporarily in one patient and advised on an alternate day in another patient | Cm (2) | Cm (1) | Cm (1) | — |
| Peripheral neuropathy | Cs | 14 (5.2) | All patients were counselled and prescribed *duloxetine* and *vit B6* dose was increased | None | | | |
| Anorexia | — | 7 (2.58) | All patients were prescribed *appetizers* and *multivitamins* | None | | | |
| Hypothyroidism | PAS | 5 (1.84) | All were counselled and prescribed *thyroxine*. Use of the offending agent was stopped in one patient and dose was reduced in another patient | PAS (2) | PAS (1) | | PAS (1) |
| Dizziness | Z, Cs | 4 (1.47) | Patients were counselled. The dose of *Vit B6* was increased in all patients. Z was advised to be taken on an alternate day in one patient. one patient was prescribed *Prochlorperazine*, and another patient was prescribed *Betahistine* | Z (1) | Z (1) | | |
| Hemoptysis | | 3 (1.1) | Patients were counselled. All three patients were prescribed *Tranexamic acid* | None | | | |
| Anemia | PAS | 2 (0.7) | Patients were counselled. One patient was prescribed for iron supplement and one patient was advised for blood transfusion along with the temporary withdrawal of the offending agents | PAS (2) | | PAS (2) | |
| Nephrotoxicity | Cm | 2 (0.7) | Patients were counselled and prescribed prednisolone along with the removal of the offending agent permanently in one patient and replaced with *Lzd* in another patient | Cm (2) | | | Cm (2) |

(Continued on following page)

**TABLE 5 |** (*Continued*) Identification of suspected drugs, frequency, and management of ADRs among DR-TB patients (*n* = 271).

| Adverse drug reaction | Suspected drugs | ADR frequency (%) | Action taken | Modified RR/MDR-TB regiment | Type of Action taken | | |
|---|---|---|---|---|---|---|---|
| | | | | | Dose reduction | Temporary withdrawal | Permanent withdrawal |
| Palpitations | | 2 (0.7) | Counselling was provided to the patients. *Beta-blockers* were prescribed | None | | | |
| Gynecomastia | | 2 (0.7) | *NSAIDs* were added to patients' treatment along with counselling | None | | | |
| Menstrual irregularities | Eto | 1 (0.36) | The patient was counselled and referred to a gynecologist | None | | | |
| Photosensitivity | Eto | 1 (0.36) | The patient was prescribed a higher dose of *Vit B6* | None | | | |
| Swelling | | 1 (0.36) | The patient was counselled and prescribed a *diuretic* | None | | | |

*H, isoniazid; Cs, cycloserine; Eto, ethionamide; PAS, para-amino salicylic acid; Z, pyrazinamide; Am, amikacin; Cm, capreomycin; S, streptomycin; NSAID, non-steroidal anti-inflammatory drugs; Lzd, linezolid; vit, vitamin.*

**TABLE 6 |** Univariate analysis of risk factors associated with adverse drug reactions.

| Variable | Odds ratio (95% CI) | *p*-value |
|---|---|---|
| Gender | | |
| Female | Referent | 0.567 |
| Male | 0.876 (0.454–1.542) | |
| Age (years) (Mean ± SD = 36.75 ± 15.69) | | |
| 18–35 years | Referent | **0.011** |
| 36–50 years | 0.48 (0.231–0.996) | **0.049** |
| >50 years | 0.314 (0.144–0.682) | **0.003** |
| Patient weight at baseline (kg) (Mean ± SD = 45.44 ± 11.61) | | |
| <40 kg | Referent | 0.898 |
| ≥40 kg | 0.958 (0.496–1.849) | — |
| Marital Status | | |
| Married | Referent | **0.006** |
| Unmarried | 3.5 (1.426–8.590) | |
| Residence | | |
| Rural | Referent | 0.607 |
| Urban | 0.852 (0.462–1.570) | |
| Smoking history | | |
| Non-smoker | Referent | 0.742 |
| Active and ex-smoker | 1.186 (0.431–3.263) | |
| Duration of illness prior to DR-TB diagnosis | | |
| Less than 6 months | Referent | 0.397 |
| 6–12 months | 0.653 (0.298–1.430) | 0.286 |
| 1–2 years | 0.422 (0.158–1.130) | 0.086 |
| More than 2 years | 0.625 (0.150–2.612) | 0.519 |
| Treatment category | | |
| New | Referent | 0.403 |
| Relapse | 0.188 (0.03–1.16) | 0.072 |
| Treatment after failure | 0.816 (0.318–2.093) | 0.672 |
| Treatment after loss to follow up | 1.031 (0.26–4.086) | 0.965 |
| Others | 0.375 (0.029–4.821) | 0.452 |
| Previous TB treatment | | |
| No | Referent | 0.655 |
| Yes | 0.809 (0.318–2.055) | |
| Resistance to All FLDs | | |
| No | Referent | 0.657 |
| Yes | 1.413 (0.306–6.521) | |
| Previous use of SLDs | | |
| No | Referent | 0.294 |

(Continued on following page)

**TABLE 6 |** (*Continued*) Univariate analysis of risk factors associated with adverse drug reactions.

| Variable | Odds ratio (95% CI) | *p*-value |
|---|---|---|
| Yes | 0.558 (0.187–1.661) | |
| Resistance to any SLDs | | |
| No | Referent | 0.822 |
| Yes | 0.924 (0.466–1.833) | |
| Co-morbidity | | |
| No | Referent | 0.541 |
| Yes | 1.312 (0.549–3.135) | |
| Patients' family TB history/status | | |
| No TB | Referent | 0.183 |
| DS-TB | 0.801 (0.215–2.989) | 0.741 |
| DR-TB | 0.218 (0.043–1.118) | 0.068 |
| Hemoglobin level at baseline | | |
| Normal | Referent | **0.028** |
| Less than normal | 2.023 (1.079–3.793) | |
| Baseline sputum grading | | |
| Negative | Referent | 0.855 |
| Scanty[a], +1[b] | 0.881 (0.275–2.817) | 0.83 |
| +2[c], +3[d] | 1.056 (0.322–3.455) | 0.929 |
| Lung cavitation at baseline | | |
| No cavitation | Referent | |
| Cavitation | 4.086 (2.067–8.076) | **0.00** |
| Body mass index (BMI) | | |
| Under weight | Referent | 0.386 |
| Normal | 1.935 (0.743–5.039) | 0.176 |
| Overweight | 1.323 (0.584–2.994) | 0.502 |

*SLDs, second line anti-TB drugs; DS-TB, drug susceptible TB; DR-TB, drug resistant TB; kg, kilogram; SD, standard deviation.*
[a]*1–9 Acid-fast bacilli (AFB)/100 high power field (HPF).*
[b]*10–99 AFB/100HPF.*
[c]*1–9 AFB/HPF.*
[d]*>9 AFB/HPF; FLDs, first-line anti-TB drugs.*
*Bold values means that p-value is significant.*

## Resistance Pattern Among Study Patients

Among all the patients, RR-TB, MDR-TB, XDR-TB, and PDR-TB patients constituted 134 (49.45%), 128 (47.23%), 8 (2.95%), and 1 (0.3%), respectively.

## Types of ADRs, Their Frequency, and Management

Among all the patients who were enrolled in the study, a total of 718 ADRs were observed. The occurrence and frequency of various ADRs were reported during the treatment. Gastrointestinal disturbances (66.7%), nervous system disorders (59.4%), and electrolyte disturbances (55.7%) remained the highest reported ADRs during therapy. These ADRs were followed by arthralgia (49.1%), ototoxicity (24%), pruritic reactions/rash (12.9%), dyspnoea (12.5%), and tinnitus (8.8%). A small number of patients reported some less frequent ADRs such as nephrotoxic, peripheral neuropathy, gynecomastia, menstrual cycle irregularities, memory loss, haemoptysis, visual disturbances, anaemia, anorexia, dizziness/vertigo, and photosensitivity. Life-threatening ADRs were not common. Arthralgia was associated with hyperuricaemia in only one patient out of 137. The majority of the ADRs reported were during the intensive phase and were managed with ancillary or symptomatic treatment. Identification of suspected drugs, frequency, and management of ADRs among DR-TB patients has been described in **Table 5**.

## Factors Associated With the Occurrence of Adverse Drug Reactions

The variables that emerged with possible association of occurrence of ADRs included age, being unmarried (*p*-value = 0.006) OR 3.5; 95% CI (1.426–8.590), hemoglobin level at baseline less than normal (*p*-value = 0.028) OR 2.023; 95% CI (1.079–3.793), and lung cavitation at baseline (*p*-value = 0.000) with OR 4.086; 95% CI (2.067–8.076) as mentioned in **Table 6**. When multivariate binary logistic regression was applied as given in **Table 7**, lung cavitation at baseline (*p*-value = 0.001) OR 3.419 (1.694–6.902) emerged as the only variable associated with the occurrence of ADRs.

# DISCUSSION

The emergence of drug resistance in TB has posed a global threat due to its infectious nature and is considered fatal. The complex combination of drug therapy with associated ADRs has made it quite difficult to efficiently manage patients. In the present study, 220 (81%) patients experienced ADRs. However, the majority of the ADRs were resolved with collective efforts of physician-led interventions combined with psychologist and family support, and none of the ADRs progressed to any permanent termination of therapy among study participants.

**TABLE 7 |** Multivariate analysis of risk factors for occurrence of adverse drug reactions.

| Variable | B | S.E. | OR (95% CI) | *p*-value |
|---|---|---|---|---|
| Age (18–35) years | | | Referent | 0.306 |
| 36–50 years | −0.067 | 0.443 | 0.935 (0.392–2.23) | 0.88 |
| >50) years | −0.618 | 0.457 | 0.539 (0.22–1.32) | 0.176 |
| Unmarried | 0.892 | 0.542 | 2.441 (0.844–7.061) | 0.1 |
| Baseline hemoglobin level | 0.499 | 0.342 | 1.648 (0.843–3.222) | 0.144 |
| Baseline lung cavitation | 1.229 | 0.358 | 3.419 (1.694–6.902) | **0.001** |

*Bold values means that p-value is significant.*

The frequency of ADRs in the current study was found to be in line with already published studies from Russia (73.3%) (Shin et al., 2007), Pakistan (72%) (Ahmad et al., 2018), Turkey (69%) (Törün et al., 2005), and India (57.6%) (Dela et al., 2017). A higher frequency was reported in a study where nearly all of the patients (99%) experienced at least one ADR (Ganiyu et al., 2021). The present study was supported by some other studies conducted in Latvia (79%) (Bloss et al., 2010), China (90.7%) (Zhang et al., 2017), Indonesia (70%) (Nilamsari et al., 2021), and Italy (89%) (Gualano et al., 2019). Likewise, three studies reported from Pakistan also reported the occurrence of ADRs ranging from 63% to 77% (Ahmad et al., 2018; Javaid et al., 2018; Atif, 2021). Contrary to already mentioned, studies from South Africa (38.9%), Ethiopia (51%) (Merid et al., 2019), and India (47%), where lower ADRs frequency was reported. The varying differences in the frequency of ADRs in reported studies may be due to differences in attitudes towards therapy, such as lack of treatment adherence, default rate, differences in opinions of patients and physicians with respect to ADRs reporting, ability to detect, drug use pattern, differences in a support program, early assessment, and management of ADRs (Li et al., 2014; Akshata et al., 2015a; Hoa et al., 2015; Kelly et al., 2016; Dela et al., 2017; Zhang et al., 2017; Prasad et al., 2019). Nutritional practices, geographic location, age, patient awareness, and nature of co-morbidity with DR-TB are some of the patient-relevant factors (Zhang et al., 2017; Merid et al., 2019). A lack of harmony regarding the ADRs reporting among patients and physicians was reported in one of the studies. Patients had reported more ADRs than those documented by the clinicians (Kelly et al., 2016). This reflected the perception differences about ADRs between physicians and patients. Another study reported the lack of provision of the required information about the regimen (Atif et al., 2016). Inadequate knowledge about drugs and drug-induced ADRs leads to patients' erroneous ADRs reporting (Partnership, 2015). The complex nature of the regimen with the presence of co-morbidity leads to a higher risk of ADRs occurrence, as widely reported in published literature (Furin et al., 2001; Mouton et al., 2016; Schaaf et al., 2016; Merid et al., 2019).

In our study, gastrointestinal disturbances [$n$ = 181 (66.7%)] appeared as one of the most reported ADRs. Our findings are consistent with the studies reporting prevalence ranging from 10 to 100% in various groups undergoing DR-TB treatment (Hoa et al., 2015; Ahmad et al., 2018; Furin et al., 2001; Lakhani et al., 2019; Ganiyu et al., 2021). These disturbances were reported with an incident rate of 32%, according to a meta-analysis of 28 studies comprising approximately 4000 DR-TB patients (Wu et al., 2016). Subgroup disturbances included gastritis (53%), nausea and vomiting (10.7%), diarrhea (1.47%), and a few cases of oral ulcers and hiccups. Similar findings with higher frequency were reported in studies reported from Pakistan (42%) (Ahmad et al., 2018), Ethiopia (59%) (Bezu et al., 2014), India (71%) (Akshata et al., 2015a), and Russia (75%) (Shin et al., 2007). Among all the patients who reported gastrointestinal disturbances, regimen modification was considered in only two patients. The suspected drug was replaced in one patient, and the dose of the suspected drug was reduced in the other. All other patients managed these ADRs with ancillary drugs comprising antiemetics, prokinetics, and proton pump inhibitors. Similar management was reported in another study conducted among MDR-TB patients in Pakistan (Ahmad et al., 2018). Even though gastrointestinal disturbances occur more frequently as compared to any other ADR, most patients need symptomatic therapy due to the mild to moderate nature of severity, thus avoiding termination of the causative agent (Nathanson et al., 2004; Carroll et al., 2012; Furin et al., 2001; Prasad et al., 2019).

Nervous system disorders were reported in 59.4% of the study cohort. Among these, depression (27.6%), sleep disturbances (17.7%), psychosis (10%), aggression (1.84%), visual disturbances (1.47%), and memory loss (0.7%) were reported. These findings are supported by similar findings reported in Pakistan (29%) (Ahmad et al., 2018) and Egypt (26.5%) (Elmahallawy et al., 2012). The psychiatric disorder prevalence was found to be in a range of 4% to 36% in individual studies among DR-TB patients (Furin et al., 2001; Hoa et al., 2015). Anti-TB drugs suspected of psychiatric complications include isoniazid, fluoroquinolones, ethionamide, and cycloserine (Carroll et al., 2012; WHO, 2014b; Gupta et al., 2020). Apart from ADRs, societal stigma attached to the disease, the length of therapy, financial problems, and any previous therapy experiences also severely affect patients (Tandon et al., 1980; Barnhoorn and Adriaanse, 1992; Kiecolt-Glaser and Glaser, 2002; Rajeswari et al., 2005; Furin et al., 2014). Reported studies have mentioned the usefulness of discontinuation of cycloserine in some patients (Prasad et al., 2016; Dela et al., 2017; Ahmad et al., 2018). The psychological and psychiatric disturbances of lesser severity can be managed by a specialized healthcare professional, social support, or by prescribing anti-depressants to DR-TB patients. In severe cases, the offending drug can be terminated or replaced with other alternatives (Gupta et al., 2020). In our research, cycloserine was suspected to be the main culprit drug. It was temporarily removed from therapy in two patients, whereas it was permanently removed for one patient diagnosed with psychosis. The dose was also reduced for one patient. The rest of the patients were managed with counselling and prescribing anti-psychotic drugs, which led to the resolution of psychosis in all patients. All patients (75) diagnosed with depression were counselled by a psychologist and were prescribed SSRIs. Cycloserine was withheld temporarily in one patient while the dose was reduced in another depression patient. One of the meta-analyses suggested for removal of cycloserine without compromising the treatment outcome among DR-TB patients and recommended clofazimine, fluoroquinolones, or bedaquiline

use if the DST results do not recommend otherwise (Lan et al., 2020).

Other frequently reported nervous system disorder was difficulty in sleeping. Around 17.7% of patients reported sleep disturbances. Similar findings were reported from a study held in Egypt (22.5%), while another study from Bangladesh reported 44% sleep disturbances (Ibrahim et al., 2017; Masuma et al., 2018). The differences in various studies may be attributed to the patient-reported versus physician-documented ADRs as reported in a study from the United States, where insomnia was the most common reported ADR (67%) by the patients, while clinicians documented only 2% of the sleep disturbances (Kelly et al., 2016). All patients were counselled and reassured for therapy continuation. Benzodiazepines were prescribed for sleep disturbances without the need for treatment modification.

Despite the higher frequency of electrolyte disturbances (55%), hypokalemia was diagnosed in only two patients who were advised for potassium-rich food and the addition of potassium supplements in their treatment regimen without causing any treatment modification. The low incidence of hypokalemia may be attributed to the aggressive and efficient management of DR-TB therapy with continuous monitoring.

Arthralgia was reported in 49% of the study participants with varying degrees of severity during anti-TB therapy (Wu et al., 2016; Sineke et al., 2019; Gupta et al., 2020; Tornheim et al., 2021). Similar findings of higher frequency were reported in studies conducted in Russia (47%) (Shin et al., 2007) and China (56.4%) (Zhang et al., 2017), whereas a lower incidence was reported in studies from Namibia (26%) (Sagwa et al., 2013) and Ethiopia (34%) (Bezu et al., 2014). Joint pain was among the most reported ADR while evaluating the health-related quality of life in the DR-TB cohort (Sineke et al., 2019). Bedaquiline, fluoroquinolones, streptomycin, ethambutol, and pyrazinamide are thought to be involved in arthralgia by causing hyperuricemia (Gerdan et al., 2013; Wu et al., 2016; Gupta et al., 2020; Lan et al., 2020). Joint pain developed during therapy subsides with non-steroidal anti-inflammatory drugs (NSAIDs), uric acid lowering agents, or taking sufficient rest (Gupta et al., 2020). In the current study, all the patients were prescribed *NSAIDs* for symptomatic relief. One patient was prescribed *Allopurinol*, and the dose of pyrazinamide was reduced in another patient.

Hearing loss was reported in 24% of the patients in the present study, which is in line with the already reported 28.3% incidence in a cohort of 12793 DR-TB patients. The occurrence of hearing loss was highest among patients using amikacin and lowest in patients using capreomycin (Wrohan et al., 2021). Similar findings were reported in studies conducted elsewhere (Wu et al., 2016). Higher dose per body weight on a monthly basis [adjusted odds ratio (aOR)] 1.15, 95% CI 1.04–1.28 and longer duration of amikacin (aOR1.98, CI 1.04–2.12) use are associated with the development of ototoxicity (Modongo et al., 2014). Amikacin was the causative agent for this disability of mild to moderate severity in the current study. Amikacin was replaced with capreomycin in thirty-three patients, and the dose was reduced in nine patients. Use was withheld temporarily and permanently in one and three patients, respectively. Nine patients were kept without management because they had completed their injectable treatment and the ADR subsided gradually. None of the patients developed any permanent loss.

Pruritis, rash, or acne was reported in 35 (12.9%) patients. Similar findings have been reported with varying frequencies ranging from 45% to 2.64% (Bezu et al., 2014; Akshata et al., 2015b; Rathod et al., 2015; Nagpal et al., 2018). Pyrazinamide and amikacin were suspected as the causative agents. Antihistamine and hydrocortisone therapy was prescribed with the use of skin emollients. Fusidic acid was prescribed for one patient. Two patients were prescribed anti-acne therapy.

Dyspnea was observed in 12.5% of the patient with mild to moderate severity. All patients were counselled and were prescribed bronchodilators. Tinnitus was reported by 9% of the patients. All patients were prescribed betahistine. Capreomycin was stopped temporarily in one patient and was advised to be taken on alternate days in another patient. Anemia was reported in two patients; one patient was prescribed an iron supplement, and the other was advised for blood transfusion along with the temporary withdrawal of para-amino salicylic acid.

Peripheral neuropathy was reported in a relatively small number (5.2%) of patients that adversely affects the daily quality of life. Higher frequency was reported in studies in Bangladesh (28%) (Masuma et al., 2018), Russia (13%) (Shin et al., 2003), and India (18.75%) (Tiwari et al., 2015). Comparable findings to the current study were reported from Pakistan (2.2%) (Ahmad et al., 2018). Anti-TB drugs such as linezolid, cycloserine, isoniazid, fluoroquinolones, SLDs, ethambutol, and ethionamide are blamed for peripheral neuropathy (Gupta et al., 2020). These drugs interfere with pyridoxine metabolism by various mechanisms (Ebadi et al., 1982; Cohen, 2001). In the present study, only cycloserine was suspected of causing neuropathy. Pyridoxine has been prescribed for the management of peripheral neuropathy along with a tricyclic antidepressant, usually amitriptyline. In cases of severity, one or more offending drugs were terminated or temporarily removed (Shin et al., 2007; Brust et al., 2013; Gupta et al., 2020). All patients were prescribed duloxetine for nerve pain and fibromyalgia. The dose of vitamin B6 was increased, and no modifications were made to the regimen.

Nephrotoxicity was not common in our study, with only 2 (0.7%) patients having toxic effects of anti-TB drugs as mentioned in the literature (Shin et al., 2007; Bezu et al., 2014; Furin et al., 2001; Ahmad et al., 2018). A study from Bangladesh reported an increased creatinine level among 3% of the DR-TB patients (Masuma et al., 2018). The most common nephrotoxic drug used for DR-TB treatment was capreomycin, followed by kanamycin and amikacin (Shibeshi et al., 2019). Patients were counselled and prescribed prednisolone along with the permanent removal of the offending agent in one patient and replacement with linezolid in another patient.

Hypothyroidism was also a less frequent observation (1.84%), and patients were counselled and were prescribed thyroxine. The use of para-amino salicylic acid was stopped in one patient, and the dose was reduced in another patient. Gynecomastia, menstrual cycle irregularities, haemoptysis, memory loss, visual disturbances, anorexia, dizziness/vertigo, and photosensitivity were some of the lower frequency ADRs in

this cohort. Encouragingly, no case of hepatotoxicity was reported in our cohort.

In our study, after statistical analysis, lung cavitation at the baseline was linked to the higher probability of ADRs among DR-TB patients. Patients with cavitation are at higher odds of developing ADRs than those without pulmonary cavitation, which is consistent with the findings already reported among DR-TB patients in Pakistan (Javaid et al., 2018). Identification of predictors for factors that may contribute to the probability of occurrence of ADRs can help to develop individual and focused monitoring plans, which may result in enhanced patient compliance and better disease management. The present study also found that successful outcomes had a significant correlation with the occurrence of ADRs. It is considered that patients may terminate therapy due to ADRs and sometimes may miss the dose of the suspected drug without informing the physician. The analysis of predictors for successful treatment outcomes was not in the scope of this study.

One of the limitations of our study is the absence of documentation of the severity of ADRs, which would have helped to assess ADR severity impact on the treatment outcome. Another limitation may be the absence of medication records for co-morbidities in patients having any co-morbidity. One of the key areas of ADRs reporting is discord between physicians and patients about certain ADRs, such as nausea, vomiting, dizziness, body pain, and headache (Kelly et al., 2016). The 69% treatment outcome of this study is quite below the WHO criterion of 75%; therefore, it is recommended to put all possible efforts into better and enhanced management of treatment plans, especially for loss to follow-up patients. Although this was the first prospective study at the current study site, it is emphasized to have multicenter prospective studies for better assessment of the treatment efficacy. Regular clinical monitoring and quality laboratory analysis along with multidisciplinary approaches are needed to avoid the unsuccessful outcomes.

## CONCLUSION

ADRs were highly prevalent in the current study but most of them were managed with pharmacological, non-pharmacological, and psychological approaches with limited modifications in treatment plan. The higher frequency of amikacin-related temporary hearing loss leading to the treatment modification among patients is of concern. This necessitates regular audiometry to avoid any permanent hearing loss. Fewer cases of replacement of suspected drugs with alternatives, without adversely impacting the treatment outcome were observed. Hence, it highlights the importance of individualized and continuous monitoring throughout the therapy.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethical Review Board (IRB) of Nishtar Medical University Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

AM: Data collection and preliminary drafting. SS: Supervision and draft review. NA: Supervision, manuscript design, analysis, and draft review. MS: Facilitator at the study center, review and supervision. AK: Project design, supervision, and draft review.

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# Implementation of *HLA-B*15:02* Genotyping as Standard-of-Care for Reducing Carbamazepine/ Oxcarbazepine Induced Cutaneous Adverse Drug Reactions in Thailand

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**Objective:** This study aimed to investigate the clinical impact of *HLA-B*15:02* pharmacogenomics (PGx) testing before carbamazepine (CBZ)/oxcarbazepine (OXC) prescriptions and to determine whether this PGx testing was associated with the reduction of CBZ/OXC-induced cutaneous adverse drug reactions (CADRs) in Thailand.

**Methods:** This retrospective observational cohort study was conducted by obtaining relevant *HLA-B*15:02* PGx-testing and clinical data from electronic medical records during 2011–2020. 384 patient data were included in this study to investigate the clinical decision on CBZ/OXC usage before and after the *HLA-B*15:02* PGx testing, and 1,539 patient data were included in this study to demonstrate the incidence of CBZ/OXC-induced SCARs and SJS between *HLA-B*15:02* tested and non-tested patients. To analyze and summarize the results, descriptive statistics were employed, and Fisher exact test was used to compare the clinical difference between the *HLA-B*15:02* positive and negative groups and to compare the differences of SCARs incidence.

**Results:** 384 patients were included in this study as per the inclusion criteria. Of these, 70 patients carried *HLA-B*15:02,* of which 63 and 65 patients were not prescribed with CBZ/OXC before and after the availability of genotyping results, respectively. In the remaining *HLA-B*15:02* non-carriers, 48, and 189 patients were prescribed CBZ/OXC before and after genotyping results were available, respectively. The findings of this study showed that

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the incidence of SCARs of CBZ/OXC was significantly lower ($p < 0.001$) in the *HLA-B*15:02* screening arm than in the non-screening arm.

**Conclusion:** *HLA-B* pharmacogenetics testing influenced the selection of appropriate AEDs. The presence of mild rash in the *HLA-B*15:02* negative group indicates that other genetic biomarker (*HLA-A*31:01*) and/or non-genetic variables are involved in CBZ/OXC-induced CADRs, emphasizing that CBZ/OXC prescriptions necessitate CADR monitoring. The hospital policy and clinical decision support (CDS) alert system is essential to overcome the barriers associated with the utilization of PGx guidelines into clinical practice.

**Keywords: carbamazepine, *HLA-B* risk alleles, pharmacogenomics, cutaneous adverse drug reactions, precision medicine**

## INTRODUCTION

Carbamazepine (CBZ) is a first-generation antiepileptic drugs (AEDs) used to treat a variety of neurological and psychiatric problems, including epilepsy, trigeminal neuralgia, and bipolar disorders. In Thais, there has been a well-documented association between *HLA-B*15:02* and CBZ-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Hung et al., 2006; Locharernkul et al., 2008; Tassaneeyakul et al., 2010; Tangamornsuksan et al., 2013; Sukasem et al., 2018; Sukasem et al., 2021b). In 2013, the government launched a policy requiring *HLA-B*15:02* pharmacogenetic (PGx) testing before the start of CBZ in Bangkok as a pilot study (Department of Medical Sciences, 2013). Subsequently, national policy screening for *HLA-B*15:02* was reinforced by the National Health Security Office (NHSO) in 2018 throughout Thailand (Ang et al., 2017; Chang et al., 2020; Sukasem et al., 2021a; Jantararoungtong et al., 2021). Besides *HLA-B*15:02*, some other variants such as *HLA-B*15:08*, *HLA-B*15:11* and *HLA-B*15:21* may also affect the safety of CBZ and found to be other *HLA-B* risk *alleles* associated with CBZ-induced cutaneous adverse drug reactions (CADRs) (Jaruthamsophon et al., 2017; Volpi et al., 2018; Kloypan et al., 2021).

In addition, Chen et al. reported a strong association between the *HLA-B*15:02* allele and oxcarbazepine (OXC)-induced SJS/TEN in Chinese and Thai populations (Chen et al., 2017). Consequently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline recommended to avoid the prescription of CBZ and OXC in *HLA-B*15:02* carrier (Phillips et al., 2018).

Although knowledge and research on PGx testing in Thailand have been rapidly expanding in recent years (Jaruthamsophon et al., 2017), there has been no longitudinal research on the application of *HLA-B*15:02* genotype results in daily clinical practice, including documentation of severe cutaneous adverse drug reactions (SCARs) and new adverse drug reactions (ADRs) in electronic medical records, patterns of AEDs prescriptions based on genotype results, and assessment of the CADRs. This is the first research of its kind in Thailand, and it focuses on these fascinating topics.

The goal of this study was to investigate how PGx testing (*HLA-B*15:02*) affected the CBZ/OXC prescriptions and the reduction of CBZ/OXC-induced SCARs in Thais. The findings of this study have the potential to help physicians regarding the prescription of appropriate AEDs in clinical practice for those patients carrying *HLA-B*15:02* CBZ/OXC-risk alleles and to support NHSO Thailand's *HLA-B*15:02* screening as the national policy.

## METHODOLOGY

### Study Population

This was a retrospective cohort study conducted at the Ramathibodi Hospital of the Faculty of Medicine. In order to determine the influence of *HLA-B*15:02* PGx testing in clinical practice, 1,020 patients with performed *HLA-B*15:02* PGx testing between 2011 and 2020 were included. Among 1,020 patients, 636 patients were excluded due to incomplete data (n = 266), PGx tested for other AEDs (n = 51), repeated PGx order (n = 53), and less than 15 years of age (n = 266) (**Figure 1**). This study did not include *HLA-B* genotyping that was performed to test the association of drug induced CADRs. Subsequently, 384 patients were enrolled for analysis. Patients' demographic information, such as age, gender, diagnosis, and drug-related information, such as the number of CBZ prescriptions and their association to *HLA-B*15:02* genotyping results, CADRs types, drug allergic history, PGx testing, number of comorbidities, types of comorbidities, and alternative drugs utilized were recorded. All CADRs were diagnosed and confirmed by a dermatologist at Ramathibodi Hospital in Thailand.

To demonstrate how prospective *HLA-B*15:02* testing likely reduces the occurrence of hypersensitivity reactions to CBZ/OXC, we recruited 1,539 patients data who were prescribed CBZ/OXC for a period of 2013–2021 and further classified them as tested for *HLA-B*15:02* group or not tested for *HLA-B*15:02* group. We retrospectively collected CBZ/OXC prescribing data, *HLA-B*15:02* testing data, and SCARs occurrence data for this part of the study.

To exemplify the overall trend of *HLA-B*15:02* testing requests within and outside of Ramathibodi Hospital, we collected overall *HLA-B*15:02* PGx testing for CBZ/OXC that was performed during 2011–2020 and presented them in percentage as per year (**Figure 2**).

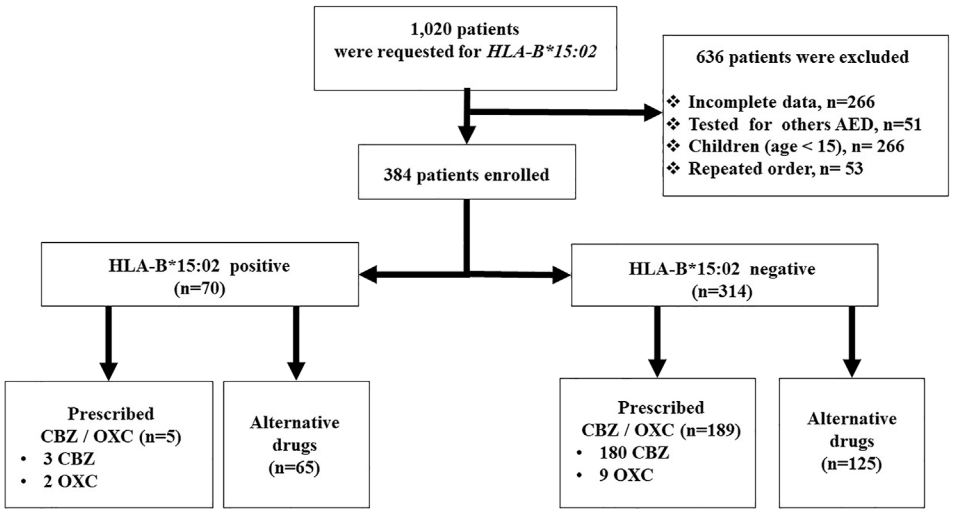


**FIGURE 1 |** The flowchart of patients recruitment and clinical decision in *HLA-B*15:02* positive (n = 70) and *HLA-B*15:02* negative (n = 314) in Ramathibodi Hospital, Bangkok.

The studies involving human participants were reviewed and approved by the Ethical Review Committee on Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University. The patients provided written informed consent to participate in this study.

## *HLA-B* genotyping

Genomic DNA samples were isolated from EDTA blood, using the MagNAprue Compact Nucleic Acid Isolation kits (Roche Applied Science, Mannheim, Germany). The quality of genomic DNA was measured by NanoDrop® ND-1000 (Thermo Scientific, Wilmington, United States). *HLA-B* alleles were analyzed by the polymerase chain reaction-sequence specific oligonucleotide probe (PCR-SSOP) assay and Luminex™ Multiplex Technology with well established protocols.

In brief, the DNA sample obtained from patients was amplified by polymerase chain reaction (PCR). The PCR product was then hybridized against a panel of sequence specific oligonucleotide probes on coated polystyrene microspheres that had sequences complementary to stretches of polymorphism within the target *HLA-B*. The amplicon-probe complex was then visualized using a colorimetric reaction and fluorescence detection technology by the Luminex®IS 100 system (Luminex Corporation, Austin, Texas, United States). Analysis of the *HLA* class I alleles were performed using HLA fusion software version 2.0 (One Lambda, Canoga Park, CA, United States). For each allele, the results were reported as either *HLA-B*15:02* positive or negative.

## Data Analysis

Descriptive statistics were employed to summarize and analyze the collected data. The Fisher exact test was used to compare the clinical characteristics of the *HLA-B*15:02* positive (positive group) and *HLA-B*15:02* negative (negative group) and to calculate the difference of the SCARs incidence between the *HLA-B*15:02* tested group and non-tested groups.

# RESULTS

## Patients Characteristics, Diagnosis, Comorbidities, Adverse Drug Reactions (ADRs), Drug Allergy

Out of 1,020 patients undertaking *HLA-B*15:02* genotyping tests during 2011–2020, only 384 patients were included as per the inclusion criteria in this study (**Figure 1**). Incomplete data (n = 266), tested for other AEDs (n = 51), Patients' data under the age of 15 (n = 266), and repeatedly requested data (n = 53) were excluded from this study. Our study population consists of 243 (63.28%) females and 141 (36.72%) males. The age range of this population was 15–95, with a mean age of 49.23 ± 19.79 (SD). Out of 384 patients, 112 (29.16%) were diagnosed with different types of epilepsy. The second most common disease for the CBZ indication was trigeminal neuralgia (n = 95, 24.74%). Neuropathic pain (n = 64, 16.67%), hemifacial spasm (n = 14, 3.65%), tonic spasm (n = 13, 3.39%), and bipolar disorder (n = 23, 5.99%) were the other commonly diagnosed diseases for which CBZ was prescribed in this study. Sixty-three cases were in miscellaneous categories (**Table 1**).

Comorbidities were discovered in 108 (28.12%) patients, 17 (17/70, 24.29%) of them were *HLA-B*15:02* positive and the remaining 91 (91/314, 28.98%) were *HLA-B*15:02* negative. The CBZ was prescribed in doses ranging from 50 to 800 mg, while the OXC was prescribed in doses ranging from 300 to 600 mg.

According to the findings, 36.46% (n = 140) of the patients had previous ADR history, while 18.49% (n = 71) had previously experienced CADRs. *HLA-B*15:02* positive patients had higher CADRs than *HLA-B*15:02* negative patients (18/70, 25.71% vs 53/314, 16.88%, $p = 0.09$), however, the difference was insignificant.

**TABLE 1 |** Patients characteristics, diagnosis, comorbidities, adverse drug reactions (ADRs), drug allergy.

| Parameter | Total | *HLA-B*15:02* Positive | *HLA-B*15:02* Negative | p-value[a] |
|---|---|---|---|---|
| Number of Patients (%) | 384 | 70 (18.23) | 314 (81.77) | |
| Age (year) | | | | |
| Range | 15–95 | 15–94 | 15–95 | - |
| Mean±SD | 49.23 ± 19.79 | 46.34 ± 20.25 | 49.89 ± 19.66 | - |
| Gender (%) | | | | |
| Male | 141 (36.72) | 32 (45.71) | 109 (34.71) | <0.0001[c] |
| Female | 243 (63.28) | 38 (54.29) | 205 (62.29) | |
| Diagnosis (%) | | | | |
| Epilepsy | 112 (29.16) | 20 (28.57) | 92 (29.30) | - |
| Trigeminal Neuralgia | 95 (24.74) | 18 (25.71) | 77 (24.52) | - |
| Neuropathic pain | 64 (16.67) | 14 (20.0) | 50 (15.92) | - |
| Hemifacial spasm | 14 (3.65) | 0 | 14 (4.46) | - |
| Tonic spasm | 13 (3.39) | 1 (1.43) | 12 (3.82) | - |
| Bipolar disorder | 23 (5.99) | 4 (5.71) | 19 (6.05) | - |
| Miscellaneous | 63 (16.40) | 13 (18.57) | 50 (15.92) | - |
| CBZ/OXC Dosage (mg) | CBZ50-800/OXC300-600 | CBZ200-800/OXC300-600 | CBZ 50–800/OXC300-600 | - |
| ADR History (%) | 140 (36.46) | 33 (47.14) | 107 (34.08) | 0.05 |
| CADRs and Non CADRs (%) | | | | |
| CADRs | 71 (18.49) | 18 (25.71) | 53 (16.88) | 0.09 |
| Non-CADRs | 69 (17.97) | 15 (21.43) | 54 (17.20) | - |
| CBZ/OXC prescription (%) | | | | |
| Prescribed | 194 (50.52) | 5 (7.14) | 189 (60.19) | <0.0001 |
| Not prescribed | 190 (49.48) | 65 (92.86) | 125 (39.81) | - |
| Comorbidities (%) | 108 (28.12) | 17 (24.29) | 91 (28.98) | 0.46 |
| Types of Comorbidities (%) | | | | |
| SLE | 9 (2.34) | 3 (4.29) | 6 (1.91) | - |
| RA | 3 (0.78) | 2 (2.86) | 1 (0.31) | - |
| CA | 15 (3.90) | 3 (4.29) | 12 (3.82) | - |
| HIV | 4 (1.04) | 1 (1.43) | 3 (0.96) | - |
| DM | 9 (2.34) | 2 (2.86) | 7 (2.23) | - |
| CNS infections | 6 (1.56) | 1 (1.43) | 5 (1.59) | - |
| Thyroid | 6 (1.56) | 1 (1.43) | 5 (1.59) | - |
| Others | 56 (14.58) | 4 (5.71) | 52 (16.56) | - |
| Past Drug Allergy (%) | 140 (36.46) | 33 (47.14) | 107 (34.08) | 0.05 |
| Other AEDs | 48 (12.50) | 13 (18.57) | 35 (11.15) | - |
| Other Drugs | 92 (23.96) | 20 (28.57) | 72 (22.93) | - |
| Past PGx testing (%) | 40 (10.42) | 4 (5.71) | 36 (11.46) | 0.06 |
| *B*13:01* | 14 (3.65) | 1 (1.43) | 13 (4.14) | - |
| *B*57:01* | 2 (0.52) | 1 (1.43) | 1[b] | - |
| *B*58:01* | 16 (4.17) | 1 (1.43) | 15 (4.78) | - |
| *B*35:05* | 9 (2.34) | 1 (1.43) | 8 (2.55) | - |
| Number of CADRs in CBZ/OXC used (%) | 21 (5.47) | 0 | 21 (6.69) | 0.01 |
| Mild | 19 (4.95) | 0 | 19 (6.05) | - |
| Severe | 2 (0.52) | 0 | 2 (0.64) | - |
| Number of non-CADRs in CBZ/OXC used (%) | 22 (5.73) | 0 | 22 (7.01) | 0.01 |

*CBZ, Carbamazepine; OXC, Oxcarbazepine; RA, Rheumatoid arthritis; HIV, Human immunodeficiency virus; SLE, Systemic Lupus Erythromatous; CA, Carcinoma; DM, Diabetes Mellitus; ADR, Adverse drug reactions; CADRS, Cutaneous adverse drug reactions; AEDs, Antiepileptic Drugs; PGx, Pharmacogenetic Testing; SD, Standard Deviation.*

[a]*p value calculated using fisher exact test*

[b]*one patient had 2 PGx testing history*

[c]*p value calculated between male and female.*

**TABLE 2 |** Clinical decision on CBZ/OXC usage before and after received the *HLA-B*15:02* PGx testing.

| Therapeutics | Before the *HLA-B*15:02* Testing | | | | After Received the *HLA-B*15:02* reports | | |
|---|---|---|---|---|---|---|---|
| | +ve (n = 70) | -ve (n = 314) | Total (n = 384) | Hold CD | +ve (n = 70) | -ve (n = 314) | Total (n = 384) |
| CBZ/OXC | 7 (10.00%) | 48 (15.29%) | 55 (14.32%) | 329 (85.67) | 5 (7.14%) | 189 (60.19%) | 194 (50.52%) |
| Alternative drugs | 63 (90.00%) | 266 (84.71%) | 329 (85.68%) | - | 65 (92.86%) | 125 (39.80%) | 190 (49.48%) |

*CD, Clinical Decision; CBZ, Carbamazepine; OXC, Oxcarbazepine; +ve, HLA-B*15:02 positive; -ve, HLA-B*15:02 negative.*

**TABLE 3 |** Cases of CBZ/OXC-induced SCARs and fixed drug eruption after received CBZ without PGx testing.

| Case | Gender | Age | *HLA-B* Genotype | ADRs type | Year of Report |
|---|---|---|---|---|---|
| 1 | F | 51 | *B*15:02/46:01* | SJS/TEN | 2013 |
| 2 | F | 32 | *B*15:02/44:03* | SJS/TEN | 2014 |
| 3 | M | 93 | *B*40:01/58:01* | DRESS | 2015 |
| 4 | M | 35 | *B*15:02/39:09* | SJS | 2015 |
| 5 | M | 64 | *B*15:02/58:01* | SJS | 2015 |
| 6 | F | 38 | *B*27:06/58:01* | DRESS | 2016 |
| 7 | F | 40 | *B*15:02/18:01* | SJS | 2016 |
| 8 | F | 43 | *B*15:02/46:01* | SJS | 2016 |
| 9 | F | 19 | *B*15:02/15:02* | SJS/TEN | 2017 |
| 10 | M | 23 | *B*15:02/15:25* | SJS | 2018 |
| 11 | M | 54 | *B*15:02/40:01* | TEN | 2018 |
| 12 | F | 57 | *B*15:02/46:01* | TEN | 2019 |
| 13 | F | 56 | *DNA not available* | FDE | 2019 |

*ADRs, Adverse drug reactions; CBZ, carbamazepine; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; SCARs, Severe cutaneous adverse drug reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.*

48 of the 384 patients had a prior history of AED allergy, with 18.57% (13/70) and 11.15% (35/314) belonging to the *HLA-B*15:02* positive and negative groups, respectively ($p = 0.05$).

## Clinical Decision on CBZ/OXC Usage Before and After the *HLA-B*15:02* PGx Testing

**Table 2** shows the status of a clinical decision on CBZ/OXC prescription. Because all of the patients were scheduled to receive CBZ/OXC therapy, *HLA-B*15:02* testing was performed as per the national policy. Out of 384 patients, the clinical decision on CBZ/OXC was put on hold for 85.67% of patients and requested the *HLA-B*15:02* testing prior prescription. Because of the clinical urgency, 55 patients were prescribed CBZ/OXC while the *HLA-B*15:02* testing was ordered. *HLA-B*15:02* carriers were found in 70 of the 384 cases. This accounts for 18.23% of the overall study population. Fortunately, CBZ was not prescribed in 63 of 70 patients with *HLA-B*15:02* carriers before the genotyping results were available; and after receiving the *HLA-B*15:02* results, CBZ/OXC was not prescribed in 65 of 70 patients. Only 48 patients in the negative group received CBZ/OXC before the *HLA-B*15:02* requested, but 189 patients with *HLA-B*15:02* negative were prescribed CBZ/OXC following the results available in the electronic medical record (EMRs) (**Table 2**). In this cohort, five patients were remain treated with CBZ/OXC-based regimen since they were received this regimen for longer than 3 months and had no CADRs. On the other hand, 189 patients in *HLA-B*15:02* negative group were administered CBZ/OXC as recommended. Surprisingly, 21 patients with negative *HLA-B*15:02* had CADRs, of which 2 patients (9.52%) were SCARs (one DRESS and one SJS cases) and 19 patients (90.48%) were mild rash. Non-CADRs were also observed in 22 patients with negative *HLA-B*15:02*, with dizziness being the most common ADRs (**Table 1**).

## Cases of Carbamazepine-Induced SCARs Without PGx Testing

In this study, 13 cases were reported as CBZ-induced SCARs after received CBZ without PGx testing during 2013–2021 (**Table 3**). Among them, the patients were diagnosed as SJS/TEN (n = 10), Drug rash with eosinophilia and systemic symptoms (DRESS, n = 2) and fix-drug eruption (FDE, n = 1). Remarkably, *HLA-B*15:02* were positive in all SJS/TEN cases (10/10, 100%), where as negative in DRESS and FDE cases. Two patients with CBZ-induced DRESS showed no *HLA-B*15:02* positive (*HLA-B*27:06/58:01* and *HLA-B*40:01/58:01*).

## Incidence of SJS-TEN Between Tested and Non-tested Patients Who Prescribed With CBZ/OXC

Available data demonstrated that prospective *HLA-B*15:02* probably reduces the incidence of hypersensitivity reactions to CBZ/OXC (**Table 4**). Of the 1,539 patients who were prescribed for CBZ/OXC, 916 (59.5%) were tested for the *HLA-B*15:02* allele and 623 (40.5%) were not tested. The incidence of clinically diagnosed SCARs to CBZ/OXC was significantly lower ($p < 0.001$) in the screening arm (0.22%) when compared to the non-screening arm (1.93%). Moreover, 10 of 623 (1.61%) of non-tested patients suffered from SJS/TEN, while only 1 of 916 (0.22%) was observed in tested patients ($p < 0.001$).

## Trend of *HLA-B*15:02* Testing Requested by Out-Side and In-Side of Ramathibodi Hospital

The Laboratory for Pharmacogenomics (PPM), Ramathibodi Hospital has been established as the first reference laboratory for PGx testing in Thailand. **Figure 2** illustrates the trend of *HLA-B*15:02* testing in the country and also hospital during 2011–2020. Totally, 5,191 PGx testing for CBZ/OXC were performed during 2011–2020 in Thailand whereas 1,020 (19.64%) patients were requested *HLA-B*15:02* for CBZ/OXC treatment in Ramathibodi Hospital. Interestingly, only 58 samples were requested by clinicians in 2011, but the number of PGx testing was escalated to 1,002 and 1,277 in 2014 and 2015, respectively. The similar trend was found in Ramathibodi Hospital; it started with three patients in 2011 and has gradually risen in 2014 (n = 278) and dropped in 2015 (n = 116), 2016 (n = 108), 2017 (n = 106), 2018 (n = 138), 2019 (n = 104) and 2020 (n = 117). Totally, 696 (13.27%) and 170 (16.67%) *HLA-B*15:02* carriers were detected in Thailand and Ramathibodi Hospital, respectively.

## Alternative Drugs Prescription in Patients With *HLA-B*15:02* Positive

In order to prevent the SJS/TEN from CBZ/OXC, the alternative AEDs choices were prescribed in *HLA-B*15:02* carriers as per the Thailand Clinical Practice Guidelines for Epilepsy and also NHSO policies. **Figure 3** depicts the alternative medications

**TABLE 4 |** Incidence of CBZ/OXC-induced SCAR and SJS between *HLA-B*15:02* tested patients and non-tested patients.

| Variable | Prescripted with CBZ/OXC | No *HLA-B*15:02* Testing | Testing for *HLA-B*15:02* | P-Value[a] |
|---|---|---|---|---|
| Number of Patients (%) | 1,539 | 623 (40.5) | 916 (59.5) | - |
| CBZ/OXC-induced SCARs (no.) | 14 | 12 | 2 | 0.0001 |
| Incidence of CBZ/OXC-induced SCARs (%) | 0.91 | 1.93 | 0.22 | - |
| CBZ/OXC-induced SJS-TEN (no.) | 11 | 10 | 1 | 0.0003 |
| Incidence of CBZ/OXC-induced SJS-TEN (%) | 0.71 | 1.61 | 0.11 | - |

[a]*p value (<0.05) calculated using fisher exact test between tested and non-tested patients.*

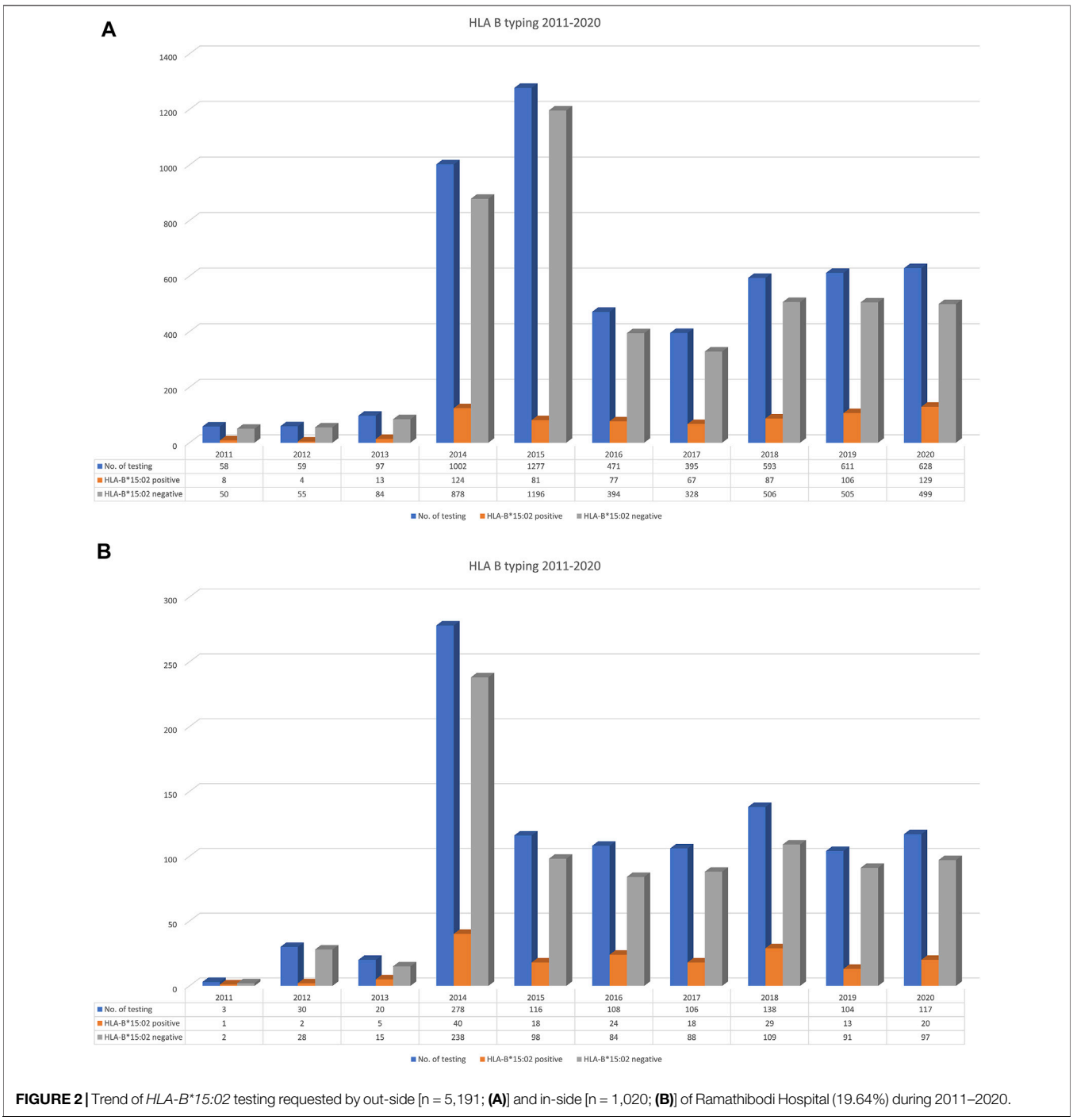


**FIGURE 2 |** Trend of *HLA-B*15:02* testing requested by out-side [n = 5,191; **(A)**] and in-side [n = 1,020; **(B)**] of Ramathibodi Hospital (19.64%) during 2011–2020.

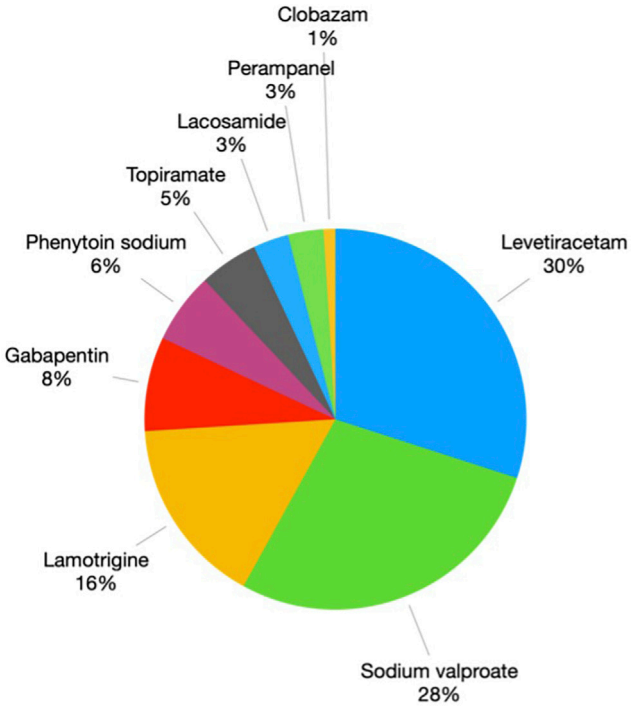


**FIGURE 3 |** Alternative drugs were prescribed in patients with *HLA-B*15:02* positive.

that were utilised in place of CBZ/OXC. The most widely utilised alternative AEDs were levetiracetam (30%), valproate (28%) and lamotrigine (LTG) (16%).

## DISCUSSION

This is the first retrospective cohort study in Thailand to determine the clinical impact of pharmacogenomics (PGx) testing on carbamazepine/oxcarbazepine (CBZ/OXC) prescribing. The female preponderance was seen in the PGx testing population in this study, and it may be because of the higher incidence of hypersensitivity reactions among females (Saksit et al., 2017). Many earlier research studies support this fact. For example, a study conducted by Alvestad et al. (2007) reported that a striking difference in the incidence of hypersensitivity was seen between males (8%) and females (19%) with $p < 0.001$. This association is highly dependent on the age group; reproductive years 20–50 are the most significant age group. The explanation for this is that sex hormones alter the immunological process of rash. Androgens limit the inflammatory response more than endogenous glucocorticoids, whereas female sex hormones enhance the immunological response both pathologically and physiologically (Talal, 1987; Da Silva, 1999; Osman, 2003).

Pharmacogenomic testing for *HLA-B*15:02* is now standard practice in Thailand. In this study, physicians requested the PGx testing for CBZ/OXC and hold the prescription until received the PGx report for 85.67% of 384 patients. This was complying with Clinical Practice Guidelines for Epilepsy (2018) of Epilepsy Society of Thailand and the Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update (Epilepsy Society of Thailand, 2018; Phillips et al., 2018). Do not use CBZ in naïve-patients that are positive for *HLA-B*15:02*. If patient used CBZ for longer than 3 months without incidence of adverse reactions, consider use with caution (Phillips et al., 2018). However, seven patients were found to receive CBZ/OXC while requesting the *HLA-B*15:02* PGx testing. Two of them were CBZ naïve-patients and prescribed with CBZ due to clinical urgency and five were identified as CBZ/OXC-treated patients (used CBZ/OXC for longer than 3 months). Therefore, alternative drugs were prescribed in 65 (92.86%) patients who carried *HLA-B*15:02* (positive group).

Among the 314, negative *HLA-B*15:02* group, 60% were prescribed with CBZ/OXC, whereas the remaining 40% switched over to other AEDs overall before and after the PGx test. The retrospective follow up analysis showed that lengthy *HLA-B* testing results turnaround time and/or lengthy reach out time of the available PGx testing results to physicians were the two important reasons for it. This is a very common barrier while translating the PGx into the real clinical world (Krebs and Milani, 2019). Thailand has recently seen a lot of technological improvement in genetic analysis but we used samples from 2011 in our research. This could explain why clinician prescribed CBZ/OXC without waiting for the PGx results in 55 (14.32%) patients. Physicians, on the other hand, awaited for the PGx results of 329 patients before making a clinical decision. This supports our hypothesis that physician CBZ/OXC prescribing decisions were influenced by *HLA-B*15:02* genotyping. Moreover, 92.85% (65/70) of *HLA-B*15:02* risk allele carriers were avoided by CBZ/OXC, so it can be assumed that the risk population is separated and SCARs are prevented in this population.

However, the screening for *HLA-B*15:02* is not a compulsory testing in Thailand prior to initiation of CBZ treatment. During 2013–2019, CBZ-induced SCARs were reported from 13 patients who received CBZ without PGx screening in Thai-SCARs cohort. Remarkably, *HLA-B*15:02* were positive in all SJS/TEN cases (n = 10, 100%), where as negative *HLA-B*15:02* in DRESS and FDE. Assumably, these patients can be prevented from SJS/TEN if the *HLA-B*15:02* PGx testing was required as a mandatory testing for CBZ prescription. Additionally, the hospital policy and clinical decision support (CDS) alert system is essential to overcome the barriers associated with the utilization of PGx guidelines into clinical practice. The PGx-CDS should be integrated into EMRs and pop-up alert in the therapeutics order system recommending the clinician to order a PGx screening test prior initiation of preventable drug-induced SCARs such as CBZ/OXC (*HLA-B*15:02*), allopurinol (*HLA-B*58:01*), abacavir (*HLA-B*57:01*) and cotrimoxazole/dapsone (*HLA-B*13:01*) (Sukasem et al., 2016; Sukasem et al., 2020; Kloypan et al., 2021; Satapornpong et al., 2021).

An earlier study in Thailand reported that out of 214 SCARs-treated patients over a period of 10 years, 23 patients (10.6%) were treated with CBZ, and this shows that

CBZ is the major culprit for SCARs. If MPE and other mild-moderate level reactions were included, this number could go higher than this. However, it cannot be assumed that all the risk allele carriers will have CBZ-induced CADRs. In this study, 7.14% of patients who carried *HLA-B*15:02* allele did not manifest any CADRs. Because the frequency of SJS/TEN is substantially lower than the frequency of the risk allele in these groups, previous studies have shown that the test's positive predictive value is poor (1–5%). Although having *HLA-B*15:02* increases the risk of CBZ/OXC induced SJS/TEN by up to >700-fold compared to non-carriers, the vast majority of patients with *HLA-B*15:02* (95%–99%) do not develop SJS/TEN from CBZ/OXC (Amstutz et al., 2014).

However, in this study if the mild reactions are included this rate goes up to 11%. The reason could be that 29% of the negative patients were reported with multiple comorbidities and most of them were immune related disorders like Systemic lupus erythematosus (SLE), hypo/hyperthyroid, cancer, rheumatoid arthritis (RA), diabetes mellitus (DM), hypertension (HTN), and central nervous system (CNS) infections. Earlier studies showed that some non-clinical risk factors may be involved in the initiation of CADRs (Campos-Fernández Mdel et al., 2005; Patel et al., 2014; John et al., 2021).

Unexpectedly, 2 cases with CBZ-induced SCARs (DRESS and SJS) were reported among 189 patients with *HLA-B*15:02* negative after CBZ/OXC treated patients. Likewise, 2 cases with CBZ-induced DRESS were reported after CBZ treatment without *HLA-B*15:02* PGx testing. Commonly, the *HLA-B*15:02* allele has been reported to be specifically associated with CBZ-induced SJS/TEN in Asian populations, and no associations have been reported for drug-induced MPE and DRESS (phenotype-specific biomarker) (Sukasem et al., 2021b). In contrast, *HLA-A*31:01* was reported to be associated with CBZ-induced DRESS and MPE (Mockenhaupt et al., 2019; Ahmed et al., 2021). US-FDA recommended that *HLA-B*15:02* and *HLA-A*31:01* genotypes should be detected to stratify the high risk patients prior CBZ prescription. The use of CBZ should be avoided in patients who test positive for the *HLA-A*31:01* or *HLA-B*15:02* alleles (US Food and Drug Administration, 2009). However, conflicting evidence has been found in this study, one SJS patient was reported from negative of *HLA-B*15:02* group. This suggested that other genetic and clinical factors may also influence a patient's risk for adverse reactions.

PGx testing has been implemented in many hospitals throughout the world over the last decade to guarantee that the best treatment is chosen. For example, 27 institutions in the United States have established numerous PGx implementation programmes (Dunnenberger et al., 2015; Volpi et al., 2018), while other PGx implementation programmes in Europe and East Asia include EU-funded Ubiquitous Pharmacogenomics (U-PGx), PREemptive Pharmacogenomic testing for the prevention of Adverse Drug Reactions (PREPARE) (van der Wouden et al., 2017), and the Southeast Asian Pharmacogenomics Research Network (SEAPharm) (RIKEN, 2012; Chumnumwat et al., 2019).

We discovered that the number of *HLA-B*15:02* tests per year has increased significantly since 2013 in Thailand. The reason for the high PGx testing could be because of the implementation of a pilot project for *HLA-B*15:02* PGx testing before prescribing CBZ in Bangkok by the Department of Medical Sciences, Ministry of Public Health, Thailand. This phenomenon was emphasised later by NHSO announcement for implementation of national screening policy in 2018.

In the *HLA-B*15:02* positive group, levetiracetam, sodium valproate, LTG, gabapentin, and phenytoin (PHT) sodium were the most prescribed as alternative AEDs in epilepsy. The reason that levetiracetam and sodium valproate were used is that they are non-aromatic AEDs with a low rate of cross-reactivity with CADRs. In 2014, Li et al. (2015) reported a significant association between *HLA-B*15:02* and PHT or LTG-induced SJS/TEN. Nevertheless, our study found that LTG and PHT were prescribed in *HLA-B*15:02* positive patients without any ADRs. The reason could be the strength of the association is much weaker than it was for CBZ/OXC-related SJS/TEN. A study from Thailand reported a moderate association (limited evidence) (Locharernkul et al., 2008) and a case report of Han Chinese also showed a weak association (insufficient evidence) (Shi et al., 2012).

Although the retrospective nature of this study is its limitation, this is the first large cohort study in Thailand that provides valuable information on the real clinical impact of *HLA-B*15:02* PGx testing for CBZ prescription and associated CADRs in Thai patients.

## CONCLUSION

The selection of appropriate AEDs was influenced by pharmacogenomic testing of *HLA-B*15:02* risk alleles. *HLA-B* genotyping can guide the physician in selecting CBZ/OXC and other AEDs prescriptions rationally. The number of *HLA-B*15:02* screening has increased significantly in Thailand. In 85% of cases, physicians waited for *HLA-B*15:02* testing to make clinical decisions on CBZ/OXC prescribing. However, physicians have administered CBZ/OXC without PGx testing in the urgent cases. Though there were no CADRs in the *HLA-B*15:02* positive group, CBZ-induced SJS/TEN were reported from *HLA-B*15:02* carriers who received CBZ without PGx screening before prescription. The presence of mild rash in the *HLA-B*15:02* negative group indicates that other genetic biomarker such as *HLA-A*31:01* and/or non-genetic variables are involved in CBZ/OXC-induced CADRs, emphasizing that CBZ/OXC prescriptions necessitate CADRs monitoring even in patient without *HLA-B*15:02* risk alleles.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Ramathibodi Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

KT, SJ, and CS: wrote the manuscript; AB, NK and CS designed and conceptualization the research; All authors performed the research; KT and SJ formal analysis and curation the data; CS, NK and AB: Validation and finalized the study.

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