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Reducing the harm of medication - recent trends in pharmacovigilance, volume II

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Reducing the harm of medication - recent trends in pharmacovigilance, volume II

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Editorial: Reducing the harm of medication–recent trends in pharmacovigilance (volume II)

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Adverse drug effect, medication without harm, pharmacovigilance, pharmacoepidemiology, causality assessment, adverse drug reaction

Editorial on the Research Topic
Reducing the harm of medication–recent trends in pharmacovigilance (volume II)

This Research Topic is the *Volume II of Reducing the harm of medication–recent trends in pharmacovigilance*. Ramírez et al. (Ramírez E, González-Munoz M, Kulkarni C, de Abajo FJ. Editorial: Reducing the Harm of Medication-Recent Trends in Pharmacovigilance. Front Pharmacol. 2022 Aug 30;13:964125. doi: 10.3389/fphar.2022.964125). In 2017, the World Health Organization (WHO) launched the third global health challenge, Drugs Without Harm, to achieve a reduction in harm related to iatrogenic drugs by 50% in 5 years. In this Research Topic, our objective was to evaluate strategies to improve the safety in the use of medicines to achieve this objective.

A set of standards, regulations, guidelines and standard operating procedures constitute the fundamental basis of an efficient pharmacovigilance system as part of health policies. Several nations implemented pharmacovigilance systems in the early 1960s and continually introduce new legislation to strengthen their existing medication safety systems. However, the development and implementation of pharmacovigilance systems is very uneven throughout the world. Khan et al. performed a semi-structured exploratory interview with stakeholders to assess their perceptions of the current adverse drug reactions (ADR) reporting system and to identify pharmacovigilance policy issues and effective coordination issues in Pakistan. The results obtained are similar to those of other low- and middle-income countries that identify the lack of a regulatory framework as the main gap in the reporting system for ADRs. These findings highlight differences compared to the pharmacovigilance systems of high-income countries. Rehman et al. performed a survey to determine the perception and effects of intervention on patients regarding ADRs in public hospitals in Islamabad revealed that most of the participants were interested in medical consultation for medication use; some were willing to report ADRs in the future and called for the establishment of a hospital-level pharmacovigilance system. Pakistan felt the need for an effective and robust pharmacovigilance system after one of the deadliest medication-related tragedies that caused more than 300 deaths in 2012. The country established its

national pharmacovigilance system center in 2015 and joined the WHO International Drug Program Monitoring in 2018 as a full member. Khan et al. in a descriptive cross-sectional study conducted by providing a questionnaire administered by an interviewer from the pharmacovigilance system through a convenience sampling method using the Indicator-Based Pharmacovigilance Assessment Tool concluded that despite receiving funding from the Global Fund, none of the National Public Health Programs have pharmacovigilance system centers or associated activities. A two-phase strategy is proposed encompassing non-financial and financial interventions to improve pharmacovigilance system systems at the national, provincial, Public Health Programs and hospital levels.

The databases of adverse event reporting systems are public tools available on the web that provide access to search for information related to adverse events in humans. FDA Adverse Event Reporting System (FAERS) is a public web-based tool providing access to search for information related to human adverse events reported to the FDA by the pharmaceutical industry, healthcare providers and consumers. This type of database with all its limitations (duplicate reports where the same report was submitted was submitted by a consumer and by the sponsor, there is no certainty that the reported event was due to the product) offers interested parties stakeholders possibilities for signals mining of possible adverse reactions of many medications. A FAERS-based study was conducted to compare adverse reaction reports and bleeding signals for ticagrelor and clopidogrel. Tang et al., using system organ classes and preferred terms from the Medical Dictionary of Regulatory Activity, analyzed the adverse reaction signals of ticagrelor and clopidogrel.

Most hospitals participate in pharmacovigilance through spontaneous reporting systems. However, spontaneous reporting systems have limitations, such as the difficulty of recognizing ADRs, the uncontrolled nature of the reporting method, and underreporting. For these reasons, retrospective and prospective surveillance methods are considered more effective than spontaneous reporting systems. Valdés-Garicano et al. retrospectively evaluated the performance of a proactive pharmacovigilance system using laboratory alerts as a method to detect serious ADRs using hyponatremia and rhabdomyolysis as case studies. The authors found moderate sensitivity and high specificity for both ADRs.

Diagnosis of delayed-type ADRs is complex and is usually done after recovery. The ADR study includes medical history, causality algorithms, skin tests, and suspected medication rechallenge tests, and helps to identify the immunological mechanisms and culprit medications involved. The identification of the guilty medication is of great importance in the diagnosis, allowing an adequate management of the patient and avoiding a possible re-exposure in the future with serious consequences. The diagnosis based on the clinical history is especially difficult and in many cases it is not easy to establish an accurate time sequence between the administration of the medication and the onset of adverse symptoms. The information that skin tests can provide in the diagnosis of immune-mediated ADRs is limited because their sensitivity and specificity depend on the medication and the clinical manifestations, and their sensitivity is low. Therefore, the gold standard for confirming the diagnosis of severe ADRs and identifying the culprit medication is re-exposure to the suspected medications. However, it raises serious ethical concerns in severe ADRs. One of the approaches that has been explored to improve the diagnosis of ADRs is *in vitro* tests that are safe for patients. Two papers addressed the use of *in vitro* tests in the identification of the culprit medication involved in hypersensitivity ADRs. Bellon et al. carried out a case-control study to evaluate the diagnostic tools in medication induced eosinophilia and systemic symptoms (DRESS) induced by vancomycin in Spanish cases. The evaluation included causality algorithms, the lymphocyte transformation test, and HLA testing. The results confirmed the association of the HLA-A*32:01 risk allele with vancomycin-induced DRESS and support lymphocyte transformation test as a reliable tool for determining vancomycin sensitization. Elzagallaai et al. evaluated the lymphocyte toxicity assay to diagnose and capture a serum sickness-like reaction due to ß-lactam antibiotics. The authors found that there was a significant concentration-dependent increase in cell death in cells isolated from patients compared to cells from healthy controls. The results of both studies suggest that *in vitro* tests could play a role in the diagnosis of hypersensitivity ADRs.

The search for predictors of medication-related problems (MRPs) is an approach that may improve current knowledge regarding the prediction of adverse drug events. Taylor et al. have developed two tools to identify patient, medication, and emergency department (ED) presentation related predictors for MRPs across the continuum of ED care that may require specialist input to identify, manage or prevent. These screening tools were applied (or implemented) at and during the ED presentation (Presentation Tool), and shortly after emergency department or short-stay unit (SSU) discharge (Discharge Tool). Preliminary scoring cutoffs and associated screening tool performance have been proposed. The authors state that MRP predictors are readily available at the bedside and can be used to detect patients at increased risk on presentation to the ED and upon discharge from the ED or SSU at community.

Potentially inappropriate medicines (PIMs) are a major concern in pharmacovigilance and are a well-known public health problem. In this volume, two papers related to potentially inappropriate medication in cancer patients were presented. China is currently the country with the largest population of elderly people with cancer in the world, and cancer, as a chronic disease, places a heavy burden on the elderly. Older cancer patients may suffer from a higher rate of comorbidity, frailty, and geriatric syndrome, putting them at high risk for polypharmacy and PIM use. In the multicenter cross-sectional study, Wang et al. evaluated potentially hazardous drug-drug interactions (DDIs) associated with prescribed oral antineoplastic agents in tertiary care teaching hospital settings without computerized DDI detection programs. Potentially hazardous DDI associated with oral antineoplastic agents were analyzed by using the United States Food and Drug Administration-approved labeling. Nearly 300 DDIs were identified in about 14,000 enrolled patients, with proton pump inhibitors, dexamethasone, and fluoroquinolones being the most frequently dangerous DDIs involved with oral antineoplastic agents. Multivariate analysis revealed younger age, increasing number of medications, and targeted therapy-treated patients were the main risk factors for a DDI. In the other study with cancer patients Tian et al. evaluated the use of potentially inappropriate medication in elderly patients seen in tertiary hospital outpatients with cancer with

multimorbidity according to Chinese Geriatrics Association criteria, American Geriatrics Society (AGS)/Beers criteria and the Screening Tool for Prescribing for the Elderly (STOPP) and the Screening Tool to Alert the Right Treatment (START) criteria. The authors found a high prevalence of PIM use in older Chinese cancer outpatients with multimorbidity and low to moderate concordance among the three criteria used. The low concordance between the different criteria highlights the need to develop special PIM detection criteria for older cancer patients.

Evidence-based medicine integrates clinical experience and patient values and aims to use the best evidence to make decisions about the care of individual patients. The patients' values, which reflect their subjective cognition and demand, have been proposed to be considered as a reliable clinical guide. In the case of pediatric patients, their guardians are responsible for their values. Yang et al. conducted a cross-sectional survey for pediatricians and guardians of children with tic disorders in Myanland, China, Macao, and Hong Kong to analyze information on physician behavior and medication choices and on the Guardians' knowledge of tic disorder, medical treatment behaviors, and medication. Options and needs. The study revealed that pediatricians in China often follow clinical guidelines when selecting tic disorder medications, but rarely consider guardians' preferences, highlighting a gap in treatment optimization. In addition, the patients' guardians lack sufficient knowledge about tic disorders and medication options, requiring more physician-initiated dialogue.

Randomized Controlled Trials (RCTs) are considered the most scientifically rigorous method for regulatory decision making. However, real-world evidence (RWE) is playing an increasing role in healthcare decisions. RWE enables monitoring of post-marketing safety and the assessment of comparative treatment effectiveness, which can be of utmost importance to develop guidelines and decision support tools for use in clinical practice. Jang et al. proposed that RWE has the potential to provide evidence for future regulatory decision-making in an environment where RCTs cannot be performed. Its objective was to investigate to what extent the safety of empagliflozin from the RWE study in Korea is different from that of the RCT emulating the design of a foreign RCT. The results of their study suggest that RWE emulating foreign RCTs has the potential to provide evidence for future regulatory decision-making.

We appreciate the good acceptance of Reducing the Harm of Medication - Recent Trends in Pharmacovigilance series as shown by the interesting contributions to its two volumes. As in the first volume, we make some suggestions to encourage future Pharmacovigilance activities. The first is based on the need for continuous improvement of pharmacovigilance systems, and on the positive involvement of patients in spontaneous reporting systems of possible ADRs. Public adverse event reporting databases (FAERS, Eudravigilance, WHO) make it easier for researchers with data mining skills to use these tools to generate new medication safety signals. As we already said in the first volume, it is necessary to improve diagnostic tools, causality algorithms and other *in vitro* tests in the diagnosis of ADRs. Current methods of diagnosis of severe ADRs, often rare medication hypersensitivity reactions by frequency and mechanism, lack clear diagnostic criteria. Given their safety and good predictive value, lymphocyte transformation test and lymphocyte toxicity assay *in vitro* tests have great potential to be a useful diagnostic tool for severe ADRs. On the other hand, the implementation of tools to reduce potentially dangerous medications in older patients with cancer, drug interactions and inappropriate medications is urgently needed. The electronic medical record has proven to be more useful for evaluating problems already detected, allowing the implementation of prevention and early detection tools that minimize the risk of ADR. The use of large automated databases, including demographic data, diagnoses, procedures, and medication use, can generate real-world evidence (RWE) about the benefits and risks of medications and could even emulate a randomized clinical trial (RCT) with the advantages of providing longer follow-ups of patients with less exclusion criteria and higher external validity. However, RWE-based studies are more prone to systematic errors than RCTs which should be taken into account when assessing causal inference medication. For all these reasons, it is necessary to have a critical mass of specialists for the early detection, diagnosis and management of ADRs who, in collaboration with the authorities and patients, develop and implement the tools that make it possible to reduce severe medication-related harm.

Author contributions

ER has been involved in drafting the manuscript and revising it critically for important intellectual content. MG-M, CK, and FD have been involved in revising the manuscript critically for important intellectual content.

Conflict of interest

Author Chanda Kulkarni is employed by the company iDD Research Solutions Pvt Ltd.

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

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Assessment of the Current State of Pharmacovigilance System in Pakistan Using Indicator-Based Assessment Tool

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Objectives: Pakistan felt the need for an effective and robust pharmacovigilance (PV) system after one of the deadliest drug-related tragedies causing more than 300 deaths in 2012. The country set up its national PV center in 2015 and joined WHO's Program for International Drug Monitoring (PIDM) in 2018 as a full member. The current study was aimed to evaluate the PV system's functionality, identify the gaps, areas of improvement, and a strategy to lead a functional PV system in Pakistan.

Methods: The descriptive cross-sectional study was conducted by providing an interviewer-administered questionnaire of the PV system across Pakistan by utilizing the Indicator based Pharmacovigilance assessment tool (IPAT). By a convenience sampling method 36 study participants were selected from the Drug Regulatory Authority of Pakistan (DRAP), drug administration of provincial health departments of 4 provinces and federally affiliated areas, 5 national public health programs, and 23 public and private hospitals. The assessment includes document review, interviews of the key informants by structured open-ended questions, and a review of websites of relevant organizations.

Results: Drug Regulatory Authority of Pakistan (DRAP) with a national PV center received a 75% overall performance score on IPAT. To be regarded as "minimally functioning," a country's PV and drug safety system must meet all core indicators. DRAP scored 80.76% on the core indicators so cannot be deemed functional at this time. The only province with a regional PV center, Punjab, had scored 72.13% on relevant parameters. Despite receiving funding from the Global Fund, none of the National Public Health Programs (PHPs) have PV centers or associated activities. All hospitals except two private hospitals could not qualify the minimum requirements for functional PV. The absence of a legal framework for mandatory ADR reporting, lack of drug information center, budgetary constraints, no active surveillance activities, the nonexistence of pharmacovigilance risk assessment expert committee, and insufficient coordination among stakeholders were identified as major gaps.

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Conclusion: The results of the study reveal that Pakistan's PV system is not fully functional at all levels. A two-phased strategy encompassing the non-financial and financial interventions is proposed to improve the PV systems at the national, provincial, PHPs, and hospitals levels.

Keywords: pharmacovigilance, system, adverse drug reactions, IPAT, public health, Pakistan, medicine safety, DRAP

INTRODUCTION

While medicines have benefits, they are also considered to have harmful effects. Though preventable, adverse drug reactions (ADRs) are among the major reasons for death (WHO, 2004). To reduce the risks involved with medicines, pharmacovigilance is considered a key instrument in public health and medical practice (WHO, 2006; 2010). Pharmacovigilance (PV) is a wider discipline and is defined as "*the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems*" (WHO, 2002). After the thalidomide catastrophe, there was a global need for speedy transmission of ADR information. As a result of the disaster, several policies, regulations, and amendments, in addition to the WHO Program for International Drug Monitoring (PIDM), were implemented. Several issues emerged in the incident including the hesitant approach of regulatory authorities, poor regulations, and weak review processes. This incident highlighted the significance of a thorough evaluation process and many countries introduced new regulations and strengthened existing drug safety systems and legislation (WHO, 2002; Rice, 2007; Lembit and Santoso, 2010; Beninger and Ibara, 2016).

The scope of pharmacovigilance has been expanding throughout the years from the unrecognized adverse drug reactions to post-market drug surveillance, medication errors, drug quality and therapeutic ineffectiveness (Nwokike and Joshi, 2010), illegal online sale of medicines, unreliable donation of prescription drugs, the growing practice of self-medication, and the sale of counterfeit and fake medicines (WHO, 2002). Pharmacovigilance has evolved as a regulatory activity, through collaboration between the World Health Organization (WHO), the Council for International Organizations of Medical Sciences, and the International Conference on Harmonization (Beninger and Ibara, 2016). Quick approval, prioritization, and expedited review for novel medications have all become more popular in recent years (Darrow et al., 2020). New accelerated and conditional approval routes necessitate more comprehensive and interactive PV, as well as more frequent and creative risk management strategies. FDA is taking extra measures to tackle the new challenges (Pitts, 2015).

Mahmood et al. (2011) underlined the importance of implementing a PV system in Pakistan to reduce drug-related mortality and illness (Mahmood et al., 2011). Until 2012 the country did not have an established PV system. More than 300 people died at the Punjab Institute of Cardiology (PIC) in Lahore in 2011 as a result of tainted medicine Isotab (Isosorbide mononitrate 20 mg). Later, a Judicial Inquiry Tribunal (JIT) was formed to examine the causes of fatalities, and it was discovered that the lack of a PV system and the hospital's ADR reporting system were the major causes of drug-related adverse events. The Judicial Inquiry Tribunal (JIT) also suggested that PV centers be established at all levels of the health administration department to collect and submit ADRs for rapid risk assessment, appraisal, and management (LHC, 2012).

Pakistan's PV research is predominantly focused on Knowledge Attitude and Practices (KAP) surveys regarding ADR reporting. Health care professionals (HCPs) have a positive attitude toward medicine safety. However, ADRs are underreported by Pakistani healthcare providers due to poor knowledge of the national ADR reporting system, training, and communication gaps between the hospitals and the regulatory authorities (Iffat et al., 2014; Atif et al., 2016; Hussain et al., 2018; Nisa et al., 2018; Syed et al., 2018). Iftikhar et al. (2018) found a high percentage of Adverse Drug Events (ADEs) among Pakistani adult and pediatric patients with 59.9 and 40.1%, respectively. The study further revealed that most of the ADEs were preventable and associated with medication errors (Iftikhar et al., 2018). Shamim et al. (2016) reported that there were few PV systems at tertiary care level hospitals (Shamim et al., 2016). No study has been conducted on the PV systems of PHPs and health facilities of Pakistan.

In 2021, Pakistan's total population is expected to be around 212.48 million (Statista, 2021), with a pharmaceutical industry worth around USD 3.2 billion (The Pakistan Business Council, 2021). More than 600 drug manufacturing licenses (DRAP 2021a) and 80,000 product registrations (DRAP 2021c) have been granted by DRAP. First National PV Center was established in 2015 and DRAP received full membership of Uppsala Monitoring Center (UMC) in 2018 (UMC, 2021a) (**Figure 1**). The WHO emphasizes the importance of conducting a thorough analysis of the strengths and shortcomings of current PV systems to improve their effectiveness (WHO, 2015). In 2015, Danya found that Pakistan had an ADR collection system in place as well as a PV center (Qato, 2018). Other studies explained that the PV system of Pakistan is at its initial stage of development (Hussain et al., 2018) and needs strengthening and improvement (Shakeel et al., 2014). However, the progress of Pakistan's current PV system has never been evaluated systematically over time. This study aims to assess Pakistan's PV system. According to our knowledge, this study is the first of its kind to use the IPAT data collection tool to assess Pakistan's PV system at the national and provincial levels from its inception through 2020.

MATERIALS AND METHODS

Study Settings

Pakistan has four provinces, i.e., Baluchistan, Khyber Pakhtunkhwa (KPK), Punjab, and Sindh. It has separate health

FIGURE 1 | Events of establishment of the national pharmacovigilance center of Pakistan with timelines.

administration for Islamabad Capital Territory (ICT), and two federally affiliated areas, Azad Jammu and Kashmir (AJK) and Gilgit Baltistan (GB). Private and public sectors deliver health services in Pakistan. The health care delivery system is three-tired. The system comprises more than 1200 public sector hospitals, above 5500 basic health units, around 685 rural health centers, and over and above 5800 dispensaries. A large number of private hospitals and stand-alone clinics operate separately. The workforce comprises 195,896 doctors, more than 95,000 lady health workers, 99,228 nurses, and 34,000 pharmacists (Muhammad et al., 2021; WHO, 2021a).

Study Design and Sampling

We conducted structured interviews of key informants of PV for our descriptive cross sectionals study across Pakistan during July-December 2020. By convenience sampling method 36 study participants were selected from DRAP, drug administration of provincial health departments, ICT, AJK, and GB, Public Health Programs (PHPs), and public and private hospitals (see **Supplementary Table**). The majority of respondents were pharmacists working in federal and provincial drug administrations, the chief pharmacists working in hospitals, logistic support managers, and program managers in PHPs.

PV activities at the DRAP and five PHPs, including the National Malaria Control Program (NMCP), the National Aids Control Program (NACP), the National Tuberculosis Control Program, the Expanded Program on Immunization (EPI), and the Pakistan Polio Eradication Initiative (PPEI) were evaluated at the national level, while each administrative unit of Pakistan, including AJK, Baluchistan, GB, ICT, KPK, Punjab, and Sindh, was evaluated at the provincial level.

IPAT suggests sampling of 10–15 health facilities, to collect representative data on PV activities at all levels of health delivery. A total of 23 health facilities, including 8 private and 15 public or government hospitals, were selected. Private hospitals include Agha Khan University Hospital (AKUH) Karachi, Quaid-e-Azam International Hospital (QIH), and Shifa International Hospital (SIH) in Islamabad, Shaukat Khanum Memorial Cancer Hospital (SKMCH) in Lahore, Rehman Medical Institute (RMI) Peshawar, Agha Khan Medical Center (AKMCG) Gilgit, Baluchistan Institute of Nephrology and Kidney Transplant (BINIQ) Quetta, and Riaz Hospital (RHM) Mirpur, AJK. While government hospitals include Allied Hospital (AH) Faisalabad, Benazir Bhutto Shaheed Hospital (BBH), District Headquarter Hospital (DHH) and Holy Family Hospital (HFH) in Rawalpindi, Federal Government Polyclinic Hospital (FGPH), and Pakistan Institute of Medical Sciences (PIMS) in Islamabad, Children Hospital (CH), Jinnah Hospital (JH), and Punjab Institute of Cardiology (PIC) in Lahore, Jinnah Postgraduate Medical Centre (JPMC) and National Institute of Child Health (NICH) in Karachi, Hayatabad Medical Complex (HMC) Peshawar, DHQ Hospital (DHQHG) Gilgit, Bolan Medical Complex Hospital (BMCH) Quetta, and DHQ Teaching Hospital (DHQTH) Mirpur AJK. This research is carried out without patients, carers, or members of the public.

Data Collection

Data Collection Tool

Data was collected using the IPAT developed and validated by "management sciences for health (MSH)" under a USAID program to examine PV systems in developing countries. IPAT consists of a total of 43 indicators with 26 core and 17 supplementary indicators. These indicators focus on five areas of the PV system, i.e., (1) policy, law, and regulation (four indicators); (2) systems, structures, and stakeholder coordination (15 indicators); (3) signal generation and data management (six indicators); (4) risk assessment and evaluation (eight indicators); and (5) risk management and communication (10 indicators). The indicators are further categorized by "structure," "process," and "outcome." The tool's objective is to make PV assessment easier by asking questions about the PV system (SPS Program, 2009).

The first section ("policy, law, and regulation") is intended to assess the National Regulatory Authority as DRAP. As a result, only the four other sections are relevant to provincial drug administration, PHPs, and health facilities. For our study, we selected the following relevant indicators according to the study settings.

- 42 indicators for DRAP (1.1–1.4, 2.1–2.11, 2.13–2.15, 3.1–3.6, 4.1–4.8, 5.1–5.10)
- 37 indicators for Provincial Health Department (2.1–2.11, 2.13–2.14, 3.1–3.6, 4.1–4.8, 5.1–5.10)
- 30 indicators for health facilities
- 31 indicators for Public Health Programs

Data Collection Process

We approached participants directly and over the phone before data collection to ask them if they would participate in the study. Participants were interviewed in-person to provide information on the indicators that were featured on the IPAT tool they used. There were also open-ended questions about the current PV

TABLE 1 | Drug regulatory authority of Pakistan.

Pharmacovigilance indicators at the national level		Core/ supplementary	Score
1	Policy, law, and regulation		
1.1	Existence of a national policy document addressing pharmacovigilance	C	2
1.2	Specific pharmacovigilance provisions in national medicines or similar laws	C	2
1.3	Legal requirements require marketing licensors to report all serious adverse reactions to the national drug regulator	S	0
1.4	Legal requirement for the marketing authorization holder to conduct post-marketing surveillance activities	S	0
Subtotal score (%)			4/6 (66.6)
2	Structures, systems, and stakeholders coordination		
2.1	Pharmacovigilance center exists	C	2
2.2	Clear mandate, structure, roles, and responsibilities of pharmacovigilance center exists	C	2
2.3	Medicine information service exists	C	0
2.4	Separate staff for pharmacovigilance	C	2
2.5	A dedicated budget for pharmacovigilance exists	C	0
2.6	National medicine safety advisory committee exists	C	0
2.7	National pharmacovigilance guidelines exists	C	2
2.8	SOPs for safe use of medicines exists	C	2
2.9	Basic communication tools provided for reporting and information on the safety of medicines	C	2
2.10	Drug safety bulletin exists	C	2
2.11	Reference materials available in pharmacovigilance center	S	1
2.13	Training of healthcare professionals on pharmacovigilance during the previous year	S	1
2.14	Countrywide platform or plan for coordinating pharmacovigilance initiatives	C	2
2.15	Membership of national pharmacovigilance center of WHO International Drug Monitoring program	S	1
Subtotal score (%)			19/25 (76)
3	Signal generation and data management		
3.1	A mechanism for coordinating and compiling pharmacovigilance data from all sources across the country	C	2
3.2	Database for tracking pharmacovigilance activities exists	C	2
3.3	A form for reporting suspected ADRs exists	C	2
3.4	A form for reporting suspected product quality issues exists	C	2
3.5	A form for reporting suspected medication errors exists	C	2
3.6	A form for reporting suspected treatment failure exists	C	2
Subtotal score (%)			12/12 (100)
4	Risk assessment and evaluation		
4.1	Last year, a medicine utilization review performed	S	0
4.2	Within the previous 5 years, a survey for pharmaceutical product quality undertaken	S	1
4.3	Medication errors quantified in the last year	S	0
4.4	Number of ADR reports collected in the last year	C	2
4.5	Active surveillance activities conducted during the last 5 years	C	0
4.6	Public health programs reported ADEs for patients in the last year	C	2
4.7	Public health programs modified the treatment of patients due to ADRs in the last year	C	0
4.8	Public health programs reported serious ADEs of patients in the last year	S	0
Subtotal score (%)			5/12 (41.66)
5	Risk management and communication		
5.1	Risk mitigation plans targeted at high-risk medicines	S	0
5.2	Prequalification schemes for procurement of medicines	S	1
5.3	In the last year, medicine safety information requests received and addressed	S	1
5.4	Medicine safety bulletin published in the last year	S	1
5.5	Medicine safety issues addressed on external information	S	1
5.6	Safety alerts including "Dear healthcare professional" developed and distributed in the last year	S	1
5.7	The average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to healthcare workers and the public	C	2
5.8	Percentage of Drug and Therapeutics Committees that handled medicine safety issues during last year	C	2
5.9	Last year's public or community education initiatives on medication safety	S	0
5.10	Medicines sampled in the last year that passed product quality tests	C	2
Subtotal score (%)			11/13 (84.61)
Total			51/68 (75%)

system in the questionnaires, apart from the indicators-related items. As evidence supporting the interviews, PV-related documents were obtained from the participants. Additional information was gathered from the websites of participating organizations and reviews of documents such as the Drugs Act 1976, the DRAP Act 2012, Pakistan National PV guidelines, the draft PV Rules 2020, DRAP's Newsletter, Punjab PV plans 2017 and 2019, the fundamentals of PV and its emergence in Punjab, Punjab drug information bulletins, Guidelines of PHP, and National Health Vision Pakistan 2016–2025.

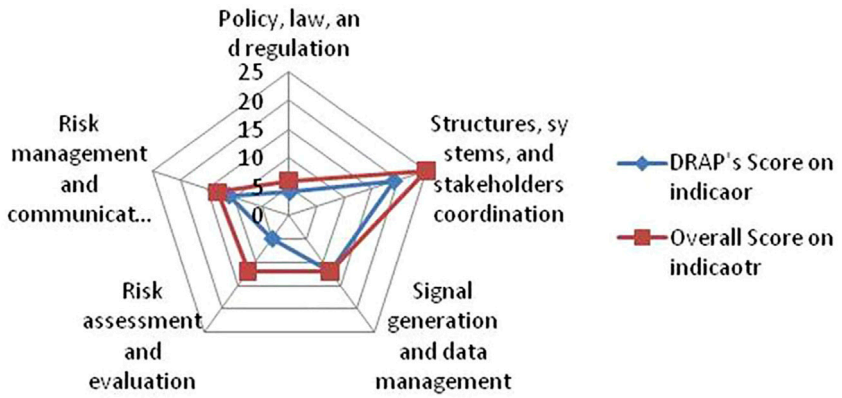

FIGURE 2 | Five-axis spider-diagram (0–25 score) showing the DRAP's scores on five main indicators of IPAT.

Data Analysis

Microsoft Excel was used to calculate the results, following quantitative and qualitative analyses of the data. Each IPAT data collection tool indicator has a number and percentage with suggested criteria. The responses of participants are recorded as either a "Yes" or a "No." Any fulfilled core indicator is given 2 points, supplementary indicator 1 point, and any unfulfilled indicator is given 0 points. The maximum points for core and supplementary indicators are 52 and 17, respectively. These numerical values have been assigned according to IPAT tool scoring. The threshold for various quantitative indicators (2.13, 4.4, 5.3, 5.4, 5.5, 5.6, 5.7, and 5.10) was not set due to the small values of the data. Finally, the response data is tabulated and also displayed as a column-chart and radar chart to allow for visual identification of progress over time. The value was multiplied by 100 after the final score was calculated by combining the scores of all indicators and dividing it by the aggregate score of all indicators.

RESULTS

The Drug Regulatory Authority of Pakistan

The Drug Regulatory Authority of Pakistan (DRAP) was evaluated for 42 PV indicators which contain 26 core and 16 supplementary indicators, for a total score of 68. DRAP achieved an aggregate score of 75% (**Table 1**) with breakup into four categories: (1) "policy, law, and regulation" (66.6%), (2) "Structures, systems, and stakeholder's coordination" (76%), (3) "Signal generation and data management" (100%), (4) "Risk assessment and evaluation" (41.66%), and (5) "Risk management and communication" (84.61%), (**Figure 2**). Overall, the DRAP met (21/26) 80.76% of the core and (9/16) 56% of supplementary indicators.

According to the study findings, DRAP has established a national PV center with seven designated staff members, standard operating procedures, and guidelines. With full membership of the WHO PIDM in 2018, the collected data is transferred to the VigiBase. In addition to the DRAP MED Vigilance E-Reporting System and the Web-RADR Med Safety mobile application, the National PV Center has provided online and manual ADR reporting forms. Safety alerts and advisories are issued on DRAP's website and social media accounts. During 2016–2018 DRAP has taken several regulatory actions on external safety information (**Table 2**). Since its establishment, 6587 ADR reports (116 in 2018, 2415 in 2019, and 4056 in 2020) have been received by the NPC. The majority of reports are from pharmaceutical firms, with 124 ADRs coming from Punjab's PV center. Not a single ADR report from the public has been reported.

DRAP lacks legal provisions requiring medicine registration holders to report ADRs to the DRAP, a medicine information center, and a dedicated budget for PV-related activities. Pharmacovigilance Risk Assessment Expert Committee is also missing, however, an internal "Causality Assessment and Signal Review group" comprised of DRAP officers has been notified.

Pharmacovigilance Activities at Provincial Health Departments

It was found that except Primary & Secondary Healthcare Department (PSHD) Punjab and Health Department of Islamabad Capital Territory (ICT) all health departments of other administrative units of Pakistan have no PV center and therefore no PV-related activities are carried out. The PSHD Punjab was assessed on 37 PV indicators, with 24 core and 13 supplemental indicators aggregating 61 points. Punjab scored (45/61) 72.13% overall (**Table 3**), with the following categories: (1) "structures, systems, and stakeholder coordination" (83.33%), (2) "signal generation and data management" (100%), (3) "risk assessment and evaluation" (25%), and (4) "risk management and communication" (69.23%) (**Figure 3**). Overall, Punjab satisfied 79.16% of the core indicators (19/24) and 53.84% of the supplemental indicators (7/13) in total.

The provincial drug control unit of PSHD Punjab has established a provincial pharmacovigilance center (PPC) along with designated five officers, PV guidelines, and SOPs. A monthly Punjab drug safety newsletter is published regularly. Punjab also has constituted an ADR risk management and scrutiny committee

TABLE 2 | Regulatory actions by DRAP.

S. No.	Drug	Basis for action	Source of information	Action taken
1.	Systemic fluoroquinolones (DRAP, 2016)	Risk of disabling adverse effects of tendons, muscles, joints, and central nervous system	US-FDA FDA	Prescribing information and labeling information updated, black box warning
2.	Hydroxyzine hydrochloride (DRAP, 2017b)	Abnormal cardiac rhythm	European Medicine Agency (EMA), United Kingdom (MHRA), PMDA (Japan), Health Canada	Prescribing information updated and daily dose reduced
3.	Direct acting hepatitis cantiviral (DRAP, 2017a)	Risk of hepatitis b virus (hbv) reactivation	PMDA (Japan) US-FDA	Prescribing information updated and box warning
4.	Irrational combination of Paracetamol 500 mg, Thioridazine 3 mg, and caffeine 70 mg (DRAP, 2016)	Withdrawn of Thioridazine worldwide by the brand leader Novartis. Combination not registered in any Stringent Regulatory Authority	Internal review and Novartis Pharma	Cancellation of Registration
5.	Oral ketoconazole (DRAP, 2016)	Potential to cause severe liver injuries	USFDA, European Medicines Agency's Committee (EMA), Health Canada	Cancellation of Registration
6.	Clarithromycin (DRAP, 2018)	A possible increase in the risk of heart disease	US-FDA	Prescribing information updated
7.	Canagliflozin (DRAP, 2018)	Risk of amputation of lower limb	US-FDA. European Medicines Agency (EMA)	Prescribing information updated, black box warning

to scrutinize the Individual Case Safety Reports (ICSRs). Drug Safety Alerts are posted on a Drug Control Unit's webpage. Punjab also uses Facebook and Twitter to disseminate safety information. Furthermore, KPK is in the process of developing an ADR collection system, while Baluchistan has yet nominated focal persons at the provincial and district levels. In 2018, ICT drug administration set up a PV center and signed MOU with 11 private hospitals of Islamabad for ADR reporting. Nearly 23 focal persons from the hospitals were trained on PV-related activities; despite all these efforts, the PV Center of ICT has not received any ADR.

Pharmacovigilance Activities at Public Health Programs

The quantitative results have not been computed because only a few indicators of assessment tools were verified in each program. That is why the findings are not summarized in a table or shown as a chart. The key informants were interviewed with a structured IPAT questionnaire and for additional information, the program manager and procurement officer/logistic support officer were interviewed through unstructured questions, and results are presented through the qualitative description. All vertical programs except EPI and Initiative for the eradication of polio have pharmacists in their staff.

National Malaria Control Program

The Directorate of NMCP has no PV unit and designated staff responsible for data management. No form to report ADR, problems with product quality, medication error, and treatment failure was available. The procurement of medicines is based on WHO prequalification criteria due to global fund requirements. The strategic plan for malarial control in Pakistan (2015–2020) does not account for ADRs reporting or medicine safety. Two separate studies were conducted including an assessment of therapeutic efficacy and safety of an anti-malarial drug (Directorate of malaria control Pakistan, 2017) and the quality of anti-malarial drugs. In one of the survey-based studies, the clinical safety of an anti-malarial drug was assessed.

National Tuberculosis Control Program

NTBCP also lacks a PV center; however, the procurement officer who is a pharmacist is assigned the additional responsibility of monitoring medicine-related issues. There is a form available for reporting suspected treatment failure (TB-07) and ADRs; however, the separate subset of other forms is not available for product quality-related problems and medication errors. The data for the number of ADR reports during last year was not available. Only treatment failure information was collected which was 3% last year. Only one medicine, i.e., vitamin B-6 was withdrawn from the market in 2018 due to quality-related issues.

National AIDS Control Program

The pharmacovigilance center and designated staff are not provided in the NACP. Quality assurance guidelines contain the statement regarding ADRs reporting. It is the responsibility of the antiretroviral therapy physicians to report any ADR. An internal form is available for reporting ADRs, product-related quality issues, medication errors, and suspected treatment failure. Less than 1% of patients had treatment failure during the last year. The procurement is mandated through WHO qualification.

Pakistan Polio Eradication Initiative

The PV center is not physically present. There is no ADR reporting form, however, through the online "contact us" form, anyone can submit a query related to the polio vaccine and its suspected effects.

Expanded Program on Immunization

There is no formal PV center, however, a monitoring and evaluation (M&E) wing is responsible for AEFIs. The WHO's SOPs for vaccine safety are being used. A quarterly bulletin is published since August 2017 and provinces issue their bulletins. During the last measles vaccination campaign the vaccinators

TABLE 3 | Primary and secondary healthcare department Punjab.

Pharmacovigilance indicators at the provincial level		Core/ supplementary	Score
2	Structures, systems, and stakeholders coordination		
2.1	Pharmacovigilance center exists	C	2
2.2	Clear mandate, structure, roles, and responsibilities of pharmacovigilance center exists	C	2
2.3	Medicine information service exists	C	0
2.4	Separate staff for pharmacovigilance	C	2
2.5	A dedicated budget for pharmacovigilance exists	C	0
2.6	National medicine safety advisory committee exists	C	2
2.7	National pharmacovigilance guidelines exists	C	2
2.8	SOPs for safe use of medicines exists	C	2
2.9	Basic communication tools provided for reporting and information on the safety of medicines	C	2
2.10	Drug safety bulletin exists	C	2
2.11	Reference materials available in pharmacovigilance center	S	1
2.13	Training of healthcare professionals on pharmacovigilance during the previous year	S	1
2.14	Countrywide platform or plan for coordinating pharmacovigilance initiatives	C	2
Subtotal score (%)			20/24 (83.33)
3	Signal generation and data management		
3.1	A mechanism for coordinating and compiling pharmacovigilance data from all sources across the country	C	2
3.2	Database for tracking pharmacovigilance activities exists	C	2
3.3	A form for reporting suspected ADRs exists	C	2
3.4	A form for reporting suspected product quality issues exists	C	2
3.5	A form for reporting suspected medication errors exists	C	2
3.6	A form for reporting suspected treatment failure exists	C	2
Subtotal score (%)			12/12 (100)
4	Risk assessment and evaluation		
4.1	Last year, a medicine utilization review performed	S	0
4.2	Within the previous 5 years, a survey for pharmaceutical product quality undertaken	S	1
4.3	Medication errors quantified in the last year	S	0
4.4	Number of ADR reports collected in the last year	C	2
4.5	Active surveillance activities conducted during the last 5 years	C	0
4.6	Public health programs reported ADEs for patients in the last year	C	0
4.7	Public health programs modified the treatment of patients due to ADRs in the last year	C	0
4.8	Public health programs reported serious ADEs of patients in the last year	S	0
Subtotal score (%)			3/12 (25%)
5	Risk management and communication		
5.1	Medicine safety bulletin published in the last year	S	0
5.2	Medicine safety issues addressed on external information	S	0
5.3	Safety alerts including "Dear healthcare professional" developed and distributed in the last year	S	1
5.4	The average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to healthcare workers and the public	S	1
5.5	Percentage of Drug and Therapeutics Committees that handled medicine safety issues during last year	S	1
5.6	Last year's public or community education initiatives on medication safety	S	1
5.7	Medicine safety bulletin published in the last year	C	2
5.8	Medicine safety issues addressed on external information	C	2
5.9	Safety alerts including "Dear healthcare professional" developed and distributed in the last year	S	0
5.10	Medicines sampled in the last year that passed product quality tests	C	2
Subtotal score (%)			9/13 (69.23)
Total			45/61 (73.77%)

were trained at the Union Council level for reporting AEFIs. There are case reporting forms and case investigation forms. A total of 2272 cases of AEFIs were reported in 2018. Most of the ADRs were coincidental. The WHO prequalification is not mandatory for procurements. An AEFI review committee is established at the national level.

Pharmacovigilance Activities at Health Facilities (Hospitals)

PV activities were assessed at 23 different health facilities that were selected at random. A hospital is considered a minimally functional health facility if it achieves a score of 38 on the IPAT data collection tool for health facilities, which consists of 30 PV indicators, 19 core, and 11 supplementary indicators. Since one private and two public hospitals [Agha Khan University Hospital (AKUH), Jinnah Hospital (JH) Lahore, and Children Hospital (CH) Lahore, respectively] did not respond to the IPAT data collection tool, the response rate of health facilities was observed to be 87%.

In contrast to the majority of private-sector hospitals, four private [i.e., Quaid-e-Azam International Hospital (QIH), Agha Khan Medical Center (AKMCG) Gilgit, Baluchistan Institute of Nephrology and Kidney Transplant (BINIQ) Quetta, and Riaz

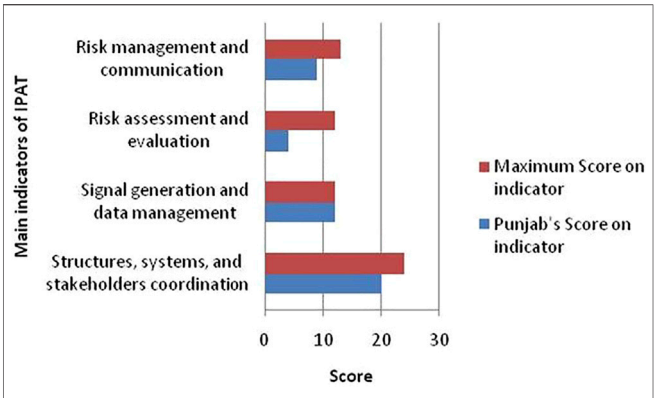

FIGURE 3 | Score of Punjab PV center on main indicators of IPAT.

Hospital (RHM) Mirpur, AJK] and nine public hospitals [i.e., Benazir Bhutto Shaheed Hospital (BBH), District Headquarter Hospital (DHH), and Holy Family Hospital (HFH), Federal Government Polyclinic Hospital (FGPH), and Pakistan Institute of Medical Sciences (PIMS) in Islamabad, Punjab Institute of Cardiology (PIC) Lahore, DHQ Hospital (DHQHG) Gilgit, Bolan Medical Complex Hospital (BMCH) Quetta, and DHQ Teaching Hospital (DHQTH) Mirpur AJK] at both the federal and provincial levels were found to be lacking in PV centers and related activities, so no response was tabulated or displayed in the radar chart. However, three private [i.e., Rehman Medical Institute (RMI), Shifa International Hospital (SIH), and Shaukat Khanum Memorial Cancer Hospital (SKMCH)] and four public [i.e., Allied Hospital (AH), Hayatabad Medical Complex (HMC), Jinnah Postgraduate Medical Centre (JPMC), and National Institute of Child Health (NICH)] hospitals responded to the IPAT data collection tool, and their responses are tabulated in **Table 4**. PV activities of healthcare facilities decrease in the following order: Hospital [score (%)]: SKMCH [41 (83.6)] > SIH [38 (77.5)] > AH [29 (59)] > NICH [23 (46.9)] > HMC and RMI [14 (28.5)]. SKMCH received the highest scores, SIH is a minimally functional health facility, while AH, and HMC, NICH, and RMI received lower scores than a minimally functional health facility. Private hospitals that do have PV systems do not share ADR-related data with national or provincial PV centers.

DISCUSSION

The study examines Pakistan's present PV system. Although no performance criterion has been set to define an effective PV system in a specific country, however, IPAT recommends that the PV system of a country must meet all of the core indicators to be considered minimally functional (SPS Program, 2009). DRAP attained (21/26) 80.76% score of the core indicators and, therefore, at the moment cannot be considered functional. Similar results are reported during the evaluation of PV systems for two African countries (Kabore et al., 2013; Constant Allabi and Nwokike, 2014) and Nepal by using the IPAT (Jha et al., 2021). However, in comparison to the survey conducted by Danya (2015) DRAP has improved few indicators of risk assessment and evaluation (Qato, 2018).

The NPC currently employs seven officers. This figure is insufficient in comparison to the number of registered medications in the country and the growing number of ADR reports. A study found less than 10 trained personnel in more than 80% of study participant countries (Olsson et al., 2010). The scarcity of trained staff affects the data management and performance of PV systems (Wilbur, 2013) and is the reason for unsuccessful experiences (Chejor, 2018).

The DRAP's NPC has received 6587 ADR reports in total. However, this number is much lower than required as per WHO standards which indicate that over 200 reports per one million inhabitants are produced annually by the countries with the best reporting rates. Considering more than 200 million people, the size of Pakistan's population, a total of 40,000 reports annually are predicted (Syed et al., 2018). Not a single ADR is received from the general population, however, a limited number of ADRs were reported by HCPs, which indicates a need for their PV education, awareness, and training. DRAP has provided an e-reporting system and Android application for ADR reporting, and it is obligatory to explore the reasons and barriers for non-reporting by the general public. An annual increase in the number of ADR reports can be seen from 2018 to 2020. The number of reports received in 2019 is 20 times higher than in 2018, and nearly two times higher in 2020 compared with 2019. It may be implied that as Pakistan's PV system advances, the number of ADR reports will increase. The WHO's threshold of ADR reports per million can be achieved in Pakistan over a certain period of time provided that a sustainable PV system is implemented. Similarly, another study reveals that long-term tradition of ADR reporting increases the number of reports (Glamočlija et al., 2018). The low number of ADR reports in Pakistan is due to various factors including non-reporting by the physicians. Hussain et al. (2021) informed that physicians and nurses of a teaching hospital did not report any ADRs during 1 year (Hussain et al., 2021). Other studies show similar results (Bäckström et al., 2000; Oshikoya and Awobusuyi, 2009). In various studies conducted in Pakistan, physicians, pharmacists, and nurses all cited fear of legal consequences as a major barrier to reporting (Khan et al., 2015; Nisa et al., 2018; Hussain et al., 2018).

Both DRAP and the directorate of drug control, PSHD Punjab issue newsletters, communicate safety alerts on their websites (DRAP 2021b; 2019; Provincial Quality Control Unit Punjab, 2021) and social media accounts like Facebook and Twitter which can help in improving the ADR reporting as several studies suggest that designated social media websites/apps like Twitter and WhatsApp connected with national and regional PV centers can help in collecting ADRs (Daley et al., 2018; Shrestha et al., 2019; Hussain, 2021; Meher, 2021).

Measurement in PV has shifted from the traditional measurement of operational performance to measuring the specific regulatory action. The stringent regulatory authorities are focusing on risk minimization measures. The ultimate test for the PV system is a demonstration of public health benefits. DRAP

TABLE 4 | Health facilities pharmacovigilance indicators.

30 Pharmacovigilance indicators			Health facilities							Total*	Achieving indicator (% HF)**
			A	B	C	D	E	F	G		
1	(2.1)	Pharmacovigilance center exists	2	2	2	2	2	0	0	1.42	71
2	(2.2)	Clear mandate, structure, roles, and responsibilities of Pharmacovigilance center exists	2	2	0	0	2	0	0	0.85	42.5
3	(2.3)	Medicine information service exists	2	2	0	2	2	2	2	1.71	85.5
4	(2.4)	Separate staff for pharmacovigilance	2	2	2	2	2	0	0	1.42	71
5	(2.5)	A dedicated budget for pharmacovigilance exists	0	0	0	0	0	0	0	0	0
6	(2.8)	SOPs for safe use of medicines exists	2	2	0	0	2	2	2	1.42	71
7	(2.9)	Basic communication tools provided for reporting and information on the safety of medicines	2	2	2	2	2	0	0	1.42	71
8	(2.10)	Drug safety bulletin exists	0	2	0	0	2	0	0	0.57	28.5
9	(2.11)	Reference materials available in pharmacovigilance center	1	1	1	1	1	1	1	1	100
10	(2.13)	Training of healthcare professionals on pharmacovigilance during the previous year	1	1	0	0	1	0	0	0.42	42
11	(3.3)	A form for reporting suspected ADRs exists	2	2	2	2	2	2	2	2	100
12	(3.4)	A form for reporting suspected product quality issues exists	0	0	0	0	2	2	2	0.85	42.5
13	(3.5)	A form for reporting suspected medication errors exists	2	2	0	0	2	2	2	1.42	71
14	(3.6)	A form for reporting suspected treatment failure exists	0	0	0	0	2	0	0	0.28	14
15	(4.1)	Last year, a medicine utilization review performed	0	1	0	1	1	0	0	0.42	42
16	(4.3)	Medication errors quantified in the last year	0	1	1	1	1	0	0	0.57	57
17	(4.4)	Number of ADR reports collected in the last year	0	2	0	0	2	0	0	0.57	28.5
18	(4.5)	Active surveillance activities conducted during the last 5 years	0	2	0	2	0	0	0	0.57	28.5
19	(4.6)	Public health programs reported ADEs for patients in the last year	2	0	0	0	2	0	0	0.57	28.5
20	(4.7)	Public health programs modified the treatment of patients due to ADRs in the last year	2	2	0	0	2	0	0	0.85	42.5
21	(4.8)	Public health programs reported serious ADEs of patients in the last year	1	1	1	0	1	0	0	0.57	57
22	(5.1)	Risk mitigation plans targeted at high-risk medicines	1	1	1	1	1	1	1	1	100
23	(5.3)	In the last year, medicine safety information requests received and addressed	1	0	0	1	1	0	0	0.42	42
24	(5.4)	Medicine safety bulletin published in the last year	0	1	0	0	1	0	0	0.28	28
25	(5.5)	Medicine safety issues addressed on external information	0	1	0	0	1	0	0	0.28	28
26	(5.6)	Safety alerts including "Dear healthcare professional" developed and distributed in the last year	0	1	0	0	1	0	0	0.28	28
27	(5.7)	The average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to healthcare workers and the public	2	2	2	2	2	2	2	2	100
28	(5.8)	Percentage of Drug and Therapeutics Committees that handled medicine safety issues during last year	2	2	0	2	0	0	0	0.85	42.5
29	(5.9)	Last year's public or community education initiatives on medication safety	0	1	0	0	1	0	0	0.28	28
30	(5.10)	Medicines sampled in the last year that passed product quality tests	0	0	0	2	0	0	0	0.28	14.8
Total score for minimally functional health facility (38)/Total maximum score (49)			29	38	14	23	41	14	14	—	—

*A, Allied Hospital, Faisalabad; B, Shifa International Hospital, Islamabad; C, Jinnah Postgraduate Medical Centre, Karachi; D, National Institute of Child Health, Karachi; E, Shaukat Khanum Memorial Cancer Hospital, Lahore; F, Hayatabad Medical Complex, Peshawar; G, Rehman Medical Institute, Peshawar; 0, absence of core/supplementary indicator; 1, presence of supplementary indicator; 2, the presence of core indicator. *Total = Average sum/7; **Percent health facility achieving indicator = 100 x total/a (a = 1 or 2 for supplementary or core indicator, respectively).*

always takes into account the safety reports coming from outside sources for regulatory actions (**Table 2**). It shows DRAP pledges to patient safety and access to quality medicines.

A country's commitment to medicines' safety can be gauged with the existence of PV policy. Similarly, the enactment of regulations ensures the legal cover to the monitoring and compliance by all stakeholders (Nwokike and Eghan, 2010). There is a clear policy of DRAP on medicine safety. However, the legislation requiring mandatory ADR reporting by stakeholders is missing. The ADR reporting system in Pakistan is voluntary. At the moment DRAP cannot enforce mandatory reporting by all stakeholders until the federal government of Pakistan approves the draft pharmacovigilance rules.

To provide independent scientific advice and guidance on medication safety a functional national advisory committee is required. The Pharmacovigilance Risk Assessment Expert Committee (PRAEC) is not established since the establishment of NPC in 2015. However, a "Causality Assessment and Signal Review group" comprised of DRAP officers defining the internal working has been notified. The absence of PRAEC is one of the major reasons that no safety signal has been generated on ICSRs by Pakistan (UMC, 2021b).

The WHO recommends that a better way of collecting spontaneous ADR reports is by using regional PV centers. Communication regarding medicine safety also works well at regional centers with short communication lines with HCPs (UMC, 2000). Pharmacovigilance centers are also absent from all provincial health departments except for Punjab. Only Punjab is sharing medicines safety reports with DRAP where half of the country's population lives. PV activities are believed to be solely the responsibility of the DRAP by provincial health administrative units; this perception needs to be altered, potentially through education, training, and active interactions.

Even though most Pakistan's national health programs are funded by the global fund (The Global Fund, 2020), the formal PV system is lacking in all programs. According to the WHO, PV should be a part of every PHP, to optimize the usage of limited health resources and avoid possible medicine-related catastrophe (WHO, 2006). One of the reasons for the absence of PV activities at PHPs is that PV is not duly included in the funding proposal as

seen in the strategic plan for the Malaria Control Program Pakistan, 2015–2020 (Directorate of malaria control Pakistan, 2014), which lacks any provision for reporting ADRs. Likewise, Stergachis et al. (2010) assessed proposals and operational plans of 15 countries for global fund malaria and the US president's malaria initiative and found that PV-related activities and financial support requests are not included adequately and consistently (Stergachis et al., 2010).

Allegations of vaccine-related adverse events that are not promptly and thoroughly addressed can erode vaccination faith and have far-reaching implications for immunization coverage and disease incidence (WHO, 2021b). Pakistan is one of the two countries along with Afghanistan that is struggling to get polio-free. Conspiracy rumors about the polio vaccine ADRs also play a pivotal role in the public for not trusting the vaccine. In a controversy that emerged in 2019 in Peshawar, Pakistan, hundreds of children rushed to hospitals with abdominal problems and fainting following the immunization. The angry protesters torched a health center. The government responded immediately and a key conspirator was arrested for his involvement in spreading the rumors. To gain the trust of parents on immunization it was proposed to disseminate information on the number of administered vaccine doses and their ADRs (Ali et al., 2019). This incident highlighted the importance of risk management and communication.

To our knowledge, no research has ever been undertaken to evaluate the PV systems of health facilities in Pakistan. The majority of the studies are conducted to measure the knowledge attitude and practices of HCPs (Iffat et al., 2014; Raza and Jamal, 2015; Atif et al., 2016; Hussain et al., 2018; Nisa et al., 2018; Syed et al., 2018; Muhammad et al., 2021) PV systems are found missing in almost all of Pakistan's public sector hospitals. This may be because of the non-availability of ADR forms in hospitals (Nisa et al., 2018; Syed et al., 2018), poor knowledge and ADRs reporting practices of health care professionals (Nisa et al., 2018), lack of knowledge about ADR reporting systems in the country, the gap between hospitals and regulators in terms of training and communication (Hussain et al., 2018), and concerns over legal responsibility (Mustafa et al., 2013). The irony is that the Punjab Institute of Cardiology where the Isotab tragedy took place has no PV system or activities. Our results show that not all hospitals have a budget set aside for PV-related activities. Similar findings are explained in a study conducted in the south-south zone of Nigeria (Opadeyi et al., 2018).

It was observed that DRAP responded to the Isotab (isosorbide mononitrate 20 mg) (LHC, 2012) and Tyno cough syrup (chlorpheniramine maleate and dextromethorphan 15 mg/5 ml) (Tribune, 2012) events but not in the same way that the rest of the world has to the thalidomide tragedy. We proposed two stages of framework for the advancement of the PV system in Pakistan. The approval of draft PV Rules and the establishment of a Pharmacovigilance Risk Assessment Expert Committee require no financial investment at the first level. Step two involves initiatives such as the development and strengthening of PV centers at national, provincial, PHPs, and hospitals levels, the recruitment of trained staff, planned PV training programs, and developing alliances with universities to perform a drug utilization review or active surveillance activities, all of which entail financial investment.

There are some limitations of the study. To verify the information, the respondent's replies are considered unless verified from the documentary evidence. IPAT carries some inherent limitations related to the non-establishment of sensitivity and specificity of indicators. Due to convenience sampling, the data may not represent the whole country. Despite all these facts, the study provides a basis for further research to explore challenges and barriers in the approval of PV regulation through in-depth interviews.

In conclusion, the study revealed that the pharmacovigilance system of Pakistan is not meeting the minimum standards. Public health programs and health facilities need to set up PV systems and integrate them with the national PV center.

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 study involving human participants was reviewed by the Institutional ethics review board of Health Services Academy, Islamabad, Pakistan. Before the interviews, consent and time for the interview were confirmed telephonically from participants in the study. To maintain privacy, the data were processed anonymously.

AUTHOR CONTRIBUTIONS

M.K. conceptualized, collected data, analyzed the results, and drafted the manuscript. S.H. conceived the idea, interpreted results, edited and revised the manuscript, T.R. contributed to data analysis, manuscript editing, and revision. Z-U-D.B. contributed to manuscript development, data analysis, results interpretation, and manuscript revision. The final version of the manuscript was checked and accepted by all contributors.

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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.2021.789103/full#supplementary-material

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Potentially Hazardous Drug-Drug Interactions Associated With Oral Antineoplastic Agents Prescribed in Chinese Tertiary Care Teaching Hospital Settings: A Multicenter Cross-Sectional Study

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Background: Oral administration increases the risk of interactions, because most oral antineoplastic agents (OAAs) are taken on a daily basis. Interactions can increase exposure to antitumoral agents or cause treatment failure. Potential drug–drug interactions (DDIs) are commonly observed in patients with cancer, while the extent to which OAAs related hazardous DDIs remains unclear.

Methods: We studied the contraindication patterns between oral antineoplastic agents and other medications among cancer patients in two tertiary care teaching hospitals in China. A total of 20 clinically significant hazardous DDI pairs that involved 30 OAAs were identified based on the predetermined criteria. Patient medications were checked for DDIs by using the US Food and Drug Administration approved labeling. Descriptive statistics and uni- and multivariate logistic regression analyses were carried out.

Results: In this study, 13,917 patients were included and a total of 297 DDIs were identified. The results revealed that proton pump inhibitors (PPIs), dexamethasone and fluoroquinolones were the most often involved hazardous DDIs with OAAs. The most prevalent contraindication is the simultaneous use of certain molecular targeted agents and PPIs. In the result of the multivariate analysis, younger age (0–20 group), increasing number of drugs and patient treated with targeted therapy had a higher risk for DDIs.

Conclusion: The prevalence of OAAs related hazardous DDIs appears to be low in the cancer patients. However, physicians and clinical pharmacologists should be aware of the potential hazardous DDIs when prescribing OAAs, especially certain pH-dependent molecular targeted agents and potential QTc prolonging drugs.

Keywords: oral antineoplastic agents, cancer, drug-drug interaction (DDI), prevalence, adverse drug events (ADE)

INTRODUCTION

Cancer patients are at a higher risk of drug-drug interactions (DDIs), because they usually take multiple medications. Moreover, the majority of cancer patients are elderly individuals who require additional medications due to comorbidities (Riechelmann et al., 2007; Targownik et al., 2007; Shinohara et al., 2018; Herrmann, 2020). Studies have shown that 0.6–5% of hospitalizations related to adverse drug events (ADEs) are because of drug interactions, which is generally believed to account for a significant proportion of ADEs (Becker et al., 2007; Roughead et al., 2010). Additionally, approximately 4% of cancer-related deaths were assessed to be brought about by DDIs (Buajordet et al., 2001). DDIs involving oral anticancer therapies may reduce the effectiveness or increase the risk of toxicities resulting in unexpected treatment outcomes (Riechelmann et al., 2007).

A risky DDIs would have a negative impact on most patients taking the combination, or the risks far outweigh the potential benefits. Cancer patients in hospital settings are usually treated with multidrug regimens that increase the likelihood of dangerous interactions when anticancer drugs are needed. A review showed that 34% of cancer patients treated with chemotherapy have experienced at least one severe DDIs (defined as life-threatening or irreversible damage) that can have serious clinical consequences (van Leeuwen et al., 2011). The increased burden of treatment for cancer patients increases the risk of such prescriptions. Therefore, prevention of adverse interactions is one of the most important factors to consider in terms of efficacy and safety when deciding on drug prescription (Chen et al., 2005). Although several studies have evaluated the prevalence of potential drug interactions in cancer patients (Riechelmann et al., 2007; van Leeuwen et al., 2011), the prevalence of potential DDIs associated with oral antineoplastic agents (OAAs) is unknown. We systematically analyzed the risk patterns between OAAs and other medications that occurred over a three-year period (2018–2020) to determine whether these warnings were contraindicated according to drug labeling in the Chinese hospitals.

MATERIALS AND METHODS

A two-center cross-sectional study of contraindications patterns between OAAs and other patient medications was conducted in 2018–2020 for all cancer patients in the two Chinese tertiary care hospitals (The Second Affiliated Hospital of Xi'an Jiaotong University and Yan'an People's Hospital). Computerized drug interaction screening programs do not exist in either hospital. The study protocol was approved by the ethics committees of both hospitals. All medical data were collected from the electronic hospital data management system of each selected hospital from January 2018 to December 2020.

All patients were treated with OAAs in the hospital settings. Analysis was limited only to patients who received two or more than two drugs where at least one of them was oral antineoplastic agents (**Supplementary Table S1**). Potentially hazardous drug interactions that did not include oral chemotherapy were excluded from the study. We also removed interactions with products that were not identifiable from the hospital's electronic data, such as herbal medicines, over-the-counter drugs, alcohol, orange and grapefruit juices, and the topical medications for skin conditions. The hazardous drug combinations were tested when the exposure period for two medicines was matched. We defined co-prescribing as one or more overlapping days of supply between the OAAs and DDI drugs. If a drug contained more than one pharmacologically active ingredient, each drug was counted separately in the analysis. If a patient took the same drug in two or more formulation (e.g., i.v. or oral moxifloxacin for infections control), the drug was counted only once.

An initial list of hazardous combinations of any oral antineoplastic agent with any medication was checked for DDIs using the Micromedex drug–drug interaction program (Buajordet et al., 2001; Micromedex Solutions). DDI pairs were considered clinically important in the study if they were listed on Micromedex with a justification assessment that was established or may be contraindicated, major, or moderate. After extensive screening of drug information software, the Food and Drug Administration (FDA)-approved product labeling was used to determine the final list of hazardous combinations as a second screening. The terms "contraindicated", "avoid" or "do not be co-administered" were used to identify the presence of hazardous drug-drug interactions within the FDA-approved label. Only the specific drugs listed on the FDA-approved label were used to identify the DDI pair in the analysis. OAAs have been defined as all cytostatic, antihormonal and molecular targeted drugs to treat malignancies. The hazardous combinations were counted only once when patients were given the same type of drug in succession, since the interaction mechanism of these drugs on oral antineoplastic agents is same, such as lansoprazole and omeprazole. DDIs can be categorized by mechanism in two major groups: pharmacokinetic DDIs and pharmacodynamic DDIs.

Descriptive statistics were applied to characterize the entire study sample in terms of demographics, cancer type, length of hospital stay, type of anticancer agents, comorbidities, number of drugs per patient, and interaction characteristics. Patients were divided into five age groups: pediatric (0–20 years old), 21–40 years old, 41–60 years old, 61–80 years old, and over 81 years old. Univariate and multivariate logistic regression analyzes were performed to identify the potential risk factors for the occurrence of contraindicated interactions. The occurrence of at least one potentially adverse interaction per patient was the dependent variable. And the explanatory variables were age, number of drugs, number of comorbidities, type of tumor (haemato-oncology/oncology), length of hospitalization and type of treatment. Gender was not included as a covariate variable due to the fact that certain types of cancer are only found in males or females. For binary or nominal variables, the lower risk group was chosen as the referent. Variables with univariate p values < 0.05 were included in the multivariate analysis. In the multivariate analysis, a p value of <0.05 was considered statistically significant.

RESULTS

Overall, a total of 13,917 patients were investigated during the 3-years study period, with a mean age of 57 years (range 4–95 years) and

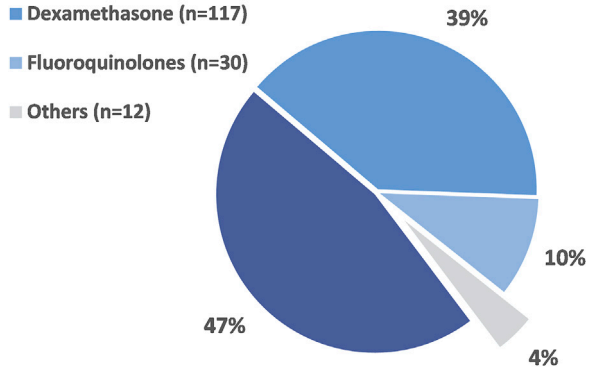

FIGURE 1 | The proportion of different drug classes associated with potentially hazardous DDIs in the studied population.

9,301 patients (66.8%) were female. The median number of drugs used per person was 7 (range 1–63 drugs) and the median hospital stay was 5 days (range 1–90 days). The median number of comorbidities per patient was 0.5 (range 0–8) and 30.1% of all patients had at least one comorbidity. Demographic characteristics are listed in **Supplementary Table S2**. To evaluate drug interactions, the drugs as a victim drug and perpetrator drug were included both in the analysis, but no contraindicated DDIs for the perpetrators were identified. The antineoplastic agents used as the victim drugs were not strong CYP3A4 inducers or inhibitors and therefore had no significant effect on other drugs.

Drug–Drug Interactions

A total of 297 DDI contraindications were identified in 285 patients (2.0%) considering for oral antineoplastic agent. Pharmacokinetically hazardous DDIs were found in 87.5% of all cases. Potentially hazardous DDIs associated with oral anticancer drugs and other agents are listed in **Supplementary Table S3**. The class of drugs most frequently associated with hazardous DDIs with oral antineoplastic agents were PPIs (47%), dexamethasone (39%) and fluoroquinolones (10%) (**Figure 1**). The most common contraindications were the concomitant use of PPIs with certain molecularly targeted agents. PPIs involved in dangerous DDIs with oral chemotherapy may require multiple days of exposure to be clinically relevant. In our study, these long-term drug exposure-related DDIs accounted for 46.5% of all hazardous DDIs. The next most common combination was toremifene, imatinib or axitinib with dexamethasone and potential QTc prolonging oral anticancer drugs with fluoroquinolones or domperidone.

Potential Risk Factors

All patients were included in the binary logistic regression analysis. In the unadjusted analysis, age, number of comorbidities, number of drugs, number of days hospitalized, tumor type and patients receiving targeted therapy were associated with an increased risk for hazardous DDIs. **Supplementary Table S1** shows the results of the univariate and multivariate binary logistic regression analyses. After adjustment for confounders, age [age –020, odds ratio (OR) 0.95 (95% confidence interval (CI) 99.6–1,186.8)], number of drugs [OR 1.08 (95% CI 1.06–1.1)] and treatment type [targeted therapy, OR 4.83 (95% CI 1.45–16.04)] remained statistically significant.

DISCUSSION

Our study found that PPIs, dexamethasone and fluoroquinolones were the most commonly reported DDIs along with OAAs. Factors such as increased number of medications, younger age, longer hospital stays and targeted therapy are associated with an increased risk of dangerous DDIs. We observed that a prevalence of hazardous DDIs with 2% of all patients being exposed to at least one DDI. The finding that increasing number of medications was a risk factor for potential drug interactions in our population is consistent with the results of previous studies (van Leeuwen et al., 2013). This can be explained by the fact that the number of medications is likely to increase as the length of stay for treatment increases. Remarkably, young age has been identified as a risk factor for contraindicated DDIs. A plausible explanation for this is that patients receiving targeted therapy are much younger than other type of therapy. The highest prevalence was attributed to targeted therapy, accounting for up to 60% of all contraindicated DDIs.

The most commonly used drugs with potentially hazardous interactions with OAAs were PPIs. Patients undergoing cancer treatment often use acid-reducing agents such as PPIs, H_2-receptors antagonists, and antacids for gastroesophageal reflux disease, dyspepsia, or gastritis associated with chemotherapy (Budha et al., 2012). Acid-reducing agents are prescribed in about 20–33% of cancer patients, and among them, PPI is the most prescribed. However, the use of these agents also increases the risk of potential DDIs, as the dissolution and subsequent absorption of many orally administered, molecularly targeted anticancer drugs exhibit pH-dependent solubility. There are many factors that affect the absorption of anticancer drugs, but pH-dependent solubility is one of the main determinants and the oral bioavailability of these drugs can be significantly altered when administered with PPIs (Smelick et al., 2013; van Leeuwen et al., 2017). The risk of death in cancer patients increased by 16% in combination with various molecularly-targeted anticancer drugs and PPIs therapy (Sharma et al., 2019). In a retrospective study, overall survival in patients with advanced non-small cell lung cancer treated with erlotinib plus acid suppression was significantly different from that of the no-acid-suppression group (12.9 vs. 16.8 months; p = 0.003) (Chu et al., 2015). Consequently, the potential for absorption-related drug interactions with these oral targeted oncolytic agents is often observed in hematology/oncology practice, and it is important to understand the impact of these interactions to avoid the reduction of drug efficacy (Budha et al., 2012).

Prolongation of the QTc interval is one of the known but relatively rare side effects of many anticancer drugs including several molecular targeted drugs (including sorafenib, crizotinib and nilotinib) and antihormonal drug (toremifene). These

anticancer therapies have properties known to induce QTc interval prolongation through various mechanisms, including direct effects on ion channels and indirectly *via* intracellular signaling pathways (Chandrasekhar and Fradley, 2019). Fluoroquinolones and domperidone are commonly used to treat cancer patients with infections, nausea or vomiting. However, cardiac adverse events such as QTc prolongation and amplified risk of torsades de pointes (TdP) have also been observed in patients taking fluoroquinolones or domperidone (Rossi and Giorgi, 2010; Douros et al., 2015). Although the incidence of cardiac events is low with the use of fluoroquinolones or domperidone alone, the concurrent use of drugs that potentially prolong the QTc interval may markedly increase the risk of pro-arrhythmic effects (Haverkamp et al., 2012; Biewenga et al., 2015; Ehrenpreis et al., 2017; Brunetti et al., 2019). Therefore, the administration of these anticancer drugs should be carefully monitored during concurrent use of other potential QTc prolonging drugs. If possible, an alternative drug that do not affect the QTc interval should be selected (Briasoulis et al., 2011). Electrocardiogram (ECG) monitoring during initiation of these QTc-interval-prolonging anticancer drugs is only necessary in patients who have an underlying condition that predisposes them to TdP or are receiving concomitant medications that may prolong the QTc interval.

Dexamethasone is widely used in the treatment of breast cancer to combat the side effects of chemotherapy and to treat symptoms related to advanced cancer. Although FDA-approved labeling indicates contraindications to the use of toremifene, sorafenib, or imatinib with dexamethasone, it is unclear whether DDIs between dexamethasone and these anticancer drugs has a clinical relevance. Evidence may reflect *in vitro* data indicating that dexamethasone is a relatively weak inducer compared to the prototype inducer and the ligand of the pregnane X receptor activator rifampicin (Revollo and Cidlowski, 2009). In clinical trials, erlotinib is known as a substrate for CYP3A4, and even short-term administration of 4 mg of dexamethasone for 3 days did not affect erlotinib concentrations (Ranson et al., 2010). Moreover, dexamethasone as a weak inducer is not contraindicated on the FDA-approved labeling of other known substrate of CYP3A4 anticancer drug substrates. Therefore, the existence of clinically significant drug interactions between dexamethasone and some anticancer drugs requires further clinical studies.

A major limitation of this study is that the clinical consequences of these drug interactions have not been investigated because of the limited information available in our dataset. We studied DDIs only while patients were hospitalized, and there are currently no studies on whether patients will continue to use them after discharge. It is unclear whether short-term contraindications affect the overall effectiveness of cancer treatment. Another limitation relates to FDA-approved labeling to identify all potentially hazardous drug combinations. Due to the large amount of screening data, we mainly use only the specific drugs listed to determine DDI pairs in the analysis based on the FDA labeling and do not include the entire class of such drugs, which may likely to miss some clinically relevant DDIs for identification. Nevertheless, drug labeling is an important resource that provides detailed information on contraindicated drug combinations information and is an important aid in clinical decision-making. Additionally, several contraindicated drug combinations, including OTC drugs, may have been missed, and herbal medicines used in hospitals could not be identified in this study due to lack of information in computer system records. Some foods containing enzyme inhibitors (including grapefruit juice) were not available in our hospital system, which may significantly affect the metabolism of some OAAs.

In our study, only 2% of the 13,917 patients included in the study were identified using potentially hazardous interacting medicines. However, high-risk patients, such as those receiving targeted therapy or those receiving a growing number of drugs, especially patients taking pH-dependent molecularly targeted agents and potential QTc prolonging drugs, should be concerned about potential drug interactions. To maximize the safety and efficacy of oral antineoplastic agents concurrently with other medications, clinicians and clinical pharmacologists should to be more aware of these potential contraindications in hematology/oncology and work closely to identify and treat these DDIs before the start and during anticancer treatment.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conception and study design: HW; data collection: all; data analysis: HW and JX; writing original draft: HW and SF; editing and final approval: all.

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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.2022.808848/full#supplementary-material

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Prescription of Potentially Inappropriate Medication Use in Older Cancer Outpatients With Multimorbidity: Concordance Among the Chinese, AGS/Beers, and STOPP Criteria

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Objectives: Age-related multimorbidity is a general problem in older patients, which increases the prevalence of potentially inappropriate medication (PIM) use. This study aimed to examine the prevalence and predictors of PIM use in older Chinese cancer outpatients with multimorbidity based on the 2017 Chinese criteria, 2019 AGS/Beers criteria, and 2014 STOPP criteria.

Methods: A cross-sectional study was conducted using electronic medical data from nine tertiary hospitals in Chengdu from January 2018 to December 2018. The 2017 Chinese criteria, 2019 AGS/Beers criteria, and 2014 STOPP criteria were used to evaluate the PIM status of older cancer outpatients (age ≥65 years), the concordance among the three PIM criteria was calculated using kappa tests, and multivariate logistic regression was used to identify the risk factors associated with PIM use.

Results: A total of 6,160 cancer outpatient prescriptions were included in the study. The prevalence of PIM use was 34.37, 32.65, and 15.96%, according to the 2017 Chinese criteria, 2019 AGS/Beers criteria, and 2014 STOPP criteria, respectively. Furthermore, 62.43% of PIMs met table 2, 0.27% of PIMs met table 3, 34.68% of PIMs met table 4, 2.62% of PIMs met table 5 of 2019 AGS/Beers criteria, respectively. According to the three criteria, 84.93%, 82.25%, and 94.61% of older cancer outpatients had one PIM. The most frequently used PIM in cancer outpatients was estazolam. The Chinese criteria and the STOPP criteria indicated poor concordance, whereas the 2019 AGS/Beers criteria showed moderate concordance with the other two criteria. Logistic regression demonstrated that age ≥ 80, more diseases, polypharmacy, irrational use of drugs, and lung cancer were positively associated with PIM use in older cancer outpatients.

Conclusion: The prevalence of PIM use in Chinese older cancer outpatients with multimorbidity is high in China, and poor-to-moderate concordance among the three criteria was observed. Research on building PIM criteria for the older cancer population is necessary in the future.

Keywords: potentially inappropriate medications, cancer, older, criteria, outpatient

INTRODUCTION

With the global population aging, the total number of people aged 60 years and older in the world is expected to reach 2 billion by 2050. China is the most populous country in the world, and the older population is also the largest (Jia et al., 2020). Older adults are more likely to suffer from multiple diseases, especially chronic diseases requiring complex treatments, such as taking many different medicines (Cojutti et al., 2016). Polypharmacy (defined as more than five medicines) is associated with the prescription of inappropriate medications, and a growing body of evidence links polypharmacy with negative outcomes (Field et al., 2001; Ferner and Aronson, 2006; Maddison et al., 2011; Weng et al., 2013; LeBlanc et al., 2015).

However, alterations in age-related pharmacokinetics and pharmacodynamics of older adults have led to an increased risk of drug–drug interactions and drug–disease interactions (Fried et al., 2014; Payne, 2016). Cancer patients are particularly prone to unintended consequences of polypharmacy because chemotherapy may carry a risk of drug–drug interactions and adverse drug events, which may include chemotherapy-related toxicity (Maggiore et al., 2014; Woopen et al., 2016). Some studies have shown that older cancer patients could suffer from a higher rate of comorbidity, frailty, and geriatric syndrome, putting them at high risk of polypharmacy and inappropriate medication use (Wildiers et al., 2014; Koczwara et al., 2022).

Potentially inappropriate medication (PIM) is a public health issue that can be defined as medications that should be avoided and may outweigh the expected clinical benefit, such as adverse drug events, hospitalization, disability, and economic burden (Hyttinen et al., 2016; Muhlack et al., 2017; Wallace et al., 2017). The American Geriatrics Society (AGS)/Beers criteria were the first expert consensus on geriatric PIM (Beers et al., 1991). The AGS, through an expert US-based panel, has undertaken the task of regular review and updating of AGS/Beers criteria, which are now in their sixth iteration (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). There were some substantial changes in the categories, and some medications were dropped or added. Because Beers criteria were not organized according to physiological systems, University College Cork organized experts from many disciplines to formulate the screening tool of old persons' prescriptions to alert to the right treatment (STOPP/START criteria) through the Delphi method, and the second edition was updated in 2014 (O'Mahony et al., 2015; O'Mahony, 2020). Two criteria have been widely used in PIM use application surveys in communities, clinics, and hospitals worldwide. China formulated the criteria for judging the potentially inappropriate medication use of older adults by an expert panel in 2017, including medication risk and medication risk under disease status (Rational Drug Use Branch of Chinese Association of Geriatric, 2018). These country-specific criteria were divided into high-risk and low-risk medications according to experts' evaluation.

Some previous reports examined PIM use in older Chinese patients based on the three criteria. However, no study has specifically reported on the concordance among the three criteria. The prevalence and the risk factors associated with PIM use according to the three criteria in older Chinese cancer patients are unclear. The concordance of different criteria often led to large differences in the results. Besides, country-specific and non-country-specific criteria significantly impact PIMs in older cancer patients. Therefore, in this study, we extracted prescriptions of cancer outpatients treated at tertiary hospitals in Chengdu, China. PIMs were screened based on the 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria. The concordance among the three PIM criteria was calculated, and the prevalence and the risk factors associated with PIMs were explored. It is hoped that this study will provide relevant evidence for follow-up research.

METHODS

Setting and Sample

The cross-sectional study was performed to examine the concordance between the 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria on the detection of PIM use among older cancer outpatients with multimorbidity in tertiary hospitals in Chengdu, a capital city in southwest China, which covers an area of 12,390 square kilometers, with a permanent population of 16.0 million in 2017. The prescriptions of older (aged ≥65) cancer outpatients with multimorbidity (cancer with other diseases) were cluster sampled from a hospital prescription analysis cooperation project led by the Chinese Pharmaceutical Association between 1 January and 31 December 2018. All data were retrospectively encoded without any possibility of identification and treated.

Data Collection

The data were collected by diagnoses type as follows: 1) basic information (region, prescription number, and department source); 2) patient characteristics (age, gender, and diagnosis); and 3) medication characteristics (generic name, trade name, specification, dosage form, administration route, number of prescriptions, prescription expenditure dosage, and frequency of administration).

Evaluation Criteria

The 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria were used to evaluate PIM use for older cancer outpatients outside of palliative care and hospice service. The prescription in this study was evaluated as potentially inappropriate with PIM use in older adults (table 2), PIM use in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (table 3, drugs to be used with caution in older adults (table 4, and potentially clinically important drug–drug interactions that should be avoided in older adults (table 5 of 2019 AGS/Beers Criteria. The 2014 STOPP criteria were used (not including a screening tool to alert to right treatment criteria). The 2017 Chinese criteria contained two tables about PIM use in Chinese older adults and PIM use in Chinese older adults under disease states. PIM was divided into high-risk and low-risk medications and divided into A and B

categories according to defined daily doses. Researchers (FY Tian, RN Yang) independently reviewed the medications of each patient and assessed prescription expenditure. Prescription expenditure refers to the expenditure of all drugs in the prescription. The irrational use of the drugs was evaluated by two clinical pharmacists (FY Tian, ZY Chen). Prescription comments were done according to the Chinese Prescription Administrative Policy. Nonstandard prescriptions, inappropriate prescriptions, and supernormal prescriptions referring to medication without indications were classified as irrational prescriptions. Any inconsistencies between the two researchers were submitted to a third professional and then resolved through collective discussion.

Statistical Analysis

Categorical data were described using frequency, and the χ^2 test was used to compare categorical variables between groups. Continuous data subject to a normal distribution are expressed as the mean ± standard deviation (SD), and continuous data subject to a nonnormal distribution are expressed as M (P_{25}, P_{75}). We defined gender, age, number of diseases, polypharmacy, rational prescriptions, expenditure, and type of cancer as risk factors. The associations between risk factors and PIM use (non-PIM = 0, PIM = 1) were performed through multivariate logistic regression analysis to determine the influence on PIM-related risk. Statistical analyses were conducted using SPSS version 26.0 (Armonk, NY: IBM Corp.). A comparative analysis was performed between the results obtained for the three PIM identification tools, and the agreement between them was determined through weighted kappa concordance tests (values of kappa >0.60 indicate good to excellent agreement, values between 0.40 and 0.60 indicate moderate agreement, and values < 0.40 indicate poor agreement) (Landis and Koch, 1977). Logistic regression used the enter method strategy and likelihood ratio method. The results of the logistic regression analysis are presented with odds ratios (ORs) and 95% confidence intervals (CIs); $p < 0.05$ was considered statistically significant.

Ethics Approval

This study protocol was approved by the Sichuan University West China Hospital Research Ethics Board. All procedures performed in this study conformed to the standards of the 1964 Helsinki Declaration and subsequent relevant ethics.

RESULTS

Basic Characteristics of Patients

A total of 6,160 cancer outpatient prescriptions were included in this study, of which 46.53% (2,866) were female. The median age was 72 (IQR: 68, 78) years old, ranging from 65 to 99, with the oldest (≥80 years of age) cancer patients accounting for 18.72% (1,153). The median number of medical diagnoses was 3 (IQR: 2, 5). Regarding medication of prescriptions, the median number prescribed was 3 (IQR: 2, 4), and 22.53% (1,388) of older cancer outpatients had polypharmacy. The prevalence of rational prescriptions was 93.93% (5,786). The median prescription expenditure was 814.62 (IQR: 274.65, 1,638.95) Chinese Yuan (CNY). In this study, 20.70% (1,275) of the patients had lung cancer, 18.83% (1,160) had breast cancer, 16.36% (1,008) had colorectal cancer, 12.76% (786) had prostate cancer, and 6.38% (393) had gastric cancer The characteristics of the basic information in this study are listed in **Table 1**.

Concordance Between the Three Criteria

Considering the three PIM classification tools applied, the 2017 Chinese criteria had 1335 PIM prescriptions in common with the 2019 AGS/Beers criteria and 726 PIM prescriptions in common with the 2014 STOPP criteria. In contrast, the 2019 AGS/Beers criteria had 919 PIMs in common with the 2014 STOPP criteria. The kappa statistic for the 2017 Chinese and STOPP criteria was 0.320, indicating poor concordance. In contrast, the 2019 AGS/Beers criteria showed moderate concordance with the 2017 Chinese criteria and the 2014 STOPP criteria (κ = 0.469 and 0.509, respectively) (**Table 2**).

Prevalence of PIMs and the Most Frequent PIMs

Among the 6,160 older cancer outpatient prescriptions, 2,117 (34.37%) outpatient prescriptions were identified with at least one PIM, and a total of 2,477 PIMs were detected by the 2017 Chinese criteria. Of the patient prescriptions with PIM, 84.93% received one PIM, 13.04% received two PIMs, and 2.03% had at least three PIMs according to the criteria (**Table 3**). Overall, the most consumed PIMs according to the 2017 Chinese criteria were estazolam, clopidogrel, and tramadol at 20.65%, 14.00%, 13.68%, respectively (**Table 4**).

According to the 2019 AGS/Beers criteria, 2011 (32.65%) outpatient prescriptions were identified with at least one PIM, and a total of 2,630 PIMs were detected. Among them, 62.43% met table 2, 0.27% met table 3, 34.68% met table 4, and 2.62% met table 5 of 2019 AGS/Beers criteria, respectively. Of the patient prescriptions with PIM, 82.25% received one PIM, 10.69% received two PIMs, and 7.06% had at least three PIMs according to the criteria (**Table 3**). Overall, the most consumed PIMs according to the 2019 AGS/Beers criteria were estazolam, tramadol, and hydrochlorothiazide, which were 20.97%, 13.89%, 9.85%, respectively (**Table 4**).

Based on the 2014 STOPP criteria, 983 (15.96%) outpatient prescriptions were identified with at least one PIM, and 1,036 PIMs were detected. Of the patient prescriptions with PIM, 94.61% received one PIM, 4.17% received two PIMs, and 1.22% were had at least three PIMs according to the criteria (**Table 3**). Overall, the most consumed PIMs according to the 2014 STOPP criteria were estazolam, glimepiride, and alprazolam at 49.80%, 17.61%, and 15.75%, respectively (**Table 4**).

Risk Factors for PIM Use

Based on the three criteria, PIM use was the dependent variable (non-PIM = 0, PIM = 1). Logistic regression demonstrated that age ≥ 80 years (OR: 1.322 by 2017 Chinese criteria, OR: 1.238 by 2019 AGS/Beers criteria, OR: 1.386 by 2014 STOPP criteria),

TABLE 1 | Basic characteristics of older cancer outpatients.

Characteristics	Total	2017 Chinese criteria			2019 AGS/Beers criteria			2014 STOPP criteria		
		PIM group	Non-PIM group	*p*-value	PIM group	Non-PIM group	*p*-value	PIM group	Non-PIM group	*p*-value
N (%)	6,160	2,117 (34.37)	4,043 (65.63)		2011 (32.65)	4,149 (63.35)		983 (15.96)	5,177 (84.04)	
Sex, n (%)				<0.001			0.023			0.016
Male	3,294 (53.47)	1,228 (58.01)	2066 (51.10)		1,117 (55.54)	2,177 (52.47)		491 (49.95)	2,803 (54.14)	
Female	2,866 (46.53)	889 (41.99)	1977 (48.90)		894 (44.46)	1972 (47.53)		482 (49.03)	2,374 (45.86)	
Age, years (IQR), n (%)	72 (68, 78)			<0.001			<0.001	743 (75.58)	4,264 (82.36)	<0.001
65–79	5,007 (81.28)	1,631 (77.04)	3,376 (83.50)		1,580 (78.57)	3,427 (82.60)		240 (24.42)	913 (17.64)	
≥80	1,153 (18.72)	486 (22.96)	667 (16.50)		431 (21.43)	722 (17.40)				
No. of diseases (IQR)	3 [2, 5]			<0.001			0.002			<0.001
2	1941 (31.51)	567 (25.58)	1,374 (33.98)		581 (28.89)	1,360 (32.78)		210 (21.36)	1731 (33.44)	
3-4	2,619 (42.52)	897 (42.37)	1722 (42.59)		860 (42.76)	1759 (42.40)		402 (40.90)	2,217 (42.82)	
≥5	1,600 (25.97)	653 (30.85)	947 (23.42)		570 (28.34)	1,030 (24.83)		371 (37.74)	1,229 (23.74)	
No. of medications (IQR), n (%)	3 [2, 4]			<0.001			<0.001			<0.001
1–4	4,772 (77.47)	1,391 (65.71)	3,381 (83.63)		1,400 (69.61)	3,372 (81.27)		615 (62.56)	4,157 (80.30)	
≥5	1,388 (22.53)	726 (34.29)	662 (16.37)		611 (30.38)	777 (18.73)		368 (37.44)	1,020 (19.70)	
No. of rational prescriptions, n (%)				<0.001			<0.001			<0.001
Rational prescriptions	5,786 (93.93)	1928 (91.07)	3,858 (95.42)		1828 (90.90)	3,958 (95.40)		859 (87.39)	4,927 (95.17)	
Irrational prescriptions	374 (6.07)	189 (8.93)	185 (4.58)		183 (9.10)	191 (4.60)		124 (12.61)	250 (4.83)	
No. of prescription expenditures [(QR), n (%)	814.62 (274.65, 1,639.95)									0.813
<500 CNY	2,322 (37.69)	874 (41.28)	1,448 (35.81)	<0.001	939 (46.69)	1,383 (33.33)	<0.001	378 (38.45)	1944 (37.55)	
500–1000 CNY	1,108 (17.99)	376 (17.76)	732 (18.11)		321 (15.96)	787 (18.97)		171 (17.40)	937 (18.10)	
>1000 CNY	2,730 (44.32)	867 (40.95)	1863 (46.08)		751 (37.34)	1979 (47.40)		434 (44.15)	2,296 (44.35)	
Type of chronic disease, n (%)										
Lung cancer	1,275 (20.70)	554 (26.17)	721 (17.83)	<0.001	544 (27.05)	731 (17.62)	<0.001	264 (26.86)	1,011 (19.53)	<0.001
Breast cancer	1,160 (18.83)	251 (11.86)	909 (22.48)	<0.001	253 (12.58)	907 (21.86)	<0.001	157 (15.97)	1,003 (19.37)	0.012
Colorectal cancer	1,008 (16.36)	376 (17.76)	632 (15.63)	0.032	384 (19.09)	624 (15.04)	<0.001	184 (18.72)	824 (15.92)	0.03
Prostate cancer	786 (12.76)	315 (14.88)	471 (11.65)	<0.001	247 (12.28)	539 (12.99)	0.434	132 (13.43)	654 (12.63)	0.493
Gastric cancer	393 (6.38)	114 (5.38)	279 (6.90)	0.021	114 (5.67)	279 (6.72)	0.112	56 (5.70)	337 (6.51)	0.339
Liver cancer	379 (6.15)	109 (5.15)	270 (6.68)	0.018	99 (4.92)	280 (6.75)	0.005	30 (3.05)	349 (6.74)	<0.001
Esophageal cancer	298 (4.84)	74 (3.50)	224 (5.54)	<0.001	74 (3.68)	224 (5.40)	0.003	15 (1.53)	283 (5.47)	<0.001
Uterine cancer	130 (2.11)	35 (1.65)	95 (2.35)	0.071	37 (1.84)	93 (2.24)	0.304	21 (2.14)	109 (2.11)	0.951
Kidney Cancer	125 (2.03)	49 (2.31)	76 (1.88)	0.25	43 (2.14)	82 (1.98)	0.673	23 (2.34)	102 (1.97)	0.451
Thyroid cancer	117 (1.90)	35 (1.65)	82 (2.03)	0.306	27 (1.34)	90 (2.17)	0.026	21 (2.14)	96 (1.85)	0.553

PIM, potentially inappropriate medication; IQR, interquartile range; CNY, Chinese yuan.

more diseases (OR: 1.348 by 2017 Chinese criteria, OR: 1.193 by 2019 AGS/Beers criteria, OR: 2.229 by 2014 STOPP criteria), polypharmacy (OR: 3.09 by 2017 Chinese criteria, OR: 2.52 by 2019 AGS/Beers criteria, OR: 2.087 by 2014 STOPP criteria), and irrational use of drugs (OR: 1.679 by 2017 Chinese criteria, OR: 1.762 by 2019 AGS/Beers criteria, OR: 2.857 by 2014 STOPP criteria) were positively associated with PIM use in older cancer outpatients. Lung cancer patients (OR: 1.281 by 2017 Chinese criteria, OR: 1.344 by 2019 AGS/Beers criteria, OR: 1.421 by 2014 STOPP criteria) were also more likely to have PIMs. However, when the prescription expenditure (OR: 0.524 by 2017 Chinese criteria, OR: 0.416 by 2019 AGS/Beers criteria, OR: 0.634 by 2014

TABLE 2 | Concordance between the 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria.

2019 AGS/Beers criteria	2017 Chinese criteria		κ	P
	Yes	No		
Yes	1,335	676	0.469	<0.001
No	782	3,367		
2014 STOPP criteria	**2017 Chinese criteria**			
	Yes	No		
Yes	726	257	0.320	<0.001
no	1,391	3,786		
2019 AGS/Beers criteria	**2014 STOPP criteria**			
	Yes	No		
Yes	919	1,092	0.509	<0.001
No	64	4,085		

κ, kappa coefficient; P, probability value, based on kappa test.

STOPP criteria) was higher, PIM use in older cancer outpatients was lower (**Table 5**).

DISCUSSION

To the best of our knowledge, this is the first study assessing the concordance of three PIM-detecting tools—the 2017 Chinese criteria, the 2019 AGS/Beers criteria, and the 2014 STOPP criteria—in older Chinese cancer outpatients. Although these criteria were developed for different populations and with different aims, they are the most commonly used in older Chinese patients. Because multiple comorbidities are frequent among older cancer patients, a tool focusing on cancer outpatients should be implemented to alert doctors to an eventual PIM prescription. Our study found that the 2017 Chinese and the 2014 STOPP criteria indicated poor coherence, whereas the 2019 AGS/Beers criteria showed moderate concordance with the other two criteria, which was a little different from another study on Chinese older inpatients (Ma et al., 2018). Moreover, a Portuguese study performed in inpatients 65 or more years of age showed poor concordance among the 2019 AGS/Beers criteria, 2014 STOPP criteria, and the EU(7)-PIM list (Perpétuo., 2021). The low concordance between different criteria highlights the need to develop special PIM-detecting criteria for older cancer patients exposed to many PIMs and reinforces the fact that older cancer outpatients are also at risk of PIM. This will provide a basis for rational drug use for cancer patients and reduce outpatient prescription expenditure. The poor concordance between the Chinese and the STOPP criteria can be due to the applicability requirements of each list. The overlap between the Beers criteria and the other two criteria regarding medication risk irrespective of conditions was relatively high. However, the Chinese criteria contained clopidogrel and mixed insulin not included in the Beers criteria. In order to determine one PIM with the STOPP criteria, it is imperative to know the entire medication history and clinical information of the patient. These reasons may lead to moderate concordance between the Beers criteria and the other two criteria.

China is currently the country with the largest older cancer population in the world, and cancer as a chronic disease places a heavy burden on the elderly. Older cancer patients can suffer from a higher rate of comorbidity, frailty, and geriatric syndrome, putting them at a high risk of polypharmacy and PIM use (Pamoukdjian et al., 2020; Kleckner et al., 2022). To the best of our knowledge, this is the first cross-sectional study on the prevalence and risk factors for PIM use in Chinese older cancer outpatients according to the three criteria. The prevalence of PIM use was 34.37%, 32.65%, and 15.96%, according to the 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria, respectively. There is little difference between the 2017 Chinese and 2019 AGS/Beers criteria. However, the prevalence of PIM use of the 2014 STOPP criteria was lower than the other two criteria. According to the 2017 Chinese criteria, to consider the medicine as a PIM, it is only necessary to know the status of medication and disease in

TABLE 3 | The number of PIMs used by older cancer outpatients in the PIM group.

Characteristics	2017 Chinese criteria	2019 AGS/Beers criteria	2014 STOPP criteria
PIM prescription	2,117	2011	983
PIMs, n (%)	2,477	2,630	1,036
1 PIM	1798 (84.93)	1,654 (82.25)	930 (94.61)
2 PIMs	276 (13.04)	215 (10.69)	41 (4.17)
≥3 PIMs	43 (2.03)	142 (7.06)	12 (1.22)

PIM, potentially inappropriate medication.

TABLE 4 | The five most consumed PIMs used by older cancer outpatients.

Number	2017 Chinese criteria	N = 2,464 (%)	2019 AGS/Beers criteria	N = 2,427 (%)	2014 STOPP criteria	N = 1,022 (%)
1	Estazolam	509 (20.65)	Estazolam	509 (20.97)	Estazolam	509 (49.80)
2	Clopidogrel	345 (14.00)	Tramadol	337 (13.89)	Glimepiride	180 (17.61)
3	Tramadol	337 (13.68)	Hydrochlorothiazide	239 (9.85)	Alprazolam	161 (15.75)
4	Mixed insulin	201 (8.16)	Glimepiride	180 (7.42)	Zolpidem	29 (2.84)
5	Insulin glargine	189 (7.67)	Alprazolam	161 (6.63)	Flupentixol and melitracen	24 (2.35)

TABLE 5 | Multivariate logistic regression analysis of factors associated with PIM use.

	2017 Chinese criteria 2			2019 AGS/Beers criteria				2014 STOPP criteria			
Characteristics	**OR**	**95% CI**	***p*-value**	**Characteristics**	**OR**	**95% CI**	***p*-value**	**Characteristics**	**OR**	**95% CI**	***p*-value**
Sex				Sex				Sex			
Female	References		Female	References		Female	References				
Male	1.026	0.895–1.176	0.714	Male	0.934	0.814–1.073	0.337	Male	0.754	0.634–0.897	0.001
Age				Age				Age			
65–79	References		65–79	References		65–79	References				
≥80	1.322	1.146–1.525	<0.001	≥80	1.238	1.071–1.431	0.004	≥80	1.386	1.164–1.652	<0.001
No. of diseases				No. of diseases				No. of diseases			
2	References		2	References		2	References				
3-4	1.205	1.053–1.380	0.007	3-4	1.157	1.157–1.193	0.035	3-4	1.5	1.244–1.815	<0.001
≥5	1.348	1.152–1.579	<0.001	≥5	1.193	1.017–1.399	0.03	≥5	2.229	1.815–2.737	<0.001
No. of medications				No. of medications				No. of medications			
1–4	References		1–4	References		1–4	References				
≥5	3.09	2.667–3.58	<0.001	≥5	2.52	2.169–2.927	<0.001	≥5	2.087	1.747–2.493	<0.001
No. of rational prescriptions				No. of rational prescriptions				No. of rational prescriptions			
Rational prescriptions	References		rational prescriptions	References		rational prescriptions	References				
Irrational prescriptions	1.679	1.339–2.104	<0.001	irrational prescriptions	1.762	1.408–2.205	<0.001	irrational prescriptions	2.857	2.233–3.657	<0.001
No. of prescription expenditures				No. of prescription expenditures				No. of prescription expenditures			
<500 CNY	References		<500 CNY	References		<500 CNY	References				
500–1000 CNY	0.665	0.566–0.782	<0.001	500–1000 CNY	0.488	0.414–0.576	<0.001	500–1000 CNY	0.714	0.578–0.882	0.002
>1000 CNY	0.524	0.454–0.604	<0.001	>1000 CNY	0.416	0.360–0.480	<0.001	>1000 CNY	0.634	0.527–0.7630	<0.001
Type of chronic disease				Type of chronic disease				Type of chronic disease			
Lung cancer	1.281	1.067–1.538	0.008	Lung cancer	1.344	1.066–1.694	0.013	Lung cancer	1.421	1.125–1.794	0.003
Breast cancer	0.514	0.412–0.640	<0.001	Breast cancer	0.598	0.462–0.776	<0.001	Breast cancer	-	-	0.084
Colorectal cancer	—	—	0.243	Colorectal cancer	—	—	0.545	Colorectal cancer	—	—	0.557
Prostate cancer	—	—	0.346	Prostate cancer	—	—	0.876	Prostate cancer	—	—	0.298
Gastric cancer	0.62	0.476–0.808	<0.001	Gastric cancer	0.721	0.535–0.970	0.031	Gastric cancer	—	—	0.469
Liver cancer	0.757	0.577–0.993	0.044	Liver cancer	—	—	0.072	Liver cancer	0.54	0.354–0.825	0.004
Esophageal cancer	0.542	0.399–0.736	<0.001	Esophageal cancer	0.57	0.407–0.798	0.001	Esophageal cancer	0.31	0.177–0.7542	<0.001
Uterine cancer	0.631	0.411–0.969	0.035	Uterine cancer	—	—	0.126	Uterine cancer	—	—	0.599
Kidney cancer	—	—	0.392	Kidney cancer	—	—	0.392	Kidney cancer	—	—	0.871
Thyroid cancer	0.624	0.407–0.958	0.031	Thyroid cancer	0.48	0.299–0.771	0.002	Thyroid cancer	—	—	0.988

older patients. In addition, Chinese criteria were made based on drug utilization of the older Chinese population, so it is more suitable for Chinese individuals. The AGS/Beers criteria judge each medicine as a PIM based not only on the medication profile of a patient but also on the pathologies of the patients, as well as the laboratory results (O'Mahony et al., 2015). In order to apply the STOPP criteria, it is imperative to know the entire medication history, clinical information of the patient, and laboratory (O'Mahony et al., 2015; O'Mahony, 2020; Perpétuo et al., 2021). Based on the 2019 AGS/Beers criteria, our study found that the prevalence of PIM use among older Chinese cancer patients was 32.65%, which was lower than the prevalence of 80.4% reported by a study on Korean cancer patients according to the 2019 AGS/Beers criteria (Suh et al., 2021). The older Korean patients received anti-neoplastic therapy with emergency department (ED) visits, the prevalence of polypharmacy in the patients was observed in 80.4%, and the prevalence was 22.53% in our study. Taking more medications was the reason for the higher prevalence of PIM use compared to our study. Based on the 2014 STOPP criteria, our study found that the prevalence of PIM use among older cancer outpatients was 15.96%, which was lower than Japanese with a prevalence of 31.9% (Hakozaki et al., 2021). Older advanced non–small cell lung cancer (NSCLC) patients and those on oral molecular-targeted anticancer agents were included in the study. According to our research, the prevalence of PIM use in lung cancer patients was higher. The high prevalence of PIM use is that older cancer outpatients are usually in serious condition both physically and mentally, and the willingness of patients to take medicine is relatively strong, not only for antitumor drugs but also for analgesic drugs and sedative-hypnotic drugs. Another potential reason was that the adverse outcomes in older cancer patients were highly associated with PIM use, and the poor clinical outcome of cancer patients will further aggravate the prevalence of PIM use (Mohamed et al., 2020; Chen et al., 2021).

In our research, the most frequent PIM in Chinese older cancer outpatients was estazolam, according to the three criteria. Sleep disorder is common with advancing age and affects 36%–70% of older adults (Hishikawa et al., 2017; Patel et al., 2018), and it is further aggravated in older cancer patients. Consequently, estazolam is a benzodiazepine frequently used by older Chinese cancer patients. However, benzodiazepines are also linked to risks of mortality, falls, fractures, and depression among older adults (Kripke et al., 2002; Stone et al., 2008; Yaffe et al., 2014). Therefore, the risk of this category of medication use should be further evaluated for older cancer patients.

According to the results of logistic regression analysis, PIM-associated factors were the same among the three sets of criteria; older cancer outpatients who were ≥80 years of age, had more diseases, had polypharmacy, and had an irrational use of drugs and those who had lung cancer were more likely to receive PIMs. Furthermore, compared with other identified factors, polypharmacy is the most strongly associated independent risk factor. Patients with polypharmacy had more than two to three times the risk of PIM use compared with patients with one to four medications. In this study, the polypharmacy of older cancer outpatients was 22.53%, which is slightly little lower than the result of our other study (Tian et al., 2021), and this was similar to the results of Hsu et al.'s study, in which polypharmacy prevalence was lower in those with than without a cancer history (Hsu et al., 2021). Older cancer patients with age more than 80 generally have worse health and more multimorbidity than the general cancer population of older adults, and they are more likely to be exposed to PIM use (Lai et al., 2018). Our study found that, with the increase in multimorbidity in Chinese older cancer patients, the risk of PIM use gradually increased. This phenomenon is similar to older Chinese patients with other chronic diseases in some studies (Li et al., 2021; Zhao et al., 2021). The growth was more obvious with the 2014 STOPP criteria, as the PIM use of these criteria was more affected by the disease. In addition, unreasonable prescribing carries a higher risk of PIM use in Chinese older cancer outpatients. However, with the increase in prescription expenditures for cancer patients, the prevalence of PIM gradually declined. This was because the high expenditure on cancer prescriptions was mostly due to the use of antitumor drugs. However, the three criteria rarely involve antitumor drugs. Among all cancer diseases, only lung cancer was associated with PIM use. One study showed that at least half of patients with lung cancer have comorbidities, which would increase the risk of PIM use (Pluchart et al., 2021). Through these results, we suggested reducing unnecessary medications and performing medication reconciliation carefully for older cancer outpatients with taking multiple medications from the doctor or the pharmacist. At the same time, the criteria could be more refined according to the risk factors, such as the formation of special criteria for the outpatients who were ≥80 years of age and older lung cancer patients. This will further improve the feasibility and accuracy of the criteria.

Several limitations should be noted in this study. It was an observational study conducted in China, which is likely to cause some deviations in the results. These results need to be further confirmed by multicenter clinical trials. Second, there are no follow-up data for these older cancer patients when investigating PIM use by electronic medical data, so the correlation between PIM use and further clinical outcomes is not known. Finally, the patients attending outpatients of tertiary hospitals were the main focus of the study, and cancer outpatients who were in nursing homes and communities were not evaluated.

CONCLUSION

This study investigated the use of PIMs in older cancer outpatients with multimorbidity in Chengdu based on the 2017 Chinese, 2019 AGS/Beers, and 2014 STOPP criteria. The results showed that the prevalence of PIM use was high in Chinese older cancer outpatients; poor-to-moderate concordance among the three criteria was observed; and age ≥80, more diseases, polypharmacy, irrational use of drugs, and lung cancer were risk factors for PIM use.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion 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 this study protocol, which was approved by the Sichuan University West China Hospital Research Ethics Board. Written informed consent from participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conception and design: FT. Administrative support: FT. Provision of study materials or patients: FT, MZ, and RY. Collection and assembly of data: FT, RY. Data analysis and interpretation: FT and ZC. Manuscript writing: all authors. Final approval of manuscript: all authors.

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Medication Choices in Children With Tic Disorders in Mainland China, Macao, Hong Kong, and Taiwan: Perspectives of Guardians and Physicians

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Objective: Survey pediatricians and guardians of children with tic disorder on medication needs and choices.

Methods: We designed a cross-sectional survey for pediatricians in mainland China, Hong Kong, Macao, and Taiwan, as well as for the guardians of patients with tic disorder from West China Second University Hospital. We collected and analyzed information on clinicians' medical behavior and medication choices and on guardians' knowledge of tic disorder, medical treatment behaviors, and medication choices and needs.

Results: We collected responses from 242 physicians and 610 guardians. For patients with tic disorder and without comorbidities, the first-line drugs selected by physicians were tiapride (60.74%), clonidine (32.64%), haloperidol (25.62%), aripiprazole (16.53%), and sulpiride (12.4%). Physicians reported making medication choices by considerations such as clinical guidelines, clinical efficacy, a low incidence of adverse drug reactions, sufficient clinical research evidence, convenient dosage forms, and patient adherence. Guardians reported making medication choices by considerations such as a low incidence of adverse drug reactions, physician recommendations, clinical efficacy, dose, dosage forms, and the convenience and steadiness of obtaining the medication. However, guardians exhibited insufficient knowledge of tic disorder and treatment options.

Conclusions: Physicians and patient guardians differ in their considerations when selecting medications, highlighting a gap in optimizing treatment.

Keywords: pediatricians, aripiprazole, tiapride, doctors, dose

Abbreviations: TD, tic disorder.

1 INTRODUCTION

Tic disorder (TD) is a common childhood neuropsychiatric disorder characterized by motor or vocal twitching in one or more parts of the muscles and is sudden, involuntary, repeated, rapid, and purposeless (Yang et al., 2020). TD is categorized as transient, chronic, Tourette syndrome, or undefined (Liu et al., 2020).

The prevalence of transient TD, chronic TD, and Tourette syndrome in children has been estimated at 2.99, 1.61, and 0.77%, respectively, and appears to be more than four times higher in boys (1.06%) than in girls (0.25%) (Knight et al., 2012). In China, the prevalence of transient TD, chronic TD, and Tourette syndrome has been reported as 1.7, 1.2, and 0.3%, respectively (Yang et al., 2016).

TD patients often suffer from comorbidities that affect their physical and mental health. Approximately 30–50% of patients with TD are diagnosed with attention-deficit/hyperactivity disorder, and 10–50% of patients are estimated to have obsessive-compulsive disorder (Kurlan et al., 2002; Hirschtritt et al., 2015). Other comorbidities include sleep disorders, learning difficulties, anxiety, and depression. Patients with TD have an overall lower quality of life than children without TD (Conelea et al., 2011; Eddy et al., 2011; Evans et al., 2016).

Drug therapy is the main treatment to control the symptoms of TD in children, but medication choices vary by country and physician preferences (Waldon et al., 2013). A survey of 22 European experts (Roessner et al., 2011) recorded support for risperidone, clonidine, aripiprazole, and pimozide. A survey of Canadian physicians (Cothros et al., 2019) reported that aripiprazole, risperidone, and clonidine were the most commonly prescribed drugs for TD, but the use of risperidone was decreasing. A survey of 110 Chinese physicians (Lu et al., 2020) showed support for clonidine, aripiprazole, and tiapride as the preferred drugs for newly diagnosed TD cases with moderate chronic TD. Other surveys of drug choices for TD did not investigate factors related to medication choice and polled physicians but not patient guardians.

In addition, patient and guardian awareness of TD is important for controlling the condition, but research has rarely focused on guardian awareness of the disorder, medical treatment behaviors, medication choices, or patient needs. Therefore, we assessed these factors from the perspective of both guardians and physicians so as to improve guardian participation in treatment decision-making and the clinical outcomes.

2 MATERIALS AND METHODS

2.1 Participants

Pediatricians from major hospitals in China who were members of child development and behavior groups of the Chinese Pediatric Society in Chinese Medical Association were included in the survey. Pediatricians were included if they were in active medical practice, without limitation of professional title or age, and if they prescribed medication for patients with TD. Interns, medical students, and trainees receiving standardized training were excluded.

Patients with TD from the outpatient department of pediatric neurology of West China Second University Hospital, Sichuan University, were included. Patients under 18 years of age who had been diagnosed with TD according to DSM-IV diagnostic criteria and whose guardians agreed to participate and sign the informed consent were included. Patients were excluded if they exhibited cerebral palsy, meningitis, motor language development lags, nail-biting, restless legs syndrome, myasthenia gravis, Brown syndrome, or other neuropsychiatric conditions.

2.2 Data Collection

Questionnaires for physicians collected data in three categories: basic information (sex, education level, professional title, years of medical service, and province), medical behavior (tic assessment methods, common treatment methods, and treatment goals), and prescribing behavior (preferred drugs and considerations in selecting drugs). Questionnaires for guardians collected data in three categories: basic information (patient age, disease duration, family history, type of tic, and comorbidities), guardian's cognition of TD (understanding TD pathways, TD classification, symptoms and characteristics, pathogenic factors, common treatment methods, and treatment duration), and guardian's medical behavior and medication choices (department of first visit, time to first treatment, treatment methods, and involvement in medication choices).

2.3 Data Analysis

Questionnaires with incomplete contents were excluded from the analysis. The mean (± standard deviation) or median was used to describe quantitative variables. The frequency or composition ratio was used for categorical variables. Tic assessment methods, treatment goals, and treatment strategies were assigned a numeric score of 1 ("very unimportant"), 2 ("not important"), 3 ("neutral"), 4 ("important"), or 5 ("very important"). Factors in medication choice were evaluated on the same scale. Data analyses were performed in SPSS version 22 (IBM SPSS, Armonk, NY, United States).

2.4 Ethical Considerations

The study protocol conformed to the Helsinki Declaration and was approved by the Office of Research Ethics Committees of West China Women's and Children's Hospital. All participants voluntarily took part in the study and provided informed consent.

3. RESULTS

3.1 Survey of Physicians

3.1.1 Physician Information

A total of 242 questionnaires were collected, and all contained complete information (effective rate: 100%). Participating physicians were from 24 provinces in eastern, central, and western China and from Hong Kong, Macao, and Taiwan. Almost three quarters (73.55%) were female, and almost all (97%) possessed at least one university degree. Sixty percent of participating physicians had professional titles of deputy senior or above, 69% had been practicing medicine for more than 10 years, and 75.21% worked at Grade III, Level A hospitals (**Table 1**).

TABLE 1 | Demographic information of pediatricians (N = 242).

Content	Number (n)	Constituent ratio (%)
Sex		
Male	64	26.45
Female	178	73.55
Education background		
Bachelor's degree	125	51.65
Master	85	35.12
PhD	32	13.22
Professional title		
Junior title	37	15.29
Intermediate title	59	24.38
Deputy senior title	77	31.82
Senior title	69	28.51
Time spent in clinical work		
1–5 years	34	14.05
6–10 years	41	16.94
11–20 years	75	30.99
≥21 years	92	38.02
Grade of affiliated hospital		
Grade III, Level A hospital	182	75.21
Grade III, Level B hospital	8	3.31
Grade II, Level A hospital	26	10.74
Grade II, Level B hospital	15	6.20
Others	11	4.55
Affiliated departments		
Pediatric neurology department	12	4.96
Child psychiatry department	10	4.13
Department of developmental behavioral	17	7.02
Child psychological counseling department	9	3.72
Department of children healthcare	62	25.62
Pediatric department	127	52.48
Others	5	2.07

TABLE 2 | Evaluation methods, treatment goals, and treatment strategies of tic (N = 242).

Topic/Option	Very Unimportant n (%)	Unimportant	Neutral	Important	Very Important	Average
Evaluation Methods of Tic						
Observe tic symptoms	5 (2.07)	1 (0.41)	10 (4.13)	67 (27.69)	159 (65.7)	4.55
Reference to past medical history	5 (2.07)	1 (0.41)	19 (7.85)	86 (35.54)	131 (54.13)	4.39
Tic comorbidities scale	7 (2.89)	7 (2.89)	51 (21.07)	101 (41.74)	76 (31.40)	3.96
Various functional examinations	6 (2.48)	8 (3.31)	54 (22.31)	107 (44.21)	67 (27.69)	3.91
Tic specificity scale	9 (3.72)	13 (5.37)	50 (20.66)	94 (38.84)	76 (31.40)	3.89
Treatment goals						
Improve overall function	5 (2.07)	3 (1.24)	14 (5.79)	83 (34.30)	137 (56.61)	4.42
Reducing tic frequency	5 (2.07)	1 (0.41)	17 (7.02)	90 (37.19)	129 (53.31)	4.39
Alleviating comorbidities	4 (1.65)	2 (0.83)	24 (9.92)	100 (41.32)	112 (46.28)	4.30
Eliminate tic	9 (3.72)	6 (2.48)	56 (23.14)	80 (33.06)	91 (37.60)	3.98
Treatment strategies						
Provide strategies to help patients manage tics	5 (2.07)	2 (0.83)	21 (8.68)	80 (33.06)	134 (55.37)	4.39
Oral or written education of parents	6 (2.48)	3 (1.24)	26 (10.74)	78 (32.23)	129 (53.31)	4.33
Drug treatment	7 (2.89)	3 (1.24)	35 (14.46)	103 (42.56)	94 (38.84)	4.13
Surgery	111 (45.87)	39 (16.12)	55 (22.73)	17 (7.02)	20 (8.26)	2.16

3.1.2 Medical Behavior

The most common methods for evaluating tics used by pediatricians were observation of tic symptoms (4.55 points) and reference to past medical history (4.39 points), followed by the tic comorbidities scale (3.96 points), functional examinations (3.91 points), and the tic specificity scale (3.89 points). Most common treatment goals were improving overall function (4.42 points), reducing tic frequency (4.39 points), alleviating comorbidities (4.30 points), and eliminating tics (3.98 points). The most commonly used treatment tactic reported was providing strategies to help patients manage tics (4.39 points), followed by oral or written education of parents

TABLE 3 | Preferred drugs during treatment (N = 242).

Drugs	TD patients without Comorbidities		TD patients with ADHD	
	Number(n)	Ratio (%)	Number(n)	Ratio (%)
Tiapride	147	60.74	123	50.83
Sulpiride	30	12.40	28	11.57
Haloperidol	62	25.62	61	25.21
Pimozide	5	2.07	6	2.48
Clonidine	79	32.64	79	32.64
Guanfacine	1	0.41	5	2.07
Aripiprazole	40	16.53	52	21.49
Risperidone	15	6.20	31	12.81
Ziprasidone	1	0.41	2	0.83
Olanzapine	6	2.48	7	2.89
Quetiapine	0	0.00	5	2.07
Topiramate	15	6.20	27	11.16
Sodium valproate	30	12.40	44	18.18
Levetiracetam	16	6.61	27	11.16
Aatomoxetine	-	-	61	25.21
Methylphenidate	-	-	36	14.88

TABLE 4 | Considerations of choosing in selecting drugs (N = 242).

Factors	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	Average score
Clinical guideline recommendations	6 (2.48)	2 (0.83)	18 (7.44)	44 (18.18)	172 (71.07)	4.55
Recommended by experts	9 (3.72)	10 (4.13)	58 (23.97)	93 (38.43)	72 (29.75)	3.86
Sufficient clinical evidence	6 (2.48)	8 (3.31)	28 (11.57)	79 (32.64)	121 (50.00)	4.24
Better clinical efficacy	7 (2.89)	4 (1.65)	18 (7.44)	59 (24.38)	154 (63.64)	4.44
Fewer adverse drug reactions	8 (3.31)	5 (2.07)	19 (7.85)	65 (26.86)	145 (59.92)	4.38
Convenient use of dosage forms	9 (3.72)	10 (4.13)	38 (15.7)	73 (30.17)	112 (46.28)	4.11
Smaller drug dose	14 (5.79)	24 (9.92)	59 (24.38)	56 (23.14)	89 (36.78)	3.75
Better drug tastes	22 (9.09)	27 (11.16)	61 (25.21)	51 (21.07)	81 (33.47)	3.59
Better drug appearance	77 (31.82)	51 (21.07)	52 (21.49)	35 (14.46)	27 (11.16)	2.52
Cheaper drug price	19 (7.85)	35 (14.46)	89 (36.78)	49 (20.25)	50 (20.66)	3.31
More plentiful supplies in hospital	20 (8.26)	13 (5.37)	69 (28.51)	64 (26.45)	76 (31.40)	3.67
Patients' demands	12 (4.96)	29 (11.98)	80 (33.06)	72 (29.75)	49 (20.25)	3.48
High degree of patient recognition	7 (2.89)	17 (7.02)	63 (26.03)	85 (35.12)	70 (28.93)	3.80
Better patient adherence	6 (2.48)	7 (2.89)	43 (17.77)	88 (36.36)	98 (40.50)	4.10

Note: 1 point means very unimportant, 5 points means very important.

(4.33 points), drug treatment (4.13 points), and surgery (2.16 points; **Table 2**).

Preferred treatment methods for patients without comorbidities were psycho-behavioral therapy (86.36%, 209/242), educational interventions (73.97%, 179/242), and drug therapy (68.18%, 165/242). For children with TD and comorbidities, the commonly used treatment methods were drug therapy (89.26%, 216/242), psycho-behavioral therapy (85.12%, 206/242), and educational interventions (71.49%, 173/242).

3.1.3 Preferred Drugs and Influencing Factors

For patients without comorbidities, the first-line drugs were tiapride (60.74%), clonidine (32.64%), haloperidol (25.62%), aripiprazole (16.53%), and sulpiride (12.40%). For patients with TD and attention-deficit/hyperactivity disorder, the preferred drugs were tiapride (50.83%), clonidine (32.64%), haloperidol (25.21%), Aatomoxetine (25.21%), and aripiprazole (21.49%; **Table 3**).

When selecting therapeutic drugs, physicians cited the following factors as priority considerations: clinical guideline recommendations (4.55 points), better clinical efficacy (4.44 points), fewer adverse drug reactions (4.38 points), sufficient clinical evidence (4.24 points), convenient dosage forms (4.11 points), and better patient adherence (4.10 points; **Table 4**).

3.2 Survey of Patient Guardians

3.2.1 Patient Information

A total of 621 questionnaires were collected, of which 610 contained complete responses (effective rate: 98.2%). Three quarters (77.90%, 475/610) of patients with TD were male. Patient age ranged from 2.20 to 15.98 years (mean: 7.86 ± 2.38 years). The mean course of TD disease was 1.44 ± 1.48 years, and 26.10% (159/610) of the patients had comorbidities. Disease types were transient TD (322/610, 52.80%), chronic TD (27.20%, 166/610), other (11.80%, 72/610), and Tourette syndrome (8.20%, 50/610).

TABLE 5 | Guardian's cognition of TD (N = 610).

Option	Number(n)	Proportion (%)
Understanding TD Pathways (Multiple Choices)		
Medical staff's information	327	53.60
Discovery by themselves	319	52.30
Other patients' information	59	9.70
The Internet	16	2.60
Don't understand the disease	11	1.80
Books	3	0.50
What type of disease is TD?		
Neuropsychiatric disease	497	81.50
Psychological disease	50	8.20
Not a disease	31	5.10
Otolaryngology disease	13	2.10
Ophthalmic disease	10	1.60
Unclear	5	0.80
Respiratory diseases	4	0.70
TD symptoms and Characteristics (multiple choices)		
The involuntary, sudden and rapid contraction movement of the head, face, trunk and limbs	498	81.60
The sound like burping or coughing through the nose, mouth and throat	354	58.00
TD mostly started in childhood	267	43.80
New forms of tic may appear	182	29.80
It can occur when the motor system functions normally	122	20.00
Causes of TD (multiple choices)		
Neurotransmitter imbalance	510	83.60
Infectious immune factor	155	25.40
Genetic factor	150	24.60
Organic factor	59	9.70
Stress	19	3.10
Psychological factors	10	1.60
Malnutrition	6	1.00
Factors aggravating tic symptoms (multiple choices)		
Stress	495	81.10
Shock	441	72.30
Being reminded	315	51.60
Fatigue	301	49.30
Focusing attention	123	20.20
Infections	8	1.30
Colds	5	0.80
Watching television or using electronic devices	5	0.80
TD common treatment (multiple choices)		
Drug therapy	543	89.00
Psychobehavioral therapy	477	78.20
Educational intervention	179	29.30
Physical therapy	119	19.50
Surgery	9	1.50
TD treatment time		
About 1 month	58	9.50
About half a year	193	31.60
About 1 year	176	28.90
About 3–5 years	156	25.60
About 10 years	17	2.80
About 20 years	1	0.20
Lifetime	9	1.50

3.2.2 Guardians' Knowledge of TD

More than half of the guardians had learned about TD through medical staff (53.60%, 327/610) and self-education (52.30%, 319/610). Most guardians (81.50%) thought that TD was a neuropsychiatric disease, while 5.10% (31/610) thought that TD was not a disease. More than 80% of the guardians believed that the cause of TD was neurotransmitter imbalance. The factors that guardians thought would aggravate tic symptoms were stress (81.10%, 495/610), shock (72.30%, 441/610), being reminded (51.60%, 315/610), fatigue (49.30%, 301/610), concentration (20.20%, 123/610), infections (1.30%, 8/610), colds (0.80%, 5/610), and watching television or using electronic devices (0.80%, 5/610). As for common treatments for TD, most guardians were aware of drug therapy (89%, 543/610) and psycho-behavioral therapy (78.20%, 477/610), but fewer knew about educational interventions (29.30%, 179/610),

TABLE 6 | Guardian's medical behavior and medication choices (N = 610).

Option	Number(n)	Ratio (%)
For TD, which Department did You Go to at the First Time?		
Neurology department	379	62.10
Ophthalmology department	93	15.20
Pediatric department	34	5.60
Developmental-behavioral pediatrics	30	4.90
Otolaryngological department	27	4.40
Psychiatry department	26	4.30
Pneumology department	15	2.50
Psychological counseling department	4	0.70
Traditional Chinese medicine department	1	0.20
Other	1	0.20
The time between the onset of TD and the time to seek medical treatment		
More than 1 year	112	18.40
Several months	238	39.00
A few weeks	174	28.50
Immediately	86	14.10
Involvement in medication choices		
Yes	314	51.50
No	213	34.90
Uncertain	83	13.60
Whether you expressed your personal medication preferences to your physicians		
yes	237	38.90
No	265	43.40
Uncertain	108	17.70
Do you consider the child's medication preference		
Yes	405	66.40
No	100	16.40
Uncertain	105	17.20
Correct medication for TD (multiple choices)		
Take medicine on time and in regular dose	411	67.40
Consult your doctor or pharmacist immediately if any new symptoms occur during medication	407	66.70
drug use should be discontinued or reduced when symptoms improved were alleviated	144	23.60
medication was unnecessary because disease they could manage the disorder themselves	60	9.80
Medication only needs to be taken during an onset of tic	14	2.30

physical therapy (19.50%, 119/610), or surgery (1.50%, 9/610). More than half of the guardians believed that TD treatment lasted 6–12 months (**Table 5**).

3.2.3 Medical Behavior and Drug Provision by Guardians

Only 14.10% (86/610) of patients had received medical treatment immediately after the first onset of tics, and more than half of patients first received medical treatment at a neurology department (62.10%, 379/610). Only 51.50% (314/610) of the guardians participated in medication choices: 38.90% (237/610) of the guardians had expressed their medication preferences to physicians, and 66.40% (405/610) of the guardians took their children's medication preference into consideration. In terms of medication behavior, 67.40% (411/610) of guardians thought that medication should be taken on time and at a regular dose, 66.70% (407/610) of the guardians immediately consulted medical staff when they observed new symptoms, and 23.60% (144/610) of the guardians thought that drug use should be discontinued or reduced when symptoms were alleviated. Moreover, 9.80% (60/610) thought that medication was unnecessary because they could manage the disorder themselves, and 2.30% (14/610) thought that medication was only necessary at the onset of tics (**Table 6**).

3.2.4 Medical Preferences of Guardians

When selecting medications, guardians placed emphasis on drugs with fewer adverse reactions (4.52 points), recommendations from physicians (4.44 points), better clinical efficacy (4.29 points), lower drug doses (4.27 points), more convenient dosage forms (4.01 points), and sufficient supplies at the hospital (3.95 points; **Table 7**).

4. DISCUSSION

4.1 Main Findings

The majority of physicians we polled thought that the most important treatment goals for patients with TD were to improve their overall function, reduce the frequency of tics, and control comorbidities. The most important treatment strategies include the provision of effective strategies to manage TD, oral or written education of both patients and guardians, and medication. Psycho-behavioral therapy, educational interventions, and medication are the main treatment methods. The first-line drugs include selective D2 dopamine receptor antagonists (e.g., tiapride), α-adrenergic agonists (e.g., clonidine), and antipsychotics (haloperidol and

TABLE 7 | Factors to consider in the medication choices of the patient's guardian (N = 610).

Factor	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	Average score
Recommended by physicians	4 (0.7)	5 (0.8)	32 (5.2)	244 (40.0)	325 (53.3)	4.44
Recommended by other patients	22 (3.6)	132 (21.6)	214 (35.1)	180 (29.5)	62 (10.2)	3.21
Better clinical efficacy	3 (0.5)	10 (1.6)	59 (9.7)	275 (45.1)	263 (43.1)	4.29
drugs with fewer adverse reactions	6 (1.0)	0 (0.0)	35 (5.7)	198 (32.5)	37 (60.8)	4.52
Convenient use of dosage forms	2 (0.3)	27 (4.4)	128 (21.0)	259 (42.5)	194 (31.8)	4.01
Smaller drug dose	3 (0.5)	10 (1.6)	66 (10.8)	271 (44.4)	260 (42.6)	4.27
Better drug tastes	9 (1.5)	99 (16.2)	249 (40.8)	168 (27.5)	85 (13.9)	3.36
Better drug appearance	53 (8.7)	264 (43.3)	216 (35.4)	53 (8.7)	24 (3.9)	2.56
Cheaper drug price	11 (1.8)	78 (12.8)	212 (34.8)	205 (33.6)	104 (17.0)	3.51
More plentiful supplies in hospital	3 (0.5)	33 (5.4)	119 (19.5)	299 (49.0)	156 (25.6)	3.95

Note: 1 point means very unimportant, 5 points mean very important.

aripiprazole). Clinical guidelines, better clinical efficacy, fewer adverse drug reactions, sufficient clinical evidence, convenient dosage forms, and better patient adherence are the important factors influencing the medication choices of pediatricians. Haloperidol was used for patients with severe tics, which was recommended as a second-line drug in Chinese guideline (Liu et al., 2020), and weak recommendations are made for the use of haloperidol in Canadian guideline (Pringsheim et al., 2012), doctors also prescribed trihexyphenidyl to reduce extrapyramidal reactions caused by haloperidol in China. Chinese pediatricians' drug choices for treating TD generally follow clinical recommendations (Pringsheim et al., 2012; Pringsheim et al., 2019; Liu et al., 2020), but they do not fully consider guardian preferences and medication prices when selecting drugs. This may reflect the heavy workload of physicians and the short time allotted to each patient visit, precluding in-depth communications between physicians and patients or guardians, further improvements and optimizations are required in future medical practice. Tiapride is not a very common medicine in western countries, but it was recommended as a first-line drug for TD in Chinese guideline (Liu et al., 2020), adequate clinical research evidence showed that the drug is effective and safe, and it is also very cheap in China, so it is widely used.

We found that guardians had a poor understanding of the disease, especially its classifications, symptoms, and characteristics, factors aggravating tic symptoms, and the length of treatment. In addition, the guardians were not sufficiently aware of educational interventions, physical therapy, or surgical options, and some guardians even misunderstood treatment needs. Because of the guardians' poor understanding of TD, some patients did not receive timely medical attention when needed, delaying treatment. Therefore, more effective education should be provided to patients and their guardians to enhance their cognition of TD. Moreover, some guardians did not understand the nature of the drug therapy, believing that medication could be discontinued or the dose reduced when symptoms were alleviated; some even believed that medication was only required at the onset of tic. In terms of medication choices, both guardians and clinicians preferred drugs with fewer adverse effects and better clinical efficacy, but guardians also considered factors such as smaller drug dose, more convenient dosage forms, and a steady and convenient supply. However, guardians reported that most physicians did not consider patients' treatment needs, underscoring the importance of physicians listening to guardians' input when making medication choices.

4.2 Comparisons With Other Studies

A Japanese survey from 2019 (Yu et al., 2019) found that the most important factor considered in the decision to begin pharmacotherapy in children with TD was functional impairment caused by tic symptoms, and this finding is consistent with ours. Aripiprazole and risperidone were the first- and second-line medications for TD, as α-adrenergic agonists are seldom prescribed in Japan, although they are widely used in China. This difference in clinical practice may result from the fast-acting receptor agonist clonidine being the only α-adrenergic receptor agonist officially accepted for treatment of hypertension in Japan. In addition, Aatomoxetine was a first-line drug because the use of methylphenidate is restricted in Japan.

A cross-sectional study of TD medications prescribed in Korea between 2009 and 2016 (Choi et al., 2019) reported that aripiprazole was the most commonly prescribed drug, the use of risperidone was declining, and the number of prescriptions written increased over time. Other commonly used drugs were benzatropine and haloperidol. The widespread use of aripiprazole might be related to the mounting body of evidence that indicates that aripiprazole has good efficacy and tolerability. In China, physicians' drug choices are similar, with the exception of benzatropine and haloperidol, which are rarely used because of the high incidence of adverse drug reactions.

Lu et al. (2020) recently surveyed 110 pediatricians in China on drug treatment of patients with newly diagnosed TD and comorbidities. Their findings were consistent with ours, although their sample was smaller and they did not report factors that influenced medication choices. Geng et al. (2016) surveyed 57 guardians on their knowledge of TD; 71.90% believed that TD was a disease, but 73.70% still adopted inappropriate measures when tics occurred, indicating that guardians had a poor understanding of TD, similar to our findings. However, the study did not investigate patients' medication needs or factors in medication choices.

4.3 Limitations of the Study

Our study has some limitations. First, we did not sample at random, but we did include physicians from 24 provinces and Hong Kong, Macao, and Taiwan. Guardians were recruited from the largest women and children's hospital in southwestern China, so the results were of good representativeness. Second, we used a cross-sectional design to identify the factors influencing medication choices, so causal inference could not be made. Third, patient medications were reported by guardians. Although this can reflect patients' medication needs to a certain extent, some information bias was inevitable. Fourth, this study is from a specific region, so the extrapolation has certain limitations. Future research should overcome these limitations.

4.4 Conclusion

We found that pediatricians in China typically follow clinical guidelines in selecting medications for TD but seldom consider guardian preferences, highlighting a gap in optimizing treatment. Moreover, patient guardians lack sufficient knowledge of TD and medication choices, requiring more physician-initiated dialogue.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Office of Research Ethics Committees of West China Women's and Children's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CY and YY: designed the review, collected data, carried out analysis and interpretation of the data and wrote this study. LlZ and LiZ: designed the review, collected data, checked the data and wrote the study.

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A Qualitative Study of Stakeholders' Views on Pharmacovigilance System, Policy, and Coordination in Pakistan

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Objectives: Due to the absence of necessary rules, poor coordination, and various challenges, the pharmacovigilance system of Pakistan is not optimally functional at all levels of the health system. The objective of the study was to assess the stakeholders' perceptions of the current ADR reporting system and to identify the pharmacovigilance policy issues and problems of effective coordination.

Methodology: Stakeholders from a broad range of disciplines, academia, regulatory authorities, the pharmaceutical industry, international health organizations, as well as pharmacovigilance experts, and healthcare professionals were included in the study. A total of 25 stakeholders throughout Pakistan were interviewed during exploratory semi-structured interviews. The interviews were recorded digitally, transcribed, coded, compared, and grouped according to their similarity of themes. Participants provided insights into gaps, limitations, and challenges of Pakistan's current ADR reporting system, issues with proposed pharmacovigilance rules, and coordination difficulties.

Results: The majority of the participants considered the ADR reporting system in Pakistan to be improving but in a nascent phase. The identified gaps, challenges, limitations of the system, and barriers to reporting were labeled as reasons for limited functioning. Almost all stakeholders were aware of the existence of draft pharmacovigilance rules; however, participants in the industry were familiar with the contents and context of draft pharmacovigilance rules. Bureaucratic red tape and lack of political will appeared to be the top reasons for delaying the approval of the pharmacovigilance rules. Wider consultation, advocacy, and awareness sessions of policymakers and HCPs were suggested for early approval of rules. Participants unanimously agreed that the approval of rules shall improve the quality of life and reduce the economic burden along with morbidity and mortality rates. The need for greater and collaborative coordination among the stakeholders in promoting medicines' safety was highlighted. All participants suggested the use of media and celebrities to disseminate the safety information.

Conclusion: Participants showed partial satisfaction with the way pharmacovigilance in Pakistan is moving forward. However, stakeholders believed that engagement of multi-stakeholders, approval of pharmacovigilance rules, and the establishment of

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pharmacovigilance centers in provinces, hospitals, and public health programs (PHPs) shall support in achieving the desired results.

Keywords: pharmacovigilance, adverse drug reactions, views, perceptions, regulation, coordination, public health, Pakistan

INTRODUCTION

The thalidomide incident in 1961 marked a paradigm shift in the field of medicine safety (Fornasier et al., 2018). The World Health Assembly during its 16th session in 1963 adopted a resolution (WHA 16.36) that reaffirms the need for rapid dissemination of information regarding adverse effects resulting from medicines. This resolution paved the path to the formation of the World Health Organization Programme for International Drug Monitoring (PIDM) (Pal, 2013).

In 1978, the Uppsala Monitoring Center (UMC) was established to support the PIDM. All member states sent the individual case safety reports (ICSR) to the central database called VigiBase (UMC, 2022). The UMC is responsible to manage and maintain the VigiBase. It is a database with more than 28 million safety reports. The basic idea behind establishing this center was to collect adverse reaction reports from multiple sources across the globe to identify potential hazards related to medicine safety (UMC, 2018; WHO, 2022).

A national pharmacovigilance regulatory framework is considered an integral part of medicines policy in a country (Mehta et al., 2017). A set of rules, regulations, guidelines, and standard operating procedures are required for an efficient pharmacovigilance system to ensure medicine safety and data integrity. Similarly, the enactment of regulations ensures the legal cover for monitoring and compliance by all stakeholders (Nwokike and Eghan, 2010). The lack of a pharmacovigilance policy is seen as a contributory factor that medicines' safety and quality may be compromised (Rasheed et al., 2019). The thalidomide disaster pointed out the inadequate regulations and the flaws in the regulatory processes adopted by the regulatory agencies. As a result, several countries have therefore introduced new legislation to reinforce their existing drug safety systems (WHO, 2002; Rice, 2007; Lembit and Santoso, 2010; Beninger and Ibara, 2016). The United States Food and Drug Administration in 1962 introduced the amendments which require safety and efficacy data on medicines prior to the premarketing submission. The United Kingdom introduced the Yellow card scheme to report suspected ADRs by healthcare professionals in 1964. Patients had access to submit yellow cards since 2005 (MHRA, 2022). In 1965, the European Union developed its first legislation applicable to its member states. A pharmacovigilance system at the EU level was established in 1995 and last strengthened with further regulations were implemented in 2012 which was a revolutionary step in the field of medicines regulation (Bahri and Arlett, 2014; EMA, 2022). These regulations strengthened transparency, stakeholders' engagement, and safeguarding of public health. However, the regulatory framework and pharmacovigilance activities are not harmonized across various countries. Hans and Gupta (2018) found inconsistency and variance among regulatory functions of the United States, Canada, the United Kingdom, and India (Hans and Gupta, 2018).

The drug regulatory authorities around the globe have introduced user-friendly online ADR reporting systems including USFDA MedWatch (FDA, 2022), Yellow Card Scheme in the United Kingdom(MHRA, 2022), and mobile applications to effectively identify and address serious drug-related problems. The studies have shown that these systems are underutilized due to their voluntary nature in reporting ADRs (Hazell and Shakir, 2006). In the United States, less than 10% of ADRs are reported through MedWatch (Lasser et al., 2002). The countries which introduced patient reporting earlier, that is, the Netherlands, Denmark, and the United Kingdom, showed high reporting rates, while countries that introduced patient reporting recently, including Hungary, Portugal, and Malta, have low levels of ADR reporting (Inácio et al., 2017).

Similar to the thalidomide disaster, the Isotab tragedy in Pakistan highlighted the importance and need for introducing an ADR reporting system at all levels of healthcare establishments (LHC, 2012). The use of contaminated cardiac medicine took the lives of more than 300 patients. The judicial inquiry tribunal (JIT) established to determine the causes of deaths in the Punjab Institute of Cardiology, Lahore, observed that there was no system of ADR reporting in the hospital and supplier firm. It was further found there is no pharmacovigilance system that exists in the country. The JIT recommended introducing a system of yellow slips for reporting ADRs to the hospital committees set up for the said purpose. Moreover, it was also suggested to set up pharmacovigilance centers at the level of the health department to process and share information regarding drug reactions and other related matters with health professionals and hospitals (LHC, 2012). In 2015, Drug Regulatory Authority of Pakistan (DRAP) established the national pharmacovigilance center. This was in order to collect the ADR reports from all stakeholders (Qato, 2018). Consequent to this, DRAP became a full member of the UMC in 2018 (WHO, 2022). A study (Khan et al., 2022) revealed that the pharmacovigilance system in Pakistan is not fully functional at all levels. Presently, ADR reporting is voluntary. Currently, there is a med vigilance E-reporting system (DRAP, 2018) and Web-RADR med-safety mobile application for reporting ADRs (DRAP, 2020). However, the collected number of ADRs related to medicines is not sufficiently corresponding to the population of the country (Syed et al., 2018; Khan et al., 2022). A recent study also identified gaps in the pharmacovigilance system including the absence of the pharmacovigilance legal framework that will require mandatory ADR reporting by the stakeholders (Khan et al., 2022).

In Pakistan, majority of the physicians are not aware of the ADR reporting system, and there is inadequate coordination between the physicians and other healthcare professionals

TABLE 1 | List of stakeholders contacted and participated in the study.

Stakeholders	Stakeholders contacted and invited (n)	Stakeholders who accepted the invitation (n)
Federal ministers (current and former)	3	0
Bureaucrats/civil service officers (federal and provincial)	2	0
Government officers as pharmaceutical regulators (federal and provincial)	11	6
Academia, pharmacy/medical (public and private sector)	4	3
Pharmacovigilance consultants	5	4
Pharmaceutical practice and policy expert	1	1
Representatives of international health organizations	2	2
Physicians	2	2
Nurses	2	1
Public health program	1	1
Pharmaceutical industry (multinational and national)	5	5
Total	38	25

(Hussain et al., 2020b) and other stakeholders (Khan et al., 2022). Some studies have investigated only the barriers to ADR reporting (Hussain et al., 2018, 2020a, 2020b; Nisa et al., 2018; Syed et al., 2018), while no study has been conducted to explore the other issues related to the ADR reporting system, pharmacovigilance policy and legal framework, and stakeholder's coordination.

This study aimed to fill this gap and explore the multi-stakeholder views and perceptions about the pharmacovigilance system in Pakistan. The study also aimed to explore the pharmacovigilance stakeholder's opinions and perceptions regarding challenges, barriers, limitations, and the gaps related to the ADR reporting system in the country.

METHODOLOGY

Study Design

Through an inductive qualitative approach (Thomas, 2006), in October–December 2021, the study was conducted using semi-structured interviews (Kaae and Traulsen, 2015). A deductive approach was applied to frame the interview guide questions.

Participant Selection

A purposive sampling technique was used for this study (Campbell et al., 2020). A list of potential participants for the study was prepared from various fields including present and former federal ministers, bureaucrats (senior officers in Ministry/Health Department), and technical officers working in the federal and provincial drug authorities, academia, experts on medicine safety and pharmaceutical policy and practice, pharmaceutical industry (multinational and national), physicians, and nurses (**Table 1**).

The inclusion criteria included: a) participants working or involved in Pakistan's healthcare system (doctors, pharmacists, and nurses); b) participants having a current or minimum of 5 years of experience or involvement in the policy development and ADR reporting or medicine safety activities; c) participants who were fluent in the English language. The participants represent the larger sample of all the persons involved in pharmacovigilance in Pakistan. The participants were recruited through phone calls, WhatsApp messages, and emails. Thirty-eight participants were contacted, out of which 35 responded to the invitation. Three participants did not reply to the email and subsequent reminders. Five participants initially agreed to participate but later showed reluctance to record the interviews. Furthermore, five participants had issues with the availability of time for the interview. This resulted in 25 participants.

Information sheets and consent forms (see supplementary material) were sent to the participants who gave consent for the interview. The range of duration of the interviews was between 16 and 55 min. The mean interview time was 33 min.

Interview Guide Development

We conducted a comprehensive literature review to determine the existing knowledge about the current ADR reporting system, pharmacovigilance policy/rules/regulations, and coordination among stakeholders. The literature search was conducted by using the keywords "pharmacovigilance, adverse drug reactions, ADR, policy, regulation, qualitative study, policy analysis, coordination, and stakeholders" on search engines such as Google Scholar, ScienceDirect, HINARI, and PubMed. This literature review fed to develop the guide (Ritchie and Lewis, 2003; DiCicco-Bloom and Crabtree, 2006; Guion and Mcdonald, 2006; Turner, 2010; Babar et al., 2012; Babar and Francis, 2014; Hussain et al., 2018, Hussain et al., 2020b; Phillips et al., 2021; Khan et al., 2022).

The following broad themes were identified, and subsequent sets of questions were developed. These included 1) perception of the current ADR reporting system in Pakistan, including participants' awareness, understanding, opinions, and views on challenges, gaps, limitations, barriers, and approaches for improvement; 2) role of the pharmaceutical industry in the promotion of medicine safety; 3) future research needs; 4) views on draft pharmacovigilance rule, participants' awareness, understanding, opinions, and impact on public health; 5) perception on coordination, stakeholder engagement and communication; gaps in stakeholders selection, placement of the National Pharmacovigilance Center, and DRAP are

TABLE 2 | Themes and sub-themes.

Theme	Subtheme	Details
General views on the ADR reporting system of Pakistan	Understanding of the current ADR reporting system	Perceptions about gaps, limitations, challenges, and barriers to the ADR reporting system
Views to improve the current pharmacovigilance system Future pharmacovigilance research needs in Pakistan	Future ideas on pharmacovigilance research requirements	
Role of the Pharmaceutical industry in the promotion of medicines' safety	Knowledge about pharmacovigilance activities conducted by the pharmaceutical industry	—
Views on draft pharmacovigilance rules in Pakistan	Familiarity and understanding of the issues of draft pharmacovigilance rules	Knowledge of draft pharmacovigilance rules Factors involved in delaying the approval of the pharmacovigilance rules Expediting the approval process of pharmacovigilance rules Impact on public health and medicine safety after implementation of pharmacovigilance rules
Coordination, stakeholder engagement, and communication	Need for greater harmonization	Description of coordination between DRAP and other stakeholders Explanation of personal experience of contacting DRAP for safety information Knowledge sharing and stakeholder engagement
Gaps in the selection of effective stakeholders	Identification of key stakeholders to improve the pharmacovigilance system Placement of national industry Pharmacovigilance center	
Media and medicine safety	Role of media in medicine safety promotion	Selection of media for medicine safety promotion

aiming to promote public health and the issues related to unethical medicine promotion by the pharmaceutical industry; and 6) the role of media in promoting medicine safety (**Table 2**).

The interview guide was tested for its validity and reliability by two experienced researchers at the Health Services Academy, Islamabad, and Quaid-i-Azam University Islamabad, Pakistan. The interview guide was piloted by one pharmacist from the Drug Regulatory Authority of Pakistan (DRAP) and another one from the World Health Organization with involvement in policy development and the ADR reporting system.

After the verbal consent, an information sheet with a consent form (see supplementary material) was sent to the participants through email. The interviews were conducted on Zoom video conferencing (https://zoom.us/) and were recorded after permission by the respondents. The interviews were transcribed verbatim (space fillers were omitted). Both participants were sent their audios and transcripts to edit and approve. The interview guide was amended after the pilot interviews (see appendix-A supplementary material). One question was deleted, and three questions were added based on information received from the respondents.

Data Collection

Twenty-five stakeholders were interviewed (**Figure 1**). Ten interviews were conducted in person, 14 on zoom video conferencing, and one on a mobile phone. Before conducting the interviews, the participants were briefed on the study and

TABLE 3 | Stakeholder's characteristics: Stakeholders n = 25.

Stakeholder	Designated in thesis
Federal government service	FGS-I FGS-II FGS -III FGS–IV
Provincial government service	PGS-I PGS-II
Academic pharmacy	AP-I AP-II
Academic physician	APhy-I
Physician	Phy-I Phy-II
Pharmacovigilance experts (PE)	PE-I PE-II PE-III PE-IV
Pharmaceutical policy and practice expert	PPPE-I
Pharmaceutical industry (PI)	PI-I PI-II PI-III PI-IV PI-V
International Health Organization (IHO)	IHO-I IHO-II
Nurse	N-I
Public health program	PHP-I

TABLE 4 | Stakeholders' characteristics.

Details	Number of participants
Public sector employees	8
Private sector employees	12
Freelance consultants	5
Profession	
Doctors	8
Pharmacist	16
Nurse	1
Gender	
Male	21
Female	4
Age of participants	
<40	7
40–60	13
60 +	5
Experience (years)	
10>	5
10–20	5
20 +	15

were informed that interviews are voluntary and they have the right to withdraw from the interview at any time. Consent was taken before the recording of the interviews. All interviews were conducted in the English language. The interviews were recorded on mobile phone and Zoom video conferencing application and saved on a password-protected computer. Coding was carried out on the interviewees to ensure anonymity (**Table 3**). No financial compensation was offered to the participants. The interviews were transcribed intelligent verbatim (McMullin, 2021).

Data Analysis

Thematic analysis was performed according to the process explained by Braun and Clark (Braun and Clarke, 2012). A team of experts performed a staged analysis of the interviews. Initially, transcripts were read thoroughly to take notes and to record the key themes and codes. Subsequently, a basic coding framework was developed outlining the subthemes, categories, codes, and quotes. In the last stage, the group of researchers further refined the codes.

RESULTS

A total number of 30 participants showed willingness to participate in the research, and 25 interviews were conducted. Demographic information including age, gender, profession, and length of experience was also recorded (**Table 4**). The majority of the participants (n = 16) were pharmacists by training: one-fourth were medical doctors (n = 8) and one was a nurse. More than 80% participants (n = 21) were male, while less than 20% (n = 4) were female. Out of 25, eight participants were government employees, 12 were from private organizations, and five were consultants. The results are listed as follows.

Theme No. 1: General Views on the ADR Reporting System of Pakistan

The majority of the participants felt that the ADR reporting system in Pakistan is evolving but it is in its infancy. Some participants thought that the pharmacovigilance system is only limited to tertiary care hospitals and immunization programs.

> "To be honest with you, the ADR reporting system in Pakistan has been in a transition . . . the ADR system which is in process at the moment looks very potential very promising. And we will only know about its impact once it starts to take hold and starts to grow roots in the system, which may not be the case at the moment (PPPE -I)".

Presently, 50 to 55 firms are reporting ADRs, and 60% of reports are coming from the expanded program for immunization. The perception of a few participants about DRAP had changed during the COVID-19 vaccine roll-out. A participant from the public health program acknowledged the good work of DRAP during the pandemic.

> "Our views have basically strengthened or we have our perception has been cleared during the COVID vaccination rollout. Before that, we were not clear about how was DRAP working or how were we supposed to report to DRAP (PHP-I)".

The absence of a proper pharmacovigilance regulatory framework is identified as the major gap in the ADR reporting system. Almost all participants mentioned that without the implementation of pharmacovigilance rules how one can expect stakeholders to report ADRs. A policy expert was "not satisfied the way it has been handled" (PE-III).

According to a pharmaceutical policy and practice expert, "the biggest gap would be the reporting by the health system into a national database" (PPPE-I). The connection between hospitals, community pharmacies, and central and provincial pharmacovigilance centers is missing. A physician stated that he was aware of some vaccine monitoring networks that keep track of adverse events (AEs) associated with their vaccines as a requirement of principle manufacturers, but they are not integrated with the national system. A similar statement of a tertiary care hospital nurse is as follows:

> "We actually report different medical errors, different adverse reactions, and all these things to our control system for HMIS. And then this will go to the quality department and then I don't know where'd they go? That I don't know (N-I)".

Few participants thought that the absence of a causality assessment committee and not having the capacity of the national pharmacovigilance center to evaluate individual case safety reports (ICSRs) are essential gaps in the system.

> "They have extensive AEFI reporting systems; at least for this COVID vaccination, they have 50,000 AEFI data, but the capacity of the DRAP to collect these data and generate the safety signals that is also lacking. (IHO-II)".

Several participants commented that pharmacovigilance should be included in the curriculum of medical and pharmacy undergraduate degree programs. A participant thought that the pharmacy's curriculum does not address these issues (PE-III). He further added that community pharmacies have not been engaged in the collection of ADR reports.

> "85% of our drug consumption is at the community pharmacies. And I'm not sure if they have been brought into the loop on this important element. I think mostly, we have been focusing on some hospitals in the country. (PE-III)".

Underreporting is identified as a major limitation to the ADR reporting system in Pakistan by the participants. The factors which contribute to the under-reporting are lack of awareness and training of healthcare professionals (HCPs), education of patients and consumers, noncoordination between regional and national pharmacovigilance centers, lack of communication among HCPs, no or limited private sector engagement, lack of information on drug exposure, mistrust on the system, no use of technology or the resources through which the reports had to channelize to the centers, shortage of skilled human resource, no mandatory requirement of ADR reporting, and lack of training and the understanding of the ADRs. Many participants believed that filing an ADR report and receiving no response or feedback from the regulator is very discouraging for future reporting.

> "It is not clear what is to be reported and where and then that feedback is never given back to the people, what happened to it and all so, those the two-way communication isn't there (Phy-II)".

Two participants considered the devolution of the health sector in 2011 from the federal domain to the provincial domain, a challenge for coordination among federation and provinces regarding medicine safety. Another participant felt that regarding medicines safety there is "no active listening".

> "There is a system in the making of the ADR reporting system. I hope that would actually soon be smart enough and listening enough so that patient responses could be actually picked up early enough and completely enough. But at the moment, there's no communication system, whereby reports could actually be communicated back into the system where it could be actually aggregated at a larger level (PPPE-I)".

The participants talked about other challenges of the current ADR reporting system, including the weak surveillance system, reluctance in reporting, low quality of the reported data, and biases in reporting. Lack of awareness, communication channels, trained staff, infrastructure, and facilities, are additional challenges of the ADR reporting system. According to a federal regulator, fewer experienced technical staff is the reason for a lower number of reports sent to the global system. A participant informed that the pharmaceutical industry is reluctant to implement a pharmacovigilance system because they have no profit coming from this activity. An expert considered less understanding of patients and attendants as a primary challenge to the ADR reporting system because patients and their attendants are not able to distinguish between the symptoms of disease and adverse effects of the medicines.

> "I think the primary challenge in ADR reporting comes from the one: the patient himself; ourselves, which where they may not actually be able to determine whether whatever is happening to them, if it is a strange phenomenon if that is because of intake of medicine, and then while reporting back, they may not be very clear about what their experience has been (PPPE-I)".

For all participants who were working in hospitals or the pharmaceutical industry, the leading barrier to ADR reporting is the fear of punitive action, punishment, and regulatory action, fear of losing a job, and public protest in case any ADR happened to the patient. A former hospital pharmacist thought that a "lack of trust in the system" hinders the HCPs to report while a physician commented that there is a disincentive in reporting with a feeling that "if I shall report, I shall get caught" (Phy-I).

> "The main barrier is that the person who is supposed to report is the person who's administering the drug or the vaccine. So what happens is that they're very scared of punitive action or anything that might go against them and reporting an ADR (PHP-I)".

An industry representative mentioned that "doctors are absolutely very, very busy with their practice for a large number of patients. So they do not have time to report adverse events"(PI-III). A federal regulator considered the illiteracy of people and the language of reporting forms as the biggest barriers to reporting.

> "The biggest barrier in Pakistan is, of course, due to low literacy rate is communication in language query using; the language used by the regulators or the HCPs is most often the official language English however, the patients are unable to understand these things in that language (FGS-I)".

The participants suggested various interventions and strategies to improve the current ADR reporting system. Early approval of pharmacovigilance rules, the establishment of provincial pharmacovigilance centers and ADR reporting centers in hospitals, giving priority to the subject, training of

HCPs, capacity building of hospitals and the pharmaceutical industry, and awareness of HCPs and patients are the most important aspects to improve the pharmacovigilance system in Pakistan.

Two participants suggested initiating the behavioral change communication strategies among all stakeholders to encourage the culture of reporting ADRs. An academic pharmacist recommended involving the religious clerics to advocate the ADRs reporting during Friday prayer sermons.

> "Behavioral change communication, a lot of good campaigns, which would actually aim at consumers, doctors, paramedics, system operators, would need to be actually carried out so that they are willing to share information and other barriers (PPPE-I)".

All stakeholders should adopt a joint strategy regarding the need to strengthen liaison and confidence among all. The infrastructure of pharmacovigilance centers in the industry requires improvement. Doctors and pharmacists should provide counseling and education to patients and relatives. There is a need to convince people on the grounds who are directly dealing with patients to report. One participant proposed media campaigns on medicine safety. Both physicians thought that there should be no punitive action against a person who has honestly reported the ADRs.

An academic pharmacist emphasized that for the promotion of the pharmacovigilance culture in the country, institutional purchase of medicines should be linked with the existence of a pharmacovigilance system. Few participants proposed the information and behavioral change exercises, the active role of civil society, and the training of provincial officers. An academic physician suggested developing the culture of community pharmacies in the country.

> "I have seen in other countries that they have this facility extended right into their communities, the community pharmacies, their pharmacist, visits the homes of the patient, chronically ill patients, and provides them the proper advice about the safe use of the drugs. So that is something which we just can't dream of, in this country (APhy-I)".

A participant among the federal government officers recommended training the regulator and the HCP on the Urdu version of all terminologies related to ADR to remove the language barrier. He further suggested people should be sensitized about ADR reporting in their languages. Added to this, at least those companies which are introducing new medicines should appoint pharmacovigilance officers to make liaison with the HCPs and analyze the reported data.

One participant argued that DRAP should analyze the reports it receives and a federal government officer identified a missing link of the regulatory authority that is not publishing the received information.

> "My advice to DRAP would be that please analyze those reports, after the company submits those reports, please analyze those reports (PE-III)".

A federal regulator stressed the provision of a dedicated budget at every level of the healthcare system. He stated that funds are required for spreading awareness, training of HCPs, equipment, and human resources. There should be no frequent transfers of the employees working in pharmacovigilance departments.

A physician from the industry suggested that in hospitals, a team of doctors and pharmacists should work together in the pharmacovigilance department.

> "We need to have a very you know, kind of way cross-pollinated system where pharmacists and doctors should have a very important team. The person who is working on pharmacovigilance should either be supervised by a doctor in any pharmaceutical company (PI-II)".

Theme 2: Role of the Pharmaceutical Industry in the Promotion of Medicine Safety

All participants believed that the pharmaceutical industry plays a key role in the promotion of the safety of medicines because it is their "social responsibility" to report about the safety of medicines. Many believed pharmacovigilance activities performed by the industry are limited to routine surveillance. Two participants commented that in Pakistan, multinational firms are reporting ADRs to DRAP because of their obligation toward their parent company while local companies are still not at par. Few participants argued that there is a disincentive for the industry in reporting because of the "huge investment," "low understanding of the ADR reporting system," and "no obligation" by the law. A federal regulator thought that the industry's role is not more than 15% because HCPs and the public report to the regulatory authority not to the industry. Another federal regulator commented that funds are required to run the ADR reporting system while financial support required to collect such data is neither supported by the governments nor by the pharmaceutical industries. The limited information is not sufficient to take any regulatory decisions.

> "Currently, almost 40 or 50 pharmaceutical companies are reporting to the DRAP, but the data is not so much what you can say so much big that you can take the decisions based on that data (FGS-II)".

Few participants thought that the industry is only interested in profit-making. A physician while sharing his experience of attending the medical conferences said that the industry never shares a bad side of the medicine. His statement is as follows:

> "If you want me a blank answer, they have a role, but they don't follow a good roleplay. I have been dealing with so many companies, and they always come and

> praise about their medicine, they never tell you this, you know, this side effect (Phy-I)".

A nurse thought that the pharmaceutical industry only "hires doctors" and never arranges educational seminars for the nurses, despite being important stakeholders. A doctor from public health program thought the pharmaceutical industry gives very little importance to telling the message.

> "If you've had the chance to look at the ads, for an over-the-counter drug, there is only at the end of the ad, they have a very small slot for saying that all medicines should be kept away from children. They may have effects, side effects, or anything. But the thing is that that message is completely lost in the entire promotion of the medicine itself (PHP-I)".

Theme 3: Future Pharmacovigilance Research Needs of Pakistan

There is a limited collaboration between academia, industry, regulator, and HCPs regarding medicines' safety. On enquiring from participants about future research needs of pharmacovigilance in Pakistan, one participant stated that the biggest need in Pakistan is how various study designs are developed and implemented.

> "In many of the hospitals, you might have retrospective data on some reporting, but it has not been collected not has been studied in a cohort manner. Neither there is a regulatory obligation for that nor the industry is interested in that and the HCPs themselves do not perform such studies because of the lack of interest from their side because their interest is more on the clinical side. So, this is one thing that you need to establish ADR linked with the study design especially the active surveillance and the passive surveillance study design. This shall also be propagated through the academicians as well as HCP levels (FGS-I)".

A public health expert talked about research on the off-label use of medicines. Two participants emphasized the need for local clinical trials and safety data. A physician said, "if research is done in other parts of the world, it does not mean that the same research is effective on our population" (Phy I). A pharmaceutical industry representative pointed out that the local medicine safety newsletters contain only information related to international signals and product quality issues. The information is not from Pakistan in the local aspect, and all of the signals or the box warnings are from the international data. The statement of the academic physician is as follows.

> "Yes, particularly, the local data is very, very important, because with the new medicines, which are being introduced, now, the importance of genetic factor is becoming more and more important. So, we just cannot rely on the data of other countries, we have to have our own data as well. So, if we have this data available, this will help us to make our own guidelines. And we can also issue instructions about the safe use of these drugs (APhy-I)".

Theme 4: General Views on Draft Pharmacovigilance Rules in Pakistan

The majority of the participants (n = 22) were aware of the existence of draft pharmacovigilance rules except for three participants: two physicians and one nurse did not know about the existence of such rules.

Most of the participants accepted that they have seen the initial drafts and have not reviewed them recently. The reasons they explained were that the "rules were shared long ago" and "no new stakeholder consultation" was arranged by the regulator. Only the participants from the pharmaceutical industry were aware of the context and contents of the rules. A pharmacovigilance expert said:

> "I've come across really, but I have not gone through the very fine tooth comb scape? I have not looked at line by line, but I think I'm reasonably aware of it. Yeah. If you ask me, have you read it? My answer would be no (PE-III)".

There were conflicting opinions among the participants if the draft rules are aligned with the international best practices. The current and former employees of multinational pharmaceutical companies found the rules aligned with the international standards with no shortcomings. According to them, draft rules are adapted from EMA and FDA regulations and WHO guidelines. The participants from federal government services also believed the rules are drafted as per international practices. Some participants argued that rules are adapted from international regulations and are not made in the local context. A statement of an expert is as follows:

> "They might be aligned with international standards. So, but that's the cut and paste situation. But are they relevant to our country? I have my doubts about that (PE-III)".

Some participants pointed out that the rules are complicated, and they do not define the roles and responsibilities of stakeholders. One participant from the pharmaceutical industry suggested that a qualified person for pharmacovigilance should be free from "commercial bias." A participant from the federal government service informed that to ensure transparency, an independent chairman of the risk assessment committee (not from DRAP) has been proposed in amendments to the rules. Few stakeholders thought that shortcomings cannot be pointed out, and rules cannot be improved without implementing them.

> "Rules cannot be improved until they are implemented. Once implemented limitations come and with the passage of time to know the problems hurdles in

these rules, and that's why with the passage of time amendments are made in the rules to make them better and better (FGS-II)".

A pharmacovigilance expert who is also a pharmacist sees bias and conflict of interest in the whole system. He thought that rules are drafted by the pharmacists, and the objective of the whole exercise looks to promote pharmacists, not patients' safety. The participants from international health organizations suggested wider dissemination of the rules before approval and include the role of the healthcare commissions in the proposed rules.

Almost all stakeholders rated "bureaucratic red tape" as the top reason for delaying the approval of the pharmacovigilance rules. One participant believed that the bureaucracy does not understand the importance of the issue.

"I think that it might be a bureaucratic red taping because if it were, it had been drafted in 2017 and now it is 2021 and still it hasn't been notified (FGS-III)".

Many participants stated the "lack of political will" for the delay in the approval of pharmacovigilance rules. They think that the government is not clear in taking steps and that its commitment to medical safety is not there. Several participants mentioned that there is no willingness from stakeholders, that pharmacovigilance is not on the agenda, and policymakers are not competent. The pharmacovigilance job is usually assigned as additional work to the officers in provinces and hospitals or given to the junior and inexperienced officers and it usually does not work. One participant thought that pharmacovigilance is not the priority of the policy and decision-makers.

"The only and only thing is that, as I already shared with you, that pharmacovigilance system and ADR reporting is never, never a priority for any of us, for our policymakers, for the people who are involved and who are at the helm of affairs in the health ministry, even DRAP everywhere (PGS-I)".

Two participants doubted the immediate implementation of the pharmacovigilance rules due to lethargy and the capacity of the system. Some stakeholders think that it shall be an economic burden on the industry to set up the pharmacovigilance system and hire the services of qualified pharmacovigilance experts.

"...Pharmaceutical companies also don't like these rules to be implemented, because it's a burden for them as well in an implementation that really related to the resources related to the system related to the implementation overall(PI-III)".

On questioning how the process of approval of pharmacovigilance rules be expedited, some participants proposed to arrange formal consultations of all stakeholders, giving it a priority and setting the timelines. Several participants believed to initiate advocacy, as well as sensitizing the political leadership and bureaucracy.

A participant suggested that leadership be sensitized to pharmacovigilance to achieve WLA (WHO listed authorities) status. The participants from the pharmaceutical industry believed that the involvement of trade bodies can strengthen the proposed rules.

"Hopefully, we are going for the WLA (WHO listed authorities) and in these aspects rules, approval of rules can be accelerated because the higher management should show the commitments that DRAP shall achieve the WLA and WLA is not possible without promulgation of pharmacovigilance rules. It is one of the basic requirements and it is the level one indicator (FGS-II)".

Most participants were confident that approval and implementation of pharmacovigilance rules shall not only ensure early detection of medicine-related risks but also can minimize their harm, can reduce morbidity and mortality rates, as well as the economic burden.

"If pharmacovigilance system starts to take hold in Pakistan and if the reports coming back, properly analyzed, if the issues are being identified, and that would be the start. And if after that, you can work backward, to prevent ADRs on a larger scale. So that would actually have a major impact on public health (PPPE-I)".

Some participants believed that with the implementation of the rules, the number of ADRs shall increase to contribute to the global pharmacovigilance system, and a good enforcement mechanism shall be in place. One participant thought that if few regulatory decisions will be taken based on reported ADRs, then definitely public health will be affected by these rules. The public will be gradually aware that their reports have an effect on the regulatory system in Pakistan.

"In Pakistan, many rational formulations were registered in the past which do not exist in the stringent regulatory authorities. But they continue because there is no established ADR reporting system in Pakistan, but after these rules, if the ADRs are reported there might be some deregistration cases (FGS II)".

A participant from the multinational pharmaceutical industry thought that rules will be just another bureaucratic layer over the system, while another believed that because of their inability to comply with the requirements of the rules, the industry will backlash.

One of the academic pharmacists' opinions is that it will have a great impact on prescribing, dispensing, and administration of medication, health outcomes of the patient, as well as it will increase patients' confidence in the healthcare system.

Theme 5: Coordination, Stakeholder Engagement, and Communication

The majority of the participants thought that the collaboration between DRAP and stakeholders was not at an optimal level. Participants believed that inappropriate selection of stakeholders, lack of coordination between various regional and national pharmacovigilance centers, limited representation of stakeholders from civil society, and lack of understanding and where and how to report ADRs are some of the potential barriers.

> "The coordination is far from ideal or the desired level. And the main reason for that I don't blame anyone for that I can see that the DRAP does not have the required manpower and resources where they can outreach and contact the stakeholders and have more frequent interaction with the stakeholders (APhy-I)".

Recently, DRAP has demonstrated an active role and conducted a series of seminars and training sessions for stakeholders other than healthcare professionals and patients because they are informed through the safety alerts. For some participants, the coordination between DRAP and stakeholders is good. A pharmacist from an international health organization said, in the recent past, DRAP is very active in coordinating with the stakeholders (IHO-I). There is a need for a coordination mechanism within the provinces and hospitals.

For some participants, the coordination between DRAP and stakeholders is not friendly. An academic physician understands that DRAP is facing a shortage of manpower and other resources. A participant from the provincial government service informed that there are two or three drug information centers, and all are in the private sector. In the absence of the DIC, how anyone could contact DRAP for the information remains unknown. The participants other than DRAP were asked about their experience in contacting DRAP for safety information. Most stakeholders were satisfied with their personal experience in contacting DRAP, but they think that it cannot be generalized.

> "If you ask my personal experience, it has always been blurred, I could always reach out, but I don't think that is something that I would say across the board (PI-I)".

The participants who work with the government were asked to share their experience of contacting the industry for safety information. A federal government official stated that it was a bad experience.

> "...There was a manufacturer from which I needed some information on the vaccine safety and I contacted that particular manufacturer, but they were not able to collect the data because they were not collecting that data from the endpoints. So, their vaccine was distributed in the government sector as well as in the public sector. However, they had this whole system on the paper, but it was not implemented. And the reason for being not implemented is that there was no regulatory binding on it. So, this was a bad experience (FGS-I)".

The participants were asked to identify the key stakeholders to get engaged in the improvement of pharmacovigilance. The majority of the stakeholders proposed to involve multiple stakeholders including DRAP, PHPs, provincial governments, pharmaceutical physicians, district health officers or someone who has control over hospitals, healthcare commission, medical specialized associations, international health partners, journalists, media, and religious leaders. One participant recommended that "we should convince the doctors first. And we should convince the heads of the medical institutions. Either private or public" (AP-II), while another suggested conducting continuous consultative meetings.

> "The person who confronts the patients, who is involved with the drugs, the patient? Who really interact with the key stakeholder? who are the key stakeholder the nurse, doctor, and the patients. He should be involved, somebody there who's a day in and day out dealing with the drugs and the patients and the customers and the consumers (PE-III)".

Few participants found gaps in the stakeholder's selection during the development of the pharmacovigilance system. A pharmacist from an international health agency believed that the stakeholder's selection for the pharmacovigilance system is limited, and the civil society is not involved in the process.

> "I believe that the civil society's role is very important. Fortunately, it's not, you know, the representation is very limited, although I do agree, we have, you know, representation, but it needs to be expanded (IHO-I)".

An academic pharmacist argued that media is another stakeholder as far as patients and consumer rights are concerned. The participants from pharmacy academia were of the view that policymakers do not consider them as stakeholders.

> "...the only stakeholder they see is the pharmaceutical industry, which is very unfortunate. They need to broaden the understanding of stakeholders and the biggest stakeholder is the consumer, is the patient you need to go back then the nurse then the pharmacist than the doctor(AP I)".

The key role of regulatory authority in promotion of the public health was described by many participants. An academic pharmacist found DRAP in a dilemma between promoting public health, as well as the goals of the pharmaceutical industry.

One of the inherent issues in our drug regulatory system is that DRAP was really struggling between the two camps. One is public health, and the second is regulating and promoting the pharmaceutical industry. My view is that the DRAP should take the role of somebody who is responsible for public health and not somebody who is promoting the pharmaceutical industry. (AP-I).

The participants who were pharmacists proposed that the pharmacovigilance center should be independent of DRAP and be placed in research or academia settings.

> ". . .It should be independent of DRAP because DRAP is looking at the registration, and licensing of a product. The regulator is doing its own monitoring. My view is that it should be an independent function of from DRAP (AP-I)".

If I were a doctor, I would not like to talk anything negative about what has happened to my patients. And particularly, they will not like to tell to DRAP. So DRAP is a regulator. That' is the police. Now, how would a doctor like to talk about an offense to the police? (PPPE-I).

> "National and provincial committees on pharmacovigilance can serve as a think-tank on pharmacovigilance and arrange more advocacy sessions. Few participants suggested engaging media and celebrities disseminate the information".

The academic and practicing pharmacists thought that community pharmacies have a bigger role in educating and also in reporting ADRs. If community pharmacists are offered incentives the number of ADR reports can be increased. Another academic pharmacist and a physician from the pharmaceutical industry recommended incentives and recognition certificates to doctors and heads of hospitals.

> "Just a simple sign (Board), If I take this medication, if you take this medication, you experience any good or bad thing, kindly come and talk with your pharmacist or come or talk with this patient (AP-I)".

Theme 6: Medicine Safety and Role of Media

There was a unanimous consensus over the role of media in promoting medicine safety. The participants believed that media can be involved through news briefings, writing articles, arranging talk shows, cartoon commercials, social mobilization campaigns, medicine safety campaigns, advertisements, commercials, and dramas to create awareness and dissemination of information. An academic pharmacist emphasized the need to train the media persons with the right knowledge. The role of cartoon journalism and cartoon stories to promote medicine safety was highlighted by both academics from the pharmacy.

> "If media can spread the political awareness, why not the medical awareness and why not about the ADRs (APhy-I)".

Not everyone sees the positive role of media. The participant from the public health program and the pharmaceutical industry highlighted the negative role of the media.

The participants suggested choosing the right media for medicine safety whether it is electronic media, print media, and social media. One of the participants preferred social media over others because it is popular and free. Another participant suggested placing information banners at the different OPDs of the hospitals. One of the participants suggested that the DRAP should have a strong communication team to spread safety information.

DISCUSSION

The study set out to explore the views of stakeholders on the ADR reporting system of Pakistan, issues with policy, and coordination among stakeholders. The majority of the participants consider the pharmacovigilance system of Pakistan evolving but it is in its infancy. To see if it has an impact, it must get a foothold in the system and start to build roots. Similar findings were observed in the study by Kiguba et al., (2022) on pharmacovigilance in low- and middle-income countries. This is when compared with the high-income countries, the majority of low- and middle-income countries' regulatory pharmacovigilance systems are nascent or nonexistent.

Often concerns are raised regarding DRAP for poor ADR reporting in the country (Hussain et al., 2018; Atif et al., 2020). Although during 2017–19 the number of ADR reports was not as expected (Khan et al., 2022); however, more than 50,000 adverse events following immunization (AEFIs) reports related to the COVID-19 vaccine have been received by DRAP in the last 2 years. Many participants acknowledged the efforts put in place by the DRAP to improve medicine safety, especially during the COVID-19 pandemic. Due to a shortage of trained staff and the absence of a causality assessment committee, the analysis of received reports is another challenge for the regulatory authority. Pakistan's pharmacovigilance system is facing the challenges of budgetary constraints, and there is some support from international organizations (Junaidi, 2021). Similar findings were recorded in a study that most LMIC face financial issues, and they rely on the donor's support (Kiguba et al., 2022).

The participants identified a lack of regulatory framework i.e., pharmacovigilance rules as the major gap in the ADR reporting system which is similar to the findings of a recently conducted quantitative study (Khan et al., 2022). Stakeholders also stated other gaps which include lack of integration among the various components of the health system including hospitals, pharmacies, lack of awareness and knowledge gap, communication gaps between doctors and pharmacists, absence of a causality assessment committee, and the incapacity of the national pharmacovigilance center to evaluate individual case safety reports. Various other studies have mentioned the same gaps in the ADR reporting system of Pakistan (Hussain et al., 2018; Atif et al., 2020; Khan et al., 2022).

Underreporting is generally considered a key limitation to any pharmacovigilance system. Few stakeholders recognized that reporting is discouraged when the reporter does not receive any feedback from the pharmacovigilance center. A randomized study conducted in Sweden explains that feedback from the doctor influences the ADR reporting rate (Wallerstedt et al., 2007). Various other studies also support this notion that the ADR reporting rate is affected by the feedback and some reporters require personal response (Oosterhuis et al., 2011;

Rolfes et al., 2015; Al Dweik et al., 2017). One of the challenges discussed by the participants was that there is no active listening going on regarding medicines' safety. Paying attention to patient voices in vaccine safety has drawn the attention of the researchers. It involves active listening techniques to understand how others assess and perceive risk, and then use this information to empower better decision making (Holt et al., 2016). In response to a question, a participant gave feedback that pharmaceutical companies are reluctant to implement a pharmacovigilance system since this activity does not create profit. A study expressed that in Europe, pharmacovigilance infrastructure is becoming increasingly established, and the high cost of its implementation is being borne by drug manufacturers (Milmo, 2014).

Fear of punitive action among all stakeholders surpasses all barriers to reporting ADRs. Several studies stated the same factors that contribute to hurdles related to ADRs reporting (Al Dweik et al., 2017; Ali et al., 2021; Sharif et al., 2022). The quality of the language and completeness of reports can impede the understanding of the ADR (Hazell and Shakir, 2006). It was also discussed that the English language is one of the barriers among the Pakistani population. The long ADR forms are not in the same language which patients, their attendants, and few healthcare professionals understand these forms. Pakistan may provide ADR reporting forms in regional languages as the Indian pharmacovigilance center has provided consumer reporting forms in 10 languages to tackle the language barrier in ADR reporting (Kalaiselvan et al., 2015).

The pharmaceutical industry is often accused of unethical promotion of medicines. Marketing drugs to physicians including sponsored medical conferences may influence their perception (Kaczmarek, 2022). All stakeholders other than industry representatives also discussed the role of the pharmaceutical industry in profit-making than promoting medicines' safety. A physician was of the view that the pharmaceutical industry or medical representatives never inform regarding the adverse effects of medicines during medical conferences or personal visits. This has also been observed in the literature (Fickweiler et al., 2017).

To make sure that drug safety monitoring processes are implemented and sustained, the country's drug regulatory mechanisms should be framed to incorporate pharmacovigilance measures (Alomar et al., 2019). DRAP started consultations on the initial draft of pharmacovigilance rules in 2017. The first draft was prepared in 2018. Since then it has been in the draft format and has not become part of the regulations.

Except for two physicians and one nurse, all participants were aware of the existence of draft pharmacovigilance rules. These findings are similar to what is observed in the literature as studies found that majority of the Pakistani physicians and nurses were not aware of the ADR reporting center and activities in Pakistan (Hussain et al., 2018; 2020a). Some participants have the view that draft rules are as par as international standards. However, some others believed that draft rules are adapted from the international guidelines and not made in the local context and this will not work. Their stance is supported by a study that states that some laws adapted or copied from developed countries are not compatible in the contexts of developing countries (Umeokafor, 2020).

In addition to officers from DRAP, only the representatives of the pharmaceutical industry were aware of the context and contents of the proposed rules. This shows how the pharmaceutical industry in Pakistan watches its interests. There are several studies depicting how the pharmaceutical industry has influenced medicines advertising and promotion in the country (Caudill et al., 1992; Abraham, 2002; Babar et al., 2011; Fugh-Berman and Homedes, 2018; Hailu et al., 2021). One of the pharmacovigilance experts described the policy process as being driven by pharmacists. This is being deduced that the intention of the process is to promote the pharmacists rather than the patient safety.

Generally, politicians initiate policy formulation in areas of major political concern while the permanent bureaucracy has significant power in policy formulation (Buse et al., 2005). Participants believed that bureaucratic red tape and lack of political will are the major reasons for not approving the draft pharmacovigilance rules. According to Bashir's (2011) analysis, Pakistan's government sector's ineffectiveness is mainly due to the high level of red-tapism (Bashir, 2011). Another researcher recommended removing or reducing the red tape from government organizations to improve the efficiency and economy (Rauf, 2020). Various studies support the creation of sustainable budgets for pharmacovigilance staff, routine training, and the development of national pharmacovigilance policies through a political will (Biswas, 2013; Olsson et al., 2015). Political will and sustainability of the pharmacovigilance system are linked in several studies (Abiri and Johnson, 2019). Participants also stated to initiate training and advocacy sessions to convince the political leadership and bureaucracy to bring the pharmacovigilance on agenda and get the rules approved and implemented. A similar framework for communication among doctors, pharmaceutical companies, patients, and DRAP is required. This is similar to what is being developed by the researchers from the Royal College of Physicians of London (RCP) (Allan, 2009).

According to an academic pharmacist, DRAP is attempting to promote public health and the pharmaceutical industry at the same time. A similar observation was shared in a study that states that support from the government for the pharmaceutical industry have not had a positive impact on the quality of medicines. Balance must be established between public health objectives and economic interests. The pharmacy academia suggested placing the national pharmacovigilance center in any academic clinical institution instead of DRAP. They have the view that DRAP is issuing licensing of medicines, hence monitoring of medicines' side effects would be a conflict; however, this does not hold much substance. Also, the WHO recommends that for a pharmacovigilance center, a government health authority or drugs regulatory agency is the place to govern or establish a pharmacovigilance center.

The COVID vaccine rollout has enhanced the value of global coordination among the stakeholders (Naniche et al., 2021). Although DRAP has shown improvement in coordination with stakeholders during the pandemic, it still lacks harmony

and collaboration. Previous studies identified the lack of coordination among the stakeholders (Hussain et al., 2020b; Khan et al., 2022). The public health programs (PHPs) in Pakistan are not integrated with DRAP, except for the expanded program for immunization (EPI). The coordination with EPI is improved because EPI was managed by the COVID vaccine rollout program. As soon as pharmacovigilance rules are approved, all public health programs will need to develop pharmacovigilance systems and integrate them with the DRAP's national center.

It was also observed that the stakeholders' selection was not uniform during the development of the pharmacovigilance system and drafting rules with limited or no participation of civil society and academia. Before formulating any policy, it is essential to conduct a stakeholder analysis and engage stakeholders (Adenuga et al., 2020). The role of patient organizations in pharmacovigilance has evolved, with many activities that increase member awareness of and involvement in drug safety, but there are still internal and external barriers to their involvement (Edwards and Graedon, 2010). The representation of the civil society or patient groups in the pharmacovigilance system in Pakistan is none or very limited. This might be due to a lack of awareness and a culture of nonparticipation by the patients and consumers.

Media represents and influences societies in both positive and negative ways. A recent study demonstrated that media coverage may lead to increased adverse event reporting. A balanced approach by the media to cover harm caused by medicines is essential (Edwards and Graedon, 2010). In Pakistan, pharmaceutical companies alleged that they are sometimes blackmailed by the media if any incident occurred due to their medicine. This shows the dark side of yellow journalism (Ricchiardi, 2012; Kurambayev, 2017). A similar study showed how media creates hypes in case of mass casualty incidences (Musharraf et al., 2022). Due to the growing popularity of the use of social media the participants also suggested the promotion of medicine safety. The same was suggested by Yasir Al-Worafi (2020) that social media could be used to strengthen the pharmacovigilance systems.

The participants presented a number of strategies to improve the pharmacovigilance system of Pakistan, as presented in recent studies (Hussain et al., 2020a; Atif et al., 2020; Shchory et al., 2020; Bahri and Pariente, 2021; Khan et al., 2022). The participants also proposed that the healthcare practitioners who interact with patients should be involved to improve the pharmacovigilance system in the country. The role of nonpharmacists in community pharmacies is also neglected and they also needed to be brought into the discussion. Community pharmacists can also play a pivotal role in increasing the number of ADR reports. Linking institutional purchases with the availability of pharmacovigilance systems can also improve the culture of pharmacovigilance.

For a robust and functional pharmacovigilance system in Pakistan, the study participants proposed 1) immediate approval of pharmacovigilance rules, 2) training and advocacy sessions to pursue the political leadership and bureaucracy, 3) establishment of a Pharmacovigilance Risk Assessment Expert Committee, 4) recruitment of trained staff, 5) allocation of a separate budget for pharmacovigilance activities, 6) capacity building and integration among the various components of the health system including hospitals, pharmacies, public health programs with provincial or central pharmacovigilance centers, 7) to update medical, pharmacy, and nursing curriculum with the inclusion of pharmacovigilance, 8) involving media to promote medicine safety, 9) involving nonpharmacists at community pharmacies, and 10) conducting local clinical trials to generate local safety data. This is the first ever inductive qualitative study conducted in Pakistan on the ADR reporting system, policy, and coordination involving a broad range of stakeholders. Any review of the pharmacovigilance policy of Pakistan by policymakers can get help from findings from the current study as a crucial component.

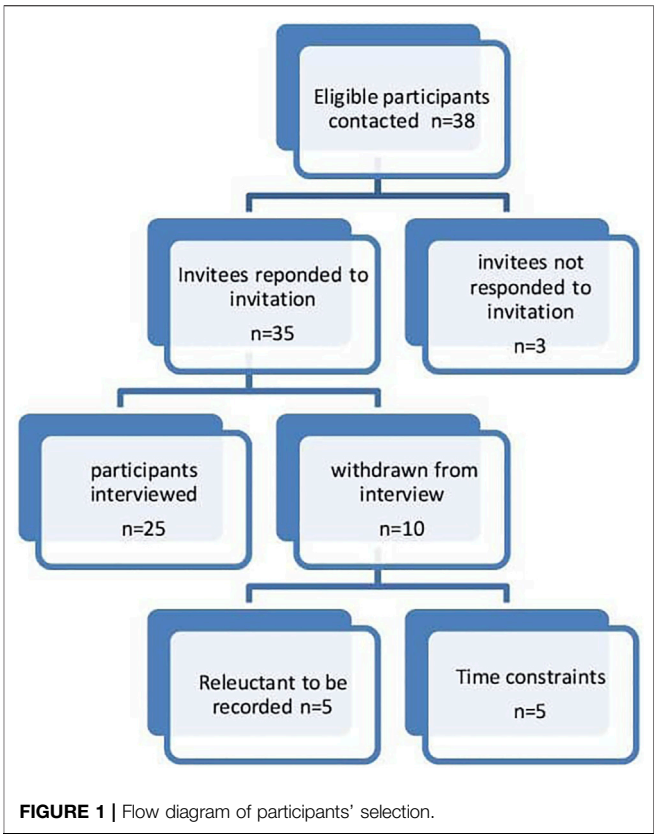

FIGURE 1 | Flow diagram of participants' selection.

Limitations to the Study

The study sample did not include key informants from individual Pakistani provinces where there is no ADR reporting system in place. These provinces are Sind, Khyber Pakhtunkhwa, Baluchistan, and federally administered areas Gilgit Baltistan and Azad Jammu and Kashmir. Participants' selection was purposive, and we do not know if the views and experiences of participants who have withdrawn from the

study differ from those of their colleagues. Not including patient support groups and media may also have restricted the range of stakeholders.

CONCLUSION

The study concluded that the stakeholders were partially satisfied with the progress made with the current pharmacovigilance system. Although the pharmacovigilance rules are available in the draft format, there is a need for the approval of the legal framework. However, before approval and implementation, a wider consultation of multi-stakeholders including the patient groups and journalists will help address the policy issues. Through advocacy and training of stakeholders, removing barriers of red-tape, having a political will, and motivating the willingness of HCPs are the major objectives to be achieved. By engaging stakeholders, technology, and media, the medicines' safety information can be disseminated to the masses to improve the safety of medicines.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion 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 ethics review board of the Health Services Academy. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK conceptualized, developed an interview guide, collected data, analyzed the results, and drafted the manuscript. SH conceived the idea, improved the interview guide, interpreted results, edited and revised the manuscript, and SK and MS contributed to data analysis, manuscript editing, and revision. Z-U-DB contributed to the interview guide and manuscript development, data analysis, result interpretation, and manuscript revision. Z-U-DB also edited the manuscript for clarity. The final version of the manuscript was checked and accepted by all contributors.

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Utility of a Laboratory Alert System for Detecting Adverse Drug Reactions in Hospitalised Patients: Hyponatremia and Rhabdomyolysis

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Background—Adverse drug reactions (ADRs) are a public health issue, due to their great impact on morbidity, mortality, and economic cost. The use of automatized laboratory alerts could simplify greatly its detection.

Objectives—We aimed to evaluate the performance of a laboratory alerts system as a method for detecting ADRs, using hyponatremia and rhabdomyolysis as case studies.

Methods—This is a retrospective observational study conducted in 2019 during a 6-month period, including patients hospitalized at the Hospital Universitario de La Princesa. Patients were identified using altered laboratory parameters corresponding to the two signals: "rhabdomyolysis" (creatine phosphokinase >5 times the upper limit of normality (ULN): >1000 U/L for men and >900 U/L for women) and "hyponatremia" (<116 mEq/L) were detected. In cases where ADR was suspected, causality assessment was performed using the algorithm of the Spanish Pharmacovigilance System (SEFV).

Results—During the study period, 180 patients were studied for the "rhabdomyolysis" signal, 6 of them were found to have an ADR (3.3%). The sensitivity of the test was 60%, specificity 97%, and positive predictive value 41%. 28 patients were studied for the "hyponatremia" signal, and 11 patients were found to have an ADR (39.3%), with a sensitivity of 76.9%, a specificity of 93.3%, and a positive predictive value of 88.2%. We found no relationship between altered laboratory values and risk of ADR in any of the cases studied.

Conclusion—A pharmacovigilance program based on automatized laboratory signals could be an effective method to detect ADR. The study of the "hyponatremia" laboratory alert is more efficient than "rhabdomyolysis". The evaluation of the hyponatremia alert allows the identification of 12 times more ADRs than the rhabdomyolysis alert, which means less time spent per alert evaluated to identify an ADR.

Keywords: pharmacovigilance, adverse drug reaction, safety, rhabdomyolysis, hyponatremia

INTRODUCTION

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as a harmful, unintended reaction to medicines that occur at doses normally used for treatment (WHO, 2002; Safety of Medicines, 2002). ADRs are a frequent cause of illness, disability, or death, and in some countries, they are even among the 10 leading causes of mortality (WHO, 2004).

A meta-analysis of prospective studies conducted in U.S. hospitals by Lazarou et al. (1998) estimated that the overall incidence of serious ADRs in hospitalized patients was around 6.7% and the incidence of deaths from ADRs was about 0.3%. Furthermore, ADR treatment places a largely unrecognized but considerable financial burden on the healthcare system. The need for these additional medical interventions may be avoidable (WHO, 2002). Therefore, mechanisms to assess and monitor the level of safety provided by the clinical use of medicines are essential to prevent or reduce adverse drug effects and improve public health (WHO, 2004).

In hospitals, the most common method used for ADR detection is spontaneous reports. However, this system is subjected to several limitations, notably the existence of a high under-reporting of ADRs (Neubert et al., 2013). Currently, the WHO and the European Medicines Agency (EMA) propose complementing spontaneous reports with specific pharmacovigilance programs to identify drug safety problems as early as possible (Ramirez et al., 2010).

Methods to identify ADRs should be tailored to local needs. In our center, active pharmacovigilance activities include the review of all patients admitted to the hospital but data related to ADRs not apparent at the time of admission or arising during hospitalization are lost. In addition, the diagnosis of ADRs is not always straightforward and tools to facilitate their early identification are part of the strategy to improve patient safety.

In recent years, the availability of computerized databases associated with electronic medical records has made it possible to develop different programs for the detection of ADRs. The methods used by these programs differ between hospitals due to the specific characteristics of each clinical setting (Ramirez et al., 2010). ADR detection systems based on signals generated using laboratory information stand out. Several studies have identified these programs as effective (Levy et al., 1999; Ramirez et al., 2010; Neubert et al., 2006; Dormann et al., 2004; Tegeder et al., 1999; Dormann et al., 2000). In addition, they can be used as a tool for the early detection of ADRs, thereby reducing hospital length of stay and costs caused by ADRs (Dormann et al., 2000). The software developed at our hospital allows the automatic detection of clinically relevant altered analytical values, such as elevation of liver enzymes, amylase, creatine phosphokinase (CK), hematologic alterations and hyponatremia.

The primary research objective of this study was to evaluate the performance of a laboratory alerts system as a method of detecting ADRs, using hyponatremia and rhabdomyolysis as case studies. Secondary objectives were to evaluate the performance of these laboratory signals, estimate the incidence of identified ADRs, and describe the characteristics of patients in whom an ADR has been identified.

MATERIALS AND METHODS

Study Population and Study Design

A retrospective observational study was conducted at the Hospital Universitario de La Princesa, a tertiary level university hospital, including all medical specialties except for pediatrics and gynecology-obstetrics. It has 524 beds and currently covers a population of 323,000 people in Madrid (Basic Information, 2020).

The study population was all patients hospitalized in the hospital during the study period. The study period was 6 months (1 July 2019 to 31 December 2019). These dates were chosen, despite the existence of time periods closer to the study (September 2020–April 2021) to avoid the possible contaminating effect that the SARS-CoV-2 Global Pandemic could have on the validity of the data collected. The data collected were limited to the laboratory signals of "rhabdomyolysis" and "hyponatremia".

The methodology proposed by Ramirez et al. (2010) was used as a reference, with some modifications:

- Definition of the laboratory signals: rhabdomyolysis (value of creatine phosphokinase [CK] >5 times the upper limit of normality (ULN): >1000 U/L for men and >900 U/L for women) and hyponatremia (<116 mEq/L) (Letmaier et al., 2011; Ramírez et al., 2019; Sosa Medellin, 2016; Torres et al., 2015; Arébalo-López et al., 2015).
- Detection of laboratory signals using the "LABORATORY SIGNALS" application developed by the Bioinformatics Department of our hospital.
- Review of medical records when a suspected case was detected. The analysis was not continued in cases whose signal was attributed to the patient's primary diagnosis or any underlying disease [see **Supplementary Annex**].
- For the remaining patients, causality assessment was performed using the algorithm developed by the Spanish Pharmacovigilance System (SEFV) (Aguirre and García, 2016). In each patient with suspected ADR, the causality algorithm was applied to each suspected drug by two investigators (MV and GM). Both investigators had clinical experience but one of them had less experience in drug safety assessment. To calculate the sensitivity, specificity and positive predictive value (PPV), the differences in the causality results of the SEFV algorithm of the two evaluators were taken into account. This made it possible to identify some cases in which the result differed and, after discussion of the discrepancies, it was determined whether the alert met ADR criteria or not.
- Suspected adverse reactions that were ultimately not considered as adverse reactions were considered as false positives.
- ADRs detected were reported to the SEFV.

TABLE 1 | Patients with a rhabdomyolysis alert who met exclusion factors due to underlying diseases that explained the analytical alteration.

	No. (% of Total) N = 180	CK Levels (U/L, Mean ± SD)	Age (Mean ± SD)	Male Sex (No. and %)
Myocardial infarction	58 (32.2)	3.203 ± 2,785	61 ± 14.5	37 (63.8)
Surgery for reasons other than myocardial infarction	24 (13.3)	2.287 ± 1,636	65.8 ± 14.7	16 (66.7)
Surgery due to myocardial infarction	20 (11.1)	2,054 ± 1,084	68.6 ± 9.6	16 (80)
Muscle compression due to a prolonged fall	17 (9.4)	2,943 ± 2,673	82.8 ± 8.1	7 (41.2)
Infections	11 (6.1)	11,231 ± 20,031	73.1 ± 15.3	7 (63.6)
Drug intoxication	10 (5.6)	15,713 ± 29,184	50.5 ± 24.8	6 (60)
Major trauma	8 (4.4)	2,639 ± 2,073	51.3 ± 17.74	8 (100)
Seizures	8 (4.4)	2,623 ± 2,387	40.1 ± 8.8	8 (100)
Acute vascular thrombosis	8 (4.4)	2,506 ± 1,603	77.1 ± 17.1	4 (50)
Extreme physical exercise	4 (2.2)	13,280 ± 16,508	33 ± 11.2	2 (50)
Myositis and other genetic and metabolic disorders	1 (0.6)	3,762	53	1 (100)
Losses from the study	1 (0.6)	7,171	30	1 (100)
Total	170 (94.4)	4,345 ± 9,649	65.4 ± 18.0	113 (66.5)

CK: creatine-phosphokinase enzyme; SD: standard deviation.

The SEFV algorithm comprises 7 criteria (Aguirre and García, 2016), which are assessed for every drug-ADR pair: 1) Time sequence (chronology between the start of treatment with the suspected drug(s) and the appearance of the adverse effects); 2) Identification of plausible adverse drug reactions using knowledge extracted from the literature; 3) Withdrawal effect: evolution of the adverse effect after withdrawal of the suspected medication; 4) Re-exposure effect: reaction after re-administration of the suspected drug; 5) Alternative explanation for the observed effects; 6) Contributing factors favoring the causal relationship (e.g. renal failure and relative overdose of a drug with predominantly renal elimination); 7) Complementary explorations: serum drug levels, biopsies, positive radiological examinations, positive specific skin tests, etc. The maximum possible score is 12.

Based on the obtained scores, the causal relationship is classified as: unrelated (<1), conditional (1–3), possible (4–5), probable (6–7) and definitive (>7). Only those classified as possible, probable, or defined were considered as drug related.

Data Analysis

The statistical analysis was accomplished using Microsoft Excel 2021 and the SPSS 22.0 statistical software (SPSS Inc., Chicago, Illinois). The average, standard deviation (SD) and interquartile range (IQR) were calculated for each quantitative variable studied. The incidences of ADRs detected were estimated from the cases with each signal. PPV were calculated for analytical values where possible (primarily by reviewing all data collected, to identify false negatives while minimizing variability). PPV is defined as the number of times an alert is issued with respect to a particular rule and an ADR is confirmed (true positives), divided by the number of times an alert is issued with or without confirmation of an ADR (sum of true positives and false positives) (Handler et al., 2008). The Number of laboratory signals Needed to be Evaluated (NNE) was estimated by determining the number of cases evaluated to detect one ADR. Hypothesis testing for independent samples was performed with SPSS for those variables that were attempted to be correlated in the two groups (age, sex, level of the analytical value, and the possibility of ADR).

Ethics

The project was approved by the Ethics Committee for Research on Medicines (CEIm) of the Hospital Universitario de La Princesa. As all the information was registered from the electronic medical record without interviewing the patients, it was not necessary to request patients' informed consent. Researchers respected the confidentiality of every data obtained during the conduct of the study.

RESULTS

Rabdomyolysis

In the study of laboratory signal for "rhabdomyolysis", the "LABORATORY SIGNALS" application detected 388 laboratory alerts from 180 different patients. In 170 patients an alternative cause was found to justify the high CK levels (see **Table 1**). In 4 of them, no alternative cause was identified but causality with drugs could not be established, and in 6 of them, 1 ADR was detected. No significant differences regarding age, sex, or CK levels were detected between the different groups.

The underlying diseases or primary diagnoses that were exclusion criteria for the patients to be studied (Garro Ortiz, 2014; Li et al., 2014; Torres et al., 2015; Deljehier et al., 2018) are detailed in **table 1**, being myocardial infarction the most common. A patient was lost from the study: it was a foreign patient who returned to his country of origin after the laboratory alteration was detected, with a strong suspicion of suffering from myositis, without any complementary studies.

Therefore, the total number of cases assessed using the SEFV Causality Algorithm was 10, constituting 5.6% of the total of 180 patients with this signal. A possible ADR was found in 6 of them (3.3%), caused by the following drugs: atorvastatin, lorazepam, risperidone, olanzapine, and rapid insulin, which are detailed in **Table 2**.

TABLE 2 | Cases of rhabdomyolysis assessed using the SEFV Algorithm.

Category	No. (% of Total) N = 180	Drugs Responsible for ADR	Originating Service	Peak CK Levels (U/L, Mean ± SD)	Age (Mean ± SD)	Sex (%)
No causality was detected, although they did not meet exclusion factors	4 (2.2)	N/A	ED (3) PSQ	3,543 ± 2,765	67 ± 23.4	2F (50) 2M (50)
"Possible" causality (score SEFV: 4–5)	4 (2.2)	Rapid insulin	ICU	4,516	43	F
		Lorazepam	ICU	7,518	53	M
		Olanzapine	ED	1,256	59	F
		Risperidone	PSQ	8,337	63	M
"Probable" causality (score SEFV: 6–7)	2 (1.1)	Atorvastatin	IM	6,508	84	M
		Lorazepam	ED	5,282	60	F
"Definitive" causality (score SEFV: ≥8)	0	N/A	N/A	N/A	N/A	N/A
Total patients with ADR	6 (3.3)	N/A	N/A	4,911 ± 2,308	60.3 ± 13.6	3F (50) 3M (50)
Total number of cases assessed with the SEFV Algorithm	10 (5.6)	N/A	N/A	4,364 ± 2,451	63 ± 17.2	5F (50) 5M (50)

SD: standard deviation. N/A: Not applicable. ICU: Intensive Care Unit. ED: emergency department. PSQ: psychiatry department. IM: Internal Medicine Department. F: female. M: male.

Most patients experienced a drop in CK levels from the moment it was diagnosed, taking 2–7 days to reach normal values. In patients with ADRs, the drop in CK levels followed drug withdrawal, with a latency period of 1.5 days until the start of its normalization. In addition, 100% of patients with ADR suffered from renal dysfunction due to rhabdomyolysis, which resolved in all cases after the discontinuation of the precipitating agent.

There were 4 false positives, those cases in which a sufficient score in the SEFV algorithm was not achieved after agreement of all investigators, although no alternative cause could be found to justify the CK levels, and there were no false negatives. This second review was understood as gold standard, as it minimizes the variability, in order to make the following calculations: the sensitivity of the test was defined as 60%, the specificity was estimated at 97% and the PPV of the test was over 40.8% (with a confidence level of 95%). The prevalence of this ADR in patients with rhabdomyolysis was 3.3%.

Hyponatremia

In the case of ADRs due to "hyponatremia", the "LABORATORY SIGNALS" application detected 50 laboratory levels with concentration of sodium (Na) in blood serum below 116 mEq/L, in 28 different patients. There were 11 confirmed ADR cases (39.3%). In 17 patients (60.7%) ADR was excluded as an alternative cause of hyponatremia was present (see **Table 3**). No significant differences regarding age, sex, or hyponatremia levels were found between these groups of patients.

The underlying diseases or primary diagnoses that were excluded (Letmaier et al., 2011; Ramírez et al., 2019), are listed in **Table 3**, being the most common diarrhea.

Regarding the drugs causing the ADRs: 18 drugs were found that met causality criteria to be defined as ADRs, in 11 different patients. The demographic characteristics of each patient and their clinical service and the assessment of causality of the SEFV algorithm for each drug, are shown in **Table 4**. In 7 of the 11 cases, it was not possible to determine the drug causing the ADR because there were 2 drugs that could be responsible, either because of concomitant administration of both separately, or because the pharmaceutical presentation included both, in which case the label of the combined drug was evaluated. These cases of combined administration of two drugs in a single tablet were: trimethoprim-sulfamethoxazole, amiloride-hydrochlorothiazide, and losartan-hydrochlorothiazide. It is noteworthy that 8 of the 11 drugs involved were diuretics.

Treatment was required in 92.9% of the patients studied. Hyponatremia was corrected within 1–3 days in 89.3% of cases,

TABLE 3 | Patients with hyponatremia who met exclusion factors due to underlying diseases that explained the analytical alteration.

	No. (% of Total) N = 28	Na Levels (mEq/L, Mean ± SD)	Age (Mean ± SD)	Female Sex (No. and %)
Diarrhea and other gastrointestinal disorders	5 (17.9)	110.6 ± 4.6	72.6 ± 14.3	4 (80)
Major surgeries	4 (14.3)	111.3 ± 5.8	66.3 ± 15.8	2 (50)
Congestive heart failure[a]	3 (10.7)	107.1 ± 7.0	89.3 ± 8.0	2 (66.7)
Potomania	3 (10.7)	114.7 ± 0.6	76 ± 19	2 (66.7)
Liver cirrhosis	1 (3.6)	115	58	0
Pneumonia	1 (3.6)	116	49	1 (100)
Total	17 (60.7)	111.4 ± 5.1	72.4 ± 16.2	11 (64.7)

Na: sodium. mEq/l: milliequivalents per liter. SD: standard deviation.

[a]Heart failure was considered an alternative explanation of ADR, because it affects the ability to excrete ingested water by increasing antidiuretic hormone levels and is therefore a cause of hyponatremia.

TABLE 4 | *Cases of hyponatremia assessed using the SEFV Algorithm.*

Category	No. (% of Total) N = 28	Drugs Responsible for ADR		Clinical Service	Na Levels (mEq/L)	Age	Sex (%)
		Drug 1	Drug 2				
"Possible" causality (score SEFV: 4–5)	8 (28.6)	Chlorthalidone	Enalapril	ED	114	58	F
		Hydrochlorothiazide	Amiloride	ED	111	94	F
		Hydrochlorothiazide	Enalapril	REU	114.8	85	F
		Hydrochlorothiazide	Losartan	ED	115.3	83	F
		Hydrochlorothiazide	N/A	ED	116	84	M
		Furosemide	N/A	ED	116	75	F
		Mirtazapine	Gabapentin	IM	115	86	F
		Trimethoprim	Sulfamethoxazole	ED	102	53	M
"Probable" causality (score SEFV: 6–7)	2 (7.14)	Furosemide	N/A	ED	115.6	97	F
		Methotrexate	N/A	ED	116	19	F
"Definitive" causality (score SEFV: ≥8)	1 (3.57)	Furosemide	Spironolactone	ED	109	61	F
Total with sufficient score SEFV ≥4	11 (39.28)	N/A	N/A	N/A	113.2 ± 4.3	72.3 ± 22.9	9F (81.8) 2M (18.2)

N/A: Not applicable. ED: Emergency Department. REU: Rheumatology Department. IM: Internal Medicine Department. F: female. M: male.

lasting up to 5–7 days in 3 cases. Two of the patients (none with suspected ADRs) died during the episode (both due to sepsis). In the case of ADRs, the recovery of the analytical value after drug withdrawal did not require more than 2 days in any case.

After a subsequent review of the results by a second investigator, three false positives (in which an alternative cause was finally found, therefore they are represented in **Table 3**) and one false negative were found. After the relevant calculations, the sensitivity of the test was defined as 76.9%, the specificity as 93.3%, and the PPV of the test as 88.2%. The prevalence of ADRs in patients with hyponatremia was 39.2%.

Comparison of the Two Signals

During 2019 there were 15,898 admissions at our hospital, so the annual incidence of these ADRs is 75.5 cases of rhabdomyolysis per 100,000 admissions and 138.4 cases of hyponatremia per 100,000 admissions. With respect to the parameter "Number of laboratory signals Needed to be Evaluated" (NNE), 30 cases (180/6) need to be reviewed to find an ADR in the case of the laboratory signal "rhabdomyolysis", and 2.5 cases (28/11) in the case of the signal "hyponatremia". Therefore, the evaluation of the hyponatremia alert allows the identification of 12 times more ADRs than the rhabdomyolysis alert, which means less time spent per alert evaluated to identify an ADR.

DISCUSSION

The prevalence of possible ADRs found when studying the analytical signal of "rhabdomyolysis" was 3.3%, a result similar to that found in other similar studies (Haerian et al., 2012). Female sex is a risk factor for suffering ADRs (Rubio Mirón and Sánchez Rubio, 2008), and in the present study there was a marked increase in the proportion of women over men in the group with ADRs versus those with non-drug-related CK elevation (50% compared to 33%), although no significant differences were found (which would be expected to be found if the sample size were larger). Nor was it possible to find significant differences in age or a correlation between CK levels and the likelihood of ADR.

As for the drugs causing ADRs, all of them were reported in the literature to cause rhabdomyolysis as a side effect (Rubio Mirón and Sánchez Rubio, 2008; Oshima, 2011; Arébalo-López et al., 2015; Torres et al., 2015). Only three of them listed rhabdomyolysis as an adverse effect in the corresponding drug label: risperidone, atorvastatin, and olanzapine. The remaining 2 drugs involved (lorazepam and rapid insulin) do not mention rhabdomyolysis as an adverse effect, but this is explained by the much lower frequency of these adverse reactions in these cases (Oshima, 2011; Haerian et al., 2012; Torres et al., 2015). This leads us to believe that more active pharmacovigilance could provide data that would allow these ADRs to be better characterized, possibly including rhabdomyolysis as an adverse reaction in the drug label in the future.

It is noteworthy that, although statins are usually the most frequent pharmacological group causing rhabdomyolysis (Oshima, 2011; Garro Ortiz, 2014; Torres et al., 2015), in our study only 1 of the 6 drugs found was a statin. However, about 60% of patients who suffered a myocardial infarction, underwent surgery, or suffered a muscle compression due to a fall, were on statin treatment. All these patients had some underlying disease that explained the CK elevation, which could in some cases mask an ADR.

Regarding the hyponatremia signal: based on the results obtained (prevalence close to 40%, sensitivity of 76%, specificity of 93%, and PPV of 88%), there is a high correlation between the patients studied and patients who truly present an ADR, demonstrating the usefulness of its routine study. In this case, no significant differences were found in the age, sex, or sodium levels of patients with ADRs compared to those with hyponatremia produced by alternative causes.

Of the drugs that met the causality criteria for ADR, 72.2% were diuretics, as it is one of the most frequent drug groups that causes hyponatremia as ADR (Ramirez et al., 2010; Spasovski et al., 2014). However, diuretics are part of the therapeutic strategies used in heart failure, which is in itself a cause of hyponatremia, so there is a confounding parameter in the assessment of this ADR.

Of the drugs involved, only methotrexate did not have hyponatremia as a possible adverse effect listed on the drug label but it was reported in the literature (Liamis et al., 2016; Spasovski et al., 2014). Additionally, 6 cases were found that appeared to be due to a drug-drug interaction. In all cases, each drug was described as a potential cause of hyponatremia on its own, thus ruling out the possibility that the ADR only occurred in the case of interaction, and in any case, raises a possible potentiation of the ADR. The drug combinations were trimethoprim-sulfamethoxazole, furosemide and spironolactone, hydrochlorothiazide and amiloride, chlorthalidone and enalapril, enalapril and hydrochlorothiazide, and mirtazapine and gabapentin.

The drugs associated with the two ADRs evaluated are different, as is their prevalence of use in the general population. In addition, more drugs are associated with hyponatremia than with rhabdomyolysis. Nevertheless, the aim of this work is to evaluate the possibility of detecting ADRs using the laboratory's alert program.

If we consider the approximation of "NNE" that was calculated (it is necessary to review 30 patients with rhabdomyolysis to find an ADR, and 2.5 patients with hyponatremia to find an ADR), the study of the laboratory signal "hyponatremia" is more efficient than that of "rhabdomyolysis" for detecting ADRs. Moreover, it is also simpler: for the "hyponatremia" signal, 90% (10/11) of ADRs included in the discharge report a statement regarding the pharmacological origin of the alteration, compared to 16% (1/6) in the case of "rhabdomyolysis". This could indicate that there is greater awareness among medical staff on the possibility of ADRs in the case of hyponatremia, raising the possibility of studying whether there is an association between the best-known adverse reactions with better treatment, and with faster recovery and lower morbidity and mortality for the patient. One could even consider the need for further training of physicians in these issues so that they can suspect less prevalent and less known adverse reactions.

In terms of limitations of the study, as the data were not compared to a gold standard, the sensitivity and specificity of the signals were calculated by comparing a first and second review of the data. About the causality algorithm application, it is necessary to highlight that there is no internationally validated algorithm and that the algorithm of SEFV is only one tool for evaluation. These algorithms depend closely on the physician's clinical experience. There were several discrepancies between the results of the two evaluators, so the PPV for the both laboratory signals studied were very low. However, we believe that this measure can be improved with specific training and experience. In this regard, we recommend clinicians to keep up to date with drug safety surveillance, which will allow early identification and treatment of ADRs.

It is important to consider that the incidence of ADRs is low, that resources to evaluate alerts are limited and that we are interested in detecting a greater number of ADRs with the least possible effort. Therefore, specificity has been prioritized over sensitivity of the method. The cut-off points have been established to rule out mild cases, detect serious ADRs and obtain a manageable number of alerts to evaluate. Although this may be a limitation of the study, being less restrictive in the evaluation cut-off points could generate a lot of noise, making it difficult to identify and manage ADRs in a timely manner.

For most borderline cases, it would have been necessary to re-expose the patient to the drug to conclude causality between the altered laboratory results and a possible ADR. The ethical aspects of this measure should be taken into consideration, as it is not a simple decision to expose the patient to a potentially harmful medication, without any other clinical or therapeutic reason to justify the re-exposure. This aspect should be taken into account in future studies as a limitation.

As this was a retrospective analysis, the information contained in the medical records was sometimes incomplete and it was not possible to contact the patient or specialist to obtain additional information.

Although the population attended in our hospital during the study period was approximately 8,000 patients, a series of limitations have risen such as the selection bias that might have occurred when limiting the study to 6 months in a single hospital in Madrid. As a consequence, the data obtained could only be extrapolated to a population with similar characteristics.

CONCLUSIONS

A pharmacovigilance program based on automatized laboratory signals could be an effective method to detect ADRs in hospitalized patients. The Causality Algorithm of the Spanish Pharmacovigilance System is suitable for this purpose. The application used allows to identify ADRs and to help clinicians in the specific management of the ADR if required.

The study of the laboratory signal "hyponatremia" is more efficient than that of the signal "rhabdomyolysis", as it requires a smaller number of cases to be examined to find an ADR. The prevalence of ADR found for each of the signals is 39.3% for "hyponatremia" and 3.3% for "rhabdomyolysis". In neither case has it been possible to establish a relationship between the magnitude of the alteration in the laboratory value and the possibility that it was caused by drugs.

The study of adverse drug reactions using automatized laboratory signals can be very useful to obtain information that may be missed during the clinical assessment. To be able to do this properly, healthcare professionals must be meticulous when completing a patient's clinical history, avoiding missing data that could be useful afterwards.

Knowledge about the potential for a drug to cause a particular adverse reaction makes it easier to recognize, resulting in optimal treatment for the patient.

It is important to continue active pharmacovigilance to collect more information on adverse drug reactions, as the less frequent ones may still be largely unknown.

In addition, pharmacovigilance activities include the notification of these ADRs to the SEFV, which groups and evaluates ADR notifications from all over the country with the aim of identifying new risks derived from the use of drugs. Thus, optimizing the reporting activity indirectly leads to improvements in the safe use of the drugs and in the health of the population.

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 Ethics Committee for Research on Medicines (CEIm) of the Hospital Universitario de La Princesa. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MVG, GMA, and FAS contributed to conception and design of the study. MVG and GMA organized the database. MVG performed the statistical analysis. MVG and GMA wrote the first draft of the manuscript. DC, RPG and FAS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

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Development of Screening Tools to Predict Medication-Related Problems Across the Continuum of Emergency Department Care: A Prospective, Multicenter Study

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Background: Medication-related problems (MRPs) occur across the continuum of emergency department (ED) care: they may contribute to ED presentation, occur in the ED/short-stay unit (SSU), at hospital admission, or shortly after discharge to the community. This project aimed to determine predictors for MRPs across the continuum of ED care and incorporate these into screening tools (one for use at ED presentation and one at ED/SSU discharge), to identify patients at greatest risk, who could be targeted by ED pharmacists.

Methods: A prospective, observational, multicenter study was undertaken in nine EDs, between July 2016 and August 2017. Blocks of ten consecutive adult patients presenting at pre-specified times were identified. Within 1 week of ED discharge, a pharmacist interviewed patients and undertook a medical record review to determine a medication history, patient understanding of treatment, risk factors for MRPs and to manage the MRPs. Logistic regression was undertaken to determine predictor variables. Multivariable regression beta coefficients were used to develop a scoring system for the two screening tools.

Results: Of 1,238 patients meeting all inclusion criteria, 904 were recruited. Characteristics predicting MRPs related to ED presentation were: patient self-administers regular medications (OR = 7.95, 95%CI = 3.79–16.65), carer assists with medication administration (OR = 15.46, 95%CI = 6.52–36.67), or health-professional

administers (OR = 5.01, 95%CI = 1.77–14.19); medication-related ED presentation (OR = 9.95, 95%CI = 4.92–20.10); age ≥80 years (OR = 3.63, 95%CI = 1.96–6.71), or age 65–79 years (OR = 2.01, 95%CI = 1.17–3.46); potential medication adherence issue (OR = 2.27, 95%CI = 1.38–3.73); medical specialist seen in past 6-months (OR = 2.02, 95%CI = 1.42–2.85); pharmaceutical benefit/pension/concession cardholder (OR = 1.89, 95%CI = 1.28–2.78); inpatient in previous 4-weeks (OR = 1.60, 95%CI = 1.02–2.52); being male (OR = 1.48, 95%CI = 1.05–2.10); and difficulties reading labels (OR = 0.63, 95%CI = 0.40–0.99). Characteristics predicting MRPs related to ED discharge were: potential medication adherence issue (OR = 6.80, 95%CI = 3.97–11.64); stay in ED > 8 h (OR = 3.23, 95%CI = 1.47–7.78); difficulties reading labels (OR = 2.33, 95%CI = 1.30–4.16); and medication regimen changed in ED (OR = 3.91, 95%CI = 2.43–6.30). For ED presentation, the model had a C-statistic of 0.84 (95% CI 0.81–0.86) (sensitivity = 80%, specificity = 70%). For ED discharge, the model had a C-statistic of 0.78 (95% CI 0.73–0.83) (sensitivity = 82%, specificity = 57%).

Conclusion: Predictors of MRPs are readily available at the bedside and may be used to screen for patients at greatest risk upon ED presentation and upon ED/SSU discharge to the community. These screening tools now require external validation and implementation studies to evaluate the impact of using such tools on patient care outcomes.

Keywords: emergency department, medication management, risk factors, patient transfer, workforce

INTRODUCTION

Transitions from the community into the emergency department (ED), to a hospital ward or back to the community, are transitions associated with medication-related problems (MRPs) (Claydon-Platt et al., 2012; Roughead et al., 2016; Marotti et al., 2011; Cornish et al., 2005; Galvin et al., 2013). MRPs may contribute to ED presentations or occur due to care provided in ED, for example, initiating new medications without fully understanding patients' medical and medication history.

Approximately one half of MRPs associated with the ED setting go unrecognized or unaddressed by non-pharmacist ED clinicians (Hohl et al., 2005; Cavin and Sen, 2005). Increasingly, pharmacists are smoothing medication-related transitions of care (Bond and Raehl, 2007; deClifford et al., 2007; Patanwala et al., 2011; Patanwala et al., 2012; Cesarz et al., 2013; Proper et al., 2015; Tong et al., 2016), although many more patients present to ED than can be seen by this workforce. Screening tools could assist in identifying patients at greatest risk for MRPs, who pharmacists could focus upon. Such tools should identify patients at risk for MRPs across the continuum of ED care, not only those contributing to ED presentation. They should be quick for non-pharmacists to administer, use readily available information relevant to the broad range of patients who present to ED and have simple parameter definitions to optimize inter-rater reliability. Good specificity and sensitivity are important to detect patients at risk for MRPs but not have sizable numbers of patients receiving an intervention (e.g., being seen by an ED pharmacist) that they do not require.

Several screening tools have been developed to identify patients at risk for MRPs. Some specifically assist in identifying patients with MRPs that contribute to the ED presentation (Hohl et al., 2005; Hohl et al., 2018). Others identify MRPs that occur when patients are admitted to hospital, but these often require pathology results and detailed past medical or medication history, which are time-consuming to accurately identify in ED (DeWinter et al., 2017; Parekh et al., 2020). Some tools are based upon expert opinion, rather than occurrence of actual MRPs (Kumar et al., 2011; Kaufmann et al., 2015). Our study aimed to develop two tools to identify patient, medication, and ED presentation related predictors for MRPs across the continuum of ED care that may require specialist input to identify, manage or prevent: at and during the ED presentation (Presentation Tool), and shortly after ED or short-stay unit (SSU) discharge (Discharge Tool) (**Figure 1**). The Presentation Tool could be used early in the ED presentation (e.g., by nurses during the ED cubicle assessment), to identify patients who could benefit from a specific focus on medications taken prior to presentation. Early identification of an accurate medication history and medication review could identify and manage medication-related contributors to the presentation, prevent patients from missing critical medications during their ED/SSU stay and advise on therapeutic decisions being made in ED. For those admitted to hospital, early review could ensure that the admission medication regimen is accurately prescribed. The Discharge Tool, to be used for patients returning to the community from ED/SSU, could detect patients at risk for MRPs related to medication regimen changes made in ED/SSU. Pharmacists could provide these patients with detailed medication education and ensure comprehensive clinical handover to community healthcare

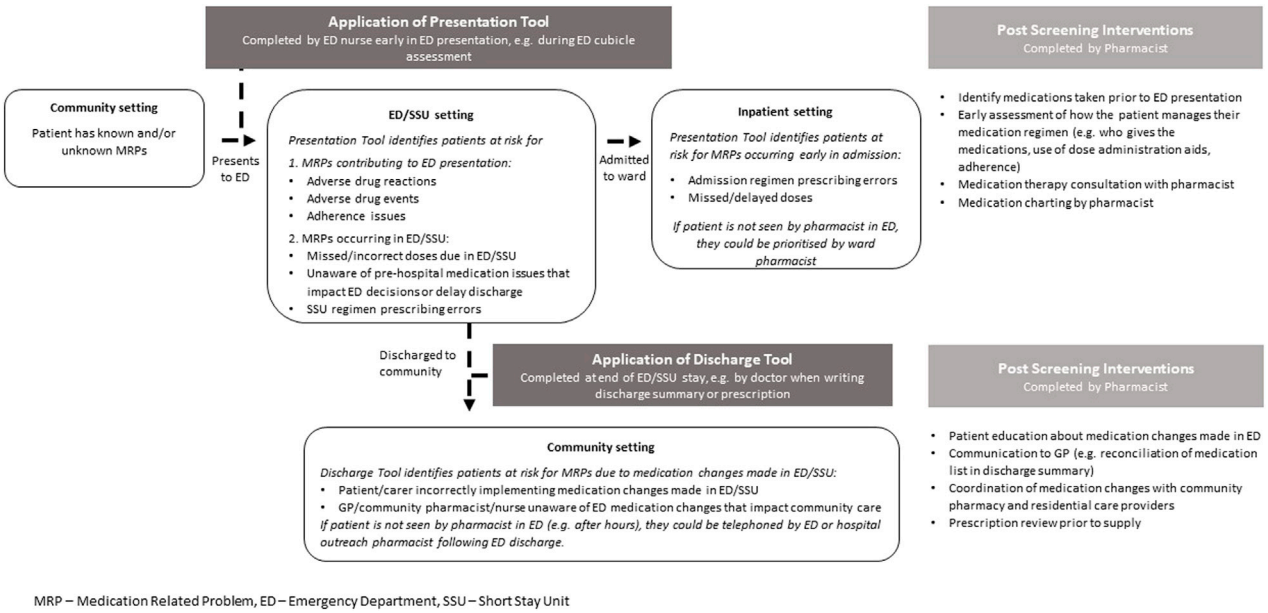

FIGURE 1 | Medication-related problems occurring across the ED patient journey.

providers. As the two tools detect different types of MRPs, the relevant variables within each tool could differ.

MATERIALS AND METHODS

Study Design and Setting

We undertook a prospective observational study in the EDs of nine Australian metropolitan and regional hospitals in the states of Victoria, New South Wales and Tasmania. Patient presentations to each ED in 2016 ranged from 25,000 to 92,000. Patient recruitment was undertaken between July 2016 and August 2017. The lead hospital ethics committee approved the study and each participating hospital provided governance approval before study commencement at each site.

Patient Involvement

Patients were involved in piloting the data collection tool and informed the feasibility and acceptability of the study methodology. Patients and carers were interviewed after ED discharge to identify medication concerns and requirements for health professional follow-up.

Selection of Participants

At each site, blocks of ten consecutive adult patients presenting to ED at pre-specified times across all days of the week were identified by pharmacist investigators. The times were determined randomly, prior to study commencement and covered the 24-h period. Patients were excluded if they did not wait to be seen by a clinician, were transferred from ED to another hospital, died in ED, a pharmacist was involved in their ED care or where it was deemed inappropriate to interview patients within 7 days of their presentation (e.g., severe mental health crisis). Patients interviewed face-to-face on a hospital ward did not provide consent as the medication review and data collection was undertaken as part of standard care. Patients discharged from ED or SSU provided verbal consent before undertaking the telephone interview.

Development of the Data Collection Tool

Identification of the list of patient, medication-related and ED presentation variables that were potential predictors of MRPs was an iterative process. Four investigators (ST, AH, DT, EzM) drew on their extensive clinical practice experience in the ED and experience in undertaking medication safety research to derive an initial list. In developing the initial lists, investigators considered the resources produced by the Australian Commission on Quality and Safety in Health Care, specifically the classification of high-risk medicines and the Medication Risk Identification checklist of the Medication Management Plan (Australian Commission on Quality and Safety in Healthcare, 2013 and 2022). Two investigators (ST and EzM) undertook a narrative review of the literature for potential variables reported in previous studies (Claydon-Platt et al., 2012; Roughead et al., 2016; Marotti et al., 2011; Cornish et al., 2005; Galvin et al., 2013; Hohl et al., 2005; Cavin and Sen, 2005; Patanwala et al., 2011; Patanwala et al., 2012; Cesarz et al., 2013; deClifford et al., 2007; Kumar et al., 2011; Kaufmann et al., 2015; Saedeer et al., 2016; Fitzgerald et al., 2015). Related variables were grouped, then the four investigators worked together to come to a consensus as to the specific variables to include in the data collection tool. The literature search did not yield any additional variables over and above those initially identified by the investigators, however the literature search did assist with precisely defining variables and

sparked discussion about the rationale for excluding variables that had been included in previous publications. Variables identified in the literature that were excluded, were excluded on the basis that they were imprecise (e.g., Kumar et al. included "other" under the list of comorbidities) or would be difficult to quickly measure at the bedside (e.g., variables with complex definitions, such as severity of organ dysfunction). Laboratory and diagnostic tests were avoided because not all ED patients require these tests routinely. Specific medications were not listed to avoid dating the screening tools as therapeutics evolve.

The data collection tool comprised three components: the first collected data from the hospital medical record (including information required by the pharmacist as part of the medication review and information required to measure some predictor variables), the second section included information that formed part of the pharmacists' medication review to identify MRPs (documentation of a best possible medication history, identification of MRPs that required management) and the third section included a series of questions asked of the patient/carer to measure the predictor variables or confirm predictor variable information recorded in the medical record. Data were collected on 13 patient related variables including age, sex, presenting complaint, government benefit card status, social/living situation (living at home alone or with others) and cognitive and sensory issues. A total of 16 medication related variables were included, including the number and type of medications patients were taking prior to ED presentation, allergy status, who organizes the medications at home, medication adherence and what medications were prescribed in ED. Data were collected for 11 ED environment related variables, including triage category, the time of presentation, duration of ED stay and mode of presentation (e.g., *via* ambulance/emergency service or self-presenting). Further details are available in **Supplementary Appendix S1**. The data collection tool was piloted in 50 ED patient interviews, undertaken by an ED pharmacist at the lead site, before applying for ethical approval for the multisite study.

Data Collection

Within 24–48 h after ED discharge, investigator pharmacists collected initial data from medical records. Following this, a patient and/or carer interview was undertaken by a pharmacist, face-to-face, for patients admitted to an inpatient ward, or *via* telephone, for patients discharged from ED/SSU to the community. If this interview could not be undertaken within 7 days of leaving ED, patients were deemed lost to follow-up. During the interview, data from the medical record review was verified, a best possible medication history was determined, patients' understanding of ED medication regimen changes was assessed and a medication review was undertaken to identify, manage or prevent potential MRPs. Responses to a list of patient, medication-related and ED presentation variables that were potential predictors of MRPs was completed to ensure these were systematically recorded for each patient.

An MRP was defined as any medication error or adverse drug event that may require specialist input, such as an ED pharmacist, to identify, manage or prevent. Medication error was defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer" (National Coordinating Council for Medication Error Reporting and Prevention, 2022). Medication errors could occur at any stage of the medication management pathway, including the decision to prescribe, prescribing, dispensing, administration, monitoring or clinical handover to other health professionals. An adverse drug event was defined as an injury that occurred due to a medication; such adverse events could be preventable (e.g., due to a medication error) or non-preventable (e.g., idiosyncratic allergy). MRP types were classified according to the presence of a prescribing or administration error occurring prior to or in ED, an adverse drug event(s) or adverse drug reaction and/or presence of significant knowledge deficits and/or non-adherence to their prescribed medication regimen that may require specialist input to identify, manage or prevent (the specific types of MRPs are defined further in **Supplementary Appendix S2**). Two senior ED pharmacists independently reviewed all MRPs identified by investigator pharmacists during the patient interviews and medication reviews. MRPs were classified according to whether they could have been identified, managed or prevented by screening at ED presentation or ED discharge. MRP severity was classified according to a consequence-probability matrix (Society of Hospital Pharmacists of Australia, 2013). Discrepancies of opinion were resolved by consensus.

Examples of MRPs included in the ED presentation model were those that caused the presentation to ED, those that involved failure to prescribe and/or administer a time critical medication in ED (often a pre-admission medication that was not related to the reason for presentation but that had the potential to or did delay ED discharge if not given in a timely way) and prescribing errors on the hospital admission medication chart related to pre-admission medications. Examples of MRPs included in the ED discharge model included where a medication was initiated in ED that the patient was expected to take after leaving ED, but the patient failed to implement this change as intended. The implementation failure could be due to the patient not understanding the change that was intended, failing to have the medication dispensed or failure to handover medication information from ED to the general practitioner to assist with a smooth continuum of care.

Primary Outcomes

The first primary outcome was the set of predictor variables that were significantly associated with MRPs that could be identified, managed, or prevented by evaluation of medication management at the time of ED presentation. This set informed the development of the Presentation Tool.

The second primary outcome was the set of predictor variables that were significantly associated with MRPs that could be identified, managed, or prevented at the time of ED/SSU discharge to the community. This set informed the development of the Discharge Tool.

Data Analysis

We estimated that each site could recruit at least 100 patients. With a target sample size of 900, we would be 95% certain that the incidence of MRPs would lie ±1.8% of an incidence of 7.5% obtained in our pilot study. The precise number of patients

recruited varied according to each site's capability. The aim was to recruit more than 5 to 15 patients per explanatory variable (Tabachnick and Fidell, 1989); as the number of cases increased there was increased likelihood that the results obtained would be stabilized following regression analysis.

Statistical analysis was undertaken at the patient level. Univariate associations were examined between the presence of one or more MRPs and the patient, medication, and ED presentation-related predictor variables. Thirty variables were taken through to the multivariable regression analysis. Variables were excluded if there were difficulties collecting variables (due to >5% of missing data, or feedback from pharmacists that data was difficult to precisely collect during the interview) or if the prevalence was very low or if other variables captured similar information. Further details are provided in **Supplementary Appendix S1**. For the small amount of missing data, the more prevalent response was entered.

Multivariable logistic regression was undertaken using the backward Wald method recommended by Sun (Sun et al., 1996). Receiver operator characteristic (ROC) curves were constructed to determine the specificity and sensitivity of the models to predict MRPs. To identify weighted scores for screening tool predictor variables, beta-coefficients from the multivariable regression were multiplied by ten and rounded to the nearest whole number in a method used by Moore (Moore et al., 2012). Internal validation of the models was undertaken using bootstrapping of 1,000 resamples to assess reliability of the coefficients of regression (Danial et al., 2019). Standard errors were used to calculate the 95% bootstrap confidence intervals of the odds ratios. Data were analyzed using IBM SPSS (version 25).

RESULTS

Characteristics of Study Subjects

Overall, 1730 patients were screened; 1,238 patients met all inclusion criteria, 277 were lost to follow-up and 57 patients declined consent. Demographic parameters for the 904 adult patients included 457 (50.6%) male, 134 (14.8%) aged 80 years and older, 292 (32.3%) brought to ED by an emergency service, and 409 (45.2%) taking four or more regular medications. Almost one third of patients (288, 31.9%) were hospitalized, whilst 616 (68.1%) were discharged from ED or SSU to the community.

One or more MRPs were identified during the pharmacist medication review in 381/904 (42.1%) patients. One or more MRPs of high, moderate, or low significance occurred in 60 (6.6%), 179 (19.8%) and 220 (24.3%) patients, respectively. High risk MRPs mostly involved high risk medications, particularly anticoagulants, strong opioids, and insulin. Further details have been published elsewhere (Taylor et al., 2020).

Predictor Variables for Occurrence of MRPs Related to ED Presentation

One or more MRPs that could have been identified, managed, or prevented by screening early in the ED presentation were identified in 284/904 (31.4%) patients. The ED presentation was medication-related for 68 (7.5%) patients. The types of MRPs included in the ED presentation model are outlined in **Table 1**. One hundred and seventy-one (18.9%) patients had one or more MRPs classified as prescribing errors, whilst 155 (17.1%) had one or more MRPs classified as adherence or knowledge issues. Univariate associations between predictor variables and MRPs are detailed in **Supplementary Appendix S3**, **Table 1**.

Significant predictors of MRPs in the multivariable logistic regression are summarized in **Table 2**. Eight predictor variables were significantly associated with increased risk of MRPs that could be addressed by screening at ED presentation: age, gender, pharmaceutical benefit (pension or concession) cardholder, who administers the medications at home, medication adherence, medication-related ED presentation, medical specialist seen recently and recent hospital admission. If patients had difficulty reading medication labels, this was protective for MRPs (OR = 0.63, 95%CI = 0.40–0.99). The ED presentation model provided an area under the curve (AUC) for the ROC curve of 0.84 (95% CI = 0.81–0.86). At a sensitivity of 80%, the model had a specificity of 70%, whilst at a sensitivity of 90%, specificity was 57% (**Figure 2A**).

Predictor Variables for Occurrence of MRPs Related to ED Discharge

One or more MRPs that could have been identified, managed, or prevented by screening at the time of ED/SSU discharge to the community were identified in 112/616 (18.2%) patients. The types of MRPs included in the ED discharge model are summarized in **Table 1**. Fifty-nine (9.6%) patients had one or more MRPs classified as adherence or knowledge issues, whilst 46 (7.5%) patients were noted to have inadequate clinical handover to the general practitioner. This included medications being prescribed in ED that the general practitioner was going to need to monitor or re-prescribe, where the general practitioner was not provided with the details as to what was prescribed in ED (for example, insulin, oxycodone, new anticoagulation or antiarrhythmics). Univariate associations between predictor variables and MRPs are detailed in **Supplementary Appendix S3**, **Table 2**.

Four variables were significant predictors of increased risk of MRPs that could be addressed by screening at ED discharge: patient adherence, difficulty reading medication labels, ED length of stay greater than 8 h and ED/SSU changes to the medication regimen (**Table 3**). The model for MRPs related to ED discharge provided an AUC for the ROC curve of 0.78 (95% CI = 0.73–0.83). At a sensitivity of 82%, specificity was 57% (**Figure 2B**).

Internal Validation

After conducting logistic regression with 1,000 sample bootstraps, results showed that the bootstrapping procedure did not change significant variables observed. Standard errors obtained for explanatory variables were similar to those obtained following bootstrapping, which indicated internal model validation.

TABLE 1 | Types of medication-related problems included in the ED presentation and ED discharge models.

Type of MRP	Number of Patients with ≥1 of these MRPs overall[a] (%) (n = 904)	Number of Patients with ≥1 of these MRP types included in ED presentation model[a] (%) (n = 904)	Number of Patients with ≥1 of these MRP types included in ED discharge model[a] (%) (n = 616)
Prescribing error	171 (18.9)	163 (18.0)	9 (1.4)
Adherence/knowledge issue	155 (17.1)	103 (11.4)	59 (9.6)
Adverse drug reaction	40 (4.4)	37 (4.1)	3 (0.4)
Drug-drug interaction	14 (1.5)	13 (1.4)	2 (0.3)
Medication administration error in ED	10 (1.1)	10 (1.1)	0 (0)
Clinical handover deficiency[b]	46 (5.1)	0	46 (7.5)
Other	12 (1.3)	8 (0.9)	4 (0.6)
Total number of patients with ≥1 MRP of any type	381 (42.1)	284 (31.4)	112 (18.2)

[a]*Some patients had more than one type of problem or had problems included in the ED, presentation and ED, discharge models.*
[b]*Failure to inform general practitioner of significant prescription in ED, that patient was to take after discharge (for example, insulin, asthma inhalers, oxycodone, anticoagulant, antibiotic).*

TABLE 2 | ED Presentation Screening Tool: summary of multivariable regression analysis of predictor variables for medication-related problems that could be identified/managed/prevented by screening early in the ED presentation (n = 904).

MRP Predictor variables	Odds ratio	95% confidence interval	Regression coefficient	Score assigned[1]
Medication related ED presentation	9.95	4.92–20.10	2.297	23
At home, medication administered by				
Self-administers	7.95	3.79–16.65	2.073	21
Carer assists	15.46	6.52–36.67	2.738	27
Health professional administers	5.01	1.77–14.19	1.611	16
No medications prior to ED	1.0	—	0	0
Patient age				
80 + years	3.63	1.96–6.71	1.289	13
65–79 years	2.01	1.17–3.46	0.699	7
40–64 years	1.60	0.97–2.65	0.472	5
18–39 years	1.0	-	0	0
Medication adherence	2.27	1.38–3.73	0.819	8
Patient reports to sometimes or usually miss taking their medication doses				
Seen a medical specialist in the past 6 months	2.02	1.42–2.85	0.701	7
Pharmaceutical benefit (pension/concession) card holder[2]	1.89	1.28–2.78	0.636	6
Recent admission: Inpatient in previous 4 weeks	1.60	1.02–2.52	0.472	5
Sex, male	1.48	1.05–2.10	0.394	4
Patient/carer who administers the medications has difficulties reading medication labels[3]	0.63	0.40–0.99	negative	0

[1]*Regression coefficient multiplied by 10 and rounded to the nearest whole number.*
[2]*Pharmaceutical benefit card holders are those receiving income means tested Australian government benefits and entitles patients to more extensive medication cost subsidies than general patients.*
[3]*The person who administers the medications has difficulties reading labels due to language barrier, intellectual difficulties, or visual acuity.*

Weighted Scoring for Screening Tools

The beta coefficients and weighted scoring assigned for each predictor variable are reported in **Tables 2** and **3**. **Tables 4** and **5** describe how these tools could be operationalized for use and scoring at the bedside. Potential scoring cut points and their corresponding sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are also described.

For the Presentation Tool, potential scores range from a minimum of 0 and to a maximum of 93. Using the scoring approach outlined in **Table 4**, the median (interquartile range) score in the derivation dataset was 34 (18–44). Using a score cut-off score of above 30, the sensitivity, specificity, PPV and NPV, with associated 95% confidence intervals were 0.90 (0.86–0.93), 0.55 (0.51–0.59), 0.48 (0.44–0.52) and 0.92 (0.89–0.95), respectively.

For the Discharge Tool, potential scores range between a minimum of 0 and maximum of 53. Using the scoring approach outlined in **Table 5**, the median (interquartile range) score was 12 (0–14). Using a score cut-off score of above 12, the sensitivity, specificity, PPV and NPV, with associated 95% confidence intervals were 0.72 (0.63–0.80), 0.57 (0.53–0.62), 0.27 (0.22–0.33) and 0.90 (0.86–0.93), respectively.

DISCUSSION

Statement of Principal Findings

Key predictor variables for MRPs that could be identified, managed, or prevented by screening at the time of ED presentation and as patients were discharged from ED/SSU to the community have been identified.

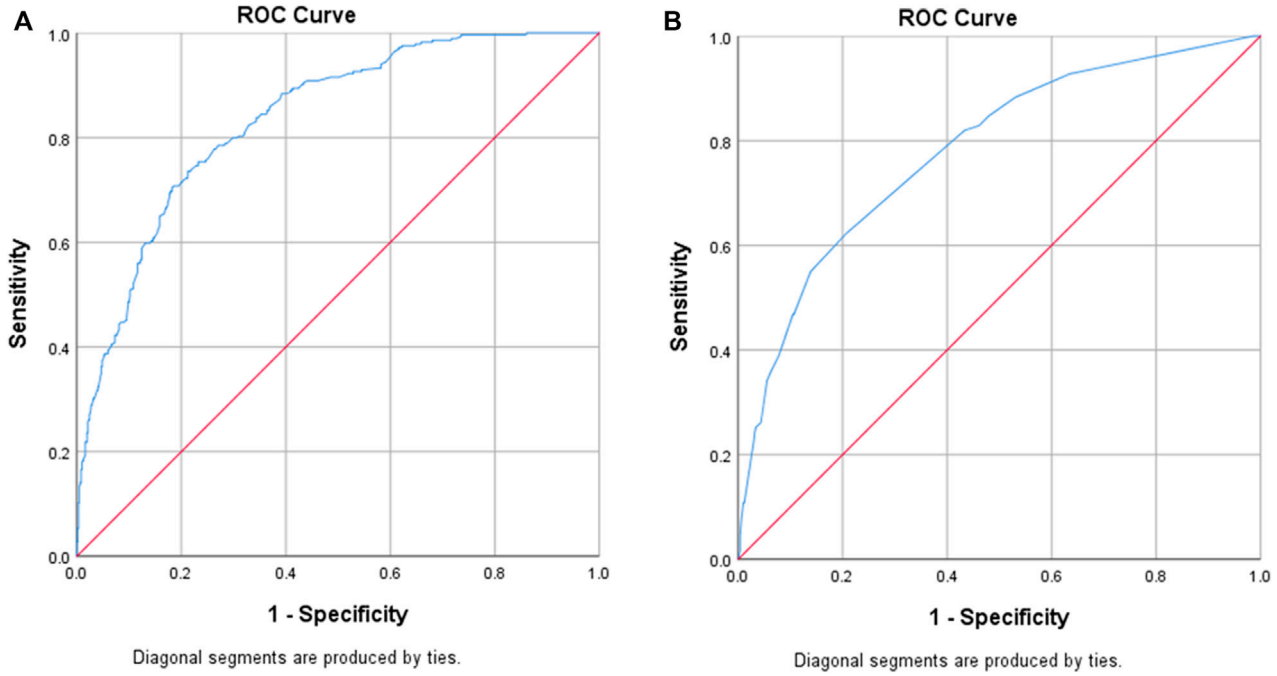

FIGURE 2 | Receiver Operating Characteristic (ROC) curves for each model. **(A)** ED Presentation screening tool: AUC of ROC curve = 0.84 (95% CI = 0.81–0.86), [sensitivity 80%, specificity 70%]. **(B)** ED Discharge screening tool: AUC of ROC curve = 0.78 (95% CI =0.73–0.83), [sensitivity 82%, specificity 57%]

TABLE 3 | ED Discharge Screening Tool: summary of multivariable regression analysis of predictor variables for medication-related problems that could be identified/managed/prevented by screening at the time of ED discharge (n = 616).

MRP Predictor variables	Odds ratio	95% confidence interval	Regression coefficient	Score assigned[1]
Medication adherence Patient reports to sometimes or usually miss taking their medication doses	6.80	3.97–11.64	1.917	19
Medication regimen change in ED or short stay unit New medication started, pre-ED medication stopped or dose changed	3.91	2.43–6.30	1.363	14
ED length of stay				
>8 h	3.23	1.47–7.78	1.171	12
4–8 h	1.37	0.80–2.35	0.314	3
Patient/carer who administers the medications has difficulties reading medication labels[2]	2.33	1.30–4.16	0.845	8

[1]*Regression coefficient multiplied by 10 and rounded to the nearest whole number.*
[2]*The person who administers the medications has difficulties reading labels due to language barrier, intellectual difficulties or visual acuity.*

These predictor variables are readily collected at the bedside and have been incorporated into two screening tools to capture patients at risk for MRPs across the ED continuum of care. A weighted scoring system has been developed and using some preliminary score cut-points, the scoring tools' performance characteristics are reported. Overall, the models have similar predictive characteristics to other published models (Hohl et al., 2018; DeWinter et al., 2017; Kumar et al., 2011; Kaufmann et al., 2015; Geeson et al., 2019), but either screen for a broader range of MRPs or are more practical for ED use.

Presentation Tool MRP Predictors

Increasing patient age was associated with increasing risk of MRPs, which is consistent with previous studies (DeWinter et al., 2017; Geeson et al., 2019; Parekh et al., 2020). Being older and very much older were associated with increased risk of MRPs, independent of the number of medications taken before presentation.

Several predictors related to patients' ability to manage their medications at home and to communicate their medication history in ED. Patients with carers assisting with medication administration were at particularly high risk for MRPs related to ED presentation. High-risk medications were significant predictors in the univariate analysis but did not remain significant in the multivariable analysis. These high-risk medications may not predict a patients' risk of MRPs if they are capable of accurately articulating to a health professional how they take these medications at home. If the

TABLE 4 | ED Presentation medication-related problem screening tool.

Question	Potential response	Score
Patient age	o 18–39 years	0
	o 40–64 years	5
	o 65–79 years	7
	o ≥ 80 years	13
Patient sex	o Female	0
	o Male	4
Pension or concession card holder? (Do they pay the pension/concession amount for their community prescriptions?)	o No	0
	o Yes	6
Who administers the medications at home?	o No regular medications taken at home	0
	o Patient themselves	21
	o Family, friend or carer helps	27
	o Health professional e.g., nurse	16
Is the ED presentation potentially medication-related (e.g., allergy, side effect, overdose, poor adherence)?	o No	0
	o Yes	23
Is there a potential medication adherence problem? "People often have difficulty taking their pills for one reason or another. How often do you miss taking a dose of your medicines?"	o No (Never/rarely/very occasionally/doesn't take medicines)	0
	o Yes (Sometimes/Usually)	8
Has the patient visited a medical specialist as an outpatient in the last 6 months? (e.g., surgeon, cardiologist, psychiatrist, doctor other than their local doctor)?	o No	0
	o Yes	7
Recent admission: Was the patient in hospital within the past 4 weeks?	o No	0
	o Yes	5

Score cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
30 or less/Greater than 30	0.90 (0.86–0.93)	0.55 (0.51–0.59)	0.48 (0.44–0.52)	0.92 (0.89–0.95)
40 or less/Greater than 40	0.63 (0.57–0.69)	0.83 (0.80–0.86)	0.63 (0.57–0.68)	0.83 (0.80–0.86)

95%CI, 95% confidence interval.

carer who assists with medication administration is not available in ED, it may be difficult for ED clinicians to accurately elicit this history, thus putting this patient group at higher risk of MRPs (WHO, 2014).

Being a government pharmaceutical benefit cardholder may be a marker of socioeconomic status. One published screening tool excluded socioeconomic status because it was difficult to measure reliably (Geeson et al., 2019). Some markers of socioeconomic status are confronting for health professionals and may not be appropriate to ask in ED. Patients are routinely asked about their benefit status when a community prescription is dispensed, therefore this may be a feasible method to identify this potential predictor of MRPs.

The person who administers the medications at home having difficulties reading medication labels being a protective factor for having an MRP related to presentation was unexpected. The upper level of the 95% confidence interval for the odds ratio was 0.99, therefore this variable is at the margin of our definition of a variable that would be retained within the multivariable model. It is possible that this variable may fall outside of the criteria for inclusion in a future validation sample. If this variable is retained within the model, it is possible that patients and carers who are aware of their difficulties reading labels may take more care and use other resources to minimize the risk of medications errors.

Discharge Tool MRP Predictors

Key predictors of MRPs relevant to patients being discharged from ED/SSU to the community were whether there was a medication regimen change made in ED/SSU that the patient needed to implement, whether there was evidence of poor adherence and whether they had difficulties reading medication labels (due to English language, intellectual or visual acuity problems of the person administering the medications). In addition, longer duration of ED stay, may indicate a more complex presentation or presentation at a time when the ED capacity was stretched such that staff were unable to provide adequate discharge education or clinical handover.

Interpretations Within the Context of the Wider Literature

Kumar (Kumar et al., 2011) developed an ED pharmacist referral tool in their emergency SSU using patient characteristics based upon expert-panel opinion. Their tool identified patients at risk for MRPs across the continuum of ED care. Patients with a medication-related presentation; newly prescribed warfarin; over 70 years, taking five or more medications, and with three or more comorbidities, were identified to be at high risk for medication

TABLE 5 | ED Discharge medication-related problem screening tool.

Question	Response	Score
ED length of stay: Duration of stay in ED? (excluding short stay unit)	o Up to 4 h o Between 4–8 h o More than 8 h	0 3 12
Medication regimen change: In ED/short stay unit, was a new medication started, a pre-ED medication stopped or dose changed?	o No o Yes	0 14
Reading difficulties: Does the patient (or the person who helps with the medication routine) have difficulty reading medication labels?	o No o Yes	0 8
Is there a potential medication adherence problem? "People often have difficulty taking their pills for one reason or another. How often do you miss taking a dose of your medicines?"	o No (Never/rarely/once in a while/doesn't take medicines) o Yes (Sometimes/Usually)	0 19

Score cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
12 or less/Greater than 12	0.72 (0.63–0.80)	0.57 (0.53–0.62)	0.27 (0.22–0.33)	0.90 (0.86–0.93)
20 or less/Greater than 20	0.36 (0.27–0.45)	0.90 (0.87–0.93)	0.45 (0.35–0.56)	0.86 (0.83–0.89)

95%CI, 95% confidence interval.

misadventure. This tool had good levels of specificity and sensitivity of 78 and 83%, respectively. However, whilst the list of comorbidities was pragmatic, it is infinite, and the comorbidities were poorly defined. Warfarin use is declining as newer options become available; specifying particular medications within a tool has the potential to date the tool as therapy evolves. During routine ED care, it is not possible to systematically identify all potential comorbidities and whether they are active issues, therefore, co-morbidities were not included in our models.

Two decision rules were developed in three Canadian EDs, to identify patients presenting to ED with moderate/severe adverse drug events (ADEs) (Hohl et al., 2018). The following factors were associated with presentation with ADEs: rule 1 comprised having a pre-existing medical condition or having taken antibiotics within 1 week of presentation; rule 2 comprised age over 80 years or having a medication change within 28 days. These rules would be practical to administer in the ED, but only detected those patients at risk for presenting to ED with an MRP. The rules had a sensitivity of 91.3% and specificity of 37.9%. At a sensitivity of 80%–82%, our models have greater specificity (57%–70%), although ideally our models would also have greater specificity. With low levels of specificity, some patients may be unnecessarily seen by a pharmacist, which has workforce implications.

A prospective study undertaken on adult medical wards of two United Kingdom hospitals (Geeson et al., 2019) developed a 12-item prognostic model to prevent MRPs of at least moderate severity, with a sensitivity of 90% and a specificity of 30%. The model included the number of regular medications prescribed on the first full day of admission, which is not feasible for ED patient screening. It included pathology results to estimate renal function and white cell counts, which are not universally measured in ED patients.

A study by DeWinter et al. (2017) developed a decision rule to identify which admitted patients needed medication reconciliation. This rule only identified MRPs in admitted patients, rather than considering MRPs across the continuum of ED care. It did not include patients discharged from ED to the community, who comprise the greatest proportion of patients who present to an ED. Administering the rule required detailed knowledge of medication groups taken by patients, which would be time-consuming to complete during an ED cubicle assessment. Likewise, a rigorously designed United Kingdom study identified hospitalized patients at risk for MRPs (Kaufmann et al., 2015). They used a mixed-methods approach comprising a literature search and expert-panel using the nominal group technique. Eighty-five risk factors for MRPs were narrowed to 27 judged to be 'important' or 'rather important'. Accurately gathering this number of variables in ED would be problematic, even if this tool could be automated.

Implications for Policy, Practice, and Research

The screening tools developed in relation to this study may assist ED pharmacists to ensure they see higher-risk patients, may help ward staff to prioritize patients for early ward review, and highlight to ED nurses and doctors, which patients need greater medication-related support at or shortly following ED discharge.

Predictors in both models are amenable to being incorporated into electronic patient management systems with some auto-populated information. Some parameters will need ED clinicians to check-off, such as who administers the medications at home and how often medication doses are missed. Once completed, pharmacist follow-up could be electronically triggered (DeWinter et al., 2017; Geeson et al., 2019). At risk patients identified outside of clinical pharmacy hours could be followed up by telephone after ED discharge or be prioritized to be seen by ward pharmacists. The tool score cut-off points could be varied depending upon the availability of the pharmacist workforce to follow-up patients identified to be at risk.

Tool validation is required in indigenous populations, private hospital ED patients and hospitals with poorly developed clinical

pharmacy services. Although speculative, indigenous patients may require additional variables to be included, such as whether they live remotely or in a metropolitan area. In addition, the age categories may need to be reduced to younger years of age as is required for several health interventions in this population, such as vaccination eligibility (Australian Technical Advisory Group on Immunisation (ATAGI), 2018) and interventions for cardiovascular disease (Reath and O'Mara, 2018).

The PROGRESS framework (Steyerberg et al., 2013) for prognosis research outlines the stepwise process for the development and evaluation of prognostic or predictive tools. This stepwise process involves model development, followed by external validation of the model using a new dataset, then impact evaluation to assess the impact of tool implementation on health outcomes. Our study describes the initial step in this process. External, prospective validation and impact evaluation are required to determine the performance of the tools in practice. Also, assessment of inter-rater reliability is required.

Strengths and Limitations

The tools were developed using multicenter prospective data and outcomes relevant for patients and clinicians. To minimize selection bias but also maintain the depth of medication review for each patient (to optimize data accuracy and completeness), blocks of ten consecutive adult ED patients who presented to a range of EDs, at different times of the day across 7 days of the week were included. MRPs associated with ED care were identified for patients discharged from ED as well as those who were hospitalized. Using an objective approach to patient recruitment, rather than only those seen by ED pharmacists minimizes selection bias and enables identification of patients at risk for MRPs, and those not at risk. Predictors are readily determined at the bedside. By not including specific medications in the tools, a detailed medication history is not required at the point of screening, and the tools are less prone to becoming dated as medication prescribing practices evolve.

Some patients were lost to follow-up, particularly those discharged directly from ED. The tools may not identify all patients likely to benefit from clinical pharmacist review, e.g., patients with sepsis where an ED pharmacist could facilitate timely provision of the first antibiotic dose (Roman et al., 2018). MRPs due to dispensing and administration errors may have been under-estimated if not documented during the ED presentation. MRPs related to patient/carer knowledge deficits and non-adherence are likely under-estimated, as these MRPs were identified during the pharmacist interview/review in a process that mirrored routine care, rather than using specific tools validated to identify patient knowledge and adherence issues. The definition required that a knowledge deficit be one where the patient may be harmed by the knowledge deficit, therefore only the most serious knowledge deficits were included.

The data collection process, involving experienced pharmacists undertaking comprehensive medication reviews and reconciling data with several sources of information maximized the completeness of the data collection process. For the majority of variables taken through to the multivariable regression analysis there were no missing data. Of over 27,000 pieces of data taken through to the multivariable regression analysis there was a total of 103 pieces of missing data. The variable with the greatest prevalence of missing data was whether a medical specialist had been seen in the previous 6 months (there were 35 (3.9%) patients missing this data element). For patients missing this data variable, patients had often seen a specialist but found it difficult to recall whether it was within 6 months or within the past 6–12 months. So as not to over-estimate the potential risk, patients with missing data were coded as not having seen a specialist within the previous 6 months (this was also the most prevalent response). All patients had a comprehensive assessment of the MRP outcome variables and no patient had missing outcome data.

Ideally the tools would have greater specificity, but this highlights the broad range of ED MRPs and their multifactorial etiology. Preliminary scoring cut-points and associated screening tool performance have been proposed using this derivation dataset. These performance outcomes need to be further evaluated using a separate validation dataset.

CONCLUSION

In conclusion, predictors of MRPs that are readily available within the ED have been identified and built into tools to screen for patients at greatest risk for MRPs across the ED continuum of care. Future studies are required to prospectively validate these tools and evaluate their impact in practice.

DATA AVAILABILITY STATEMENT

The data underlying this article may be shared on reasonable request to the corresponding author and approval of the approving Human Research and Ethics Committee.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Austin Health Human Research and Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conception and design: ST, AH, DT, and EzM; Data acquisition: ST, EsM, AH, AW, LA, PL, DL, DS, RS, SL, HC; Analysis and interpretation: ST, EsM, AH, DT, AW, LA, PL, DL, DS, RS, SL, HC, ET, EzM; Drafting manuscript and critical appraisal: ST, EsM, AH, DT, AW, LA, PL, DL, DS, RS, SL, HC, ET, EzM; Statistical expertise: DT, ET, EzM; Acquisition of funding: ST, AH, DT, EzM.

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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.2022.865769/full#supplementary-material

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The role of *in vitro* testing in pharmacovigilance for ß-lactam-induced serum sickness-like reaction: A pilot study

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Background: Current pharmacovigilance (PV) methods for detection of adverse drug reactions (ADRs) fail to capture rare immune-mediated drug hypersensitivity reactions (DHRs) due to their scarcity and the lack of clear diagnostic criteria. Drug-induced serum sickness-like reactions (SSLRs) are rare type of DHRs that occur in susceptible patients 1–3 weeks after exposure to the culprit drug with ß-lactam antibiotics being the most associated drugs. The diagnosis of drug induced SSLR is difficult due to the lack of safe and reliable diagnostic tests for identifying the culprit drug. The lymphocyte toxicity assay (LTA) is an *in vitro* test used as a diagnostic tool for drug hypersensitivity reactions (DHRs).

Objective: To evaluate the role of the LTA test for diagnosing and capturing SSLR due to ß-lactam antibiotics in a cohort of patients.

Methods: Patients were recruited from patients referred to the Drug Hypersensitivity Clinic at Clinic at London Health Science Centre with suspicion of drug allergy. Twenty patients (10 males and 10 females) were selected to be tested to confirm diagnosis. Demographic data was collected form the patents and blood samples were withdrawn from all patients and from 20 healthy controls. The LTA test was performed on all subjects and data is expressed as percentage increase in cell death compared to control (vehicle without the drug).

Results: In the result of LTA tests performed on samples from the selected 20 patients. There was a significant ($p < 0.05$) concentration-dependent increase in cell death in cells isolated from patients as compared to cells

Abbreviations: AH, antihistamine; Amox, amoxicillin; Ceph, cephalexin; EM, Erythema multiforme; JP, Joint pain; JP&S, Joint pain and swelling; MP, Maculopapular; NA, not available; St, steroids; UM, Urticaria multiforme.

from healthy controls when incubated with the drug in the presence of phenobarbitone-induced rat liver microsomes.

Conclusion: Giving its safety and good predictive value the LTA test has very strong potential to be a useful diagnostic tool for ß-lactam-induced SSLR. The test procedure is relatively simple and not overly costly. Further studies including other drug classes are needed to evaluate the utility of the LTA test for SSLR due to other drugs.

KEYWORDS

drug hypersensitivity, pharmacovigilance, beta-lactam agents, serum sickness-like reaction, adverse drug reaction

Introduction

Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the science and activities relating to detection, assessment, understanding and prevention of adverse effect or any other medicine-related problem (WHO, 2014). The importance of the discipline of PV is generally considered to have been established by the release of the Kefauver-Harris Amendment (Drug Efficacy Amendment) to the Federal Food and Cosmetic Act in the United States in 1962. The law required drug manufacturer to provide proof of effectiveness and safety of their drugs before approval (Peltzman, 1973). The terms "pharmacovigilance" and "drug safety" are commonly used in the field to describe the systematic collection and review of post-marketing drug safety data to guide drug use (Beninger, 2018). However, PV activities also include reviewing reports submitted by clinical investigators early during the drug development process and during selection of first safe human dose.

Adverse drug reactions (ADRs) are one of the leading causes of death in the developed world and represent a heavy cost burden on the healthcare system causing many hospital admissions and extended hospitalizations (Bates et al., 1997). ADRs cause one death every 5 min and cost over $136 billion annually in the United States (Johnson and Bootman, 1995). In the European Union, ADRs are estimated to be responsible for 5% of hospital admissions and cases 197,000 deaths annually (Bouvy et al., 2015). ADRs can either be type A, which are predictable from the drug pharmacology and dose dependent and type B, which are unpredictable, unrelated to the drug's known pharmacology and do not have clear dose dependency. Type B ADRs include immune-mediated drug hypersensitivity reactions (DHRs; drug allergy) and non-immune mediated DHRs (also called pseudoallergy). They represent smaller fraction of total ADRs (−15%–20%) with some types of reactions lie under the rare and very rare categories (i.e., incidence between ≥1/10,000 to 1,000 and <1/10,000 of drug exposure, respectively). Rare and very rare ADRs cannot be captured during the pre-marketing stages of drug development due to the underpowered sample size (Chan et al., 2015). In addition, it is always not feasible nor practical to study unpredictable (type B) ADRs in prospective, interventional, and clinical trial studies due to their unpredictability and rare occurrence. Another inherited problem associated with these reactions is the difficulty in defining cases based on clinical presentation and associated signs and symptoms (Uetrecht and Naisbitt, 2013). Many of these rare ADRs are underreported due to poor case definition and lack of diagnostic methods (Lopez-Gonzalez et al., 2009). In fact, it is estimated that over 95% of ADRs go unreported (Bailey et al., 2016). This is a major problem as the only way to fully evaluate drug safety in real world is though robust pharmacovigilance studies and data collection. Many drugs have met all the regulatory efficacy and safety requirements only to be later withdrawn from the market due to efficacy or safety concerns jeopardizing patient safety and costing the drug developers and the healthcare systems billions of dollars (Qureshi et al., 2011). It is therefore extremely important to develop sensitive and specific methods to detect and report ADRs in the early stages of clinical use. The current PV systems, which largely depends on spontaneous voluntarily reporting lack such robustness and fundamentally inefficient to detect signal from noise due to lack of reliable diagnostic test to identify cases (Salvador et al., 2022). We propose that a reliable *in vitro* diagnostic test for rare and very rare idiosyncratic ADRs would help capture and report them enhancing PV and ADR surveillance. Efficiency of surveillance is particularly essential for rare and very rare ADRs; for instance, missing one case of an ADRs with 5% prevalence may not have a significant effect on the overall surveillance process but missing one case 1 in 10,000 exposures may result in failure to detect the ADR leading to unsafe exposure of a large number of patients to the drug.

DHRs are divided, according to the immune mechanism and type of immune cells involved, into type I (IgE-mediated), type II (cytotoxic reactions mediated by drug-specific IgG), type III (immune complex-mediated), and type IV reactions (delayed reactions, T-cell-mediated) (Elzagallaai and Rieder, 2015). Serum sickness (SS), which belongs to type III immune-complex mediated reaction, was first described by von Pirquet and Schick in 1951 (von Pirqet and Schick, 1951). It was later found that circulating immune complexes and complement activation is important in the pathophysiology of these immune-mediated reactions (Vaughan et al., 1967). Serum sickness-like reaction (SSLR) is clinically similar reaction that mostly triggered by drugs. They are most associated with ß-lactam antibiotics (especially cefaclor and amoxicillin), sulfonamides, fluoroquinolones, aromatic

anticonvulsants, tetracyclines, minocycline, metronidazole, bupropion, and other drugs including biologicals (Lawley et al., 1984; Platt et al., 1988; Heckbert et al., 1990; Weiss and Smith, 2020). This type of reactions can also develop as a result of vaccine administration including recent cases of SSLR to inactivated COVID-19 vaccine (Chung et al., 2021; Chaijaras et al., 2022). The condition is defined by sudden appearance of skin rash (usually urticaria-like) and arthritis usually manifested 1–3 weeks after drug exposure, which can be accompanied by fever, lymphadenopathy, eosinophilia, and rarely renal involvement (Del Pozzo-Magana et al., 2021). It is uncommonly seen in clinical practice, but its incidence appears to be on the rise since the introduction of biologic drugs (Finger and Scheinberg, 2007; Khan, 2016). It has been estimated that the incidence of SSLR associated with cefaclor is between 0.024% and 0.2% per course (Knowles et al., 2000). The diagnosis of SSLR is challenging due to other possible causes (Schryver, 2015). The exact prevalence of SSLR due to ß-lactam antibiotics is not known, however, studies have estimated it to complicate 0.4%–0.5% of antibiotic courses (Reynolds, 1996; Isaacs, 2001). In a 10-year retrospective cohort study we found that SSLR represent 15.4% of all patients with cutaneous ADRs referred to our clinic, 0.02% of all cause of consult, and 0.9% of all sudden skin rashes seen in the our institution pediatric emergency department. The most commonly implicated drugs were ß-lactam antibiotics including amoxicillin (87%) and cephalosporins (8.5%) (Del Pozzo-Magana et al., 2021). Type B ADRs also include "pseudoallergy", which is non-immune-mediated. Examples of the latter reactions are opioids-induced pruritis and NSAIDs-induced pseudoallergy (Zhang et al., 2018). Another example of pseudoallgy is complement activation-related pseudoallergy (CARPA) (Szebeni, 2005).

The precise details of the pathophysiology of drug-induced SSLR is not well understood. However, in delayed onset drug hypersensitivity the generation of cytotoxic reactive metabolites from drug molecules *in vivo* is believed to be the first step in a cascade of events leading to the immune-mediated reaction (Elzagallaai et al., 2017). These reactive metabolites are capable of adducting (hapenating) endogenous macromolecules produced an antigen recognized by the immune system as non-self. They may also cause local or systemic cell damage resulting in releasing 'danger signals', which prime immune cells to mount the reaction (Matzinger, 1994; Pichler et al., 2010x). Diagnosis of drug-induced SSLR is challenging, mainly based on clinical presentation and medication history, and no reliable and safe diagnostic test is available. Case definition for management and pharmacovigilance purposes is therefore challenging giving the fact that presenting signs and symptoms are often variable.

The lymphocyte toxicity assay (LTA) is an *in vitro* test that has been proven to have a significant value in the diagnosis of drug-induced hypersensitivity reactions (DHRs) but most of the validation work has been focused on type IV T-cell-mediated delayed DHRs (Elzagallaai et al., 2013; Dhir et al., 2021). The test has been shown in a study involving 51 patients with DHRs to have a sensitivity of 99% and specificity of 75% (Naranjo et al., 1994). In another study, Neuman et al. used the test to investigate DHRs in 86 patients with suspected reaction to sulfamethoxazole and 62 patients with suspected reactions to anticonvulsants (Neuman et al., 2000). They estimated the test sensitivity and specificity to be 98% and 89%, respectively. Other studies have estimated the positive predictive value of the LTA in cases of DHRs to sulfonamides to be between 80% and 90% (Neuman et al., 2002; Neuman et al., 2007). Using re-exposure as a gold standard test in a small cohort (22 patients), we calculated the overall sensitivity and specificity of the LTA test to be 40% and 90%, respectively, but that depended on the suspected drug (Elzagallaai et al., 2010). In this study we explored the potential role of the LTA *in vitro* test for diagnosis of ß-lactam-induced SSLRs for the purpose of optimizing and improving pharmacovigilance to these rare types of DHRs.

Materials and methods

Materials

Penicillin, cephalexin, tetrazolium salt 3-(4, 5-dimethylthiazol-2-yl) 2, 5 diphenyl-tetrazolium bromide (MTT), hydrogen peroxide (H_2O_2), 2′,7′-dichlorofluorescin diacetate (DCFH-DA), Histopaque® -1077 (Ficoll), Hank's balanced salt solution (HBSS) and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St, Louis, MO, United States). RPMI 1640 and trypan blue were purchased from Invitrogen™, Life Technologies Inc. (Burlington, ON, Canada). Phenobarbitone-induced pooled male Sprague-Dawley rat liver microsomes were purchased from BioIVT (Westbury, NY, United States). All other chemicals used in this study were the highest purity commercially available.

Subjects

Informed consent was obtained from all participants and the study protocol was approved by the Western University Research Ethics Board for Human Subjects (REB No. 11883E). Two groups of individuals were included in our study. The first group consisted of patients who had experienced a β-lactam antibiotic-induced SSLR. The diagnosis of SSLR was established by revising patients' files by two clinicians (AMA and BD-M), who have experience in managing patients with DHRs. Any ambiguity in the diagnosis was confirmed by a third clinician (MJR). The general criteria for diagnosis include development of skin rash and joint inflammation with or without fever after exposure to the culprit drug (De Schryver and Ben-Shoshan, 2015; Del Pozzo-Magana et al., 2021). The inclusion criteria of this group include: 1) Having a history of SSLR related to the administration of a ß-lactam antibiotics (penicillins or cephalosporins); 2) symptoms developed are highly suggestive of SSLR and should include skin rash and joints involvements; 3) the patient consents to participate in the study and provides a sufficient blood sample. We excluded patients with any underlying rheumatological conditions (e.g., lupus, rheumatoid arthritis,

TABLE 1 Characteristics of patients included in the study.

Patient #	Sex	Age (Y, years; M, months)	Drug involved	Onset of reaction (Days)	Type of skin rash	Presence of fever	Other symptoms	Time to resolution	Treatment
1	F	18M	Amox	7	MP	Y	JP&S	4	St
2	M	3Y	Amox	10	MP	N	JP&S	6	St
3	F	2Y	Amox	7	MP	Y	JP&S	5	St
4	M	32Y	Amox	10	MP	NA	JP&S	6	St
5	F	30M	Amox	3	UM	Y	JP	5	St
6	M	2Y	Amox	6	MP	N	JP&S	5	NA
7	M	29M	Amox	7	MP	N	JP	5	St
8	F	5.5Y	Amox	7	MP	Y	JP	5	St
9	F	19M	Amox	7	UM	NA	JP	5	AH
10	M	67Y	Ceph	NA	MP	NA	NA	NA	NA
11	F	3Y	Amox	7	EM	NA	JP	15	St
12	M	50Y	Amox	NA	MP	NA	JP&S	14	St
13	F	2Y	Amox	10	EM	Y	JP	6	St
14	M	6Y	Amox	10	MP	N	JP&S	14	St
15	M	8Y	Ceph	7	MP	y	Jp	5	St
16	M	2Y	Amox	7	EM	NA	JP&S	5	AH
17	F	2Y	Amox	5	MP	NA	JP&S	&	AH
18	M	11M	Amox	7	MP	NA	JP&S	5	AH
19	F	3Y	Amox	7	MP	Y	JP&S	3	AH
20	F	2Y	Ceph	8	MP	Y	JP&S	4	St

dermatomyositis, spondyloarthropathies, Sjogren's disease. Juvenile idiopathic arthritis, and polymyalgia rheumatica). The second group is composed of 20 healthy individuals, who denied any history of DHRs to ß-lactam antibiotics. Overall, 20 patients between the age of 11 months and 67 years were recruited. The patients' characteristics are summarized in Table 1.

Blood collection and isolation of cells

Thirty milliliters of peripheral venous blood samples were collected from each participant by venipuncture into heparinized syringes and processed immediately. To isolate peripheral blood monocytes (PBMCs), blood was diluted 1: 1 with phosphate-buffered saline (PBS, 10 mM NaH_2PO_4, 2 mM KH_2PO_4, 137 mM NaCl, 2.7 mM KCl; pH 7.2) and 30 ml were layered over 15 ml of Ficoll-Paque density gradient and centrifuged at 500 g for 20 min. The interface layer (buffy coat) was then collected. Cells were washed twice with PBS and adjusted to 1×10^6 cell/mL in HEPES [4-(2-hydroxyethyl)-1-piperazine] ethanesulfonic acid buffered saline containing 15 mM HEPES, 125 mM NaCl, 6 mM KCl, 1.2 mM $MgSO_4$, 1.0 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 10 mM glucose; pH 7.4).

In vitro toxicity testing

The LTA was performed as described previously (Elzagallaai et al., 2010; Elzagallaai et al., 2011). Briefly, PBMCs were plated in flat-bottom 96-multi-well plates at a density of 1×10^5 cells per well in quadruplicate and treated with a final concentration of 6.25–125 µg/ml of either amoxicillin or cephalexin depending on the suspected drug. Drug solutions were freshly prepared in dimethyl sulfoxide (DMSO) and diluted in culture media to give the desired final concentration (DMSO final concentration is always kept at ≤1%). Microsomal protein was added at a concentration of 0.25 mg/ml, followed by addition of the NADPH-generating system (nicotinamide adenosine dinucleotide phosphate [NADP] 0.6 mM, glucose-6-phosphate 2.4 mM, glucose-6-phosphate dehydrogenase 2 U/ml). Preparations were incubated for 2 h at 37°C in a 5% CO_2 humidified atmosphere. A standard curve for measuring cell death was generated by seeding cells at 25%, 50%, 75% or 100% of cell populations in culture media in quadruplicate. After incubation, drugs in solution were removed by centrifugation at 500 *g* for 10 min. Then, cells were suspended in 100 µl fresh RPMI-1640 media supplemented with 10% FBS, 100U/ml penicillin G sodium and 100 µg/ml streptomycin sulfate, and left to recover for 18 h in an atmosphere of 5% CO_2 at 37°C. Cell

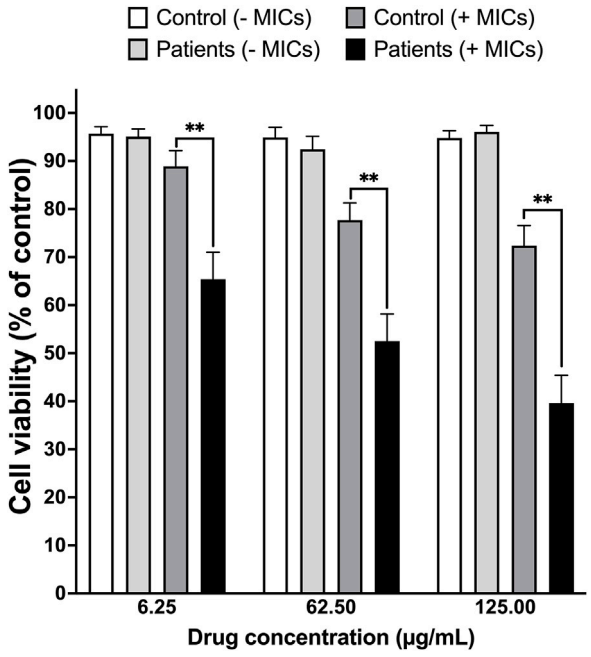

FIGURE 1
Summary of the LTA test results for 20 SSLR patients and 20 healthy controls. Lymphocytes isolated from health controls were incubated with drug either without microsomes (MICs, white bars) or with drug and MICs (light grey bars) and cells isolated from SSLR patients were incubated with drug either without MICs (dark grey bars) or with MICs (black bars). Y axis represents cell viability expressed as a percentage from incubating the corresponding cells with control vehicle without the drug. **, $p < 0.001$.

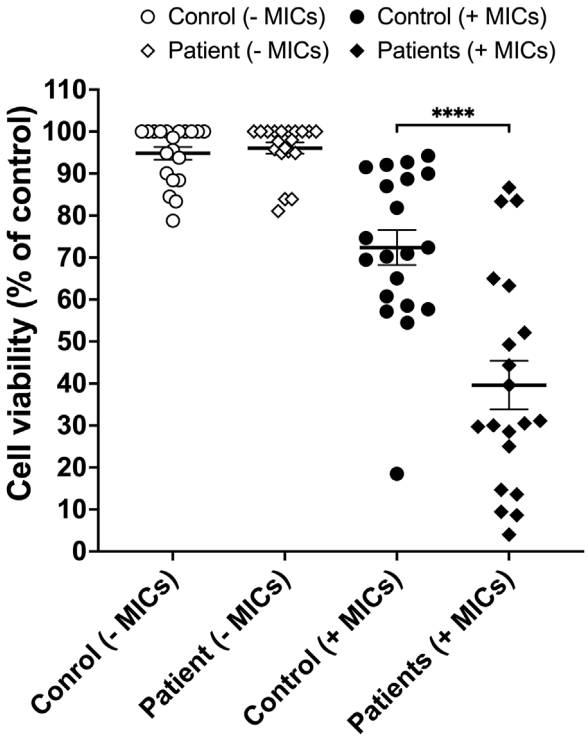

FIGURE 2
Cell viability (expressed as % of control) of PBMCs from healthy volunteers without microsomes (MICs, open circles), SSLR patients without MICs (open diamonds), healthy controls with MICs (closed circles) and SSLR patients with MICs (closed diamonds). Mean ± SEM. ****, $p < 0.0001$.

viability was quantified using MTT staining as described previously. (Elzagallaai et al., 2010).

Statistical analysis

Statistical analysis was performed using Prism GraphPad software. The numbers of dead cells were expressed as a percentage of control (vehicle without drug) and blotted as mean ± standard error (SEM). Significant differences were determined by two-tailed Student's t-test. A probability of more than 95% ($p \leq 0.05$) was considered significant. Correlations were made using Pearson correlation analyses. Unless otherwise indicated, values are presented as mean ± standard error (SEM).

Results

Twenty patients (10 males and 10 females) presented with symptoms that meet our inclusion criteria for SSLR to beta-lactam antibiotics (penicillins and cephalosporins). Clinical symptoms included cutaneous lesions (maculopapular, EM, urticaria) and joint inflammation (arthritis) that included hands, feet, or both. Eight of the 20 patients also developed fever as part of the hypersensitivity syndrome. The mean age of the patients was 9.9 years and ranged from 11 months to 67 years. The characteristics of the patient population is summarized in Table 1. All patients had positive LTA test results using a cut-off value of 20% increase in cell death (Figure 1). At 125 µM of the drug and in the presence of MICs, degree of cell death was significantly higher ($p < 0.0001$) in cells isolated from ß-lactam-induced SSLR patients (Mean: 60.37%) than cells from healthy controls (Mean: 27.61%). Difference between means (controls and patients) ± SEM = 32.76 ± 7.117 (95% confidence interval: 47.17 to 18.35) (Figure 2).

Discussion

Case definition in PV studies require applying rigorous criteria, which in cases of idiosyncratic reactions are almost always lacking. In addition, use of PV algorithms in the

diagnosis of DHRs in general is not accurate because of the often lack of sufficient information for scoring (Benahmed et al., 2005). An alternative would be a reliable and safe *in vitro* test with adequate sensitivity and specificity to detect true cases among the suspected cohort of patients. It is understandable that these criteria can only be applied in prospective PV studies but can be used for PV surveillances.

Drug-induced SSLR represent a major problem to healthcare—along with other idiosyncratic hypersensitivity reactions—due to the difficulty in diagnosis and accurate identification of the culprit drug. Approximately 10% of the general population report an allergy to β-lactam antibiotics; however, 90% of reported allergies to β-lactam antibiotic cannot be ruled out immunologically (Surtees et al., 1991). Such false labeling of patients puts them at greater risk of adverse reaction due to the use of less safe alternative drugs with inferior effectiveness to treat their infection which increases length of hospital stay and worsen the outcome. Furthermore, false labeling result in the use to non-beta-lactam antibiotics leading to cost increases and contributes to worsening the bacterial resistance problem. Capturing true cases of ß-lactam-induced SSLR using available clinical criteria is difficult due to lack of reliable diagnostic tests. On the other hand, for newly marketed drugs, especially biologicals, capturing IDRs for safety evaluation is utmost important for proper PV monitoring. All the available diagnostic aids including skin testing and oral re-challenge have their risks and shortcomings and are not always feasible to perform either due to lack of expertise or fear of inducing a severe reaction in the patient. The LTA has the advantage of being safe as an *in vitro* test and can be used both as a diagnostic test and an investigative tool for the pathophysiology of SSLRs. Kearns et al. (Kearns et al., 1994) tested 19 patients (10 male and 9 females) suspected of developing SSLR to cefaclor and found that subjects with SSLR exhibited an increase in cell death of 50%–167% above baseline. The effect was specific to cefaclor and was not produced by incubation of isolated cells with another cephalosporin (cephalexin) along with metabolic activation system (Kearns et al., 1994). In another study, the same group also tested 10 patients with SSLR to cefaclor using the LTA test. The degree of cell death in the patient pollution was highly positive and ranged from 40% to 140% increase above baseline (Kearns et al., 1998). In a validation study for the LTA test using systemic re-exposure as a gold standard to determine the predictive value of the test for diagnosis of hypersensitivity reactions (HSRs) to different groups of drugs, we tested 11 patients with HSRs to beta-lactam antibiotics (6 to amoxicillin and 5 to cefaclor) (Elzagallaai et al., 2010). When the results of the re-exposure were compared to the LTA results, all except one patient had complete agreement.

The main pitfall associated with evaluating the role of *in vitro* toxicity testing for pharmacovigilance monitoring of rare drug-induced reactions is the lack of large studies looking at the predictive value of these tests (Elzagallaai et al., 2009). We speculate that one of the main reasons for this is the technical skills and special equipment required to perform the test restricting it to highly sophisticated research centers. We have introduced a more simplified version of the LTA test—the *in vitro* platelet toxicity assay (iPTA)—using blood platelets as a surrogate cell model for toxicity testing (Elzagallaai et al., 2011). The iPTA test has been proven to be less technically demanding and less expensive than the LTA with potentially better predictive value (Elzagallaai et al., 2013).

Data from this pilot study points to the value of the LTA (and potentially the iPTA) both as a diagnostic tool for beta-lactam-induced SSLRs and as a PV monitoring tool. Further research with larger numbers of patients is needed to further explore the pathophysiology and biology of SSLR to β-lactam antibiotics.

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 REB of the University of Western Ontario. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AE designed the study, analyzed the data and wrote the manuscript. AA Collected data and blood samples and performed the *in vitro* testing, BD recruit patients and collected clinical data. EM recruited patients and healthy controls to the study and revised the manuscript. MR contributed to the original design of the study, recruitment of patients and writing of the manuscript.

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Conflict of interest

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

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Using real-world data for supporting regulatory decision making: Comparison of cardiovascular and safety outcomes of an empagliflozin randomized clinical trial versus real-world data

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Aims: In countries where a randomized clinical trial (RCT) is difficult to perform, a real-world evidence (RWE) study with a design similar to an RCT may be an option for drug regulatory decision-making. In this study, the objective was to find out to what extent the safety of empagliflozin from the RWE study in Korea is different from the one in RCT by emulating the design of foreign RCT. The outcome covers various safety outcomes including cardiovascular safety.

Methods: The EMPA-REG OUTCOME trial (NCT01131676) was selected for comparison. The inclusion/exclusion criteria and follow-up method for the RWE were matched to the comparison RCT. Major adverse cardiovascular events (MACEs) were used as a primary outcome and 15 other outcomes were also included for analysis.

Result: We followed 23,126 matched patients with type 2 diabetes mellitus (11,563 empagliflozin users and 11,563 sitagliptin users) for 2.7 years (median). Empagliflozin use was associated with a significantly decreased risk of MACEs [EMPA-REG DUPLICATE RWE: adjusted HR 0.87, 95% confidence interval (CI) 0.79–0.96]. The predefined estimate agreement, regulatory agreement, and standardized difference for RCT duplication were achieved [EMPA-REG OUTCOME RCT: adjusted HR 0.86, 95% (CI) 0.74–0.99]. According to the predefined criteria for 15 outcomes, 10 outcomes were evaluated as good, and three as moderate.

Conclusion: Our study results suggest that RWE in one country in comparison with an RCT has the potential for providing evidence for future regulatory decision-making in an environment where RCT could not be performed.

KEYWORDS

real-world evidence, randomized controlled trial, emulation analysis, diabetes mellitus, sitagliptin, empagliflozin

Introduction

Randomized controlled trials (RCTs) are generally regarded as the gold standard for regulatory decision makings. Given the growing trend of globalization and the need to make new or extended-use medicines rapidly available to patients worldwide, the RCTs are usually conducted in multi-regional clinical settings (Quan et al., 2017). However, since most clinical trials are conducted in the US and Europe, the proportion of Asians is relatively low. It has been reported that the proportion of clinical trials in Korea among the total clinical trial is about 3% (ClinicalTrials.gov, 2022). Data from multi-regional clinical trials (MRCTs) are submitted to regulatory agencies, which currently find it difficult to evaluate such data for drug approval (Sohn et al., 2019). The main reason is that clinical trial subjects are of different races. Furthermore, it is difficult to conduct additional clinical trials for regulatory decisions like expanding drug indications or adding side effects information, due to time and cost (Revicki and Frank, 1999; Garrison et al., 2007).

Real-world evidence (RWE) is clinical evidence concerning the potential benefits or risks of a medication derived from analysis of real-world data (RWD). RWE has a relative advantage over RCTs because it enables a long-term follow-up study or research on rare populations. In the United States, the 21st Century Cures Act, passed in 2016, placed additional focus on the use of RWE to support regulatory decision making, including adding/modifying an indication, use in a new population, and adding comparative effectiveness or safety information (Food-and-Drug-Administration-FDA, 2018a; Food-and-Drug-Administration-FDA, 2018b; Food-and-Drug-Administration-FDA, 2019a; Food-and-Drug-Administration-FDA, 2019b). With a rise in observational COVID-19 study dissemination, this trend is being accelerated (Pundi et al., 2020). Rather than performing additional RCT in every country to verify new indications or side effects, performing an RWE study in other races and medical-practice conditions could be an alternative way. If the design and analysis method of the RWE study are implemented as closely as possible with the RCT, it will be easier to make regulatory decisions based on comparisons of results of RWEs and RCTs.

Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor drug approved by US Food and Drug Administration (FDA) in 2014 for the treatment of type 2 diabetes (T2DM). After its approval for T2DM, several RCTs have been performed to demonstrate the safety of empagliflozin for other outcomes (Zinman et al., 2015; Packer et al., 2020). New indications such as reducing the risk of cardiovascular death in adults with T2DM and established cardiovascular disease and hospitalization for heart failure in adults with heart failure were added under FDA approval (Dailymed-Prescribing-information, 2022). However, the Ministry of Food and Drug Safety (MFDS) in Korea has not yet recognized the safety of empagliflozin for cardiovascular disease. This is because sufficient evidence has not been provided for whether the indication, "reducing the risk of cardiovascular death" could be demonstrated for Koreans as well. For this reason, empagliflozin has not yet been approved for reducing the risk of cardiovascular disease (MFDS-Prescribing-information, 2021).

In this study, we aimed to investigate to what extent the safety of empagliflozin from the RWE study in Korea is different from the one in RCT by emulating the design of foreign RCT. The outcome covers various safety outcomes including cardiovascular safety. We applied a RCT emulation analysis process that would be acceptable for regulation (Franklin and Schneeweiss, 2017; Franklin et al., 2020). If there were any discrepancies between the RCT and RWE, we investigated the circumstances under which this inconsistency occurs.

Methods

Study design and data sources

The study drug was selected through a pre-determined process (Supplementary Figure S1). Firstly, drugs that need to be re-evaluated under MFDS (date of announcement: 2021-01-24) were assessed (number of drugs: 498) (Supplementary Table S1). Secondly, according to the selection criteria set by the research team, 91 drugs were considered having high demand for safety evaluation. Of those, the anti-diabetic medications consisting largest number of drugs (number of drugs: 7) were selected (Supplementary Table S2) An additional selection process was carried out with considering each drugs' adverse reaction profiles. Finally, empagliflozin and its pivotal study (EMPA-REG Outcome) were selected as a target drug and a target trial, respectively. This 1:1 matched cohort study included patients with type 2 diabetes mellitus and high cardiovascular risk, using the same inclusion/exclusion criteria, follow-up method and outcome definitions of a target RCT. The study assessed the effect of empagliflozin versus sitagliptin on cardiovascular and several safety outcomes of empagliflozin. The EMPA-REG OUTCOME trial (NCT01131676) (Zinman et al., 2015) was selected to target emulation (Franklin et al., 2020; Franklin et al., 2021). The EMPA-REG OUTCOME study provided strong evidence that the SGLT2 inhibitor empagliflozin protects against major adverse cardiovascular events (MACEs) and other secondary outcomes (Zinman et al., 2015).

The analyzed health insurance data was officially provided by the Korean Health Insurance Review & Assessment Service (HIRA) (Kim et al., 2017). The insurance data included demographic, diagnosis, procedure, and prescription data of

patients. The requirement for written informed consent from participants was waived because all participants were anonymized using a randomized identification number. This study was approved by the institutional review board of Seoul National University (IRB No. E2101/001-003). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (von Elm et al., 2014).

Study patients

The target population is patients with T2DM and established cardiovascular disease. Patients who had been diagnosed with T2DM were included from 2011 to 2020, with a 3 years of study index period between May 2016 and May 2018. The period between January 2011 to May 2016 was used as a screening period for applying inclusion/exclusion criteria. Patients were selected according to the same inclusion/exclusion criteria as a RCT (Supplementary Table S3). All patients (≥18 years) had established cardiovascular disease and received empagliflozin or sitagliptin for the first time. Note that according to 2013 American College of Cardiology and American Heart Association guideline, patients who have been diagnosed with an established cardiovascular disease are classified as a high-risk group (Karmali et al., 2014). Therefore, included patients were considered as having high cardiovascular disease risks. We selected an active comparator (sitagliptin) as a proxy for the placebo, because it is well known for observational studies, that a non-user comparator group can differ substantially from actively treated patients, unlike RCTs (Food-and-Drug-Administration-FDA, 2013). Many other studies have also selected Dipeptidyl peptidase-4 inhibitors as comparators for assessment of SGLT-2 safety (Kim et al., 2018; Douros et al., 2020; Lee et al., 2020; Seong et al., 2020; Han et al., 2021). The index date was defined as the very first date each drug was prescribed.

Key variables

Individuals were followed-up until May 2020, and outcomes were recorded between each individual's index date and May 2020. MACEs outcome from the EMPA-REG OUTCOME trial was used as a primary outcome. Since HIRA does not provide cause of death information, modified MACEs (all-cause death, myocardial infarction (MI), and stroke) was applied (Yeom et al., 2015). A total of seven cardiovascular outcomes were analyzed: all-cause death, MI, hospitalization for unstable angina, coronary revascularization procedure, stroke, transient ischemic attack, and hospitalization for heart failure.

Eight safety outcomes were also analyzed: hypoglycemic events, urinary tract infections (UTIs), genital infections, volume depletion, acute kidney injury (AKI), diabetic ketoacidosis (DKA), thromboembolic events, and bone fracture. The operational definitions of outcomes were defined using the Korean Standard Classification of Diseases-9 codes or procedure codes and were directly matched to each Regulatory Activities Preferred Term (MedDRA PT) in the RCT (Supplementary Table S4). To minimize confounding variables (e.g., selection bias) as much as possible, 72 covariates were included viz. Demographics, comorbidities, and disease/outcome specific variables. Of those, the main variables included are as follows: Seven types of glucose-lowering therapies (Metformin, Insulins, Sulfonylureas, Glitazones, Glucagon-like peptide-1 agonists, Alpha-glucosidase inhibitors, and Meglitinides) [Diabetes treatment strategies], time since type 2 diabetes mellitus [Duration of continuous enrolment], number of inpatient/outpatient visit [Indicators of health care utilization of the patients], five types of cardiovascular risk factors (Coronary artery disease (CAD), Multi vessel CAD, MI, Coronary Artery Bypass Graft, and Stroke with proper cardiovascular procedures) [history of cardiovascular procedures]. All covariates within the preceding 1 year of index date were evaluated.

Statistical analysis

Statistical analyses were performed for the intention-to-treat population. Each time an outcome was analyzed, a new cohort was constructed after excluding patients with a history of the corresponding outcome. Patients were followed up until the earliest of events, the date of last follow-up, the date of switching diabetic medication to the other comparison group, or the end of the study period. The maximum follow-up period was set at 48 months (same as in the RCT). Empagliflozin users were matched 1:1 to sitagliptin users and the distribution of the propensity score was inspected (Parsons, 2001). A standardized difference >0.1 was regarded as a sign of imbalance (NCSS-statistical-Software, 2017). As same with RCT, the age and sex-adjusted multivariate Cox proportional hazard regression was used to estimate the hazard ratio (HR) of empagliflozin for the cardiovascular outcome, with a 95% confidence interval (CI). For a safety outcome model, logistic regression was used to the odds ratio (OR) of empagliflozin.

Sensitivity analyses were performed the same as with the RCTs in two ways. First, patients who received at least one dose of the study drug were observed until ≤30 days after a patient's last intake of medication. Additionally, we followed up patients who received the study drug for ≥30 days (cumulative) including events that only occurred ≤30 days after a patient's last intake of medication ("as-treated" analysis). Analyses were performed with SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, United States).

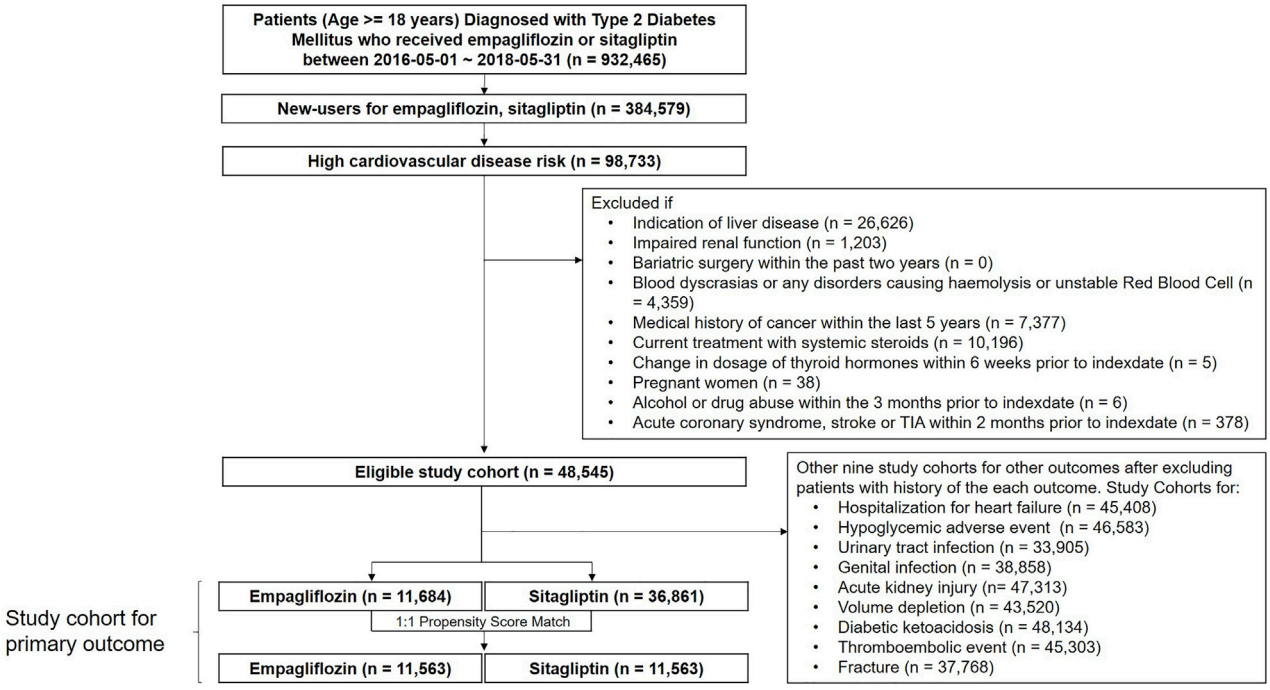

FIGURE 1
Study flow chart.

RCT-RWE agreement assessment

We defined three metrics below to make a binary decision on whether an RCT was successfully emulated, considering statistical significance, directionality, and CIs associated with the corresponding RWE study. The agreement criteria suggested by Franklin *et al.* were used for determining each agreement (Franklin et al., 2020). First, we defined regulatory agreement (RA) as the ability of the RWE study to emulate the direction and statistical significance of the randomized trial finding. A secondary agreement metric was the estimate agreement (EA), defined as an RWE estimate that lies within the RCT 95% CI. We also conducted hypothesis tests to evaluate whether there was a difference in findings by calculating the standardized difference (SD) between the RCT and RWE effect estimates. We considered a p-value < 0.05 (where SD is greater than 1.96) statistically significant for the SD agreement. For comparison of results, HRs for cardiovascular outcomes and ORs for safety outcomes were calculated and compared (HRs were not provided for safety outcomes in an RCT). We defined the emulation result as "good" or "moderate" if all three agreements or two of three agreements were achieved, respectively. If the emulation result achieved ≤ one of the agreements, we defined the result as 'fail'.

Results

A total of 932,465 patients (age ≥18 years) diagnosed with diabetes who received empagliflozin or sitagliptin were identified. New empagliflozin or sitagliptin users (n = 384,579) were selected (Figure 1). Among 98,733 patients who have high cardiovascular disease risks, an eligible study cohort with 48,545 patients remained after excluding patients who do not meet predefined inclusion criteria. Sitagliptin users were older and visited clinics more frequently (inpatient/outpatient) than empagliflozin users (Table 1). A later index date of empagliflozin users was observed compared to sitagliptin users. Compared to sitagliptin users, empagliflozin users were more often diagnosed with coronary artery disease (including coronary revascularization) and had fewer strokes.

After 11,563 empagliflozin users were matched to sitagliptin users, the above differences (age, number of clinic visits, index date, cardiovascular risk factors, comedications, and comorbidities) were reduced, and both groups were well balanced. Standardized differences were well below 0.1 for all 72 covariates. Median length of follow-up (2.7 years; median duration of anti-diabetic medications prescription during follow-up [1.7 (interquartile range 0.5–2.4) years]; and mean age of patients [55.6 years; men: 58.9% (n = 13,628)] were shown. In the other nine study cohorts for evaluating safety outcomes, the two drug user groups were also well balanced after 1:1 matching (Supplementary Tables S5–S13).

TABLE 1 Baseline characteristics.

Variables	Pre-Match			Post-Match		
	Sitagliptin N = 36,861	EmpagliflozinN = 11,684	STD	Sitagliptin N = 11,563	Empagliflozin N = 11,563	STD
Sex	20,289 (55)	6,913 (59.2)	−0.04	6,799 (58.8)	6,829 (59.1)	−0.004
Age	60.4 ± 11.4	55.4 ± 11	−0.4	55.5 ± 11.3	55.6 ± 10.9	0.008
Insurance type						
Normal	34,434 (93.4)	11,065 (94.7)	0.06	10,927 (94.5)	10,950 (94.7)	0.01
Medicaid	2,234 (6.1)	583 (5)		595 (5.2)	577 (5)	
No charge	193 (0.5)	36 (0.3)		41 (0.4)	36 (0.3)	
Number of Inpatient visit	0.8 ± 2.2	0.5 ± 1.2	−0.2	0.5 ± 1.1	0.5 ± 1.2	0.01
Number of outpatient visit	28.1 ± 27.5	25.5 ± 23.9	−0.1	25.3 ± 23.1	25.6 ± 23.9	0.01
Time since type 2 diabetes mellitus						
≤1 year	18,197 (49.4)	5,045 (43.2)	0.1	5,043 (43.6)	5,008 (43.3)	0.007
>1–5 years	16,927 (45.9)	5,941 (50.9)		5,827 (50.4)	5,866 (50.7)	
>5 years	1737 (4.7)	698 (6)		693 (6)	689 (6)	
Index year						
2016	10,568 (28.7)	2,247 (19.2)	0.2	2,281 (19.7)	2,247 (19.4)	0.01
2017	18,283 (49.6)	6,336 (54.2)		6,286 (54.4)	6,270 (54.2)	
2018	8,010 (21.7)	3,101 (26.5)		2,996 (25.9)	3,046 (26.3)	
Charlson comorbidity index						
0	1,521 (4.1)	473 (4.1)	0.03	469 (4.1)	468 (4.1)	0.004
1	3,361 (9.1)	1,144 (9.8)		1,150 (10)	1,138 (9.8)	
2	4,937 (13.4)	1,644 (14.1)		1,634 (14.1)	1,629 (14.1)	
3	27,042 (73.4)	8,423 (72.1)		8,310 (71.9)	8,328 (72)	
CV risk factor						
CAD	32,597 (88.4)	10,817 (92.6)	0.1	10,657 (92.2)	10,699 (92.5)	0.01
Multi vessel CAD	16,230 (44)	6,161 (52.7)	0.2	5,944 (51.4)	6,056 (52.4)	0.02
MI	1920 (5.2)	911 (7.8)	0.1	836 (7.2)	877 (7.6)	0.01
CABG	7,665 (20.8)	3,341 (28.6)	0.2	3,195 (27.6)	3,264 (28.2)	0.01
Stroke	5,299 (14.4)	1,062 (9.1)	−0.2	1,030 (8.9)	1,057 (9.1)	0.008
PAD	2,376 (6.5)	666 (5.7)	−0.03	687 (5.9)	661 (5.7)	−0.010
DM circulation	4,921 (13.4)	1802 (15.4)	0.06	1760 (15.2)	1775 (15.4)	0.004
DM foot	3 (0.0)	4 (0.0)	0.02	3 (0.0)	1 (0.0)	−0.01
DM nephropathy	2,365 (6.4)	1,009 (8.6)	0.08	965 (8.4)	985 (8.5)	0.006
DM neuropathy	5,274 (14.3)	1,591 (13.6)	−0.02	1,620 (14)	1,574 (13.6)	−0.01
DM other Complications	27,326 (74.1)	8,353 (71.5)	−0.06	8,288 (71.7)	8,287 (71.7)	0.000
Hyperglycemia	694 (1.9)	159 (1.4)	−0.04	160 (1.4)	154 (1.3)	−0.005
Comorbidities						
Hypertension	28,872 (78.3)	9,208 (78.8)	0.01	9,095 (78.7)	9,108 (78.8)	0.003
Edema	3,490 (9.5)	1,066 (9.1)	−0.01	1,065 (9.2)	1,056 (9.1)	−0.003
Kidney stone	585 (1.6)	168 (1.4)	−0.01	189 (1.6)	167 (1.4)	−0.02
Osteoarthritis	13,169 (35.7)	3,580 (30.6)	−0.1	3,561 (30.8)	3,568 (30.9)	0.001
Other arthritis	9,104 (24.7)	2,570 (22)	−0.06	2,484 (21.5)	2,554 (22.1)	0.02
PUD	9,380 (25.5)	2,828 (24.2)	−0.03	2,733 (23.6)	2,796 (24.2)	0.01
Pancreatitis	342 (0.9)	103 (0.9)	0.00	105 (0.9)	102 (0.9)	−0.003
UC	59 (0.2)	12 (0.1)	−0.02	10 (0.1)	12 (0.1)	0.006
Crohn	15 (0.0)	5 (0.0)	0.00	5 (0.0)	5 (0.0)	0.000
Asthma	5,421 (14.7)	1,626 (13.9)	−0.02	1,596 (13.8)	1,602 (13.9)	0.002
COPD	1,349 (3.7)	296 (2.5)	−0.07	300 (2.6)	295 (2.6)	−0.003
Bladder stone	29 (0.1)	5 (0.0)	−0.01	5 (0.0)	5 (0.0)	0.000
Dementia	5,993 (16.3)	1,153 (9.9)	−0.2	1,141 (9.9)	1,150 (10)	0.003
Electrolyte Imbalance	2,353 (6.4)	608 (5.2)	−0.05	585 (5.1)	600 (5.2)	0.006
Glaucoma/Cataract	10,509 (28.5)	3,176 (27.2)	−0.03	3,127 (27)	3,152 (27.3)	0.005

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics.

Variables	Pre-Match			Post-Match		
HONK	285 (0.8)	64 (0.6)	−0.03	65 (0.6)	63 (0.5)	−0.002
HTN nephropathy	166 (0.5)	54 (0.5)	0.00	40 (0.4)	51 (0.4)	0.02
Hyperthyroid disease	704 (1.9)	225 (1.9)	0.00	226 (2)	224 (1.9)	−0.001
Hypothyroid disease	1802 (4.9)	602 (5.2)	0.01	597 (5.2)	594 (5.1)	−0.001
Osteomyelitis	282 (0.8)	66 (0.6)	−0.02	56 (0.5)	66 (0.6)	0.01
Pneumonia	2,872 (7.8)	770 (6.6)	−0.05	749 (6.5)	763 (6.6)	0.005
Skin infection	1,438 (3.9)	459 (3.9)	0.00	459 (4)	455 (3.9)	−0.002
Glucose-lowering therapy						
Metformin	25,836 (70.1)	8,466 (72.5)	0.05	8,422 (72.8)	8,382 (72.5)	−0.008
Insulins	6,312 (17.1)	2,118 (18.1)	0.03	2098 (18.1)	2074 (17.9)	−0.005
SUs	16,898 (45.8)	5,499 (47.1)	0.02	5,428 (46.9)	5,441 (47.1)	0.002
Glitazones	3,280 (8.9)	1,328 (11.4)	0.08	1,309 (11.3)	1,301 (11.3)	−0.002
GLP-1 agonists	112 (0.3)	81 (0.7)	0.06	78 (0.7)	74 (0.6)	−0.004
AGIs	1,532 (4.2)	364 (3.1)	−0.06	366 (3.2)	362 (3.1)	−0.002
Meglitinides	253 (0.7)	85 (0.7)	0.00	83 (0.7)	82 (0.7)	−0.001
Co-medications						
Anticoagulants	1,650 (4.5)	564 (4.8)	0.02	523 (4.5)	550 (4.8)	0.01
Antiplatelets	24,499 (66.5)	8,232 (70.5)	0.09	8,111 (70.2)	8,141 (70.4)	0.006
Heparins	1,287 (3.5)	354 (3)	−0.03	338 (2.9)	352 (3)	0.007
Thrombolytics	58 (0.2)	10 (0.1)	−0.02	7 (0.1)	10 (0.1)	0.01
Statins	25,978 (70.5)	9,459 (81)	0.3	9,287 (80.3)	9,343 (80.8)	0.01
Other lipid Lowerings	3,903 (10.6)	1,678 (14.4)	0.1	1,627 (14.1)	1,633 (14.1)	0.002
Nitrates	6,264 (17)	2,441 (20.9)	0.1	2,378 (20.6)	2,393 (20.7)	0.003
Digoxin	5,390 (14.6)	2,134 (18.3)	0.1	2060 (17.8)	2087 (18.1)	0.006
ACEIs	2,127 (5.8)	963 (8.2)	0.1	929 (8)	927 (8)	−0.001
ARBs	21,506 (58.3)	7,292 (62.4)	0.08	7,171 (62)	7,198 (62.3)	0.005
Entresto	6 (0)	17 (0.2)	0.05	6 (0.1)	8 (0.1)	0.007
Other Anti HTNs	24,131 (65.5)	8,132 (69.6)	0.09	8,017 (69.3)	8,025 (69.4)	0.002
Loop diuretics	4,310 (11.7)	1,364 (11.7)	0.00	1,292 (11.2)	1,327 (11.5)	0.01
Other diuretics	10,016 (27.2)	3,223 (27.6)	0.01	3,076 (26.6)	3,165 (27.4)	0.02
Antianxieties	14,982 (40.6)	4,215 (36.1)	−0.09	4,133 (35.7)	4,183 (36.2)	0.009
Antipsychotics	1800 (4.9)	302 (2.6)	−0.1	299 (2.6)	301 (2.6)	0.001
Antidepressants	6,667 (18.1)	1771 (15.2)	−0.08	1777 (15.4)	1759 (15.2)	−0.004
Dementia	5,993 (16.3)	1,153 (9.9)	−0.2	1,141 (9.9)	1,150 (10)	0.003
Antiparkinsons	1,139 (3.1)	179 (1.5)	−0.1	164 (1.4)	179 (1.6)	0.01
Anticonvulsants	934 (2.5)	186 (1.6)	−0.07	200 (1.7)	186 (1.6)	−0.01
NSAIDs	28,032 (76.1)	8,810 (75.4)	−0.02	8,757 (75.7)	8,733 (75.5)	−0.005
Bisphos-phonates	1765 (4.8)	373 (3.2)	−0.08	379 (3.3)	371 (3.2)	−0.004
Opioids	16,376 (44.4)	4,778 (40.9)	−0.07	4,720 (40.8)	4,732 (40.9)	0.002

Values are represented as mean ± standard deviation or number (%); ACEis, angiotensin-converting enzyme inhibitors; AGIs, α-glucosidase Inhibitors; ARBs, angiotensin II, receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; HONK, hyperglycaemic hyperosmolar nonketotic coma; HTN, hypertensive; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral artery disease; PUD, peptic ulcer disease; STD, standardized difference; SUs, sulfonylureas; UC, ulcerative colitis.

Comparison of baseline characteristics between RCT and RWE

A lower proportion of men and a lower mean age were observed in our RWE cohort than in the corresponding RCT. (Table 2). Compared to the RCT, the RWE cohort was more often diagnosed with coronary artery disease (including coronary revascularization) and had fewer MIs, strokes, and peripheral artery disease. Rates of patients receiving glucose-lowering therapies were generally similar between the RCT and the RWE, except for the use of insulin. However, the proportions of patients who have been more than 5 years since their diagnosis of T2DM were 82.0 and 6.0% in RCT and RWE, respectively (p-value < 0.001).

TABLE 2 Comparison of baseline characteristics between RCT and RWE.

Characteristics	EMPA-REG outcome® (RCT)		EMPA-REG Duplicate (RWE)	
	Placebo N = 2,333	Empagliflozin N = 4,687	Sitagliptin N = 11,563	Empagliflozin N = 11,563
Age	63.2 ± 8.8	63.1 ± 8.6	55.5 ± 11.3	55.6 ± 10.9
Male—no. (%)	1,680 (72.0)	3,336 (71.2)	6,799 (58.8)	6,829 (59.1)
CV risk factor				
Coronary artery disease	1763 (75.6)	3,545 (75.6)	10,657 (92.2)	10,699 (92.5)
Multi-vessel coronary artery disease	1,100 (47.1)	2,179 (46.5)	5,944 (51.4)	6,056 (52.4)
History of myocardial infarction	1,083 (46.4)	2,190 (46.7)	836 (7.2)	877 (7.6)
Coronary artery bypass graft	563 (24.1)	1,175 (25.1)	3,195 (27.6)	3,264 (28.2)
History of stroke	553 (23.7)	1,084 (23.1)	1,030 (8.9)	1,057 (9.1)
Peripheral artery disease	479 (20.5)	982 (21.0)	687 (5.9)	661 (5.7)
Glucose-lowering therapy				
Metformin	1734 (74.3)	3,459 (73.8)	8,422 (72.8)	8,382 (72.5)
Insulin	1,135 (48.6)	2,252 (48.0)	2098 (18.1)	2074 (17.9)
Sulfonylurea	992 (42.5)	2014 (43.0)	5,428 (46.9)	5,441 (47.1)
Thiazolidinedione	101 (4.3)	198 (4.2)	1,309 (11.3)	1,301 (11.3)
Glucagon-like peptide-1 agonist	70 (3.0)	126 (2.7)	78 (0.7)	74 (0.6)
Time since diagnosis of type 2 diabetes				
≤1 year	52 (2.2)	128 (2.7)	5,043 (43.6)	5,008 (43.3)
>1 to 5 years	371 (15.9)	712 (15.2)	5,827 (50.4)	5,866 (50.7)
>5 years	1910 (81.9)	3,847 (82.1)	693 (6.0)	689 (6.0)
Anti-hypertensives	2,221 (95.2)	4,446 (94.9)	9,625 (83.2)	9,685 (83.8)
Diuretics	988 (42.3)	2047 (43.7)	3,689 (31.9)	3,698 (32.0)
Lipid-lowering	1864 (79.9)	3,820 (81.5)	9,616 (83.2)	9,655 (83.5)
Anti-coagulants	2090 (89.6)	4,162 (88.8)	8,351 (72.2)	8,422 (72.8)

Values are represented as mean ± standard deviation or number (%); CV, cardiovascular; RCT, randomized clinical trial; RWE, real-world evidence.

RCT-RWE agreement on cardiovascular outcomes

From the results of RWE, empagliflozin was associated with a significantly decreased risk of MACEs (HR 0.87, 95% CI 0.79–0.96), all-cause mortality (HR 0.78, 95% CI 0.67–0.91), and heart failure (HR 0.85, 95% CI 0.75–0.95) comparing to sitagliptin (Table 3). MI, stroke, hospitalization for unstable angina, coronary revascularization, and transient ischemic attack were not significantly associated with empagliflozin use. As mentioned above, empagliflozin was related to a significantly decreased risk of MACEs [EMPA-REG DUPLICATE RWE: adjusted HR 0.87, 95% confidence interval (CI) 0.79–0.96]. The predifined estimate agreement, regulatory agreement, and standardized difference for RCT duplication were achieved (Figure 2) [EMPA-REG OUTCOME RCT: adjusted HR 0.86, 95% (CI) 0.74–0.99]. All of the eight cardiovascular outcomes except stroke achieved three agreements (RA/EA/SD) (point estimate HR in RCT and RWE = 0.86:0.87 [MACEs], 0.68:0.78 [all-cause death], 0.87:0.91 [MI], 0.99:0.94 [hospitalization for unstable angina], 0.86:0.94 [coronary revascularization], 0.85: 0.88 [transient ischemic attack], and 0.65: 0.85 [hospitalization for heart failure]). For stroke, the HR estimate of RWE 0.89 was in the opposite direction to that of RCT (disagreement of RA [point estimate HR of RCT: 1.18]), and two of three agreements (EA/SD) were achieved.

RCT-RWE agreement of safety outcomes

For safety outcomes from RWE, empagliflozin was associated with lowered risk of hypoglycemia (OR 0.70, 95% CI 0.59–0.84), UTI (OR 0.87, 95% CI 0.81–0.94), AKI (OR 0.70, 95% CI 0.59–0.82), and volume depletion (OR 0.84, 95% CI 0.76–0.94) comparing to sitagliptin. Alternatively, the risk of genital infections significantly increased (OR 1.49, 95% CI 1.35–1.65) compared to sitagliptin. No significant associations were identified in DKA, thromboembolic event, and fracture (Table 4).

TABLE 3 RCT-RWE agreements for MACEs and each cardiovascular outcome component.

Outcomes	EMPA-REG Outcome® (RCT)		EMPA-REG Duplicate (RWE)		STD	Agreement		
	Rate/1,000 Patient-yr	HR (95%CI)	Rate/1,000 Patient-yr	HR (95%CI)		RA	EA	SD
MACEs								
Sitagliptin	43.9	0.86 (0.74–0.99)	25.5	0.87 (0.79–0.96)	0.1	Y	Y	Y
Empagliflozin	37.4		22.5					
All-cause death								
Sitagliptin	28.6	0.68 (0.57–0.82)	12.0	0.78 (0.67–0.91)	1.0	Y	Y	Y
Empagliflozin	19.4		9.5					
Myocardial infarction								
Sitagliptin	19.3	0.87 (0.70–1.09)	8.7	0.91 (0.76–1.08)	0.3	Y	Y	Y
Empagliflozin	16.8		7.9					
Stroke								
Sitagliptin	10.5	1.18 (0.89–1.56)	9.1	0.89 (0.75–1.05)	−1.7	N	Y	Y
Empagliflozin	12.3		8.2					
Hospitalization for unstable angina								
Sitagliptin	10.0	0.99 (0.74–1.34)	50.5	0.94 (0.88–1.01)	−0.3	Y	Y	Y
Empagliflozin	10.0		48.1					
Coronary revascularization								
Sitagliptin	29.1	0.86 (0.72–1.04)	36.9	0.94 (0.87–1.02)	0.8	Y	Y	Y
Empagliflozin	25.1		35.2					
Transient ischemic attack								
Sitagliptin	3.5	0.85 (0.51–1.42)	9.2	0.88 (0.74–1.04)	0.1	Y	Y	Y
Empagliflozin	2.9		8.0					
Hospitalization for heart failure								
Sitagliptin	14.5	0.65 (0.50–0.85)	20.5	0.85 (0.75–0.95)	1.8	Y	Y	Y
Empagliflozin	9.4		17.4					

EA, estimate agreement; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; RA, regulatory agreement; RCT, randomized clinical trial; RWE, real-world evidence; SD, standardized difference; STD, standardized difference; Y, yes; N, no.

In regulatory agreement, empagliflozin showed significantly lowered risk in RWE, whereas the RCT reported a non-significant effect on the hypoglycemic adverse event, UTI, and volume depletion. An estimate agreement was achieved for 6 of the 8 emulations, with the exception of a hypoglycemic adverse event (OR: 0.70) and genital infections (OR: 1.49) where the emulation estimates were below the lower 95% CI bound from the RCT (OR: 1.00; 95% CI: 0.89–1.11 and OR: 3.74; 95% CI: 2.70–5.19 for hypoglycemic adverse event and genital infection, respectively). Statistically significant disagreements in SDs were shown (SD: −3.3 and −5.3 for hypoglycemic adverse event and genital infections, respectively).

Sensitivity analyses

After follow-up of patients who received at least one dose of study drugs until ≤30 days after the last intake of medication, similar results (HR for MACEs: 0.88; 95% CI: 0.77–0.99) were obtained (Supplementary Table S14). Additional sensitivity analysis (including patients who received study drugs for ≥30 days including only events that occurred ≤30 days after a patient's last intake of medications) did not produce meaningful changes in the study findings (HR for MACEs: 0.87; 95% CI: 0.79–0.96) (Supplementary Table S15). All three agreements remained 'Y' for MACEs in both sensitivity analyses. In the same sensitivity analyses for eight safety outcomes, at least two of the three agreements were achieved in six safety outcomes (UTI, AKI, volume depletion, DKA, thromboembolic event, and fracture) (Supplementary Tables S16, S17). The hypoglycemic adverse event and genital infections still failed to show sufficient agreements, as in the main analysis.

Discussion

Our study analyzed patients with high cardiovascular disease risks that were prescribed empagliflozin or sitagliptin for

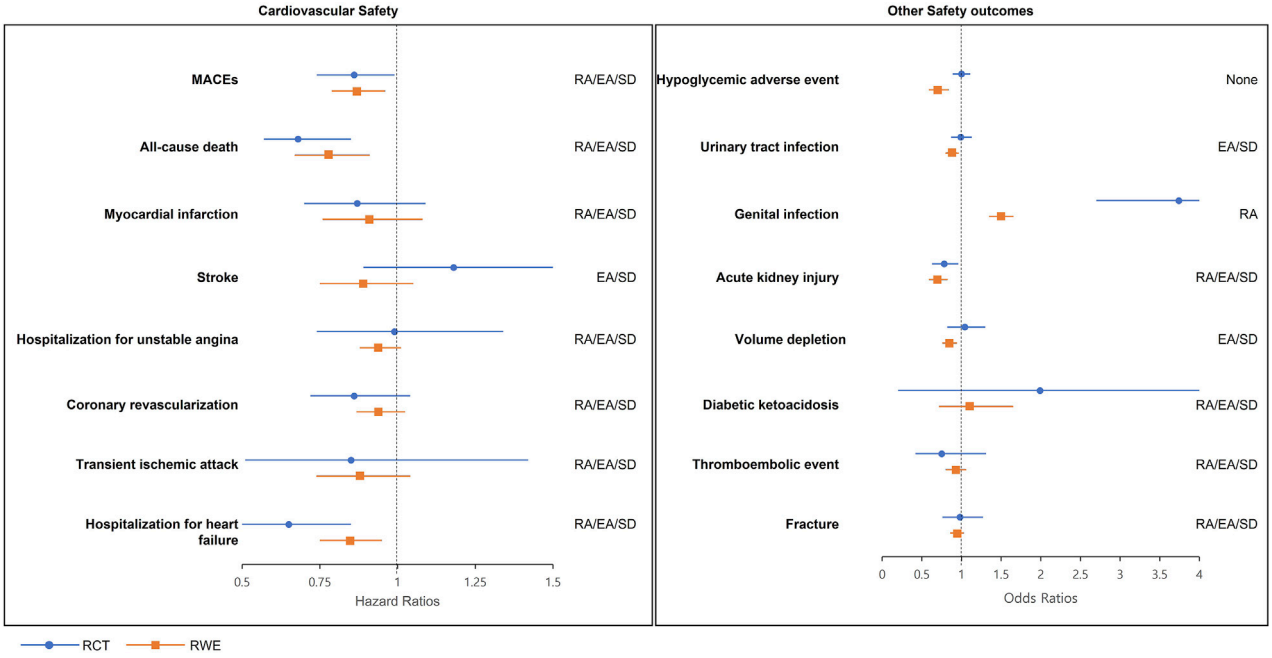

FIGURE 2
RCT-RWE agreements plots. EA, estimate agreement; MACEs, major adverse cardiovascular events; RA, regulatory agreement; RCT, randomized clinical trial; RWE, real-world evidence; SD, standardized difference.

emulation of a pre-existing RCT. The primary objective of the study was to evaluate to what extent the safety of empagliflozin from the RWE study in Korea is different from the one in RCT by emulating the design of foreign RCT. This study emulated the cardiovascular outcomes including other safety outcomes of the EMPA-REG OUTCOME RCT in Korea. According to pre-specified agreement standards, successful agreements were achieved in cardiovascular disease including MACEs. For all outcomes, 14 of the 16 RCT outcomes including safety outcomes were successfully reproduced (graded as "good" or "moderate"). Our study results suggested that RWE can emulate RCT results satisfactorily and have the potential for providing evidence for future regulatory decision-making when RCT evidence is not available in Korea.

As shown in other studies, one must always keep in mind that some discrepancies may occur due to differences in study samples, study designs, or statistical methods. To date, various RWE studies have reported on the safety of SGLT-2 inhibitors including empagliflozin. There were discrepancies between findings, for example, the beneficial effect of SGLT-inhibitors on MACEs has been reported (Persson et al., 2018; Filion et al., 2020; Dave et al., 2021). However, two other studies have reported non-significant results in MACEs (Norhammar et al., 2019; Jeon et al., 2021). In other safety outcomes, Lega *et al.* reported a decreased risk of UTIs (Lega et al., 2019), while another study reported an association with an increased risk of UTI (Han et al., 2021). SGLT2 inhibitor use was associated with an elevated DKA risk (Wang et al., 2019); however, this study was not in Korea (Kim et al., 2018). We found both adverse (Ueda et al., 2018) and beneficial (Toulis et al., 2018) effects on fracture, although most results were non-significant. Most studies have reported decreased risks of SGLT2 inhibitors on AKI or impairment in renal function (Nadkarni et al., 2017; Cahn et al., 2019; Heerspink et al., 2020; Koh et al., 2021). Therefore, our study focused on emulating an existing RCT design and thereby confirming that the same results can be obtained from RWE. We have demonstrated SGLT-2 inhibitors' associations with decreased cardiovascular outcomes including reducing MACEs and heart failure. Our results were consistent with the results of the target trial, and other studies including RCTs [MACEs (Mascolo et al., 2021) and heart failure (Kramer et al., 2010; Mascolo et al., 2021; Requena-Ibanez et al., 2021; Santos-Gallego et al., 2021; Ferreira et al., 2022; Neuen et al., 2022; Requena-Ibanez et al., 2022; Sauer, 2022)] which show that SGLT could induce reverse cardiac remodeling and improving quality of life, and also reduce myocardial fibrosis.

However, despite the substantial effort, there were disagreements between the RCT and RWE in several outcomes. Stroke is a well-known disease that can be captured with a high accuracy because of its seriousness. The incidence rates were similar between RCT and RWE results. However, our study result suggested that empagliflozin was associated with a decreased risk of stroke (although not significant) unlike its non-significant increase in the RCT. Several meta-analyses including all trials do show reductions

TABLE 4 RCT-RWE agreement for each safety outcome.

Outcomes	EMPA-REG Outcome® (RCT)		EMPA-REG Duplicate (RWE)		STD	Agreement		
	Rate (%)	OR (95%CI)	Rate (%)	OR (95%CI)		RA	EA	SD
Hypoglycemic adverse event								
Sitagliptin	27.9	1.00 (0.89–1.11)	2.6	0.70 (0.59–0.84)	-3.3	N	N	N
Empagliflozin	27.8		1.9					
Urinary tract infection								
Sitagliptin	18.1	0.99 (0.87–1.13)	23.3	0.87 (0.81–0.94)	-1.7	N	Y	Y
Empagliflozin	18.0		20.9					
Genital infection								
Sitagliptin	1.8	3.74 (2.70–5.19)	7.9	1.49 (1.35–1.65)	-5.3	Y	N	N
Empagliflozin	6.4		11.4					
Acute kidney injury								
Sitagliptin	6.6	0.78 (0.63–0.96)	3.3	0.70 (0.59–0.82)	-0.8	Y	Y	Y
Empagliflozin	5.2		2.3					
Volume depletion								
Sitagliptin	4.9	1.04 (0.82–1.30)	7.1	0.84 (0.76–0.94)	-1.7	N	Y	Y
Empagliflozin	5.1		6.1					
Diabetic ketoacidosis								
Sitagliptin	0.04	1.99 (0.2–17.8)	0.38	1.09 (0.72–1.64)	-0.5	Y	Y	Y
Empagliflozin	0.1		0.42					
Thromboembolic event								
Sitagliptin	0.9	0.75 (0.42–1.31)	4.3	0.92 (0.80–1.05)	0.7	Y	Y	Y
Empagliflozin	0.6		3.9					
Fracture								
Sitagliptin	3.9	0.98 (0.76–1.27)	13.8	0.94 (0.87–1.03)	-0.3	Y	Y	Y
Empagliflozin	3.8		13.1					

EA, estimate agreement; HR, hazard ratio; CI, confidence interval; MACEs, major adverse cardiovascular events; RA, regulatory agreement; RCT, randomized clinical trial; RWE, real-world evidence; SD, standardized difference; STD, standardized difference; Y, yes; N, no.

in hemorrhagic stroke (Tsai et al., 2021) and in total stroke (Mascolo et al., 2021), which supports our results. Also, SGLT-2 inhibitors seem to reduce atrial fibrillation (Pandey et al., 2021), which can also explain the stroke protection. It seems reason for the discrepancy is not clear. Ethnic factors may have been involved because over 70% of patients were Caucasian, and only 20% were Asian in the RCT (Zinman et al., 2015). Asians are reported to have a lower risk of cardiovascular disease than other races (Jung et al., 2015). As this study was conducted on Koreans, the proportion of patients with a history of severe diseases such as MI or stroke was small at baseline, and the age and severity of diabetes (time since onset of T2DM) were also lower than those of the RCT. In the subgroup analysis reported by the RCT, empagliflozin was reported to have a HR of 0.88 and 1.48 for Caucasians and Blacks for MACEs respectively and 0.68 for Asians (Zinman et al., 2015). Another study showed the protective effect of the SGLT-2 inhibitors against stroke in Koreans (Han et al., 2021); therefore, racial factors may have influenced our findings.

Another hypothesis includes a possibility of physicians' reluctance to prescribe empagliflozin because of its known side effects. It has been reported that cardiologists may be reluctant to prescribe SGLT2 inhibitors due to concerns of adverse effects (Vardeny and Vaduganathan, 2019). Owing to incomplete knowledge of its benefits and/or risks (Das et al., 2018), concerns with SGLT2 inhibitors have led to decreased use in clinical practice (Vaduganathan et al., 2018). The drug approval date of empagliflozin was May 2016 in Korea, and physicians may have paid attention to prescription in the early stages of approval during the index period (2016–2018) of this study. Typically, patients tend not to use drugs when they are not in good health (Glynn et al., 2001) and this phenomenon can be observed in a study that reported excessively large protective effects on cardiovascular disease by using statins (Glynn et al., 2006). In the case of a new drug, this point should be taken into account because physicians often intend to prescribe the medication to a person who is expected to be relatively healthy and has a good prognosis. This trend is expected to be more prominent in outcomes such as stroke and genital infection in which the point estimate was reported as one or higher in RCTs. The HR point estimate of such an outcome in RWE is either reversed or

much lower than the value reported in the RCT. Stroke and genital infection showed HRs and ORs of 1.18 and 3.74 in the RCT, and 0.89 and 1.49 in our RWE study, respectively. Therefore, there is a possibility that undetected selection bias exists in our study.

In the hypoglycemic event, there was a >10-fold difference between the incidence in a RCT and that in RWE. The hypoglycemic event was less likely to be captured in real-world claim data, as shown in the event rates. Kim et al. reported that there is a possibility of underestimating the frequency of the hypoglycemic events when using HIRA data (Kim et al., 2016). Other studies share similar problems, showing the accuracy of diagnosis could be low owing to the nature of claims data because hypoglycemic events that can be self-treated do not need any medical management (Task Force Team for Basic Statistical Study of Korean Diabetes Mellitus of Korean Diabetes Association et al., 2013; Park et al., 2018). It appears that physicians in Korea consider hypoglycemic events to be temporary and do not often record a diagnostic code. Similarly, two observational studies in Korea showed low event rates of hypoglycemia (6.3%, self-reported outcome) (Hong et al., 2019), and 2.4 per 100 person-year (insurance claim data) (Han et al., 2021). The discrepancy in event rates could have led to the disagreement in treatment effect estimates. The event rate appears to be an important factor when conducting the RCT emulation study.

The intention-to-treat approach was applied in our study, and the median duration of observation time was 2.7 and 3.1 years in RWE and RCT studies, respectively. Adherence to medications in the RWE is often poor compared with the RCT (Freemantle et al., 2013), and the median duration of treatment was 1.7 (RWE) and 2.6 (RCT) years in this study. In sensitivity analysis, as-treatment analyses were performed to test whether our main outcome was affected by adherence. Similar results were obtained, and shorter duration of use for empagliflozin provided a benefit on several outcomes.

There are several limitations in our study. We tried to emulate as much of an RCT as possible, including inclusion and exclusion criteria, exposures, and results; however, because of the limitations of the healthcare database, accurate emulation was not possible. Our study is a retrospective cohort design and not all information is included in the HIRA data (e.g., lab results for blood glucose test, urine culture test, or body weight). Therefore, although we adjusted for all possible confounders, there still may be residual confounding factors present. There were regulatory disagreements in UTIs and volume depletion outcomes, indicating potential for residual confounding factors related to these outcomes. Additionally, note that unlike RCT, RWE cannot provide the exact cause and effect, and it could only show a significant association. The ultimate goal of our study was to utilize relevant RWE for regulatory decisions when no RCT evidence is available. The results of RCT and RWE are not always consistent. As mentioned above, event rates for testing specificity of outcome definition should be addressed. In addition, consideration of characteristics such as study participants, real-world clinical settings, and data availability might be important for enhancing the validity of study.

Our study results suggest that RWE emulating foreign RCT has the potential for providing evidence for future regulatory decision-making in an environment where RCT could not be performed. Further research is needed to determine whether RWE findings can be reliable evidence in various clinical settings or specific patient groups.

Data availability statement

The datasets presented in this article are not readily available because Viewing of data that shows all the records of a patient are difficult to share owing to the policy of the Korean National Health Insurance Service. It can only be viewed in anonymized form when analyzed. Therefore, if there is a request for original data, the statistical data obtained after the desired statistical processing on the server will be shared. Requests to access the datasets should be directed to National Health Insurance Service, nhiss. nhis.or.kr.

Ethics statement

The studies involving human participants were reviewed and approved by the Seoul National University (IRB No. E2101/001-003). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HJ contributed to the conception and design of the study, data acquisition, analysis and interpretation of results, drafted, and revised the manuscript. JO and I-WK contributed to the conception and design of the study, analysis and interpretation of results, and revised the manuscript.

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Conflict of interest

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

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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.2022.928121/full#supplementary-material

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Adverse reaction signals mining and hemorrhagic signals comparison of ticagrelor and clopidogrel: A pharmacovigilance study based on FAERS

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Background: Ticagrelor and clopidogrel are commonly used antiplatelet agents, and we conducted a pharmacovigilance analysis using the Food and Drug Administration Adverse Event Reporting System (FAERS) to provide a reference for safe and reasonable clinical use.

Methods: Data were collected in FAERS from 2012 Q1 to 2022 Q2 for data cleaning. We used system organ classes (SOCs) and prefer terms (PTs) from the Medical Dictionary of Regulatory Activity (MedDRA version 25.1). Adverse event reports were retrieved at the PT level. Adverse reaction (ADR) signals of ticagrelor and clopidogrel were mined by calculating reporting odds ratios (ROR), proportional reporting ratios (PRR), information component (IC) and empirical Bayesian geometric mean (EBGM). After that, further analysis of the hemorrhagic signals and their clinical information were performed.

Results: The number of ADR reports where the primary suspect (PS) drugs were 15,133 for ticagrelor and 23,860 for clopidogrel. Significant ADR signals were identified by the SOC analysis for ticagrelor including cardiac disorders (ROR 4.87, PRR 4.46), respiratory disorders (ROR 2.45, PRR 2.28), and vascular disorders (ROR 2.22, PRR 2.16). Clopidogrel included blood disorders (ROR 2.86, PRR 2.77), vascular disorders (ROR 2.71, PRR 2.61), and cardiac disorders (ROR 2.29, PRR 2.22). At the PT level, the more frequent ADR signals for ticagrelor were dyspnoea, contusion, and haemorrhage, while clopidogrel were gastrointestinal haemorrhage, anaemia, and drug interaction. The hemorrhagic signals of both were mainly focused on the SOC level of gastrointestinal disorders, injury disorders and vascular disorders and nervous system disorders. The death and life-threatening rate of ticagrelor was 7.76 percentage higher than that of clopidogrel.

Conclusion: Clinicians need to pay attention to not only common ADRs but also be alert to new ADR signals when choosing to use ticagrelor and clopidogrel.

This study provides a reference for the reasonable and safe clinical use of ticagrelor and clopidogrel.

KEYWORDS

ticagrelor, clopidogrel, FAERS, pharmacovigilance, adverse events, hemorrhagic signals

Introduction

Ticagrelor and clopidogrel are commonly used P2Y12 receptor inhibitors in clinical practice. In patients with acute coronary syndrome (ACS) and after percutaneous coronary intervention (PCI), dual antiplatelet therapy with aspirin combined with one of these is the basis of antithrombotic therapy. The mechanism differs between the two, with ticagrelor exerting its antiplatelet effect by reversibly and non-competitively directly inhibiting the P2Y12 receptor and limiting the ADP-mediated conversion of glycoprotein IIb/IIIa to the activated form (Capodanno et al., 2010). Clopidogrel, on the other hand, irreversibly blocks the P2Y12 receptor, thereby exerting its antiplatelet effect (Hollopeter et al., 2001).

Ticagrelor was approved for marketing by the U.S. Food and Drug Administration (FDA) on 20 July 2011, and clopidogrel was approved for marketing in June 1998, and ADRs were gradually reported during the clinical application of both drugs. Common adverse effects of ticagrelor include bradycardia and AV block, dyspnea, and risk of bleeding (Gurbel et al., 2009; Goldberg et al., 2015; Scirica et al., 2018; Pujade et al., 2020; Escaned et al., 2021). Clopidogrel resistance occurs in approximately 30% of patients (Tantry et al., 2018; Ma et al., 2021). Common adverse reactions of clopidogrel are risk of bleeding, gastrointestinal complications, rash, fever and neutropenia (Doogue et al., 2005; Kang et al., 2015; Chan et al., 2019). A study that was based on FAERS database conducted by Serebruany VL et al. at the annual meeting of the European Society of Cardiology (ESC 2017) demonstrated significantly higher ticagrelor-related mortality than clopidogrel and prasugrel, which was not consistent with the results of previous PLATO study (Cannon et al., 2010). At the same time, due to the lack of sufficient evidence-based data on the efficacy and safety of ticagrelor and clopidogrel, there is still some confusion among clinicians regarding the choice of ticagrelor or clopidogrel.

In this study, the latest reported data from FAERS database were used to perform pharmacovigilance analysis of ticagrelor and clopidogrel to provide a reference for safe and reasonable clinical use.

Materials and methods

Data sources and procedures

The data for this study was obtained from the FAERS database of ADR reports from the first quarter of 2012 through the second quarter of 2022. The FEARS database is a publicly available database of self-reported ADRs from healthcare professionals, drug manufacturers, and patients in many countries around the world, with data updated quarterly (Zhai et al., 2019).

We imported all data into SQL Server 2019 to build the ADR database. To ensure that there was no duplicate data, we performed a two-step deduplication process (Omar et al., 2021). The data was first normalized and cleaned, and all duplicate rows were removed. After that, if the CASEID and FDA_DT were the same, deduplication was performed based on the latest FDA_DT (Hu et al., 2020). The ADRs with ROLE_COD listed as PS were further screened as the background basis for the whole study. The search terms for ticagrelor were BRILINTA, TICAGRELOR, BRILIQUE and AZD6140, and for clopidogrel were CLOPIDOGREL and PLAVIX.

ADRs were classified and described according to the PT and the SOC in the International MedDRA, version 25.1 (Peng et al., 2020).

Statistical analysis

ROR and PRR were used in the proportional imbalance method for data mining (Evans et al., 2001; van Puijenbroek et al., 2002). The larger the ROR and PRR were, the stronger the ADR signal was, indicating a stronger statistical relationship between the target drug and the target ADR. The ADR signals were significant if a ≥ 3, ROR or PRR ≥ 2.0 and 95% confidence interval (95% CI) value exceeds 1.0. To reduce false-positive ADR signals, we also used EBGM and IC to confirm the ADR signals we found (Bate et al., 1998; Szarfman et al., 2002; Karahoca, 2012). The equations and criteria for the four algorithms are shown in Table 1 (Shao et al., 2021; Zhou et al., 2021). We used R 4.2.1 software to perform the statistical analysis of the data.

TABLE 1 Summary of four algorithms used for signals detection.

Algorithms	Equation	Criteria
ROR	$ROR = ad/bc$	ROR ≥ 2
	$95\%\ CI = e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)0.5}$	95% CI > 1
PRR	$PRR = a\ (c + d)/(a + b)/c$	PRR ≥ 2
	$\chi^2 = [(ad-bc)2](a + b + c + d)/[(a + b)\ (c + d)\ (a + c)\ (b + d)]$	$\chi^2 \geq 4$
BCPNN	$IC = \log_2(a(a+b + c + d)/(a+b)/(a+c))$	IC025 > 0
	$IC025 = e^{\ln(IC)-1.96(1/a+1/b+1/c+1/d)0.5}$	
MGPS	$EBGM = a(a + b + c + d)/[(a+b)\ (a+c)]$	EBGM05 > 2
	$EBGM05 = e^{\ln(EBGM)\ -1.64(1/a+1/b+1/c+1/d)0.5}$	

Result

ADR reports and clinical information

Finally, we obtained 10252782 reports of PS drugs, and 15,133 and 23,860 ADRs of ticagrelor and clopidogrel, respectively. The clinical information of the two drugs are shown in Table 2. The proportion of male patients was slightly higher for ticagrelor (59.59%) than for clopidogrel (46.90%), but clopidogrel had a high value of missing sex (19.21%). Ticagrelor was mainly used in ACS, myocardial infarction and stent placement in patients with a median age of 67 years. Clopidogrel was primarily indicated for antiplatelet therapy, stent placement, and prophylaxis in patients with a median age of 72 years. The majority of patients in both were elderly patients between the ages of 65–84.

TABLE 2 ADE reports and clinical information.

	Ticagrelor	Clopidogrel
Total	15,133	23,860
Gender, n (%)		
Male	9,018 (59.59)	11,191 (46.90)
Female	5,272 (34.84)	8,085 (33.89)
Missing	843 (5.57)	4584 (19.21)
Age (years)		
Median (IQR)	67 (59-75)	72 (63–80)
<18	15 (0.10)	66 (0.28)
18–64	4267 (28.20)	5,037(21.11)
65–84	5,352 (35.36)	9,982 (41.84)
≥85	455 (3.01)	2,241 (9.39)
Missing	5,044 (33.33)	6,534 (27.38)
Outcome		
Death	1,883 (16.57)	2,578 (11.67)
Life-Threatening	1,241 (10.92)	1,935 (8.76)
Hospitalization	5,771 (50.79)	11,535 (52.20)
Disability	315(2.77)	764(3.46)
Indication		
Acute coronary syndrome	3,305 (27.86)	811 (4.09)
Myocardial infarction	2.018 (17.01)	687 (3.46)
Stent placement	1,764 (14.87)	1,210 (6.10
Antiplatelet therapy	202 (1.70)	1637 (8.25)
Prophylaxis	62 (0.52)	935 (4.71)

In addition, we also visualized the overall outcome metric data for ticagrelor and clopidogrel, as shown in Figure 1A. The overall lethality of ticagrelor (16.57%) was slightly higher than that of clopidogrel (11.67%), with a smaller difference in life-threatening, hospitalization and disability.

System organ classes disproportionality analysis

In the disproportionate analysis of SOCs, the significant signals for ticagrelor were cardiac disorders (ROR 4.87, PRR 4.46), respiratory disorders (ROR 2.45, PRR 2.28), and vascular disorders (ROR 2.22, PRR 2.16). Significant signals for clopidogrel were blood and lymphatic system disorders (ROR 2.86, PRR 2.77), vascular disorders (ROR 2.71, PRR 2.61), and cardiac disorders (ROR 2.29, PRR 2.22). As shown in Table 3, cardiac disorders and vascular disorders were common to both.

Adverse reaction frequency analysis

We performed a deeper analysis, the disproportionality analysis at the PT level. PTs related to ticagrelor and clopidogrel indications were removed from the analysis and ranked in descending order of the frequency and ROR of PTs. In Table 4, the top significant safety signals for ticagrelor and clopidogrel are shown separately, while we compared them with the adverse reactions spelled out in the drug instructions, using * to mark those not mentioned in the instructions. The 95% CI for ROR only shows the lower limit of the 95% two-sided CI of the ROR.

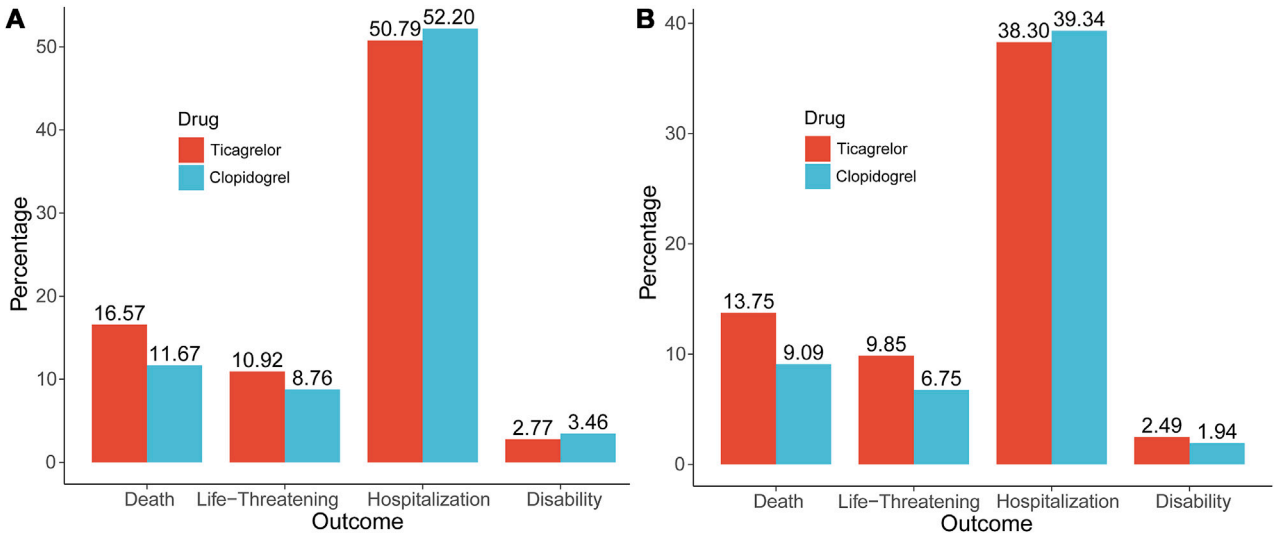

FIGURE 1
The Outcome indicators of ticagrelor and clopidogrel. **(A)** Overall outcome indicators; **(B)** Outcome indicators of hemorrhagic signals.

TABLE 3 Significant safety signals on the SOC level.

SOC	ROR (95%CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Ticagrelor				
Cardiac disorders	4.87 (4.72–5.02)	4.46 (12479.14)	2.15 (2.08)	4.44 (4.33)
Respiratory disorders	2.45 (2.38–2.52)	2.28 (3619.78)	1.19 (1.15)	2.28 (2.22)
Vascular disorders	2.22 (2.12–2.32)	2.16 (1247.42)	1.11 (1.06)	2.16 (2.08)
Clopidogrel				
Blood and lymphatic system disorders	2.86 (2.77–2.96)	2.77 (4120.12)	1.46 (1.41)	2.76 (2.68)
Vascular disorders	2.71 (2.63–2.79)	2.61 (4367.90)	1.38 (1.34)	2.60 (2.53)
Cardiac disorders	2.29(2.22–2.36)	2.22 (2880.23)	1.15 (1.11)	2.22 (2.16)

The frequent adverse safety signals for ticagrelor were dyspnoea, contusion, and haemorrhage, the largest ROR values were paroxysmal atrioventricular block, tooth pulp haemorrhage and cheyne-Stokes respiration. The adverse signals not mentioned in the instructions were intentional product misuse, paroxysmal atrioventricular block, tooth pulp haemorrhage, cheyne-Stokes respiration, sinus arrest, gastrointestinal vascular malformation, ventricle rupture, rhythm idioventricular, dressler's syndrome, sinoatrial block. The frequent adverse reaction signals of clopidogrel were gastrointestinal haemorrhage, anaemia and drug interaction. The signals of adverse reactions not mentioned in the instructions were preternatural anus, capillary fragility test, metallosis of globe, cullen's sign, orbital compartment syndrome, insulin autoimmune syndrome, multiple injuries, CYP2C19 polymorphism, oesophageal intramural haematoma and haemorrhagic thyroid cyst. The analysis of real-world study based on the FAERS database also provides great reference value for the revision of the instructions for ticagrelor and clopidogrel.

Comparison of hemorrhagic signals

The main effect of ticagrelor and clopidogrel were antiplatelet, and our deeper comparison assessed their significant adverse hemorrhagic signals. Ticagrelor had a total of 125 PT level hemorrhagic ADR signals, and clopidogrel had a total of 256, mainly focused on gastrointestinal disorders, injury disorders, nervous system disorders and vascular disorders. The overall incidence of bleeding events was slightly lower with ticagrelor than with clopidogrel (9.70% vs. 12.65%). Both

TABLE 4 Top significant signals on the PT level (*: The instruction does not mention).

PT	SOC	Freq	ROR (95%CI)	PRR (χ^2)
Ticagrelor (Sorted by frequency)				
Dyspnoea	Respiratory, thoracic and mediastinal disorders	2,359	5.96 (5.72)	5.69 (9132.68)
Contusion	Injury, poisoning and procedural complications	717	10.34 (9.60)	10.18 (5873.07)
Haemorrhage	Vascular disorders	488	7.20 (6.58)	7.12 (2550.54)
Intentional product misuse*	Injury, poisoning and procedural complications	421	5.10 (4.63)	5.06 (1356.83)
Anaemia	Blood and lymphatic system disorders	417	7.44 (6.75)	7.38 (2279.22)
Product use issue	Injury, poisoning and procedural complications	379	2.60 (2.35)	2.58 (367.69)
Gastrointestinal haemorrhage	Gastrointestinal disorders	369	5.43 (4.90)	5.391312.01)
Blood pressure increased	Investigations	256	2.33 (2.06)	2.32 (192.68)
Ticagrelor (Sorted by frequency) Dyspnoea	Respiratory, thoracic and mediastinal disorders	2,359	5.96 (5.72)	5.69 (9132.68)
Cerebral haemorrhage	Nervous system disorders	240	9.20 (8.10)	9.15 (1723.77)
Haemoglobin decreased	Investigations	228	3.07 (2.69)	3.06 (316.28)
Clopidogrel				
Gastrointestinal haemorrhage	Gastrointestinal disorders	3162	27.58 (26.59)	26.50 (73189.45)
Anaemia	Blood and lymphatic system disorders	1622	6.29 (5.99)	6.18 (6959.36)
Drug interaction	General disorders and administration site conditions	1239	6.39 (6.04)	6.30 (5459.49)
Cerebral haemorrhage	Nervous system disorders	1134	24.94 (23.48)	24.60 (24293.19)
Haemorrhage	Vascular disorders	1028	8.35 (7.85)	8.25 (6436.63)
Haematochezia	Gastrointestinal disorders	815	11.84 (11.04)	11.72 (7789.85)
Melaena	Gastrointestinal disorders	788	27.71 (25.78)	27.44 (18877.33)
Multiple injuries*	Injury, poisoning and procedural complications	681	242.68 (220.89)	240.57 (104118.10)
Rectal haemorrhage	Gastrointestinal disorders	678	11.82 (10.95)	11.72 (6479.08)
Epistaxis	Respiratory, thoracic and mediastinal disorders	666	6.45 (5.97)	6.41 (2997.94)
Ticagrelor (Sorted by ROR)				
Paroxysmal atrioventricular block*	Cardiac disorders	3	139.19 (40.7)	139.18 (349.84)
Cheyne-Stokes respiration*	Respiratory, thoracic and mediastinal disorders	12	86.06 (47.40)	86.04 (909.42)
Haemorrhage coronary artery	Cardiac disorders	3	65.73 (20.20)	65.73 (176.51)
Sinus arrest*	Cardiac disorders	59	64.72 (49.60)	64.63 (3416.23)
Gastrointestinal vascular malformation*	Gastrointestinal disorders	3	63.95 (19.70)	63.95 (171.95)
Ventricle rupture*	Cardiac disorders	4	55.35 (20.00)	55.35 (199.47)
Rhythm idioventricular*	Cardiac disorders	10	50.57 (26.60)	50.56 (456.52)
Dressler's syndrome*	Cardiac disorders	4	50.08 (18.20)	50.08 (180.90)
Sinoatrial block*	Cardiac disorders	16	44.93 (27.10)	44.91 (649.89)
Clopidogrel				
Preternatural anus*	Congenital, familial and genetic disorders	9	965.82 (297.42)	965.71 (2668.74)
Capillary fragility test*	Investigations	7	429.24 (150.56)	429.20 (1495.22)
Metallosis of globe*	Injury, poisoning and procedural complications	3	429.22 (86.63)	429.20 (640.81)
Cullen's sign*	Skin and subcutaneous tissue disorders	6	257.54 (93.60)	257.52 (958.22)
Orbital compartment syndrome*	Eye disorders	7	250.39 (98.58)	250.37 (1098.07)
Insulin autoimmune syndrome*	Immune system disorders	54	246.73 (176.54)	246.56 (8388.07)
Multiple injuries*	Injury, poisoning and procedural complications	681	242.68 (220.89)	240.57 (104118.10)
CYP2C19 polymorphism*	Congenital, familial and genetic disorders	5	238.46 (79.91)	238.45 (760.02)
Oesophageal intramural haematoma*	Gastrointestinal disorders	15	222.04 (119.04)	222.00 (2175.07)
Haemorrhagic thyroid cyst*	Endocrine disorders	3	214.61 (53.67)	214.60 (425.21)

gastrointestinal disorders and nervous system disorders dominated. As shown in Table 5, for a single SOC item we list the three PTs with the highest frequency. The most frequent of ticagrelor's gastrointestinal disorders were gastrointestinal haemorrhage, rectal haemorrhage and gastric ulcer, and those for clopidogrel were gastrointestinal haemorrhage,

TABLE 5 Major hemorrhagic signals.

SOC (n, %)	PT (Top 3)	ROR (95%CI)	PRR (χ^2)	IC (IC025)	EBGM (EBGM05)
Ticagrelor					
Gastrointestinal disorders (42, 33.60)	Gastrointestinal haemorrha	5.43 (4.90)	5.39 (1312.01)	2.42 (2.18)	5.36 (4.92)
	Rectal haemorrhage	3.96 (3.33)	3.95 (278.39)	1.98 (1.66)	3.93 (3.40)
	Gastric ulcer	8.34 (6.93)	8.34 (6.93)	8.34 (6.93)	8.34 (6.93)
Injury, poisoning and procedural complications (17, 13.60)	Contusion	10.34 (9.60)	10.18 (5873.07)	3.33 (3.09)	10.07 (9.46)
	Subdural haematoma	7.01 (5.63)	7.00 (413.23)	2.80 (2.25)	6.95 (5.79)
	Post procedural haemorrhage	5.96 (4.50)	5.95 (200.28)	2.56 (1.93)	5.91 (4.67)
Nervous system disorders (15, 12.00)	Cerebral haemorrhage	9.20 (8.10)	9.15 (1723.77)	3.18 (2.80)	9.06 (8.14)
	Haemorrhage intracranial	14.69 (12.50)	14.63 (1983.49)	3.85 (3.29)	14.39 (12.62)
	Haemorrhagic stroke	11.00 (8.69)	10.98 (626.67)	3.44 (2.72)	10.85 (8.91)
Vascular disorders (8, 6.40)	Haemorrhage	7.20 (6.58)	7.12 (2550.54)	2.82 (2.58)	7.07 (6.56)
	Haematoma	4.91 (4.02)	4.90 (299.73)	2.29 (1.88)	4.88 (4.13)
	Shock haemorrhagic	7.90 (5.94)	7.89 (285.92)	2.97 (2.23)	7.82 (6.16)
Clopidogrel					
Gastrointestinal disorders (69, 26.95)	Gastrointestinal haemorrhage	27.58 (26.59)	26.50 (73189.45)	26.50 (73189.45)	26.50 (73189.45)
	Haematochezia	11.84 (11.04)	11.84 (11.04)	11.84 (11.04)	11.84 (11.04)
	Melaena	27.71 (25.58)	27.44 (18877.33)	4.69 (4.36)	25.85 (24.33)
Injury, poisoning and procedural complications (35, 13.67)	Multiple injuries	242.68 (220.89)	240.57 (104118.13)	7.27 (6.62)	154.52 (142.82)
	Contusion	4.42 (4.07)	4.42 (4.07)	4.42 (4.07)	4.42 (4.07)
	Subdural haematoma	19.54 (17.67)	19.45 (6681.97)	4.22 (3.82)	18.65 (17.14)
Nervous system disorders (26, 10.16)	Cerebral haemorrhage	24.94 (23.48)	24.60 (24293.19)	4.54 (4.27)	23.32 (22.17)
	Haemorrhage intracranial	12.48 (10.99)	12.45 (2517.64)	3.60 (3.17)	12.13 (10.91)
	Hemiparesis	8.26 (7.15)	8.24 (1187.11)	3.02 (2.62)	8.11 (7.19)
Vascular disorders (19, 7.42)	Haemorrhage	8.35 (7.85)	8.25 (6436.63)	3.02 (2.84)	8.11 (7.70)
	Haematoma	13.38 (12.21)	13.31 (5212.45)	3.69 (3.37)	12.94 (11.98)
	Shock haemorrhagic	12.98 (10.98)	12.95 (1520.71)	3.66 (3.10)	12.60 (10.96)

haematochezia and melaena. Table 5 allows us to directly compare the strength of the hemorrhagic adverse reaction signals, and also greatly facilitates the comparison and deeper excavation of the major hemorrhagic adverse reaction signals of both.

After that, this study went deeper to compare the clinical information of the hemorrhagic signals, as shown in Table 6. In total, there were 3,640 patients with ticagrelor and 13,099 patients with clopidogrel. Regarding the gender of the patients, the number of males was much higher than that of females in both, but clopidogrel had a higher missing gender values, 22.03% vs. 4.12%. In terms of age, the median value of ticagrelor (68 years) was smaller than that of clopidogrel (73 years), and both drugs were used to treat the largest proportion of patients between 65 and 84 years. Ages from both also had large missing values, 27.67% for ticagrelor and 25.25% for clopidogrel.

We then counted the outcome indicators for all patients, as shown in Figure 1B, and the lethality rate was higher for ticagrelor (13.75%) than for clopidogrel (9.09%), with a difference of 4.66% points. The life-threatening rate was also higher for ticagrelor (9.85%) than for clopidogrel (6.75%), with a difference of 3.10% points. The difference between the two hospitalization rates (38.30% vs. 39.34%), was not much. Death and life-threatening events were the more serious adverse outcome events, and ticagrelor was 7.76% points higher than clopidogrel.

Disscussion

Based on data from the FAERS database from 2012Q1 to 2022Q2 quarters, the study used ROR and PRR as the primary assays, IC and EBGM as confirmation methods to perform a pharmacovigilance analysis of ticagrelor and clopidogrel to provide a reference for safe and reasonable clinical use of the drugs. ADR signals and hemorrhagic events provided the real-world based reference value.

For ticagrelor and clopidogrel, it is also important to understand the clinical application scenarios for which they

are better suited. In patients with acute myocardial infarction, ticagrelor was significantly more effective than clopidogrel (p <0.05), and the incidence of ADR was significantly lower than that of clopidogrel (p <0.05). The effect of ticagrelor on acute myocardial infarction patients is significantly better than clopidogrel, and has higher safety (Ma et al., 2020). Ticagrelor has beneficial effects in clinical application, while it has a higher incidence of dyspnoea and major bleeding compared to clopidogrel (Steiner et al., 2013).

In this study, we concluded that the overall mortality of ticagrelor was higher than that of clopidogrel (16.57% vs. 11.67%), which is not consistent with previous research. For patients with ACS, the proportion of death and life-threatening events with ticagrelor was more than with clopidogrel (25.54% vs. 22.28%). For patients with stent placement, the proportion of death and life-threatening events with ticagrelor was less than with clopidogrel (11.61% vs. 14.21%). For patients with myocardial infarction, the proportion of death and life-threatening events with ticagrelor was lower than with clopidogrel (19.62% vs. 21.91%). The choice of ticagrelor or clopidogrel in different clinical scenarios can reduce the incidence of death and life-threatening events to a certain extent.

The FAERS database also has certain limitations, such as duplicate reporting, incomplete reporting, irregular reporting, and mixed reporting of indications and adverse reactions. We cleaned the collected data more thoroughly, so that the quality of the data obtained was more reliable and the analysis results were more accurate.

TABLE 6 Clinical information associated with hemorrhagic signals.

	Ticagrelor	Clopidogrel
Total	3640	13,099
Gender, n (%)		
Male	2153 (59.15)	6162 (47.04)
Female	1337 (36.73)	4052 (30.93)
Missing	150 (4.12)	2885 (22.03)
Age (years)		
Median (IQR)	68 (60–76)	73 (63–81)
<18	3 (0.08)	29 (0.22)
18–64	1001 (27.50)	2662 (20.32)
65–84	1471 (40.41)	5818 (44.42)
≥85	158 (4.34)	1445 (11.03)
Missing	1007 (27.67)	3145 (24.01)
Outcome		
Death	614 (13.75)	1,688 (9.09)
Life-Threatening	440 (9.85)	1,254 (6.75)
Hospitalization	1,710 (38.30)	7,303 (39.34)
Disability	111 (2.49)	361 (1.94)

System organ classes level analysis

In the disproportionate analysis of SOC levels, ticagrelor focused on cardiac disorders, respiratory disorders, and vascular disorders, which was in high agreement with the PLATO study in which the most common adverse effects in patients were dyspnea and haemorrhage (Cannon et al., 2010). The adverse effect of bradycardia in cardiac disorders has also been a cause of great alarm (Turgeon et al., 2015; Pujade et al., 2020). Clopidogrel focused mainly on blood and lymphatic system disorders, vascular disorders, and cardiac disorders, which was also in high agreement with the most common haemorrhage and hematologic abnormalities in the instructions (Kohriyama et al., 2014). In the SOC level analysis, cardiac disorders were somewhat biased because the applicable disorders were also grouped into PTs.

New adverse reaction signals

After obtaining the results of all PT level ADR signals for ticagrelor and clopidogrel, the signals were ranked according to their frequency and ROR, mainly focusing on gastrointestinal disorders. The higher the frequency was the more valuable is the excavation. After comparing with the drug instructions, it was found that both showed new ADR signals that were not mentioned in the instructions.

ADR signals not mentioned in the ticagrelor specification were intentional product misuse, paroxysmal atrioventricular block, tooth pulp haemorrhage, and Cheyne-Stokes respiration. The unmentioned intentional product misuse (ROR 5.10, PRR 5.06) and the mentioned product use issue (ROR 2.60, PRR 2.58) both suggested that the use of ticagrelor can be more problematic in patients, and if taken in strict accordance with medical advice, it may be possible to somewhat reduce the associated ADRs. ADR signals not mentioned in the clopidogrel instructions were multiple injuries, preternatural anus, capillary fragility test, metallosis of globe. Multiple injuries (ROR 242.68, PRR 240.57) had high frequency and strong signal and alert us to pay close attention to this adverse reaction while using clopidogrel.

Comparison of hemorrhagic signals and clinical information

A deeper analysis was a summary of all significant hemorrhagic signals for both. It can be seen that bleeding events of ticagrelor occurred mainly in the gastrointestinal tract (33.60%) and injury, procedural complications (13.60%) and clopidogrel mainly in the gastrointestinal tract (26.95%) and injury, procedural complications (13.67%). Two clinical information analyses were performed in this study. The

outcome events from the first clinical information are shown in Figure 1A, where ticagrelor was more lethal and more life-threatening than clopidogrel.

The second clinical information focused on all patients who experienced hemorrhagic adverse events because both drugs are antiplatelet agents and haemorrhage is their most common and predominant adverse effect. As shown in Figure 1B, the lethality and life-threatening rate of ticagrelor was 7.76% points higher than that of clopidogrel. The difference in hospitalization rates between the two was not much. By the above analysis, considering all significant hemorrhagic signals alone, ticagrelor produced higher rates of lethality and life-threatening events.

Conclusion

In this study, the FAERS database was used to perform the pharmacovigilance analysis of ticagrelor and clopidogrel, and the ADR signals at the SOC and PT levels were detected using the disproportionality method, provided some complementary ADR signals that are not mentioned in the instructions. Then by further analysis of hemorrhagic events, ticagrelor produced higher rates of lethality and life-threatening events. Clinicians need to be aware of not only common ADRs but also new ADR signals when choosing to use ticagrelor and clopidogrel. This study provides a reference for the reasonable and safe clinical use of ticagrelor and clopidogrel.

Data availability statement

The Publicly available datasets can be found here: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Author contributions

ST and XZ were responsible for the design of the whole study. ZW and LX were responsible for data acquisition and processing analysis. ST, XZ, and QW performed all data checking and review. ZW was responsible for drafting the article. All authors critically reviewed the manuscript, interpreted the results, and all approved the study.

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Conflict of interest

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

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LTT and HLA testing as diagnostic tools in Spanish vancomycin-induced DRESS cases: A case-control study

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe T-cell-mediated off-target adverse reaction. DRESS cases caused by vancomycin have often been reported. The HLA-A*32:01 allele has been associated with genetic susceptibility to vancomycin-induced DRESS in US citizens of European descent. We have analyzed the association of the HLA-A*32:01 allele in 14 Spanish DRESS cases in which vancomycin was suspected as the culprit drug, and the lymphocyte transformation test (LTT) as an *in vitro* assay to evaluate vancomycin sensitization. The results were compared to vancomycin-tolerant control donors. LTT was performed in 12 DRESS cases with PBMCs from resolution samples available and in a group of 12 tolerant donors. ROC curves determined that LTT is a suitable tool to identify patients sensitized to vancomycin (AUC = 0.9646; $p < 0.0001$). When a stimulation index >3 was regarded as a positive result, contingency tables determined 91% sensitivity, 91.67% specificity, 91% positive predictive value, and 91.67% negative predictive value ($p = 0.0001$, Fisher's exact test). The HLA A*32:01 allele was determined by an allele-specific PCR assay in 14 cases and 25 tolerant controls. Among the DRESS cases, five carriers were identified (35.7%), while it was detected in only one (4%) of the tolerant donors, [odds ratio (OR) = 13.33; 95% CI: 1.364–130.3; $p = 0.016$]. The strength of the association increased when only cases with positive LTT to vancomycin were considered (OR = 24.0; 95% CI: 2.28–252.6; $p = 4.0 \times 10^{-3}$). Our results confirm the association of the risk allele HLA-A*32:01 with vancomycin-induced DRESS in Spanish cases, and support LTT as a reliable tool to determine vancomycin sensitization.

KEYWORDS

drug hypersensitivity, DRESS, HLA, LTT, severe cutaneous adverse reactions, vancomycin, drug causality algorithm

Introduction

Adverse drug reactions are a frequent problem in clinical practice. Among them, skin reactions are observed in 2–3% of hospitalized patients, of which only 2–5% are considered severe (Gomes et al., 2019). Severe cutaneous adverse reactions (SCARs) are T-cell-mediated type IV hypersensitivity reactions. Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DiHS) are the conditions of serious concern as, albeit rare diseases, they carry significant morbidity and mortality rates.

In particular, DRESS/DiHS has a mortality rate between 2 and 10 percent (Chen et al., 2010; Cacoub et al., 2011; Kardaun et al., 2013). It typically develops 2–8 weeks after the initiation and continuous drug intake and presents with a variety of cutaneous manifestations, hematological abnormalities such as eosinophilia or atypical lymphocytes, adenopathy, fever, and involvement of one or more organs. The liver is the organ most frequently involved, with the kidneys being second. The heart, lung, pancreas, and central nervous system can also be affected in a small proportion of patients. Sequential reactivation of human herpesvirus (HHV) has been described, particularly HHV-6 and cytomegalovirus (CMV), and it is frequently associated with disease severity (Mizukawa et al., 2019; Shiohara and Mizukawa, 2019). Diagnosis can be challenging as not all the symptoms develop simultaneously (Stirton et al., 2022). The score classifications developed by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (JSCAR) (Shiohara et al., 2007; Shiohara and Kano, 2007) and the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group (Kardaun et al., 2007) are currently used for diagnosis. A few biomarkers such as soluble OX40 (Mitsui et al., 2022) and decreased frequencies of plasmacytoid dendritic cells (pDC) (Hsu et al., 2021) have been recently proposed for diagnosis and prognosis of HHV-6 reactivation.

Aromatic anticonvulsants, allopurinol, and sulfonamides such as sulfamethoxazole or sulfasalazine are common culprit drugs in DRESS cases. However, antimicrobials have also been repeatedly incriminated (Kardaun et al., 2013; Cabañas et al., 2014; Cabañas et al., 2018; Lee et al., 2022).

Pharmacogenetic studies have identified some HLA-I alleles as genetic risk factors for well-characterized type IV hypersensitivity reactions in relationship with certain drugs such as abacavir, carbamazepine, and allopurinol in selected populations, and genetic tests are being implemented to avoid their use and prevent severe reactions in patients at risk (Su et al., 2016; Kuruvilla et al., 2022; Wang et al., 2022); HLA-B*57:01 testing has been conducted prior to prescription in HIV patients (the prototypical case) due to its 100% negative predictive value (NPV) and 55% positive predictive value (PPV) to predict abacavir hypersensitivity (Phillips and Mallal, 2009). Nonetheless, there are no specific biomarkers available for most of the drugs inducing SCARs, and active research is being conducted to identify suitable biomarkers for common inducers of severe reactions.

Vancomycin is a glycopeptide antibiotic extensively used to treat infections caused by gram-positive microbes. It has been frequently reported as a causative agent in DRESS cases (Kardaun et al., 2007; Del Pozzo-Magaña et al., 2022; Madigan and Fox, 2019; Lin et al., 2014).

An analysis of HLA genotypes in North American patients of European descent presenting with vancomycin-associated DRESS identified *HLA-A*32:01* as a risk allele to develop this condition (Konvinse et al., 2019). Moreover, it was estimated that only 75 patients would need to be tested to prevent one case. These findings are of high interest for other European populations. As with other genetic associations, the findings would need to be replicated in independent cohorts.

Ascertaining a causative drug is mandatory in severe delayed drug hypersensitivity reactions, due to the high morbidity and mortality upon re-exposure to the culprit drug. However, such identification is often a difficult task, in particular when multiple medications are concomitantly used. Moreover, multiple drug sensitization, including sensitization to drugs introduced during the acute reaction, is frequent in DRESS cases (Gex-Collet et al., 2005; Barbaud et al., 2013). Clinical judgment is not always a reliable tool for drug causality assessment in DRESS. Algorithms such as the Naranjo score (Naranjo et al., 1981) have been developed as an alternative approach to determine the causality likelihood of drugs taken by a given patient (Macedo et al., 2006); however, no DRESS-specific algorithm has been developed yet.

The ENDA/EAACI Drug Allergy Interest Group advises that an LTT should be performed before *in vivo* tests in severe reactions with a suspected T-cell mechanism (Mayorga et al., 2016). Recent results from our group showed that LTT presented a sensitivity of 73% and a specificity of 82% in DRESS cases associated with a variety of drugs when the test was performed after recovery, using the algorithm of the Spanish

pharmacovigilance system (ALSEFV) as the gold standard to identify the culprit drugs (Cabañas et al., 2018).

The aim of this study is twofold: 1) to evaluate the usefulness of LTT to vancomycin to support drug causality assessment in DRESS cases in whom this was suspected to be the inducing agent; and 2) to estimate, in a Spanish-European population, the association HLA-A*32:01 with the risk of DRESS induced by vancomycin.

Methods

Vancomycin-induced DRESS cases and tolerant control subjects

Fourteen patients recorded in the Spanish registry PIEL*enRed* with a diagnosis of DRESS, in whom vancomycin was considered as the suspected inducing drug, and from which biological samples were available, were included in the study. The diagnosis was validated in all of them by an expert committee (blinded to medications) and classified as possible, probable, or definite cases (a score of two or more) using the DRESS scoring system proposed by RegiSCAR (Kardaun et al., 2014).

Drug causality was assessed using the algorithm of the Spanish pharmacovigilance system (ALSEFV) (Capellà and Laporte, 1993; Cabañas et al., 2018), as recommended by the Spanish guidelines for the management of DRESS (Cabañas et al., 2020). Vancomycin was considered to be related to the adverse reaction when it scored ≥4 in ALSEFV (corresponding to the categories "probable" or "very probable").

As controls, we selected 25 consecutive patients who completed the treatment with vancomycin without any sign of skin adverse reaction.

LTT assay

Lymphocyte transformation tests (LTT) were performed following standard procedures in order to confirm the culprit drug (Pichler and Tilch, 2004; Cabañas et al., 2018). The test was performed after the resolution of the clinical symptoms and at least 4 weeks after the end of steroid treatment. Briefly, peripheral blood mononuclear cells (PBMCs) were isolated from anti-coagulated whole blood, and triplicate cultures were established for six days in RPMI culture medium plus 5% autologous serum, in the presence or absence of increasing concentrations (10–200 μg/ml) of vancomycin. ^{3}H-thymidine (0.5 μCi/well) was added to the cultures 18 h before harvesting. Proliferation was estimated as ^{3}H-thymidine uptake measured in counts per minute (cpm), incorporated into DNA as assessed by liquid scintillation in a β counter (MicroBeta TriLux, Wallac, and PerkinElmer). A stimulation index (SI) was calculated as the ratio of mean cpm values between drug-stimulated and unstimulated cell cultures.

HLA typing

DNA samples were analyzed by HLA-A*32:01 allele-specific PCR (AS-PCR)/melting curve following the previously published protocol and primers (Rwandamuriye et al., 2019) with minor modifications. Internal control primers were used to amplify the housekeeping gene galactosylceramide (GALC) as described. Primers are shown in Supplementary Table S1. Briefly, the real-time PCR reaction contained 2 μl (100 ng) of total DNA, 1x SYBR Green Master mix (Quantimix Easy kit, Biotools), 250 nmol/L of each HLA-A*32 specific primer, and 50 nmol/L of each GALC primer in a 15 μl final volume. The PCR was performed in 96-well optical plates on a BioRad CFX96 qPCR machine (BioRad Laboratories), and results were analyzed using CFX Manager software (BioRad). In some experiments, amplification products were also visualized on a 1.5% agarose gel.

Preliminary experiments were performed in DNA samples that had previously undergone high-resolution, full allelic HLA typing in the settings of previous studies (Ramírez et al., 2017; Balas et al., 2020) with confirmation that HLA-A*32:01 was amplified only in those cases previously identified as carriers of the allele.

Statistical analysis

The quantitative data are described as mean and standard deviation, or median, interquartile range (IQR), minimum, and maximum. The qualitative data are described as frequency and percentage.

The nonparametric Mann–Whitney *U* test was applied to compare continuous variables. Fisher's exact test was used to compare the results of the LTT (positive/negative) in cases with the results in tolerant control donors. Sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) of LTT were calculated using 2 × 2 contingency tables. Receiver operating characteristic (ROC) curves were plotted using a nonparametric method to assess the diagnostic capacity of LTT to vancomycin.

Allele and population frequencies of HLA-A*32:01 were calculated. The association of DRESS with vancomycin exposure was assessed by calculating the odds ratio (OR) and its 95% confidence interval (CI). Fisher's exact test was used to assess the statistical significance of the differences found between the proportion of individuals carrying the HLA allele among cases and vancomycin-tolerant controls. A p-value of <0.05 (two-tailed) was considered statistically significant. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were computed using 2 × 2 contingency

TABLE 1 Demographics and main results in DRESS cases.

Case	Sex	Age	Ethnic origin	DRESS RegiSCAR score	DRESS RegiSCAR diagnostic	ALSEFV score of vancomycin causality	Time from reaction to LTT	Maximum SI in LTT	HLA-A*32:01 AS-PCR
P_1	Male	83	European	5	Probable	8	NA	NA	Negative
P_2	Female	73	European	7	Definite	4	14 months	31.44	Negative
P_3	Female	39	Mixed	4	Probable	2[a]	8 months	15.13	Negative
P_4	Male	88	European	3	Possible	4	33 days	5.54	Negative
P_5	Female	38	Mixed	3	Possible	4	49 days	9.71	Negative
P_6	Female	58	European	7	Definite	4	38 days[b]	11.97	Positive
P_7	Male	74	European	3	Possible	9	3 months	2.03	Negative
P_8	Female	30	European	4	Probable	5	NA	NA	Negative
P_9	Female	3	European	5	Probable	7	5 months	9.67	Positive
P_10	Male	32	European	6	Definite	4	3 months	3.94	Negative
P_11	Female	12	European	5	Probable	5	3 months	73.03	Positive
P_12	Female	6	European	4	Probable	5	19 months	3.25	Negative
P_13	Female	75	European	4	Probable	6	22 months	38.71	Positive
P_14	Male	6	European	2	Possible	5	84 days	9.87	Positive

NA, not available; AS-PCR, allele-specific PCR.
[a]Positive delayed intradermal test to vancomycin.
[b]Similar results were obtained two years and 10 years post-reaction.

tables. We estimated that the sample size of the study would provide a power ≥80% to detect an OR>5 with a type I error of 0.05.

Statistical analyses were performed using GraphPad Prism v 9.0 (La Jolla, CA, United States).

Ethical approval

The Research Ethics Committee of University Hospital "Príncipe de Asturias" granted approval for the whole PIELenREd registry and biological sample collection (code PER-MED-2010-01, date: 28 July 2010), under which the present study was carried out. All patients, cases, and controls alike, or their legal representatives provided specific written informed consent for the collection of both personal data and biological samples.

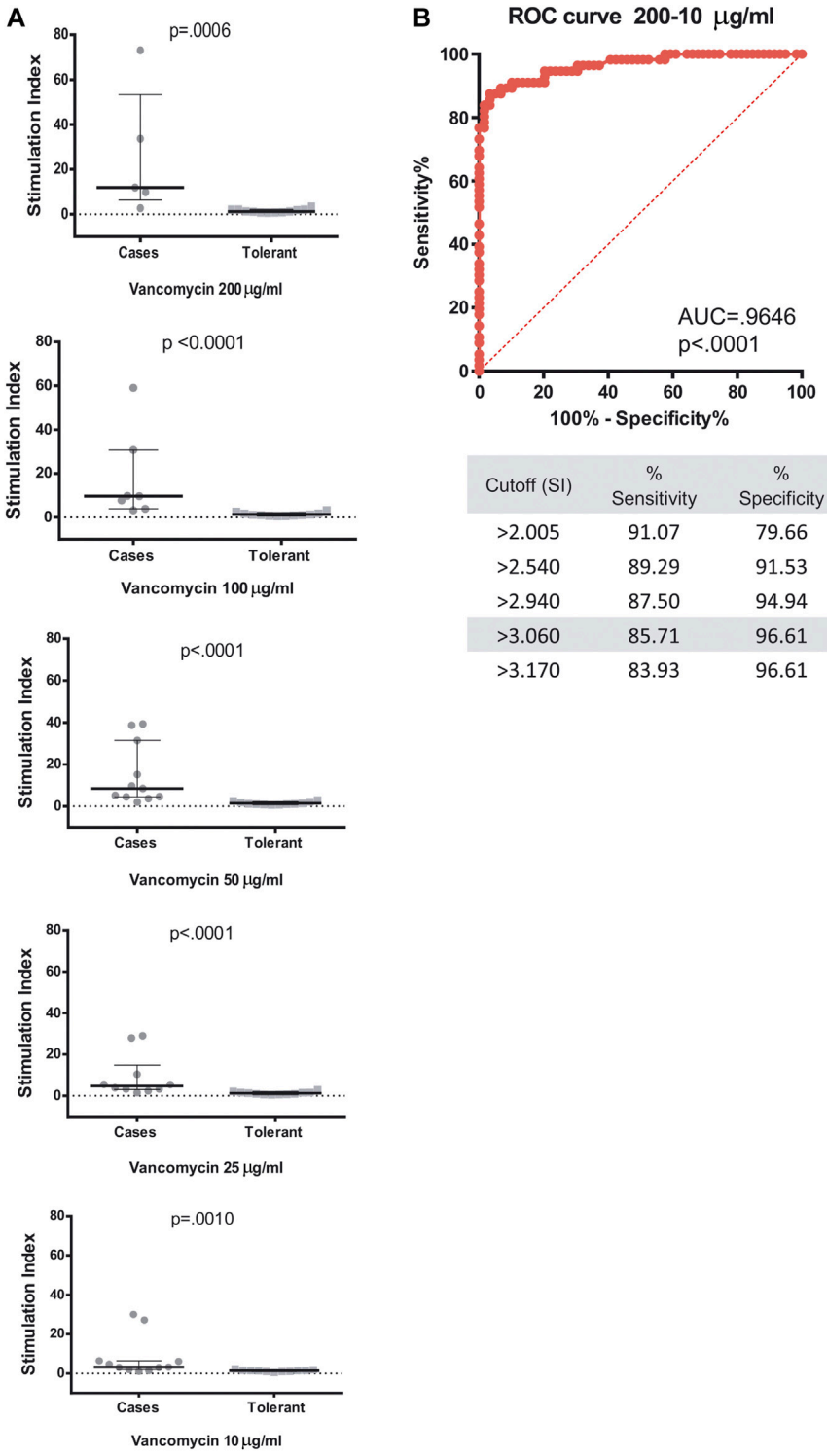
Results

Characteristics of patients and controls

Fourteen patients with DRESS associated with vancomycin exposure were included (four possible, seven probable, and three definite DRESS). Drug causality assessment using the ALSEFV identified vancomycin as the possible culprit (score 4–5) in nine cases, probable in two cases (score 6–7), and definite in two cases (score >8). We also included an additional case (P 3) in which ALSEFV scored low on the causal relationship with vancomycin (score = 2), but presented an intradermal test with a positive result in delay reading, thus confirming vancomycin sensitization. Ten (71.4%) were adults and four (28.6%) were children, with an overall median age of 38.5 years (range 3–88), while the median age of the adult population was 66.5 years (range 32–88); nine (64.3%) were women (Table 1). Twenty-five patients who completed the vancomycin treatment (mean exposure time: 14.4 ± 10.2 days) without any sign of skin adverse reaction were included as vancomycin-tolerant controls, with a median age of 64 years (range 28–78), and nine (36%) of them were women (Supplementary Table S2).

LTT as a diagnostic tool for vancomycin-induced DRESS

Out of 14 cases, we were able to perform the proliferation assays in 12 patients with DRESS attributable to vancomycin (11 with ALSEFV score ≥4 and one with a positive intradermal test). In the remaining two cases, no blood samples during the recovery phase were available (Table 1). LTT was performed in 12 vancomycin-tolerant controls from whom fresh blood samples could be obtained as well. Vancomycin-induced proliferation was tested in a range of five concentrations (10, 25, 50, 100, and 200 μg/ml). Statistically significant differences between cases and controls were found in the proliferative



Cutoff (SI)	% Sensitivity	% Specificity
>2.005	91.07	79.66
>2.540	89.29	91.53
>2.940	87.50	94.94
>3.060	85.71	96.61
>3.170	83.93	96.61

FIGURE 1
LTT results and ROC curve analysis of LTT to vancomycin. **(A)** PBMCs from 12 patients with a diagnostic of DRESS and vancomycin involvement or from 12 vancomycin-tolerant control donors were isolated and cultured *in vitro* with 10, 25, 50, 100, or 200 µg/ml of vancomycin. Stimulation indices were calculated as described in the methods section. Median and interquartile ranges are shown. Mann–Whitney *U* test was applied for statistical analysis. **(B)** ROC curve analysis, sensitivity, and specificity of grouped results for the five concentrations tested.

TABLE 2 Summary of sensitivity and specificity of LTT to vancomycin during the recovery phase of DRESS patients according to different cutoff points considered for positivity.

Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Fisher's exact test
SI ≥ 3	90.9	91.67	90.9	91.67	$p = 0.0001$
SI ≥ 2	100	58.33	68.75	100	$p = 0.0046$

response of lymphocytes at all concentrations (Figure 1A). ROC curves showed a good performance in all concentrations (Supplementary Figure S1). Overall, when results at all concentrations were analyzed together, LTT reached a sensitivity of 85.71% and a specificity of 96.61% when a stimulation index (SI) of >3.06 was considered for positivity (Figure 1B).

Contingency table analysis of LTT results from cases and controls revealed 90.9% sensitivity and 91.67 specificity when the cutoff point for positivity of SI was set at ≥ 3.0, with 90.9 % PPV and 91.67% negative predictive value (NPV). On the other hand, when the SI cutoff point was set at ≥ 2.0, sensitivity and NPV increased to 100%, but specificity decreased to 58.33% and PPV was 68.75% (Table 2 and Supplementary Table S3).

HLA associations with vancomycin-induced DRESS

To validate the AS-PCR HLA-A*32:01 typing assay (Rwandamuriye et al., 2019) in our laboratory, DNA from 43 donors previously genotyped for HLA-I alleles with high resolution in previous studies involving SCARs to anticonvulsants (Ramírez et al., 2017) or benznidazole (Balas et al., 2020) was tested using real-time PCR as described in the Methods section. Samples were identified as positive or negative based on the presence or absence of HLA-A*32:01-specific melt peaks and confirmed in agarose electrophoresis (Supplementary Figure S2). Only three samples from patients previously identified as carriers of the HLA-A*32:01 allele were accurately identified as positive, and all the remaining 40 donors were negative. HLA alleles previously identified in negative samples are listed in Supplementary Table S4. AS-PCR assays were subsequently performed in all 14 DRESS cases associated with vancomycin, to check for the presence of the risk HLA-A*32:01 allele. Five cases (35.7%) were identified as carriers. Interestingly, 75% (3/4) of pediatric cases were carriers of the risk allele, while it was identified in only 20% of adults (40% of adults if only probable or definite DRESS cases with positive LTTs are included). As a general population group for comparison, we considered a published group of 253 hematological Spanish donors with a population frequency of 9.5% carriers of the allele (Balas et al., 2011). The difference between the DRESS group and the general population group was statistically significant ($p = 0.011$; Fisher's exact test), representing an OR 5.30 (95% CI: 1.64–17.10).

The odds ratio was slightly higher (OR 6.36) when only DRESS cases with a probable or definite diagnosis (DRESS score ≥4) were considered in the analysis. When we restricted the analysis to the subset of eight cases with a DRESS score ≥4 and a SI ≥ 3 in LTT, the frequency of HLA-A*32:01 carriers rose to 50% and the OR increased to 9.54 as compared to the general population ($p = 0.0056$).

The presence of the risk HLA-A*32:01 allele was also investigated by AS-PCR assay in 25 vancomycin-tolerant control donors, being identified in only one of them (4%). When compared to such a tolerant group, the association between the risk allele and vancomycin-induced DRESS yielded an OR of 13.33 (95% CI: 1.36–130.30; $p = 0.016$), and was stronger when only cases with positive LTT (SI ≥ 3) were considered (OR 24.0; 95% CI: 2.28–252.60; $p = 0.0040$). Similar results were found when only probable or definite DRESS cases were included in the analysis (OR 24.0; 95% CI: 2.10–273.86; $p = 0.0076$) (Table 3).

Discussion

The main findings of the present case-control study are the following: 1) LTT as a diagnostic tool to identify vancomycin sensitization showed high sensitivity and specificity, as well as positive predictive and negative predictive values (all of them over 90%) when the cutoff point of SI for positivity was set at ≥ 3, using the ALSEFV drug causality algorithm as the gold standard; 2) the presence of HLA-A*32:01 allele was strongly associated with validated DRESS cases in whom vancomycin was suspected to be the culprit drug, when compared to both population controls and vancomycin-tolerant controls, confirming it as a relevant biomarker of susceptibility in a European-Spanish population.

SCARs are T-cell-mediated type IV hypersensitivity reactions that cannot be predicted based on the pharmacological characteristics of the drug alone, and are responsible for significant morbidity, mortality, and socioeconomic costs (Gomes and Demoly, 2005). The key to

TABLE 3 HLA-A*32:01 frequency in vancomycin-induced DRESS cases as compared to population controls and vancomycin-tolerant controls.

Population control

	HLA-A*32:01 allele frequency		OR (95% CI)	*p*-value[b]
	DRESS	General population[a]		
DRESS score ≥2	5/14 (35.7%)	24/253 (9.5%)	5.301 (1.643–17.102)	0.011
DRESS score ≥4	4/10 (40%)	24/253 (9.5%)	6.361 (1.677–24.129)	0.014
LTT vancomycin SI > 3				
DRESS Score ≥2	5/11 (45.45%)	24/253 (9.5%)	7.95 (2.257–28.022)	0.0033
DRESS score ≥4	4/8 (50%)	24/253 (9.5%)	9.54 (2.241–40.62)	0.0056

Vancomycin-tolerant control

	HLA-A*32:01 allele frequency		OR (95% CI)	*p*-value[b]
	DRESS	Vancomycin tolerant		
DRESS score ≥2	5/14 (35.7%)	1/25 (4.%)	13.33 (1.36–130.30)	0.016
DRESS score ≥4	4/10 (40%)	1/25 (4%)	16.0 (1.50–170.62)	0.017
LTT vancomycin SI > 3				
DRESS score ≥2	5/11 (45.45%)	1/25 (4%)	24.0 (2.28–252.60)	0.0040
DRESS score ≥4	4/8 (50%)	1/25 (4%)	24.0 (2.10–273.86)	0.0076

[a]From Balas et al. tissue antigens (2011).
[b]Fisher's exact test.

prevention from further exposure to the culprit drugs involves the correct identification of the causative drug through a combination of *in vitro* and/or *in vivo* tests (Alfirevic and Pirmohamed, 2017; Ardern-Jones and Mockenhaupt, 2019; Pirmohamed, 2019) and, therefore, allow patients to receive treatments that otherwise might not have been permitted in the future if the patient is labeled as being allergic. Rechallenge *in vivo* tests are contraindicated in DRESS cases. On the other hand, cutaneous tests have high specificity but low sensitivity. In this scenario, *in vitro* tests are recommended as a first approach to determine the culprit drugs (Mayorga et al., 2016). In a previous study, we found that *in vitro* LTT tests have good specificity and sensitivity in DRESS cases when performed upon resolution of the clinical symptoms (Cabañas et al., 2018). Nonetheless, vancomycin-specific LTT showed lower specificity, and previous reports had suggested non-specific induction of lymphocyte proliferation by vancomycin (Pichler and Tilch, 2004). In the present study, the ROC curve analysis in cases and vancomycin-tolerant controls confirmed the suitability of the LTT as a tool to evaluate vancomycin sensitization in DRESS cases, with good sensitivity, specificity, PPV, and NPV when a SI ≥ 3 is considered as the cutoff point. In our previous study, tolerant donors were not analyzed, and we used ALSEFV scores as standard and SI ≥ 2 as criteria for positivity, which results in lower specificity and PPV.

No specific algorithm has been developed for drug causality assessment in DRESS. The Naranjo score (Naranjo et al., 1981) has been classically used to evaluate adverse drug reactions. We have used the algorithm of the Spanish pharmacovigilance system (ALSEFV) as recommended by the Spanish guidelines for the management of DRESS (Cabañas et al., 2020). There are no data available on the specificity of the ALSEFV to accurately determine the culprit drugs; however, a previous study suggested a good agreement with rechallenge results in a variety of non-immediate drug reactions including mild reactions (Cabañas et al., 2018). Nonetheless, not all mild delayed reactions are necessarily T-cell mediated. Our LTT results, after comparison of cases with tolerant donors, suggest that LTT is a sensitive and specific tool to identify individuals with DRESS reactions to vancomycin when performed after resolution of the clinical symptoms.

Genetic testing has a potential role among strategies used for prevention in identifying whether an individual may be susceptible to developing a serious adverse reaction from a particular drug, as pharmacogenomic studies have revealed strong associations between SCARs and genes encoding HLA molecules in a drug and ethnicity-specific pattern (Su et al., 2016; Phillips, 2018; Kuruvilla et al., 2022). Thus, pharmacogenetic testing in SCARs has been proposed for prevention, monitoring, and diagnosis (Pirmohamed, 2019). We used the recently

published HLA-A*32:01 AS-PCR assay (Rwandamuriye et al., 2019) to confirm the feasibility of this specific test for identifying carriers of the risk allele and to evaluate its association with vancomycin-induced DRESS in a group of Spanish-European patients. Our study confirms that HLA-A*32:01 AS-PCR is a reliable assay, as well as the previously described association, although with lower OR than that in US citizens of European descent (OR 70 in US cases vs. 24 in Spanish cases). The strongest associations were found when cases were restricted to those showing positive LTT results (SI > 3). However, even when only the more strict criteria (only probable or definite DRESS cases with LTT SI > 3) were used for analysis, only 50% of Spanish cases were carriers of the allele as compared to 82.6% in the American group. Interestingly, we observed a higher proportion of carriers of the risk HLA-A*32:01 allele among children with vancomycin-induced DRESS. Given that only four children were included in the analysis, further studies including larger cohorts would be needed to draw specific conclusions in pediatric cases and to explore the underlying mechanisms in case of confirmation of this finding. On the other hand, as LTT specificity is not 100%, we cannot rule out the possibility of including a false-positive adult patient in the analysis that, due to the small sample size, could skew the results. Nonetheless, the discrepant strength of the association in the whole population may also be related to a dissimilar frequency of other HLA alleles that might also be involved in the presentation of vancomycin to specific TCRs. Glycopeptide antibiotics contain a heptapeptide core structure, and molecular docking analysis predicted the binding of vancomycin within the peptide-binding groove of HLA molecules in the absence of other peptides (Konvinse et al., 2019). Moreover, vancomycin, as well as other glycopeptide antibiotics such as teicoplanin and telavancin, were also predicted to bind HLA-DQ (DQA1*01:01, DQB1*05:03) as the molecular basis for cross-reactive T-cell responses (Nakkam et al., 2020). It is thus possible that additional HLA class I or class II alleles present in our population might be responsible for vancomycin-specific DRESS, and this issue deserves further research. In this sense, only one of our cases (P14) was tested for teicoplanin with a maximum SI = 7.0, strongly suggesting cross-reactivity with teicoplanin. The patient was a carrier of HLA-A*32:01. However, no information is available regarding other HLA class I or HLA class II alleles, and to speculate about the possible cross-reactivity among glycopeptide antibiotics in our cases would be too risky. Among the limitations of the study, we should mention the following: first, the number of cases analyzed was small, though it proved enough to detect statistically significant strong associations; second, we used the algorithm of the Spanish pharmacovigilance system (ALSEFV) as the gold standard to identify vancomycin as the culprit drug which is a tool far from perfect, and thus, the parameters estimated for LTT and HLA-A*32:01 performance can only be considered as approximate estimates in the absence of a better gold standard; third, the sample of vancomycin-tolerant controls were selected in a consecutive manner, but not at random, and it may not be representative enough of the whole population exposed to vancomycin; however, it is important to note that the HLA-A*32:01 allele frequency among population controls was fairly similar, which reinforces the validity of the results obtained.

In conclusion, our study confirms HLA-A*32:01 association with vancomycin-induced DRESS in an independent group of European cases, and suggests that the combination of HLA-A screening for this allele as well as *in vitro* LTT test could be useful to identify DRESS patients sensitized to vancomycin. Although a negative AS-PCR test does not exclude vancomycin sensitization, a positive test could be helpful to identify cases before LTT can be performed. Moreover, PCR is a technique widely available in clinical laboratories. Furthermore, research is needed to confirm these findings in other European populations. Finally, it is important to stress that the usefulness of testing the alleles to prevent vancomycin-induced type IV hypersensitivity reactions should be specifically examined in prospective studies.

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 Research Ethics Committee of University Hospital "Principe de Asturias" which granted approval for the whole PIELenREd registry and biological sample collection (code PER-MED-2010-01, date: 28 July 2010), under which the present study was carried out. All patients, cases, and controls alike, or their legal representatives provided specific written informed consent for the collection of both personal data and biological samples. Written informed consent to participate in this study was provided by the participant's legal guardian/next of kin.

Author contributions

All authors helped to perform the research; TB's contribution included manuscript drafting, writing conception and design, and performing procedures and data analysis; CM performed DNA extraction and PCR analysis; FA contributed to writing the manuscript; VL, JG, CE, AF, RB, MB, and RC contributed to sample collection; VL collected clinical, medication, and demographic data; and JG and ER calculated drug causality

algorithms. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

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

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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.2022.959321/full#supplementary-material

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Patients' perception of the pharmacovigilance system: A pre-diagnostic and post-interventional cross-sectional survey

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Background and objective: The risk of adverse reactions necessitated the pharmacovigilance system for patient safety. A literature search documented better health literacy of patients through intervention. This investigation aims to assess the perception and the effect of an intervention on patients regarding adverse reactions caused by drugs.

Methods: A pre-diagnostic and post-interventional cross-sectional investigation was designed with a sample size of 423 patients in hospitals of Islamabad. The proportion of patients was selected based on a stratified probability technique. A prevalidated tool was used to collect the response twice through a health promotion brochure with counseling, which was applied as an intervention.

Results: The outcome of the investigation revealed that the prerequisite of the pharmacovigilance center in the hospital among respondents was improved significantly by 41.2% after intervention. Knowledge, communication, and practice were significantly different with respect to gender. There was a moderate Pearson correlation between diagnostic and interventional responses of patient's knowledge of adverse reactions by drugs ($r = 0.66$, $p < 0.01$) and patient's communication in pharmacovigilance ($r = 0.62$, $p < 0.01$) and a strong correlation between diagnostic and interventional responses of patient's practice in the pharmacovigilance system ($r = 0.72$, $p < 0.01$).

Conclusion: The finding of the investigation provided evidence that patient awareness was significantly improved by the health promotion model. Patient participation in the reporting of adverse reactions of drugs will complement the hospital staff reporting. These reports will construct an authentic, cross-checked database for rational drug safety practices in Pakistan.

KEYWORDS

patients, perception, pharmacovigilance, health promotion, intervention

Introduction

Adverse reactions by drugs are significant healthcare threats to public health worldwide (Karimian et al., 2018). The adverse complications are escalating in patients due to disease co-morbidities that cause a forever-increasing demand for drugs (Chen et al., 2019). Drug-related complications were due to genetic variation, substandard medicine, under or overconsumption of prescribed dosage, irrational medicine usage, environmental conditions, lack of patient counseling, and non-adherence by patients (Belayneh et al., 2018). Adverse reactions by the same medication may differ between individuals and situations (Roden et al., 2011). Risk of adverse reactions necessitated the pharmacovigilance system for patients' safety. Adverse reaction by drugs was one of the major causes of deaths associated with new hospitalizations worldwide (Giardina et al., 2018). Patients' health care costs may be increased due to hospitalization for anti-dote therapy. Adverse reactions by drugs are indeed a financial burden to the patients, hospital administration, and the government (Sultana et al., 2018). The heavy cost of drug adverse responses may be envisaged that the patient's belief is lost in the healthcare delivery system (Inacio et al., 2019).

The World Health Organization has reported that adverse reactions are often a reaction by the drug that is noxious and undesirable and usually develop at normal doses in disease diagnosis, prophylactic treatment, drug therapy, or to modify physiological processes (WHO, 2002). Pharmacovigilance is defined by the World Health Organization as "the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems" (WHO, 2002). An adverse event or experience is defined as 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment (WHO, 2002). Patients are an important part of pharmacovigilance since they suffer from adverse drug reactions. The importance of adverse reactions by drugs is undoubtedly evident, but the adverse reactions are generally not documented or considerably under-reported by healthcare stakeholders (Adisa et al., 2019).

The main limitations in reporting were insufficient awareness about pharmacovigilance, non-availability of reporting documents in hospitals, and lack of knowledge about online reporting systems in patients. The patient-accessible online facility for adverse drug reaction reporting was offered by VigiBase, Uppsala Monitoring Center, Sweden; Food and Drug Administration, United States of America; MedWatch Yellow Card Scheme by the United Kingdom; and the Drug Regulatory Authority of Pakistan (Weigmann, 2016; Hussain and Hassali, 2019). Lack of pharmacovigilance awareness was observed in patients, and educative intervention was proposed to enhance responsiveness in Nepal (Jha et al., 2014).

The adverse drug reaction monitoring system is progressive in developed nations with the existence of a pharmacovigilance system at the hospital, regional, and national levels. The successful pharmacovigilance program of the Netherlands noticed dissimilarities in several reports by healthcare staff and patients due to differences in opinions about the severity and outcomes of adverse drug reactions (De et al., 2008). Patient reporting may initially be voluntary in low-income countries, but it must be mandatory after some time for a viable pharmacovigilance system. All of the stakeholders' involvement may identify risk factors in a limited time to prevent or minimize adverse reactions (Pal et al., 2013).

Pakistan is the 134th Uppsala Monitoring Center participant in Sweden to record the pharmacovigilance activities (Hussain and Hassali., 2019). Health policy based on the Pakistan constitution considers health as an essential right of all the people. The Pakistan's healthcare system is built on the national health policy (Jooma and Sabatinelli., 2013). Punjab Cardiology Institute, Lahore, recorded casualties of more than a hundred cardiac patients in 2012 as a result of adverse drug reactions from contaminated Isotab. This incident endorsed patient contributions in the reporting of adverse drug reactions in its true perspective to ensure rational drug use in the country (Hussain and Hassali., 2019). The purpose of patient involvement is to increase patient safety as being the actual target of these reactions. The scarcity of research in Pakistan related to the patient's perception of the pharmacovigilance system provided evidence for an investigation. Therefore, a research survey was planned to determine the perception and effects of the intervention on patients regarding adverse reactions caused by drugs in hospitals of Islamabad.

Materials and methods

Survey design and population

A pre-diagnostic and post-interventional cross-sectional investigation was designed. The current survey was carried out in all the public sector tertiary care hospitals in the capital city of Pakistan. The hospital administration and institutional research review boards of the Pakistan Institute of Medical Sciences, Capital Development Authority Hospital, Federal Government, Chak Shahzad Hospital, Federal Government Polyclinic Hospital, and Social Security Hospital permitted the survey. The majority of the population of Islamabad visited outpatient departments of these hospitals for the treatment of diseases. All the tertiary care private healthcare facilities refused to allow the investigation in their premises. The survey populace involved both genders visiting the general medicine and general surgery outpatient departments. All the patients who gave willingness according to the recruiting strategy were involved in the survey.

TABLE 1 Sample size calculation of patients from each hospital.

Name of the hospital	Average monthly patient visitors' general medicine	Sample	Average monthly patient visitors' general surgery	Sample
Pakistan Institute of Medical Sciences, Sector G 8	1,908	104	1,292	70
Federal Government Polyclinic Hospital, Sector G 6	1,802	98	1,248	68
Capital Development Authority Hospital	722	39	228	12
Federal Government, Chak Shahzad Hospital	229	12	71	4
Social Security Hospital	188	10	112	6
Total population	4,849	263	2,951	160

Sampled population size and technique for sampling

The sampled population size was assumed to be at 50% awareness prevalence with a 5% allowable error and confidence interval limits of 95% due to the non-availability of any published investigation in the country. The addition of a 10% non-responsive population in the Z formula resulted in 423 survey participants. The survey was based on quantitative research, and therefore probability techniques for sampling were considered. Because the hospital had average monthly records of patients' visits, patients from each hospital were calculated by stratified random sampling as presented in Table 1. Patients from each stratum were chosen by a systematic random sampling technique. The first patient on the survey day was randomly chosen by the Sobol software method from the visitor's token area/register, and then the regular interval "k" that was calculated for each hospital was added until the sample size was completed. If the nominee refused, then the next patient was contacted in turn. The refusal rate was quite high. The response rate in patients was 58%, as 423 questionnaires were received back twice out of 726 questionnaires distributed. The number of patients calculated from each hospital is elaborated in Table 1.

Instrument for collecting data

The survey was based on a pre-validated instrument used in Nepal adopted from the Malaysian research study on pharmacovigilance. (Alshakka et al., 2007; Palaian et al., 2010; Jha et al., 2014). The questionnaire used in this survey was divided into four sections: patients' demographics, patients' knowledge of adverse reactions by drugs (patient's immediate action after suffering from a disease, guidance provided by a healthcare professional for safe drug usage, patient's compliance with healthcare guidance, patient's understanding about the adverse reaction by drugs, patient's perception regarding the purpose of reporting adverse reactions by drugs, vulnerable population for developing adverse reactions by drugs, appropriate person in the healthcare team for reporting adverse reactions by drugs, do you have the knowledge of pharmacovigilance as the science of detecting adverse drug reactions, and knowledge of online forms for reporting drug reactions), patient's communication in pharmacovigilance (discussion with the physician about the probability of adverse drug reactions before taking medication, discussion with the physician about dose frequency and timing of medicines, discussion with the physician about precautions and instructions related to prescription, show compliance to prescriber instructions, and did/will you review the drug brochure about the adverse reaction of the drugs before taking the medication?), and patient practice in the pharmacovigilance system (experience of adverse drug reactions during the lifetime, did you report adverse drug reaction to anyone, I will be reporting adverse drug reactions in future, the prescribing and dispensing times should be improved to prevent adverse drug reactions, have you noticed/remembered any adverse drug reactions reported in the media, is there a need of pharmacovigilance center in hospitals, reporting of adverse reactions by drugs is beneficial for the populace as it reduces re-occurrence, and adverse drug reactions are a serious concern for healthcare stakeholders in Pakistan). The tool was modified on recommendations of expert professionals according to the local pharmacovigilance needs, in consistent with the literature published (Mahmood et al., 2011). A five-person expert committee was established, with members who have experience working for the Pakistani Drug Regulatory Authority, hospital staff members, and public health professionals. They were given the prevalidated research instrument and the intervention leaflet and were encouraged to make additional alterations. They suggested adding items such as adverse drug reactions are a serious concern for healthcare stakeholders in Pakistan and knowledge of online forms for reporting adverse drug reactions in the questionnaire with verbal inquiry about awareness of drug regulatory authority online reporting forms during intervention and counseling about availability as well as the reporting mechanism during the intervention. The committee decided on a format for the length and development of each item and reviewed and revised each newly proposed item. Ten patients from each institution

participated in the initial pilot testing, which was followed by another review by an expert panel. Face validity of the instrument was judged by committee experts, and construct validity was analyzed using Pearson correlation. According to the Statistical Package for Social Sciences, the amended instrument's reliability coefficient Cronbach's alpha value was 0.90. Finally, these pilot results were included in the results as the total sample collected from each hospital.

Health promotion model

The educational intervention took an average of 30 min excluding filling the time of pre- and post-intervention questionnaires. The interventional activity was completed during the waiting time of the patients in the outpatient department of the hospitals. The educational brochure comprised basic information regarding pharmacovigilance activities, awareness regarding side effects and adverse reactions to drugs, the procedure for suspected adverse reaction reporting, healthcare personnel's role in monitoring and treatment, self-reporting websites, and the importance of reporting drug adverse reactions. After 10 min of the distribution of information brochures, counseling activity was conducted by trained pharmacists related to the information brochure.

Statistical analysis and variables

Entry and analysis of data were based on SPSS software. The Statistical Software Package for Social Sciences version 21 was used (Dembe et al., 2011). The descriptive statistical analysis involved frequency and percentage calculations. The inferential investigation of data was computed on continuous variables formulated by summing identical items in an eight-item subscale for the awareness of adverse drug reactions by drugs, an eight-item subscale for the practice of adverse drug reactions by drugs, and a five-item subscale was formulated for communication in pharmacovigilance among patients. The Shapiro–Wilk test was performed to test the normality of the distribution. The chi-squared test, Pearson correlation, and paired *t*-test were applied on data for inferential inference.

Ethics approval

The Ethics Review Board of the Health Services Academy, Islamabad, Pakistan, and institutional review boards/hospital administrators permitted the survey. The survey participants were informed about the project, and consent was obtained in writing.

TABLE 2 Patient demographics.

Patient demographic	Frequency (percentage)
Age of respondents	
18–40 years	162 (38.3%)
41–60 years	145 (34.3%)
61 years and above	116 (27.4%)
Gender of respondents	
Male	193 (45.6%)
Female	230 (54.4%)
Residence of respondents	
Urban	301 (71.2%)
Rural	122 (28.8%)
Educational level of respondents	
Uneducated	161 (38.1%)
Up to intermediate level of education	154 (36.4%)
Graduate and above	108 (25.5%)
Monthly income of respondents(in Pakistani rupees)	
Less than 50,000	146 (34.5%)
50,000–100,000	160 (37.8%)
More than 100,000	117 (27.7%)

Results

Patient demographics

Patient demographic data comprised patient's age, gender, educational level, place of residence, and monthly income in Pakistani rupees. The respondents were divided into three main categories based on their age, education, and monthly income. The majority of the sampled population was in younger age groups (38.3%), uneducated (38.1%), and urban population (71.2%). Nearly half of the survey participants were female (54.4%). The majority (37.8%) earned between 50,000 and 100,000 Pakistani rupees every month. The patient demographics are represented in Table 2.

Patient's knowledge of adverse reactions by drugs

The questionnaire subsection related to patient's knowledge by adverse reactions by drugs revealed that 74.2% of patients immediately consult doctors when suffering from the disease before the intervention, despite the fact that 16.1% replied that they will do self-medication when suffering from the disease in the future after counseling sessions and brochure intervention. The outcomes of the guidance provided by healthcare professionals for safe drug usage presented negligible improvement from 64.1% of patients to 68.8%. Patients' compliance with the healthcare guide by the healthcare professionals was fully followed by 51.8% initially and

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TABLE 3 Patients' knowledge of adverse reactions by drugs and patients' communication in pharmacovigilance.

Characteristic	Diagnostic response	Interventional response
	n (%)	n (%)
Patients' knowledge of adverse reactions by drugs		
Patients' immediate action after suffering from a disease		
a. Immediately consult the doctor for a prescription	314 (74.2%)	355 (83.9%)
b. Practice self-medication	109 (25.8%)	68 (16.1%)
Guidance provided by a healthcare professional for safe drug usage		
a. Yes	271 (64.1%)	291 (68.8%)
b. No	152 (35.9%)	132 (31.2%)
Patients compliance with healthcare guidance		
a. Completely	215 (50.8%)	260 (61.5%)
b. Not entirely	107 (25.3%)	89 (21%)
c. Not followed	101 (23.9%)	74 (17.5%)
Patients' understanding about adverse reactions by drugs		
a. Harmful response by a drug*	149 (35.2%)	318 (75.2%)
b. Routine side effect	67 (15.8%)	57 (13.5%)
c. Desired response	59 (13.9%)	48 (11.3%)
d. Do not know	148 (35%)	0
Patients' perception regarding the purpose of reporting adverse reactions by drugs		
a. Drug safety improve by reporting	80 (18.9%)	270 (63.8%)
b. Reoccurrence will be prevented	150 (35.5%)	107 (25.3%)
c. Prerequisite in the hospital setting	62 (14.7%)	42 (9.9%)
d. Enable physicians for early diagnosis	131 (31%)	4 (0.9%)
Vulnerable population for developing adverse reactions by drugs		
a. Child populace	139 (32.9%)	112 (26.5%)
b. Adult population	49 (11.6%)	31 (7.3%)
c. Old age people	82 (19.4%)	53 (12.5%)
d. All of the above	153 (36.2%)	227 (53.7%)
Appropriate person in the healthcare team for reporting adverse reactions by drugs		
a. Physician	84 (19.9%)	145 (34.2%)
b. Pharmacist	42 (9.9%)	58 (13.7%)
c. Nurse	42 (9.9%)	57 (13.5%)
d. All of the above	107 (25.3%)	163 (38.6%)
e. Do not know	148 (35.0%)	0
Do you have the knowledge of pharmacovigilance as the science of detecting adverse drug reactions?		
a. Yes	121 (28.6%)	414 (97.9%)
b. No	302 (71.4%)	9 (2.1%)
Knowledge of online forms for reporting drug reactions		
a. Yes	242 (57.2%)	420 (99.3%)
b. No	181 (42.8%)	3 (0.7%)
Patients' communication in pharmacovigilance		
Discussion with the physician about the probability of adverse drug reactions before taking medication		
a. Yes	204 (48.2%)	317 (74.9%)
b. No	219 (51.8%)	106 (25.1)

(Continued on following page)

TABLE 3 (*Continued*) Patients' knowledge of adverse reactions by drugs and patients' communication in pharmacovigilance.

Characteristic	Diagnostic response	Interventional response
	n (%)	n (%)
Discussion with the physician about dose frequency and timing of medicines		
a. Yes	252 (59.6%)	403 (95.3%)
b. No	171 (40.4%)	20 (4.7%)
Discussion with the physician about precautions and instructions related to prescription		
a. Yes	267 (63.1%)	359 (84.9%)
b. No	156 (36.9%)	64 (15.1%)
Show compliance with prescriber instructions		
a. Yes	315 (74.5%)	359 (84.9%)
b. No	108 (25.5%)	64 (15.1%)
Did/will you review the drug brochure about the adverse reaction of the drugs before taking the medication?		
a. Yes	219 (51.8%)	370 (87.5%)
b. No	204 (48.2.%)	53 (12.5%)

*Correct response.

61.5% of the respondents in the final response. A total of 35.2% respondents knew that adverse reactions by the drug were the harmful response, while 75.2% participants identified correctly in the interventional survey. The data about the patient's knowledge of adverse reactions by drugs in the pre-post analysis are presented in Table 3.

Patient's communication in pharmacovigilance

A total of 48.2% of the sampled population discussed the probability of adverse reactions by drugs before taking medication in the pre-survey, while the response was increased to 74.9% in the post-survey. As regards discussion about dose frequency and timing of medicine, 59.6% of participants before the intervention intended to discuss while 95.3% aimed to discuss it with the prescriber in future conversation. Precautions/instructions related to prescription were conversed with the physician by 63.1% of patients before the counseling session, and 84.9% of the patients intended to converse it with the prescriber in the forthcoming discussion. The data related to communication in pharmacovigilance among patients are presented in Table 3.

Patient practice in the pharmacovigilance system

A total of 45.9% of the participants experienced adverse reactions by drugs during their lifetime, but the reporting rate was only 30.2%. The attitude toward reporting was modified by pharmacist counseling sessions and health brochure intervention, and 99.3% of respondents showed the intention to report in the future. Media reports were recalled by 56.7% of the patients in the initial response and 60.8% in the final response. The prerequisite of the pharmacovigilance center in hospitals was improved significantly from 56.7% to 97.9%. The data about pharmacovigilance practice among patients are described in Table 4.

The patient's knowledge of adverse reactions by drugs, patient's communication in pharmacovigilance, and patient's practice in the pharmacovigilance system were correlated with the intervention response. The findings of the bivariate Pearson correlation coefficient showed that there is a strong correlation between diagnostic and intervention responses of patient's practice in the pharmacovigilance system and a moderate correlation between diagnostic and intervention responses of patient's knowledge of adverse reactions by drugs and diagnostic and intervention responses of patient's communication in pharmacovigilance. The outcome of intervention on paired variables showed significant differences ($p \leq 0.05$). The results of pre-diagnostic and post-interventional assessments using the paired *t*-test are displayed in Table 5.

The perception difference related to age, gender, and education of participants was computed by applying chi-squared statistics. The findings of the research investigation revealed that all the variables except the interventional response of communication in pharmacovigilance were

TABLE 4 Patients' practice in the pharmacovigilance system.

Characteristic	Diagnostic response	Interventional response
	n (%)	n (%)
Experience of adverse drug reactions during the lifetime		
a. Yes	194 (45.9%)	194 (45.9%)
b. No	229 (54.1%)	229 (54.1%)
Did you report adverse drug reactions to anyone?		
a. Yes	127 (30.02%)	127 (30.02%)
b. No	296 (69.98%)	296 (69.98%)
I will be reporting adverse drug reactions in future		
a. Yes	242 (57.2%)	420 (99.3%)
b. No	181 (42.8%)	3 (0.7%)
Prescribing and dispensing time should be improved to prevent adverse drug reactions		
a. Yes	252 (59.5%)	332 (78.5%)
b. No	171 (40.5%)	91 (21.5%)
Have you noticed/remembered any adverse drug reactions reported in the media?		
a. Yes	240 (56.7%)	257 (60.8%)
b. No	183 (43.3%)	166 (39.2%)
Is there need of pharmacovigilance centers in hospitals?		
a. Yes	240 (56.7%)	414 (97.9%)
b. No	183 (43.3%)	9 (2.1%)
Reporting of adverse reactions by drugs is beneficial for the populace as it reduces re-occurrence		
a. Yes*	260 (61.5%)	374 (88.4%)
b. No	163 (38.5%)	49 (11.6%)
Adverse drug reactions are a serious concern for healthcare stakeholders in Pakistan		
a. Yes*	226 (53.4%)	418 (98.8%)
b. No	197 (46.6%)	5 (1.2%)

*Correct response.

TABLE 5 Pre-diagnostic and post-interventional assessments using the paired *t*-test.

Variable	Response	Mean	SD	Mean difference	Correlation r-value	*p*-value	t-value df (422)	*p*-value
Patient's knowledge of adverse reactions by drugs	Diagnostic response	18.33	4.49	4.94	0.66	<0.01	30.03	<0.01
	Interventional response	13.39	2.71					
Patient's communication in pharmacovigilance	Diagnostic response	6.97	1.72	1.25	0.62	<0.01	18.90	<0.01
	Interventional response	5.72	0.89					
Patient's practice in the pharmacovigilance system	Diagnostic response	11.80	2.46	1.80	0.72	<0.01	20.89	<0.01
	Interventional response	10.00	1.27					

significant for the age of the contributors. There were significant differences in gender among all variables. Communication in pharmacovigilance was only non-significant for education. The chi-squared statistics related to perception differences constructed on age, gender, and education are explained in Table 6.

Discussion

Patients' perception of the disease and drugs plays a vital role in the successful therapy model in health management. Patients' education involves counseling that is important for disease understanding and awareness of pharmacological and non-

TABLE 6 Perception differences based on age, gender, and education.

Variable	Patient's knowledge of adverse reactions by drugs						
	Response	Diagnostic response	χ^2	*p*-value	Interventional response	χ^2	*p*-value
Age							
15–30 years	Don't know	64.8%	63.61	<0.01*	61.6%	11.09	<0.01*
	Yes	35.2%			38.4%		
31–45 years	Don't know	81.5%			43.2%		
	Yes	18.5%			56.8%		
46 and above years	Don't know	33.9%			48.3%		
	Yes	66.1%			51.7%		
Gender							
Male	Don't know	37.4%	95.28	<0.01*	32.3%	55.01	<0.01*
	Yes	62.6%			67.7%		
Female	Don't know	83.6%			68.4%		
	Yes	16.4%			31.6%		
Education in years							
Uneducated	Don't know	58.3%	52.53	<0.01*	56.4%	5.79	0.05
	Yes	41.7%			43.6%		
Matric and intermediate	Don't know	81.9%			43.9%		
	Yes	18.1%			56.1%		
Graduate and above	Don't know	38.1%			55,2%		
	Yes	61.9%			44.8%		
Patient's communication in pharmacovigilance							
	Response	**Diagnostic response**	**χ^2**	***p*-value**	**Interventional response**	**χ^2**	***p*-value**
Age							
15–30 years	Don't know	42.8%	7.47	0.02	51.6%	0.44	0.80
	Yes	57.2%			48.4%		
31–45 years	Don't know	57.5%			49.3%		
	Yes	42.5%			50.7%		
46 and above years	Don't know	44.9%			53.4%		
	Yes	55.1%			46.6%		
Gender							
Male	Don't know	13.6%	180	<0.01*	30.8%	62.56	<0.01*
	Yes	86.4%			69.2%		
Female	Don't know	79.1%			69.3%		
	Yes	20.9%			30.7%		
Education in years							
Uneducated	Don't know	41.7%	5.17	0.07	49.1%	4.28	0.11
	Yes	58.3%			50.9%		
Matric and intermediate	Don't know	54.2%			47.7%		
	Yes	45.8%			52.3%		
Graduate and above	Don't know	50.5%			60%		
	Yes	49.5%			49%		

(Continued on following page)

TABLE 6 (*Continued*) Perception differences based on age, gender, and education.

Patient's practice in the pharmacovigilance system							
	Response	**Diagnostic response**	χ^2	***p*-value**	**Interventional response**	χ^2	***p*-value**
Age							
15–30 years	Don't know	54.7%	77.79	<0.01*	80.05%	37.40	<0.01*
	Yes	45.3%			19.5%		
31–45 years	Don't know	8.2%			47.3%		
	Yes	91.8%			52.7%		
46 and above years	Don't know	45.8%			58.5%		
	Yes	54.2%			41.5%		
Gender							
Male	Don't know	23.7%	24.92	<0.01*	58.6%	2.94	0.05
	Yes	76.3%			41.4%		
Female	Don't know	47.1%			66.7%		
	Yes	52.9%			33.3%		
Education in years							
Uneducated	Don't know	49.7%	78.89	<0.01*	71.2%	26.25	<0.01*
	Yes	50.3%			28.8%		
Matric and intermediate	Don't know	9.0%			47.1%		
	Yes	91.0%			52.9%		
Graduate and above	Don't know	55.2%			73.3%		
	Yes	44.8%			26.7%		

Note: * (significant at ≤ 0.05 *p*-value).

pharmacological approaches in the treatment. Compliance with therapy may be improved by effective active and passive counseling of the patients. Active counseling involves face-to-face conversation, while passive counseling involves the use of written information (Saood et al., 2020). The current investigation involved a mixed method of face-to-face counseling sessions with health brochure intervention. A total of 423 patients from the targeted outpatient departments were evaluated for the survey. The majority of the sampled population was women because of the high incidence of disease, also testified by Gove (1984). Self-ingestion of medicines without physician consultation was reported as one of the significant etiological cause of adverse drug reaction (Mahmood et al., 2011). The present research investigation reported a decrease in patient's intention toward self-medication when they suffered from disease after the intervention.

The World Health Organization documented that the majority of the patients globally fail to take medicines correctly (World Health Organization, 2004). The poor drug adherence contributing factors are related to patients and physicians. The barrier in communicating with the physician and lack of communication in pharmacovigilance were the most important physician-contributing factors (Brown et al., 2011). Similar results were reported by the majority of the patients in this survey. The suboptimal level of health literacy in patients evoked poor compliance (Millar et al., 2016). The instructions of the prescriber were fully followed by less than 62% of the patients after intervention. Low health literacy of the patients may be linked with uneducated and less educated participants in the survey. The majority of the respondents were not able to recognize the concept of adverse reactions by drugs in the diagnostic survey. Perception regarding adverse drug reactions was also low in some areas of Nepal and Nigeria (Jha et al., 2014; Adisa et al., 2019). The understanding of adverse drug reactions was improved in two-thirds of the participants after health communication. Almost half of the counseled respondents correctly identified vulnerable populations to develop adverse drug reactions. The literature search also nullified the concept that the children were most susceptible to adverse reactions by drugs. Everyone may be endangered to adverse reactions by drugs, irrespective of age group, sex, race, and other factors (Mahmood et al., 2011; Inacio et al., 2017). The familiarity of the pharmacovigilance concept was less in 1/3rd of the sampled population in the diagnostic survey also reported in fifty nations' metanalysis reports on adverse drug reactions (Margraff et al., 2014). The intervention created awareness in more than 95% of the participants. The knowledge of patients regarding an appropriate person in the healthcare team is a prerequisite for

reporting. Healthcare team members of all specialties were involved in signal detection in pharmacovigilance systems globally. The majority of the patients did not appropriately recognize the responsible person for reporting adverse drug reactions in the diagnostic survey, but after the intervention, they were able to identify the health personnel's involvement in adverse drug reactions. Patients' reporting had generated positive outcomes in the previous literature and is a prerequisite of the day for patient's safety (Mahmood et al., 2011).

The Eric's report declared that drug safety data need to be transmitted effectively for educating healthcare stakeholders, so that the risk–benefit data of medicines may be interpreted timely, and the exchange of such data at the international and national levels should be recommended (Hugman, 2006). The health conversation of patients with prescribers related to the effects of adverse drug reactions was aimed to be less than 75% in the future response. The Patient–physician communication of dose and timing is important because type A reactions are dose-dependent (Coleman and Pontefract, 2016). Dose and timing of medication conversation with the physician were improved significantly to 95.3% in the final response. The lack of patient compliance with therapy resulted in resistance to treatment, therapy failure, deaths, prolonged hospital duration, and increased expenditure on healthcare. Chronic medication adherence was detected 50% in patients (DiMatteo et al., 2002). The patients' compliance with prescriber's instructions was increased to 10.4% in the final response. The drug leaflet guide is a source for providing relevant information to consumers (Adepu and Swammy, 2012). The percentage of future drug literature reviewers increased to 35.8% after intervention.

A substantial number of participants (45.9%) declared that they experienced adverse reactions by drugs, and only 30.2% documented that to health personnel. Medical professionals' poor knowledge in signal detection and rare practice of reporting are major constraints in a viable pharmacovigilance system in the countries (Fernandopulle and Weerasuriya, 2003; AlShammari and Almoslem, 2018). The majority of patients intended in both surveys for future reporting of adverse reactions by drugs. Medical professionals' underreporting in developing nations will be supplemented by an autonomous patient pharmacovigilance reporting practice. The consumer reporting of adverse reactions may be a beneficial project for safety assurance. The majority of the patients were able to recall media reports; therefore, the potential of the media should be utilized in Pakistan for the dissemination of pharmacovigilance reports (Van Hunsel et al., 2009). Patients believed that physician's prescribing time and pharmacist dispensing time should be improved for a better understanding about drugs. Mostly, patients proposed a hospital-based pharmacovigilance system in the country for effective health communication among stakeholders for patients' safety (Saqib et al., 2019) The personalized drug model proposed by Wertheimer may guide for efficient, suitable, economical, and safe drug usage globally (Wertheimer, 2017).

The findings of this survey revealed that diagnostic and interventional response variables were moderately and positively correlated in patient's knowledge and patient's communication and strongly and positively correlated in patient's practice in the pharmacovigilance system. There was a significant average difference between diagnostic and interventional responses in all the three testing components. The mean values were higher for diagnostic responses, and the differences were statistically significant. The average difference in patients' knowledge was 4.94, whereas it was 1.25 in patients' communication and 1.80 in patients' practice. The majority of the population started choosing correct responses after intervention. There was little variation in average and standard variation in comparison to the diagnostic response.

Limitations

There are some limitations to this survey: first, only public sector hospitals in the federal capital permitted the study; therefore, the information may not represent the patients from the private hospitals. Second, due to time limitation, only general surgery and general medicine departments were included. However, this pioneer survey of the fifth most populated nation may provide a basis for further investigations related to patients. The research was carried out in Pakistan's federal capital, and the results will only be cautiously extrapolated to the nation as a whole. There is a need for further research to investigate the predictors, promoters, and barriers in adverse reaction reporting among patients in Pakistan.

Conclusion

The results of the pioneer survey concluded that health literacy improved significantly in the interventional survey, but the baseline results indicated a low awareness level of pharmacovigilance among patients in the federal capital of Pakistan. The survey revealed that the majority of the participants were interested in physician consultation for drug use; some were willing to report adverse drug reactions in the future and demanded the establishment of a pharmacovigilance system at the hospital level. Patients' participation in the reporting of adverse reactions of drugs will complement the hospital staff reporting. These reports will construct an authentic, cross-checked database for rational drug safety practices in Pakistan.

Data availability statement

The raw data supporting the conclusion 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 Review Board of the Health Services Academy. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AR, SNK, RZ, and MZ: Conceptualized the study. AR and UH: Contributed to data collection, SNK, RZ, MZ, and FF: Supervised the work and supported in data analysis. AR, RZ, and UH: Drafted the manuscript. All authors contributed to revising the manuscript and approved the final manuscript.

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Conflict of interest

The 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.

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