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Medication safety and interventions to reduce patient harm in low- and middle-income countries

Edited by
Mansour Adam Mahmoud, Brian Godman, Ahmed Awaisu, Ahmed Ibrahim Fathelrahman, Hisham Aljadhey, Joseph O. Fadare, Johanna Catharina Meyer and Fahad Saleem

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Medication safety and interventions to reduce patient harm in low- and middle-income countries

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Editorial: Medication safety and interventions to reduce patient harm in low- and middle-income countries

Mansour Adam Mahmoud [1], Johanna C. Meyer [2,3]*, Ahmed Awaisu [4], Joseph Fadare [5,6], Ahmed Ibrahim Fathelrahman [7], Fahad Saleem [8], Hisham Aljadhey[9] and Brian Godman [2,10,11]

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Editorial on the Research Topic
Medication safety and interventions to reduce patient harm in low- and middle-income Countries

The safe and rational use of medicines is crucial, especially from the context of low- and middle-income countries (LMICs) where medicine spending accounts for a considerable proportion of healthcare costs, and much of this is out-of-pocket expenditure (Cameron et al., 2009; Ofori-Asenso and Agyeman, 2016). Consequently, medicines should not be over-used or misused as seen with antibiotics in ambulatory care among patients with self-limiting illnesses or in hospitals for patients with COVID-19 (Godman et al., 2020; Langford et al., 2021), as this increases antimicrobial resistance (AMR) with its considerable impact on morbidity, mortality, and cost (Hofer, 2019; Antimicrobial Resistance Collaborators, 2022; GBD, 2023). Similarly, efforts are needed to improve medicine use in patients with chronic non-communicable diseases, including enhancing adherence to prescribed medicines, to improve outcomes and reduce complications (Kirk et al., 2017; Rezende Macedo do Nascimento et al., 2020; Chan et al., 2021; Nowak et al., 2022). Alongside this, reducing the potential for drug-drug interactions (DDIs) especially among patients with multiple co-morbidities. Furthermore, increased knowledge about possible adverse drug events (ADE) can reduce medication errors and adverse drug reactions (ADRs), with their substantial impact on morbidity, mortality and cost (Chan et al., 2016; Mouton et al., 2016; Formica et al., 2018). However, major issues with medication safety, including ADRs and medication errors, are severely hampered by inadequate patient education and counselling, low health literacy and considerable under reporting of ADRs (Mahmoud et al., 2014), with issues of medication misadventure more prevalent in

LMICs. It was against this background, that the need for this Research Topic was identified, which resulted in 19 original research papers. It is hoped that this collection of original papers will provide future guidance to reduce patient harm, improve the care of patients and their quality-of-life.

ADR reporting is an issue across countries, especially in the ambulatory care setting (Ampadu et al., 2016; Gidey et al., 2020; Haines et al., 2020; Sefah et al., 2021; Mahmoud et al., 2022). This was identified by Karuppannan et al. with many pharmacists, especially community pharmacists, not reporting ADRs even when identifying them (Karuppannan et al.). However, it was reassuring to note the study by Jiang and colleagues, in which they documented the extent of current ADRs in their hospital over a 10-year period, stratified according to the severity of the ADRs (Jiang et al.). In addition, the extent of ADRs caused by DDIs was similarly reported. The investigators concluded that increased training can assist physicians with their knowledge of ADRs and associated DDIs to improve patient safety and care outcomes (Jiang et al.). Alsheikh and Alasmari also found that community pharmacists in Saudi Arabia were knowledgeable about ADRs. Furthermore, they had good attitude and practices concerning pharmacovigilance and ADR reporting (Alsheikh and Alasmari), which is encouraging. These findings contrast with those of Hu et al. in China, who found that whilst hospital pharmacists typically had a positive attitude towards ADR reporting, there were concerns with their actual knowledge and practices (Hu et al.). This is a concern since hospital pharmacists are key role players in LMICs, educating physicians regarding the importance of monitoring and reporting of ADRs to improve patient care and safety (Terblanche et al., 2018).

In their study, Yang and co-authors showed a positive impact of drug and therapeutic committees (DTCs) in hospitals on reducing prescribing errors and inappropriate prescribing of antibiotics as well as associated AMR through antimicrobial stewardship (AMS) activities, alongside reducing costs (Yang et al.). This is important given concerns with currently a limited number of active DTCs and their impact across LMICs, including encouraging ADR reporting and improving antimicrobial use through AMS activities, due to resource constraints, limited training and other issues; however, this is changing (Cox et al., 2017; Matlala et al., 2017; Fadare et al., 2018; Siachalinga et al., 2022).

Trained community pharmacists can also play a key role in reducing unnecessary purchasing of antibiotics without a prescription, especially for self-limiting conditions such as acute respiratory infections (Marković-Peković et al., 2017; Mukokinya et al., 2018). This is an issue in countries and regions such as post-conflict zones in Pakistan where there is currently poor knowledge, attitude and practices among citizens towards antibiotics and AMR (Khan et al.). Previous studies have demonstrated high rates of purchasing of antibiotics without a prescription in Pakistan, including 'reserve' antibiotics as per the WHO AWaRe classification (Sharland et al., 2018), which needs to be urgently addressed as part of national action plans, if Pakistan is to achieve its desired goals (Saleem et al., 2018; Atif et al., 2019; Saleem et al., 2020). In the case of children, pictorial storybook telling can assist with enhancing their knowledge regarding the rational use of medicines, including antibiotics (Bakaruddin et al.), which is a consideration for the future. In a number of LMICs, especially among African and Asian countries, such activities are needed to address rising AMR and its consequences, including increasing the use of 'Watch' antibiotics (Klein et al., 2021; Antimicrobial Resistance Collaborators, 2022).

The timely identification of risk factors associated with ADEs is also important to improve future patient care. In their study, Khan et al. found that the prescribing of bedaquiline alongside other active treatments lowered the chance of ADEs in patients with multidrug-resistant *tuberculosis* (TB) (Khan et al.). Alongside this, elderly patients, active smokers and those experiencing a delay in treatment were more prone to ADEs. The care of TB patients can also be improved through information provided regarding the rational use of medicines, early detection and management of ADEs as well as general counselling from clinical pharmacists (Khan et al.).

Improving the prescribing of medicines to treat cardiovascular disease in the elderly to reduce potentially inappropriate prescribing (PIP) in LMICs, and their associated consequences, is becoming critical with growing prevalence and mortality rates (WHO, 2021). Xingwei and colleagues discuss the development of a learning-based risk warning model to aid physicians in identifying key factors in this population that could result in PIP to provide future guidance (Xingwei et al.). In their study, Očovská et al. highlighted the importance of both effectiveness and safety when treating patients to help reduce drug-related hospital admissions (DRA) (Očovská et al.). This is especially the case with diuretics and antithrombotic medicines which are both effective; however, both are among the most common classes of medicines causing DRA (Očovská et al.).

Conducting research to identify ways to improve adherence to medicines in patients with long-term diseases is also important. This is especially the case during pandemics with their impact on clinic closures and associated concerns with the subsequent monitoring of patients (Kluge et al., 2020). Ahmed and colleagues identified key enablers to enhance adherence to prescribed medicines in patients with HIV/AIDS to assist with this (Ahmed et al.). They also identified key barriers to adherence, which included lack of social support, stigma and COVID-19 related lockdown measures (Ahmed et al.), which need to be addressed going forward.

In their study, Liu et al. demonstrated the considerable concerns regarding the management of patients with presumptive asthma among primary care providers in rural China (Liu et al.). In their vignette, only 10% of providers prescribed the correct medicines, whilst 65% prescribed antibiotics, which were considered unnecessary. Furthermore there was high use of injections, which was also unnecessary among asthma patients, calling for a considerable re-think of incentives and educational approaches to improve the future care of these patients (Liu et al.). Sharing of medicines is also a problem across countries, including unused medicines left over from a course of treatment (Mahlaba et al., 2022), as this can delay diagnoses, enhance DDIs and ADRs as well as AMR with antibiotics (Song et al.). The authors showed this was a considerable problem in South Korea, which calls for greater public education campaigns similar to other countries (Song et al.).

On a positive note, Yi et al. demonstrated that the introduction of collaborative pharmaceutical care services among patients with Parkinson's disease in China can reduce drug-related problems as well as improve patients' medication regimens, including dosage adjustments where needed, and adherence thereby improving their quality-of-life (Yi et al.). Consequently, providing a rationale for further improving pharmacy services across China and other LMICs with ageing populations.

Some papers in this Research Topic also focussed on very specific issues. For instance, Bibi and colleagues found in their observational cohort study that biodegradable polymer drug-eluting stents had comparable clinical outcomes to durable polymer stents when used for primary percutaneous coronary interventions (Bibi et al.). Studies such as this will assist policymakers and clinicians in their decision-making, especially in resource-constrained settings. In their study, Zhang et al. were concerned that the prescribing of urate-lowering-therapy (ULT) would adversely influence the progression of kidney function in patients with asymptomatic hyperuricemia. Encouragingly, they found that ULT did not delay the progression of kidney function; although further studies are needed (Zhang et al.). Chai and associates were concerned that the increasing use of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors in patients would increase the risk of fractures among patients with type 2 diabetes (Chai et al.). This is an issue with increasing rates of diabetes globally combined with a growing prevalence of complications in sub-optimally controlled patients (Chan et al., 2021). Nevertheless, the authors believed an association was unlikely based on their network meta-analysis (Chai et al.).

Mushtaq and co-authors were concerned with the emergence of resistant strains in patients with hepatitis C virus infection, despite the effectiveness of direct-acting antivirals (DAAs) (Mushtaq et al.). Based on their findings, they advocated that direct resistance testing should be encouraged in the future to optimise re-treatment strategies in patients failing on DAA therapy, given the importance of effectively treating these patients (Mushtaq et al.). This is likely to be followed up in the future. Finally, Mei et al. found that Nao-Xue-Shu, a traditional Chinese medicine, combined with nifedipine showed improved effectiveness in patients with hypertensive intracerebral haemorrhage compared with the other combinations, and Nao-Xue-Shu combined with nimodipine may be more effective in reducing proinflammatory factor expression in these patients (Mei et al.).

In conclusion, there were a considerable number of papers in this Research Topic. Strengthening pharmacovigilance policies and standards in LMICs is crucial to increase ADR reporting and improve patient safety. A continuous development program among healthcare professionals concerning pharmacovigilance along with participation in advocacy for ADR reporting are both key to improving pharmacovigilance in practice. There is certainly a need to reduce DDIs and associated AMRs, to improve future patient care and reduce healthcare costs. Community and hospital pharmacists, as well as physicians, have a key role to play to encourage further reporting to improve patient care. Improving adherence to medicines is also a key area for the future, alongside the potential for collaborative pharmaceutical care services. Finally, concerted efforts are needed to improve appropriate prescribing and dispensing of antibiotics across sectors in an attempt to curb the menace of AMR. Antimicrobial stewardship programmes are key in this respect.

Author contributions

MM, JM, AA, JF, AF, FS, HA, and BG developed the concept for this Research Topic and actively engaged in ensuring the quality of manuscripts accepted. BG wrote the first draft of the editorial. All authors reviewed the editorial and approved the submitted version.

Conflict of interest

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

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Impact of a Collaborative Pharmaceutical Care Service for Patients With Parkinson's Disease

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Objective: To identify the impact of a collaborative pharmaceutical care service (CPCS) on medication safety and establish the impact of the CPCS on patient reported outcomes for Parkinson's disease (PD) patients.

Methods: Initially, PD outpatients receiving the CPCS between March 2017 and March 2019 were compared with PD patients receiving standard of care to identify differences in management. Pharmacist interventions data were coded and patients with PD receiving the CPCS were compared with those receiving standard of care to determine differences in medicines prescribed and dosage associated with these. Following this, data of patients receiving CPCS at baseline and 3-months follow-up were collected using a questionnaire consisting of validated measures of two patient-reported outcomes [adherence and quality of life (QoL)]. Mean scores for continuous variables were calculated, with descriptive analysis of categorical variables consisting of frequency counts and percentages. Change in adherence score before and after CPCS was investigated using a Wilcoxon sign rank sum test, spearman correlation analysis was used to correlate the changes in QoL before and after CPCS with the number of interventions, and $p < 0.05$ indicates that the difference is statistically significant.

Results: A total of 331 PD outpatients received CPCS over 490 outpatient visits with an average age of 71.83 (±12.54). Five hundred and forty-five drug related problems were recorded as pharmacist interventions, of which most involved change to dosage ($n = 226$, 41.47%), adverse drug reactions ($n = 135$, 24.77%), and change in a medication ($n = 102$, 18.72%). Compared with those receiving standard of care, patients receiving CPCS were significantly less likely to have been prescribed pramipexole (18.52 versus 23.77%, $p < 0.001$) and more likely to have been prescribed amantadine (5.40 versus 3.70%, $p = 0.02$) and selegiline (17.36 versus 11.64%, $p < 0.001$). Lower dosages of levodopa/benserazide (0.51 ± 0.31 g versus 0.84 ± 0.37 g, $p < 0.001$), levodopa/carbidopa (0.33 ± 0.23 g versus 0.66 ± 0.47 g, $p < 0.001$), pramipexole (1.14 ± 1.63 mg versus 1.27 ± 0.69 mg, $p = 0.01$), and entacapone (130.00 ± 79.76 mg versus 173.09 ± 97.86 mg, $p < 0.001$) were also recorded. At baseline 119 PD outpatients with an average age of 69.98 (±9.90) were

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recruited for the longitudinal study. At 3-month follow-up, participants reported improvement in bodily pain subscale (baseline versus 3-months follow-up, 30.04 ± 22.21 versus 23.01 ± 20.98, p = 0.037) and medication adherence (6.19 ± 1.50 versus 6.72 ± 1.73, p = 0.014). Frequency of CPCS use was related to activity of daily living subscale (p = 0.047), the bodily pain subscale (p = 0.026), and medication adherence (p = 0.011). Total score of PDQ-39 was associated with patient education (p = 0.005) and usage and dosage combined with patient education (p = 0.006), while medication adherence score was associated with usage and dosage (p = 0.005).

Conclusion: The CPCS was effective in resolving drug-related problems and in improving patients' medication regimens, medication adherence, and QoL through patient education and dosage adjustments. This is the first step in the development and feasibility testing of pharmacy services for PD patients in China.

Keywords: Parkinson's disease, pharmaceutical service, quality of life, drug-related problems, medication adherence

1 INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease, with an estimated incidence rate of 37.55 per 100,000 person-years (95% CI 26.20–53.83) in females aged 40 and over and 61.21 (95% CI 43.57–85.99) in males aged 40 years and older, with incidence increasing with age (Hirsch et al., 2016). Patients with PD are likely to be prescribed a large number of medicines to treat motor and non-motor symptoms as well as a number of co-morbid conditions, with levodopa and dopaminergic agonists most commonly prescribed, together with medicines for comorbidities, such as asorthostatic hypotension (McLean et al., 2017). As a consequence of being prescribed multiple medicines, patients with PD face problems with regards to polypharmacy, such as an increased risk of missing doses, and harmful drug related problems (DRPs) associated with drug interactions, as well as reduced quality of life (QoL) and increased treatment burden (Klietz et al., 2019). High levels of polypharmacy associated with complex drug regimens among patients with PD have been linked to poor adherence, reducing therapeutic benefits such as improved mobility, activity, emotional wellbeing, cognition, communication, and body comfort (Daley et al., 2012; Daley et al., 2014). Given this poor adherence to therapy, it is important to understand the causes of this—both to reduce medicines wastage and so that patients get the best possible outcomes from their medicines (Wei et al., 2014).

As a member of the medical team, pharmacists have a key role in ensuring medicines optimisation, especially for patients prescribed multiple medicines and/or those prescribed low therapeutic index drugs (Avery et al., 2012). While to date there is a lack of evidence regarding the contribution of pharmacists to patient outcomes in China, where the role of pharmacists has tended to focus more on medicines supply than on supporting patients to get the best outcomes from their medicines (Yi et al., 2016), studies undertaken in other countries such as Brazil and the United States have demonstrated the contribution of pharmacists to medicines management of patients with PD with patients' adherence and QoL improved through pharmacists' interventions (Poon et al., 2012; Foppa et al., 2016). Given this evidence that pharmacists can effectively have a positive clinical impact on patients' OoL and drug related problems, an innovative service for patients with PD was developed at a 2,024-bed tertiary academic-teaching hospital in Beijing, the collaborative pharmaceutical care service (CPCS).

The CPCS involves a physician and a pharmacist collaborating in providing patient care, with pharmacists working with physicians in the diagnosis and management of patients to provide individualised care for patients. The service is provided in a clinic in the outpatients department. Initially, patients have a consultation with a physician and a pharmacist at the same time. Patients subsequently have a consultation with the pharmacist alone where the pharmacist reviews the patient's notes to identify drug related problems (DRPs) including potential drug interactions, monitor adverse events (AEs), respond to patient-related medication questions, and provide patient education so that patients get the right medicines and know how to take them correctly, with the intention of improving medicines safety, reducing medicines waste, and of enhancing patient outcomes (quality of life and adherence). During the patient education session, pharmacists provided a leaflet of usage and dosage for patients. Any interventions made by the pharmacist including identification of DRPs are recorded in the pharmacist's intervention records.

The aim of the study reported here was to investigate the impact of the CPCS. This has been achieved through addressing the following objectives:

1) To identify the impact of the CPCS pharmacist interventions on medication safety by comparing pattern of prescribed medications between CPCS patients and patients receiving standard of care;
2) To establish the impact of the CPCS on patient reported outcomes (adherence and quality of life [QoL]) by comparing

the changes seen from baseline to 3-months post-intervention among patients receiving CPCS.

2 MATERIALS AND METHODS

2.1 Overview of Study Design

To address the first study objective, records of patients with PD taking part in the CPCS were compared with records of patients with PD receiving standard of care. Patients who received standard of care only visited the physicians without consultation with the pharmacist. For the second study objective, longitudinal analysis of patient reported outcomes (adherence and QoL) captured at baseline (enrolment in the CPCS) and at 3-months follow-up was undertaken to determine impact.

2.2 Impact of CPCS on Medication Safety

To identify the impact of the CPCS pharmacist interventions on medication safety (Objective 1) recorded drug related problems (DRPs) and pharmacist interventions were extracted from pharmacist intervention records for the period March 2017 to March 2019. These data were merged with patient demographic information (age, gender, etc.) extracted from outpatient records, with additional data related to patient medication history derived from the hospital electronic prescription information system to create a dataset consisting of patients with PD receiving the CPCS. DRPs and pharmacist interventions data within the dataset were then coded using a validated framework for categorizing pharmaceutical care activities contributing to reducing patient harm associated with detecting DRPs and resolving them (Schaefer, 2002). Severity of AEs was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as Grade 1 to 5 which was widely used in previous studies (Common Terminology Criter, 2017; Smith et al., 2021). Severity of drug-drug interactions was evaluated with Lexi-Interact online (Lexicomp. Drugs interacti, 2021).

Those patients with PD receiving the CPCS were compared with those receiving standard of care to determine differences in medicines prescribed and dosage associated with these. Data related to patients with PD receiving standard of care were obtained from the electronic prescribing database from January 1, 2016, to August 15, 2018.

Data were entered into Microsoft Excel, and the distributions of DRPs and drug use were tabulated. Mean scores for continuous variables were calculated, with descriptive analysis of categorical variables consisting of frequency counts and percentages.

2.3 Impact of CPCS on Patient-Reported Outcomes

To establish the impact of the CPCS on adherence and quality of life, data were collected using a questionnaire consisting of validated measures of these patient-reported outcomes. Relevant factors affecting patients' QoL or medication adherence found in previous studies, such as gender, age, Hoehn-Yahr (H&Y, corrected) grading scale for the evaluation of severity of PD, and other disease related information, were considered at baseline patient characteristics (Schrag et al., 2000; Straka et al., 2018). The H&Y stages 1–2 indicated early stage, H&Y stages 2.5–3 medium stage, and H&Y stages 4–5 advanced stage of PD.

2.4 Inclusion Criteria for the CPCS on Patient-Reported Outcomes

Inclusion criteria for the CPCS was as following: (1) patients diagnosed with PD; (2) patients able to communicate; (3) patients able to consent to participate in the study. Patients with dementia or diagnosed with PD symptoms only were therefore not eligible to take part.

Patients with PD receiving the CPCS were followed up 3 months after the baseline measure on the basis of our systematic review on pharmaceutical service for patients with PD expert opinions and the time period used for repeat prescriptions in China.

2.5 Patient-Reported Outcomes and Validation

Patients' adherence was measured using a questionnaire including eight items, in which six items were scored as "yes" = 0 and "no" = 1, another item was "yes" = 1 and "no" = 0; and the last item was by adopting a 5-point Likert scale, namely "never," "occasionally," "sometimes," "frequently," "always," corresponding to scores of 1, 0.75, 0.50, 0.25, and 0, respectively. The reliability of the adherence scale was tested with half-reliability test. Change in adherence score before and after CPCS was investigated using a Wilcoxon sign rank sum test, and $p < 0.05$ indicates that the difference is statistically significant.

Patients' QoL was investigated using the 39 item PDQ-39 scale which consists of eight subscales: mobility (10 items), activity of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily pain (3 items) (Martinez-Martin et al., 2011). For the PDQ-39, a higher score indicates a poorer QoL. Among the influencing factors of patients' QoL scores, independent variables were used for Mann-Whitney Test U test for dichotomous variables; spearman correlation analysis was used for continuous variables; and changes in QoL before and after pharmacological services were measured with Wilcoxon sign rank sum test. Spearman correlation analysis was used to correlate the changes in QoL before and after pharmacological services with the number of interventions, and $p < 0.05$ indicates that the difference is statistically significant.

2.6 Sample Size

Sample size was calculated using PASS 11.0 software, with adherence the primary outcome and QoL the secondary outcome. Based on previous literature, where the mean ± standard deviation (SD) of change in adherence score before and after pharmacist intervention was −1.13 ± 0.96 (a lower the adherence score indicates higher adherence) (Zhang et al., 2018),

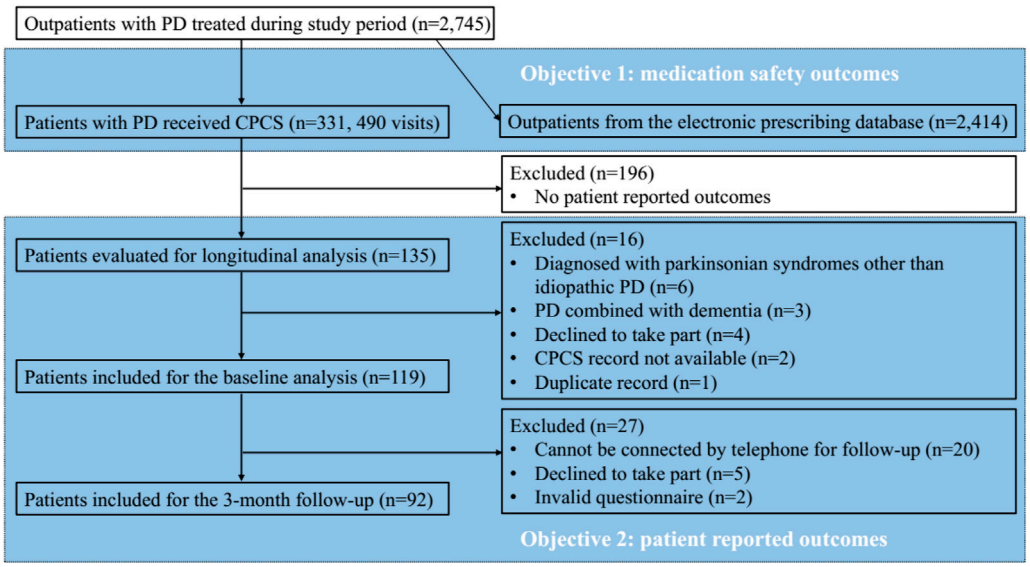

FIGURE 1 | Study participants.

and taking the test level α as 0.05 and the power as 0.90, a sample size of $n = 6$ was calculated for the primary outcome. For the secondary outcome, the results of a meta-analysis were used, where findings indicate that the emotional well-being subscale of PDQ-39 before and after the intervention of the pharmacist may have benefits, with a change value of −6.51 ± 24.34 (Mynors et al., 2007). With the test level α at 0.05, and the power is 0.80, the sample size here is $n = 87$. In view of the fact that older patients with PD may have a higher drop-out rate, a 30% increase in the sample size was considered and the final sample planned to be included was 113 patients.

3 RESULTS

3.1 Impact of the CPCS on Medication Safety

3.1.1 Participants' Demographics

A total of 331 patients with PD with an average age of 71.11 (±10.24 years old) received the CPCS. The service was delivered during 490 outpatient visits; 104 patients had multiple episodes of care. Most were over 65 years-old ($n = 244$, 73.7%) and male ($n = 181$, 54.7%).

In comparison, 2,414 patients with PD received standard of care. These patients were an average age of 71.83 (±12.54); and as with those receiving CPCS, most were male ($n = 1,319$; 54.64%). There were no statistically significant differences in age ($p = 0.317$) or gender ($p = 0.988$) between those patients receiving the CPCS and those who received standard of care (**Figure 1**).

3.2 Drug Related Problems

A total of 545 DRPs (mean 1.65 per patient) were recorded and interventions made by the pharmacist, of which 226 (41.47%) involved change to dosage, 135 (24.77%) related to AEs, 102 (18.72%) to change in a medication, 51 (9.36%) involved patient education, 18 (3.30%) interventions related to drug-drug interactions, 8 (1.47%) of special complications, and 5 (0.92%) to drug information. Among AEs, 38 (28.1%) were mild AEs (Grade 1) and the rest (71.9%) were moderate AEs (Grade 2). Ninety-nine (73.3%) interventions to AEs were fully accepted and implemented. Among the drug-drug interactions, five (27.8%), two (11.1%), nine (50.0%), and two (11.1%) were classed as "no known interactions," "no action needed," "monitor therapy," and "consider therapy modification," respectively. All interventions to the drug-drug interactions were fully accepted and implemented.

3.3 Prescribed Medicines

Comparing between those receiving the CPCS and receiving standard of care, some difference in medicines were found.

Across all patient age groups, patients receiving the CPCS were significantly less likely to have been prescribed pramipexole [18.52% (223/1,204) versus 23.77% (7,150/30,078), $p < 0.001$] and more likely to have been prescribed amantadine [5.40% (65/1,204) versus 3.70% (1,114/30,078), $p = 0.02$] and selegiline [17.36% (209/1,204) versus 11.64% (3,502/30,078), $p < 0.001$].

Among patients under 65, patients receiving the CPCS were significantly more likely to have been prescribed pirbedil [16.29%, (50/307) versus 11.64% (826/7,096), $p = 0.014$] and selegiline [25.08% (77/307) versus 14.66% (1,040/7,096), $p < 0.001$] and significantly less likely to have been prescribed pramipexole [11.07% (34/307) versus 20.49% (1,454/7,096), $p < 0.001$] and levodopa compound [30.29% (93/307) versus 36.81% (2,612/7,096), $p = 0.02$].

For patients over 65, those receiving the CPCS were significantly less likely to have been prescribed pramipexole than those receiving standard of care [21.07% (189/897) versus 24.78% (5,696/22,982), $p = 0.011$] and more likely to have been

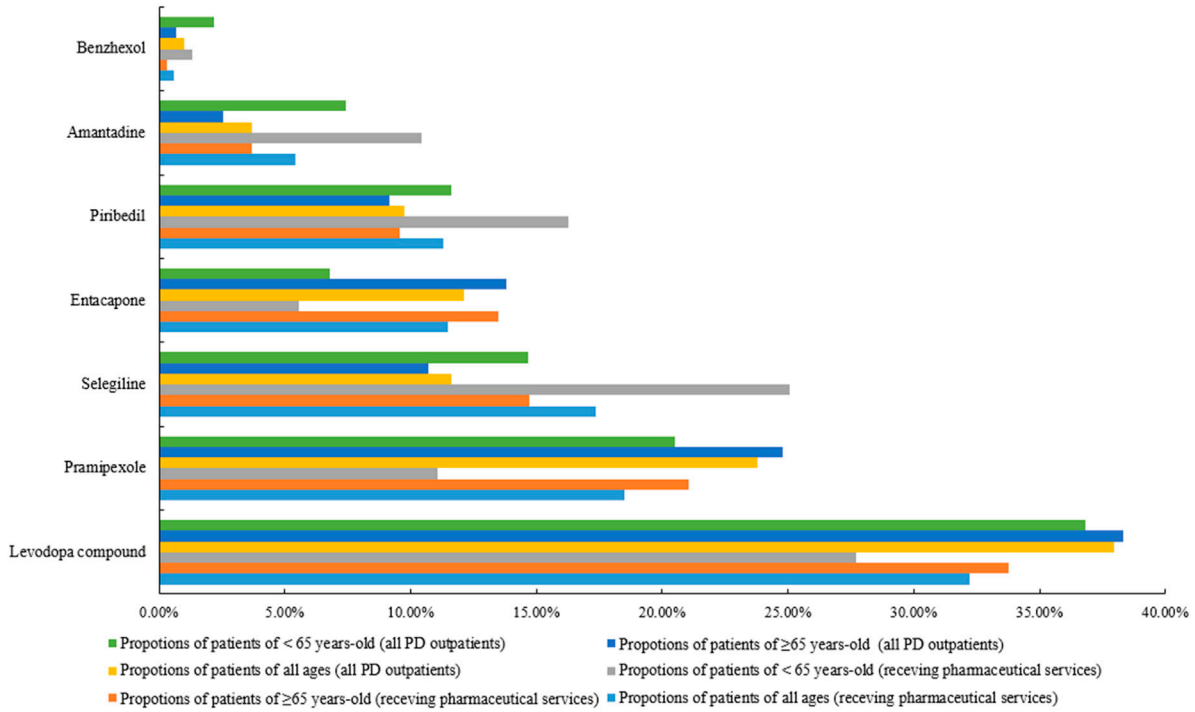

FIGURE 2 | Comparison of prescribing for patients receiving CPCS with patients receiving standard of care.

prescribed selegiline [14.72% (132/897) versus 10.71% (2,462/22,982), $p = 0.011$].

No statistical significant difference was found in the proportion of prescribed benzhexol and entacapone (**Figure 2**).

3.4 Medicines Dosage

Compared with patients with PD receiving standard of care, those receiving CPCS were prescribed significantly lower dosages of levodopa/benserazide (0.51 ± 0.31 g versus 0.84 ± 0.37 g, $p < 0.001$), levodopa/carbidopa (0.33 ± 0.23 g versus 0.66 ± 0.47 g, $p < 0.001$), pramipexole (1.14 ± 1.63 mg verusu 1.27 ± 0.69 mg, $p = 0.01$), and entacapone (130.00 ± 79.76 mg versus 173.09 ± 97.86 mg, $p < 0.001$).

3.5 Impact of the CPCS on Patient Reported Outcomes

3.5.1 Participants' Demographics

A total of 135 patients were invited to take part in this study. Of these 119 were enrolled, with patients excluded for the following reasons: six were diagnosed with parkinsonian syndromes other than idiopathic PD, three had a diagnosis of PD combined with dementia and hence lacked capacity to consent to participate, 4 declined to take part, two did not have CPCS records, and one duplicated record. The average age of participants was 69.98 years old (±9.90) with a median disease duration of 3.92 years; just over half (53.8%) were male. The median H&Y stage was 2.50, indicating that most participants were in the early stages of PD (see **Table 1** for details).

From the 119 participants followed up with consent, 92 took part in the second round of data collection. The reasons for loss to follow-up included: 20 not being available and 5 declined to take part. Among the 92 patients, the average age was 69.69 years old (±9.73) and just over half (53.3%) were male, which was similar to the baseline.

3.6 Medication Adherence

The half-reliability coefficient of the medication adherence scale was 0.454.

Of the included 122 patients, eight patients were not evaluated for medication adherence because they did not take any medication, and thus 114 patients were included in this analysis.

3.7 Related Factors of Medication Adherence

Univariate analysis found that the main influencing factor of medication adherence was mental health (whether combining with depression, anxiety, bipolar disorder, hallucinations, delusion, cognitive impairments) ($p < 0.001$) and hyposmia ($p = 0.032$).

3.8 Changes of Medication Adherence

The adherence score improved at 3-months follow-up (**Table 2**).

3.9 Frequency of CPCS and Medication Adherence

Frequency of receiving the CPCS was related to improvements in medication adherence, with a statistically significant difference

TABLE 1 | Participant profile at baseline.

Items	Sample size	Category and number
Gender	119	Male/Female: 64/55
Age (year, mean ± SD)	119	69.98 ± 9.90
Course/year (median, interquartile range)	113	3.92 (2.00,6.21)
H&Y scale (median, interquartile range)	119	2.50 (1.50,3.00)
Marital status	109	Married/widowed: 96/13
Education level	119	College and above: 61 Junior high to high school (including technical secondary school): 51 Primary and below: 7
Type of jobs	117	Individual, business, enterprise (service staff): 16 Technology, medical, teachers: 51 Executive: 17 Workers: 17 Farmers/Housewives: 9 Other: 7
Employment status	118	In-service: 7 Unemployed: 6 Retirement: 105
Payment methods	118	Health Insurance: 84 New Rural Cooperative: 6 Public expense: 25 Own expense: 3
Monthly household income	114	< 5,000 : 54 5,000–12,000 : 51 ≥12,000 : 9
Swallowing disorder	119	Yes/No: 23/96
Sleep disorder	119	Yes/No: 61/58
Mental symptoms	107	Yes/No: 45/62
Dysuria	119	Yes/No: 66/53
Constipation	119	Yes/No: 84/34 Colon cancer: 1
Hyposmia	119	Yes/No: 57/62
Wearing off phenomenon	119	Yes/No: 55/64
On/off phenomenon	119	Yes/No: 22/97

TABLE 2 | Medication adherence of patients with Parkinson's disease at baseline and 3-months follow-up.

Items	Baseline (n = 114)		3-months follow-up (n = 92)		p
	Mean ± standard deviation	Median, interquartile range	Mean ± standard deviation	Median, interquartile range	
Adherence	6.19 ± 1.50	6.75 (4.75,7.56)	6.72 ± 1.73	7.00 (6.38,8.00)	0.014

p *values refer to differences in means.*

between patients who received the CPCS twice (p = 0.011), three or more times (p = 0.026), and patients who received CPCS only once.

3.10 Association Between CPCS Components and Medication Adherence

Medication adherence was associated with the following components: medication information (n = 1, 0.87 points), usage and dosage (n = 54, 0.53 points), and medication selection (n = 24, 0.16 points). In combination, the following intervention components were also associated with medication adherence: usage and dosage plus medication information (n = 1, 1.25 points), medication selection plus medication information (n = 1, 1.25 points), medication selection plus usage (n = 14, 0.79 points), usage and dosage plus adverse reactions (n = 21, 0.73 points), medication selection plus patient education (n = 7, 0.64 points), adverse reactions plus patient education (n = 9, 0.36 points), usage and dosage plus patient education (n = 14, 0.30 points). However, only usage and dosage (p = 0.005) reached statistical significance.

3.11 Quality of Life (PDQ-39)

The baseline PDQ-39 total scores were 16.26 ± 10.52.

At 3-month follow-up, the number of outpatient visits to receive the CPCS ranged from 1 to 9, with most patients receiving it once (n = 60, 49.18%) or twice (n = 26, 21.31%). In terms of what was delivered during the CPCS, the most frequently occurring components of the intervention were changes to usage and dosage (57 cases, 36.31%), identification of adverse drug reactions (37 cases, 23.57%), patient education (32 cases, 20.38%), medication selection (24 cases, 15.29%), combined medications/interactions (6 cases, 3.82%), and provision of drug information (1 case, 0.64%).

TABLE 3 | Quality of life of patients with Parkinson's disease at baseline and 3-months follow-up.

Items	Baseline (n = 119)		3-months follow-up (n = 92)		p
	Mean ± standard deviation	Median, interquartile range	Mean ± standard deviation	Median, interquartile range	
Mobility	21.45 ± 26.24	10.00 (2.50,30.00)	22.74 ± 24.65	15.00 (2.50,35.00)	0.301
Activity of daily living	21.95 ± 22.83	16.67 (4.17,33.33)	23.96 ± 21.70	20.83 (8.33,37.50)	0.188
Emotional well-being	11.13 ± 17.54	4.17 (0.00,16.67)	12.41 ± 19.71	4.17 (0.00,13.54)	0.968
Stigma	12.08 ± 19.84	0.00 (0.00,18.75)	10.87 ± 17.87	0.00 (0.00,18.75)	0.297
Social support	3.22 ± 10.01	0.00 (0.00,0.00)	5.98 ± 12.62	0.00 (0.00,0.00)	0.028
Cognitions	23.16 ± 17.57	25.00 (6.25,31.25)	25.41 ± 17.60	25.00 (12.50,37.50)	0.319
Communication	7.07 ± 13.32	0.00 (0.00,8.33)	7.43 ± 13.89	0.00 (0.00,8.33)	0.827
Bodily pain	30.04 ± 22.21	25.00 (16.67,41.67)	23.01 ± 20.98	16.67 (0.00,41.67)	0.037
PDQ-39 total score	16.26 ± 10.52	14.48 (8.65,21.61)	16.48 ± 10.97	14.56 (8.06,23.10)	0.696

p *values refer to differences in means.*

The 3-months follow-up PDQ-39 total scores was 16.48 ± 10.97 (**Table 2**).

3.12 Factors Related to Quality of Life

After univariate analysis, it was found that the main factor affecting the PDQ-39 total QoL was age (≥70 years) (p < 0.001), H&Y stages (p < 0.001), constipation (p = 0.002), dysphagia (p = 0.002), dysuria (p = 0.001), "on-off" phenomenon (p = 0.003), and "wearing-off" phenomenon (p = 0.001). In general, those who were older (≥70 years) and reported dysphagia, constipation, "on-off" phenomenon, "wearing-off" phenomenon, and higher H&Y stage reported poorer QoL.

3.13 Changes of Quality of Life

At 3-month follow-up, participants reported improvement in bodily pain subscale (baseline versus 3-months follow-up, 30.04 ± 22.21 versus 23.01 ± 20.98, p = 0.037). No statistically significant differences were found in patients' PDQ-39 total score and mobility, activity of daily living, emotional well-being, stigma, cognitions, and communication subscales when subscales were adjusted (**Table 3**).

3.14 Frequency of Patients Receiving CPCS and Quality of Life

Frequency of CPCS use was related to activity of daily living subscale (r = 0.208, p = 0.047) and the bodily pain subscale (r = 0.232, p = 0.026), with statistically significant differences among patients who received the CPCS three or more times and patients who received CPCS for once (p = 0.013) or twice (p = 0.047). Frequency of receiving the CPCS was not related to PDQ-39 total score (p = 0.260), mobility subscale (p = 0.539), emotional well-being subscale (p = 0.359), stigma subscale (p = 0.274), social support subscale (p = 0.616), cognitions subscale (p = 0.395), and communication subscale (p = 0.416).

3.15 Association Between CPCS Components and Quality of Life

Total score of PDQ-39 was associated with the following components: patient education (n = 32, −0.38 points), adverse reactions (n = 37, −0.36 points), usage (n = 57, −0.36 points), and medication selection (n = 24, −0.16 points). In combination, the following intervention components were also associated with PDQ-39: usage and dosage plus patient education (n = 14, −1.94 points), medication selection plus usage (n = 14, −1.02 points), medication selection plus patient education (n = 7, −0.85 points), usage and dosage plus adverse reactions (n = 22, −0.84 points), adverse reactions plus patient education (n = 9, −0.80 points). However, only patient education (p = 0.005) and usage and dosage combined with patient education (p = 0.006) reached statistical significance.

4 DISCUSSION

The purpose of this study was to investigate the impact of the CPCS on medication safety and patient reported outcomes. Two databases were used as well as questionnaires consisting of validated measures. For medication safety, the study found that the CPCS could resolve DRPs, improve prescribed medicines, and lower medicines dosages. For patient reported outcomes, the CPCS improved bodily pain subscale and patient adherence, while no significant difference was found in the PDQ-39 total scores and other subscales.

The CPCS was effective in reducing medication risk for PD patients. This is important as movement complications caused by levodopa (such as dyskinesia), which usually occur at about 2–5 years with the medication, could be reduced as a consequence of the CPCS (Turcano et al., 2018; Bressman and Saunders-Pullman, 2019). A randomized double-blind study indicated dosage as a risk factor for motor complications (Olanow and Stocchi, 2018). A Japanese study on data from medical insurance database during 2005–2016 showed the equivalent daily dose of levodopa as 500.0 mg for patients with a PD course of 5–7.5 years (Kasamo et al., 2019). Dosages of levodopa/benserazide in patients receiving CPCS in our hospital was similar to that of these Japanese patients (average daily dose 0.51 ± 0.31 g); compared with patients receiving standard of care, the average dosage was lower, suggesting that the CPCS played a role in adjusting medication dosages and thus reducing the risk of motor complications.

The CPCS as an intervention was intended to improve adherence and QoL (Martinez-Martin et al., 2015). The study

found that the CPCS needs to involve frequent contact with patients in order to affect patient outcomes, and highlights a role for pharmacists in following-up service delivery for PD patients. This is not surprising, as previous studies have found that it is important for interventions to be delivered over time and not just on a single occasion to have a sustained effect (Rigotti et al., 2014). As previous studies have found that Chinese patients valued information about their medicines usage and dosage (Yi et al., 2015), during CPCS, pharmacists provided a leaflet of usage and dosage for patients. Our study also found that CPCS components in usage and dosage could improve patients' medication adherence, which indicated a further strengthened in the future.

Our study also found that patient education or a combination of dosage and patient education can improve patients' PDQ-39 scores; however, it was not possible to investigate the subscales of this, due to a small sample size in relation to the six intervention components. While this is a limitation of this study, a previous study of PDQ-39 scale in mainland China found that the PDQ-39 scale retesting reliability of the stigma, social support, and cognitive subscales was poor (Luo et al., 2010). Moreover, although some changes in PDQ-39 scores were made and that the scale was validated for Chinese patients, it may not be the most culturally sensitive tool for this population. Other scales for quality of life may be more useful for future studies, such as health-related quality of life (Rajan et al., 2020).

Our study is the first to evaluate the outcomes of CPCS for PD patients using the MRC framework for the development and evaluation of complex interventions (Developing and evaluating, 2019). Prior to undertaking the study reported here we conducted an extensive search of the evidence-base to identify suitable evaluation indicators and outcomes, follow-up time, and intervention components (Yi et al., 2020e2075). As a consequence of this we were able to design a robust investigation incorporating multiple outcome measures, overcoming the limitations of previous studies. We have also been able to establish whether frequency of CPCS delivery has an impact on outcomes, and which intervention components are associated with these, thus providing us with insight into likely intervention mechanisms that can be investigated in more detail in future studies.

Despite this, our study has some limitations. Firstly, not all PD patients could be followed up to capture repeated measures of adherence and PDQ-39 scales, which means that those proving two sets of data may not be representative of all patients. Patients with a higher H&Y stage or combined with non-motor symptoms tended to decline to take part at follow-up, which may have introduced bias in patient selection. Furthermore, the acceptability of and satisfaction with the CPCS was not evaluated in the study, the implications of interventions on DRPs were not recorded. Thirdly, due to limited number of pharmacists providing CPCS, the number of patients who received CPCS is relatively small considering the prevalence of PD in China. Fourthly, although there were no statistically significant differences in age or gender between those patients receiving the CPCS and those who received standard of care, the participants receiving CPCS and standard of care may not be comparable. CPCS was a pharmacist initiated quality improvement campaign and the study was a post-hoc evaluation of its effectiveness, not a study designed in a prospective manner, thus the treatment and measurement were not implemented concurrently for these two groups. Nevertheless, we were not aware of major environmental differences during this period. All study participants were recruited and managed within the single institution.

5 CONCLUSION

A pharmaceutical care intervention designed to support patients with PD can successfully address drug treatment-related problems, improve medication regimens, patients' QoL, and medication adherence when delivered on two or more occasions. Intervention components consisting of medication dosage adjustments and patient education contributed most to observed intervention outcomes. However, a randomized controlled study is needed to confirm the current findings and explore the mechanisms of interventions.

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 author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Peking University Third Hospital Ethics Committee. Written informed consent for participation was exempt for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

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

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SYSTEMATIC REVIEW
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Effect of Urate-Lowering Therapy on the Progression of Kidney Function in Patients With Asymptomatic Hyperuricemia: A Systematic Review and Meta-Analysis

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Background: Hyperuricemia is involved in the risk of chronic kidney disease (CKD). However, whether urate-lowering therapy (ULT) can influence the progression of kidney function in patients with asymptomatic hyperuricemia is still controversial. We conducted a systematic review and meta-analysis to evaluate the effect of ULT on the progression of kidney function in asymptomatic hyperuricemia patients.

Methods: The MEDLINE, EMBASE and Cochrane databases were searched without language, national or ethnic restrictions for randomized controlled trials published prior to November 30, 2020, that compared ULT with controlled therapy in patients with asymptomatic hyperuricemia.

Results: Eleven studies were included for qualitative synthesis. ULT did not ameliorate eGFR slopes (WMD 0.36 ml/min/1.73 m^2 per year, 95% CI: −0.31, 1.04), or lead to reductions in kidney events (RR 1.26; 95% CI: 0.80, 2.00) or all-cause mortality (RR 1.00; 95% CI: 0.65, 1.55), although ULT resulted in a decrease in serum uric acid levels (WMD −2.73 mg/dl; 95% CI: −3.18, −2.28) and lowered the incidence of gout episodes (0.9 vs 2.7%, RR 0.38; 95% CI: 0.17, 0.86).

Conclusion: In patients with asymptomatic hyperuricemia, ULT did not decay the progression of kidney function. Long-term and larger sample studies are needed to verify the results.

Systematic Review Registration: [www.crd.york.ac.uk/PROSPERO/#recordDetails], identifier [CRD42020204482].

Keywords: urate-lowering therapy, asymptomatic hyperuricemia, eGFR slopes, kidney events, chronic kidney disease

INTRODUCTION

Hyperuricemia is often accompanied by traditional metabolic abnormalities, such as cardiovascular diseases, type 2 diabetes, hypertension and obesity, and was shown to be an independent risk factor for all-cause and cardiovascular mortality with a mild elevation of serum uric acid levels in a nationwide community-based population followed up for 7 years (Konta et al., 2020). Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities of the kidney lasting for more than 3 months. Cardiovascular disease, end-stage renal disease requiring renal replacement therapy (RRT), and mortality increase with a decrease in the glomerular filtration rate (GFR) (Gansevoort et al., 2013). It is essential to detect and mitigate the possible risk factors for kidney function deterioration. Several studies have shown that uric acid is an independent risk factor for the occurrence and progression of kidney diseases (Bellomo et al., 2010; Li et al., 2014; Oh et al., 2019; Zhou et al., 2019) and is associated with a significant decrease in kidney function (Tsai et al., 2017). Hyperuricemia is involved in the risk of incident RRT and all-cause mortality in patients with stage 3–5 CKD (Lee and Wang, 2019). However, correlational relationships do not represent causation.

Asymptomatic hyperuricemia and gout are continuous pathological processes of hyperuricemia. Performing interventions to treat gout in patients with CKD can have benefits such as delaying and ameliorating renal function(Novella-Navarro et al., 2020). This issue has been affirmed and recommended by guidelines in China and America. However, whether asymptomatic hyperuricemia should be treated in patients with CKD remains controversial. A randomized controlled trial (RCT) with a follow-up of 6 months showed that febuxostat had the ability to delay decreases in the GFR in patients with asymptomatic hyperuricemia and CKD by decreasing serum uric acid levels (Sircar et al., 2015). Nevertheless, an RCT with a duration of 108 weeks of follow-up demonstrated that febuxostat did not delay the advancement of kidney function in patients with similar conditions (Kimura et al., 2018). The guidelines of America did not recommend treatment for these patients (Fitzgerald et al., 2020). In China's guidelines, it is suggested that patients with asymptomatic hyperuricemia should be treated with urate-lowering drugs when the level of serum uric acid ≥540 μmol/L or 480 μmol/L with one of the following comorbidities: hypertension, abnormal lipid metabolism, diabetes, obesity, stroke, coronary heart disease, cardiac insufficiency, urinary acid nephrosis, or renal function damage (≥CKD stage 2) (Chinese Society of Endocrinology, 2020). A Cochrane systematic analysis showed that in patients with or without CKD, ULT may prevent the development of CKD (Sampson et al., 2017). Su et al. (Su et al., 2017) performed a meta-analysis and demonstrated that ULT can reduce the relative risk (95% CI, 31, 64) of kidney failure events by 55% in patients with CKD. Unfortunately, these studies did not distinguish between patients with gout and those with asymptomatic hyperuricemia, which may muddle the interpretation of the results.

We performed a systematic review and meta-analysis to evaluate the efficacy of urate-lowering therapy on the progression of kidney function in patients with asymptomatic hyperuricemia.

METHODS

Protocol

We carried out the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol of our study was registered in PROSPERO (No. CRD42020204482).

Search Strategies and Selection Criteria

The MEDLINE, Embase and Cochrane databases were searched until November 30, 2020, without limitations on language, country, or race.

The following terms and their relevant formations were used: "xanthine oxidase inhibitor OR allopurinol OR febuxostat OR topiroxostat OR pegloticase OR probenecid OR puricase OR urate lowering therapy" AND "asymptomatic hyperuricemia" OR "hyperuricemia" AND "randomized controlled trial".

Inclusion and Exclusion Criteria

Studies meeting the following criteria were included: 1) patients aged more than 18 years old with asymptomatic hyperuricemia (serum uric acid concentration ≥6.8 mg/dl (Fitzgerald et al., 2020) or uric acid level of women ≥360 umol/L), if the mean serum uric acid level ≥6.8 mg/dl in all included patients, the study was included; 2) patients have had subcutaneous tophi or have had gout, but no acute episodes in the past 1 year; 3) randomized controlled trials lasted more than 3 months and compared urate-lowering therapy with placebo or traditional treatment. The exclusion criteria were as follows: 1) patients currently experiencing gout; 2) trials compared the efficacy of different urate-lowering therapies or different doses of the same drugs.

Outcome Measures of Efficacy and Safety

The primary outcome of efficacy was the change of eGFR slopes. The secondary endpoints were changes in estimated GFR (eGFR), kidney events (kidney failure (defined as GFR< 15 ml/min/1.73 m^2) or end stage kidney disease (ESKD) (defined as treatment with maintenance dialysis or kidney transplantation) or established surrogate end point: doubling of serum creatinine (equivalent to 57% decline in eGFRcr) or more than 40% estimated GFR decline) (Levey et al., 2014; Kanda et al., 2018), uric acid levels, and blood pressure, gout episodes and all-cause mortality.

Data Extraction and Risk of Bias

Based on the inclusion and exclusion criteria, two researchers (XM and KA) independently screened the full text of the eligible studies and carried out data extraction. Baseline patient demographics, interventions, outcomes and adverse events

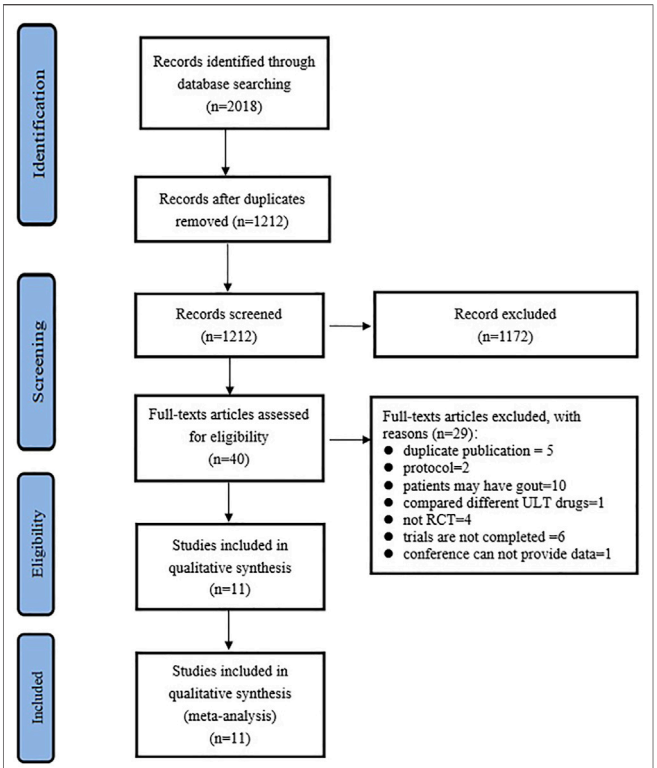

FIGURE 1 | PRISMA Flow diagram of the study.

were extracted. Any inconsistencies between them were resolved by further discussion in consultation with a third reviewer if necessary (LZ).

MZ and QS used the Cochrane Collaboration's risk of bias tool to conduct the methodological quality assessment shown as risk of bias of the included RCTs (Higgins et al., 2011), including assessments of random sequence generation, allocation concealment, blinding of outcome assessors, selective outcome reporting, and other items. Studies were rated as having either a low, high, or unclear risk of bias. Any disagreements were resolved by discussion and consultation with a third reviewer (S.Q.L.).

Data Synthesis and Analysis

Data synthesis was conducted with RevMan (version 5.2). Weighted mean differences (WMDs), 95% confidence intervals (CIs) for continuous effects and risk ratios (RRs) for dichotomous effects were calculated. If more than two arms were included in one intervention in one study, the effect sizes were combined to obtain a mean difference. When the standard deviation (SD) of continuous data changes was not reported in the study, it was calculated according to the equation provided in the Cochrane System Review Handbook. The I^2 value was used to assess the heterogeneity between the included studies; low, moderate and high heterogeneity were indicated when the I^2 value was less than 25%, 25%–50% and more than 50%, respectively. A random effects model was selected regardless of the I^2 value for statistical analysis. Begg's funnel graph was used to evaluate the potential publication bias by Stata (version 14, StataCorp. 2015) due to the subjectivity of inspecting the symmetry, Egger's test was also performed to assess the bias. Publication bias may exist when Begg's funnel diagram is considered asymmetrical and when Egger's test has a p value less than 0.05. Subgroup analysis for changes in eGFR was employed based on the number of participants ("less than or equal to" or more than 100 patients in each group). Sensitivity analysis was employed to appraise the stability of the pooled WMD of uric acid levels.

RESULTS

Search Results

The PRISMA selection flow chart is shown in **Figure 1**. Through the database searching, a total of 2,018 records were identified. A total of 1212 records were identified after duplicate removal, and 40 full-text articles were assessed for eligibility. Finally, 11 studies (Siu et al., 2006; Liu et al., 2015; Sircar et al., 2015; Takir et al., 2015; Golmohammadi et al., 2017; Jalal et al., 2017; Kimura et al., 2018; Mukri et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020) were included for qualitative synthesis.

Clinical Characteristics

The patients' baseline demographics, characteristics, intervention arms, and study duration are exhibited in **Supplementary Table S1**. A total of 1,551 and 1,544 subjects were included in the uric-lowering therapy group and control group, respectively. The duration of the studies was between 12 weeks and 3 years. The uric-lowering drugs were allopurinol (Siu et al., 2006; Liu et al., 2015; Takir et al., 2015; Golmohammadi et al., 2017; Jalal et al., 2017; Badve et al., 2020) and febuxostat (Sircar et al., 2015; Kimura et al., 2018; Mukri et al., 2018; Kojima et al., 2019; Tanaka et al., 2020). The included trials were either multicenter trials (Jalal et al., 2017; Kimura et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020), or single-center trials (Siu et al., 2006; Liu et al., 2015; Sircar et al., 2015; Takir et al., 2015; Golmohammadi et al., 2017; Mukri et al., 2018). Serum uric acid levels ranged from 7.26 ± 0.15 to 9.92 ± 1.68 mg/dl, and the eGFR ranged from 20.84 ± 5.80 to 90.1 ± 18.4 ml/min/1.73 m^2. The eGFR in the included patients was less than 60 ml/min/1.73 m^2 in eight studies (Sircar et al., 2015; Golmohammadi et al., 2017; Jalal et al., 2017; Kimura et al., 2018; Mukri et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020), more than 60 ml/min/1.73 m^2 in one study (Liu et al., 2015), and not mentioned in detail in two studies (Siu et al., 2006; Takir et al., 2015).

Risk of Bias of Included Studies

The risk of bias of the included studies was estimated by the Cochrane Collaboration's risk of bias tool (**Supplementary Figure S1**). Nine studies (Siu et al., 2006; Liu et al., 2015; Sircar et al., 2015; Jalal et al., 2017; Kimura et al., 2018; Mukri et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020) described random sequence generation clearly. Blinding of participants and personnel (performance bias) was mentioned in three studies (Sircar et al., 2015; Jalal et al., 2017; Badve et al.,

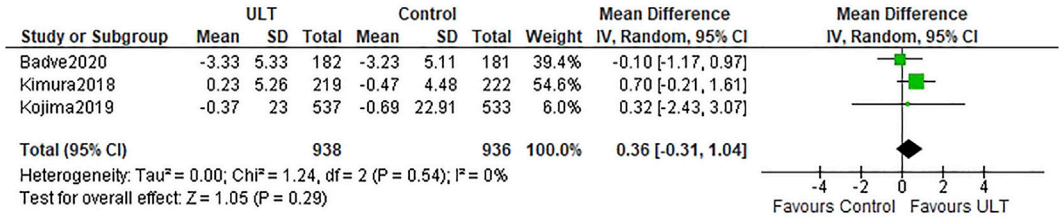

FIGURE 2 | eGFR slopes: ULT vs control group.

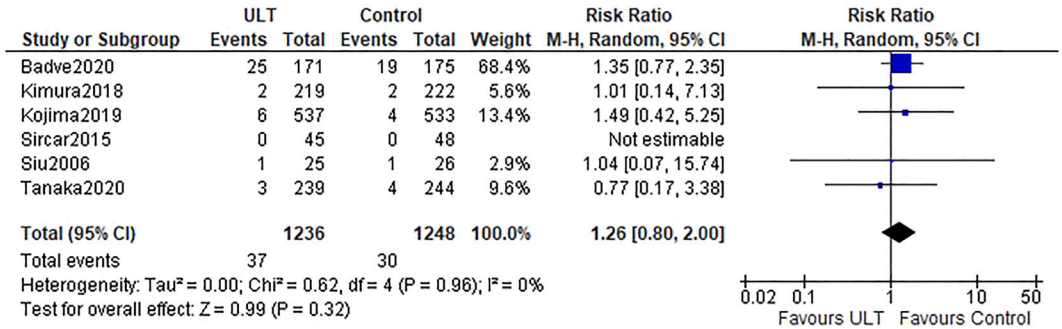

FIGURE 3 | Kidney events: ULT vs control group.

2020), unclear in one study (Golmohammadi et al., 2017); hence seven studies (Siu et al., 2006; Liu et al., 2015; Takir et al., 2015; Kimura et al., 2018; Mukri et al., 2018; Kojima et al., 2019; Tanaka et al., 2020) had a high risk of bias for this aspect. Allocation concealment was unclear in six studies (Siu et al., 2006; Liu et al., 2015; Takir et al., 2015; Golmohammadi et al., 2017; Kimura et al., 2018; Mukri et al., 2018).

eGFR Slopes

Three studies (Kimura et al., 2018; Kojima et al., 2019; Badve et al., 2020) described the eGFR slopes. There was no difference in the eGFR slopes between the ULT group and the control group (WMD 0.36 ml/min/1.73 m^2 per year; 95% CI: −0.31, 1.04) (**Figure 2**).

eGFR

Seven studies (Liu et al., 2015; Sircar et al., 2015; Golmohammadi et al., 2017; Jalal et al., 2017; Kimura et al., 2018; Mukri et al., 2018; Tanaka et al., 2020) presented the results or changes in eGFR before and after interventions. The results were presented as median (IQR) in one study (Mukri et al., 2018). We could not obtain the mean and standard deviation, hence the study was not included in our statistical analysis. The pooled results showed that ULT could improve renal function compared with control groups (WMD 2.93 ml/min/1.73 m^2; 95% CI: 1.00, 4.87) with obvious heterogeneity (I^2 = 80%) (**Supplementary Figure S2**).

However, the other studies did not provide the change of eGFR, especially in the study of Kojima et al., which included a large number of subjects and did not show the difference between febuxostat and control groups. These may lead to the bias of evaluating the effect of ULT on eGFR. When the studies with the number of participants≤100 in each group were excluded, ULT did not ameliorate eGFR (WMD 0.56 ml/min/1.73 m^2; 95% CI: −0.42, 1.53) with no heterogeneity (I^2 = 0%) (**Supplementary Figure S3**).

Kidney Events

Six studies (Siu et al., 2006; Sircar et al., 2015; Kimura et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020) referred to the kidney events. Overall, there were 37 (37 of 1,236 patients, 3.0%) and 30 (30 of 1,248 patients, 2.4%) kidney events in the ULT and control groups, respectively. There was no difference between the ULT and control groups (RR 1.26; 95% CI: 0.80, 2.00) (**Figure 3**).

Uric Acid

All the studies reported uric acid levels before and after intervention. Compared with the control group, ULT significantly lowered serum uric acid levels (WMD -2.73 mg/dl; 95% CI: −3.18, −2.28) (**Figure 4**). Both allopurinol and febuxostat notably decreased serum uric acid levels.

For the Begg's plot (**Supplementary Figure S4A**) of uric acid, the studies were distributed approximately symmetrically. The *p* value for the Egger's test was 0.095 (**Supplementary Figure S4B**) and the Egger's plot shown in **Supplementary Figure S4C**, suggested a low risk of publication bias.

Sensitivity analysis was performed by excluding each study one by one; and the difference did not change, which showed the stability of the result.

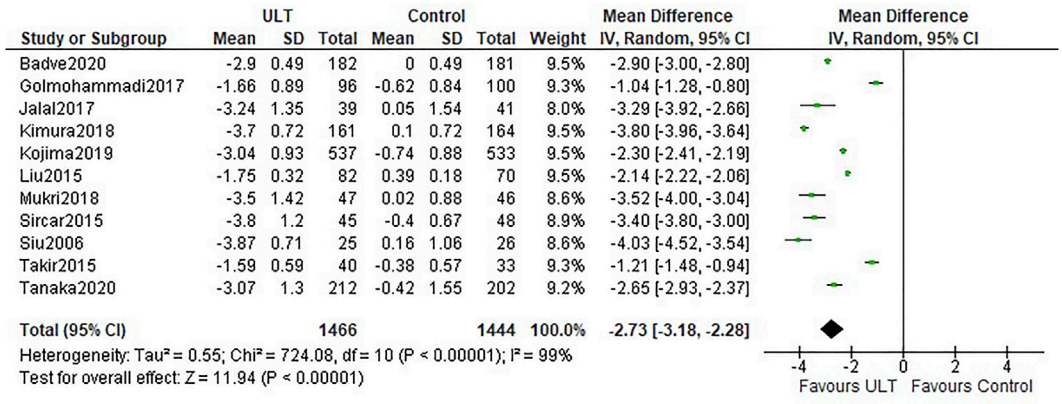

FIGURE 4 | Uric acid levels: ULT vs control group.

Blood Pressure

ULT had the ability to decrease systolic blood pressure (WMD −3.88 mmHg; 95% CI: −4.85, −2.91) (**Supplementary Figure S5**) and diastolic blood pressure (WMD −2.41 mmHg; 95% CI: −3.31, −1.52) (**Supplementary Figure S6**).

Gout Episodes

Five studies (Jalal et al., 2017; Kimura et al., 2018; Kojima et al., 2019; Badve et al., 2020; Tanaka et al., 2020) reported the incidence of gout episodes. The incidence of gout episodes was 0.9% (11/1,216) and 2.7% (33/1,221) in the ULT and control groups, respectively. Urate-lowering treatment seemed to decrease the incidence of gout episodes when compared with the control (RR 0.38; 95% CI: 0.17, 0.86) (**Supplementary Figure S7**).

All-Cause Mortality

Eight studies provided information on the incidence of all-cause mortality. Forty patients died in each of the groups i.e., ULT (3.1%) and control (3.0%). There was no difference in all-cause mortality between the ULT and control groups (RR 1.00; 95% CI: 0.65, 1.55) (**Supplementary Figure S8**).

DISCUSSION

Our meta-analysis evaluated the kidney outcomes of ULT in patients with asymptomatic hyperuricemia and found that compared with the control group, ULT did not ameliorate eGFR slopes, or lead to reduction in kidney events or all-cause mortality, although ULT resulted in a decrease in serum uric acid levels and lowered the incidence of gout episodes.

There is consensus on initiating ULT when a patient has gout. Nevertheless, this may not be the case in patients without gout or asymptomatic hyperuricemia. Our results demonstrated that ULT did not reduce eGFR slopes or kidney events in patients without gout. Although several theoretical mechanisms provided the possibility of the damaging effects of uric acid in causing CKD (Sanchez-Lozada et al., 2002; Sanchez-Lozada et al., 2008), our results did not support them.

Gout episodes are caused by the incorporation of crystalloid salts of uric acid into the joints. With the rise of uric acid levels, the risk of acute gout episodes increases simultaneously. Our results showed that ULT lowered the incidence of gout episodes in patients without gout. Nevertheless, the incidence of gout episodes events was 1.27 and 2.71% in the ULT and control groups respectively, which was relatively low.

The impact of uric acid on hypertension is of research interest. A single-center longitudinal cohort study with nearly 20 years of follow-up indicated that elevated serum uric acid was related to the progression of hypertension (Wang et al., 2014). A meta-analysis including 25 studies with 97,824 participants showed that hyperuricemia increased the risk of incident hypertension (Wang et al., 2014). Increased uric acid concentrations were associated with a high risk of the development of hypertension (Grayson et al., 2011). ULT treatment exhibited a reduction hazard ratio and risks of hypertension (Feig et al., 2008; Lin et al., 2020) and lowered blood pressure in patients with hyperuricemia and hypertension (Gunawardhana et al., 2017; Qu et al., 2017). Our results showed the possible benefit of ULT in subjects without gout.

Hyperuricemia has been shown to be an independent risk factor for mortality in patients with chronic obstructive pulmonary disease (Zhang et al., 2015). A retrospective case-matched cohort study revealed that patients with asymptomatic hyperuricemia had an increased risk of all-cause and CVD mortality and that ULT can reduce the risk of all-cause death (Chen et al., 2015). However, this was in contrast to our result, which indicated that there was no difference between the ULT

and control groups in all-cause mortality. This finding needs to be investigated further.

Limitations

There were some limitations in our review. First, the equations for evaluating eGFR were CKD-EPI (Jalal et al., 2017; Mukri et al., 2018; Badve et al., 2020), the Japanese eGFR equation (Kimura et al., 2018; Kojima et al., 2019), MDRD (Sircar et al., 2015) or were not reported (Siu et al., 2006; Liu et al., 2015; Takir et al., 2015; Golmohammadi et al., 2017; Tanaka et al., 2020), which may influence the assessment of the real GFR of included subjects. Second, the only included ULTs were allopurinol and febuxostat, which may lead to bias in assessing the effects of ULTs. Furthermore, since only three studies mentioned blinding of participants and personnel, specifically, therefore, the possibility of performance bias may exit. In addition, some studies did not provide the change of eGFR slopes and eGFR, which may lead to bias in evaluating the efficacy of ULT.

CONCLUSION

In conclusion, our meta-analysis evaluated the effect of ULT on kidney function in patients with asymptomatic hyperuricemia. Compared with the control group, ULT did not ameliorate eGFR slopes, or lead to reductions in kidney events or all-cause mortality, although ULT resulted in a decrease in serum uric acid levels and lowered the incidence of gout episodes. Long-term and larger sample studies are needed to verify the kidney outcomes of ULT in patients with asymptomatic hyperuricemia.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Research idea and study design: LZ, SL; statistical analysis: LZ; data extraction: KA, XM; methodological quality assessment: MZ, QS, data analysis/ interpretation: All. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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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.2021.795082/full#supplementary-material

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Barriers and Enablers for Adherence to Antiretroviral Therapy Among People Living With HIV/AIDS in the Era of COVID-19: A Qualitative Study From Pakistan

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Background: With the increased availability of safe antiretroviral therapy (ART) in recent years, achieving optimal adherence and patient retention is becoming the biggest challenge for people living with HIV (PLWH). Care retention is influenced by several socioeconomic, socio-cultural, and government policies during the COVID-19 pandemic. Therefore, we aim to explore barriers and facilitators to adherence to ART among PLWH in Pakistan in general and COVID-19 pandemic related in particular.

Methods: Semi-structured interviews were conducted among 25 PLWH from December 2020 to April 2021 in the local language (Urdu) at the ART centre of Pakistan Institute of Medical Sciences, Islamabad, Pakistan. Interviews were audio-recorded in the local Urdu language, and bilingual expert (English, Urdu) transcribed verbatim, coded for themes and sub-themes, and analyzed using a phenomenological approach for thematic content analysis.

Results: Stigma and discrimination, fear of HIV disclosure, economic constraints, forgetfulness, religion (Ramadan, spiritual healing), adverse drug reactions, lack of social support, alternative therapies, and COVID-19-related lock-down and fear of lesser COVID-19 care due to HIV associated stigma were identified as barriers affecting the retention in HIV care. At the same time, positive social support, family responsibilities, use of reminders, the beneficial impact of ART, and initiation of telephone consultations, courier delivery, and long-term delivery of antiretrovirals during COVID-19 were identified as facilitators of HIV retention.

Conclusion: Improving adherence and retention is even more challenging due to COVID-19; therefore, it requires the integration of enhanced access to treatment with improved employment and social support. HIV care providers must understand these reported

factors comprehensively and treat patients accordingly to ensure the continuum of HIV care. A coordinated approach including different stakeholders is required to facilitate patient retention in HIV care and consequently improve the clinical outcomes of PLWH.

Keywords: people living with HIV/AIDS, antiretrovirals, barriers and facilitative factors, Pakistan, challenges, interventions, UNAIDS

INTRODUCTION

With significant advances in antiretroviral therapy (ART), acquired immunodeficiency syndrome (AIDS) has progressed from acute to manageable chronic human immunodeficiency virus (HIV) infection, with improved immunity, viral suppression, and improved health-related quality of life (HRQoL) of people living with HIV/AIDS (PLWHA) (Kanters et al., 2017; Ahmed et al., 2021a). However, retention in HIV care has become a significant challenge, and it is seen more difficult during the COVID-19 pandemic due to lockdown and travel restrictions (Kanters et al., 2017; Jiang et al., 2020; Mhango et al., 2020). Non-adherence to ART is a common problem among HIV patients, with rates ranging from 19% in North America and Western Europe to 40% in Latin America, 28–42% in Africa, and 40% in Asia-Pacific (UNAIDS, 2021). ART-default (loss of follow-up) has been reported as an important factor leading to viral resistance, and disease progression that leads to ultimate consequences such as co-morbid conditions and mortality (Abadiga et al., 2020; Ahmed et al., 2021). HIV outbreaks are on the rise in Pakistan, which currently accounts for 0.24 million PLWHA (NACP, 2021; Ahmed et al., 2019). As of August 2021, 46,912 PLWHA registered with the National AIDS Control Programme (NACP), Pakistan, of which 26,093 are on treatment, implying that approximately 45% are not on treatment (NACP, 2021).

The research on PLWHA affected by COVID-19 is in the infancy stage; however, a recent meta-analysis reported that PLWHA are likely to have a significantly high risk of contracting COVID-19 infection [risk ratio (RR) 1.24, 95% confidence interval (CI) 1.05–1.46)] and mortality (RR 1.78, 95% CI 1.21–2.60) compared to the general population (Ssentongo et al., 2021). According to a modelling study by World Health Organization (WHO) in the Sub-Saharan African region, impediments in the supply of antiretrovirals (ARVs) and other HIV prevention services will exacerbate the situations such as; increasing the likelihood of HIV-related morbidities and new HIV outbreaks (Jewell et al., 2020). During the pandemic, all the countries have adopted measures to reduce the spread of COVID-19 infection, thus restricting a person to person physical contact by way of social distancing (Shiau et al., 2020). The measure such as Lock-down strategy are aimed at confining residents at home, thus limiting their movement. In such scenarios, provision of healthcare services to patients with chronic conditions such as HIV is affected significantly due to disruption or restriction of hospital visits, diagnosis and ultimately hamper the treatment for PLWHA (Linnemayr et al., 2020). To date limited data is available in the context of COVID-19 restrictions pertaining to PLHWA attaining ART from HIV clinics.

Adherence to ART is a dynamically complex behaviour influenced by socioeconomic as well as cultural factors (Castro, 2005). Some qualitative studies have reported barriers that include forgetfulness, fatigue, hopelessness (Jones et al., 2015), stigma and discrimination (Wasti et al., 2012), HIV non-disclosure (Arnold et al., 2014), and religious beliefs (Holtzman et al., 2015; Medved Kendrick, 2017). Facilitators of retention to treatment include family support (Yehia et al., 2015), positive relationship with healthcare providers (Nam et al., 2008), access to affordable transportation (Yehia et al., 2015), livelihood support (Wang et al., 2020), improved knowledge about the disease (Ammon et al., 2018), reminders (Nam et al., 2008), attending a support group (Wang et al., 2020), and carrying ART while away from home (Kumarasamy et al., 2005; Croome et al., 2017). Many of the reported barriers and facilitators are implicated in the Pakistani context; however, some may be unique and not reported in the literature. Therefore, in this study we are aiming to explore factors in Pakistani context.

In Pakistan, HIV testing and treatment services are provided free of cost to all PLWHA. The protection and treatment of PLWHA during the pandemic of COVID-19 is crucial (Ahmed et al., 2020b). In comparison to other low-middle income countries (LMICs), Pakistan has a strikingly different socio-cultural environment (Ahmed et al., 2021d). The HIV epidemic is more prevalent in patients who inject drugs (PWID) and reported in deported migrants (Ahmed et al., 2019; Ahmed et al., 2020b). Prevention and treatment of the growing HIV/AIDS epidemic have been difficult in Pakistan's traditional Muslim society (Ali et al., 2021). It is difficult for PLWHA to obtain HIV testing or treatment because they are afraid of being stigmatized due to misunderstandings in traditional cultural beliefs and practices. Qualitative research is thought to be a reliable method for determining the correct cause and effect of relationships, in-depth phenomena, respondents' thoughts, and feelings (Morgan, 2017). According to the authors' knowledge, no qualitative study has been conducted in Pakistan to investigate barriers and ART facilitators, and there is a scarcity of knowledge about patients' experiences with adherence to ART throughout the literature during the COVID-19 pandemic. As a result, the purpose of this study is to explore the overall barriers and enablers of adherence to ART in PLWHA in Pakistan and specific facilitators and barriers during the COVID-19 pandemic to generate purposeful identification of factors that may improve treatment outcomes.

METHODS

Study Design and Study Setting

The research followed the COnsolidated criteria for REporting on Qualitative Research (COREQ) guidelines (attached in **Supplementary File**) to report this study (Tong et al., 2007).

The study was conducted in one of the largest ART centres in Pakistan situated in the Pakistan Institute of Medical Sciences (PIMS), Islamabad (Ahmed et al., 2021a; Ahmed et al., 2021d). More than 3600 PLWHA are registered in this centre, and approximately 15–20 HIV patients visit it daily for their ART refills and health-related issues. The most significant feature of this centre is that treatment is provided free of cost (Ahmed et al., 2021a). This ART centre also works in conjunction with the Department of Infectious Diseases to cater the HIV patients and other infectious diseases (Ahmed et al., 2021a; Ahmed et al., 2021e).

Study Participants

Adults PLWHA included in the study based on 1) receiving ART from the ART Centre for at least 1 year of diagnosis; 2) being willing to be interviewed (an audio record); 3) being able to converse in Urdu (National language of Pakistan); and 4) gave written or verbal informed consent. Participants were chosen by purposive sampling, a non-probability sampling technique in which patients were selected with broad geographical provenance and have the best knowledge on study issues and approached through the case manager in the counselling room or on a telephone call. The sample size has been determined by the principle of saturation as suggested by Mason Mark (Mason, 2010). Saturation point criteria refer to "the point when new incoming data fail to produce new information to address the research question OR no new information appeared thought to be different and significant." Patients with cognitive impairments, terminally ill, hospitalized patients, and PLWHA unwilling to participate were excluded from the study.

Interview Guide Development and Data Collection Procedure

A semi-structured interview guide was developed based on a literature review and discussions with academics and HIV treatment experts at the ART Centre PIMS, Islamabad, to ensure that all relevant issues are included in the study guide in a culturally acceptable manner. The interview guide was validated through argumentative and cumulative methods to produce a reliable interview guide (Hashmi et al., 2017). The guide was piloted on two HIV patients to ensure that the content of the interview guide sufficiently covered all aspects of the research question, and later the guide was modified accordingly. The data from pilot interviews were not included in the final thematic content analysis (TCA). Open-ended questions with appropriate probes have led the study participants to freely express their personal experiences and factors that facilitate and impede adherence to ART. Participants were encouraged to provide as much information about the subject as possible.

Because of the high stigma associated with HIV/AIDS in Pakistan (Ahmed et al., 2021d; Hussain et al., 2021), and to maintain physical distance due to the COVID-19 pandemic, the NACP of Pakistan approved the study's conduct, with all interviews to be conducted by a female nurse (MJ), who works as a health counsellor in the ART centre. PLWHA were familiar with her and were willing to participate in the study. She has a bachelor's degree in nursing and has worked as an HIV counsellor in ART centre for over 10 years. She regularly sees HIV patients and counsels them on HIV disease knowledge and progression, ARV medications, and other PLWHA concerns. Before the study, she had received specialized training in qualitative interviewing methods and data collection. She gets assistance from the HIV case manager and AA for logistic support in conducting the interviews. Interviews were conducted from December 2020 to April 2021. To avoid inter-individual variability, MJ conducted all interviews. After the initial general questions, the interviewer further explored by way of probing questions. All interviews were conducted in Urdu (Pakistan's national language) and at a time convenient for the respondents during working hours. Interviews were held using a digital audio recorder, and each interview was given a unique identifying number (pseudonym) to maintain participants' anonymity. Because of COVID-19 restrictions, the ART Centre started sending ART courier to PLWHA, for whom it was difficult to visit the clinic and have no problem receiving medicine *via* courier. HIV case manager approached these patients and offered them a telephone interview at their ease. Three PLWHA that accepted to be the part of study their interviews were conducted on telephone call. Fieldnotes of scrupulous information were also noted, and each interview lasted from 24 to 37 min. Response saturation was reached at the 22nd interview, and three more interviews were conducted to validate the saturation of responses (Saunders et al., 2018).

Data Analysis

Data processing was carried out manually using TCA as described by Braun and Clarke (Braun and Clarke, 2006) and commenced simultaneously during the data collection phase. All recorded interviews were transcribed verbatim by the AA. Verbatim English translation of all the transcribed interviews was undertaken by AA and further verified by FKH, MMU, and MJ. Researchers (AA, MMU, MJ, and FKH) listened to the audio recordings and read the transcripts many times to gain an in-depth understanding of the data. After extensive discussion with research supervisors (JAD, CLH, AA1), meaningful words, phrases, and sentences related to the study's objectives were extracted manually in Microsoft® Excel spreadsheets from each interview. A list of initial codes was generated (AA, MJ, FKH, MMU). Next, we grouped all the key codes based on similar features. We searched through the topics of codes by gathering all similar and repetitive codes into a sub-theme. Themes were generated by combining several sub-themes (AA, MJ, JAD, MMU, FKH, AA1). Cross-checking was undertaken to ensure data credibility and enhance trustworthiness. In case of any variation, the judgment given by the supervisors (AA1 and JAD) was considered final. Numerous direct quotes were included in the results to ensure that the results accurately reflect what respondents meant.

Ethical Considerations, Rigour, and Trustworthiness

Ethics approval was obtained from the National AIDS Control Programme (NACP) of Pakistan and PIMS hospital, Islamabad (Approval No; 2060). The research procedures followed the

TABLE 1 | Characteristics of study participants.

Pseudonyms	Age	Gender	Marital status	Education	Employment	Residence	Ethnicity	Time since taking ART
P1	52	Male	Married	None	No	Rural	Pashtun	9
P2	40	Male	Married	Primary	Yes	Rural	Punjabi	3
P3	24	Female	Single	Secondary	No	Urban	Punjabi	3
P4	33	Female	Married	Primary	yes	Urban	Kashmiri	2
P5	44	Female	Married	Primary	no	Rural	Pashtun	4
P6	52	Female	Widowed	None	no	Rural	Sindhi	5
P7	37	Female	Divorced	None	no	Rural	Punjabi	2
P8	64	Male	Divorced	None	no	Rural	Punjabi	6
P9	56	Male	Married	None	yes	Rural	Pashtun	5
P10	51	Male	Married	None	no	Rural	Punjabi	8
P11	69	Male	Widower	None	no	Rural	Kashmiri	7
P12	23	Male	Single	None	no	Urban	Sindhi	2
P13	19	Male	Single	None	no	Rural	Punjabi	2
P14	22	Male	Single	None	no	Rural	Pashtun	3
P15	25	Male	Single	Secondary	yes	Urban	Pashtun	2
P16	47	Male	Married	Tertiary	yes	Urban	Kashmiri	4
P17	49	Male	Divorced	Primary	yes	Rural	Punjabi	5
P18	30	Male	Single	Tertiary	yes	Urban	Kashmiri	5
P19	31	Female	Divorced	None	No	Rural	Kashmiri	3
P20	51	Female	Married	Primary	No	Rural	Sindhi	2
P21	37	Male	Single	Secondary	Yes	Urban	Kashmiri	4
P22	45	Male	Married	None	No	Urban	Kashmiri	2
P23	35	Male	Single	Primary	Yes	Rural	Punjabi	3
P24	47	Female	Married	None	Yes	Urban	Punjabi	2
P25	41	Male	Divorced	None	No	Rural	Pashtun	4

Helsinki Declaration and the WHO Guide to Good Clinical Practices (World Health Organization, 2005). Patients were introduced to the purpose of the research and were consented to the audio recording of the responses. Participants were assured to keep both their identity and data confidential (Tong et al., 2007). Several methods were used to ensure the validity and rigor of the findings (Hadi and José Closs, 2016; Amin et al., 2020), including the development of a coding system, peer review of themes, sub-themes, rapport with participants, triangulation of multiple data sources (visual materials, field notes, and interview transcripts), and the provision of a detailed description that recognizes the context of data collection.

RESULTS

Characteristics of Participants

The study included 25 PLWHA, with a mean age of 41 years (range 19–69), consisting of (n = 17) males (n = 10), living in a relationship (n = 14), having no formal education (n = 18), unemployed (n = 16), living in rural areas, and (n = 10) taking ART from 4 to 6 years (**Table 1**).

Thematic Content Analysis

The TCA yielded three major themes. 1) Patient-related factors; 2) medication-related factors and 3) COVID-19 related factors. These themes were further categorized into several subthemes, and details of these are discussed below. **Tables 2**, **3** presents the barriers and facilitators with selected patient quotes, respectively. **Figure 1**, showing the overall barriers and enablers identified in this study.

Theme 1: Patient-Related Factors

Sub-Theme 1: Disclosure of HIV Status and Social Support

Twelve participants did not even let their friends know that they were on ARVs (N = 3); admitted that their friends knew but were not having any idea about the disease. Patients' treatment was of concern when others could see them taking medicines out of their homes and be suspected of living with HIV. Some patients in rural areas usually travel long distances to hospitals in other provinces to conceal their HIV status within their communities. Social stigma is another important issue that tends HIV patients to conceal it from their family members and friends. Some participants were enthusiastic and had no reservations about sharing their status with their acquaintances because they believed it would result in positive therapy outcomes in the long run (**Table 2**).

Participants agreed that family and friends' social support helps to increase adherence to ART. If they forget to take medicine or visit the clinic, their family members (wife, children, parents, and relatives) remind them to remain adherent to ART. The lack of support from family members made it impossible for them to take medication because they would feel less important, uncomfortable, or sometimes forget to take medicine (**Table 3**).

TABLE 2 | Barriers to retention in HIV care for people living with HIV in Pakistan.

Barriers		Selected patient quotes
Themes	**Sub-themes**	
Patient related factors	Disclosure of HIV status	• "I am working in a marble factory; I take my medications carefully. Other office workers notice that I am constantly taking medications and point it out to me. I simply inform them that it is due to my diabetes. They'll probably laugh in my face if I tell them it's because of [HIV]. I may be embarrassed to get medicine and wear a mask. I'm going to die when I don't take my medicine and, I believe, it's not right for me to tell them I'm diseased [HIV Positive]." (P14, 22 years, male) • "I can't get medicine from my own province, because I don't want anyone in my community to know about my [HIV] status" (P9, 56 years, male) • "I have little trouble informing my relatives, colleagues, of my [HIV] status. When I tell them, I was encouraged to take drugs daily without suspicion and healing of my illness. However, I sometimes find it difficult to inform new colleagues because they ask many questions about how I got that [virus], and sometimes they completely avoid me in fear of getting a virus from me." (P22, 45 years, male) • "I have little trouble informing my relatives, colleagues, of my [HIV] status. When I tell them, I was encouraged to take drugs daily without suspicion and healing of my illness. However, I sometimes find it difficult to inform new colleagues because they ask many questions about how I got that [virus], and sometimes they completely avoid me in fear of getting a virus from me." (P22, 45 years, male) • "I think it would have been worse if I had told them because they would have told them [relatives] I should have said before." (P5, 44 years, female) • "I have little trouble informing my relatives, colleagues, of my [HIV] status. When I tell them, I was encouraged to take drugs daily without suspicion and healing of my illness. However, I sometimes find it difficult to inform new colleagues because they ask many questions about how I got that [virus], and sometimes they completely avoid me in fear of getting a virus from me." (P22, 45 years, male)
	Stigma and discrimination	• "I felt left and isolated in my family when I was sick [at the hospital]. During this time, I felt very strange because I have separate personal items, utensils and toiletries from those of the others in my family." (P13, 19 years, male) • "All of my family members began to stay away from me after I received a positive test of HIV. It is so obvious: there are separated foods and utensils. They even prevent my wipes because they believe that they can be transmitted by sweat. At the next [Doctor] appointment, I talked about this scenario to doctor and the doctor guided them, no need to separate utensils." (P15, 25 years, male) • "There are some [community members] who said, 'we could get infected with the disease [HIV/AIDS]." They refused to sit besides me." (P7, 37 years, female) • "Oh . . . It's my fault, I think, to get HIV infected and that's my life. I am not sure other people understand, care for and understand me about my HIV status. It is disgraceful to me for this infection, and I don't think I should tell others." (P24, 47 years, female)
	Forgetfulness and busy routine	• "I forget to take medicine when I am away from home or when I am depressed." (P1, 52 years, male) • "I'm the only caretaker of my children [family]. I'm always very busy . . . I didn't get to the hospital on time to collect medicine, I didn't have time to eat, and I missed a few doses at different times." (P5, 44 years, female) • "I usually go home late after substance abuse or alcohol intake, and no one reminds me to take ART." (P8, 64 years, male)
	Economic constraints	• "I went to Peshawar [to find a job]. I got one time a refill from [clinic]. I worked on a farm for 2 months in the jungle. I do not speak Pashto so I could not refill the medicine. When I was travelling to Islamabad with friends, robbers stole all (my) money. Therefore, I missed my medication for 1 months." (P1, 52 years, male) • "The reason for missing my medication is that . . . [Money]. Every month I must go to clinic for ART to cure my disease for that I need bus fare. Whose responsibility is this? No job! No money! I have no alternative but to stop treatment." (P8, 64 years, male) • "Earlier, I had received ensure, a supply of supplemental nutrition for free from the NGO. But the next day, the NGO's official told me they would no longer give it to me. I felt angry when I heard this and left the drug bottle. I didn't take 5 days of pills because of this." (P10, 51 years, male) • "I couldn't visit [clinic], because I have no proper cloths" (P14, 22 years, male)
	Religion	• "During Ramadan, I took a break from my treatment. I was sick and went to see my doctor, and he told me not to stop treatment at any time, so I'm taking medicine now when I'm fast." (P4, 33, female) • "During Ramadan, I only take the evening dose. I can't take the dose in the morning because we only eat at night." (P1, 52 years, male) • "Peer [Religious scholar] asked them to recite specific verses on the water daily and to drink that water daily for a specific period of time, [peer advised], no need to take drugs for the proper functioning of Dam Darood." (P10, 51 years, male)
	Alternative therapies	• "Hakim told me that the virus is nothing, it's just a weakness, he gave me some phakki (a kind of medicine) to take daily, he promised me to cure the problem fully, but after 6 months, my health started to get worse so I left the hakim phakki." (P17, 49 years, male) • "Someone outside the hospital contacted me that he had created an HIV medicine that would instantly kill the virus and boost the immune system of the body, I visited clinic of this person somewhere in the rawalpidi, the doctor gave me a supplement and asked me to take it regularly. Supplement was very

(Continued on following page)

TABLE 2 | (*Continued*) Barriers to retention in HIV care for people living with HIV in Pakistan.

Barriers		Selected patient quotes
Themes	**Sub-themes**	
		expensive, approximately 50,000 rupee for a month (314 USD). But after wasting so much for a year that I couldn't recover, he also promised me that my viral load would be negative, but nothing like that happened. So after a 14-month break, I'm going to visit the PIMS again to start ART." (P11, 69 years, male)
Medication related factors	ART Adverse effects	• "At the beginning of therapy, I had vomiting. I missed a couple of doses until I adapted to the medication." (P1, 52 years, male) • "Okay, for the first time I knew, when I started using drugs, they left you, that is, sometimes it doesn't work, I mean, even though you keep going, I know I'm in really bad mental shape the next day. They're leaving you mentally ruined. The next day, when I take drugs, I can't be alone! I have to be with someone, because it reminds me a lot of the first year I've been infected." (P2, 40 years, male) • "The beginning of ART was a trying time for me. I had persistent nausea, diarrhea, and mood swings." (P13, 19 years, male) • "I've been using ART for 6 years, in the early years I felt side effects slowly now, and now I'm used to it." (P8, 64 years, male)
COVID-19 related factors	Impact of Lockdown	• "My transportation options to the clinic have now been narrowed down due to COVID-19. Transport is still needed because it now costs more money, or the police can hinder you. Above all, transport is not available." (P13, 19 years, male) • "It's going to have an impact on my ability, of course, because I don't have to go anywhere. The transport had stopped. My only way to do this is to go to the clinic. I have also been worried about how I am going to be able to see you and how I'm going to be able to ask you for my medication. Some people say that the situation here is becoming increasingly grim." (P6, 52 years, female)
	Limited care of COVID-19 due to Stigma	• "I know that one of my HIV-positive friends, who had contracted COVID-19 and had been admitted to the hospital, had been treated badly than the other person who did not have HIV." (P18, 30 years, male)

Sub-Theme 2: Stigma and Discrimination

All PLWHA face discrimination in the family, society, and the anticipated stigma of HIV infection, which strongly impacts adherence to therapy. This includes segregation and division of personal belongings, and even food utensils are some of the common examples of discrimination and treatment faced by HIV patients by family members and friends. In case of discrimination by members of other communities, they did not sit close to PLWHA or move away from the PLWHA chairs and kept away from direct physical contact with PLWHA; this ultimately leads to stigma and discrimination that can promote loss to follow up. The factors that maintained the anticipated stigma among the participants were the fear of prejudice from other community members. As a result of this perception, they conceal their HIV status from members of their communities, failing to maintain regular follow-ups (**Table 2**).

Sub-Theme 3: Forgetfulness, Busy Routine, and Reminders

Participants reported that they frequently forgot their medications due to a hectic schedule or being away from home. Because single parents must work to meet their children's basic needs, it may be difficult for them to visit the ART centre, accounting for many non-adherence cases. PLWHA who used intravenous drugs reported forgetfulness as a result of substance abuse or alcohol consumption (**Table 2**).

Patients often said that alarms on watches or mobile phones helped them remember to take their pills. Eleven people said they were alarmed on their mobile phones or watches. Many patients did not know how to use mobile devices or the internet, etc. Not all patients were literate, and not all of them had mobile devices. Ten of the respondents are certainly illiterate. These patients depended on unusual methods, such as the Sun's location, the length of the shadows, the arrival and departure of students, Adhan sounds of mosques, and the bell rings of factories to take their pills (**Table 3**).

Sub-Theme 4: Economic Constraints

Participants reported that employers do not hire them due to their HIV status, which leads to unemployment, food insecurities, and distant movement to seek job opportunities. Most participants (N = 14) had no formal education; they often found low-wage jobs like waiters, tea boys, peons, doormen, gardeners, drivers, and sweepers at low wage rates. When they move to the countryside to find job opportunities, they face a lack of transportation, unavailability of nearby ART clinics, and language restrictions that prevent them from remaining in HIV care. Some participants reported that ART makes them drowsy, and that to combat this, they must consume expensive nutritious foods. Some also said that they are dependent on non-governmental organizations (NGOs) for the availability of food. If they found an obstruction in food, they often skip doses because they cannot tolerate medicine effects without nutritious food (**Table 2**).

Sub-Theme 5: Family Responsibility

The majority of the PLWHA were young, fertile, and had school-age children (N = 7). They are afraid of dying from AIDS, which would leave their children, orphans. According to the findings, PLWHA who have children are more committed to raising and

TABLE 3 | Facilitators to retention in HIV care for people living with HIV in Pakistan.

Facilitators		Selected patient quotes
Themes	**Sub themes**	
Patient related factors	Family responsibility	• "I have a boy who was born virus-free. As long as I'm alive, I want him to have better opportunities. I'm going to ruin his chance if I don't take or give up the medications." (P21, 37 years, male) • "I have two children, I am a single parent because my wife is dead, I have to take ART regularly to keep myself healthy, to work hard to make money for my children's growth." (P11, 69 years, male)
	Reminders	• "I've been busy with a lot of work; I think reminders are a great way to remember the pill I've got to take." (P18, 30 years, male) • "To make sure that I am taking my pills on time. I have set alarm in my mobile phone." (P16, 47 years, male) • "When I hear the Adhan, Allah ho Akbar, I take medicine." (P9, 56 years, male)
	Social support	• "Initially, I failed to take my medication for a week due to a disagreement with my family; however, a doctor and a community worker advised my family not to argue, and after that, family support was critical to my adherence to therapy." (P13, 19 years, male) • "My wife is HIV-negative, while I am HIV-positive. When she is angry with me because of family issues, she stops caring for me [rarely], so I miss a few doses. Her encouragement, on the other hand, is critical to my overall adherence [to treatment]." (P16, 47 years, male) • "Everyone in my family is extremely caring; they frequently remind me to take my medication on time." (P12, 23 years, male) • "Often my children remind me to take pills when I feel tired or busy working or sleeping at a dose stage. They're going to get me a glass of water and a bottle of prescription." (P1, 52 years, male)
Medication related factors	Beneficial impact of ART	• "I have agreed to commit myself more to antiretrovirals because of their therapeutic benefits. I was unable to walk, but now I am healthy, and I'm usually in the office today. It is all because of the pills. I must therefore continue to take medicines to prevent disease progression." (P18, 30 years, male) • "When I started the therapy, I was bedridden, having multiple diseases, high viral load, CD-4 less than 50 cells/mm^3, than the doctor prescribed me ART, I started to recover, my CD-4 cells were raised, viral was undetected, I started to regain my health, healthier and more powerful." (P16, 47 years, male)
COVID-19 related factors	Telephone consultations	• "You [Clinic] saved my time and money [travelling cost] and helped me improve my health through telephone call consultation." (P6, 52 years, female) • "I was worried about to what additional safety measures I need to take, call [from clinic] help me to get know the disease." (P17, 49 years, male)
	Dispensing of medicine for long time	• "My village is near Peshawar. I can't come every month; ART centre has given me a medicine for next 6 months" (P9, 56 years, male)
	Courier delivery of ART	• "No problem. No problem. I was not [clinic] around. Two months [drug supply] they sent me a courier, and I am supposed to return in November." (P5, 44 years, female) • "I was really excited to receive a call from the clinic because I ran out of ART, I lived 120 km away from the clinic, it was hard for me to visit the clinic, but thanks to the clinic staff, they sent me the medicine to my address." (P11, 69 years, male) • "Staff from clinic advised me not to visit [hospital] because of increased COVID-19 cases in the country and asked about my health and other health problems and sent me the drugs *via* post office." (P2, 40 years, male) • ''The clinic's nurse asked if they could send me ART by courier, but I refused because I hadn't told anyone about my HIV status and was afraid of how people would react.'' (P14, 22 years, male)
	Using ART to decrease the chances to contract COVID-19	• "I heard on TV that HIV people who do not take ART regularly are at risk of getting COVID-19. Therefore I am fully adherent to therapy." (P3, 24 years, female) • "During the telephone consultation, Doctor advised me to adhere to ART as it would help me to fight and improve immunity against HIV and COVID-19 both. (P1, 52 years, male)"

educating their children, which has aided them in taking ART more seriously (**Table 3**).

Sub-Theme 6: Religion

PLWHA, a resident of a community, usually follows the religious, cultural, and traditional rituals in their everyday lives. 96.4% of the Pakistani population practices Islam, and fasting is considered as a main pillar of Islam ($N = 11$). PLWHA reported that they fast for the entire day during Ramadan and that while fasting, they do not take medication properly and usually skip the morning dose. Some participants also seek the spiritual healing to permanently end the HIV/AIDS rather than to take ART throughout the life.

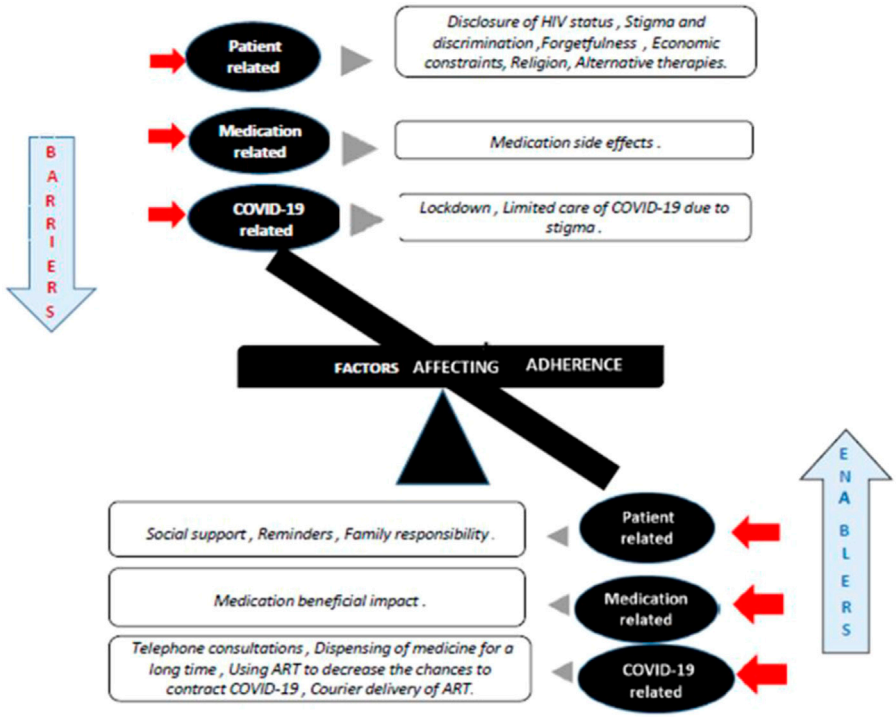

FIGURE 1 | Barriers and enablers of adherence to ART identified.

Two participants also reported visiting a peer (religious scholar) for Dam Darood (spiritual healing), preventing them from taking ART for 6 months (**Table 2**).

Sub-Theme 7: Alternative Therapies

Five out of twenty-five participants indicated that when doctors told them they had to take medication for a lifetime, they were concerned and tried other alternatives such as Tibb Unani, homeopathic therapy for treating HIV. Because of which they avoided taking ART for some time, but when their health got worse, they returned to the clinic for ART (**Table 2**).

Theme 2: Medication-Related Factors

Sub-Theme 1: Side-Effects and Adverse Effects

Side effects and the adverse effects experienced during drug therapy is a normal happening. These sometimes affect the drug-taking behaviour and are often bothersome and result in failure to comply with therapy (N = 6). PLWHA reported that when taking ART, they usually experience unexpected or intolerable side effects, such as nightmares, psychosis, diarrhoea, and misdiagnosed psychiatric side effects, which cause them to discontinue taking medications. This is particularly common in patients who are asymptomatic and believe that taking ART worsens their health (**Table 2**).

Sub-Theme 2: Beneficial Impact of ART

The HIV status of all PLWHA in our group is confirmed after a prolonged illness. They have experienced the devastating effects of disease on their bodies, had vivid illness stories, and reported significant improvement in their health after initiating the ART. Patients reported ART improved their physical health, improved appetite, increased immunity, and prolonged life. These improvements have inspired them to take their medicines further (**Table 3**).

Theme 3: COVID-19 Related Factors

Sub-Theme 1: Impact of Lockdown

To restrict COVID-19 spread government (Govt) of Pakistan imposed lockdown and interstate travel ban in March 2020, participants temporarily forced (n = 9) to become nonadherent due to finishing off their home ART stock. The most frequently reported impacts of COVID-19 restrictions were on clients' travel to HIV clinics due to inadequate transport, police abuse, and insufficient transportation funds (**Table 2**).

Sub-Theme 2: Telephone Consultations

Participants reported that after a month of COVID-19 lockdown, the ART centre contacted them for follow-up and inquired about disease conditions and ART availability. The (N = 13) participants reported that telephone consultation was a great step to help them manage and get information on how to remain safe from contracting the COVID-19 (**Table 3**).

Sub-Theme 3: Dispensing of Medicine (ART) for Longer Periods

To avoid exposure to COVID-19 and to reduce the pressure of patients visiting the hospital, the ART centre prescribed the medicines for up to one to 6 months to improve the

continuity of the medicine. This was done for patients who were living far away from the clinic (**Table 3**).

Sub-Theme 4: Limited Care of COVID-19 due to Stigma

The PLWHA expressed concern about being hospitalized if they contracted COVID-19. Participants reported they might be treated differently than non-HIV people due to the stigma and discrimination associated with HIV (**Table 2**).

Sub-Theme 5: Using ART to Decrease the Chances to Contract COVID-19

Most interviewers reported hearing from friends and family that PLWHA and other chronic disease patients are at increased risk of contracting COVID-19. Some also said that during consultation doctor also guided them to be adherent to ART as PLWHA are slightly at more risk of COVID-19 than ordinary people. They are regularly taking drugs to maintain their viral suppression and increase their immunity (**Table 3**).

Sub-Theme 6: Courier Delivery of ART

The clinic began courier delivery to PLWHA living in remote rural areas, and this service was only offered to those clients who agreed to receive the medicine by courier, and they appreciated this service and expressed that this service should be continued even after the pandemic. Some clients ($N = 4$) declined courier delivery because they were afraid to be exposed to people who did not know their HIV status (**Table 3**).

DISCUSSION

The exploratory nature of qualitative design has enabled us to use a phenomenology-based approach to explore the perspectives of PLWHA and generating rich data to identify the gaps otherwise overlooked by other methodological approaches in outcome research (Pietkiewicz and Smith, 2014; Queirós et al., 2017). Reducing HIV-related morbidity and mortality means ensuring that PLWHAs remain in antiretroviral therapy even during the COVID-19 pandemic, which can help prevent new cases of HIV infection and improve the quality of life of PLWHA (Mirzaei et al., 2021). We aimed to explore the barriers and facilitators that influence PLWHA adherence to antiretroviral therapy in Pakistan. Stigma and discrimination have been recognized as significant barriers, with fear of disclosure of HIV, economic constraints, forgetfulness, religion (spiritual healing), adverse drug reactions, lack of social support, and COVID-19 lockdown restrictions also affecting retention to therapy. In the meantime, positive social support, family responsibilities, reminders, the beneficial impact of ART, telephone consultation, courier delivery of ART, using ART to decrease the fear of contract COVID-19, and long-term drug delivery during COVID-19 have been recognized as facilitators of HIV retention. Studies in other resource-limited settings reported in line with these factors (Wasti et al., 2012; Bezabhe et al., 2014; Kuznetsova et al., 2016; Phuphanich et al., 2016; Chirambo et al., 2019). However, some findings such as spiritual healing, alternative treatment methods, traditional time management, job migration, and COVID-19 related factors like impact of lockdown, telephone consultations, dispensing of ARVs for longer period, courier delivery of ART and using ART to decrease the chances to contract COVID-19 have not been reported in other settings. This can be attributed to the differences in the socioeconomic status and socio-cultural norms of our study sample.

The most common barrier reported by most respondents was fear of disclosure of one's HIV infection status and this finding is consistent with the studies conducted in other LMICs (Wasti et al., 2012; Bezabhe et al., 2014; Chirambo et al., 2019). Studies done in Sub-Saharan countries demonstrated that covert usage of ART is to delay or miss medication that ultimately leads to ART adherence failure (Croome et al., 2017). Alternatively, a prior and full disclosure of HIV status has been associated with full retention to HIV care (Chirambo et al., 2019; Dessie et al., 2019). We suggest promoting the mutually facilitated disclosure of HIV status and increasing actions such as integrating psychological health services into ART clinics would help patients navigate through acceptance of their HIV disclosure outcomes.

Stigma and discrimination appeared to be the most general barrier to ART adherence and maintenance of care. Also, Other studies in America (Earnshaw et al., 2013; Darlington and Hutson, 2017; Gunn et al., 2021; Yabes et al., 2021), Middle East (Aghaei et al., 2020; Ballouz et al., 2020; Moradzadeh and Zamanian, 2021), Asia (Ekstrand et al., 2018; Ekstrand et al., 2020; Stephens and Surjan, 2020), Sub Saharan Africa (Jones et al., 2020; Chimoyi et al., 2021; MacLean and Wetherall, 2021; Madiba et al., 2021), and Europe (Vaughan et al., 2020; Hedge et al., 2021) have found stigma to be a significant contributor to non-adherence. In Pakistan, the stigma of HIV/AIDS is enormous (Ahmed et al., 2019; Ahmed et al., 2021a; Ahmed et al., 2021d). It's primarily due to misunderstandings about HIV risk factors and lack of knowledge of advances in treatment such that those who are treated have lowered risk of transmitting HIV (Ahmed et al., 2021f). Further, we found that PLWHA were afraid of being ostracised from their family, friends, and the public this may be attributed to poor knowledge among the public regarding the transmission of the virus. Therefore, it ultimately calls for more public education campaigns (Kumarasamy et al., 2005; Bezabhe et al., 2014; Kuznetsova et al., 2016). Discrimination towards people with HIV/AIDS is a dynamic socio-cultural phenomenon that is an outcome of viewing people with HIV/AIDS as "less than human." (Phuphanich et al., 2016).

A multi-mechanism approach that includes the provision of information, counselling, and facilitating interaction between people who are HIV-infected and the community to reduce stigma and increase care participation is an effective HIV prevention strategy (Grossman and Stangl, 2013). A systematic review and meta-analysis by Mak et al. (2017) demonstrated that there is a lack of effective stigma reduction programmes to be implemented on a larger scale. Considering different types of health inequalities in Pakistan, addressing multi-level stigma and discrimination could improve patients' adherence to ART treatment.

The present study explored the forgetfulness of HIV patients, which is quite common among chronic patients. Our findings on the forgetfulness of ART use are consistent with the Jones and Phuphanich et al. studies that attribute alcohol use and extra working hours to influencing PLWHA drug-taking behaviour (Bezabhe et al., 2014; Jones et al., 2015). The need to maintain private HIV status in alcohol use influences noncompliance with ART, resulting in avoiding ART when consuming alcohol (Fisher et al., 2007). Fear of the combined medicine toxicity and side-effects of alcohol also results in a default (Chirambo et al., 2019). We suggest that social habits should be included and explored as a continuous ART-care process (Mabweazara et al., 2018). To prevent drink and substance abuse-related nonadherence, Pakistan requires support groups and education intervention within ART programmes.

The lack of jobs, resulting in migration from home stations to find an appropriate position, affects adherence to therapy. Lack of proper clothing and food insecurity were among the main socioeconomic constraints that negatively affected retention of HIV treatment found in the present study that even got worse in the COVID-19 pandemic. These factors have also been reported in other studies conducted in Togo, Ethiopia and Kenya (Bezabhe et al., 2014; Yaya et al., 2014; Aibibula et al., 2017; Wang et al., 2020). Patients usually lose follow-up when they migrate either within Pakistan or overseas for work purposes (Ahmed et al., 2020b). Some studies have also documented the migration trend of Pakistani youth from rural to urban areas of Pakistan for work and the Middle East and Southeast Asian countries (Ahmed et al., 2020b; Khan and Cailhol, 2020). Bezabhe et al. (2014), reported patients usually stop taking ART medication when they cannot afford food or when NGOs no longer supply ration, especially when unemployed. Such factors are believed to exacerbate HIV-related problems, including stigma and prejudice, reduced physical activity, drug schedules, and indirect costs of care, which are not exceptional for HIV/AIDS patients. Strategies need to be implemented to improve access to jobs and food security for HIV-positive patients in Pakistan. Both government and non-governmental organizations need to combine efforts to address the multidimensional disadvantages of PLWHA.

It is important to note that religious fundamentalism is a very complex issue and often affects patients' preferences for antiretroviral therapy in our study and this factor was also reported by studies conducted in Zimbabwe (Mutambara et al., 2021), Nigeria (Victor-Aigbodion, 2020), Ghana (Dzansi et al., 2020), Iran (Aghaei et al., 2020) and United States (Vigliotti et al., 2020; Doolittle et al., 2021). In Ramadan, Muslims observe fasting during the daytime from sunrise to sunset. Some patients usually skip medicines to fulfil their religious duties, and a similar trend is also found in other studies (Bezabhe et al., 2014; Croome et al., 2017). Members of the religious community, governments, and NGOs should work with the health authorities to help manage therapies during fasting months.

Social support and reminders are described as key enablers in this study; similar findings have been documented in other studies (Bezabhe et al., 2014; Kuznetsova et al., 2016; Mao et al., 2018). To promote adherence, HIV counsellors in our study usually advise patients to communicate their status to family members and close friends, willing to provide social assistance, pills, financial support, and emotional assistance. Dialogue and behavioural exercises are thought to improve the disclosure act effectively; some studies have documented the significance of the above (Montalto et al., 2017; Mi et al., 2020).

Electronic devices like telephones have the benefit of reminding patients when they must take their drugs while keeping the privacy of their status. Meta-analyses have shown that the short message service (SMS) on cell phones has improved compliance with ART treatment as well as HIV care retention (Kanters et al., 2017; Shah et al., 2019). Some of the traditional approaches such as the Sun's movement during the daytime and the sounding of the prayer calls from the mosques, are usually reckoned as reminders for illiterate patients taking ART. Many HIV patients in Pakistan are illiterate and are dependent on traditional time counting methods that do not measure time by time and are influenced by many different factors. Hence, healthcare providers need to guide patients to use a quick, electronic reminder to enhance retention in care.

In our study, respondents raised difficulty reaching ART clinics during COVID-19, and a similar trend was observed in Chinese and Uganda studies (Guo et al., 2020; Linnemayr et al., 2020). Participants welcome the clinic step at COVID-19 for telephone consultations, delivery of medicine for a longer duration (up to 6 months), and appreciated the courier delivery of ART to remote patients. Similar actions have been reported by Quilantang et al. (2020) in the Philippines. Although the world has been struggling to contain the pandemic of COVID-19, millions of people are living with HIV and need constant medical supervision. There is growing concern that the response to COVID-19 may cause harm to individuals who have chronic infections.

The last decade has seen a gradual shift from hospital-based ART to primary health centres and, most recently, to the community (Kredo et al., 2013; Avong et al., 2018; Shoptaw et al., 2020). For the benefit of patients and medical professionals, community pharmacies can play a crucial role in the provision of ART services in the local community (Lelubre et al., 2018). Studies in western countries have shown that community pharmacies can play various roles in treating HIV/AIDS (Hirsch et al., 2009; Rosenquist et al., 2010; Murphy et al., 2012). Plenty of evidence suggests that trained and educated HIV pharmacists at specialized community/dispensing pharmacies and clinic-embedded pharmacist involvement in HIV care promote positive outcomes (Barnes et al., 2020). For example, Hirsch et al. (2009) found that patients who take medication therapy from trained HIV pharmacists stationed at ten community pharmacies were more likely to be classified as adherent with a medication possession ratio (MPR) of 80–120% than those who used nonspecialized community pharmacies (56.8 vs. 38.1%, $p < 0.001$) (Hirsch et al., 2009). Likewise, Cocohoba et al. (2012) compared PLWHA using HIV-focused community pharmacies with PLWHA using traditional pharmacies and found that patients using an HIV-focused pharmacy had significantly higher regimen refill adherence as measured by median MPR (90 vs. 77%, $p < 0.0001$) (Cocohoba et al., 2012). In LMICs like Pakistan, qualified clinical staff to provide optimal care, especially ART, is lacking (Ahmed et al.,

2018). Suppose community pharmacists in Pakistan receive appropriate antiretroviral training. In that case, they can assist in reducing barriers to ART adherence, such as patients travelling long distances to clinics, which places a significant financial burden on patients, long waiting lines at therapy clinics at overburdened health facilities, and better pharmaceutical care. Furthermore, community pharmacists can connect with patients in highly personalised ways; they can also help improve outcomes and reduce costs associated with non-adherence, as well as provide easy access to ART in the COVID-19 pandemic (Avong et al., 2018; Ahmed et al., 2020c; Kretchy et al., 2021).

Implications of Findings and Future Studies

There is currently very little information available on the response of people living with disabilities in the COVID-19 pandemic. Our findings highlight the key needs for the preparation of health systems to facilitate ongoing care for HIV and other chronic diseases, while transitions to normal health care are underway from the COVID-19 pandemic. We hope that the results of this qualitative study on the perceptions of ART clients about COVID-19 will provide additional valid evidence on the impact of COVID-19 on HIV care. A major advantage of this study is its contribution to a small but, hopefully, increasing literature with empirical results on how COVID-19 has a bearing on HIV care, providing first-line insights into barriers, facilitators, perception of risk, and opportunities for enhancing adherence to the PLWHA in LMICs like Pakistan. Future studies from various settings that further investigate PLWHA religious thoughts and moral stances in relation to HIV management are recommended.

Limitations

First, we did not apply Kappa to the inter-rater reliability test, but we continued to discuss the issues through coding and thematic analysis after data collection to ensure the reliability of the data. Second, we have not collected data from bedridden patients or patients with psychiatric or other problems. Third, some interviews were done on the phone call recording; maybe there is a chance of missing some non-verbal cues, but we tried to get all the non-verbal cues on the transcript as well. Fourth, it is a single-cantered study, which may limit the generalizability of the findings, but we did our best to include PLWHA of all ethnicities. Fifth, most participants were illiterate, male, unemployed, and from rural areas, as HIV outbreaks are more concentrated in these population subsets. Lastly, COVID-19 related information is rapidly changing, and this study is cross-sectional study done during the COVID-19 pandemic, so the results should be interpreted with caution. Despite limitations, we used a purposive sampling method to identify participants with different demographic characteristics and medication-taking behaviours which best represented patients' perspectives on the phenomenon under study.

CONCLUSION

In this study, we found Stigma and discrimination, fear of disclosure of HIV infection, economic constraints, forgetfulness, religious factors, ART adverse effects, lack of social support, alternative therapies, COVID-19 related lock-downs and limited care of COVID-19 due to stigma as barriers to adherence to therapy. On the other hand, social support, family responsibilities, use of reminders, the beneficial impact of ART and initiation of telephone consultations, courier delivery, and long-term supplies of drugs during COVID-19 have improved HIV retention. To facilitate optimum adherence to ART, retention of care, and improved patient outcomes during COVID-19, interventions are needed to ensure enhanced access to health care, social acceptance of HIV, the development of social policies, and improved employment through cooperation between the various stakeholders.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethics approval of study was provided from National AIDS Control Programme (NACP) of Pakistan (Approval No; 2060). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, AA1 and MMU; Data curation, AA1, MJ, MMU and FKH; Formal analysis, AA, MJ, MMU, JAD, FKH and AA2; Investigation, AA, JAD, MMU and LHC; Methodology, AA1, MJ, MMU, FKH, JAD and AA2; Project administration, AA1, MJ, JAD, MMU, FKH; Resources, AA2, JAD, MMU, LHC; Software, AA, FKH; Supervision, JAD, FKH, LHC, AA2, NC; Validation, AA1, JAD; Writing original draft, AA1; Writing review & editing, AA1, JAD, MJ, MMU, AA2, LHC, FKH, NC.

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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.2021.807446/full#supplementary-material

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Evaluation of Prescription Medication Sharing Among Adults in South Korea: A Cross-Sectional Survey

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Background: Prescription medication sharing is an inappropriate medication use behavior that can lead to medication errors and adverse drug events, posing a public health threat. The reported prevalence of prescription medication lending and borrowing varies by country, ranging from 6%–23% and 5%–52%, respectively. However, research on medication sharing is scant in Asian countries. Therefore, this study aimed to describe the rate of prescription medication sharing practices and investigate the associated behavioral factors, types of shared medications, and reasons for sharing among adults in South Korea.

Methods: A cross-sectional study was conducted using an online self-administered survey of 1,000 adults (aged 19–69 years; November 2020). A stratified sampling method was used to select survey participants from a nationwide consumer panel, which ensured a representative distribution of the Korean population by age, gender, and region. Descriptive and logistic regression analyses were used to evaluate the information related to sharing behavior.

Results: A total of 1,000 respondents participated in this study. The mean age of the respondents was 44.7 years (standard deviation [SD], 13.4), ranging from 20 to 69 years. The rate of medication sharing was 52.4%. The most prevalently shared medications were analgesic, antipyretic, and antimigraine medications. Prescription medications were shared mostly between family and relatives. Older age was a predictive factor for sharing analgesics. Lower educational level was a predictive factor for sharing ophthalmic medications.

Conclusions: Approximately one in two respondents in our study have experienced medication sharing in their lifetime. Future studies are needed to establish evidence-based strategies for patient education and improve the medication use process. Healthcare professionals should assess patients' needs for accessing medications and be ready to educate and guide them with specific action plans. Policymakers should consider patient empowerment strategies including public education and campaigns to avoid potential adverse outcomes of medication sharing.

Keywords: medication sharing, prescription medication sharing, medication lending, medication borrowing, inappropriate medication use

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INTRODUCTION

Medication sharing is defined as lending or borrowing medication (Daniel et al., 2003). Although the terms "to borrow" and "to lend" also imply returning an item to its owner, "medication sharing" in social science research is considered as the act of giving or receiving medications without returning them to the owner (Beyene et al., 2014). When the shared medication requires a prescription from healthcare providers, this phenomenon is referred to as "prescription medication sharing" (Daniel et al., 2003). The reported prevalence of prescription medication lending and borrowing varies by country, ranging from 6 to 23% and 5%–52%, respectively (Beyene et al., 2014). Prescription medication sharing is an inappropriate medication use behavior that can lead to medication errors and adverse drug events. In an aging society with many older adults having multimorbidity and polypharmacy (Golchin et al., 2015), the increased availability of medications for sharing and the vulnerability of older adults towards adverse drug events can potentially complicate the clinical consequences for individuals. Furthermore, prevalent medication sharing at the community level poses a public health threat (Goldsworthy et al., 2008).

Many studies have been conducted to investigate behaviors related to medication sharing, such as the circumstances and predictors associated with this practice. Some studies have reported that being female (Daniel et al., 2003; Goldsworthy et al., 2008); being 18–24 years of age (Petersen et al., 2008); being a non-Hispanic White, reproductive-aged female United States resident (Petersen et al., 2008); having lower income (Daniel et al., 2003); deriving health-related information from the Internet (Petersen et al., 2008); having a larger household size (Daniel et al., 2003; Petersen et al., 2008); having non-Medicare insurance (Ward et al., 2011); and having leftover medications stored at home (Beyene et al., 2019) were associated with increased medication sharing. In addition, potential reasons for sharing medication include emergency situations, inconvenience in visiting a physician, lack of trust in the physician, low accessibility to the medication, availability of medications from close acquaintances, cost saving, assisting with pain management, and maintaining good relationships with people (Markotic et al., 2017). Unintended and unexpected consequences of medication sharing caused by unsupervised and reckless medication use have also been documented, such as delayed diagnosis or treatment, incorrect perceptions of the ineffectiveness of the medication, drug interactions, adverse drug reactions, drug abuse, addiction, antibiotic resistance, and teratogenicity (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008; Markotic et al., 2017).

Medication sharing is considered an underestimated problem in the medical field (Petersen et al., 2008; Auta et al., 2011). In South Korea, research on the status of medication sharing behavior and associated factors is scant. Therefore, this study aimed to describe the rate of prescription medication sharing practices and investigate the associated behavioral factors, types of shared medications, and reasons for medication sharing among adults in South Korea.

MATERIALS AND METHODS

Study Design and Population

A cross-sectional study was conducted using an online self-administered survey to evaluate the experience of medication sharing among adults aged 19 years or above, excluding healthcare professionals. Participants were recruited using a commercially available consumer panel of a nationwide convenience sample operated by the Panel Marketing Interactive company, which included 1.59 million people, one of the biggest consumer panels in South Korea in 2020 (Panel Marketing Interactive, Seoul, South Korea; Kim et al., 2020). A more detailed description of the panel has been published elsewhere (Panel Marketing Interactive, 2021).

A stratified sampling scheme was used to select survey participants from the panel, which ensured that they were representative of the distribution of the national census statistics by age, gender, and region (Korean Statistical Information Service, 2019). Considering that the oldest panel from the marketing company was set at 69 years of age, and the relative difficulty in accessing the Internet among older adults, Koreans older than 70 years were not included. Participants were recruited through the company's website or an e-mail inviting them to participate in the study, and a link was provided in the recruitment announcement (banner) to lead them to the survey screen. The survey questionnaire included four screening questions for ensuring the participant's eligibility in terms of having non-healthcare-related jobs and other pre-determined quotas for demographic information, such as gender, age, and region. Prior to commencing the survey, all participants responded to the screening questions and those who met the eligibility criteria agreed to participate in the survey by providing informed consent. The survey was conducted between November 6 and 12 November 2020. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University (IRB No. 2009/002-012). This study has been conformed to the principles embodied in the Declaration of Helsinki.

Questionnaire Development

The questionnaire was developed following the conceptual framework of the modified Andersen behavioral model of health, which includes the outcome of health behaviors (Andersen, 1995). The model was developed to determine why families use health services, and health behavior was considered a function of three factors: 1) predisposing characteristics such as demographics, social structure, and health beliefs; 2) enabling resources from personal/family sources or the community; and 3) perceived or evaluated needs. In this study, the variable of health behavior was replaced with medication sharing behavior. The literature on medication sharing was consulted to extract factors which were then categorized into sectors in the model. The survey questionnaire comprised three themes: 1) demographic characteristics, 2) lending experience, and 3) borrowing experience. Demographic characteristics consisted of predisposing factors including gender, age, and marital status, as well as enabling resources including educational level, type of health insurance, and area of residence. Questions regarding

lending and borrowing experiences included the participants' lifetime experience of medication sharing, types of people with whom they had shared medication, types of medications shared, and reasons for sharing. The reasons for lending or borrowing medication consisted of enabling factors and need factors. The reasons for medication sharing included severity of symptoms (Goulding et al., 2011), limited access to physicians (Goulding et al., 2011; Ward et al., 2011), urgency (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008), medication potency (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008), accessibility to medication (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008; Markotic et al., 2017), altruism (Markotic et al., 2017), and having faith in the lender (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008). The list of medications that were lent or borrowed included pain or fever relievers, intestinal medications, ophthalmic medications, antibiotics, topical corticosteroids, muscle relaxants, allergy medications, hypnotics, mood medications, contraceptives, inhalers for asthma, and chronic disease medications for hypertension, diabetes, or hyperlipidemia. The list of medications was formulated based on the literature on medication sharing (Goldsworthy et al., 2008; Petersen et al., 2008; Goulding et al., 2011; Ward et al., 2011; Beyene et al., 2014) and prevalent chronic diseases in adults (Korea Centers for Disease Control and Prevention, 2018). The medication list used in the questionnaire stated the class of the medications and explained the medications in lay terms. The questionnaire also asked participants whether the medication package insert or instructions for medication use were provided during medication sharing. The consequences of taking shared medications were also assessed as an outcome factor.

After the development of the questionnaire, a face validation was conducted with five pharmacists and five non-healthcare personnel to evaluate the appropriateness, clarity, and readability of the questions. The final version of the questionnaire comprised a total of 20 questions, including four screening questions and 16 main questions, in three sections: lending experience (6 questions), borrowing experience (6 questions), and demographic characteristics (4 questions). Not all participants responded to all 20 questions; respondents with no medication sharing experience completed a total of 10 questions: four screening questions, two questions on lending and borrowing experience (yes/no), and four questions regarding demographic characteristics. The questions about lending and borrowing experiences were in separate sections. When the respondent clicked on "yes" for the question on having lending experience, additional questions regarding their lending experience were asked consecutively. If the respondent selected "no" as their response to this question, the questionnaire skipped to the borrowing experience section. When the borrowing experience section was completed, the demographic section began.

Sample Size

The target number of survey participants was calculated to evaluate the prevalence of medication sharing practices in South Korea. From the literature review, the average prevalence was found to be approximately 25% (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008; Auta et al., 2011; Goulding et al., 2011; Beyene et al., 2014), and the prevalence in our study was expected to be 30%. The sample size was calculated using the G*power 3.1.9.4 program (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) (Faul et al., 2007) based on a two-sided binomial test, with 90% power and 5% significance level, yielding 842 participants. Considering screening failure and participant dropout rate (15%), the target sample size of the study was determined to be 1,000.

Statistical Analysis

Descriptive statistics were used to summarize respondents' demographic characteristics and information related to medication sharing. Continuous variables were analyzed using student's *t*-test, while categorical demographic variables were analyzed using Pearson's chi-squared test or Fisher's exact test. Medication sharing prevalence was examined by gender, age group (20–29, 30–39, 40–49, 50–59, and 60–69 years), marital status, metropolitan status, residential area, level of education, and health insurance type. Multiple logistic regression analysis was used to identify factors associated with medication sharing behavior. Subgroup analyses were performed for each medication's lending and borrowing experience to determine the factors contributing to the sharing behavior for each medication. Statistical analyses were performed using SPSS 25 (IBM Corp, Armonk, NY) and R 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $p < 0.05$.

RESULTS

Participants' Characteristics

A total of 1,000 people participated in this study; questionnaire distribution was terminated when the target number of respondents was achieved. The mean age of the participants was 44.7 years (standard deviation [SD], 13.4), ranging from 20 to 69 years. The ratio of men to women was approximately 1:1. More than half of the respondents were married (62.9%), and most (91.4%) lived in urban areas. Over 70% of the respondents had a college degree or higher, and most of them had workplace health insurance (69.8%). The demographic characteristics are presented in detail in **Table 1**.

Reported Experience of Lending or Borrowing Prescription Medication

Among the 1,000 respondents, 524 reported having either medication lending or borrowing experiences, while 312 reported having experienced both medication lending and borrowing. The rates of medication lending and borrowing experience were 40.6% and 43.0%, respectively. The mean age of participants who had lent and borrowed medication was 45.3 years (SD: 13.4) and 44.5 years (SD: 13.5), respectively. **Table 1** presents the prevalence of medication lending and borrowing based on the respondents' demographic characteristics.

TABLE 1 | Survey respondents' demographic characteristics and the rates of lending or borrowing prescription medications (n = 1,000).

Characteristics	Number of respondents (%)*	Have lent prescription medications	Have borrowed prescription medications
		Prevalence (95% CI)	Prevalence (95% CI)
Total	1,000 (100.0)	40.6 (37.6–43.6)	43.0 (39.9–46.1)
Gender			
Female	492 (49.2)	42.1 (37.7–46.4)	42.9 (38.5–47.3)
Male	508 (50.8)	39.2 (34.9–43.4)	43.1 (38.8–47.4)
Age distribution			
20–29 years	182 (18.2)	37.9 (30.9–45.0)	42.3 (35.1–49.5)
30–39 years	187 (18.7)	36.9 (30.0–43.8)	44.4 (37.3–51.5)
40–49 years	224 (22.4)	42.9 (36.4–49.3)	45.1 (38.6–51.6)
50–59 years	232 (23.2)	44.0 (37.6–50.4)	42.2 (35.9–48.6)
60–69 years	175 (17.5)	40.0 (32.7–47.3)	40.6 (33.3–47.8)
Marital status			
Single	371 (37.1)	37.5 (32.5–42.4)	41.8 (36.8–46.8)
Married	629 (62.9)	42.4 (38.6–46.3)	43.7 (39.8–47.6)
Metropolitan status			
Urban	914 (91.4)	40.9 (37.7–44.1)	43.9 (40.7–47.1)
Rural	86 (8.6)	37.2 (27.0–47.4)	33.7 (23.7–43.7)
Residential area			
Capital	194 (19.4)	44.3 (37.3–51.3)	47.4 (40.4–54.5)
Metropolitan cities	250 (25.0)	36.4 (30.4–42.4)	41.2 (35.1–47.3)
Provinces	556 (55.6)	41.2 (37.1–45.3)	42.3 (38.2–46.4)
Level of education			
High school and below	291 (29.1)	40.9 (35.2–46.5)	43.6 (37.9–49.3)
College and above	709 (70.9)	40.5 (36.9–44.1)	42.7 (39.1–46.4)
Health insurance type			
Self-employed	239 (23.9)	41.0 (34.8–47.2)	43.1 (36.8–49.4)
Workplace	698 (69.8)	41.1 (37.5–44.8)	42.8 (39.2–46.5)
Others[a]	63 (6.3)	33.3 (21.7–45.0)	44.4 (32.2–56.7)

[a]*Others include Medical Aid, no health insurance, or unknown.*

**Percentage was calculated in column.*

CI, *confidence interval.*

Medications were primarily lent to or borrowed from family and relatives (86.9% for lending and 83.5% for borrowing) and friends (23.2% and 21.2%, respectively). These numbers were not mutually exclusive. The most frequent reason for both lending and borrowing was that the lender happened to have the medication the borrower needed (58.4% for lending and 45.3% for borrowing). The least frequent reason for lending was that the lender just wanted to help the borrower (7.1%), and that for borrowing was that the borrower wanted stronger medication (7.9%; **Supplementary Table S1**). Most of the respondents who had lent medication (91.4%) provided either a verbal explanation or an instruction sheet when they lent the medication. However, 20% of the respondents who had borrowing experience reported having received neither a verbal explanation nor an instruction sheet. Most respondents (89.4% for lending and 87.0% for borrowing) reported that the borrower's condition improved after taking the medication.

Prescription Medications Subject to Lending or Borrowing

The rankings of medications that had been lent or borrowed were similar. Pain relievers, including analgesic, antipyretic, and antimigraine medications, were the most frequently lent and borrowed ones (**Table 2**). The reported frequency of gastroduodenal ulcer medication and ophthalmic medication lending was over 20%, whereas borrowing of these medications was below 20%. Antibiotics were also shared by more than 10% of the respondents. Less than 5% of the respondents shared chronic disease medications. The details are presented in **Table 2**.

Associated Factors for Prescription Medication Lending or Borrowing

There were no statistically significant differences related to lending or borrowing experiences based on participants' demographic characteristics (**Table 1**). The mean age of the groups with and without medication lending experience and that of groups with and without medication borrowing experience showed no statistically significant differences (p = 0.208 and p = 0.763, respectively). However, some associated factors were determined for the sharing behavior for each medication type in the subgroup analyses. Among the prescription medications, the results for analgesics, gastroduodenal ulcer medications, ophthalmic medications, antibiotics, and hypnotics showed significant factors contributing to lending or borrowing behavior.

TABLE 2 | Reported frequencies and types of prescription medications that were lent and borrowed.

Type of medication	Lent prescription medications (*n* = 406), No. (%*)	Borrowed prescription medications (*n* = 430), No. (%*)
Analgesics	218 (53.7)	204 (47.4)
Antipyretics	173 (42.6)	147 (34.2)
Antimigraine	100 (24.6)	91 (21.2)
Gastroduodenal ulcer medications	99 (24.4)	73 (17.0)
Ophthalmic medications	88 (21.7)	63 (14.7)
Laxatives or antidiarrheal medications	73 (18.0)	68 (15.8)
Antibiotics	65 (16.0)	55 (12.8)
Topical corticosteroids	59 (14.5)	53 (12.3)
Muscle relaxants	41 (10.1)	38 (8.8)
Allergy medications	38 (9.4)	31 (7.2)
Hypnotics	23 (5.7)	22 (5.1)
Antihypertensives	17 (4.2)	9 (2.1)
Psoriasis medications	16 (3.9)	24 (5.6)
Diabetes medications	11 (2.7)	5 (1.2)
Hyperlipidemia medications	10 (2.5)	9 (2.1)
Mood medications	7 (1.7)	1 (0.2)
Contraceptives	6 (1.5)	2 (0.5)
Inhalers for asthma	1 (0.2)	2 (0.5)
Others	19[a] (4.7)	26[b] (6.0)

[a]*Others include decongestants, antitussives, expectorants, and medications for cold or weight loss.*
[b]*Others include decongestants, antitussives, expectorants, medications for cold, weight loss, hair loss, rhinitis, dental care, and nutritional supplements.*
**As the respondents were asked to report their lending or borrowing experience for a list of 19 medications, the numbers are not mutually exclusive.*

TABLE 3 | Factors associated with lending or borrowing experience for analgesics.

Characteristics	Have lent analgesics (*n* = 218) OR (95% CI)[a]	Have borrowed analgesics (*n* = 204) OR (95% CI)[a]
Gender		
Female	1.0	1.0
Male	1.13 (0.74–1.70)	1.17 (0.78–1.77)
Age distribution		
20–29 years	1.0	1.0
30–39 years	1.45 (0.69–3.03)	1.76 (0.84–3.69)
40–49 years	1.61 (0.78–3.32)	3.28 (1.56–6.92)†
50–59 years	1.63 (0.77–3.48)	2.09 (0.96–4.53)
60–69 years	2.47 (1.06–5.75)*	3.79 (1.63–8.81)†
Marital status		
Single	1.0	1.0
Married	1.02 (0.58–1.78)	0.90 (0.52–1.55)
Residential area		
Capital	1.0	1.0
Metropolitan cities	0.94 (0.51–1.72)	0.44 (0.24–0.80)†
Provinces	0.77 (0.46–1.30)	0.57 (0.34–0.95)*
Level of education		
High school and below	1.0	1.0
College and above	1.03 (0.64–1.65)	1.02 (0.63–1.64)
Health insurance type		
Self-employed	1.0	1.0
Workplace	1.43 (0.88–2.34)	1.23 (0.75–2.03)
Others[b]	1.65 (0.61–4.47)	1.54 (0.63–3.80)

[a]*Multiple logistic regression analysis.*
[b]*Others include Medical Aid, no health insurance, or unknown.*
*p< *0.05*
†p< *0.01.*
CI, *confidence interval;* OR, *odds ratio.*

Respondents aged 60 years or older were more likely to lend analgesics than those aged 20–29 years (odds ratio [OR], 2.47; 95% confidence interval [CI], 1.06–5.75). Respondents aged 40–49 years (OR, 3.28; 95% CI, 1.56–6.92) and 60 years and older (OR, 3.79; 95% CI, 1.63–8.81) were more likely to borrow analgesics than respondents aged 20–29 years (**Table 3**).

Respondents aged 50 years and older were more likely to lend or borrow gastroduodenal ulcer medications than respondents aged 20–29 years (**Supplementary Tables S2, 3**). Regarding ophthalmic medications, respondents who had an educational level of college and above were less likely to lend these medications than those with an educational level of high school and below (OR, 0.54; 95% CI, 0.31–0.93; **Supplementary Table S2**). In the case of antibiotics, respondents in their 30s (OR, 4.92; 95% CI, 1.68–14.44), 50s (OR, 3.36; 95% CI, 1.05–10.67), and 60s (OR, 5.65; 95% CI, 1.65–19.29) were more inclined to lend antibiotics than those in their 20s; married people were less inclined to lend antibiotics than those who were single (OR, 0.40; 95% CI, 0.19–0.81; **Supplementary Table S2**). Respondents aged 30–39 years tended to borrow more antibiotics than those aged 20–29 years (OR, 3.64; 95% CI, 1.12–11.79; **Supplementary Table S3**).

Hypnotics tended to be borrowed less by male respondents than female respondents (OR, 0.25, 95% CI, 0.09–0.69). They were borrowed more by respondents in their 30s (OR, 15.89; 95% CI, 1.70–148.34), 40s (OR, 10.87; 95% CI, 1.08–108.99), and 60s (OR, 50.87; 95% CI, 4.34–595.88) than those in their 20s. Married people were less likely to borrow hypnotics than those who were single (OR, 0.14; 95% CI, 0.04–0.47) (**Supplementary Table S3**).

DISCUSSION

To our knowledge, our study is the first of its kind to report the prevalence of prescription medication sharing, the most frequently shared medications, and their associated factors using a relatively large sample in South Korea. We believe it provided comprehensive overview of medication sharing behavior among Korean adults. Pharmacotherapy is the mainstay modality for treating many clinical conditions (Upadhyay et al., 2018). Therefore, access to medication and its appropriate use is one of the most important healthcare agendas (World Health Organization, 2017). Timely and proper access to medication has been a critical issue for improving health outcomes for patients, clinicians, and policymakers not only for enhancing legitimate access to prescription medications but also for avoiding the misuse or illicit use of medications (World Health Organization, 2021). Although many studies have addressed ways to improve clinical outcomes with appropriate use of pharmacotherapy worldwide (Whelton et al., 2018), studies on medication sharing have been conducted by researchers from limited number of countries. The majority of the published studies on the topic were from countries in Europe, America, and Oceania (Daniel et al., 2003; Sorensen et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008; Goulding et al., 2011; Ward et al., 2011; Beyene et al., 2014; Dohn and Pilkington, 2014; Markotic et al., 2017; Markotic et al., 2018; Beyene et al., 2019a; Beyene et al., 2019b; Beyene et al., 2019c), very few studies were reported from African countries and Middle East (Yousif, 2002; Jassim, 2010; Sharif et al., 2010; Auta et al., 2011; Kheir et al., 2011; Ocan et al., 2015; Asmelashe Gelayee and Binega, 2017; Mostafa-Hedeab, 2018; Obol et al., 2018; Torres et al., 2019; Alhomoud, 2020), even fewer studies were conducted from countries by researchers in Asia including Korea (Ali et al., 2010; Baber et al., 2017; Atif et al., 2019). While a few studies mentioned presence of medication sharing as a part of medication misuse (Jeong, 2017; Park and Jang, 2018), no studies were found from a literature search using keywords of medication sharing from the Research Information Sharing Service (RISS), a Korean research data search engine. Therefore, our study can serve as a point of reference highlighting overall practice of prescription medication sharing among Korean adults.

Our findings indicate that one in two Korean adults share prescription medications. The estimated prevalence is similar to that reported in Nigeria (52.7%) (Auta et al., 2011), but our observed prevalence rate was mostly higher than the rates observed in the United States and Ireland, with the reported rates of lending or borrowing ranging between 13.4% and 34.1%, respectively (Daniel et al., 2003; Goldsworthy et al., 2008; Petersen et al., 2008; Goulding et al., 2011; Ward et al., 2011; Beyene et al., 2014). The exact reasons why the rates of medication sharing differ between countries remain unclear; however, the potential reasons could be related, in part, to differences in enabling resources like access to healthcare services and prescription medication health insurance coverage, as well as to the diversity of health beliefs or culture in each society related to sharing practices (Beyene et al., 2014). Reports from the literature also indicate enabling resources like presence of leftover medications as predictors of medication sharing (Beyene et al., 2019a). In fact, in 2018, a Korean government report estimated that the cost of unused prescribed medications was 218 billion Won (USD 192,579,505 as of 2021) in South Korea (Health Insurance Review and Assessment Service, 2019). We believe that leftover medications should be explored as the potential resources for medication sharing in the future, because the most common reason for medication sharing in our study was accessibility to medication from others, especially from family and relatives.

Our findings showed that analgesics and gastroduodenal ulcer medications were the most frequently shared medications. Based on reports from the Health Insurance Review and Assessment Service in South Korea, these ranked in the top five medications that have been most frequently billed over the past 3 years (Healthcare Bigdata Hub. Health Insurance Review and Assessment Service, 2021). Further, the tendency of borrowing behavior for hypnotics was higher in women and people with older age when we explored the association between medication sharing and predisposing factors. This can be attributed to the reported strong predictors of insomnia medication use by women and older adults (Bertisch et al., 2014; Wilson et al., 2019). The increased medication usage can be linked to the possibility of medication sharing.

Studies from many countries have reported the frequent sharing of analgesics (20%–61%) (Sorensen et al., 2003; Petersen et al., 2008; Auta et al., 2011; Markotic et al., 2018). Moreover, as the prevalence of using prescription pain

medications increases with increasing age (Hales et al., 2020), sharing of analgesics may also be affected by increasing age. More attention should be paid to the potential risks of analgesic-sharing, such as missed opportunities for timely diagnosis by physicians and adverse drug reactions, including hypertension and nephrotoxicity in frail older adults (Petersen et al., 2008; Beyene et al., 2014; Wongrakpanich, et al., 2018). Along with analgesics, antibiotics are a well-known shared medication (Beyene et al., 2014). Sharing of antibiotics can complicate the efficacy and safety of the medication use process not only at the personal level but also at the public health level due to antimicrobial resistance (World Health Organization, 2020).

The prevalent sharing of analgesics and antibiotics is a major public health concern. However, less frequently shared medications with reported serious adverse consequences should also be highlighted. Ophthalmic medications may include, but are not limited to, artificial tears, antibiotics, antihistamines, eye solutions for glaucoma management, and retinal eye drops. If shared, the safety concerns of unsupervised usage may range from mild side effects, such as burning or conjunctivitis, to severe adverse reactions, such as toxic epidermal necrolysis and angina pectoris (Latanoprost. IBM Micromedex Solutions, 2021). Sharing of gastroduodenal medications could also lead to serious adverse events (Fossmark et al., 2019). Moreover, some antidiarrheal medications should be used only while following specific patient instructions on dose and treatment duration (Latanoprost. IBM Micromedex Solutions, 2021; Whittaker and Newman, 2021). As findings related to sharing of ophthalmic and gastrointestinal medications have not been reported in detail in other studies, we believe that our study highlights the special role of healthcare professionals, especially pharmacists, in conducting frequent medication reviews and educating their patients to avoid adverse consequences.

Several limitations of this study should be noted. First, our study shares an inherent weakness related to cross-sectional design with limited representativeness and generalizability as a convenience sampling method was used to recruit the survey participants. To improve the external validity and to minimize selection bias, stratification method was used during the recruitment process reflecting the national census statistics by age, gender, and region. In addition, the biggest consumer panel available in South Korea was employed (Kim et al., 2020; Panel Marketing Interactive, 2021). Second, our study included people younger than 70 year old as the study utilized an internet-based survey. The rate of Internet use among Koreans in their 30s was 99.9% and 91.5% for those in their 60s, whereas the rate dropped to 40.3% for those aged 70 and over (National Information Society Agency, 2020). With the very low rate of the internet use among aged 70 and over, we believe that including only those who were younger than 70 was a practical and reasonable approach. Third, as the survey depended on the respondents' lifetime memory, presence of the measurement bias with underreporting of the medication sharing experience can exist. Finally, although the target medications for the sharing experience was explicitly declared to prescription medications, a possibility of data contamination of their experiences with over-the-counter medications cannot be ignored.

Medication sharing is a multifaceted problem requiring astute observations of patients and persistent efforts by healthcare professionals in the care network. More research is needed to compile data on key characteristics regarding people engaging in medication sharing, types of shared medications, and circumstances surrounding medication sharing. Based on real-world evidence, healthcare professionals could reflect on their patients' needs for accessing certain medications (e.g., subjective perception of emergency situations and their needs for usage) and be ready to educate and guide them with specific action plans regarding how to appropriately access prescription medications. From the policymakers' perspective, patient empowerment strategies in the form of public education or campaigns could be considered to improve awareness and avoid the adverse ramifications of unsupervised medication sharing.

CONCLUSION

Approximately one in two Korean adults in our study had experience in lending or borrowing medications prescribed for someone else with analgesics as the most frequently shared medications. Respondents with lower educational level were more likely to share ophthalmic medications. Larger scale population based studies are needed to confirm the prevalence of medication sharing and to focus on establishing evidence-based strategies for patient education and improving the medication use process, especially for medications with potential risks when shared without appropriate supervision of healthcare professionals.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because informed consents agreed by the participants indicated that access to the data is limited to the authors and the Institutional Review Board (IRB) of Seoul National University in special conditions. Requests to access the datasets should be directed to EL.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of Seoul National University (IRB No. 2009/002-012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS and EL conceptualized the study. SS curated the data, performed the methodology and led the article writing. EL and SK contributed to the writing of the article and interpretation of data. EL, SK, and SYS reviewed the survey questions and edited the article. SS and YL performed

statistical analyses. YL supervised the statistical analyses. All authors contributed to the writing of the article and reviewed the final article.

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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.2022.773454/full#supplementary-material

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Irrational Use of Medicine in the Treatment of Presumptive Asthma Among Rural Primary Care Providers in Southwestern China

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Poor knowledge, scarce resources, and lack of or misaligned incentives have been widely documented as drivers of the irrational use of medicine (IUM), which significantly challenges the efficiency of health systems across the globe. However, there is limited understanding of the influence of each factor on IUM. We used detailed data on provider treatment of presumptive asthma cases in rural China to assess the contributions of provider knowledge, resource constraints, and provider behavior on IUM. This study enrolled 370 village providers from southwest China. All providers responded to a clinical vignette to test their knowledge of how to treat presumptive asthma. Resource constraints ("capacity") were defined as the availability of the prescribed medicines in vignette. To measure provider behavior ("performance"), a subset of providers (104 of 370) were randomly selected to receive unannounced visits by standardized patients (SPs) who performed of presumptive asthma symptoms described in the vignette. We found that, 54% (201/370) of providers provided the vignette-based patients with prescriptions. Moreover, 67% (70/104) provided prescriptions for the SPs. For the vignette, only 10% of the providers prescribed the correct medicines; 38% prescribed only unnecessary medicines (and did not provide correct medicine); 65% prescribed antibiotics (although antibiotics were not required); and 55% prescribed polypharmacy prescriptions (that is, they prescribed five or more different types of drugs). For the SP visits, the numbers were 12%, 51%, 63%, and 0%, respectively. The lower number of medicines in the SP visits was due, in part, to the injections' not being allowed based on ethical considerations (in response to the vignette, however, 65% of providers prescribed injections). The difference between provider knowledge and capacity is insignificant, while a significant large gap exists between provider performance and knowledge/capacity (for 11 of 17 indicators). Our analysis indicated that capacity constraints play a minor role in driving IUM compared to provider performance in the treatment of asthma cases in rural China. If similar findings hold for other disease cases, this suggests that policies to reduce

the IUM in rural China have largely been unsuccessful, and alternatives for improving aligning provider incentives with appropriate drug use should be explored.

Keywords: irrational use of medicine, asthma, primary care providers, clinical vignette, standardized patients

1 INTRODUCTION

The rational use of medicine requires that "*patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*" (World Health Organization, 1985). A World Health Organization (WHO) report noted that less than 40% of primary care patients in public facilities and 30% in the private sector of developing and transitional countries are treated following standard treatment guidelines (Holloway and Van Dijk, 2011). The irrational use of medicine (IUM), in particular, IUM by providers, is a major challenge that affects healthcare systems worldwide. Examples of provider IUM include polypharmacy; inappropriate use of antibiotics for non-bacterial infections; overuse of injections when oral formulations would be more appropriate; and failure to prescribe in accordance with clinical guidelines (De Vries et al., 1994; Hogerzeil et al., 2001; World Health Organization, 2021). Harmful consequences of IUM include adverse events, increasing antimicrobial resistance, and the spread of blood-borne infections, all of which can result in increased morbidity and mortality (Holloway and Van Dijk, 2011). IUM is also thought to be a significant source of unnecessary medical expenditures. Medications account for 70–75% of total health expenditures in low- and middle-income countries (LMICs), and WHO has estimated that 50–70% of these medications are not needed and constitute IUM (World Health Organization, 2008; Ofori-Asenso and Agyeman, 2016).

Existing studies suggest three main reasons for IUM in LMICs. First, inadequate knowledge and poor training of health professionals have been shown to be highly correlated with a high prevalence of IUM in LMICs (World Health Organization, 2002; Das et al., 2012; Mao et al., 2015; Mohamadloo et al., 2017; Machowska and Lundborg, 2019). Second, there is evidence that structural factors related to limited health system resources (*e.g.*, the unavailability of medical equipment, unrestricted availability of medications, high caseloads) are negatively associated with appropriate prescribing practices and the ability of providers to apply their knowledge (Das and Hammer, 2014; Giorgio et al., 2020). Third, studies of IUM in different settings have found that institutional features, including financial incentives, promotion of medications, and system-wide legislations as well as sociocultural factors and political issues, to affect the behavior of providers (World Health Organization, 2002; Holloway and Van Dijk, 2011; Mao et al., 2015; Mohamadloo et al., 2017). These institutional and other features also can amplify knowledge deficits of both providers and patients (Mao et al., 2013).

This study aimed to analyze the relative contribution of these three factors to IUM in village clinics in rural China. We used data from a survey of providers in village clinics—the most common first point of patients (Babiarz et al., 2010)—in a southwestern province to measure provider IUM in the treatment of a presumptive case of asthma. We decomposed the total scale of IUM into the *know* gap that is attributable to deficits in provider knowledge to achieve the expected level of appropriate prescription; the *know-can* gap, which is measured by the difference between provider knowledge and what they can do, given available resources; and the *can-do* gap, which is measured by the difference between what they can do and what they actually do in practice (Lange et al., 2014; Mohanan et al., 2015; Ibnat et al., 2019). The three gaps are related to the three main factors, as described above, associated with IUM in LMICs. Specifically, the *know* gap is about provider education and training; the *know-can* gap is related to structural constraints; and the *can-do* gap involves factors that influence the efforts of providers (Das and Hammer, 2014).

2 METHODS

A survey of village providers in a random sample of 370 villages in Yunnan Province (southwestern China) was used to collect information on provider knowledge (*know*), capacity (*can*), and performance (*do*) in the case of the provider's ability to prescribe medicines properly and completely for the treatment of a presumptive case of asthma. In the survey, a standardized clinical vignette was used to assess the *know* part of the study; data on clinic resources, to measure the *can* part of the study; and unannounced visits by standardized patients (SPs), to ascertain the *do* part of the study. Asthma was chosen as the disease, given its high burden in China, with more than 45 million individuals affected, coupled with the fact that previous studies have documented high rates of IUM in the treatment of the disease (Osaretin et al., 2013; GBD 2015 Chronic Respiratory Disease Collaborators, 2017; Ding and Small, 2018).

2.1 Setting

Data were collected from rural village providers in three prefectures of Yunnan Province between July 2017 and January 2018. The *per capita* gross domestic product in Yunnan Province was 34,221 RMB ($5,068 US[1]) in 2017, ranking it as the second poorest province in China. The rural population in 30 counties of the three sample prefectures was 6.5 million, out of a total rural population of 46 million in the province (Yunnan Bureau of Statistics of China, 2017).

[1]1 US$ = 6.7518 yuan (October 2017).

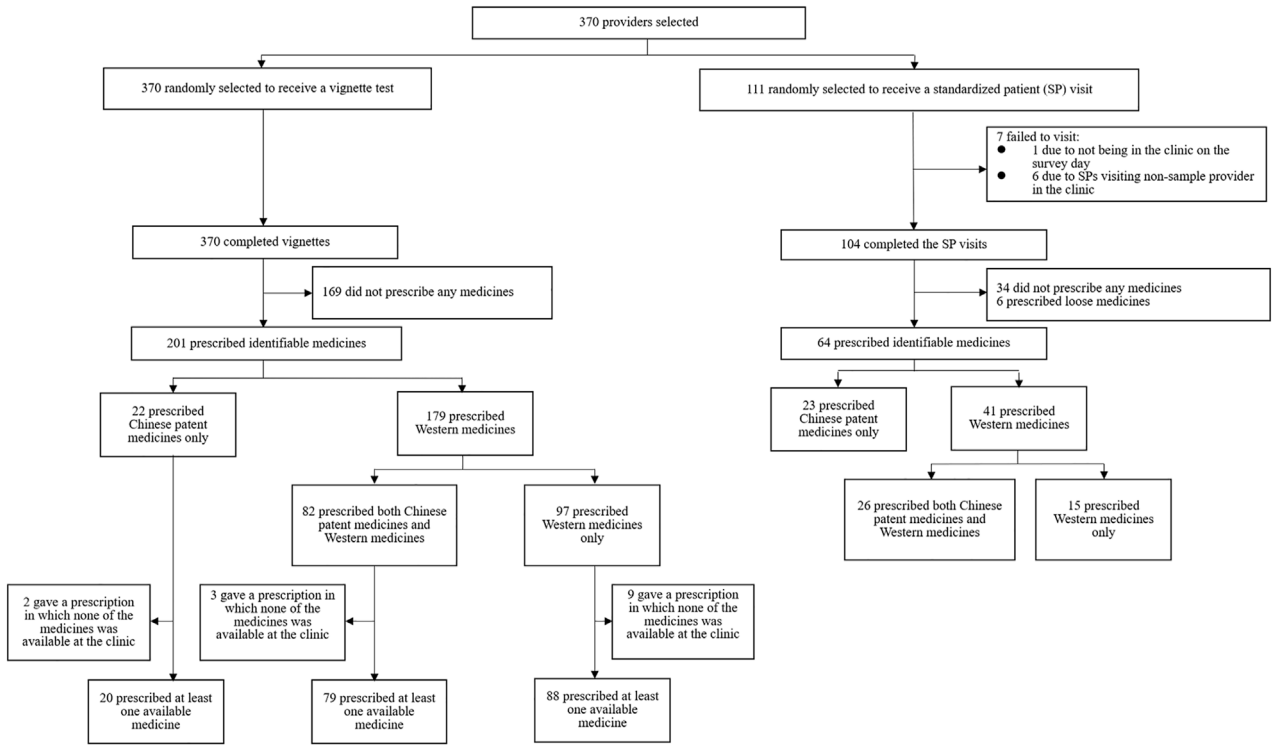

FIGURE 1 | Strobe flowchart.

China's rural primary care system is comprised of three tiers of providers—county hospitals, township health centers, and village clinics. The village clinic is the front line of the health system and is designed to provide outpatient care, the sale and dispensing of medications for common clinical conditions, and the provision of public health services. Village clinics typically function as independent for-profit entities and, at least in the past, earned part of their revenue from the sale of medications to their patients. As one of five key areas of the comprehensive health reform, the Chinese central government introduced the Zero-Markup Drug Policy (ZMDP) of the drugs on the Essential Drug List (EDL) in 2009 and has updated the EDL every 3 years since then (China, 2009; The Central Committee and the State Council of the Communist Party of China, 2009). In addition, provincial governments can add drugs to the list based on local needs. The policy intended to ensure safety in the use of medications and controls for drug-related expenditures by decoupling the compensation of healthcare providers, including government-funded village providers, from drug prescriptions and sales (China, 2009). After the comprehensive health system reform, the central government suggested a fixed quota of subsidies, which is referred to payments to village cadres, to compensate village providers, including subsidizing their loss due to implementation of the ZMDP (General Office of State Council of China, 2013). There is anecdotal evidence, however, that indicates that, after the introduction of the EDL, the drugs that village providers used to prescribe, and patients needed, were not available in village clinics (Guan et al., 2018).

2.2 Study Population

The full sample of the study comprised 370 village providers (Yi and Sylvia, 2017). To choose the sample, first, the research team randomly selected a total of 370 village clinics out of a comprehensive list of the 1,320 village clinics in the 10-county study area. Second, in each village clinic, the provider who was in charge of prescribing Western drugs and who assumed the main responsibility for outpatient care was selected. If more than one such provider was present, one was randomly selected. All 370 providers completed the provider survey instrument and clinic survey and participated in responding to the standardized asthma clinical vignette. Third, from the full sample, the research team randomly selected 111 providers who were assigned to be part of the study in which a standardized patient (SP) with presumptive asthma visited the provider's clinic (**Figure 1**).

2.3 Data Collection

The data for this study was collected through three surveys, as described below.

2.3.1 Provider and Clinic Surveys

The first survey, conducted in July 2017, was used to collect detailed information on the full sample of village providers and their clinics. The provider survey contained items in regard to the respondents' age, gender, highest level of education attained, medical certification, training in area of the diagnosis and treatment of asthma, training in the use of antibiotics,

familiarity with the term *clinical pathway*,[2] and the share of their income that was earned from their work in the clinic.

The clinic facility survey was used to collect information on the number of providers in the clinic, number of patient visits during the previous month, composition and size of the stock of Western medicines and Chinese patent medicines (CPMs), availability of medical instruments that may be used for the diagnosis of asthma, availability of intravenous drip equipment, availability of intra-muscular injection tools/equipment, whether the clinician kept medical records, any incentives from upper levels tied to prescription assessment, and implementation of the EDL and ZMDP. A translated English version of the provider survey form and clinic facility survey form are presented in **Supplementary Appendices SA, SB**.

2.3.2 Unannounced Standardized Patient Visit

The second round of the survey process, in December 2017, consisted of unannounced SP visits to selected providers. The unannounced SP method is considered the gold standard for measuring actual clinical practice in the real world (Das and Hammer, 2014; Das et al., 2016). In comparison with other methods of measuring healthcare quality, it has the advantage of enabling both case and patient mix (Das and Hammer, 2014). An SP script that presented a case of presumptive asthma, previously used in a study in India, was translated and adapted to the context in China with the assistance of respiratory specialists from the Peking Union Medical College Hospital and from People's Hospital, Peking University (Das et al., 2016). The SP script includes disease signs and symptoms, medical history, and patient background (**Supplementary Appendix SC1**).

To implement the SP protocol, five around 25-year-old women were recruited from local communities as SPs and trained intensively for approximately 2 weeks to enable them to make a consistent presentation of the disease case to providers. Before the training, the SPs had been given a physical examination in the university hospital to ensure they were healthy and had no physiological symptoms that might affect the diagnosis of village providers. The training focused on standardizing disease case presentations across SPs and on safety measures for SPs to avoid invasive procedures during clinic visits. For the latter, SPs were provided with standardized phrasing to refuse invasive procedures (**Supplementary Appendix SC2**).

The intention of the SP protocol was to make all visits as consistent as possible. The SPs were randomly assigned to providers and followed the normal procedures for any walk-in patient. Upon being presented to the provider, SPs made an opening statement of the primary symptoms of the case: "Doctor, I have a shortness of breath; I am wheezing." The SPs would respond to all questions posed by the provider, following a standardized script, purchase all medicines prescribed (which are sold by the providers), and pay the provider any fee. As noted, all of the SPs were trained to reject invasive procedures during clinic visits.

Following each visit, each SP was debriefed using a structured questionnaire, and SPs' responses were confirmed against a recording of the interaction taken, using a concealed recording device. The structured questionnaire detailed the provider's questions (which were compared to an approved checklist of appropriate/necessary questions), diagnostic examinations and tests requested, the stated diagnosis, the treatment prescribed (drugs or advice), and patient referral(s) (**Supplementary Appendix SC3**). In terms of drugs, the information included the name of the medicine, dosage form, nature/form of administration, and the dosage regimen (the time between doses and the amount of a medicine to be given at each specific time).

2.3.3 Standardized Clinical Vignettes

In January 2018, enumerators returned to sample clinics to administer a standardized clinical vignette to the sample providers. The clinical vignette was designed to present the same asthma case as was presented by the SPs, except for two changes. One was that providers were aware that they were being evaluated; (Das and Hammer, 2014) the other was that intrusive procedures (*e.g.*, injections) were allowed.

A total of 32 enumerators (2 per team, 16 teams) were trained for 7 days to present the standardized clinical vignette to the sample providers. One enumerator in a team assumed the role of a "mock patient"; the other assumed the role of "facilitator." The facilitator read the instructions to the provider, documented the interaction, and provided additional information that the patient might not know but would be helpful to the provider's diagnosis if the provider actively solicited it, *e.g.*, the results of tests or examinations. At the start of the clinical vignettes, providers were told to consult with the "mock patient" as they would a patient in their clinic but to assume that they had access to any diagnostic equipment and therapeutics they required.

During the vignette interactions with the sample providers, the enumerators documented the same information as was recorded in the structured questionnaire of SP visits. Although the team collected information about the name of the medicines and routes of administration of each drug prescribed, only detailed information was documented in regard to the dosage regimen for drugs that were available in the clinic. For those that providers prescribed, but were not available at clinic, the vignette teams did not collect such information. Data are provided in **Supplementary Appendix SD**.

2.4 Outcomes

2.4.1 Measurement of IUM

The survey data were used to produce three categories of outcome variables. Specifically, information on drug prescriptions was used to create a primary set of measures of IUM. From this information, we produced variables that included the number of

[2]Clinical pathways are document-based tools that provide a link between the best available evidence and multidisplinary clinical practice in health care (Rotter et al. (2013). It has been proposed to serve as an intervention to reduce variations in practice and improve patient outcomes in many countries including China (ibid., National Health Commission of the People's Republic of China, (2016)). In our study, we use the familiarity with the term *clinical pathway* as a proxy that village providers had better clinical knowledge.

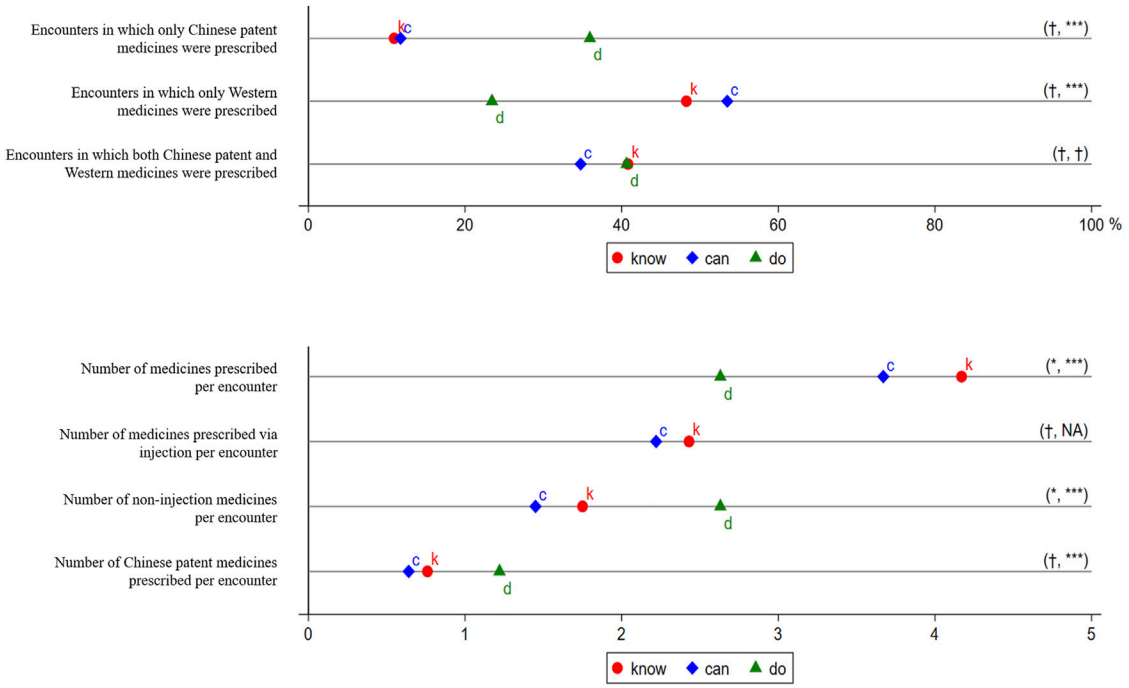

FIGURE 2 | Prescriptions in the Treatment of Presumptive Asthma. *k*, *c*, and *d* represent *know*, *can*, and *do*, respectively. The *know* gap is not measured because no well-recognized target performance is available. The distance between *k* and *c* is the *know-can* gap, and the distance between *c* and *d* is the *can-do* gap. We use t-tests to examine whether the gaps are statistically significant and report the significance of the *know-can* gap and the *can-do* gap in parentheses. †$p > 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. We did not consider Chinese patent medicines in measuring the outcomes. Injection included intravenous drip and intramuscular injection.

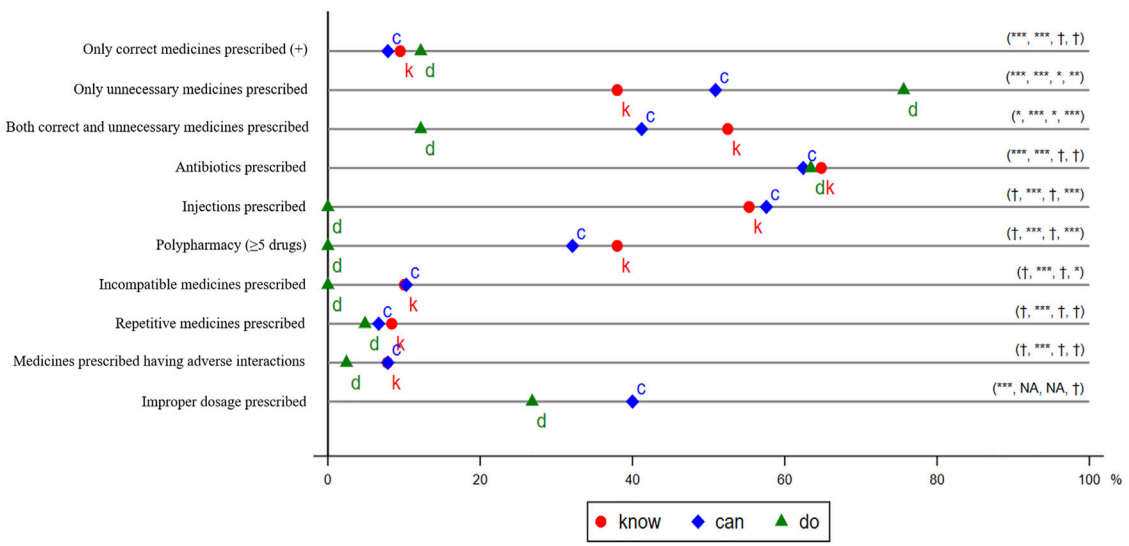

FIGURE 3 | Irrational Use of Medicine in the Treatment of Presumptive Asthma. *k*, *c*, and *d* represent *know*, *can*, and *do*, respectively. The distance between 0 and *d* and the distance between 0 and *k* is the *total* gap and the *know* gap, respectively, except that the *total* gap and *know* gap of *only correct medicines prescribed* is the distance between 100% and *d* or *k*. The distance between *k* and *c* is the *know-can* gap, and the distance between *c* and *d* is the *can-do* gap. We use t-tests to examine whether the gaps are statistically significant and report the significance of *total* gap, *know* gap, *know-can* gap, and *can-do* gap in parentheses. †$p > 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. We did not consider Chinese patent medicines in measuring the outcomes. Injection included intravenous drip and intramuscular injection.

providers who prescribe medicines, number of different drugs, origin of each (Western *vs*. CPMs), and route of administration of the medicines (**Figure 2**).

The second category outcomes were whether prescriptions followed the Chinese National Practice Guidelines to treat asthma (Asthma Workgroup of Chinese Thoracic Society and Chinese Society of General Practitioners, 2013; Asthma Workgroup of Chinese Thoracic Society, 2016). Each Western medicine on the prescription list was classified as necessary (or correct), unnecessary, or potentially harmful (**Supplementary Appendix SE**). Based on the combination of drugs in a prescription, seven indicators were reported: only correct medicines prescribed; only unnecessary medicines prescribed; only potentially harmful medicines prescribed; both correct and unnecessary medicines prescribed; both correct and potentially harmful medicines prescribed; both unnecessary and potentially harmful medicines prescribed; and correct, unnecessary, and potentially harmful medicines prescribed together (**Figure 3**).

A third category of outcome variables was defined according to Chinese Pharmacopoeia and Standards for Prescription Examination in Medical Institutions (**Figure 3**) (National Health Commission of the People's Republic of China, 2018; Commission, 2020). These indicators are widely used in recent literature on rationing use of medicines (World Health Organization, 1993; World Health Organization, 2002; Dong et al., 2010; Dhamija et al., 2013; Ventola, 2015; Ofori-Asenso and Agyeman, 2016; Rajalingam et al., 2016; Fujita et al., 2018). Specifically, we assessed whether any antibiotics were prescribed, any injections were prescribed, five or more drugs were prescribed (which we define as *polypharmacy*), medicines were prescribed without indication, incompatible medicines were prescribed, repetitive medicines were prescribed, medicines prescribed had adverse interactions, and improper dosages were prescribed. The last outcome could be assessed only for the prescribed medicines that were available in the clinics.

Two pharmacists from the Peking University Health Science Center independently evaluated and scored the prescriptions using predetermined protocols. When the scores were different, a third pharmacist would engage in discussion with them and reach a consensus. For an international comparison, CPMs were excluded in the assessment of the last two types of outcomes.

2.4.2 Measurement of *Know*, *Can*, *Do*, and Three Gaps

First, we measured the provider's *know*, *can*, and *do* for each outcome. Specifically, we used the provider's actual performance in the SP visits to measure the provider's *do*. The provider's performance in the clinical vignette was a measure of the provider's *know* (Das and Hammer, 2014). The provider's *can* was defined by the availability of the prescribed medicines during the clinical vignette in the dispensing pharmacy of the village clinic (Ibnat et al., 2019).

Then, we calculated the total gap, using the difference between the average of the providers' actual performance (*do*) and the target performance. We defined target performance as perfect adherence to prescription guidelines. We do not report the total gap for the first type of outcome because there were no available well-recognized guidelines for this outcome. In terms of the second and the third categories of outcomes, the target performance was assumed to be zero, except that it was 100% for the outcome of whether only correct medicines were prescribed.

Finally, we decomposed the total gap into three gaps. The first gap was the *know* gap, which was the difference between the average of the provider's *know* and the target performance. The *know* gap was defined as the part that could be attributed to the provider's knowledge deficiency in the total gap. The second gap was the *know-can* gap, or difference between the average of the provider's *can* and the average of the provider's *know*. An insignificant *know-can* gap indicates that the availability of drugs did not affect the rational use of medicine (RUM). The third gap was *can-do*, defined as the difference between the average of the provider's *can* and the average of the provider's *do*. The *can-do* gap reflects the part of the provider's efforts, excluding knowledge deficiency and resource constraints from the total gap.

2.5 Statistical Methods

Statistical analyses were conducted using Stata 15.1. The means and standard deviations (SDs) of continuous variables, numbers, and percentages of binary variables were reported. In addition, *t*-tests of the equality of means between *know* and *target performance* (or the *know* gap) and between *know* and *can* (or the *know-can* gap) were conducted for paired data; *t*-tests of the equality of means between *can* and *do* (or the *can-do* gap) were conducted for unpaired data. Whether a 95% confidence interval (CI) of the difference in the mean of outcomes contains 0 was used to assess the statistical significance of the gaps.

2.6 Ethics and Informed Consent

Full ethical approval for this survey was obtained from the Peking University Institutional Review Board on April 26, 2017 (IRB00001052-17033). The Board approved the verbal consent procedure, and verbal consent was obtained from local health departments and participants at the start of the survey. We collected verbal consent for the following reasons. The research presented minimal risk of harm to subjects and involved no procedures for which written consent was normally required outside of the research context, and verbal consents are more culturally acceptable than are written consents in the region.

3 RESULTS

3.1 Characteristics of Providers and Clinics

The average age of the 370 providers was 46 years, and 64% are male. In addition, 68% graduated senior high school, 26% completed junior college or a higher level of education, and 6% completed junior high school or had a lower level education. Only 8% were qualified medical practitioners or qualified associate medical practitioners, and 18% reported they were familiar with the term *clinical pathway*.

No provider received training in regard to asthma in the previous 2 years, and 54% received training in use of antibiotics. In terms of income, 95% came from working in the clinic.

Each village clinic had, on average, two providers. The number of patient visits in the previous month was 601 (SD = 1,662) with the median 303.[3] Almost all clinics implemented the ZMDP in regard to essential drugs. At the clinic, 95 brands of Western medicines and 42 brands of CPMs were available. Medical instruments and services for chest auscultation, assessment of heart rate/pulse/blood pressure, and percussion added to chest examination were available in almost all clinics, whereas those for a pulmonary ventilation test, bronchodilator test, chest X-ray examination, or blood routine test were seldom or not available. Almost all clinics provided an intravenous drip or intramuscular injection, 84% kept medical records, and 81% reported incentives tied to prescription assessment.

3.1 Prescription in the Treatment of Presumptive Asthma

3.2.1 Providers' Performance in SP Visits

As illustrated in **Figure 1**, 67% (70/104) of providers prescribed in SP visits, and six (6%) provided loose medicines (medicines taken from original packaging and did not provide a written or oral prescription) in the SP visits. Because the exact name of these medicines and related information was undeterminable, the six providers with loose medicines were excluded from the remainder of the analysis.

The descriptive statistics of prescriptions in the treatment of presumptive asthma are seen in **Figure 2**. For the composition of each prescription by the origin of medicines, we found that, in SP visits, 36% (23/64) of the prescriptions included CPMs alone; 23% (15/64), Western medicine(s) alone; and 41% (26/64), CPMs and Western medicine(s) combined (**Figure 2**, Panel A). Because injections, as an intrusive treatment, were not allowed in SP visits, only non-injectable medicines were prescribed. The number of medicines per encounter was 2.63 (±1.28), of which providers prescribed 1.22 (±0.95) CPMs per encounter in SP visits on average.

3.2.2 Providers' Know-Can Gap, and Can-Do Gap in Prescriptions

Although nearly two-thirds of providers prescribed in SP visits, fewer providers prescribed in the case of the vignette. Specifically, 54% (201/370) prescribed in a vignette (**Figure 1**), and this share fell to 51% (187/370) due to medicine unavailability. Even among 104 providers who completed both vignettes and SPs, 17 (16.3%) prescribed neither in a vignette nor an SP visit, 39 (37.5%) prescribed in both a vignette and SP visit, 17 (16.3%) prescribed only in a vignette, and 31 (29.8%) prescribed only in an SP visit. There were no significant differences in most of the characteristics between those who prescribed only in a vignette and those who prescribed only in an SP visit (**Supplementary Appendix Table S1**). An unpaired *t*-test indicated that the *know-can* gap was not statistically significant ($p > 0.05$) (**Supplementary Appendix Table S2**). The *can-do* gap, however, was statistically significant ($p < 0.01$) and suggests that providers were more likely to prescribe in an SP visit than in a vignette, without or with consideration of medicine unavailability, respectively, by 13 percentage points (by 24%) and 17 percentage points (by 33%).

We also found that providers were more likely to prescribe CPMs in an SP visit than in a vignette (**Figure 2**, Panel A). Specifically, in a vignette, 11% (22/201) of the prescriptions included CPMs alone; 48% (97/201), Western medicine(s) alone; and 41% (82/201), CPMs and Western medicine(s) combined. Even taking medicine unavailability into account, 12% (22/187) of the prescriptions included CPMs alone; 53% (100/187), Western medicine(s) alone; and 35% (65/187), CPMs and Western medicine(s) combined. Although the *know-can* gaps of prescribing CPMs alone or prescribing Western medicine(s) alone were not statistically significant ($p > 0.05$), the *can-do* gaps were statistically significant ($p < 0.001$). This shows that providers were more likely to prescribe CPMs only in an SP visit by 24 percentage points (by 200%), and less likely to prescribe Western medicines only by 30 percentage points (by 56%) than in a vignette with consideration of medicine unavailability. Neither the *know-can* gap nor the *can-do* gap of prescribing a combination of CPMs and Western medicines were statistically significant ($p > 0.05$).

The results also show that providers prescribed more medicines via other administration routes in an SP visit, where injections were not allowed, than they did in a vignette (**Figure 2**, Panel B). In vignettes, providers prescribed 4.17 (±2.47) medicines, of which 2.43 (±2.73) were prescribed via injection. Even after excluding unavailable medicines, providers prescribed 3.67 (±2.39) medicines, of which 2.22 (±2.53) were prescribed via injection. The number of non-injection medicines per encounter declined slightly, from 1.75 (±1.36) to 1.45 (±1.25), due to medicine unavailability ($p < 0.05$). Because injections were not allowed in SP visits, no medicines via injection were prescribed (even though they were deemed necessary by some providers). The number of non-injection medicines per encounter increased to 2.63 (±1.28) in SP visits, an increase of 81% ($p < 0.001$) in comparison with a vignette with consideration of medicine availability. In addition, providers prescribed fewer CPMs in a vignette without or with consideration of medicine unavailability, respectively, 0.76 ± 0.89 and 0.64 ± 0.80, than that in an SP visit (1.22 ± 0.95).

3.3 Compliance of Drug Use to Guidelines in the Treatment of Presumptive Asthma

3.3.1 Providers' Performance in SP Visits and the Total Gap

In **Figure 3**, we first present the data on whether the use of medicines followed the guidelines of the treatment of presumptive asthma. More details can be found in **Supplementary Appendix Table S3**. In SP visits, 64% (41/64)

[3]There are two outliers in this variable. After excluding the outliers, the mean and standard deviation will be 502 and 702, respectively.

of providers prescribed at least one Western medicine. Among them, 12% (5/41) prescribed only correct medicines; 76% (31/41), only unnecessary medicines; 12% (5/41), both unnecessary medicines and correct medicines; and none prescribed harmful medicines. The total gap for correct prescription was significant ($p < 0.001$), as large as 88 percentage points (the target performance is 100%), and the total gap of unnecessary prescription was −76 percentage points (the target performance is 0) and statistically significant ($p < 0.001$).

Figure 3 also presents the data for the assessment of seven frequently cited indicators of IUM. For each of these indicators, providers performed as follows in the SP visits: antibiotics prescriptions (63%), injection prescriptions (0%), polypharmacy (0%), incompatible medicine prescriptions (0%), repetitive medicine prescriptions (5%), prescriptions with adverse interaction (2%), and improper dosage prescribed (27%). A *t*-test indicated that, except for prescription of antibiotics ($p < 0.001$) and improper dosage ($p < 0.001$), the total gaps of the other five variables are statistically insignificant.

3.3.2 Decomposition of the Total Gap: Know Gap, Know-Can Gap, and Can-Do Gap

We decomposed the total gap of each outcome into three gaps: *know* gap, *know-can* gap, and *can-do* gap. We found that the total gap in correct prescription was driven mainly by the *know* gap. Specifically, in vignettes, around 10% (17/179) prescribed only correct medicines. The *know* gap of prescribing correctly was 90 percentage points and statistically significant ($p < 0.001$). Nevertheless, neither the *know-can* gap nor the can-do gap for prescribing correctly was statistically significant ($p < 0.05$).

In contrast, the total gap for prescribing unnecessarily was found to be attributable to all three gaps. In vignettes, 38% (68/179) of providers prescribed only unnecessary medicines, and the knowledge gap is statistically significant ($p < 0.001$). This share increases to 51% (84/165) when we excluded unavailable medicines. The *know-can* gap of prescribing unnecessarily was statistically significant ($p < 0.05$). Further, the statistically significant *can-do* gap ($p < 0.01$) suggests that providers were more likely to prescribe only unnecessary medicines in an SP visit than in a vignette by 25 percentage points (by 49%), even in consideration of medicine availability. We also found that the total gap for prescribing both correct and unnecessary medicines was due to all three gaps simultaneously. No gaps were found in the prescription of drugs that might be harmful to the treatment of presumptive asthma.

In terms of the third categorical outcome, we found that the total gap for antibiotics prescription, prescription of repetitive medicines, and prescription with adverse interacting medicines were driven mainly by the knowledge gap. The *know-can* and *can-do* gaps were statistically insignificant ($p > 0.05$). Although the total gaps of injection prescription, polypharmacy, and prescription of incompatible medicines were zero, this appears due to the *can-do* gap offsetting the knowledge gap. Providers' performance in the three indicators are poor in a vignette, regardless of medicine availability, and they performed perfectly in SP visits because injections were prohibited. We did not report the percentage of prescriptions with improper dosages in the vignette because we collected information only about the dosage regimen for available drugs in the clinics. An analysis of a subsample of 104 providers who completed both the vignette and an SP indicated consistent results (**Supplementary Appendix Tables S4, S5**).

4 DISCUSSION

This assessment of providers' knowledge, capacity, and performance in the use of medicines in the treatment of presumptive asthma was conducted in a rural setting, with 370 rural village providers in three prefectures in Yunnan Province. Three categorical outcomes (description on prescription, compliance with the clinical guideline to treat asthma, and widely used indicators in recent literature on rational use of medicine) consisting, respectively, of nine, seven, and seven indicators were assessed. The total gap between actual performance and target performance was decomposed into three gaps: *know* gap, *know-can* gap and *can-do* gap.

Of the second and third categorical outcomes (14 indicators) with well-defined target performance, the total gap of five indicators (only correct medicines prescribed, only unnecessary medicines prescribed, both correct and unnecessary medicines prescribed, antibiotics prescribed, improper dosage prescribed) was statistically significant. Eleven indicators were characterized by insignificant total gaps.

When we decomposed the total gap into three gaps, we found that knowledge of all indicators is statistically significant, whereas the *know-can* gap was not statistically significant in most cases. Of the assessed *can-do* gap of 17 indicators, 11 were statistically significant. Of these, six indicators were positive, indicating that providers performed better in an SP visit than they did in a vignette, and five were negative, indicating providers performed worse in SP visits than they did in a vignette.

In the clinical vignettes, the number of medicines prescribed per encounter was found to be higher than previously reported in another study in China and Vietnam as well as international standards (4.17 versus 2.19) (Mao et al., 2015). More than half of the medicines (58%; 2.43/4.17) were prescribed via injections that were unnecessary for the treatment of the case. In particular, although unnecessary, antibiotics were the most frequently prescribed medicine in our study. Prescriptions of antibiotics in this study, at 64%, revealed a much higher rate when compared to that of the WHO/International Network of Rational Use of Drugs (INRUD) (30% of prescriptions in general), (Joncheere, 2002) asthma, or angina SP visits to informal health providers in India (33%), (Das et al., 2016) or adult respiratory cases in the United States (23%) (Shapiro et al., 2014). We also noted, however, that this number is similar to that of asthma or angina SP visits to healthcare providers in primary health centers in India (64%) (Das et al., 2016) and children's asthma cases in China (50–100%) (Chen et al., 2013; Wu et al., 2020). The univariate analysis revealed an insignificant correlation ($p > 0.05$) between a prescription of antibiotics and provider characteristics, including

whether the provider received training in antibiotics. This suggests that the training might be ineffective to reduce the knowledge gap (**Supplementary Appendix Table S6**).

Providers were more likely to prescribe, in particular, CPMs in SP visits than in vignettes. On the one hand, we found that some providers (17/104; 16%) changed from prescribing in a vignette to not prescribing in an SP visit. According to earlier research, after the EDL and ZMDP, many drugs that doctors used to prescribe became unavailable (Wang et al., 2015; Yang et al., 2015). We excluded this possibility, however, because, of the 17 prescriptions, there are 16 in which at least one drug in the prescription was immediately available at the clinics. Another possibility is that providers might change to not prescribing when their diagnostic capacity is constrained by unavailable examination and testing tools in an SP visit (see limitations of this study). Further, 30% (31/104) providers changed to prescribing in SP visits from not prescribing in clinical vignettes. When we looked at the prescription by the origin of medicines, we found that the statistically significant *can-do* gap indicates higher incentives for providers to prescribe, in particular, CPMs and unnecessary medicines. There could be two explanations for the two gaps. One is that providers could earn more from selling CPMs instead of Western medicines (Zhang et al., 2015; Cai et al., 2020). The other is that providers might believe that CPMs would be "safer" than Western medicines when fewer adverse drug reaction cases were reported for CPMs (although this is not necessarily true), (Mossialos et al., 2016; National Medical Products Administration, 2020) particularly when they could not diagnose the case.

The number of encounters in which only unnecessary drugs were prescribed in an SP visit is almost twice that in a clinical vignette without (76 vs. 38%) and with (76 vs. 51%) consideration of drug availability. Inappropriate incentives for drug dispensing has been widely cited as a factor that encourages providers to prescribe more unnecessary drugs than they should (World Health Organization, 2002; Holloway and Van Dijk, 2011; Mao et al., 2015; Mohamadloo et al., 2017). Another explanation is that providers were more likely to prescribe unnecessary drugs in an SP visit because there were more uncertainties in the diagnosis due to unavailability of medical equipment for examinations and tests.

We found that, with fewer medicines prescribed per encounter in an SP visit, providers reduced the proportion of polypharmacy, medicines prescribed without indication, and incompatible medicines prescribed. The reduced number of medicines per encounter is very likely due to prohibition of injections in SP visits (due to ethical considerations). An injection prescription is a very common practice in China (Li et al., 2012; Yang et al., 2012; Mao et al., 2013; Mao et al., 2015). The medicines via injection accounted for 58% (2.43/4.17) in each encounter in clinical vignettes.

This study has three primary limitations. The first limitation concerns the measurement of capacity. The capacity of providers was defined by the availability of medicines, which may bias the capacity in uncertain ways. On the one hand, it might underestimate the capacity as, for example, providers may use a tele-medication system to improve their capacity for RUM (although anecdotally rare). On the other hand, it might overestimate providers' capacity for RUM, as we did not take providers' diagnostic capacity into account. As shown in **Supplementary Appendix Table S7**, RUM is related to the correctness of a diagnosis. Specifically, in a vignette, providers who gave a correct or partially correct diagnosis would be less likely to prescribe CPMs alone (1 vs. 16%, $p < 0.01$), to prescribe CPMs and Western medicines together (23 vs. 50%, $p < 0.001$), unnecessary medicines alone (13 vs. 53%, $p < 0.001$), antibiotics (51 vs. 73%, $p < 0.01$), and fewer CPMs per encounter (0.29 vs. 1.00, $p < 0.001$) than would whose who gave the wrong diagnosis; whereas they were more likely to prescribe Western medicines alone (75 vs. 34%, $p < 0.001$) and medicines that have adverse interactions (15 vs. 4%, $p < 0.01$) than would those who gave the wrong diagnosis. Further, we found that 25% of providers requested the results of a chest X-ray examination, but only one clinic had the needed instrument ($p < 0.001$; **Supplementary Appendix Table S8**).

The second limitation of this study is that some predetermined, inimitable and essential symptoms could be detected by the examinations and then might bias the diagnosis and results. In our study, there were seven recommended examinations for the diagnosis (**Supplementary Appendix Table S10**). For three of them, village providers would receive a similar result compared to the vignette if they implemented these examinations. Meanwhile, there were four examinations which would detect a different physiological symptom in the SP consultation when compared to the vignette consultation as SP were healthy and did not present such symptoms nor mimick them. Nevertheless, of the four examinations, two were prohibited to implement in SP visits because they were considered intrusive examination. Although percussion was allowed, no village providers performed. In SP visits, 20 (19%) village providers performed chest auscultation. Comparing those who performed chest auscultation in SP visits and those who did in vignette, we found that the rates of correct diagnosis were statistically insignificant (44 vs. 15%, $p > 0.10$ with 1,000 replications). In summary, we could reasonably conclude that the bias caused by this limitation would be negligible in this study but should be addressed in the future.

The third limitation of this study is that we excluded CPMs in measuring the second and third type of outcomes for IUM for the purpose of an international comparison. Nonetheless, we also provide the results for full prescriptions, including CPMs (**Supplementary Appendix Table S9**). These results are consistent with our findings, except for a higher incidence of improper dosage when CPMs are included (49 vs. 35%, $p < 0.01$).

5 CONCLUSION

Since 2009, China has launched major reform initiatives to improve the health sector performance for affordable, equitable, and effective health care for all by 2020. Primary

care has been a central organizing paradigm for key health system functions policy reforms. This study found that, in general, resource constraints are not a major factor that drives IUM in rural China. More investments should be focused on improving providers' knowledge and aligning provider efforts. In addition, more research is needed to build the link between policy and the narrowing of gaps. In this regard, our study has five implications for the policy reforms. First, more effective ways need to be adopted to improve providers' knowledge about RUM. Second, action is needed to shift the role of initial diagnosis from village providers to hospital-based providers to allow village providers to assume more responsibility in follow-up visits. Third, although China has implemented the EDL and ZMDP, unnecessary drug prescription is still prevalent, due mainly to inappropriate provider efforts; thus, more research is needed to explore the underlying mechanisms. Fourth, in the short run, the regulation of the prescription of injections appears to be a necessary and effective way to reduce IUM. Finally, given the wide use of CPMs, more research is necessary to assess their appropriateness.

When viewed from a broader perspective, the findings suggest that attention to improving the quality of medical care should focus on providers' education and training as well as on the governance and management of improving providers' efforts toward quality care through market-based incentives, regulations, or social accountability approaches.

DATA AVAILABILITY STATEMENT

The datasets analyzed for this study can be found in the Harvard Dataverse: https://doi.org/10.7910/DVN/U39CHC

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking University Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to this article. HY, SS, and SR designed the study. HDL, HBL, and HY participated in the analysis and interpretation of the results. HY and HDL participated in the collection of data. HY and HDL drafted the manuscript. SS, DT, and HS made substantial revisions to the draft manuscript. All authors gave their final approval for submission. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. HY is the guarantor.

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SUPPLEMENTARY MATERIAL

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Knowledge, Attitude and Practice of Hospital Pharmacists in Central China Towards Adverse Drug Reaction Reporting: A Multicenter Cross-Sectional Study

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Background: Healthcare professionals' knowledge and attitudes towards adverse drug reactions (ADRs) and ADR reporting play a significant role in pharmacovigilance. This study aims to investigate the gap between knowledge and practice in ADR reporting among hospital pharmacists.

Methods: This study is a multi-center, cross-sectional study based on a questionnaire survey. A semi-structured questionnaire was developed including knowledge, attitudes, and practices (KAP) towards ADR reporting. From October to November 2021, questionnaires were filled out on the internet by hospital pharmacists from a central province of China. The data analysis used a one-way ANOVA to analyze the differences between the pharmacist's characteristics and knowledge and attitude, respectively. The ordinal logistic regression method was used to analyze the predictors of practice.

Results: A total of 1,026 valid questionnaires from 512 medical institutions were collected. It was found that 88.8% of participants have a clear understanding of the ADR definition, while 59.6% of them have misunderstandings about the reporting time of new and serious adverse reactions. Most pharmacists showed positive attitudes towards ADR reporting. Higher education background, higher professional title, attending training, and clinical pharmacist resulted in higher knowledge scores. Higher education background, shorter working years, attending training, and from non-tertiary hospital related to higher attitude scores. In terms of practice, age, hospital type, working years, training, and pharmacist type all have significant associations with practice scores. Pharmacists' knowledge score and attitude score were significant predictors of practice score with OR being 1.19 (95% CI: 1.06, 1.33) and 1.04 (95% CI: 1.005, 1.07).

Conclusion: Although most hospital pharmacists showed positive attitudes towards ADR reporting, their knowledge and practice were still insufficient. Hospital pharmacists' knowledge and attitude are associated with their practice towards ADR reporting. The training had a significant impact on the pharmacist's knowledge, attitude, and practice.

Keywords: adverse drug reaction reporting, hospital pharmacists, knowledge, attitude, practice, China

INTRODUCTION

The World Health Organization (WHO) defines adverse drug reactions (ADRs) as harmful and unrelated to the purpose of medication when normal doses of drugs are used to prevent, diagnose, treat diseases or regulate physiological functions (Edwards and Aronson, 2000). ADR has a significant impact on the health of patients, and is a major problem that has led to an increase in global morbidity and mortality. It is estimated that about 5% of hospitalized patients are caused by ADR, and another 5% of hospitalized patients will experience ADR during hospitalization. In the European Union, ADR causes 197,000 deaths every year (Bouvy et al., 2015). In the United States, the total cost of hospitalization after adverse drug events in the intensive care unit (ICU) and non-ICU ward is estimated to be 19,685 dollars and 13,994 dollars, respectively (Cullen et al., 1997). Therefore, monitoring adverse drug reactions are critical for global health care.

In all countries, national pharmacovigilance systems rely primarily on spontaneous reporting, in which suspected adverse drug reactions are reported to a national coordinating center by health professionals, pharmaceut post-marketing ical producers, or individuals (Pal et al., 2013). Spontaneous reports of ADRs have some advantages for identifying potential safety signals, but they have apparent drawbacks, such as substantial underreporting, poor report quality, difficulty quantifying risk, and an unknown number of people who have been exposed (Alharf et al., 2018; Hazell and Shakir, 2006).

China has a nationwide ADR reporting and monitoring system, composed of four levels, which includes the National Center for ADR monitoring, 34 provincial ADR monitoring centers, and hundreds of municipal and county-level institutions (Li et al., 2018; Zhao et al., 2018). In China, the number of spontaneous ADR reports was 1.7 million in 2020, which equates to 1215 reporting per million people. With a population of 1.4 billion people, China is attempting to expand the number of spontaneous ADR reports (Song et al., 2022).

The majority of ADR reports in China come from healthcare professionals (85.4%) (NMPA, 2020). According to a survey in three provinces in China, pharmacists reported the largest proportion of ADRs (43.51%) among all sources during 2015–2017, however, the quality of ADR reporting by pharmacists was not promising, with only 11.5% of reports being of high quality (Chen et al., 2019). Another investigation showed that hospital pharmacists in a northern province of China have good knowledge and attitudes but poor practice towards ADR reporting (Su et al., 2010). To better understand the challenges pharmacists face in reporting ADRs and to offer suggestions for improving the rate and quality of ADR reporting, we conducted this survey on pharmacists' knowledge, perceptions and practice of ADR reporting.

STUDY DESIGN AND METHODS

Participants and Setting

This is a multi center, cross-sectional study based on a questionnaire survey. The questionnaire was distributed to hospital pharmacists in QQ groups and WeChat groups in Hubei Province through the questionnaire collection software (Questionnaire Star), and a statement on the research project and consent form was distributed at the same time. From October to November 2020, a total of 1,128 people participated in the survey. The data was excluded based on the following criteria: I. Pharmacists who are not hospital pharmacists; II. Invalid. The questionnaire takes less than 1 min or more than 1 h to complete. In the end, a total of 1026 valid questionnaires were obtained, with an 89.7% effective rate. Participants were from 522 hospitals in Hubei Province. Participants' responses are completely anonymous and voluntary.

Questionnaire Design

The self-administered questionnaire was composed of 25 mandatory single-choice items and one multiple-choice item, and it was developed based on scientific literature (Chatterjee et al., 2006; Al Dweik et al., 2017; Seid et al., 2018) and the practice experience of the authors. Two experts in pharmacovigilance reviewed the questionnaire draft and assessed its content validity. The questionnaire consists of five main parts: (i) Pharmacist characteristics: education, profession rank, and length of work experience, etc.; (ii) Knowledge part: definition of ADR, ADR reporting time, etc., we set multiple-choice questions, each question has a correct answer, and the correct answer receives 1 point, while the incorrect answer receives 0 point; (iii) Attitudes part: concerning and willingness about ADR reporting, this part was provided on a 5-level Likert scale (1 = "strongly disagree," 2 = "disagree," 3 = "neutral," 4 = "agree," and 5 = "strongly agree") to indicate that they disagreed or agreed.; (iv) Practice part: covers two items based on the surveyors' ADR reporting practice experience, we set up a yes or no question option, "yes" gets 2 points, "no" gets 1 point; (v) Part five: investigated the influencing factors for ADR reporting and was provided in selective form. Detailed explanations and correct answers were in **Supplementary Material S1**.

Data Processing

For describing demographic variables, descriptive statistics are used, using percentages or frequencies to demonstrate categorical variables. One-way ANOVA was used to explore the relations between pharmacists' characteristics and knowledge and attitude scores, respectively, and ordinal logistic regression was used to analyze the correlation between knowledge, attitude and practice. The characteristic factors with $p < 0.05$ in the single factor analysis results were taken as covariates in the ordinal logistic regression. SPSS 22.0 was used for statistical analysis. $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of Pharmacist

A total of 1,128 questionnaires were collected, and 1,026 of them were valid and included in the analysis. The effective rate was 89.1%. There were 335 (32.7%) males and 691 females (67.3%); 437 pharmacists (42.6%) were under the age of 35; 512

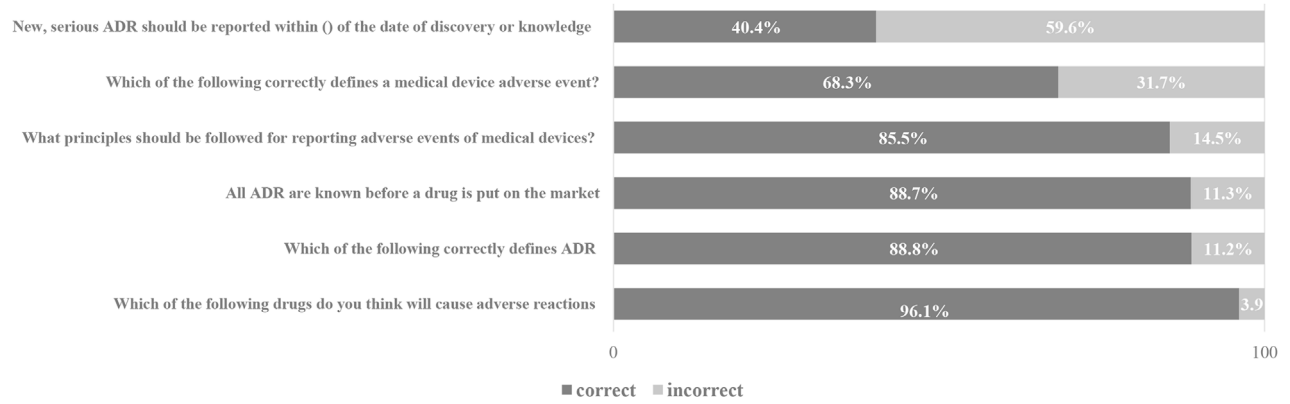

FIGURE 1 | Knowledge of pharmacists toward ADR.

TABLE 1 | Characteristics of pharmacists.

Variables	N	Percentage (%)
Respondents	1026	—
Gender		
Male	335	32.7%
Female	691	67.3%
Age (years)		
≤35	437	42.6%
36–45	277	27.0%
>45	312	30.4%
Type of Medical institution		
Tertiary hospital	514	50.1%
Non-tertiary hospital	512	49.9%
Education		
High school and below	76	7.4%
College degree	795	77.5%
Master degree and above	155	15.1%
Professional rank		
Junior	332	23.4%
Intermediate	569	55.5%
Senior	125	12.2%
Years of working		
≤5	189	18.4%
6–20	440	42.9%
>20	397	38.7%
Training attending		
Yes	778	75.8%
No	248	24.2%
Types of Pharmacists		
Clinical pharmacist	199	19.4%
Dispensing pharmacist	827	80.6%

pharmacists (49.9%) were from non-tertiary medical institution; 950 pharmacists (92.6%) have undergraduate degrees; and 569 pharmacists (55.5%) have intermediate professional titles. 837 pharmacists (81.6%) had more than 6 years of work experience; 778 pharmacists (75.8%) had participated in ADR training before; and there were 199 clinical pharmacists (19.4%). The characteristics of pharmacists are showed in **Table 1**.

Pharmacist's Knowledge of ADR

The results of pharmacists' knowledge of ADR reporting showed that 88.8% of people had a clear understanding of the definition of adverse drug reactions, while 59.6% had misunderstandings about the reporting time of new and serious adverse reactions. At the same time, 31.7% of pharmacists have cognitive errors in the definition of medical device adverse events, and 14.5% have cognitive errors in the reporting principles of medical device adverse events. The pharmacist's knowledge scores on ADR reporting are shown in **Figure 1**.

Pharmacist's Attitude Towards ADR

The results of the pharmacist's attitude towards ADR reporting indicate that the majority of pharmacists have a positive attitude towards ADR reporting. 95.1% agreed that adverse drug reaction monitoring is beneficial to public health, 84.9% believed that adverse drug reaction reporting was part of their responsibilities, 91.2% disagreed that only serious adverse drug reactions were reported, and 94.5% were willing to participate in adverse drug reaction reporting training. Regarding the issue of whether the adverse drug reaction report will generate additional workload, 48.4% of people believe that ADR reporting will generate additional workload. The results are shown in **Table 2**.

Pharmacist's Practice of ADR Reporting

According to the results of ADR reporting, 70.9% of pharmacists had encountered adverse drug reactions, of which 67.3% had reported adverse drug reactions.

Differences Between Pharmacists' Characteristics and KAP Towards ADR

The study found that there was a significant difference between pharmacists' characteristics and ADR knowledge scores. Among them, pharmacists' education, professional title, whether they participate in training, and job types have significant differences in ADR cognitive scores ($p < 0.05$). Pharmacists with a high school degree or below, junior professional titles, pharmacists who have not participated in training, and dispensing pharmacists have relatively

TABLE 2 | Attitudes of pharmacists towards ADR.

Items	Strongly agree (%)	Agree (%)	Neutral (%)	Disagree (%)	Strongly disagree (%)
You will pay attention to the possible ADR of patients	38.0	49.9	10.5	0.4	1.2
Do you agree that monitoring of ADR is beneficial to public health?	59.6	35.5	1.6	0.9	2.5
Do you agree that reporting an ADR report can also have an impact?	38.0	49.9	10.5	0.4	1.2
Do you consider reporting ADR as part of your responsibilities?	35.0	49.9	10.5	0.4	1.2
Do you think that only serious ADR should be reported?	0.9	3.6	4.4	62.4	28.8
Do you think that the ADR report will generate extra workload?	12.9	35.5	22.6	24.7	4.4
Are you willing to participate in the training of ADR reports?	38.5	56.0	4.8	0.2	0.5
Do you think that monitoring of adverse drug reactions should protect patient privacy?	38.4	56.0	4.8	0.3	0.5
Do you think that adverse drug reactions should be reported regularly?	38.5	56.0	4.8	0.2	0.5

low knowledge scores. The knowledge scores of pharmacists in non-tertiary hospitals were lower than those in tertiary hospitals ($p < 0.05$). There is a significant difference between pharmacist characteristics and ADR attitude scores. Among them, male, younger than 35 years old, non-tertiary hospital, low educational background, less than 5 years of work experience, and pharmacists with no training have relatively lower scores ($p < 0.05$). The differences in knowledge and attitude of pharmacists are shown in **Table 3**.

The Predictors of Pharmacists' Practice Toward ADR Reporting

The knowledge and attitude scores were used as predictors of pharmacists' practice toward ADR reporting to explore the relationship within KAP (**Table 4**). A significant association was observed for both knowledge [OR (95% CI): 1.19 (1.06, 1.33), $p = 0.002$] and attitude score [OR (95% CI): 1.04 (1.005, 1.07), $p = 0.023$] with the practice score of pharmacists. The covariates of the model are gender, age, hospital grade, educational background, title, working years, whether to participate in training, and job type. Pharmacist characteristics were also predictors of practice scores. The results of the multivariate model revealed that the risks of having a higher practice score were 0.60 (95% CI: 0.39, 0.94) times higher among pharmacists belonging to the age group 36–45 years, when compared with pharmacists older than 45 years. Pharmacists from non-tertiary hospitals had 1.64 (95% CI: 1.24, 2.17) times greater risk of having higher scores in practice compared with pharmacists from tertiary hospitals. The risks of having a higher practice score were 2.98 (95% CI: 1.59, 5.59) times higher among pharmacists belonging to the working year group ≤5 compared with ≥20 years. Pharmacists with training experience had 1.75 (95% CI: 1.30, 2.35) times higher practice scores compared with pharmacists with no-training experience. Dispensing pharmacists have 0.22 (95% CI: 0.14, 0.35) times higher practice scores than clinical pharmacists.

Factors Affecting Pharmacists' Reporting of ADRs

Our study also investigated the factors affecting pharmacists' ADR reporting (**Figure 2**). The investigation's findings indicated that the first three main factors affecting pharmacists' ADR reporting were the uncertainty about the suspected drug, the inability to determine whether it was an adverse drug reaction, and the report's complexity. At the same time, 24.7% of people don't know how to report.

DISCUSSION

The Importance of Hospital Pharmacists in the ADR Reporting Process

Drugs are the most common treatment for diseases, so it is necessary to pay attention to the rational use of drugs. If the safety of the drug is not considered properly, it may lead to consequences ranging from lifelong disability to death. Similarly, if a drug-related ADR is reported, the safety of the drug can be improved (Babar and Jamshed, 2008). This study aims to evaluate and compare the differences in knowledge, attitude, and practice of ADR reporting among pharmacists with different characteristics. Since many serious ADRs occur in hospitals or lead to hospitalization, pharmacists in medical institutions play an important role in ADR reporting (Lazarou et al., 1998). At the same time, most new drugs will first be used in hospitals. Therefore, the research on the knowledge, attitude, and practice of hospital pharmacists in the ADR reporting process is particularly important.

Hospital Pharmacists' Knowledge, Attitude and Practice Characteristics

In this study, we found that 11.2% of pharmacists are still unclear about the basic definition of ADR, which is similar to the results of previous research reports (Su et al., 2010). 59.6% of pharmacists have misunderstandings about the reporting time of new and serious adverse reactions. It reflects that pharmacist still lacks basic knowledge about ADR reports. Among them, pharmacists with low academic qualifications, low professional titles, and untrained pharmacists have relatively little basic knowledge related to ADR reporting. It reflects that pharmacist still lacks knowledge about ADR reporting. Among them, educational backgrounds, professional titles, and whether they have participated in the training are related to the basic knowledge related to ADR reporting. Highly educated and

TABLE 3 | The relation between the pharmacist's characteristics and KAP.

Variable	Knowledge score (0–6)			Attitude score (0–45)		
	Average	SD	*p*	Average	SD	*p*
Gender						
Male	4.74	1.11	0.29	36.83	4.37	**0.042**
Female	4.66	1.18		37.37	3.75	
Age (years)						
≤35	4.72	1.19	0.72	37.39	4.10	**0.008**
36–45	4.65	1.20		37.52	3.85	
>45	4.66	1.09		36.62	3.83	
Type of hospital						
Tertiary	4.74	1.14	0.123	37.47	4.04	**0.024**
Non-tertiary	4.63	1.18		36.91	3.89	
Education background						
High school and below	4.08	1.23	**<0.001**	35.83	3.64	**0.007**
College degree	4.66	1.18		37.27	4.00	
Master degree and above	5.10	0.85		37.45	3.89	
Professional rank						
Junior	4.51	1.29	**0.001**	37.21	4.03	0.983
Intermediate	4.73	1.11		37.17	3.92	
Senior	4.91	0.95		37.23	4.08	
Working years						
≤5	4.67	1.25	0.68	37.49	4.01	**0.033**
6–20	4.72	1.16		37.43	4.09	
>20	4.65	1.12		36.79	3.79	
Training attending						
Yes	4.73	1.18	**0.014**	37.48	4.04	**0.00**
No	4.52	1.08		36.29	3.60	
Type of pharmacist						
Clinical pharmacist	5.07	1.01	**<0.001**	37.35	4.06	0.54
Dispensing pharmacist	4.59	1.18		37.16	3.95	

The bold values are statistically significant data, mainly for ease of viewing.

trained pharmacists are more familiar with the basic knowledge related to ADR reporting. In addition, the survey showed that 40% of the pharmacists had poor knowledge about medical device adverse events. This indicates that pharmacists need to be properly trained for ADR reporting so that the quality of ADR reporting can be improved.

Pharmacists' attitude is considered the key to reporting ADR, so a positive attitude may encourage timely reporting of ADR. In the current study, pharmacists have a very positive attitude towards reporting ADR. Most pharmacists agree that ADR reporting is part of their responsibilities, which is consistent with the results of other similar studies (Hallit et al., 2019; Kopciuch et al., 2019; Al-Mutairi et al., 2021). Although most pharmacists have no significant differences in their attitudes towards ADR reporting, male pharmacists or under 35 years of age have slightly lower positive attitudes towards ADR reporting. It may be related to the new employee's relatively short length of service. Since pharmacists who have worked for a long time have been exposed to more adverse events at work, they have a better understanding of the harm that adverse events can cause to patients. And get more training and assessment related to ADR reporting in the workplace. Therefore, they pay more attention to the harmfulness of ADRs and their attitude towards ADR reporting are more positive. The positive attitude among pharmacists who have participated in ADR training is higher. Most of the participants expressed interest in ADR report training, indicating that they believe it is important to learn more about ADR reporting. In fact, it is also possible that the participants are unwilling to present their problems due to the deviation of social expectations. Because of the importance of pharmacists' knowledge and positive attitude towards ADR reporting, ADR administrative centers at all levels needs to strengthen training and education in the field of ADR.

In the current study, there is a significant difference between pharmacist characteristics and ADR practice scores. The difference of education level mainly affects the score of pharmacists' basic knowledge of adverse reactions. Among them, only pharmacists with education below senior high school have a downward trend in the score of reporting attitude towards adverse drug reactions. It indicates that the educational level of some pharmacists needs to be improved. Lower practice scores are found amount pharmacists who are over 45 years old, have less than 5 years of experience, or have not participated in ADR training. Explain that work experience and ADR

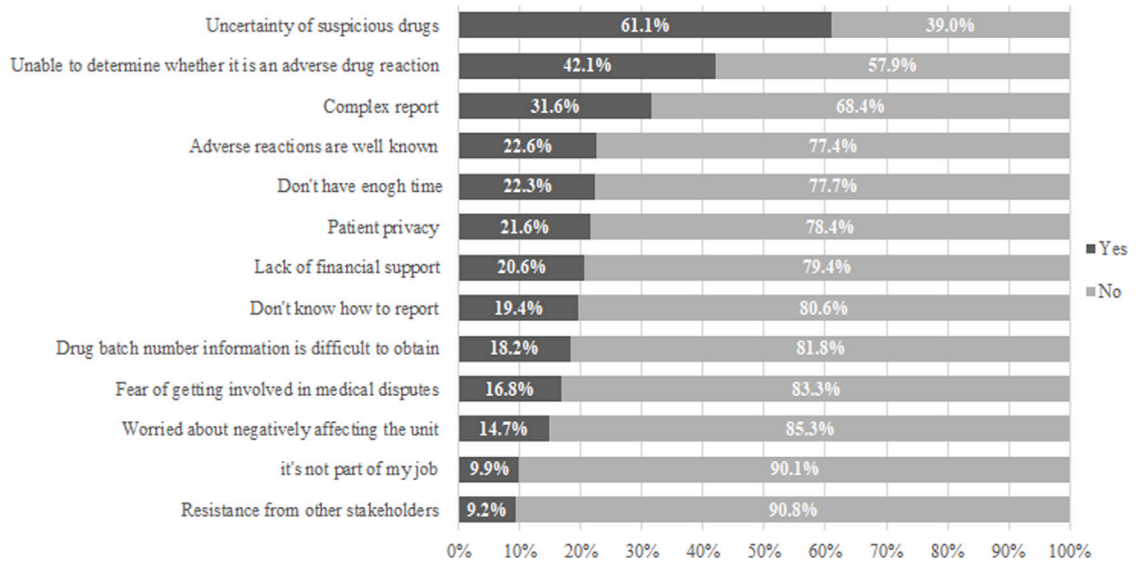

FIGURE 2 | Factors influencing the reporting of ADR among pharmacists.

TABLE 4 | Predictors of practice.

Variables	Practice score	
	OR (95% CI)	***p*-value**
Knowledge score	1.19 (1.06, 1.33)	**0.002**
Attitude score	1.04 (1.005, 1.07)	**0.023**
Gender		
Male	0.95 (0.72, 1.25)	0.718
Female	Ref	
Age (years)		
≤35	0.58 (0.33, 1.03)	0.064
36–45	0.60 (0.39, 0.94)	**0.026**
>45	Ref	
Type of hospital		
Tertiary	Ref	**0.001**
Non-tertiary	1.64 (1.24, 2.17)	
Education background		
High school and below	0.87 (0.43, 1.75	0.69
College degree	1.21 (0.78, 1.89)	0.40
Master degree and above	Ref	
Professional title		
Junior	1.64 (0.93, 2.91)	0.09
Intermediate	1.34 (0.83, 2.16)	0.23
Senior	Ref	
Working years		
≤5	2.98 (1.59, 5.59)	**0.001**
6–20	1.34 (0.84, 2.16)	0.223
>20	Ref	
Training attending		
Yes	1.75 (1.30, 2.35)	**<0.001**
No	Ref	
Type of pharmacist		
Clinical pharmacist	Ref	**<0.001**
Dispensing pharmacist	0.22 (0.14, 0.35)	

The bold values are statistically significant data, mainly for ease of viewing.

training have a greater impact on the practice of ADR reporting. Interestingly, pharmacists' practice scores in tertiary hospitals are low, which may be related to the work nature of pharmacists in tertiary hospitals. Most pharmacists in tertiary hospitals are not only engaged in pharmacotherapeutic work, but also conduct research and teach, which diverts their attention away from observing ADRs in patients. Clinical pharmacists in Chinese hospitals are typically the ones who handle ADR reporting and are better prepared than dispensing pharmacists to detect and report ADRs (Chen et al., 2015). That could explain why dispensing pharmacists have a lower ADR reporting practice score than clinical pharmacists.

The Relationship Between Pharmacist Characteristics and KAP

This study shows that both knowledge and attitude have a positive effect on the practice of pharmacists, and future improvement strategies can be carried out from the aspect of improving pharmacists' knowledge and attitude towards ADR monitoring. As a strategy to improve the ADR reporting, it should be aimed at healthcare professionals' level and the pharmacist level. In addition to encouraging pharmacists to report ADR, continuous professional development plans should be used to make up for their lack of knowledge and skills in discovering and reporting ADR. In this study, the main factors affecting pharmacists' reports of adverse reactions are the uncertainty of suspected drugs, the inability to judge whether they belong to adverse drug reactions and the complexity of the report. There is evidence that providing continuing education to health professionals can help change their behavior and attitudes towards ADR reports (Gonzalez-Gonzalez et al., 2013; Pagotto et al., 2013). The purpose of such education should not only be limited to improving pharmacists' knowledge of ADR but also be aimed at changing their attitudes and views on ADR report. The results of this study also show that pharmacists who have participated in ADR

training have higher knowledge, attitude, and practice scores. As experts, pharmacists play an important role in ensuring drug safety by detecting and reporting ADRs (Hadi et al., 2017). In the past few decades, the role of pharmacists has changed worldwide, from dispensers to guardians of drug safety (Su et al., 2010; Oreagba et al., 2011; Hadi et al., 2017). Research evidence shows that hospital pharmacists can not only detect and report ADRs but also help prevent ADR-related occurrences. In addition, pharmacists who have a clinical background and work closely with prescribers and patients can better understand suspicious ADRs (Calvert, 1999; Schlienger et al., 1999). Therefore, training and education about ADR is particularly important.

Research Limitations

The current research still has certain limitations. This study as a whole only covers one province in the central region, and the conclusions are extrapolated to other regions and need further research to confirm. At the same time, the study relied on pharmacists' self-assessment of their ADR knowledge, attitudes, and practice, which may be considered a social expectations deviation, because some participants may be unwilling to reveal practice flaws. Although we used anonymity to reduce this social expectation bias during the investigation, there may be some social expectation bias because the participants may be influenced by their hospital administrators. Therefore, the true knowledge, attitude and practice of pharmacists cannot be comprehensively summarized. Despite these limitations, we believe that our research results are reliable and may help healthcare professionals improve ADR reporting in the future.

CONCLUSION

Although most hospital pharmacists showed positive attitudes towards ADR reporting, their knowledge and practice were still insufficient. Hospital pharmacists' knowledge and practice are associated with their practice towards ADR reporting. The training had a significant impact on the pharmacist's knowledge, attitude and practice.

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 Ethics Committee of Zhongnan Hospital of Wuhan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Concept and design: HC, LL, FS, and WH. Acquisition, analysis, or interpretation of data: HC, WH, YT, YL, SG, XW, WL, and QJ. Drafting of the manuscript: WH, YT, and HC. Critical revision of the manuscript: All authors. Statistical analysis: YT.

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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.2022.823944/full#supplementary-material

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Emergence and Persistence of Resistance-Associated Substitutions in HCV GT3 Patients Failing Direct-Acting Antivirals

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Background: The hepatitis C virus has a high mutation rate, which results in the emergence of resistance-associated substitutions (RASs). Despite direct-acting antivirals (DAAs) efforts to treat chronically infected HCV genotype 3 (GT3) patients, there are concerns about the emergence and persistence of RASs in DAA failures. The objective of this study was to determine the prevalence of clinically relevant RASs in HCV NS5A and NS5B regions before and after treatment to better understand the role of RASs in treatment failures.

Methods: Viral RNA was extracted before and after treatment from serum samples. NS5A and NS5B regions of HCV were amplified by nested PCR, followed by Sanger sequencing. The nucleotide sequences were aligned against HCV GT3 reference sequences, and amino acid substitutions were analyzed using the geno2pheno [hcv] webserver.

Results: A total of 76 patients failing DAA therapy were stratified from the cohort of 1388. RASs were detected at the baseline in 15/76 patients and at relapse in 20/76 patients with cirrhosis and previously treated with interferons. The most prevalent NS5A RAS was Y93H found in all treatment-failing patients (14/54 in DCV vs. 6/22 in VEL), followed by A62S/T and A30K. No RASs were identified in NS5B. RASs that were present at the baseline persisted through the 24-week follow-up period and were enriched with emerging RASs during the treatment. The presence of RASs may be one of the causes of treatment failures in 26.3% of patients. Amino acid substitutions were present at the baseline in most of the patients with RASs against NS5A inhibitors. Patients with the baseline Y93H and/or A30K relapse more frequently than patients harboring A62S/T.

Conclusion: Treatment-failing patients harbored NS5A RASs, and the most frequent were A30K (5/20), A62S/T (20/20), and Y93H (20/20). Direct resistance testing is recommended for optimizing re-treatment strategies in treatment-failing patients.

Keywords: hepatitis C virus, genotype 3, direct-acting antiviral, relapse, resistance-associated substitutions

INTRODUCTION

Genotype 3 (GT3) of the hepatitis C virus (HCV) is the second most prevalent genotype, accounting for approximately 54 million infections globally, or 30% of all HCV cases (Messina et al., 2015). In relation to other genotypes, GT3 infection results in faster liver fibrosis (Bochud et al., 2009), a high degree of hepatic steatosis (Adinolfi et al., 2001), and an increased risk of hepatocellular cancer (Nkontchou et al., 2011), all of which necessitate urgent therapy. Pakistan is the second largest HCV burden country in the world, with 4.5–8.2% HCV seroprevalence (Iqbal et al., 2014; Umer and Iqbal, 2016). The majority of HCV infections are GT3a (69.1%), followed by GT1 (7.1%), 2 (4.2%), and 4 (2.2%) (Umer and Iqbal, 2016; Khan, 2019).

The advent of direct-acting antivirals (DAAs) has transformed the treatment landscape of hepatitis C. Despite this successful therapeutic intervention, no vaccine is available for HCV. DAA therapeutic regimens have an overall cure rate of more than 90%. Although only a small percentage of efficiently treated patients (5%) fail DAAs treatment, given the global prevalence of HCV, this translates into a substantial absolute number of patients who require retreatment. (Foster, 2016; Sarrazin, 2016). The contributing factors for DAAs treatment failure are patient adherence, suboptimal regimens, and drug resistance. Resistance-associated substitutions (RASs) are frequently detected in DAAs treatment failures (Sorbo et al., 2018). Due to the replication errors in HCV, the high rate of mutations contributes to reduced susceptibility to DAAs. If complete viral replication suppression is not achieved during DAAs treatment, previously existing strains with reduced susceptibility can be selected and result in a virological relapse after therapeutic cessation (Pawlotsky, 2011; Lontok et al., 2015). Furthermore, the presence of NS5A RASs with a high fold resistance, combined with other negative factors such as GT3a, cirrhosis, or previous treatment with non-DAAs, may reduce the efficacy of DAAs. (Lontok et al., 2015; Wyles, 2017). The combination of pan-genotypic NS5A and NS5B inhibitors (daclatasvir; DCV or velpatasvir; VEL and sofosbuvir; SOF) has shown greater therapeutic effectiveness in HCV GT3 infections, and this combination is added to "Hepatitis Control Programs" in Pakistan (Leroy et al., 2016; Wyles, 2017; Cornberg et al., 2019; Mushtaq, 2020a).

Sanger sequencing with a 15–20% cut-off level and NGS (next-generation sequencing) with a 1% cut-off level are used for the detection of the RASs in the viral population. However, a cut-off level of 10–20% for clinical relevance is recommended for detecting RASs within the HCV variants (Pawlotsky, 2016; Wyles, 2017; Pawlotsky et al., 2018).

The presence of RASs has been linked to treatment failures. RASs are found in nearly 100% of patients who experience viral breakthrough, while 50–90% in patients who relapse, depending on the genotype, DAA regimen, and the RAS analysis method (Perales et al., 2015; Sarrazin, 2016). The most commonly detected NS5A RASs in patients with therapeutic failure involved multiple amino acid positions (24, 28, 30, 31, 58, 92, and 93) with high persistence of years. On the other hand, NS5B RAS has a very short half-life due to its adverse effect on viral fitness levels. The impact and prevalence of RASs varied between HCV genotypes (Pawlotsky, 2016; Sarrazin, 2016; Zeuzem et al., 2017). The substitution Y93H is a common RAS seen in DCV-failing patients and can be found in a variety of genotypes (Dietz et al., 2018). There are currently no conclusive studies that indicate the need for baseline RAS testing; the baseline Y93H is thought to have an impact on the SOF/VEL therapy outcome in GT3 patients. Nonetheless, except in cirrhotic patients, the presence of Y93H does not appear to have a substantial impact on the outcome of VEL-based treatment. The American Association for the Study of Liver Diseases (AASLD) recommends testing for resistance to NS5A RASs Y93H in GT3-infected treatment-naive individuals with cirrhosis (Foster et al., 2015; Wyles, 2017).

Despite the fact that baseline RASs have a minor impact on overall DAAs treatment success, many examples have shown lower response rates when RASs are present. Continuing viral replication in the face of suboptimal drug pressure results in the enrichment of pre-existing RASs or the accumulation of new RASs, lowering drug susceptibility or increasing viral replicative fitness. Given that 58 million people worldwide have active HCV infections, even 2–5% treatment failure rates would lead to a large number of patients infected with resistant HCV (Howe et al., 2021).

We have evaluated the impact of baseline RASs on treatment outcomes in GT3-infected patients treated with DAAs. Furthermore, the emergence and persistence of NS5A and NS5B RASs possibly associated with drug resistance were also examined in treatment failures.

METHODS

Patients and Therapeutic Regimens

A total of 76 non-SVR HCV GT3 patients were stratified from the cohort of 1388 (January 2019 to January 2020) (Mushtaq, 2020a). HCV RNA was isolated from serum samples of non-SVR patients at the baseline and post-failure in the following two groups of SOF + DCV for 12 weeks in compensated or decompensated cirrhosis and the SOF/VEL group for 12 weeks in compensated or decompensated cirrhosis. Patients were treated with the following DAAs regimens based on the progressive availability of new DAAs and in accordance with national and international recommendations (**Figure 1**). The inclusion criteria included infection with HCV GT3a and age ≥18 years. Patients who had previously received SOF plus RBV or other DAAs were excluded.

Study Assessments

The primary outcome was sustained virological response (SVR), defined as undetectable HCV RNA in the serum at end of treatment. Non-SVR patients included non-responders or virological relapse. The virological response to treatment is used to characterize non-response (HCV RNA becomes detectable at treatment completion) or relapse (HCV RNA decreases and remains below the detection limit, but it becomes detectable if treatment is stopped) (Dieterich et al.,

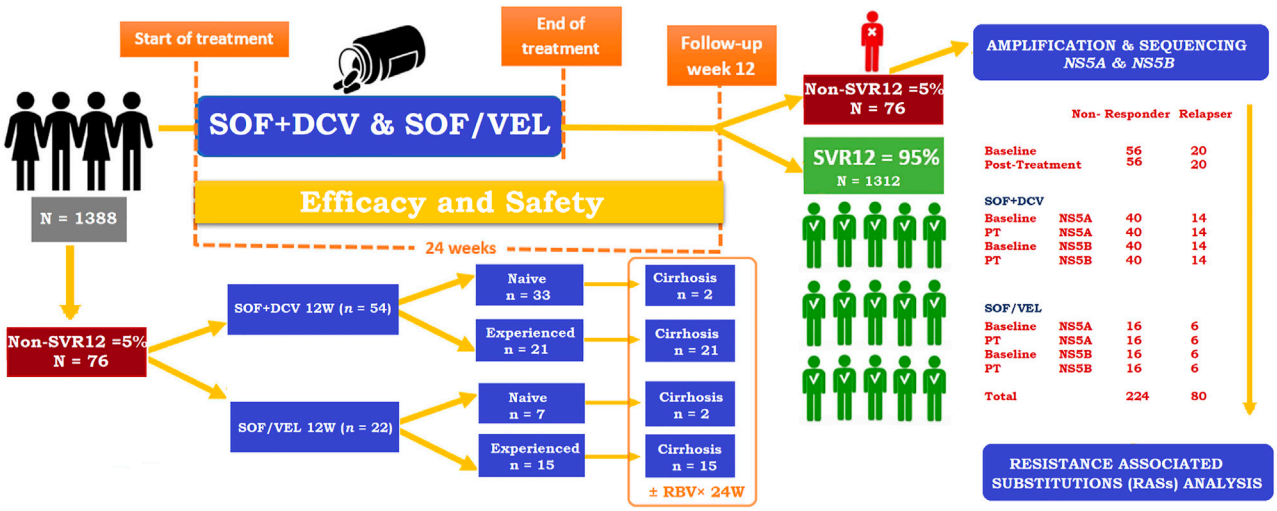

FIGURE 1 | Study flow chart of HCV GT3 patients.

2009). The COBAS TaqMan HCV test by Roche Molecular Systems with a lower limit of quantitation (LLOQ) of 25 IU/ml was used to determine HCV-RNA levels at the baseline, on-treatment 4, 8, and 12 weeks and post-treatment 16, 20, and 24 weeks. The HCV genotype, as well as the subtype, was determined using Abbott's RealTime HCV genotype II assay and confirmed by sequence analysis. Sanger sequencing was used to test for resistance in plasma samples from all patients at the baseline and from patients who had HCV-RNA levels of 1,000 IU/ml in the NS5A and NS5B genes at the end of the treatment. Serum samples of patients were stored at −80°C until the treatment was completed. Adverse event (AE) reporting, clinical laboratory tests, and vital signs were used to assess safety and tolerability.

The primary goal was to find out how common clinically relevant RASs were in DAA treatment-failing patients in both groups of DAAs therapy. Second, the distribution of patients with NS5A and NS5B baseline RASs, the prevalence of people with these baseline NS5A and NS5B RASs who are treatment-failing, and the prevalence of people with these baselines NS5A and NS5B RASs who are not treatment-failing will be determined.

Laboratory Protocols

Resistance testing of RASs (at baseline and post-treatment) was carried out at the Institute of Biomedical and Genetic Engineering (IBGE), KRL Hospital, Islamabad. The nested PCR method was used to amplify HCV genes from patient samples, which were then sequenced using the Sanger sequencing method.

HCV RNA Isolation

The Viral RNA Mini Kit by QIAGEN (Cat. No. 52904) was used to extract all of the RNA. The extracted RNA was also quantified using a NanoDrop 2000 UV-Vis spectrophotometer (Thermo Fisher Scientific). A 260/280 ratio of nearly 1.8 to 2 indicated that the RNA was pure. The RNA was aliquoted as soon as possible after quantification to avoid repeated freeze-thaw cycles.

TABLE 1 | Primers used for the nested PCR assay.

Primer	ID	Nucleotide sequence of primers (5–3)
HCVNS5A	5AEF1	CTCATCGCATTCGCATCCCGG
	5AER1	CAGGCACTTCCACATCTCGTCCC
	5AIF2	AACTGTCACTAGTCTGCTCCGGCGGTTG
	5AIR2	ATGGAGGGGATCCGCGCGCAAGGCGG
HCVNS5B	5BEF1	TGAGCTAGTGGACGCCAACTTGTTATG
	5BER1	GTTCTTCGCCATGATGGTGGTTGGAAT
	5BIF2	ACGGAGCGGCTTTACTGC
	5BIR2	CGTACCGCCCAATTAAAGAG

TABLE 2 | Thermal cycler program.

Cycle Step	Nested PCR, step I		Nested PCR, step II[a]		Cycles
	Temp. (°C)	Time	Temp. (°C)	Time	
Initial denaturation	98	30 s	98	30 s	1
Denaturation	98	10 s	98	10 s	
Annealing	66	20 s	64	20 s	35
Extension	72	4 min	72	30 s	
Final extension	72	10 min	72	10 min	1
Hold	4	Hold	4	Hold	Hold

[a]*Nested PCR, step II was performed as step I, with the following changes: 5 ul of the step I product was used as the DNA template, and primers were changed from external to internal. The annealing temperature was changed to 64°C, and the extension time was changed to 30 s.*

Complementary DNA (cDNA) Synthesis

Complementary DNA was synthesized using Invitrogen's commercial SuperScriptTM III Reverse Transcriptase (Cat. No. 18080–093) and gene-specific reverse primers. For the synthesis, 50 µL of the reaction volume was used for the final concentration of the reagents. After preparing the reaction mixture, the contents of the tube were gently mixed and incubated for 10 min at 25°C, 55 min at 50°C, and 15 min at 70°C. After incubation, the cDNA

was stored at −20°C. The cDNA was used as a template for nested PCR.

Primer Design and Nested PCR Optimization

Primers were designed manually using a consensus sequence from the alignment retrieved from the online Los Alamos HCV database. Gradient PCR was used to optimize the primer annealing temperature. Primer sequences for the selected target genes are given in **Table 1**. Nested PCR was carried out with these primers targeting NS5A and NS5B regions of HCV using Phusion™ High–Fidelity DNA Polymerase by Thermo Fisher Scientific (Cat. No. F530S) **Table 2**. The amplicons were confirmed by 2% agarose gel electrophoresis by Syngene. Before proceeding to sequencing, PCR-positive samples were purified using a MAGBIO's HighPrep™ PCR kit (Cat. No. AC-60005).

Sanger Sequencing of NS5A and NS5B

After purification of sequencing templates, the BigDye™ Terminator v3.1 Cycle Sequencing Kit by ThermoFisher (Cat. No. 4337454) was used for sequencing reactions. Sequencing reactions were further purified with MAGBIO's HighPrep™DTR (Cat. No. DT-70005) kit and resuspended in 10 μL of Hi-Di™ Formamide. At both sites, the purified products were run for capillary electrophoresis (Sanger) sequencing on a 3130 Genetic Analyzer (Applied Biosystems™, Thermo Fisher Scientific, USA) with the same primer pair used in the nested PCR.

Sequence Analysis and Interpretation of RASs

SeqScape® Software version 2.6 by Thermo Fisher Scientific was used for the alignment of forward and reverse nucleotide sequences of all samples with the reference strain of GT3a isolate NZL1 (Accession number D17763.1) to generate a consensus sequence of the HCV quasispecies, which resulted as a mixture of peaks in the electropherogram. The consensus sequences were queried in the web-based mutation detection algorithm, "geno2pheno [hcv]" for the differentiation of the clinically relevant substitutions and their evaluation for potential ramifications. RASs greater than 100X were chosen following the geno2pheno [hcv] rules. Geno2pheno [hcv] (http://hcv.geno2pheno.org) is a key tool for interpreting and assessing HCV sequences for the prediction of resistance against DAAs. (Kalaghatgi et al., 2016). The analysis was performed to look into the RASs in the NS5A and NS5B regions of HCV by comparing scores of 2018 and 2020 EASL guidelines against clinically relevant RASs (Pawlotsky et al., 2018; Pawlotsky, 2020). Furthermore, the RASs reported as affecting DAA treatment outcomes *in vitro* and *in vivo* were also evaluated (Wyles, 2017; Palanisamy et al., 2018; Sorbo et al., 2018). NS5A RASs, i.e., Y93H and A30K, were defined as clinically relevant for HCV GT3 in this study which is also been reported in the literature previously (Hernandez et al., 2013; Wyles, 2017; Di Maio et al., 2018; Dietz et al., 2018; EASL, 2018; Hezode et al., 2018; Ghany et al., 2019; Sharafi et al., 2019). The reference sequence D17763 was used for HCV GT3a. The Sanger sequences of HCV GT3a obtained in this study are available in **Supplementary Material**. However, they are deposited in the GenBank database under the following accession numbers: ON009333–ON009338.

Statistics

For data entry and analysis, SPSS (Statistical Package for Social Sciences) software was used. The results of patients' demographic and laboratory tests were expressed as a number (percentage) for binary variables and as a mean (standard deviation) for continuous variables. The baseline data of the treatment regimens administered (SOF + DCV vs. SOF/VEL) were compared. Student's t-test was used to compare two groups, and a chi-squared test was used to compare binary variables. The analysis was considered statistically significant when the p value was <0.05.

RESULTS

Patient Characteristics at the Baseline

In total, 1388 patients with HCV GT3, 972 in the SOF + DCV group and 416 in the SOF/VEL group, were assessed for treatment efficacy previously (Mushtaq, 2020a; Mushtaq, 2020b). Among them, 76/1388 (5%) failed to achieve SVR during DAAs treatment. Detailed demographic and baseline clinical characteristics of the study cohort (n = 76) are described in **Table 3**. The mean age was 53 years; most patients were females (59%), treatment-experienced (48%), and (53%) cirrhotic. The most common comorbidities at the baseline included diabetes (59%), gastrointestinal disease (89%), and kidney disease (39%). The risk factors correlated with the SVR rate were blood transfusion (92%), surgery (59%), and tobacco smoking (46%). All patients were infected mainly with HCV GT3a. As a result of assignment criteria, more patients treated with SOF/VEL were of old age (58 vs. 51, $p = 0.04$) and cirrhotic (77 vs. 43%, $p < 0.001$). Similarly, most of the patients were INF-experienced in the SOF/VEL group and SOF + DCV group (68 vs. 39%, $p = 0.02$). Significant differences were observed in relapsed patients (26 vs. 27%, $p = 0.01$) of SOF + DCV and SOF/VEL groups, respectively. The significant risk factor associated with the non-SVR was blood transfusion ($p = 0.03$). Similarly, elevated ALT was found to be a significant contributor in both groups of DAAs.

Baseline Prevalence of NS5A and NS5B Substitutions.

Sequence analysis of 76 non-SVR patients with reference showed several amino acid residue changes in both groups of DAAs at baseline, as shown in **Table 4**. For NS5A sequences in the DCV + SOF group, the most prevalent substitutions were S14M (92%), A17S (92%), A21T (92%), A62S (94%), S98G (84%), S103P (83%), D126E (80%), F127C (80%), and D172E (92%). The most prevalent substitutions in NS5B sequences of the DCV + SOF group were E258Q (16%), N307G (16%), and A338V (17%). Similarly, the most prevalent substitutions in NS5A sequences of the VEL/SOF group were S14M (92%), A17S (92%), A21T (92%), D172E (90%), H180N (90%), T183V (90%), and N307G (27%) in NS5B. The frequency of natural polymorphisms to respective

TABLE 3 | Baseline characteristics and demographics.

	SOF + DCV group (n = 54)	SOF/VEL group (n = 22)	*p* Value
Mean age, yr. (range)	51 (30–75)	58 (35–77)	0.04
Male, n (%)	21 (39)	10 (46)	—
Cirrhosis, n (%)	23 (43)	17 (77)	0.001
Mean HCV RNA, log10 IU/ml (range)	6.2 (3.9–7.1)	6.4 (4.2–7.9)	—
Previous treatment[a], n (%)	21 (39)	15 (68)	0.02
Non-responder, n (%)	40 (74)	16 (73)	
Relapsers, n (%)	14 (26)	6 (27)	0.01
Significant mutations	—	—	—
Baseline S98G, n (%)	50 (93)	20 (91)	—
Baseline Y93H, n (%)	9 (17)	4 (18)	—
Baseline A62S, n (%)	51 (95)	18 (82)	—
Baseline A30K, n (%)	1 (2)	1 (5)	—
Laboratory data, M±SD	—	—	—
HB (g/dl)	13 ± 2	13 ± 2	—
WBCs ($\times10^9$/L)	8 ± 2	7 ± 1	—
PLT ($\times10^9$/L)	203 ± 77	211 ± 80	—
AST (40U/L)	70 ± 34	69 ± 35	—
ALT (40U/L)	80 ± 60	92 ± 70	0.05
Albumin (g/L)	40 ± 3	40 ± 6	—
Creatinine (mg/dl)	99 ± 25	100 ± 26	—
INR	1 ± 0.1	1.1 ± 0.1	—
Comorbidities	—	—	—
Diabetes, n (%)	35 (65)	10 (45)	—
Gastrointestinal disease, n (%)	50 (92)	18 (80)	—
Kidney disease, n (%)	22 (40)	8 (36)	—
Risk factors			
Blood transfusion, n (%)	52 (96)	18 (81)	0.03
Surgery, n (%)	35 (65)	10 (45)	—
Tobacco smoking, n (%)	30 (55)	5 (22)	—

[a]*Pegylated interferon (Peg/INF) plus ribavirin.*
Bold values represent statistical significance.

positions of amino acids in NS5A and NS5B was higher in the SOF + DCV group and then in the SOF/VEL group receiving patients. Most of the clinically relevant RASs were (A62S/T, Y93H, and A30K) in DAAs failing patients. Second, 34.2% of patients with NS5A baseline RASs and 26.3% of people with these baseline NS5A RASs were treatment-failing, and 14.4% of people with these baseline NS5A RASs were not treatment-failing.

Treatment Characteristics and RAS Prevalence at the Baseline

Among non-SVR patients, 56/76 (74%) patients were non-responders, while 20/76 (26%) patients relapsed after treatment completion. In total, 54 patients from the SOF + DCV group and 22 from the SOF/VEL group were assessed for RAS analyses at the baseline in both genes (*NS5A* and *NS5B*). Among them, 14 patients were found to be relapsers in the SOF + DCV group and six patients from the SOF/VEL group. They were assessed for RAS analyses in both genes (*NS5A* and *NS5B*) at pre- and post-treatment. However, 40 patients were non-responders in the SOF + DCV group and 16 patients from the SOF/VEL group achieved SVR after 24 weeks of follow-up and had low viral load at week 12. But relapse patients had a high viral load at week 12. Thus, week 12 was found to be significant (p = 0.05). Regarding follow-up data, relapse patients were consistent in their therapy, and follow-ups and non-responders were inconsistent in their therapy and follow-ups. Simultaneously, 24 weeks of extended treatment and adding RBV were administered to 77% (17/22) in the SOF/VEL group compared to only 43% (23/54) in the SOF + DCV group (**Table 5**). The prevalence of RASs was relatively high in relapse patients rather than in non-responders at the baseline. Patients with a high prevalence of RASs at the baseline were further checked for RAS analysis at treatment outcome. Surprisingly, patients with baseline RASs were the majority relapsers. The main reason for treatment failure was the enrichment of RASs. The baseline Y93H was found to be a significant contributor toward resistance development in the treatment - failing patients, especially with cirrhosis and a history of IFN-based treatment. The baseline Y93H was found in 75% of patients who relapse the therapy in comparison with non-responders (16%). However, amino acid substitutions (S98G and A62S) were equally high in all non-SVR patients at the baseline.

Effect of Acquired and Persisted RASs in the NS5A Gene

For further analysis of acquired and persistent RASs against NS5A inhibitors, sequences were analyzed by geno2pheno [hcv] 0.92 algorithms (**Figure 2**) in 20 relapse patients in the

TABLE 4 | Baseline prevalence of amino acid substitutions in NS5A and NS5B.

DCV + SOF group, n (%)				VEL/SOF group, n (%)			
Substitutions	**NS5A, 54**	**Substitutions**	**NS5B, 54**	**Substitutions**	**NS5A, 22**	**Substitutions**	**NS5B, 22**
R6G	1 (1.8%)	E258Q	9 (16%)	S14M	20 (92.5%)	E258Q	4 (18%)
S14M	50 (92.5%)	N307G	9 (16%)	A17S	20 (92.5%)	N307G	6 (27%)
V15M	2 (3.7%)	A338V	9 (17%)	A21V	20 (92.5%)	A338V	4 (18%)
A17S	50 (92.5%)	Y391C	1 (1.8%)	A30K	1 (5)	—	—
K20R	3 (5.5%)	V490M	1 (1.8%)	L34V	2 (10%)	—	—
A21T	50 (92.5%)	—	—	A62T	4 (18%)	—	—
A25S	5 (9.2%)	—	—	A62S	18 (82)	—	—
I27M	10 (18.5%)	—	—	Y93H	4 (18.2%)	—	—
A30K	1 (1.8%)	—	—	S98G	20 (91%)	—	—
L34V	20 (37%)	—	—	A147P	2 (10%)	—	—
Q40H	10 (18.5%)	—	—	L158I	2 (10%)	—	—
V46G	5 (9.2%)	—	—	R170G	2 (10%)	—	—
W47R	10 (18.5%)	—	—	D172E	19 (90%)	—	—
V52A	6 (11%)	—	—	L179M	7 (31%)	—	—
P58T	4 (7%)	—	—	H180N	19 (90%)	—	—
C59Y	10 (18.5%)	—	—	T183V	19 (90%)	—	—
A62T	18 (33%)	—	—	—	—	—	—
A62S	51 (94.4%)	—	—	—	—	—	—
Y93H	9 (5%)	—	—	—	—	—	—
S98G	50 (93%)	—	—	—	—	—	—
S103P	45 (83%)	—	—	—	—	—	—
P104H	20 (37%)	—	—	—	—	—	—
V113R	20 (37%)	—	—	—	—	—	—
A114S	20 (37%)	—	—	—	—	—	—
N116S	30 (55.5%)	—	—	—	—	—	—
D126E	43 (80%)	—	—	—	—	—	—
F127C	43 (80%)	—	—	—	—	—	—
A147P	31 (58%)	—	—	—	—	—	—
L158I	32 (30%)	—	—	—	—	—	—
P163S	10 (18.5%)	—	—	—	—	—	—
R170G	10 (18.5%)	—	—	—	—	—	—
D172E	50 (92.5%)	—	—	—	—	—	—
I173H	31 (58%)	—	—	—	—	—	—
V177E	10 (18.5%)	—	—	—	—	—	—
M176T	16 (30%)	—	—	—	—	—	—
L179M	16 (30%)	—	—	—	—	—	—
H180N	32 (60%)	—	—	—	—	—	—
T183V	20 (37%)	—	—	—	—	—	—
I184L	10 (18.5%)	—	—	—	—	—	—
G185V	10 (18.5%)	—	—	—	—	—	—
S207A	20 (37%)	—	—	—	—	—	—

DCV + SOF group (n = 14) and DCV + SOF group (n = 6), respectively (**Table 6**). The results obtained from the analysis of patients' samples at the baseline revealed that all displayed one substitution on the scored position A62S/T/V (amino acid position conforming resistance) on the *NS5A* gene subjected to the selective pressure of DAA therapy. They will have reduced susceptibility to elbasvir, ledipasvir, and pibrentasvir. Most of the relapsers had RAS Y93H at the baseline which was further maintained and enriched at post-treatment failure.

All substitutions detected at the baseline on NS5A against DCV and VEL were maintained (A62S/T/V and S98G) in treatment-failing patients. However, most of the patients acquired one or two NS5A RASs: A30K, which confers resistance to daclatasvir, and Y93H, which confers resistance to all inhibitors excluding pibrentasvir. Hence, Y93H has been linked to the failure of NS5A inhibitors. The NS5B RASs that confer resistance to sofosbuvir were not identified and studied. Sequences from all 14 DCV patients and six VEL patients were analyzed for the presence of mutations known to NS5A inhibitor RASs at amino acid positions 28, 30, 31, 32, 58, 92, and 93. Before treatment, DCV patients had NS5A RASs (cut-off 20%) 1/14, 14/14, and 9/14 at positions 30, 62, and 93 of amino acids, and those after treatment were 4/14, 14/14, and 14/14. However, in six VEL patients, before treatment, NS5A RASs were 1/6, 6/6, and 4/6 in DCV patients at positions 30, 62, and 93 of amino acids, and after treatment, they were 1/6, 6/6, and 6/6, respectively. In **Table 7**, RASs that were present at the baseline persisted through the treatment period and were enriched with emerging RASs during the treatment, i.e., paired RASs (A30K + A62S + Y93H) and (A62T + Y93H) frequency 0–28.6%, 21.4–35.7% pre- and post-DCV treatment, respectively. Similarly, the paired RAS (A62S + Y93H) frequency increased from 16.6 to 50% from pre-to post-VEL treatment, respectively. Most of the paired RASs emerged during the

TABLE 5 | Treatment characteristics and RAS prevalence in non-responders vs. relapsers at the baseline.

Baseline	Non-responders, n = 54	Relapsers, n = 20	*p* Value
Treatment regimen, n (%)			
Daclatasvir + sofosbuvir	40 (74%)	14 (70%)	—
Velpatasvir/sofosbuvir	16 (30%)	6 (30%)	—
Treatment duration, wk	—	—	
4 weeks	—	3 (15%)	—
8 weeks	—	5 (25%)	—
12 weeks	52 (96%)	20 (100%)	0.05
16 weeks	40 (74%)	15 (75%)	—
20 weeks	14 (26%)	14 (70%)	—
24 weeks	9 (17%)	9 (45%)	—
Addition of ribavirin, n (%)	23 (43%)	17 (77)	—
Cirrhosis n (%)	20 (37%)	20 (100)	—
Previous treatment[a], n (%)	16 (30%)	18 (90)	—
Significant mutations	—	—	—
Baseline S98G, n (%)	50 (93%)	18 (90%)	—
Baseline Y93H, n (%)	9 (16%)	13 (65%)	—
Baseline A62S/T/V, n (%)	51 (95%)	20 (100%)	—
Baseline A30K, n (%)	—	2 (10%)	—

[a]*Previous treatment referring to pegylated interferon (Peg/INF) + RBV.*
Bold values represent statistical significance.

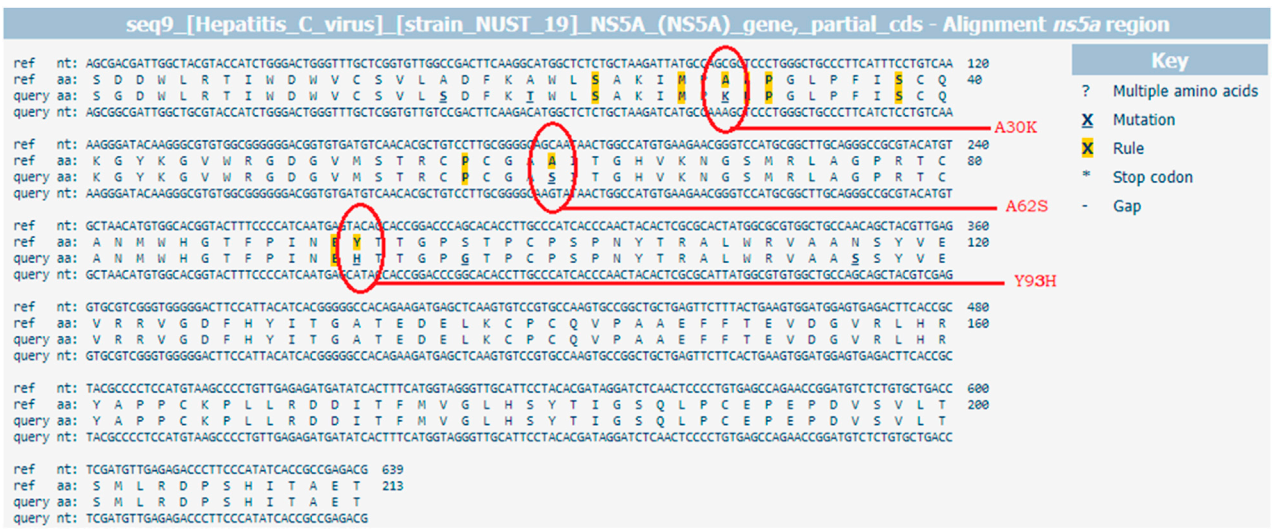

FIGURE 2 | G2P [hcv] web-based interpretation tool for RAS identification through HCV sequence alignment with the reference sequence D17763.

treatment period, indicating that they acquired under drug pressure and lead to treatment failing. All of the RASs present at the pre-treatment stage persisted throughout the treatment and appeared post treatment in the NS5A region of HCV, indicating their long half-life.

The association between the treated groups and adverse events noted in on-treatment relapse patients during the period of study is shown in **Table 8**. Both groups of treatment were well-tolerated, with no AEs requiring treatment discontinuation. There were no fatalities reported. A strong association was revealed between adverse events (Skin rashes and oral ulcers) and the treatment group. Patients receiving SOF + DCV had more adverse effects (skin rashes: 50 vs. 45% and oral ulcers: 45 vs. 40%) than those receiving SOF/VEL, respectively.

In addition, these abnormalities were not caused directly by the treatment regimens but were clinically linked to the fibrosis stage of the liver and its elevated enzymes as these patients were cirrhotic by nature.

DISCUSSION

The concept of viral resistance is the selection of viral variants that permit the substitution of an amino acid in the viral

TABLE 6 | Distribution of RASs in 20/76 treatment failing patients at pre- and post-treatment.

Patient ID	RASs	NS5A inhibitors				
		Daclatasvir	Elbasvir	Ledipasvir	Pibrentasvir	Velpatasvir
D1 baseline	A62S	RS	S	S	S	S
D1 failure	A62S and Y93H	R	R	R	RS	R
D2 baseline	A62S and A30K	R	R	R	RS	R
D2 failure	A62S, A30K, and Y93H	R	R	R	RS	R
D3 baseline	A62S and Y93H	R	R	R	RS	R
D3 failure	A62S, A30K, and Y93H	R	R	R	RS	R
D4 baseline	A62S and Y93H	R	R	R	RS	R
D4 failure	A62S, A30K, and Y93H	R	R	R	RS	R
D5 baseline	A62T	R	R	R	RS	R
D5 failure	A62T and Y93H	RS	S	S	S	S
D6 baseline	A62S and Y93H	R	R	R	RS	R
D6 failure	A62S and Y93H	R	R	R	RS	R
D7 baseline	A62T and Y93H	R	R	R	RS	R
D7 failure	A62T and Y93H	R	R	R	RS	R
D8 baseline	A62T and Y93H	R	R	R	RS	R
D8 failure	A62T and Y93H	R	R	R	RS	R
D9 baseline	A62S	RS	S	S	S	S
D9 failure	A62S, A30K, and Y93H	R	R	R	RS	R
D10 baseline	A62T and Y93H	R	R	R	RS	R
D10 Failure	A62T, Y93H	R	R	R	RS	R
D11 baseline	A62V	RS	S	S	S	S
D11 failure	A62V and Y93H	R	R	R	RS	R
D12 baseline	A62S and Y93H	R	R	R	RS	R
D12 failure	A62S and Y93H	R	R	R	RS	R
D13 baseline	A62T	RS	S	S	S	S
D13 failure	A62T and Y93H	R	R	R	RS	R
D14 baseline	A62S and Y93H	R	R	R	RS	R
D14 failure	A62S and Y93H	R	R	R	RS	R
V1 baseline	A62S	RS	S	S	S	S
V1 failure	A62S and Y93H	R	R	R	RS	R
V2 baseline	A62S	RS	S	S	S	S
V2 failure	A62S and Y93H	R	R	R	S	R
V3 baseline	Y93H	R	R	R	S	R
V3 failure	Y93H	R	R	R	S	R
V4 baseline	A62S, A30K, and Y93H	R	R	R	RS	R
V4 failure	A62S, A30K, and Y93H	R	R	R	RS	R
V5 baseline	A62T and Y93H	R	R	R	RS	R
V5 failure	A62T and Y93H	R	R	R	RS	R
V6 baseline	A62S and Y93H	R	R	R	RS	R
V6 failure	A62S and Y93H	R	R	R	RS	R

Note: Resistance analysis by using the geno2pheno algorithm. RASs, are represented by red color, and substitutions on scored positions are represented by green color. Abbreviations: R, resistance; RS, reduced susceptibility; S, susceptible.

therapeutic targets making the virus less susceptible to the inhibitory effect of the drug (Pawlotsky, 2011). HCV resistance to DAAs is driven by the selection of mutations in the targeted genes (*NS3*, *NS5A*, and *NS5B*) under the drug (DAAs) pressure (Pawlotsky, 2016). RASs are the amino acid substitutions that confer resistance, and the viral variants that carry these RASs having reduced susceptibility to the DAAs are called resistant variants (RV) (Jiménez-Pérez et al., 2016). The RAS is defined by the type of HCV (genotype and subtype), the position of amino acid, and protein of HCV *via* international recommendations (EASL, 2018). The emergence and type of RASs are determined by the genotype and the drug to which it was exposed (Dietz et al., 2018). Furthermore, it can arise from DAA exposure and exist naturally in naive patients with HCV. RASs seem to be more prevalent in GT1a and GT3a than in other genotypes (Baumert et al., 2019).

Presently, DAA-based regimens cure most HCV patients. Despite this, virological failure can result in 2–5% of patients, especially in accordance with the development of RASs. The presence of RASs in DAA-failing patients may jeopardize the efficacy of second-line treatment and hence is a major priority for successful re-treatment (Lontok et al., 2015).

This study aimed to illustrate the clinically relevant RASs in NS5A and NS5B (DAAs-targeted genes) at pre-and post-treatment among HCV GT3 patients for understanding the role of RASs in the failure of the treatment. When we began this real-world study, we hypothesized that the clinically relating RASs in GT3 should be Y93H. This is because *in vitro* data from the literature show that Y93H confers a high degree of resistance to DCV and VEL, with resistance fold-change values of 2100 and 700, respectively, when compared to GT3a wildtype replicons (Hernandez et al., 2013; Lawitz, 2016). The clinical trials of ALLY

TABLE 7 | Frequency of RASs to DAAs at pre-and post-treatment in the NS5A region of HCV GT3 treatment-failing patients.

RAS/Paired RAS	Drugs			
	Pre-treatment frequency (%)		Post-treatment frequency (%)	
	Daclatasvir	Velpatasvir	Daclatasvir	Velpatasvir
A30K	0	0	0	0
A62S	2/14 (14.2)	2/6 (33.3)	0	0
A62T	2/14 (14.2)	0	0	0
A62V	1/14 (7.1)	0	0	0
Y93H	0	1/6 (16.6)	0	1/6 (16.6)
A30K + A62S	1/14 (7.1)	0	0	0
A30K + Y93H	0	0	0	0
A62V + Y93H	0	0	1/14 (7.1)	0
A62T + Y93H	3/14 (21.4)	1/6 (16.6)	5/14 (35.7)	1/6 (16.6)
A62S + Y93H	5/14 (35.7)	1/6 (16.6)	4/14 (28.6)	3/6 (50)
A30K + A62S + Y93H	0	1/6 (16.6)	4/14 (28.6)	1/6 (16.6)

Safety and tolerability of DAAs among relapsers.

TABLE 8 | On-treatment adverse events in relapse patients.

Patients, n (%)	SOF + DCV	SOF/VEL	*p* Value
	Relapsers (n = 14)	Relapsers (n = 6)	
Skin rashes with bruising	7 (50)	3 (45)	0.01
Nausea	3 (22)	1 (17)	—
Edema	6 (40)	2 (35)	—
Weight loss	3 (22)	1 (17)	—
Fatigue	10 (71)	3 (50)	—
Oral ulcers and bleeding	6 (45)	3 (40)	0.05

Bold values represent statistical significance.

and ASTRAL proved that the presence of baseline Y93H in GT3 cirrhotic patients is associated with lower SVR rates to treatment with SOF + DCV and SOF/VEL (Foster, 2016; Goujon et al., 2020). Similarly, our findings are in alliance with these findings where baseline Y93H in GT3 cirrhotic patients (22/76) taking SOF + DCV and SOF/VEL lead to lower SVR rates.

According to the EASL guidelines, baseline RAS testing of Y93H in GT3 patients before starting the SOF/VEL treatment is recommended. The findings of the baseline Y93H will include RBV with/without extension of treatment duration. However, these guidelines were for retreatment against NS5A failures from 2014–2017 for GT3 patients (Liver, 20182018). Therefore, it was important for the study groups to evaluate treatment outcomes based on the Y93H baseline analysis. As shown in **Table 5**, 13/22 patients in both groups with baseline Y93H were DAA-failing patients. As a result, it appeared that Y93H had a negative impact on treatment outcomes. At the time of relapse, the Y93H RAS in the NS5A region was maintained and enriched with multiple mutations, including S98G and A62S/T/V. In some HCV GT3 patients with baseline Y93H, an emergent S62L and S98G substitution have been identified at treatment failure (Dietz et al., 2018). Their presence at pre-treatment can affect post-treatment sustained virological response (SVR) to DCV-based therapy (Lontok et al., 2015; Pawlotsky, 2016; Zeuzem et al., 2017; Sorbo et al., 2018).

Cirrhosis is an advance and critical condition of chronic HCV infection because it indicates a long-term viral infection accompanied by vigorous viral replication, which may result in viral fitness (Sarrazin, 2016; Smith et al., 2019). In this study, RASs were found in 20/76 DAA-failing patients, 18 of whom were cirrhotic and had previously received IFN-based treatment, and RASs Y93H were found in 20 of the cirrhotic patients. Our findings are consistent with previous research that amino acid substitutions/RASs, particularly clinically relevant RASs, are more common in patients with cirrhosis than in non-cirrhosis patients (Sarrazin, 2016; Smith et al., 2019).

The RASs against NS5A inhibitors result in treatment failure and are regarded as a major threat to HCV treatment and eradication (Zeuzem et al., 2017). In terms of behavior, NS5A RASs can cause a resistance fold-change of more than two, and those that cause a resistance fold-change of more than 100 are known as RASs >100X (Sharafi et al., 2019) For example, substitution in codon (93) can change the related amino acid in the NS5A protein from Y to H, N, and C (Y93H/N/C) and lead to resistance in many NS5A inhibitors (Issur and Götte, 2014). Nonetheless, the viral genotype/subtype is considered in determining the fold-change (Hezode et al., 2018; Liver, 20182018; Sharafi et al., 2019). In this research, baseline RASs were investigated in 76 HCV GT3a patients, the most widespread GT in Pakistan, and regarded as the "difficult-to-treat genotype" (Iqbal et al., 2014; Messina et al., 2015; Umer and Iqbal, 2016). Herein, most of the identified substitutions Y93H paired with RASs (A30K + A62S + Y93H) 0–28.6% pre-and post-DCV treatment, respectively. Similarly, the paired RAS (A62S + Y93H) frequency increased from 16.6 to 50% from pre- to post VEL treatment, respectively. According to some studies, RASs in aa 93 (Y93H) are considered a >100 resistance fold-change NS5A RAS, especially when they appeared as a paired substitution with RASs in aa 30 in HCV 3a (Kjellin et al., 2019; Smith et al., 2019). Viral populations having one or more RASs have fitness levels closer to the wild-type virus and may accumulate through the selection pressure or emerge during the suboptimal conditions of the treatment (Pawlotsky, 2016). NS5A RAS has been shown to persist for at least 1-year post-treatment failure and may impact retreatment with some NS5A inhibitor-containing regimens (McPhee, 2014). So the

identification of RASs may guide the choice of the most appropriate drugs for HCV retreatment. In our case, 19/20 patients with paired RASs were treatment-failing against NS5A inhibitors, so second-line therapy has to be different than the present.

In our study, there could be various confounding factors in terms of outcome in the DAA group. The significant negative predictors described in (**Table 3**) for treatment outcomes were found in the SOF/VEL group compared to those of the SOF + DCV group in terms of the proportion of treatment-experienced patients (68 vs. 39%), older age (58 vs. 51%), and patients with cirrhosis (77 vs. 43%). However, the SOF + DCV group had a higher rate of comorbidities and risk factors. In addition, the SOF/VEL use was less relative to SOF + DCV due to the latest DAA regimen. It has been shown in a cohort of 2824 GT3 patients that SVR rates were similar in both regimens of SOF + DCV or SOF/VEL (Belperio, 2019). However, many studies proved that SOF/VEL has greater efficacy (Sulkowski et al., 2014; Foster et al., 2015; Nelson et al., 2015; Wyles, 2017; Hezode et al., 2018; Liver, 2018). The present study resulted that both regimens SOF/VEL and SOF + DCV were less effective among cirrhotic patients in terms of RAS presence than the non-cirrhotic patients. However, in our previous studies, both regimens were equally effective in the treatment of naïve HCV patients (Mushtaq, 2020a; Mushtaq, 2020b).

Even though the likelihood of achieving SVR with these new DAAs has been increased exponentially in patients with chronic HCV infection who have previously failed HCV antiviral therapy, RASs can appear either before or after treatment with DAAs (Hernandez et al., 2013). Our findings are in alliance with these findings in terms of the presence and prevalence of RASs at the baseline in previously treated GT3 patients—30% in DCV and 90% in VEL group, respectively.

The sequencing techniques have a significant impact on the detection rate of RASs (Pawlotsky, 2020). In this study, we were unable to perform deep sequencing or NSS due to budget constraints. Despite this constraint, HCV GT3 NS5A and NS5B regions were successfully amplified, and Sanger sequencing of 224 baselines and 80 post-treatment PCR products yielded accurate and reliable detection of amino acid substitutions/RASs. Many investigators suggested that if a 15% cut-off is used for the determination of RASs by NGS, both methods can be considered equivalent. Since recent studies have shown that NGS results at a 1% level of sensitivity frequently contribute to the identification of extra RASs that are not associated with clinical failure.(Ghany et al., 2019; Chen et al., 2020), we have used Sanger sequencing for RAS identification in NS5A and NS5B regions of HCV. The NS5A RASs were found in 26.3% of patients. Moreover, many studies have shown the 10–50% baseline range for the overall proportion of NS5A RASs (Issur and Götte, 2014). As a result, the detection rate of NS5A RASs in this study is consistent with the following studies (Wyles, 2017; Dietz et al., 2018; Hernandez et al., 2013; Di Maio et al., 2018; Ghany et al., 2019; Hezode et al., 2018; Sharafi et al., 2019). Similarly, the overall proportion of amino acid substitutions at the baseline in the NS5A and NS5B regions of HCV (**Table 4**) was very high, which is consistent with prior studies (Lontok et al., 2015; Sarrazin, 2016; Gane et al., 2017; Palanisamy et al., 2018; Rahimi, 2021).

In terms of baseline RASs, the HCV genotype and subtype are among the most influential parameters. In addition, various studies have found an increased prevalence of NS5A amino acid substitutions in HCV GT3a infection, and in this study, the prevalences of NS5A amino acid substitutions were 100X (S14M (92%), A17S (92%), A21T (92%), A62S (94%), S98G (84%), S103P (83%), D126E (80%), F127C (80%), and D172E (92%) in GT3 HCV patients, which were consistent with previous findings (Sarrazin, 2016; Smith et al., 2019; Pawlotsky, 2020) and indicating HCV heterogeneity.

Sofosbuvir is a potent inhibitor against NS5B with a pan-genotypic effect on HCV that does not cause viral resistance in GT1 and 3, with cirrhosis, and a history of previous treatment. Notwithstanding being mutation prone, SOF-resistant variants may not be established or even selectable and correlated with our findings in terms of no RAS in the NS5B region of HCV (Sofia et al., 2010; Gane et al., 2017; Sorbo et al., 2018).

Similarly, both DAA regimens were well-tolerated, with no adverse events leading to discontinuation of treatment. Skin rashes with bruising and oral ulcers were high in patients taking DCV and then VEL-based regimens, respectively. Moreover, these abnormalities were not treatment-emergent but clinically related to liver-related parameters, including ALT and AST, and total bilirubin. These findings are in agreement with the results of the following studies (Hill et al., 2016; Mushtaq, 2020a; Mushtaq, 2020b).

Our findings suggest that in cirrhotic and previously treated HCV GT3 patients, a resistance profiling test should be performed before the start of the therapy. Moreover, our findings are useful, particularly in low- and middle-income countries where generic HCV treatment is becoming more widely available against a variety of genotypes (EASL, 2018; Mushtaq, 2020a).

CONCLUSION

To summarize the study's findings, we observed the important RASs in HCV patients of GT3 from Pakistan. A62S/T, A30K, and Y93H were the most common RASs against NS5A inhibitors, which indicate an increased resistance to some DAA regimens used to treat HCV. While RASs are still a common cause of DAAs failure, identifying them is crucial for optimizing re-treatment strategies. In this rapidly evolving field, stakeholders must work together to assess real-world treatment failure rates and re-treatment success rates in order to inform the field as quickly as possible about regimen selection and the potential need for baseline resistance testing in cirrhotic patients of GT3.

STUDY LIMITATIONS

We were unable to perform NGS-based sequencing, which can further highlight minority variant frequencies associated with DAAs failure. Second, genotype diversity is lacking as we worked

only on GT3. Bioinformatics analysis could reveal all attributes of both proteins, which could be useful for further research into HCV drug resistance and the development of vaccines against HCV. Moreover, cell culture studies can further confirm these pattern of RASs in GT3.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.ncbi.nlm.nih.gov; ON009333-ON009338.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics review boards of Rawalpindi Medical University and Allied Hospitals (Holy Family Hospital, Benazir Bhutto Hospital, and District Headquarter Hospital), Institute of Biomedical and Genetic Engineering (IBGE), KRL Hospital, Islamabad, and National University of Sciences and Technology (IRB-130). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. SMu and AK made substantial contributions to the acquisition and analysis of the data. SMu and AH performed the experiments. SMu drafted the manuscript while AK and SM interpreted the results. AK, SMA, and SM were involved in the critical revision for important intellectual content. The study was supervised by SM.

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SUPPLEMENTARY MATERIAL

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Assessment of Adverse Drug Events, Their Risk Factors, and Management Among Patients Treated for Multidrug-Resistant TB: A Prospective Cohort Study From Pakistan

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Background: Multidrug-resistant tuberculosis (MDR-TB) is a growing public health problem. Treatment regimens used against MDR-TB are costly, prolonged, and associated with more side effects as compared with the drug-susceptible tuberculosis. This study was framed to determine the incidence of adverse drug events, risk factors, and their management in MDR-TB patients.

Methods: This prospective follow-up cohort study was conducted at the site of programmatic management of drug-resistant TB located at the Pakistan Institute of Medical Sciences, Islamabad. All patients, irrespective of their age, gender, and ethnicity, were included in the study. Adverse drug events were observed in patients at different time points during the study. Patients enrolled for the treatment from January 2018 were prospectively followed till December 2020 up to their end treatment outcomes.

Results: Out of 126 MDR-TB patients enrolled for treatment, 116 met the inclusion criteria and were included in the final analysis. Most patients (50.9%) were between 18 and 45 years of age. A minimum of one adverse event was experienced by (50.9%) patients. Of all the adverse events, gastrointestinal disorders were more frequent (47.4%), followed by arthralgia (28.4%) and psychiatric disturbance (20.6%). Furthermore, multivariate analysis showed a significant association with the incidence of adverse events in patients with age group above 60 years (odds ratio (OR) 4.50; 95% CI 1.05-19.2), active smokers (OR 4.20; 95% CI 1.31-13.4), delayed reporting to the TB center (OR 4.03; 95% CI 1.34-12.1), and treatment without bedaquiline regime (OR 3.54; 95% CI 1.23-10.1). Most of the patients (94.6%), counseled by the pharmacist, were found to be satisfied with the information provided and looked for more pharmacist counseling opportunities in the management of MDR-TB.

Conclusion: Current findings recommend that ADEs might be well managed by timely identification and reporting. Bedaquiline coupled with other active medications lowered the chance of ADEs in MDR-TB patients. Elderly patients, active smoking behavior, and those who have a delay in the treatment initiation are more prone to ADEs. Clinical pharmacist's contribution to TB control programs may help caregivers and patients concerning the rational use of medication, early detection, and management of ADEs.

Keywords: multidrug-resistant tuberculosis, adverse drug event, management, pharmacist, patient satisfaction

INTRODUCTION

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) poses significant challenges to the control and successful eradication of TB, particularly in developing countries (Iradukunda et al., 2021). Despite all the efforts made throughout the world by the WHO, the treatment success rate for MDR-TB is still low. The WHO targets a success rate of at least 75% for MDR-TB patients; however, the most recent statistics on treatment outcomes indicate a success rate of 56% (Baluku et al., 2021; Yang et al., 2017). This is mainly because the MDR-TB therapy is costly, has low efficacy, and has more adverse drug events when compared to drug-susceptible TB (Baluku et al., 2021). One of the factors causing MDR-TB is non-compliance to the anti-MDR-TB treatment regimen. The most important independent factor underlying non-compliance to treatment is adverse events of medications (Resende and Santos-Neto, 2015; Merid et al., 2019; Sankar et al., 2021). The overall incidence of ADEs caused by anti-TB medications ranges from 5.1% to 83.5% in different populations (Kefale et al., 2020). ADEs increase patient suffering and increase substantial additional costs because of added outpatient visits, laboratory investigations, and hospitalizations, in more serious instances (Resende and Santos-Neto, 2015). Despite these difficulties, up to 80% of the treatment results can be achieved by effectively treating MDR-TB patients. Most ADEs can be controlled with over-the-counter and commonly prescribed medications. If the ADEs are mild, then proceeding with supplementary medications may be helpful (Trubnikov et al., 2021). In some cases, ADEs disappear over time and patients should be encouraged to tolerate them until the effects subside. Studies have shown that multidrug regimens can cause numerous ADEs such as nausea, vomiting, diarrhea, skin reaction, ototoxicity, peripheral neuropathy, psychiatric symptoms, nephrotoxicity, impaired vision, and hypothyroidism (Bezu et al., 2014; Merid et al., 2019).

Pakistan ranked the highest for MDR-TB burden in EMRO (Eastern Mediterranean Region of the WHO) and fourth highest country in the world (WHO, 2018; NTP, 2020). Drug-resistant tuberculosis is becoming more common in Pakistan, which highlights the need for efficient treatment regimens for MDR/XDR-TB (Javaid et al., 2018). Despite being the country with the highest burden of MDR-TB in EMRO, there is little information available about the management of adverse effects and treatment outcomes of patients with MDR-TB in Pakistan. To attain the 2025 goal of complete elimination of TB, a better understanding of the ADE of all drugs used to treat MDR-TB is an important and much-needed step in improving patient management and treatment outcomes. Therefore, close monitoring of patients is important to ensure that the ADEs are timely reported and managed. Clinical pharmacists providing pharmaceutical care services have been shown to improve adherence to therapy and reduce potential ADEs. More data on their characteristics and management are very valuable for clinicians and pharmacists. Therefore, this study was framed to determine the incidence, risk factors, and management of adverse events encountered in clinical practice.

MATERIALS AND METHODS

Study Site

This prospective case series analysis was carried out at the unit for programmatic management of drug-resistant TB (PMDT) located in the Pakistan Institute of Medical Sciences, Islamabad. Doctors, nurses, data operators, coordinators, pharmacists, psychologists, and other support personnel work at the research site to help MDR-TB patients achieve a treatment success rate of 75%.

Study Population and Eligibility Criteria

Patients enrolled for the treatment from January 2018 were followed from the baseline visit. Those registered before 2018 and still on treatment were retrospectively followed till January 2018. Afterward, all the enrolled patients were prospectively followed till December 2020 up to their end treatment outcomes. All MDR-TB patients, irrespective of their age, gender, and ethnicity, were included in the study, while the multidrug-resistant cases those were transferred out from the study center or were still on the treatment medications during the final day of analysis were excluded.

Follow-Up and Adverse Events Monitoring

Based on WHO guidelines for the treatment of MDR-TB and previous research, a standardized data-collecting form was developed. The supervisory committee and healthcare personnel at the study site also provided input. The patients were first assessed for symptoms at baseline and then reviewed and evaluated on a monthly basis by the doctor. Once the screening tests at baseline were completed, the MDR-TB patients were enrolled to be treated with the treatment regimen according to the NTP guidelines. All the drugs were

provided at their maximum prescribed dosage, which were determined by the patient body weight. The treatment of all the patients after sputum culture conversion was continued for a minimum of 18 months. The patients were closely monitored during the follow-up visits to assess the ADEs **Table 1**. Specialist clinicians, pharmacists, and data coordinators reviewed every patient once a month to make sure their treatment was as effective as possible. All the patients were being assessed on a monthly basis and were treated as outpatients. To ensure adherence to the treatment, the patients were monitored by trained treatment supporters.

Patients found resistant in the Xpert MTB/RIF diagnostic test were registered as MDR-TB cases and treated with a regimen proposed by the WHO and National TB guidelines (WHO, 2012; WHO, 2014). Baseline laboratory tests, such as complete blood count, hepatitis, HIV, blood sugar level, kidney and liver function tests, urine routine test, and thyroid function test were conducted prior to the start of the treatment. AEs were recorded after laboratory test confirmation, and only those AEs that had at least one abnormal value were considered significant. As a requirement of PMDT, on each visit, ADEs were documented based on laboratory results, self-recorded by patients, or monitored by doctors and pharmacists. All patients were assessed for scheduled follow-up visits. Moreover, free laboratory tests and medications were provided, and both patients and treatment supporters were provided with nutritional and transport allowance support.

During corona virus infectious disease (COVID-19) pandemic, protocol of the National TB Control Program (NTP) for the protection from COVID-19 was strictly followed for both patients and healthcare professionals (NTP, 2020). According to the instruction of the NTP, an isolated triage area was assigned for all patients to separate them from suspected and non-suspected COVID-19 patients. Appropriate digital and telecommunication support were provided to the patients to ensure communication if they want any consultation for the management of ADEs caused by anti-MDR-TB treatment.

Operational Definitions

According to WHO guidelines, treatment outcomes are classified as successful when the TB patient finalizes the treatment medication to indicate cure and completion, while unsuccessful treatment outcomes are classified as treatment failure, treatment defaulters, and died patients (WHO, 2021). This study assessed patients' satisfaction with pharmacist counseling services. A novel tool known as the patient satisfaction feedback on counseling (PSF) questionnaire in English and Urdu languages was used to document the satisfaction of patients following pharmacist counseling sessions (Naqvi et al., 2019).

Statistical Analysis

Distributions of participants' characteristics and the cumulative incidences of adverse events were studied using descriptive statistics. Variables having significant association in the chi-square test were further analyzed through a univariate and then a multivariate logistic regression model. Variables with a p-value of <0.15 in the univariate regression analysis were analyzed in the final multivariate regression model. The occurrence of substantial intercorrelations between two or more independent variables in a regression model is referred to as multicollinearity. We examined the collinearity and tolerance value for each variable while creating the multivariate binary logistic regression. If the variables have a strong correlation (variance inflation factor = 10 and tolerance value > 0.1), one of them was excluded from the concluding model (Pallant, 2020). The final multivariate binary logistic regression model was adjusted using the Hosmer–Lemeshow test. The odds ratios with 95% confidence intervals were considered to measure the significant ($p \leq 0.05$) relationship between variables and adverse events. We used the Statistical Package for the Social Sciences, version 26 (SPSS) in all statistical analyses.

RESULTS

Baseline Characteristics

Overall, 126 MDR-TB patients signed up for the treatment at the site during data collection for this study. A total of ten patients were omitted from the trial because they did not match the study's eligibility requirements. A total of 116 MDR-TB patients were included and followed for their therapeutic outcomes. Baseline clinical and sociodemographic characteristics of the patients are given in **Table 2**.

Most patients (50.9%) were between 18 and 45 years of age. Male and female were 80 (56.9%) and 56 (43.1%), respectively. Nearly 66% of the patients resided in rural areas, 64.7% have no formal level of education, and 83.6% patients were married. Active smokers were 21.6%, and 25.8% had one or more comorbidities, and 27.6% were those with regime containing bedaquiline. Most of the patients (69%) had a baseline body weight of above 40 kg.

Predictors of Adverse Drug Events

A statistically significant association was found between the incidence of ADEs and age, comorbidities, smoking, baseline weight, delayed reporting to the TB center, and regime plan containing bedaquiline. No statistically significant association was identified between gender, marital status, education, employment status, residency, and number of drug resistance (**Table 3**).

Furthermore, during multivariate analysis, the variables that had a significant association with the occurrence of AEs were patients with age group above 60 years (odds ratio (OR) 4.50; 95% CI 1.05-19.2), active smokers (OR 4.20; 95% CI 1.31-13.4), and delayed reporting to the TB center (OR 4.03; 95% CI 1.34-12.1). Similarly, bedaquiline regime had the lowest incidence of ADEs among amino salicylic acid, linezolid, and injectable drugs (OR 3.54; 95% CI 1.23-10.1). Exploring the impact of ADEs on TB treatment outcomes through univariate analysis, the occurrence of ADEs had a significant risk of positive association with

TABLE 1 | Definition of side effects.

Gastrointestinal disorders	Incidence of nausea, abdominal pain, vomiting, anorexia, sour taste in the mouth, flatus and cramping, diarrhea, epigastric burning or discomfort, hematemesis, melena, and positive analysis by endoscopic study
Psychiatric disturbances	Psychosis symptoms, anxiety, nightmares, delusions, suicidal ideation, depression, and visual or auditory hallucinations
Dermatologic conditions	Every skin change includes severe generalized rash, itch, bronzing, and photosensitivity reaction
Peripheral neuropathy	Peripheral neuropathy was defined as a MDR-TB patient referring to damage to the nerves located outside of the central nervous system, signs of numbness, and tingling or burning sensation in the extremities diagnosed by the physician or electromyography
Hepatotoxicity	Any elevation with or without symptoms of serum transaminases or serum bilirubin greater than 3 or 5 times than normal upper limit
Hearing disturbance	Hearing loss and signs of auditory toxicity and tinnitus
Visual impairment	Pain on moving the eye, visual changes, and vision loss
Arthralgia	Serum uric acid levels may be raised, aching around the joints, pain, and swelling in the joints

unsuccessful treatment outcomes (OR 2.33; 95% CI 1.08-5.05). However, in multivariate analysis, no level of significance was found **Table 4**.

Frequency of Adverse Events

Out of 116 patients, 59 (50.8%) experienced at least one ADE. Most ADEs occurred during the 6-month interim period of MDR-TB treatment. Among all types of ADEs, nausea and vomiting (33%), arthralgia (28.4%), psychiatric disturbance (20.6%), and gastritis (10.3%) were mostly reported by patients during clinical follow-up assessment. Similarly, hearing disturbance (11.2%), gastritis (10.3%), skin rashes (6%), headache (4.3%), peripheral neuropathy (3.4%), and visual disturbance (1.7%) were also observed (**Table 5**).

All the adverse events were managed by pharmacological, psychological, and supportive therapies. In addition, education was provided during each follow-up visit to patients regarding ADEs and their management. ADEs were thoroughly evaluated, and it was found that no drug(s) should be permanently discontinued unless they pose a life-threatening situation or causing a lasting injury to the patient. But in a worse condition, all the required changes were made according to the WHO guidelines. Among 11 (9.48%) MDR-TB patients, temporary medications were stopped, and drugs were successfully reintroduced within 4 weeks after the problem resolution. For 6 (5.1%) drug-resistant TB patients, permanent changes were made in the regimen, and for 14 (12.0%) patients dose adjustment was suggested during the study time. All of the problematic medicines that had been temporarily discontinued over the course of therapy were restarted after the ADRs had abated.

Symptomatic management was carried out for all the patients who had the gastrointestinal disorder until the problem was resolved. In case of persistent diarrhea, temporary discontinuation of para-amino salicylic acid for 1 week (n = 2) was advised by the consultant.

In case of no improvement or worsening of arthralgia, consultation with a physician withheld the suspected agent temporarily (n = 3) or dose of the offending drug (pyrazinamide) was reduced (n = 1) or permanently stopped (n = 1). In these four patients, pyrazinamide and clofazimine were replaced with ethambutol and ethionamide, respectively.

Psychiatric problems reported by drug-resistant TB patients compelled the healthcare team for modification in the treatment regimen. Cycloserine was temporary stopped in three patients, and for five patients, the dosage was reduced for 15 days, while in three patients cycloserine was completely stopped after proper consultation with a physician.

Similarly, in case of peripheral neuropathy, linezolid was stopped for 2 weeks (n = 2). In three patients with ototoxicity, frequency of amikacin was reduced, and in one patient, the regime was switched from amikacin daily to alternate day's capreomycin, with physician's consultation. In case of skin rash, the physician advised to reduce the dose of pyrazinamide and replace clofazimine with tablet linezolid for 15 days (1) **Table 5**.

Patient Satisfaction

Out of 116 MDR-TB patients, 75 patients were available for patient satisfaction feedback regarding pharmacist-counseling assessment, and the majority (94.6%) of the respondents agreed that they were able to receive consultation without having any trouble with a pharmacist. A total of 81.3% agreed that they developed the knowledge related to MDR-TB according to their needs. However, 82.7% assured that the pharmacist helped resolve their medication-related queries during the treatment session. The majority (97.3%) appeared promising to recommend counseling from a pharmacist to others and recommended that this facility should be accessible in community pharmacies in the district. More than half of the patients (65.3%) were willing to pay for this counseling service. Moreover, 73.3% of the patients appeared satisfied with the counseling **Table 6**.

DISCUSSION

Multidrug TB treatment has long therapy duration (18 months to 2 years), and the number of drugs used for the treatment is comparatively more complex than that for drug-susceptible TB (Khan et al., 2022). Numerous side effects are identified that result in patients' non-compliance and predictably poor outcomes (Tahaoğlu et al., 2001; Mukherjee et al., 2004). Therefore, monitoring and appropriate administration of drugs are of utmost significance for the successful treatment of MDR-TB patients (Zhang et al., 2017; Ahmad et al., 2018). In this current study, gastrointestinal disorders were the most

TABLE 2 | Baseline demographic and clinical characteristics of the participants (n, 116).

Variable	Frequency (n %)
Age (years)	
<18	21 (18.1)
19–45	59 (50.9)
>46	36 (31.0)
Gender	
Female	50 (43.1)
Male	66 (56.9)
Marital status	
Married	97 (83.6)
Unmarried	19 (16.4)
Education	
Illiterate (no education at all)	75 (64.7)
Literate (primary and above)	41 (35.3)
Employment	
Employment	10 (8.6)
Unemployment	46 (39.7)
House wife	27 (23.3)
Student	20 (17.2)
Self-employment	13 (11.2)
Monthly income	
<20000	65 (56)
≥20000	51 (44)
Residency	
Rural	77 (66.4)
Urban	39 (33.6)
Smoking	
Active smoking	26 (22.4)
No smoking	91 (78.6)
Baseline weight	
<40 kg	36 (31)
≥40 kg	80 (69)
Comorbidity (30)	
Diabetes	19 (15.5)
Hypertension	7 (6)
Hepatitis	3 (2.5)
HIV	1 (0.9)
Number of resistant drugs	
≥2	59 (50.9)
<2	57 (49.1)
Resistance to SLD drugs	
Yes	28 (24.1)
No	88 (75.9)
Sputum smear	
Negative/scanty	33 (28.4)
Positive	83 (71.6)
Regime containing bedaquiline	
Bedaquiline	32 (27.6)
No bedaquiline	84 (72.4)
Successful treatment outcomes (71)	
Cured	62 (53.4)
Completed	9 (7.8)
Unsuccessful treatment outcomes (45)	
Failure	4 (3.4)
Died	28 (24.1)
Lost to follow up	13 (11.2)
Adverse events	
Adverse event reported	60 (50.9)
Adverse event not Reported	56 (49.1)

SLD, second line drug.

common type of adverse events observed in patients (50.9%). The results of the present study are parallel to previously reported studies (Farazi et al., 2014; Javadi et al., 2007; Laghari et al., 2020). However, a study reported higher (71.3%) incidence of ADEs in MDR-TB patients. These differences between studies are likely due to the differences in patient characteristics, treatment regimens, and AE-monitoring approaches. In this study, ADEs were monitored prospectively following the patient-centered care approach delivered by the pharmacist. In our study, 50.9% of the patients developed ADEs of various severities during treatment, of whom 21.5% required minimal modification of the TB treatment regimen and symptomatic treatment in managing ADEs, and these results are consistent with previous studies (Javadi et al., 2007; Baghaei et al., 2011). While maximal modification in treatment was reported in few studies as compared with the current study, i.e., 55.2% from Turkey, 29% from Namibia, and 84% from Latvia (Sagwa et al., 2014; Shin et al., 2007; Törün et al., 2005). These findings point out the promising and important role of the pharmacist to manage all adverse events. All the adverse events in the study were managed by pharmacological, psychological, and supportive therapy. Those who developed gastrointestinal disorders were reassured and symptomatically managed by adding secondary drugs. Patients with adverse events such as nausea and vomiting were advised to perform liver function tests and take anti-TB medication after a light meal. To stop vomiting symptomatically, an antiemetic was added to their regimen. In the case of persistent diarrhea, para-amino salicylic acid was stopped for 1 week or until the adverse event was not resolved. Metronidazole was also prescribed by the physician for the relief of abdominal pain and diarrhea. In the current study, modification in patient's regimes due to gastrointestinal disorders was according to the previously reported studies (Merid et al., 2019; Ahmad et al., 2018). In the current study, one of the reasons for the adverse events due to gastrointestinal disorders could be that 39.7% of patients were underweight, and they might not have tolerated the multidrug regimen. Previous studies also reported that underweight patients were more prone to ADEs (Laghari et al., 2020; Zhang et al., 2017). Therefore, appetite-stimulating agents and nutritional supplements were added to increase body weight in patients who were underweight.

A significant percentage of the patients (28.4%) experienced arthralgia, inconsistent with the results from India (Qureshi et al., 2007), Japan (Inoue et al., 1999), and Namibia (Sagwa et al., 2013). However, slightly less arthralgia is reported from China (Zhang et al., 2017). In the current study, both pyrazinamide and clofazimine were reported to be the leading cause of arthralgia. The findings of this study are in line with previous studies that reported pyrazinamide as a renowned cause of arthralgia in MDR-TB treatment (Farazi et al., 2014; Abraham et al., 2006). Symptoms of arthralgia were reduced by supportive and pharmacological treatment. The approach of treatment modification applied in our study was similar to the approach used by previous studies (Gülbay et al., 2006; Yang et al., 2017; Ahmad et al., 2018). Another adverse event, the psychiatric disturbance (20.6%), was almost

TABLE 3 | Association between patients' characteristics and incidence of ADEs (n, 116).

Variable	ADE reported (n, 60)	ADE not Reported (n, 56)	*p*-value
Age (years)			0.01
<18	7 (11.7)	13 (23.2)	
19–45	25 (41.7)	31 (55.4)	
>46	28 (46.6)	12 (21.4)	
Gender			0.21
Female	31 (52.5)	35 (61.4)	
Male	28 (47.5)	22 (39.2)	
Marital status			0.12
Married	53 (88.3)	44 (78.6)	
Unmarried	7 (11.7)	12 (21.4)	
Education			0.39
Illiterate (no education at all)	40 (66.7)	35 (62.3)	
Literate (primary and above)	20 (33.3)	21 (37.7)	
Employment status			0.49
Employment	2 (3.3)	8 (14.3)	
Unemployment	26 (43.3)	20 (35.7)	
House wife	17 (28.3)	10 (17.9)	
Student	10 (16.8)	10 (17.9)	
Self-employment	5 (8.3)	8 (14.2)	
Monthly income			0.14
<20000	37 (61.7)	28 (50)	
≥ 20000	23 (38.3)	28 (50)	
Residency			0.44
Rural	39 (65)	38 (67.9)	
Urban	21 (35)	18 (32.1)	
Smoking			0.01
No smoking	41 (65)	50 (91.1)	
Active smoking	21 (35)	5 (8.9)	
Baseline weight			0.04
<40 kg	24 (40)	13 (23.2)	
≥40 kg	36 (60)	43 (76.8)	
Reported to the TB center			0.00
More than a month delay	22 (36.7)	7 (12.5)	
Less than a month delay	38 (63.3)	49 (87.5)	
Comorbidity			0.04
Yes	20 (33.3)	10 (17.9)	
No	40 (66.7)	46 (82.1)	
Number of resistant drugs			0.13
≥2	27 (45)	32 (57.1)	
<2	33 (55)	24 (42.9)	
Regime containing bedaquiline			0.01
Bedaquiline	11 (18.3)	21 (37.5)	
No bedaquiline	49 (81.7)	35 (62.5)	
Treatment outcomes			0.02
Successful outcome	31 (51.7)	40 (71.4)	
Unsuccessful outcome	29 (48.3)	16 (28.6)	

ADE, adverse drugs events; SLD, second line of drug (p ≤ 0.05).

parallel to the previous studies conducted in Turkey (21.3%) and Russia (20.5%) (Törün et al., 2005; Shin et al., 2007). The previous study also mentioned that the leading cause of the MDR-TB treatment modification was a psychiatric disturbance among patients. Cycloserine and ethionamide were recognized as the foremost drugs associated with psychiatric disorders (Leston et al., 1970; Yang et al., 2017; Zhang et al., 2017). Ototoxicity reported in our study (11.2%) was several times lower than that reported in the previous studies, viz., 55% reported in the United Kingdom (Arnold et al., 2017), and 14.5% reported in Iran (Baghaei et al., 2011)), while the cases of ototoxicity in the current study was more than that in the study conducted in Ethiopia (4.8%) (Shibeshi et al., 2019). The variability in the results might be due to the unavailability of proper audiometric assessments at regular intervals at the study site. This might have caused the under-reporting of the actual ototoxicity frequency in our study. Audiometric assessment with consistent intervals of follow-up visits must be considered in patients' AE detection. The ototoxicity signs were recognized through assessment of hearing loss, imbalance, and visual disturbance. The prevalence of skin adverse reactions was comparatively lower than that reported in previous studies (Schaberg et al., 1996; Yee et al., 2003). We also observed 3.4% of neurologic side effects, much lower than that in a study conducted in Peru (36.7%) (Furin et al., 2001). Linezolid,

TABLE 4 | Risk factors associated with adverse drugs events.

Variable	ADE reported	COR (95%CI)	AOR (95%CI)
Age (years)			
<18	7 (11.7)	References	References
19–45	25 (41.7)	2.89 [1.22–6.81]	1.95 [0.65–5.78]
>46	28 (46.7)	4.33 [1.38–13.5]*	4.50 [1.05–19.2]*
Smoking			
No smoking	41 (65)	References	
Active smoking	21 (35)	5.49 [1.90–15.8] *	4.20 [1.31–13.4]*
Baseline weight			
<40 kg	24 (40)	References	References
≥40 kg	36 (60)	2.20 [0.98–4.94]*	1.80 [0.66–4.92]
Reported to MDR-TB center			
Less than a month delay	22 (36.7)	References	References
More than a month delay	38 (63.3)	4.05 [1.56–10.4]*	4.03 [1.34–12.1]*
Comorbidity			
No	20 (33.3)	References	References
Yes	40 (51.7)	2.30 [0.96–5.48]*	1.35 [0.47–3.88]
Regime containing bedaquiline			
Bedaquiline	11 (18.3)	References	References
No bedaquiline	49 (81.7)	2.88 [1.23–6.71]*	3.54 [1.23–10.1] *
Treatment outcomes			
Successful outcome	31 (51.7)	References	References
Unsuccessful outcome	29 (48.3)	2.33 [1.08–5.05]*	1.81 [0.65–4.99]

*FLD, first line of drugs; SLD, second line of drug; *p < 0.05, **p < 0.001; reference category, unsuccessful outcomes; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; (Univariate analysis p < 0.15 is considered significant) multivariate model was significant, with chi square 37.03 DF 8, p < 0.0005; Hosmer–Lemeshow statistic chi square 4.73 (DF 7, N 116); collinearity (variance inflation factor = 10); and tolerance value > 0.10. SLD, second line of drug; ADEs, adverse drugs events.*

TABLE 5 | Prevalence and management of adverse events in patients with MDR-TB treatment.

Adverse drugs event	n % (116)	Temporarily discontinued/dose adjustment	Permanently discontinued
Gastrointestinal disorders	55 (47.4)	Managed symptomatically	Managed symptomatically
Gastritis	12 (10.3)	Managed symptomatically	Managed symptomatically
Nausea and Vomiting	36 (33)	PAS was stopped in patients for 15 days (*n* = 2)	Managed symptomatically
Diarrhea	3 (2.6)	PAS was stopped for 1 week as advised by the consultation (*n* = 2)	Managed symptomatically
Anorexia	4 (4.3)	Managed symptomatically	Managed symptomatically
Arthralgia	33 (28.4)	Temporarily stopped the Pyrazinamide for 2 weeks (*n* = 3) Dose reduction of pyrazinamide (*n* = 1)	Stopped pyrazinamide and revised regimen (*n* = 1)
Psychiatric disturbances	24 (20.6)	Stopped cycloserine for 15 days (*n* = 3) Dose reduction of cycloserine (*n* = 5)	Cycloserine was stopped completely (*n* = 3)
Peripheral neuropathy	4 (3.4)	Linezolid was stopped for 2 weeks (*n* = 2) Pyridoxine dose was increased to 200 mg/day (*n* = 3)	Managed symptomatically
Headache	5 (4.3)	Managed symptomatically	Managed symptomatically
Skin rashes	7 (6%)	Reduced the dose of pyrazinamide (*n* = 1) Replaced clofazimine with tablet linezolid (*n* = 1)	Managed symptomatically
Hearing disturbance	13 (11.2)	The frequency of amikacin was reduced (*n* = 3)	Amikacin shifted to capreomycin (*n* = 1)
Visual disturbance	2 (1.7)	Ethambutol was temporarily stopped, and clofazimine was added to the regime (*n* = 2)	Managed symptomatically

The individual could have more than one adverse drug event.

which was temporarily discontinued, was reintroduced once symptoms resolved, and the dose of vitamin B6 was increased. Elderly patients are predominantly susceptible to ADRs. According to our results, the age group of above 46 years was more significantly associated with ADRs (OR 4.50; 95% CI 1.05-19.2 $p < 0.05$). The result of this study is entirely consistent with previous study reports (Laghari et al., 2020; Bezu et al., 2014). Geriatrics patients' liver is less able to metabolize many drugs, and the kidneys are less able to eliminate the drug from the body (Merid et al., 2019). Most reported ADEs were also associated with the smokers' group as compared with nonsmokers (OR 4.20; 95% CI 1.31-13.4). This result was supported by experimental and clinical studies that smoking increases the chance of ADEs (Bezu

TABLE 6 | Patient satisfaction feedback regarding pharmacist counseling.

Patient satisfaction feedback regarding pharmacist counseling	Response	n 75 (%)
Were you able to get counseling without any difficulty?	Yes	71 (94.6)
	No	4 (5.4)
Were you able to obtain the knowledge you required?	Yes completely	61 (81.3)
	Yes, to some extent	5 (6.7)
	No, I did not get	9 (12)
Did you find the pharmacist helpful in resolving your questions?	Very helpful	62 (82.7)
	Somewhat helpful	10 (13.3)
	Not helpful	3 (4)
What is your opinion about the time duration of pharmacist counseling?	More time should be given	28 (37.3)
	Appropriate time was given	45 (60)
	My time was wasted	2 (2.7)
Will you recommend getting counseling from pharmacists to others?	Yes	73 (97.3)
	No	2 (2.7)
In your opinion, should this service be offered by pharmacies in your locality?	Yes	73 (97.3)
	No	2 (2.7)
Are you willing to pay for this counseling service?	Yes	49 (65.3)
	No	26 (34.6)
How would you rate your satisfaction with pharmacist counseling?	Very satisfied	55 (73.3)
	Satisfied	12 (16)
	Uncertain	6 (8)
	Not satisfied	2 (2.7)

et al., 2014; Chung-Delgado et al., 2011). Bedaquiline is a novel drug approved by the WHO, for the treatment of MDR TB. This study investigated the safety of bedaquiline; patients who were without a bedaquiline regime have a higher chance of adverse events (OR 3.54; 95% CI 1.23-10.1) than the other group. The results of this study are consistent with previous studies (Gao et al., 2021; Mbuagbaw et al., 2019; Lan et al., 2020). This indicates that bedaquiline added to a background regimen can improve the rate of successful outcomes and quality of life.

Most patients looked for counseling with no trouble, discovered the pharmacists being helpful, seemed happy with the information they acquired, and looked for more pharmacist counseling opportunities. The findings of our study are consistent with other studies (Alqarni et al., 2019; Naqvi et al., 2019). A higher percentage of patients were willing to pay for the service, and the satisfaction score finding is in line with studies conducted in the United States and Saudi (Poulos et al., 2008; Alshayban et al., 2020). Pharmacists need to provide appropriate, clear, and relevant information to patients about their medications. The results of this study suggest the role of the pharmacist's services in the Pakistan's TB health sector. Therefore, efforts to emphasize pharmacists' role, as a health promoter, will help attain safe and effective pharmaceutical care services.

There are several limitations in our study. First, we only evaluated patients from a single TB referral hospital that may have introduced selection bias; as a single-centered study, its results cannot be generalized. Second, the laboratory tests, especially audiometry, were not performed at the baseline level due to limited resources provided at the study site.

Despite these limitations, we believe that our study provides important information regarding the side effects of second-line anti-TB drugs in resource-poor settings.

CONCLUSION

In conclusion, we believe that adverse drug events have implications not only for the patient but also for the entire healthcare system. In the present study, ADEs were highly prevalent with second-line anti-TB therapy, but neither led to permanent discontinuation of the regime nor significantly conceited the treatment outcomes. Current findings recommend that ADEs might be well managed by sympathetic, emotional, and pharmaceutical therapy and may be provided without disturbing anti-DR-TB regime. Bedaquiline coupled with other active medications reduce ADEs in MDR-TB patients. As a result, bedaquiline usage in DR-TB patients should be promoted. The elderly patients with active smoking behavior and those who have a delay in treatment initiation are more prone to ADEs. The contribution of clinical pharmacists in TB control programs may help caregivers and patients in the rational use of medication, early identification, and management of ADEs.

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 study protocol that was approved by the Ethics Committee of the Pakistan Institute of Medical Sciences Hospital,

Islamabad, and Shaheed Zulfiqar Ali Medical University, Islamabad (F.1-1/2015/ERB/SZABMU/359), and ethically approved after scientific review. The study was also approved by Xian Jiaotong University's Health Science Center Biology Scientific and Research Ethics Committe (2019-1257). Both a written and oral consent form was obtained from every enrolled patient in this study. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FK is the principal investigator in the project and drafted the manuscript. WK, SN, JC, and AR have contributed in training and clinical supervision. AK, FK, and KH analyzed and review the final data. YF led the principal developer of the project and ongoing management of the study. All authors have read and approved the drafts of the final manuscript.

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Evaluation of Consumers Perspective on the Consumption of Antibiotics, Antibiotic Resistance, and Recommendations to Improve the Rational use of Antibiotics: An Exploratory Qualitative Study From Post-Conflicted Region of Pakistan

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Background: Antibiotics misuse is a global challenge, and the situation is likely to deteriorate in conflict zones with insufficient health services. The misuse of antibiotics is not only associated with antimicrobial resistance but may also lead to serious consequences. This study was aimed to investigate the knowledge, attitude, and practices on antibiotic consumption, antibiotic resistance (ABR), and related suggestions among residents of conflicted zones in Pakistan.

Methods: Semi-structured interviews were conducted at community pharmacies between June 2020 and January 2021. The primary findings were ascertained through thematic content analysis. Themes, sub-themes, and categories were drawn from the final analysis. Data analysis was carried out in six steps from getting to know the data to final report development.

Results: A total of 20 consumers were interviewed with a mean interview duration of 25.4 min. The average age of participants was 35.1 years, and most of them were males. ABR was unfamiliar to the participants. Most of the participants understood the term "antibiotics," but they did not know how to use them properly. The participants were unable to distinguish between bacterial and viral illnesses. Thirteen participants believed

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that antibiotics have a faster effect than any other drug. Most of the participants perceived that every antibiotic could cause diarrhea, and pharmacy staff sometimes prefer other medicines such as multivitamins. Consumer practices regarding antibiotic usage and ABR were found to be poor. Most participants recommended that health officials must ensure qualified staff at pharmacies with strict regulations. Five participants said that a leaflet with antibiotic instructions in Urdu (national language) is usually beneficial, especially when making solutions from powder.

Conclusions: This study underscored poor knowledge, attitude, and practices among residents of conflicted zones towards antibiotics and ABR. Low literacy rate, unavailability of healthcare facilities, absence of pharmacists at community pharmacies, and uncontrolled sales of antibiotics are some factors attributed to serious hazards, ABR, and irrational use of drugs.

Keywords: customers, antibiotic use, antibiotic resistance, conflict, community pharmacy

INTRODUCTION

Antibiotics are considered as life-saving drugs; although the 19th century was dubbed the "Golden Era" as a result of its discovery, the golden period did not last long due to the rise of various resistant infections (Akhund et al., 2019). ABR is a long-standing problem (Khan and Fang, 2021). ABR has drastically expanded in the twenty-first century and is primarily attributed to irrational prescription and incorrect usage. It has become a major public health hazard worldwide, especially in underdeveloped countries (Laxminarayan et al., 2013). Antibiotics are among the list of most prescribed medications, thereby possessing a substantial risk of drug abuse. According to an estimate, approximately 20–50% of antibiotics prescribed to patients are inappropriate (Ahmed et al., 2020). The poor policies for infection control, under/excessive use of antibiotics, and availability of over-the-counter antibiotics are some of the major drivers of ABR (García et al., 2011).

Between 2000 and 2015, the global use of antibiotics increased by 65%, primarily driven by increased consumption among low- and middle-income countries (LMICs) (Klein et al., 2018). Among LMICs, the highest consumption of antibiotics was observed in India, China, and Pakistan in 2015. Of particular note, antibiotic consumption increased by 65% (up to 1.3 billion Daily Defined Doses) in Pakistan in 2015 (Atif et al., 2021). If timely measures are not taken, it is estimated that ABR might cost 10 million deaths by 2050 (DeBaun et al., 2021). On the other hand, inappropriate use of antibiotics adversely affects patients by increasing the length of hospital stay with out-of-pocket expenses, which eventually diminishes the health-related quality of life (Atif et al., 2020).

It has been observed that knowledge and awareness of ABR are considerably low in countries having an increased burden of antibiotic resistance cases (Grigoryan et al., 2007). As a result, public information campaigns are launched in various countries as part of a national strategy with diverse levels of effect on the antibiotic cogent usage (Cross et al., 2017). ABR has assessed its substantial burden in Europe at €1.5 billion each year (Organization, 2018). Similarly, in the United Kingdom, one out of every four antibiotic prescriptions is erroneously filled, resulting in 10 million improper prescriptions each year (Mason et al., 2018). Understanding consumers' knowledge of antibiotics and their appropriate use is vital in identifying the public's attitude that consequently aids in shaping the campaigns and policies on this public health issue. The World Health Organization (WHO) has proposed public education as one of the key interventions to rationalize the use of antibiotics (Chang et al., 2017). Enhancing the public understanding of antibiotics is the principal strategy of the WHO`s Antimicrobial Resistance Global Action Plan (the World Health Organization, 2015).

The available body of evidence from Pakistan indicates that the use of antibiotics is still inappropriate in spite of various antimicrobial stewardship programs (Khan et al., 2021a; Khan et al., 2021b). Evidence suggests that the general public plays an essential role in curbing the growing encumbrance of ABR (Khan et al., 2020). Moreover, consumers' behaviors towards antibiotic use are of paramount importance in post-conflicted areas with poor healthcare facilities.

Due to the heavy military operations (2007–2011), infectious diseases are on the rise in the district, where respiratory tract infections are more common. Unfortunately, schools, hospitals, and roads are still destructed and have not been rebuilt even after a decade of war (Saeed Khan, 2019). The prevalence burden of infectious diseases might be attributed to the displacement and evacuation of citizens to the other parts of Pakistan where infections are more prevalent (Muzamil et al., 2021). The war in the Swat district has affected people of every walk of life and still infectious diseases are most prevalent, and this is relevant with the current study to measure the knowledge, attitude, and practices toward antibiotics and ABR.

The findings of the current study would help the policymakers to better understand the consumer perspectives toward ABR, which could be translated into appropriate strategies for strengthening the healthcare system in Pakistan.

METHODS

Study Setting

A qualitative research (semi-structured interviews) study was carried out in post-conflict areas, formally known as the "Yousufzai state of Swat (1849–1969)." The current population of Swat is 2.3 million, and it is one of the rural districts in the northern region of the Khyber Pakhtunkhwa Province, Pakistan. The majority of the people live in rural areas, comprising about 86% of the state. Swat has witnessed an extensive militancy conflict since 2007. In this study, mainly Swat district was targeted for the data collection from June 2020 to January 2021. An explorative phenomenological study design was used, based on the face-to-face interviews.

Study Design

This was a qualitative study that employed semi-structured interviews to uncover participants' perceptions about antibiotic usage and antibiotic resistance along with recommendations. Semi-structural interviews are useful tools, especially for exploratory studies. The study design offers several advantages such as the ability and flexibility to thoroughly examine the knowledge, experiences, and purpose of the participants on a specific subject. The interview schema contained several questions with sub-sections. In a profound conversation (face-to-face in-depth interviews) with the consumers, their general perceptions of antibiotics and ABR were assumed to determine. The interviews had been designed and conducted at the site of each pharmacy, and a place was reserved in the waiting area to ensure complete easiness for interviewers. All interviews were carried out in the Pashto language for the given population's convenience. It took approximately 20–30 (minutes) to complete each interview. For recording interviews, a voice recorder was utilized, and the recording had been kept and saved confidentially. The pharmacies situated in the post-conflicted/war-affected areas were selected randomly.

Inclusion Criteria

Consumers were eligible to participate in the study if they met predesigned criteria. The first was that all participants in the offered pharmacies had to be over the age of 18 years and had to have been invited on a pure volunteer basis. Second, we had approached consumers who had made their visit to selected pharmacies and made a demand for antibiotics, whether they had a prescription or not or had empty packings or strips of antibiotics. A separate space in the selected pharmacies was reserved for the participants to feel easy during the interview. Participants also had to be able to read and understand Urdu/Pashto (national/local language) and give informed consent orally or in writing. Consumers who had no physical or mental disability were included in the study. Participants who did not meet the inclusion requirements or who refused to participate in the study were excluded.

Development of Interview Guide

An interview guide was developed through an extensive literature survey based on a qualitative and explorative study design (Côté and Turgeon, 2005; Norris et al., 2013; Ancillotti et al., 2018). The final version of the semi-structured interview guide was approved by two experts and translated by a skilled academician to the local (Pashto) language. A minor revision was carried out as per the direction of the pharmacy experts. The principal investigator's first author had to compare the translated version with the original English one and achieve equivalence (Hendrickson et al., 2013). Pilot interviews were undertaken on three interviewees for the test of protocol for confirmation of understandability and validity. However, the pilot interviews were not included in the final study. The interview guide used in the current study is provided as **Supplementary File S1**. The summary of the topics for the in-depth interviews is shown in **Figure 1**. General population views about antibiotic resistance matter to know the literature gap.

Three major scenarios were established before the study. The first option was for the consumer/patient to visit the selected pharmacy with a prescription that includes antibiotics. The second option was that the consumers did not present doctor prescriptions and demanding for antibiotics. The last scenario was about the patient visiting a pharmacy to refill antibiotics without a prescription having empty strips/bottles or other medicine packaging. All the detailed scenarios with description and pharmacy staff approach are shown in **Figure 2** with rationale.

Sampling Technique

Purposive sampling is considered a basic technique of sampling and was used in the present qualitative research (Etikan et al., 2016). Moreover, the given techniques that were helpful in the representative sample and range of understandings could be obtained effectively to show the variety in the sampling (Côté and Turgeon, 2005; Etikan et al., 2016). The inclusion of the participants was purely based on their locality, age, education, and economical status. The principal investigator (FUK) visited all the selected data collection points of the community pharmacies.

The data collectors (pharmacists) were aware of the given regions and locality. The interviewers provided all the information orally and in writing to the nominees. The principal investigator arranged the interviews for the consented participants. The in-depth interviews were initiated until gaining the point of saturation. A total of 20 participants were recruited for the study, and not a single participant was dropped from the study.

Data Collection

Data were collected between September 2019 and January 2020. The criteria for saturation points had been used to establish the adequacy of the sample size. A two-stage approach was used to choose the participants. The first phase involved participants with antibiotic prescription who approached a pharmacy during working hours (9 a.m.–6 p.m.); identified and eligible participants were asked to join the study. The second stage was to choose and interview participants who agreed to engage in the study at a time and location that was pleasing to both sides. All interviews took place in Pashto. A qualified pharmacist carried out the semi-structured interviews. The

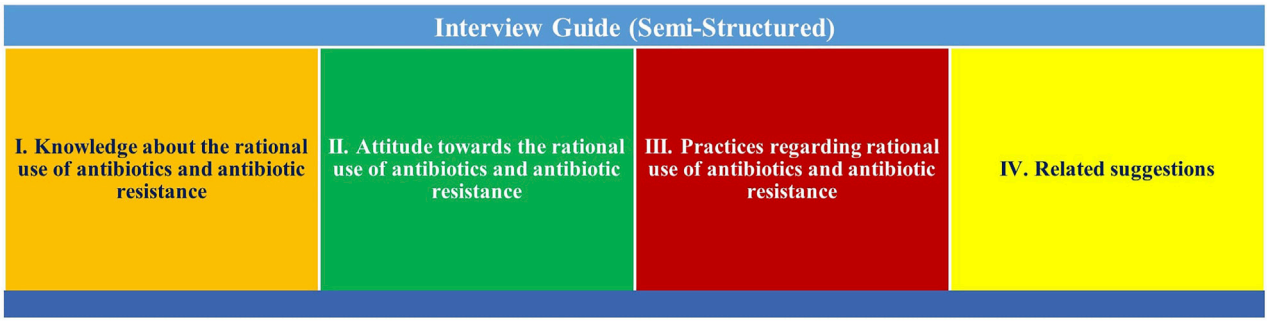

FIGURE 1 | In-depth semi-structured interview guide summary of the themes.

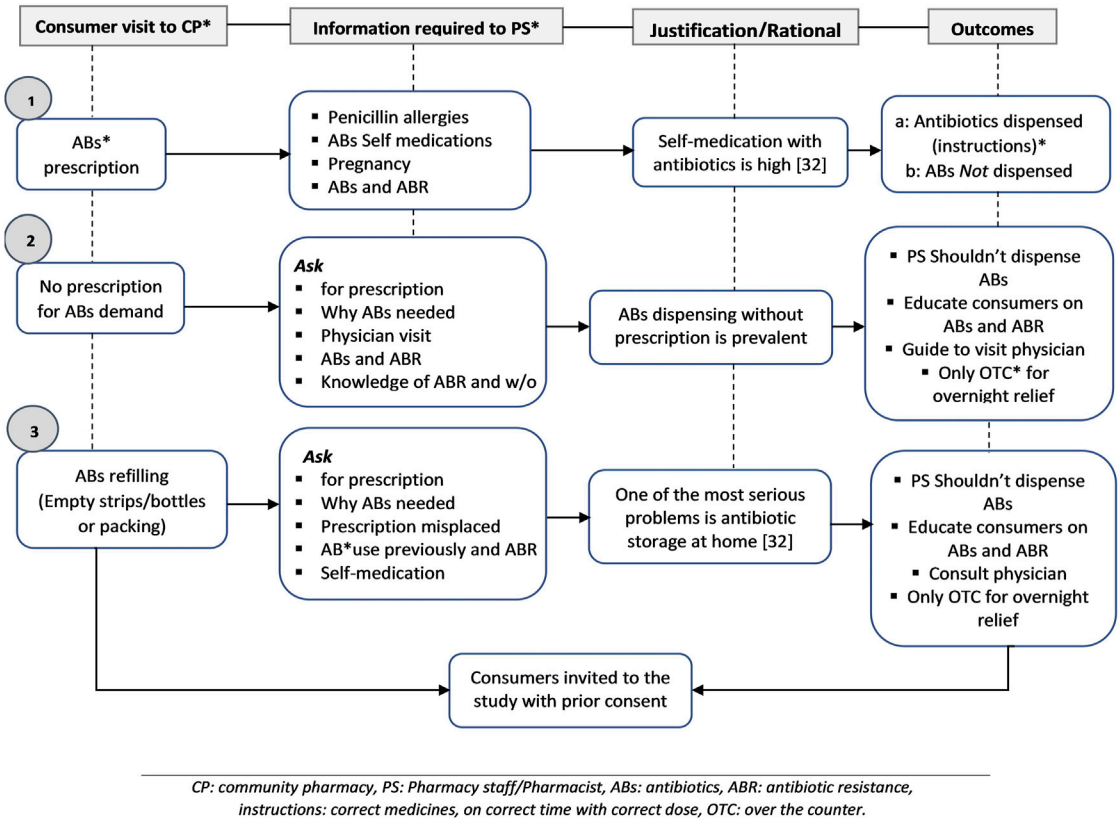

FIGURE 2 | Three scenarios for the consumer's approach to the selected community pharmacy.

transcripts and audio of the interviews were all transcribed. The participants of the study were able to read and hear taped interviews.

Analysis of Data

The analysis was carried out utilizing Braun and Clarke's thematic analytical approach (Braun and Clarke, 2006). Different steps were involved in data analytics processes from their thematic approach: knowledge of data, initial code development, thematic search, topic evaluation, identification and theme naming, and report development (Braun and Clarke, 2006). Initial data familiarization began when audio recordings were listened carefully, transcribed verbatim, and translated from Pashto to English. A forward and reverse transfer approach was tested on a group of transcripts for the translation process validation and was found to be reliable (Bowen, 2008). The initial codes for the study objectives were generated through open coding. To produce themes and sub-themes, the coded information was reduced. All authors examined the topics of the final theme. The emerging themes

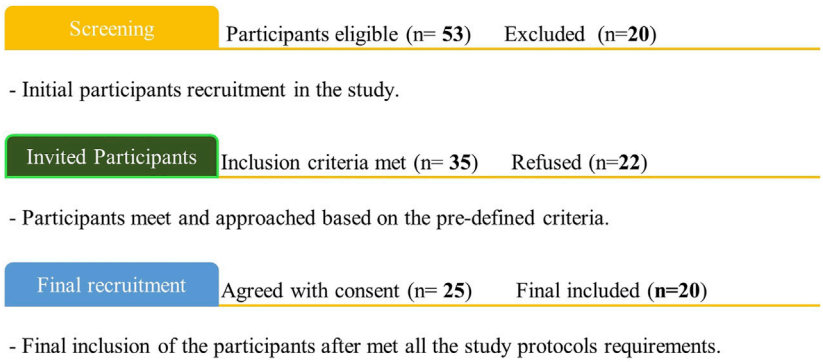

FIGURE 3 | process of the participants' recruitment.

TABLE 1 | Steps involved in data analysis.

Steps	Analysis	Accomplished task	Contribution of the research team	PI
Step-I	Getting to know the data	Recorded interviews Listening Transcription Reading and rereading	F.U.K (PI)	Reviewed the initials step
Step-II	Creating the initial codes	Codes assign to data Further code initiation	F.U.K (Farman) and THM	Finalized the codes
Step-III	Explore the themes	Classification of themes and into categories	F.U.K (PI) and S. S	Finalized the main themes
Step-IV	Themes critical review	Themes confirmation with the consistency	K.H, Z.K, and consultation with T. A	Reviewed the themes
Step-V	Identification with themes names	Themes are being refined even more	A.U.R confirmed with T. A	Final names assigned to the themes
Step-VI	Final report developed	Selection of the quotations	Y.H.K, F.U.K (PI) reviewed and confirmed by Y.F and Y.K	Final report confirmation

[a]*PI, principal investigator.*

had been cross-checked and had been concluded through frequent research team meetings (**Table 1**). For the word cloud visualization and data codings, the qualitative data analysis software (NVIVO-19) package was utilized.

RESULTS

A total of 20 in-depth interviews were conducted with a mean duration of 25.4 min. A detailed recruitment process from screening to final recruitment of the participants is described in **Figure 3**. Overall, n = 53 consumers were approached, 20 participants were excluded, and 22 refused to participate in the study. Finally, 20 participants were included in this study.

Most of the participants were males of age between 20 and 55 years (mean age of 35.1 years). The demographic parameters of study participants are described in **Table 2**.

Themes (4), sub-themes (6), and categories (31) were established, and the thematic analysis was applied. All themes included knowledge, attitude, practice, and rational use of antibiotics presented in detail. A cloud diagram was used to visualize the data as per the responses of the participants regarding antibiotics, ABR, and the perspective on the rules and regulations about the drug laws (**Figure 4**).

Participants' Knowledge

First, the participants' level of knowledge of antibiotics and the extent to which they (interviewees) understood how antibiotics were used were determined. Basic knowledge questions related to antibiotics were asked. All the respondents at three pharmacies replied with a satisfactory answer and that they had heard the word 'antibiotic.' Most of the interviewees defined the 'antibiotics' correctly (**Table 3**).

The responders' inability to explain when to take antibiotics and when to stop was the most eye-catching issue. As per their knowledge, "antibiotics should be administered if you have infections or any type of wound" without any confirmation

TABLE 2 | Respondents' (gender, age, and interview duration) details.

Respondent	Gender[a]	Age (years)	Interview (duration min)
Respondent-A	M	31	25
Respondent-B	M	43	24
Respondent-C	M	55	27
Respondent-D	M	26	30
Respondent-E	M	29	20
Respondent-F	M	31	26
Respondent-G	M	25	30
Respondent-H	M	29	27
Respondent-I	M	32	21
Respondent-J	M	38	23
Respondent-K	M	40	26
Respondent-L	M	45	29
Respondent-M	M	23	30
Respondent-N	F	47	20
Respondent-O	M	28	31
Respondent-P	M	22	30
Respondent-Q	M	26	25
Respondent-R	M	52	20
Respondent-S	M	37	23
Respondent-T	F	39	21

[a]*M, male; F, female*

that the infection-causing agent is a virus or bacterium (respondent-C).

Following basic questioning on antibiotics, queries on antibiotic usage as well as questions about ABR were asked. Overall knowledge about antibiotic resistance was poor, and after explaining the basic terms and definition of ABR to each participant, 9 out of 17 had heard the term ABR but ignored to ask from healthcare professionals. Only four respondents answered correctly, and two of them explained that ABR is a serious threat to global health.

Participants were unable to explain the exact factors behind, ABR but their knowledge about self-medication (antibiotics) was somehow satisfactory as one of the participants responded that "Many of us take antibiotics very easily without any hurdle" (respondent-J). Overall, interviewees had reported erythromycin as the most commonly used antibiotic. Self-recommendation (sharing of antibiotics with family members) of the antibiotics was common among the respondents (**Table 3**).

Participants' Attitude

Most of the participants had somehow been optimistic about antibiotics, and 13 participants believed that antibiotics had faster effect than any other medicines. Mostly everyone wanted to recover fast for daily activities, and use of antibiotics gave them extra strength, especially in infections. The majority of participants believed that many people got diarrhea after taking antibiotics and that they would rather take another medicine with the antibiotics if they got diarrhea.

Some of the interviewees had anger towards the local companies due to their low efficacy and preferred multinationally manufactured antibiotics. The participants had a favorable attitude toward the caring staff, as witnessed during the interview sessions, and the dealing person's or pharmacy staff's attitude at the pharmacy/drug outlet was important. Less than enough consumers who had a positive attitude were seen to be aware of antibiotic overuse (**Table 4**).

Participants' Practices

Participants' practice regarding antibiotics was linked with their past illness or storage of antibiotics after feeling better. Some of the interviewees visited the physician for treatment but were directed to the specific pharmacy/drug outlet to buy the prescribed medications.

Three respondents always got advice from the staff at drug stores to obtain antibiotics. Due to the unavailability of physicians, other participants easily got antibiotics by just explaining the symptoms. Most of the participants stored the leaflet and empty packs of the antibiotics if they needed the same medicines next time for the same illness as the stored strips would help to get antibiotics without a prescription.

Five interviewees responded that "we open a leaflet inside the pack of antibiotics to read the instruction in Urdu, especially for the powder form and how to make a solution correctly" (respondent-O).

Eight participants agreed that they should follow the physicians' instructions because the doctors know better. "I always listen to the physician for treatment processes and cross verify my prescription medicines with the physician once I obtain them from the pharmacy" (respondent-F).

Participants Believe in the Side Effects of Antibiotics

Ten respondents believed nausea and diarrhea occurred naturally due to any problem in the gastrointestinal system. The majority of the participants were unaware of the true cause and effects of incorrect antibiotic usage. Other interviewees explained that "because antibiotics are potent and might cause certain issues, it is recommended to take them with milk" (respondent-B) (**Table 5**).

Participants' Recommendations to Improve the Antibiotic Use

All the respondents provided many recommendations to improve the antibiotic rational/reasonable use. Ten of the interviewees' views were very positive to stop taking antibiotics from qualified healthcare professionals after physician consultation. Only a few interviewees had an answer such as "after completion of treatment, remaining antibiotics should be discarded on time" (respondent-L) (**Table 6**).

Eight participants, who belonged to the peripheral villages, responded that "the majority of the people in towns do not know about ABR." Antibiotics and resistance to antibacterial agents should be made known to the general population through public awareness initiatives. The main reason for self-medication is education, and most of the population is deprived of basic education. The government must take serious action to improve awareness about antibiotic use and resistance at the community level with a very easy medium of local languages.

The doctor is responsible for making an accurate diagnosis and prescribing the proper antibiotics as per need. The majority of respondents had never heard of a pharmacist, and only two were aware of pharmacists and their involvement in medicine dispensing.

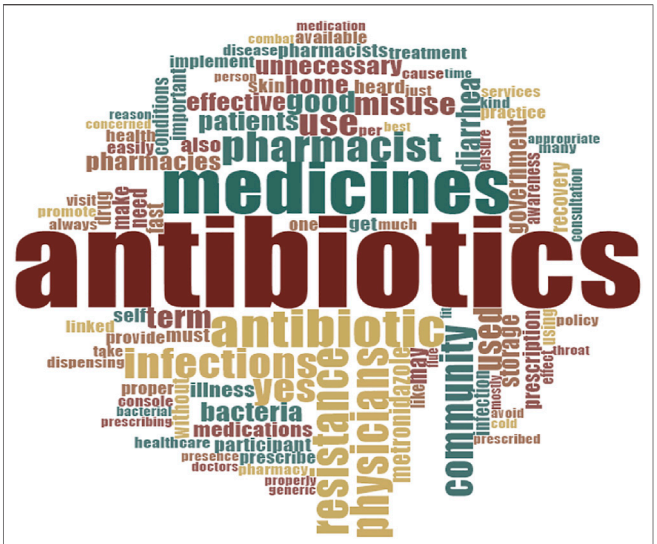

FIGURE 4 | Word cloud diagram depicting the antibiotics use and the perceptions of the participants related to antibiotic use and antibiotic resistance.

The lack of pharmacists' presence in the community pharmacies poses a threat to the spread of ABR. Most pharmacies, particularly in rural areas, are run by unqualified individuals. To limit antibiotic misuse, strict rules with severe fines implementation are required.

Antibiotic overuse can be curtailed by enforcing a policy that is implemented promptly. Three participants were well versed in the present provincial government regulations. Because the government failed to implement the new policies, five respondents did not believe in the government's policies. Every time the government attempted to implement a new policy, healthcare professionals created roadblocks to prevent the implementation of new regulations and policies.

Every pharmacy should have a pharmacist on duty who can educate consumers on how to appropriately use antibiotics. Existing regulations and a national action plan on antimicrobial resistance in Pakistan might be used to combat ABR.

DISCUSSION

This study is the first of its kind to evaluate the consumers' knowledge, attitudes, and practices toward antibiotic use and resistance in post-conflict areas of Pakistan. The AMR/ABR occurs mostly as a result of improper antibiotic use, and the current situation in Pakistan necessitates a great deal of attention. Antibiotics intake and behavior may be misinterpreted due to a lack of public understanding of self-medication with antibiotics (Alqarni and Abdulbari, 2019). Antibiotics are openly available without prescription in Pakistan, which is a unique situation to comprehend. Most people acquire and use medications based on their own needs, rather than seeing a doctor (Atif et al., 2019). ABR can be prevented by following the rules of right, i.e., using the right drugs (antibiotics) for the right patient. In healthcare settings ranging from hospitals to community pharmacies, the job of the qualified individual (pharmacist) is vital.

Our findings are in concordance with the results of other studies. According to many research reports conducted in developed and emerging EU nations, antibiotics are being misused by individuals for ordinary diseases (Väänänen et al., 2006; Kotwani et al., 2021). Antibiotic knowledge is undoubtedly complex in many aspects, yet we endeavored to give an antibiotic-related booklet to the participants in the hopes that it would have a positive impact on antibiotic attitudes and behaviors. Education is the most important factor for inappropriate antibiotic usage in a specific community, and ABR might be minimized to some extent

TABLE 3 | Participants' knowledge related to antibiotics and ABR.

Theme 1: knowledge related to antibiotics and antibiotic resistance		
Sub-themes	**Categories**	**Quotations**
Antibiotics (general) knowledge	Consumers somehow know the word antibiotics	Yes, I have heard the term antibiotics many times and mostly used when someone got injured or has wounds with peep (respondent-C)
	Believed antibiotics are always used in wounds and infections	For any type of disease (cold, fever, and flu) you can use antibiotics because of their work as per our experience and practices (respondent-M)
	The majority of the respondents were aware of common antibiotic names	The medicine erythromycin, which we use in our homes for throat illness or infection, is commonly available at drug stores (respondent-D)
	Virus and bacteria, confused recognition of the terms	Virus and bacteria are microorganisms and one can recommend antibiotics in such conditions which have referred to the virus or bacteria (respondent-B)
b) Knowledge of antibiotics resistance	Unaware of the term *"antibiotics resistance"*	Strange to know that resistance also exists in medicines, for the first time I heard 'antibiotic resistance' (respondent-A)
	Poor knowledge related to the terminology	I have heard the term antibiotics from my teacher, but I am unaware of antibiotic resistance and its mechanism (respondent-G)
	The actual cause is unknown	As per my understanding, antibiotics self-use is one of the reasons for antibiotic resistance (respondent-J)
	Wrong beliefs over misuse of antibiotics and resistance	I always use erythromycin for common cold and throat infections, as I recommend antibiotics to my family and friends (respondent-L)
		Antibiotics are the same drugs as 'paracetamol' we can get antibiotics easily (respondent-I)

TABLE 4 | Participants' attitude towards antibiotics.

Theme 2: attitude towards antibiotics		
Sub-themes	**Categories**	**Quotations**
Attitude toward antibiotic use	In many cases, a positive attitude was seen toward obtaining quality antibiotics	I always preferred multinational and good quality pharmaceutical medicine companies' antibiotics. I have experience with local companies' antibiotics, it's just a waste of money and has no effectiveness (respondent-B) I always ask about the pharmaceutical company name with its location and if the dealing person refer me local company antibiotics with a low price my trust of quality is down, then I refused to take an antibiotic (respondent-G) Whenever I need antibiotics, I go with physician prescriptions and ask for pharmacists to help but mostly pharmacists are absent at the pharmacy (respondent-H) I think the pharmacy/drug outlet staff is not concerned with the risk factors and misuse of antibiotics. The staff just looks at how much they will earn from the sale of antibiotics (respondent-A)
	Antibiotics can make a fast recovery	Antibiotics can heal infections and other conditions very quickly and that is the reason why I prefer antibiotics even for my sore throat as erythromycin works better than cold and flu medicines (respondent-I)
	To combat the diarrheal effect with metronidazole	Whenever I visit a pharmacy or drug store for antibiotics, I always request anaddition of metronidazole, which is the only prevention measure against diarrhea (respondent-G)
	The addition of paracetamol is mandatory to keep with antibiotics	I always self-add paracetamol with my antibiotics in case of fever with other conditions (respondent-C)

with increased understanding and education, according to prior research (Majumder et al., 2020). According to Khan et al., many factors, including sociological contextual factors and political and economic concerns, can play a stronger role in the fight against ABR (Krockow et al., 2019). Lack of knowledge and awareness about antibiotics is frequently the cause of antibiotic overuse (Aponte-González et al., 2019). A positive mindset, suitable information, and practices are all important factors in the proper and limited use of antibiotics (Napolitano et al., 2019). The AMR/ABR, which develops as a result of antibiotic abuse, is an issue that is currently receiving a lot of attention in Pakistan. Due to a lack of public information, attitude, and practices, antibiotic intake and behaviors may be misconstrued (Alqarni and Abdulbari, 2019). In Pakistan, antibiotics are readily available, which is a unique scenario to grasp (Atif et al., 2019). Consumers in our survey complained

TABLE 5 | Participants' practice toward antibiotics.

Theme 3: antibiotic practices		
Sub-themes	**Categories**	**Quotations**
Appropriate antibiotics consumption and healthcare professional consultation	Without consultation, antibiotics were used	The physician fee is too much for us, that is the reason we get antibiotics from drug stores without physicians and my relatives always help me in case they have antibiotics at home (respondent-C)
	The physician's charges were outranged and his direction to a specific pharmacy	I had visited a physician for my recent illness, and he directed me to buy my medicines from the nearby pharmacy inside his clinic. I have tried to purchase the same antibiotics with the brand name but could not find in other locations (respondent-J)
	The pharmacist was new to consumers and didn't ask about the medicines	Up till now, I did not even ask for the qualification from the medical/drug store staff and I do not know the pharmacist and the degree he holds (respondent-J)
	Lacking a pharmacist at the drug outlets/pharmacies	A pharmacist is a person who visits physicians to promote their products and I have never seen such a person at a medical store (respondent-I)
	The inappropriate practice of antibiotics	The pharmacy staff doesn't guide us on the appropriate use of antibiotics and just put marks on the packs, sometimes it confused me to take my medications on empty stomach or after a meal (respondent-D) Instructions in Urdu are very easy to read and follow and I do read the instructions carefully (respondent-E)
	Antibiotics without prescription from a nearby place	I can get the medicines (antibiotics) without a prescription from nearby drug outlet (respondent-C)
	Reused previous stored antibiotics and sharing of the prescription as well	I always keep the strips, leaflet, and empty bottle of antibiotics at home (respondent-K)
	No worries about nonprescription antibiotics laws and the side effects	In our hometown, you can get all the types of medicines without a prescription easily, but in a city some pharmacies ask for a doctor's prescription (respondent-E)

TABLE 6 | Suggestions for the appropriate use of antibiotics.

Theme 4: how to improve appropriate (rational) use of antibiotics		
Sub-themes	**Categories**	**Quotations**
a) Suggestions to healthcare professionals	Have moral fear for nonprescription antibiotics and put all the responsibility on the healthcare professional	It is very wrong to take nonprescription antibiotics without consultation with a physician (respondent-A)
	Need community-based awareness programs	Many of us thought whenever we get sick taking medicines and antibiotics will recover you faster (respondent-B)
		Awareness is the main factor in the reduction of antibiotic resistance at the community level, and everyone should know the danger of misuse of antibiotics (respondent-E)
	The pharmacist must educate people	Once I met a pharmacist at the main city in his pharmacy, he gave me bits of advice on my antibiotics and counseled me on the proper use of antibiotics. I appreciate such efforts made by pharmacists (respondent-C)
	A prescriber must not prescribe unnecessary antibiotics	Doctors always prescribe unnecessary medicines, especially antibiotics and we take each dose on time as per the salesman or dispensing person's instructions (respondent-D)
	Pharmacy staff must look twice at the antibiotic's prescription rather than business perspectives	Most of the time, whenever I visit to buy required medicines all the staff have more focus on dispensing. No one cares to educate the patient on the prescribed antibiotics (respondent-A)
b) Suggestions for government policies	Strict regulations must be applied as soon as possible	Doctors along with other allied health sectors always call strike if the government tries to put new changes in the healthcare system, especially the drug act (respondent-D)
	Assured qualified pharmacist presence at drug outlet	The concerned health authorities must assure qualified and well-educated people at pharmacies as most of the medical/drug stores does not have such a person to guide a layman on their medicines (respondent-C)
	Doctors should be in contact with pharmacists	The linkage between pharmacies and physicians is more important as I had an issue with my prescription and I came the other day for the prescription confirmation from my doctor (respondent-I)
	Ban on private practice	Many public sector specialists are doing private clinical practices, the government must ban such practices and doctors must be available at their concerned hospitals (respondent-J)
	Antibiotics have separate regulations	Unqualified, without a pharmacy degree, people usually dispense antibiotics which is dangerous (respondent-A)
	Awareness is the need of the time	Awareness is the key to successful treatment and I have attended some sessions related to self-medications and now I educate people and discourage self-medications (respondent-F)

that doctors or pharmacists did not freely offer comprehensive information (Lum et al., 2017). In both the developed and developing worlds, ABR is a major concern (Lum et al., 2017).

Convenience and cost savings have often been found in studies of merging nations such as China and several European countries (Melchiorre et al., 2013; Nawafleh et al., 2016; Hayat et al., 2019). Aslam et al. identified the most relevant determinants in LMICs for self-medication with antibiotics, concluding that education and mass media actions to raise public knowledge of the risks and side effects of self-medication were the most essential variables (Aslam et al., 2020). Contextual and complete research on characteristics influencing nonprescribed antibiotic usage, particularly in LMICs, is essential to effectively address antibiotic use and control the problem of ABR (Torres et al., 2019).

Even though the consumer sample was uneducated, there were variations in understanding, sensitivity, and concerns about antibiotics and ABR. Some of the inaccuracies, according to another study, suggest that clear communications from health experts, public health initiatives, and the media are essential all of the time (Lum et al., 2017). The individuals seemed to find antibiotics to be a source of hope. Antibiotics have a faster effect than any other treatment, according to more than ten participants, which is why they are not usually prescribed (Jacobs et al., 2019). According to another study, the majority of participants believed that many people get diarrhea after taking antibiotics and that if they received diarrhea, they would prefer to take another antibiotic-containing drug (Eibl et al., 2021). Other studies found that participants' usage of antibiotics was linked to previous illness or the storage of medications after they had recovered, when it comes to the usage of antibiotics, malpractices made numerous errors. As observed in both the current and previous studies, the majority of participants' activities were linked to the preservation of empty strips, packs of antibiotics for the next time usage of the same drugs for the same disease. The French Government supported an antibiotic campaign from 2002 to 2007 to reduce antibiotic use by a variety of actors, including the general public. This campaign proved successful in France, with a significant decrease in antibiotic use (Sabuncu et al., 2009). Such

initiatives and movements are required at the national level in Pakistan.

Furthermore, to avoid antibiotic scarcity, government agencies must develop strict regulations. Our findings demonstrate that most consumers are uninformed of existing antibiotics norms, laws, and national action plans, which are also misunderstood. According to a Jordanian study that made similar recommendations, controlling unnecessary antibiotics should be a key priority for physicians, pharmacists, and other regulatory organizations (Khasawneh et al., 2021). The matter must be brought to the attention of regulatory authorities, and better policy development based on our findings would be advantageous. For the culture to change, both the doctor and the pharmacist must collaborate professionally.

The lack of rigorous government laws and regulations was observed in our findings, as the interviewees were indifferent to the restrictions. ABR rates may be reduced because of community-based antimicrobial education efforts. According to studies, Pakistani physicians are supportive of antimicrobial stewardship efforts. The main problem is that rules and procedures differ from state to state (Hashmi et al., 2021; Jabeen et al., 2021).

This study is accompanied by a few limitations: first, it was conducted in post-conflict regions where the people had been through multiple military operations, and the findings may not be generalized to the other parts of the country. Second, many people have stories to tell, notably about the destruction of healthcare institutions and infrastructure in the scenic valley famed for tourism. Third, due to the cultural values of the data collection sites, fewer females took part in our study at the outset. A brief explanation of the laws and regulations, as well as Pakistan's national action plan on AMR, was provided before going on to note the suggestions on the proper use of antibiotics. Fourth, the outcome could have been influenced by consumer counsel. Furthermore, the study was only conducted in one district, but it might be expanded to other parts of Pakistan, using focus groups and interventional qualitative research. Following the in-depth interviews with the research participants, a brief intervention was conducted to present the relevant and critical information on antibiotic use, ABR, and measures to improve antibiotic consumption.

CONCLUSION

This study underscored the poor knowledge of residents from the conflicted regions regarding the appropriate use of antibiotics and ABR. Most of the study participants were aware of the term "antibiotic" without proper knowledge of antibiotic usage. However, the respondents could not grasp the concept of resistance completely. A somehow positive attitude was seen among the consumers, but the absence of a prescription, self-medication, antibiotic storage at home, and medicine sharing was found as significant contributors to incorrect antibiotic use. Malpractices in the use of antibiotics were common among the participants. It had also been observed that the leftover antibiotics were saved for future use after the therapy was completed. The absence of a qualified person, charges related to physicians visits, unnecessary prescriptions, and timely implementation of existing laws were the main areas suggested by the participants. Lack of awareness, remote health services, a shortage of pharmacists, and unregulated drug access had all been linked to insufficient antibiotic use. Further research is needed to address the issue of ABR in Pakistan's post-conflict areas.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon a reasonable request.

ETHICS STATEMENT

Ethical approval (No: 2019-1254-XJTU) has been granted by Health Science Center "Biomedical Ethics Committee" of Xi'an Jiaotong University.

AUTHOR CONTRIBUTIONS

Conceptual framework was developed by FUK (1st author); methodology and interview guide was developed by KH, TM, and YHK; thematic analysis was performed by FUK (3rd author), AUR, and TA; interpretation, and overall analysis were carried out by SS, ZK, and YK; Final draft review and editing by SKG; YF supervised the overall research project. All the authors have approved the final draft of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.881243/full#supplementary-material

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A National Survey of Community Pharmacists' Viewpoints About Pharmacovigilance and Adverse Drug Reaction Reporting in Saudi Arabia

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This study assessed the knowledge, attitudes, and practices of community pharmacists regarding pharmacovigilance and adverse drug reaction (ADR) reporting system in Saudi Arabia. A cross-sectional survey of community pharmacists from different regions in Saudi Arabia was performed through convenience sampling between November 2020 and January 2021. The responses were received from 1,172 community pharmacists. Most respondents (86.7%) were familiar with the National Pharmacovigilance and Drug Safety Center, and 830 (70.8%) knew about the ADR reporting form. The majority (94%) of the respondents agreed with the importance of reporting ADRs for patient care and national health. Although 92.2% of the participants asked their patients about ADRs, 90.2% agreed that more training programs are required to be organized by the Saudi Food and Drug Authority for healthcare professionals on the ADR detection and reporting system. Analgesic agents were the most common drug category for which ADRs were reported (67.4%). The majority (92.1%) of ADRs reportedly occurred in patients with chronic diseases. The study concluded that most community pharmacists in Saudi Arabia are knowledgeable and have good attitudes and practices regarding pharmacovigilance and ADR reporting.

Keywords: adverse drug reactions, community pharmacists, healthcare, pharmacovigilance, Saudi Arabia

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INTRODUCTION

Medication safety is an important global concern, and it is monitored and assessed using pharmacovigilance systems. Pharmacovigilance is defined as the activities linked to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) (World Health Organization, 2002). The Saudi Food and Drug Authority (SFDA) has established the Pharmacovigilance System for monitoring drug safety in Saudi Arabia under the guidance of the National Pharmacovigilance and Drug Safety Center (Alharf et al., 2018). The pharmacovigilance activities include the evaluation of ADRs, detection of signals, assessment of risks, evaluation of vaccine safety, and provision of periodic safety update reports (Alharf et al., 2018; Alwhaibi et al., 2020).

According to the World Health Organization (WHO), an ADR can be defined as any unpredictable, unintended effect of medication that is directly harmful at regular doses (Coleman and Pontefract, 2016). Globally, ADRs are recognized as the foremost cause of

morbidity and mortality (Wu et al., 2010; Silva et al., 2021). They adversely affect patients and their quality of life, leading to severe consequences such as hospitalizations, disabilities, life-threatening conditions, or even death. They also increase healthcare costs and have a negative impact on the healthcare systems (Bénard-Laribière et al., 2015; Geer et al., 2016; Veeren and Weiss, 2017; Patton and Borshoff, 2018; Alayed et al., 2019).

Giardina et al. (2018) reported an increase in hospitalization rates due to ADRs in Italy. In England, there was a 53.4% increase in the emergency admissions due to ADRs in 2014/2015 when compared to their frequency in 2008/2009 (Veeren and Weiss, 2017). In France, the incidence rate of patient hospitalizations because of ADRs was 3.6% (Bénard-Laribière et al., 2015). The incidence of ADR-related hospitalizations in Saudi Arabia has been described previously (Aljadhey et al., 2013; Alayed et al., 2019). Aljadhey et al. (2016) reported an ADR incidence of 6.1 per 100 admissions in Saudi Arabia. The medical burden of severe and fatal ADRs is high. In the United States of America and Sweden, fatal ADRs are the sixth and seventh leading causes of mortality, respectively (Lazarou et al., 1998; Wester et al., 2008). In Finland, 5% of deaths in a university central hospital was reported to be drug related (Juntti-Patinen and Neuvonen, 2002). Early detection and prevention of ADRs are urgent and should be a common goal for healthcare providers. Although there are limited methods for monitoring ADRs, they have a significant clinical impact.

Pharmacovigilance plays an important role in ensuring the safety of medications through the detection, assessment, and understanding of the adverse impact of pharmaceutical products (Härmark and Van Grootheest, 2008; Kumar et al., 2011). The most influential pharmacovigilance activity is the spontaneous reporting by healthcare practitioners (such as physicians, pharmacists, and nurses) of suspected ADRs that had not been identified during premarketing clinical trials (Güner and Ekmekci, 2019). National systems for reporting drug adverse reactions exist in almost every country. The FDA Adverse Event Reporting System (FAERS) was launched in 1998 in the United States. Healthcare professionals use the FAERS database to study the safety-related drug issues. Reporting ADRs through pharmacovigilance has been increasingly gaining attention globally (Sonawane and Hansen, 2015).

Underreporting is a significant challenge in pharmacovigilance programs (Alharf et al., 2018). The contribution of Saudi Arabia, along with other Middle Eastern countries, to global safety reporting is only 0.6% (Ahmad, 2014). This confirms that underreporting in Saudi Arabia is a significant concern, which may be attributed to the lack of knowledge and training in healthcare providers about pharmacovigilance and medication safety maintenance (Ahmad, 2014; Alshammari et al., 2017; AlShammari and Almoslem, 2018).

Studies involving community pharmacists in Saudi Arabia and assessing their understanding of ADR reporting and pharmacovigilance awareness are limited (Mahmoud et al., 2014; Ali et al., 2018; Cheema et al., 2019). The lack of pharmacovigilance as a subject of study in healthcare institutions is one of the primary reasons for healthcare providers' lack of knowledge of pharmacovigilance and ADR reporting (Mahmoud et al., 2014; Almandil, 2016). A systematic review has indicated that students' qualifications were inadequate in terms of describing ADRs or performing pharmacovigilance (Reumerman et al., 2018). However, several previous studies have indicated that pharmacy students had a higher level of knowledge than students from other healthcare schools (Sivadasan et al., 2014; Khan et al., 2015).

A community pharmacist remains the most easily accessible healthcare professional to the public and is likely the first person approached for drug information (Daly et al., 2020). The present study assessed community pharmacists' knowledge, attitudes, and practices regarding pharmacovigilance and ADR reporting in Saudi Arabia. This study confirms the presence of a certain educational gap in community pharmacists and argues for the need to facilitate specific educational programs to promote safe practices and support the pharmacovigilance environment for future community pharmacists.

MATERIALS AND METHODS

Study Design and Participants

A survey-based cross-sectional study was conducted from November 2020 to January 2021 in a convenience sample of community pharmacists from different regions of Saudi Arabia to assess their knowledge, attitudes, and practices regarding pharmacovigilance and ADR reporting.

Inclusion and Exclusion Criteria

All the registered community pharmacists in Saudi Arabia, regardless of sex and nationality, were included in this study. Community pharmacists were recruited using convenience sampling. This study excluded pharmacy technicians, hospital pharmacists, and those community pharmacists who were not registered by the Saudi Commission for Health Specialties (SCFHS).

Study Procedure

A self-administered Internet-based survey was conducted. A questionnaire was created to meet the specific objectives of this study, which was divided into four sections: demographic characteristics, knowledge, attitudes, and practices. The participants were asked to score statements based on how well they described their knowledge and training regarding the ways of ADR reporting to the SFDA using a 5-point Likert scale, starting from "not at all" = 1, "not well" = 2, "average" = 3, "well" = 4, and "very well" = 5. The score ranged 4–5, 2–3, 1–2, and <1, indicating good, fair, unsatisfactory, and poor knowledge, respectively. The questions were derived from the relevant literature and reviewed by two expert academic pharmacists from the College of Pharmacy of the Taif University. The modifications were made based on the reviewers' suggestions. The questionnaire was checked for face and content validity by five pharmacy staff members of the Department of Clinical Pharmacy at the Taif University College of Pharmacy. A pilot study was conducted with 15 community pharmacists experienced in pharmacy practice and research backgrounds. The questionnaire was

TABLE 1 | Demographic profile of the sample of community pharmacists.

Items	Measures	Frequency (n = 1,172)	Percentage (%)
Age	24–35 years	970	82.8
	36–45 years	177	15.1
	46–55 years	21	1.8
	>55 years	4	0.3
Gender	Male	1,126	96.1
	Female	46	3.9
Nationality	Saudi	94	8.0
	Non-Saudi	1,078	92.0
Educational level	BPharm	956	81.6
	PharmD	116	9.9
	Master	18	1.5
	PhD	82	7.0
Professional classification	Pharmacist	665	56.7
	Senior pharmacist	444	37.9
	Consultant pharmacist	63	5.4
Region	Western region	566	48.3
	Central Region	280	23.9
	Southern Region	214	18.3
	Eastern Region	83	7.1
	Northern Region	29	2.5
Pharmacy location	City	1,078	92.0
	Village	94	8.0
Type of community pharmacy	Chain pharmacy	1,127	96.2
	Independent pharmacy	45	3.8
Employment contract status	Full time	1,107	94.5
	Part time	62	5.3
	Temporary/casual	3	0.3
Years of experience	<5 years	312	26.6
	5–10 years	611	52.1
	11–20 years	238	20.3
	>20 years	11	0.9
Usual shift	Evening (8 a.m.–4 p.m.)	604	51.5
	Morning (4 p.m.–2 a.m.)	319	27.2
	Night (12 a.m.–8 a.m.)	249	21.2

written in both English and Arabic to avoid misunderstanding. The survey was designed to be simple, such that the participants could complete it in the shortest possible time, approximately 10–15 min.

Data Collection

A self-administered Internet-based survey was used to collect the data from pharmacists in Saudi Arabia from November 2020 to January 2021. The Google Forms survey was designed for online completion. The questionnaire link was sent to key persons in the pharmacy groups and *via* WhatsApp messenger to the Saudi Arabian community pharmacists' professional groups.

Ethical Considerations

The study received ethical approval from the Research and Ethics Committees at the Taif University (reference number: 42–144, and King Abdullah International Medical Research Center (IRB number: NRJ21J/195/08). All the participants provided informed consent, and confidentiality and anonymity were ensured. The data were anonymously downloaded in an Excel document from the Google Forms. No information was requested that could identify the participants.

Statistical Analyses

Microsoft Excel 2016 and IBM® SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, United States) were used to perform the statistical analyses. Descriptive statistics were used and presented as number (N) and percentage (%) to describe the knowledge, attitudes, and practices of the respondents related to pharmacovigilance and ADR reporting. The Chi-squared and Fisher's exact tests were performed to assess the differences in proportions, where appropriate. The statistical significance level was set a priori at $p < 0.05$.

RESULTS

Demographic Characteristics

The questionnaire was completed by 1,172 of the 1,231 contacted community pharmacists, indicating a response rate of 95.2%. The demographic profiles of the respondents are provided in **Table 1**. The majority of the respondents were 24–35 years old (970, 82.8%), men (1,126, 96.1%), non-Saudi (1,078, 92.0%), bachelor degree holders (956, 81.6%), professionally classified as pharmacists (665, 56.7%), and working in the Western region of Saudi Arabia (566, 48.3%). Most worked in cities (1,078,

TABLE 2 | Pharmacovigilance and ADR reporting related knowledge of the respondents.

Variable		Frequency (n = 1,172)	Percentage (%)
How familiar are you with the term "pharmacovigilance"?	Very familiar—I have a complete understanding	596	50.9
	Familiar—I have a basic understanding	489	41.7
	Heard of the term—cannot define it	56	4.8
	Never heard of the term	31	2.6
How familiar are you with the term "adverse effect"?	Very familiar—I have a complete understanding	649	55.4
	Familiar—I have a basic understanding	446	38.1
	Heard of the term—cannot define it	53	4.5
	Never heard of the term	24	2.0
Do you think all serious adverse effects are known before a drug is marketed?	Yes	509	43.4
	No	663	56.6
Do you know about the National Pharmacovigilance and Drug Safety Center administered by the SFDA?	Yes	1,016	86.7
	No	156	13.3
Are you familiar with the adverse drug reaction reporting form for healthcare professionals (Form No. ADR-1)?	Yes	830	70.8
	No	342	29.2
Do you know where to get the adverse drug reaction reporting form (Form No. ADR-1) from?	Yes	744	63.5
	No	428	36.5
Do you know to whom you should submit the drug reaction reports?	Yes	951	81.1
	No	221	18.9
How do you rate your knowledge and training about the method of reporting adverse drug reactions to the SFDA?	1	23	2.0
	2	46	3.9
	3	262	22.4
	4	463	39.5
	5	378	32.3
What do you think is the purpose of the National Pharmacovigilance and Drug Safety Center that is administered by the SFDA?			
To enhance patients' safety concerning the use of drugs	Yes	1,133	96.7
	No	39	3.3
To early detect and prevent frequent adverse drug reactions	Yes	1,130	96.4
	No	42	3.6
To identify predisposing factors to adverse drug reactions	Yes	1,092	93.2
	No	80	6.8
To identify rare adverse drug reactions	Yes	1,097	93.6
	No	75	6.4
To estimate the prevalence and incidence of adverse drug reactions	Yes	1,113	95.0
	No	59	5.0
To communicate with the international institutions working in pharmacovigilance	Yes	1,102	94.0
	No	70	6.0
To improve drug prescribing systems and regulations	Yes	1,096	93.5
	No	76	6.5
To access drug quality surveillance	Yes	1,091	93.1
	No	81	6.9
Which of the following scenarios would always be considered a severe adverse event by the SFDA?			
An adverse event that results in death	Yes	1,044	89.1
	No	128	10.9
An adverse event that results in hospitalization	Yes	1,046	89.2
	No	126	10.8
An adverse event that requires intervention to prevent permanent impairment/damage	Yes	1,037	88.5
	No	135	11.5
An adverse event that requires an emergency room visit	Yes	1,046	89.2
	No	126	10.8
An adverse event that results in congenital anomaly/birth defect	Yes	1,053	89.8
	No	119	10.2
An adverse event that is a life-threatening condition by a healthcare professional	Yes	1,064	90.8
	No	108	9.2
What aspect of adverse drug reaction deserves reporting by community pharmacists?			
The seriousness of the adverse drug reaction	Yes	1,028	87.7
	No	144	12.2
The unusualness of the adverse drug reaction	Yes	899	76.7
	No	273	23.2
Adverse drug reaction for the new drug only	Yes	735	62.7

(Continued on following page)

TABLE 2 | (*Continued*) Pharmacovigilance and ADR reporting related knowledge of the respondents.

Variable		Frequency (n = 1,172)	Percentage (%)
All types of adverse drug reactions	No	437	37.2
	Yes	1,001	85.4
	No	171	14.5

92.0%) and chain pharmacies (1,127, 96.2%). With respect to the employment status and experience, most had a full-time contract (1,107, 94.5%) and more than half (611, 52.1%) had 5–10 years of experience and worked in an evening shift (604, 51.5%).

Knowledge of Community Pharmacists Regarding Pharmacovigilance and Adverse Drug Reaction Reporting

The knowledge of the respondents regarding pharmacovigilance and ADR reporting is shown in **Table 2**. Half of the participants had indicated their understanding of the term "pharmacovigilance" on a 4-point Likert scale as very familiar (596, 50.9%) and the term "adverse effects" as also very familiar (649, 55.4%). More than half had indicated that not all serious adverse effects are not known before the drugs become marketed (663, 56.6%). The majority knew about the National Pharmacovigilance and Drug Safety Center administered by the SFDA (1,016, 86.7%). They were familiar with the ADR reporting form for healthcare professionals (Form No. ADR-1) (830, 70.8%), knew where to obtain it (744, 63.5%), and were aware of how the reporting form should be submitted (951, 81.1%). Less than half rated their knowledge and training about reporting ADRs to the SFDA at 4 of 5 points (463, 39.5%).

The respondents rated all the eight knowledge-related statements about the purpose of the National Pharmacovigilance and Drug Safety Center as high on a 2-point Likert scale. The majority considered the scenario of "an adverse event that is a life-threatening condition by a healthcare professional" as a severe adverse event by the SFDA (1,064, 90.8%), followed by "an adverse event that results in congenital anomaly/birth defect" (1,053, 89.8%). The aspect of adverse event reporting that was rated the highest was the "seriousness of the adverse events" (1,028, 87.7%) (**Table 2**).

There was a statistically significant effect of age on the responses of pharmacists to the question "Do you know about the National Pharmacovigilance and Drug Safety Center administered by the SFDA?" ($p < 0.05$). In addition, there were significant sex-dependent differences in the community pharmacists' perceived knowledge about the method of reporting ADRs to the SFDA ($p < 0.05$), and their responses to the questions "Do you think all serious drug reactions are known before a drug is marketed?" ($p < 0.05$) and "Do you know to whom you should submit the drug reaction reports?" ($p < 0.05$). Moreover, the perceived knowledge about the terms "pharmacovigilance" and "adverse drug reaction" was significantly affected by the educational level ($p < 0.05$), years of experience ($p < 0.05$), and professional classification ($p < 0.05$). Furthermore, there were significant differences by the educational level ($p < 0.05$) and years of experience ($p < 0.05$) in the responses of community pharmacists to the question "How do you rate your knowledge and training about the method of reporting adverse drug reactions to the SFDA?" Questions about their perceived knowledge of the ADR reporting form and to whom it was to be submitted were significantly affected by the years of experience ($p < 0.01$) and professional classification ($p < 0.05$). Work region and professional classification significantly influenced the response of the community pharmacists to the question on whether all serious adverse drug reactions were known before a drug was marketed ($p < 0.05$) (**Supplementary Table S1**).

Attitude of Community Pharmacists Toward Pharmacovigilance and Adverse Drug Reaction Reporting

The attitude of the participants toward pharmacovigilance and ADR reporting is shown in **Table 3**. The majority agreed that ADR reporting was significant for patient care (1,103, 94.1%) and positively contributed to the national health (1,108, 94.5%). However, more than half of the participants considered the ADR reporting system to be too complex and time consuming to complete (665, 56.7%). The majority asked their customers/patients about ADRs (1,081, 92.2%), agreed that the pharmacists have a professional obligation to report ADRs (1,057, 90.2%), and agreed that the SFDA should implement more training programs for the healthcare professionals related to ADRs detection and reporting (1,112, 94.9%). Less than half agreed that reporting ADRs should be voluntary for community pharmacists (527, 45.0%). The majority also believed that they would be encouraged to report more ADRs if incentives were present (932, 79.5%).

There were significant differences by age and educational level of the community pharmacists in their response to the question "In your opinion, to what extent the reporting of adverse drug reactions should be made mandatory for community pharmacists?" ($p < 0.05$). In addition, there were significant differences in the responses of the community pharmacists to the questions "Would you be encouraged to report more adverse drug reactions if there were incentives?" by age ($p < 0.05$), "Do you think that the adverse drug reaction reporting system is too complex to fill out and time consuming?" by sex ($p < 0.05$), and "Do you think adverse drug reaction reporting is significant for patient care?" by the educational level ($p < 0.05$) (**Table 4**).

Practices of Community Pharmacists

The practices of the community pharmacists regarding pharmacovigilance and ADRs reporting are shown in **Table 5**.

TABLE 3 | Attitudes of respondent pharmacists toward pharmacovigilance and ADR reporting.

Variable		Frequency (*n* = 1,172)	Percentage (%)
Do you think adverse drug reaction reporting is significant for patient care?	Agree	1,103	94.1
	Disagree	69	5.9
Do you think adverse drug reaction reporting has a positive contribution to our national health?	Agree	1,108	94.5
	Disagree	64	5.5
Do you think that the adverse drug reaction reporting system is too complex to fill out and time consuming?	Agree	665	56.7
	Disagree	507	43.3
Do you think the pharmacists should ask patients/customers about their adverse drug reactions?	Agree	1,081	92.2
	Disagree	91	7.8
Do you think that pharmacists have a professional obligation to report adverse drug reactions?	Agree	1,057	90.2
	Disagree	115	9.8
Do you think the SFDA should implement more training programs for healthcare professionals on adverse drug reaction detection and reporting?	Agree	1,112	94.9
	Disagree	60	5.1
In your opinion, to what extent the reporting of adverse drug reactions should be made mandatory for community pharmacists?	Mandatory	424	36.2
	Voluntary	527	45.0
	Not necessary to report	49	4.2
	Not sure	172	14.7
Would you be encouraged to report more adverse drug reactions if there were incentives?	Yes	932	79.5
	No	240	20.5

TABLE 4 | Attitudes of community pharmacists toward pharmacovigilance and adverse drug reaction reporting depending on the characteristics of the respondents.

Items	Comparisons				*p*-value
In your opinion, to what extent the reporting of adverse drug reactions should be made mandatory for community pharmacists?	Age				
	24–35 years	36–45 years	46–55 years	>55 years	<0.05
Mandatory	353 (36.4%)	62 (35.0%)	9 (42.9%)	0 (0.0%)	
Voluntary	433 (44.6%)	85 (48.0%)	9 (42.9%)	0 (0.0%)	
Not necessary to report	44 (4.5%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	
Not sure	140 (14.4%)	25 (14.1%)	3 (14.3%)	4 (100.0%)	
Total	970 (100.0%)	177 (100.0%)	21 (100.0%)	4 (100.0%)	
Would you be encouraged to report more adverse drug reactions if there were incentives?	24–35 years	36–45 years	46–55 years	>55 years	
Yes	788 (81.2%)	123 (69.5%)	18 (85.7%)	3 (75.0%)	<0.05
No	182 (18.8%)	54 (30.5%)	3 (14.3%)	1 (25.0%)	
Total	970 (100.0%)	177 (100.0%)	21 (100.0%)	4 (100.0%)	
Do you think that the adverse drug reaction reporting system is too complex to fill out and time consuming?	Gender				
	Male		Female		
Agree	646 (57.4%)		19 (41.3%)		<0.05
Disagree	480 (42.6%)		27 (58.7%)		
Total	1,126 (100.0%)		46 (100.0%)		
Do you think adverse drug reaction reporting is significant for patient care?	Educational Level				
	B. Pharm	Pharm. D	Master	PhD	
Agree	905 (94.7%)	104 (89.7%)	15 (83.3%)	79 (96.3%)	<0.05
Disagree	51 (5.3%)	12 (10.3%)	3 (16.7%)	3 (3.7%)	
Total	956 (100.0%)	116 (100.0%)	18 (100.0%)	82 (100.0%)	
In your opinion, to what extent the reporting of adverse drug reactions should be made mandatory for the community pharmacists?	B. Pharm	Pharm. D	Master	PhD	
Mandatory	343 (35.9%)	45 (38.8%)	3 (16.7%)	33 (40.2%)	<0.05
Voluntary	434 (45.4%)	47 (40.5%)	13 (72.2%)	33 (40.2%)	
Not necessary to report	31 (3.2%)	14 (12.1%)	0 (0.0%)	4 (4.9%)	
Not sure	148 (15.5%)	10 (8.6%)	2 (11.1%)	12 (14.6%)	
Total	956 (100.0%)	116 (100.0%)	18 (100.0%)	82 (100.0%)	

Most respondents had served more than 100 customers/patients daily (699, 59.6%). Among the respondents, 33.9% had never reported an ADR to the SFDA; however, 25.9% had reported an ADR more than three times. The frequency of observing ADRs in their customers/patients was rated as "sometimes" (549, 46.8%) and "always" (110, 9.4%). The respondents were asked to rate the frequency of ADR reporting for 18 different products on a 2-point Likert scale. ADRs were most frequently associated with

TABLE 5 | Pharmacovigilance and ADR reporting practices of respondent pharmacists.

Variable		Frequency (n = 1,172)	Percentage (%)
How many patients/customers per pharmacist are served daily?	<20	21	1.8
	20–50	71	6.1
	51–100	381	32.5
	>100	699	59.6
How often do you see adverse drug reactions among patients/customers?	Always (100%)	110	9.4
	Often (>50%)	152	13.0
	Sometimes (<50%)	549	46.8
	Rarely (≈20%)	326	27.8
	Never (0%)	35	3.0
Have you ever reported an adverse drug reaction to the SFDA?	Yes (>3 times)	304	25.9
	Yes (2 or more times)	248	21.2
	Yes (1 time)	223	19.0
	No (0 time)	397	33.9
Have you ever reported an adverse drug reaction related to the following?			
Herbal products and supplements	Yes	518	44.1
	No	654	55.8
Cosmetic products	Yes	493	42.0
	No	679	57.9
Vaccines	Yes	341	29.0
	No	831	70.9
Cardiovascular agents	Yes	575	49.0
	No	597	50.9
Respiratory tract agents	Yes	532	45.3
	No	640	54.6
Gastrointestinal agents	Yes	591	50.4
	No	581	49.5
Neurological agents	Yes	516	44.0
	No	656	55.9
Psychiatric agents	Yes	522	44.5
	No	650	55.4
Hormonal agents	Yes	439	37.4
	No	733	62.5
Diabetic agents	Yes	528	45.0
	No	644	54.9
Genitourinary agents	Yes	433	36.9
	No	739	63.0
Immunological agents	Yes	389	33.1
	No	783	66.8
Bone and joints agents	Yes	475	40.5
	No	697	59.4
Anti-infective agents	Yes	515	43.9
	No	657	56.0
Eyes, ears, nose, and throat agents	Yes	450	38.3
	No	722	61.6
Medical devices and supplies	Yes	558	47.6
	No	614	52.3
Analgesic agents	Yes	790	67.4
	No	382	32.5
Dermatological agents	Yes	501	42.7
	No	671	57.2
From your experience, who is more likely to have adverse drug reactions?			
Babies (<6 years)	Yes	839	71.5
	No	333	28.4
Children (6–18 years)	Yes	774	66.0
	No	398	33.9
Adults (men)	Yes	693	59.1
	No	479	40.8
Adults (women)	Yes	716	61.0
	No	456	38.9
Pregnant women	Yes	952	81.2
	No	220	18.7
Old people	Yes	1,034	88.2
	No	138	11.7
People with chronic disease	Yes	1,079	92.0
	No	93	7.9

TABLE 6 | Pharmacovigilance and adverse drug reaction reporting practices of community pharmacists depending on the characteristics of the respondents.

Items	Comparisons				*p*-value
How often do you see adverse drug reactions among patients?	Age				
	24–35 years	36–45 years	46–55 years	>55 years	
Always	99 (10.2%)	7 (4.0%)	4 (19.0%)	0 (0.0%)	<0.05
Often	116 (12.0%)	33 (18.6%)	3 (14.3%)	0 (0.0%)	
Sometimes	459 (47.3%)	76 (42.9%)	12 (57.1%)	2 (50.0%)	
Rarely	268 (27.6%)	56 (31.6%)	1 (4.8%)	1 (25.0%)	
Never	28 (2.9%)	5 (2.8%)	1 (4.8%)	1 (25.0%)	
Total	970 (100.0%)	177 (100.0%)	21 (100.0%)	4 (100.0%)	
Have you ever reported an adverse drug reaction to the SFDA?	Gender				
	Male		Female		
Yes (>3 times)	304 (27.0%)		0 (0.0%)		<0.05
Yes (2 or more times)	245 (21.8%)		3 (6.5%)		
Yes (1 time)	217 (19.3%)		6 (13.0%)		
No (0 time)	360 (32.0%)		37 (80.4%)		
Total	1,126 (100.0%)		46 (100.0%)		
How often do you see adverse drug reactions among patients?	Male		Female		
Always	107 (9.5%)		3 (6.5%)		<0.05
Often	149 (13.2%)		3 (6.5%)		
Sometimes	531 (47.2%)		18 (39.1%)		
Rarely	308 (27.4%)		18 (39.1%)		
Never	31 (2.8%)		4 (8.7%)		
Total	1,126 (100.0%)		46 (100.0%)		
Have you ever reported an adverse drug reaction to the SFDA?	Educational level				
	B. Pharm	Pharm. D	Master	PhD	
Yes (>3 times)	262 (27.4%)	17 (14.7%)	4 (22.2%)	21 (25.6%)	<0.05
Yes (2 or more times)	199 (20.8%)	21 (18.1%)	7 (38.9%)	21 (25.6%)	
Yes (1 time)	181 (18.9%)	19 (16.4%)	2 (11.1%)	21 (25.6%)	
No (0 time)	314 (32.8%)	59 (50.9%)	5 (27.8%)	19 (23.2%)	
Total	956 (100.0%)	116 (100.0%)	18 (100.0%)	82 (100.0%)	
Have you ever reported an adverse drug reaction to the SFDA?	Years of experience				
	<5 years	5–10 years	11–20 years	>20 years	
Yes (>3 times)	34 (10.9%)	180 (29.5%)	85 (35.7%)	5 (45.5%)	<0.05
Yes (2 or more times)	48 (15.4%)	145 (23.7%)	52 (21.8%)	3 (27.3%)	
Yes (1 time)	63 (20.2%)	122 (20.0%)	36 (15.1%)	2 (18.2%)	
No (0 time)	167 (53.5%)	164 (26.8%)	65 (27.3%)	1 (9.1%)	
Total	312 (100.0%)	611 (100.0%)	238 (100.0%)	11 (100.0%)	
How often do you see adverse drug reactions among patients?	<5 years	5–10 years	11–20 years	>20 years	<0.05
Always	31 (9.9%)	60 (9.8%)	16 (6.7%)	3 (27.3%)	
Often	36 (11.5%)	76 (12.4%)	39 (16.4%)	1 (9.1%)	
Sometimes	126 (40.4%)	306 (50.1%)	110 (46.2%)	7 (63.6%)	
Rarely	101 (32.4%)	157 (25.7%)	68 (28.6%)	0 (0.0%)	
Never	18 (5.8%)	12 (2.0%)	5 (2.1%)	0 (0.0%)	
Total	312 (100.0%)	611 (100.0%)	238 (100.0%)	11 (100.0%)	
Have you ever reported an adverse drug reaction to the SFDA?	Professional classification				
	Pharmacist	Senior pharmacist	Consultant pharmacist		
Yes (>3 times)	145 (21.8%)	135 (30.4%)	24 (38.1%)		<0.05
Yes (2 or more times)	107 (16.1%)	123 (27.7%)	18 (28.6%)		
Yes (1 time)	123 (18.5%)	93 (20.9%)	7 (11.1%)		
No (0 time)	290 (43.6%)	93 (20.9%)	14 (22.2%)		
Total	665 (100.0%)	444 (100.0%)	63 (100.0%)		
How often do you see adverse drug reactions among patients?	Pharmacist	Senior pharmacist	Consultant pharmacist		
Always	56 (8.4%)	45 (10.1%)	9 (14.3%)		<0.05
Often	90 (13.5%)	50 (11.3%)	12 (19.0%)		
Sometimes	297 (44.7%)	222 (50.0%)	30 (47.6%)		
Rarely	193 (29.0%)	122 (27.5%)	11 (17.5%)		
Never	29 (4.4%)	5 (1.1%)	1 (1.6%)		
Total	665 (100.0%)	444 (100.0%)	63 (100.0%)		

analgesic agents (790, 67.4%), followed by gastrointestinal agents (591, 50.4%), cardiovascular agents (575, 49.1%), and medical devices and supplies (558, 47.6%). ADRs were most commonly noted in people with chronic diseases (1,079, 92.1%), followed by older adults (1,034, 88.2%) and pregnant women (952, 81.2%), whereas they were least frequent in adult men (693, 59.1%) (**Table 5**).

There were statistically significant effects of age, sex, years of experience, and professional classifications of the community pharmacists on their response to the question "How often do you

see adverse drug reactions among patients?" ($p < 0.05$). In addition, sex, educational level, years of experience, and professional classifications influenced the responses of the community pharmacists to the question "Have you ever reported an adverse drug reaction to the SFDA?" ($p < 0.05$) (**Table 6**).

DISCUSSION

The present study evaluated the knowledge, attitudes, and practices of community pharmacists regarding pharmacovigilance and ADR reporting in Saudi Arabia. To the best of our knowledge, this study is the first to assess current practices in community pharmacies regarding pharmacovigilance and ADR reporting in different regions of Saudi Arabia. The results of our survey indicated that the majority of community pharmacists were aware of pharmacovigilance and ADR reporting. Their attitudes to ADR reporting were favorable. It is believed that ADR reporting must be made compulsory for all community pharmacists.

In contrast to studies conducted in Al Riyadh and Ash Sharqiyah, our study shows that community pharmacists have high awareness and knowledge regarding pharmacovigilance and methods of reporting ADRs (Bawazir, 2006; Khan, 2013; Mahmoud et al., 2014; AlRuthia et al., 2018; Al Doughan et al., 2019). Most of the respondents had 5–10 years of working experience with a full-time contract and had served more than 100 patients/customers daily. The satisfactory level of awareness might be explained by their years of experience as well as the efforts of the SFDA to establish a national platform, the National Pharmacovigilance Center (Hadi et al., 2013). This national platform aims to enforce regulations to improve current practices and adopt good pharmacy practice standards and guidelines for pharmacovigilance, as well as ADR detection and reporting processes in community pharmacists (Alshammari et al., 2017; Saudi Food and Drug Authority, 2021a).

The National Pharmacovigilance Center's collective and continued efforts to initiate and encourage online and paper reporting of ADRs have been successful and have brought several benefits (Saudi Food and Drug Authority, 2021c). In a similar context, most participants in the present study have agreed that community pharmacists have a professional obligation to report ADRs. They were familiar with the ADR reporting form (Form No. ADR-1), knew where to obtain the form, and to whom they should submit it. However, they also agreed that the SFDA should implement more continuous training programs for healthcare professionals regarding ADR detection and reporting system.

The majority agreed that ADR reporting is important for patient safety and contributes positively to national health. These results are consistent with those of previous studies (Bawazir, 2006; Khan, 2013; Mahmoud et al., 2014; AI Doughan et al., 2019). The majority (90%) of the respondents agreed that pharmacists should ask their patients/customers about ADRs and 36% indicated that reporting ADRs should be made compulsory for community pharmacists.

The good level of knowledge and positive attitudes reported in the current study are comparable with responses of community pharmacists in other countries, namely, the United Kingdom, Poland, Lebanon, and Yemen (Zimmermann et al., 2016; Al-Worafi et al., 2017; Hajj et al., 2018; Hughes and Weiss, 2019). In addition, pharmacists had the highest level of knowledge and most positive attitudes toward pharmacovigilance and ADR reporting among all healthcare professionals in many countries. In Ireland, pharmacists had higher knowledge and awareness of ADR reporting than other healthcare practitioners (O'Callaghan et al., 2018). In addition, pharmacists and pharmacist technicians exhibited the highest rate of pharmacovigilance awareness among healthcare providers in Saudi Arabia (Almandil, 2016). The level of knowledge and attitudes of the respondents in our study were better than those reported for nursing and dentistry students (Sivadasan et al., 2014; Khan et al., 2015). In particular, Sivadasan et al. (2014) stated that the level of knowledge, understanding, and awareness of pharmacovigilance and ADR reporting was better in pharmacy students than in medical students. A study by Khan et al. (2015) found that pharmacy students had better knowledge and more positive attitudes toward handling and reporting ADRs than medical students did.

Most of the participants in the current study reported that receiving an incentive would encourage them to report more ADRs. Some studies have also reported the favorable impact of various incentives on ADR reporting (Pedrós et al., 2009; Gonzalez-Gonzalez et al., 2013; Chang et al., 2017; Ali et al., 2018). It should be noted that the SFDA periodically publicly acknowledges and commends community pharmacies for their commitment to drug safety standards by monitoring ADRs and reporting (Saudi Food and Drug Authority, 2021b). Although the respondents in this study expressed good knowledge and positive attitudes toward pharmacovigilance and ADR reporting, their practice of ADR reporting was unsatisfactory and did not reflect their knowledge and attitude. This may be due to different factors, such as the high number of patients served by each pharmacist, complexity of the ADR reporting system, time factor, lack of training programs regarding ADR detection and reporting provided by the SFDA to healthcare professionals, and the absence of incentives provided to the pharmacist as encouragement to enhance ADR reporting. Underreporting of ADRs by pharmacists is common not only in Saudi Arabia but also globally. The reasons for underreporting vary in different countries, for example, the lack of time was considered the most significant reporting barrier in Australia (Li et al., 2018), whereas in Germany, the lack of good training and long forms to complete were considered as dominant negative factors (Laven et al., 2018). There is a critical need globally to resolve the reporting barriers to improve ADR reporting.

The respondents in the present study disclosed that the frequency of observing ADRs in patients/customers can be categorized as "sometimes," i.e., in less than half of cases. ADRs were most frequently observed with analgesic agents, in elderly patients/customers, and in people with chronic diseases.

These results agree with those of previous studies (Almubark et al., 2020). Although this study assessed the national knowledge, practices, and attitudes of community pharmacists toward pharmacovigilance and ADR reporting in a sample of pharmacists of a sufficient size, it was an Internet-based survey that might have been affected by reporting bias. Additionally, the respondents may not have been willing to reveal deficiencies in their practices.

The sample in the present study disclosed that the frequency of observing ADRs in their patients/customers as "sometimes". The highest category was analgesic agents, elderly patients/customers, and people with a chronic disease. These results are in agreement with prior research (Almubark et al., 2020). Although the study reported the national knowledge, practice, and attitude of community pharmacists toward pharmacovigilance and ADRs reporting with a sufficient sample size, it was an Internet-based survey which might be affected by some reporting bias. In addition, they may not have been willing to reveal their practice deficiencies.

Practical Implications

The results of this study have several practical implications. More training in pharmacovigilance and ADR reporting is required, given the importance of improving the understanding of and need to minimize drug-related problems. Lecture-based seminars on pharmacovigilance and ADR reporting may enhance the knowledge, attitudes, and practices of healthcare students. The familiarity of students with ADRs and methods to assess their cause and severity needs to be increased. The essential elements of the comprehensive pharmacovigilance curriculum were developed by the WHO and International Society of Pharmacovigilance to assist integration in the healthcare school curriculum. The integration of these initiatives is likely to improve the level of knowledge of community pharmacists regarding pharmacovigilance.

CONCLUSION

Most community pharmacists in Saudi Arabia are knowledgeable and have good attitudes and practices regarding pharmacovigilance and ADR reporting. Our findings illustrate an improvement in the knowledge, attitudes, and practices of the community pharmacists regarding pharmacovigilance and ADR reporting. The SFDA should implement good pharmacy practice guidelines and standards and adopt continuous educational programs to enhance the current practices of community pharmacists regarding pharmacovigilance and ADR reporting.

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 received ethical approval from the research and ethics committee at Taif University with reference number: 42–144 and from the King Abdullah International Medical Research Center (KAIMRC) with IRB# NRJ21J/195/08. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MYA: writing—original draft preparation, methodology, software, data curation, and analysis. MMA: conceptualization, methodology, data analysis, writing—original draft, reviewing, and editing.

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SUPPLEMENTARY MATERIAL

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Drug-Related Hospital Admissions *via* the Department of Emergency Medicine: A Cross-Sectional Study From the Czech Republic

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Background: Drug-related hospital admissions (DRAs) represent a significant problem affecting all countries worldwide. This study aimed to determine the prevalence and preventability of DRAs, identify the most common medications involved in DRAs, the most common clinical manifestations of DRAs and describe the preventability aspects of DRAs.

Methods: This cross-sectional study examined unplanned hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine in August–November 2018. Data were obtained from electronic medical records. The methodology of DRA identification was adapted from the OPERAM DRA adjudication guide.

Results: Out of 1252 hospital admissions, 195 DRAs have been identified (145 related to treatment safety, 50 related to treatment effectiveness). The prevalence of DRAs was 15.6% (95% CI 13.6–17.6). The most common medication classes involved in DRAs related to treatment safety were Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, and Beta blocking agents. The most common medication classes involved in DRAs related to treatment effectiveness included Diuretics, Antithrombotic agents, Drugs used in diabetes, Agents acting on the renin-angiotensin system, and Lipid modifying agents. Gastrointestinal disorders were the leading causes of DRAs related to treatment safety, while Cardiac disorders were the leading causes of DRAs related to treatment effectiveness. The potential preventability of DRAs was 51%. The highest share of potential preventability in medication classes repeatedly involved in DRAs related to treatment safety was observed for Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. Potentially preventable DRAs related to treatment safety were most commonly associated with inappropriate drug selection, inappropriate monitoring, inappropriate dose selection, and inappropriate lifestyle measures. On the contrary, DRAs related to treatment effectiveness were more commonly associated with medication nonadherence.

Conclusion: It should be emphasized that in most DRAs, medications were only a contributory reason of hospital admissions and that benefits and risks have to be carefully balanced. It is highlighted by the finding that the same medication classes (Antithrombotic agents and Diuretics) were among the most common medication classes involved in DRAs related to treatment safety and simultaneously in DRAs related to treatment effectiveness. The study highlighted that apart from problems related to prescribing, problems related to monitoring and patient-related problems represent significant preventability aspects.

Keywords: adverse drug event, drug-related problem, hospitalization, prevalence, preventability, Czech Republic

INTRODUCTION

Drug-related hospital admissions (DRAs) represent a significant problem affecting all countries over the world. Although many studies have focused on adverse drug reactions (ADRs) leading to hospital admissions, fewer studies have addressed broader concepts, such as adverse drug events (ADEs) and drug-related problems (DRPs).

Multiple terms and definitions are used to describe medication harm in research and clinical practice (Falconer et al., 2019). ADEs could be defined as injuries caused by drug use that encompass ADRs and harm resulting from medication errors—they are the targets of broader efforts to improve patient safety (Nebeker et al., 2004).

A DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network Europe Association, 2020). DRPs are divided into two main domains—DRPs related to treatment effectiveness (problem with the effect of the pharmacotherapy) and DRPs related to treatment safety (patient suffers, or could suffer, from an ADE). The third domain ("Other") includes unnecessary drug treatment (Pharmaceutical Care Network Europe Association, 2020).

While on the one hand, the use of medications might lead to ADEs, their use reduces hospital admissions as well. For example, the following medication classes were found to reduce emergency hospitalizations: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone receptor antagonists, statins, long-acting muscarinic antagonists, and long-acting beta-2 adrenoceptor agonists (Bobrovitz et al., 2018). Therefore, DRPs related to treatment effectiveness should also be the focus when studing DRAs.

So far, only a few studies have examined the extent to which DRPs contribute to hospital admissions. Recently, new tools (Thevelin et al., 2018; Kempen et al., 2019) have also incorporated DRPs related to treatment effectiveness. These include omission of an evidence-based drug, inappropriate selection of a drug or a dosage form, inappropriate administration, subtherapeutic dose, too short duration of treatment, medication nonadherence, inappropriate monitoring, inappropriate discontinuation, drug-drug interaction and drug-food interactions.

The concern should not only be minimizing the risks of pharmacotherapy, but also maximizing the effectiveness of pharmacotherapy (ensuring that the goals of treatment are reached). DRPs can be prevented primarily by appropriate pharmacotherapy (selection of medications and their formulation, dosing scheme, and duration of treatment—both prescribed and over-the-counter medications), appropriate use and administration of medications, appropriate medication adherence, appropriate monitoring (whether treatment goals are reached, risk factors of complications of the disease, occurrence of ADR and risk factors of ADRs), and appropriate lifestyle measures (e.g., fluid and food intake, smoking, alcohol consumption, sunscreen use).

As indicated by the definition of DRP, a DRP can be either potential (possibly leading to real problems for the patient) or actual/manifest (the problem already impacts the patient and his therapy) (Westerlund, 2019). Admission to the hospital can be a measurable outcome of manifest DRP.

Numerous studies have been conducted on DRAs from high-income countries. However, there are fewer studies from low- and middle-income countries and central and eastern Europe. This is the first study from the Czech Republic that examines DRAs without any department or age limit. In previous studies from the Czech Republic, the population studied was either from the pediatric ward (Langerová et al., 2014) or the geriatric ward (Maříková et al., 2021).

Reducing avoidable medication-related harm remains a difficult global patient safety challenge. Studies measuring the scope and nature of preventable ADEs can provide essential knowledge for the development of risk minimization measures.

The study aimed to provide information on:

a) the prevalence of DRAs to the University Hospital Hradec Králové *via* the department of emergency medicine,
b) the most common medications involved in DRAs,
c) the most common clinical manifestations of DRAs,
d) the potential preventability of DRAs,
e) medications most frequently associated with potentially preventable DRAs,
f) the most common clinical manifestations of potentially preventable DRAs, and
g) preventability aspects most frequently associated with potentially preventable DRAs.

METHODS

Study Design and Setting

This observational cross-sectional study examined hospital admissions to the University Hospital Hradec Králové *via* the

department of emergency medicine in order to identify those which are drug-related. Hospital admissions were identified using a register of all hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine. Most of the patients were admitted to the departments of internal medicine (49%), surgery (26%), neurology (10%), pneumology (4%), anesthesiology, resuscitation and intensive medicine (3%), oncology and radiotherapy (3%), orthopedics (2%), infectious diseases (1%), and psychiatry (1%). The number of hospital admissions *via* the department of emergency medicine of the University Hospital Hradec Králové is approximately 450 per month.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for the reporting of the study (von Elm et al., 2008).

Inclusion and Exclusion Criteria

The study included all patients who were admitted *via* the department of emergency medicine to any hospital ward of University Hospital Hradec Králové. Hospital admissions that took place between 12th August and 6th November 2018 were included. Visits to the department of emergency medicine without inpatient hospitalization were not included. Hospitalizations for diagnostic or elective surgical procedures for pre-existing conditions, hospitalizations with missing medical records, and hospitalizations taking less than 24 h were excluded. There were no exclusion criteria related to age or department. Patients hospitalized more than once were counted as separate cases.

Data Collection

The data collection process was retrospective. Data were obtained from electronic medical records and entered into a Microsoft Access database. The collected data included demographic characteristics, medication history, medical history, presenting complaint, admission diagnosis, laboratory values and results of clinical investigations, documented ADRs and information on medication adherence. Medications stated in medication history were counted as active substances.

Ethics Committee Approval

The study was approved by Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové. Patient informed consent was not required due to the observational design of the study and the retrospective data collection process. No personal data that could identify the patients were collected.

Methods of Assessment

The methodology of DRA adjudication was adapted from the Drug-related admissions adjudication guide developed within the OPERAM project (Thevelin et al., 2018). The DRA identification process had the following steps: data abstraction, screening for potential ADEs causing or contributing to hospital admission, causality assessment, assessment of contribution to hospital admission, and the assessment of preventability.

Potential ADEs that caused or contributed to hospital admission were identified and the causality of each ADE was assessed using WHO-UMC criteria. The modified WHO-UMC causality criteria (Klopotowska et al., 2013) described in the Drug-related admissions adjudication guide (Thevelin et al., 2018) were used to assess causality due to underuse. In addition, dosage adjustments were taken into account. ADEs with certain causal relationships had to fulfill the following criteria: 1) plausible time relationship to drug intake/dose increase, 2) plausible response to withdrawal/dose decrease, 3) cannot be explained by any disease, 4) definitive pharmacologically or phenomenologically, and 5) satisfactory rechallenge. ADEs with probable causal relationship had to fulfill the following criteria: 1) reasonable time relationship to drug intake/dose increase, 2) clinically reasonable response to withdrawal/dose decrease, and 3) unlikely to be attributed to any disease. ADEs with possible causal relationships included events with a reasonable time relationship to drug intake/dose increase that could also be explained by disease or information on dechallenge was lacking or unclear. ADEs with certain, probable, or possible causal relationships were considered confirmed ADEs.

In case of a confirmed ADE, the ADE contribution to hospital admission was accessed. According to the definition of DRA, hospitalizations due to ADEs that were the main reason for admission, as well as ADEs that were a contributory reason for admission, were considered a DRA. The main reason for admission was the primary cause of admission and was usually documented in the admission or discharge letter. A contributory reason for admission was a clinically significant contributory factor to admission—an event that worsened the main reason for admission or played a substantial role in the admission, but other factors also contributed significantly to the admission.

Drug therapeutic failure without an evident cause, drug-related laboratory deviation without clinical manifestation, intentional intoxication, and ADE that was present at hospital admission but not related to the reason of admission were not considered a DRA.

The last step was the assessment of preventability. DRAs judged to be due to medication errors were deemed to be potentially preventable. Preventability was further assessed using Hallas criteria as definitely avoidable, possibly avoidable, not avoidable, and unevaluable (Hallas et al., 1990).

Preliminary screening for potential ADEs was performed by a PhD candidate in clinical pharmacy (ZO), and the consensus assessment was performed by three board-certified clinical pharmacists (MM, JV, PS).

Classification

The identified DRAs were classified into two groups—DRAs related to treatment safety and DRAs related to treatment effectiveness. The Anatomical Therapeutic and Chemical (ATC) classification was used to code medications and medication groups (WHOCC, 2022). Medications were coded up to the fifth level. Medical Dictionary for Regulatory Activities (MedDRA) was used to classify clinical manifestations (BioPortal, 2021). MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Potentially preventable DRAs were classified according to the OPERAM DRA adjudication guide (Thevelin et al., 2018) into DRAs related to overuse, underuse, and misuse as well as the Pharmaceutical Care Network Europe Classification V 9.1 (Pharmaceutical Care Network Europe Association, 2020) into DRAs concerning the following DRPs: drug selection, dose selection, treatment duration, patient-related, patient transfer-related and other (No or inappropriate outcome monitoring). An additional category was added—inappropriate lifestyle measures.

Outcome Measures

The main outcome measure was the prevalence of DRAs (defined as the number of unplanned DRAs divided by the total number of unplanned hospital admissions). DRA was defined as a hospitalization due to an ADE, which is the main or contributory reason for hospital admission of a patient. The term ADE was defined as harm due to an ADR or a medication error related to overuse, underuse, or misuse of prescription and non-prescription medications (Thevelin et al., 2018).

The other outcomes included: the prevalence of potentially preventable DRAs (defined as the number of potentially preventable DRAs divided by the total number of DRAs), the most common medication classes implicated in DRAs, the most common clinical manifestations of DRAs, the most common medication classes implicated in potentially preventable DRAs, the most common clinical manifestations of potentially preventable DRAs and preventability aspects of potentially preventable DRAs.

Sample Size Calculation and Data Analysis

The following formula (Daniel and Cross, 2013) was used to calculate the sample size:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where p stands for the expected prevalence, Z for the standard normal variable corresponding to the confidence interval (CI), and d for precision.

A sample size of 1252 patients was required to estimate the prevalence of DRAs, based on 95% CI, precision level of 2%, and the prevalence of 15.4% [obtained from the latest systematic review (Ayalew et al., 2019)].

Categorical variables were expressed as absolute values and percentages. Continuous variables were expressed as medians with interquartile ranges.

RESULTS

Prevalence of Drug-Related Hospital Admissions and Sample Characteristics

The study included 1252 unplanned hospital admissions to University Hospital Hradec Králové *via* the department of emergency medicine. The number of patients admitted to the hospital was 1202, as some patients were admitted more than once. A total of 195 hospital admissions were identified to be drug-related. Of the 195 DRAs, 145 DRAs (74%) were related to treatment safety, and 50 DRAs (26%) were related to treatment effectiveness. The total prevalence of DRAs was 15.6% (95% CI 13.6–17.6). For the flow diagram, see **Figure 1**.

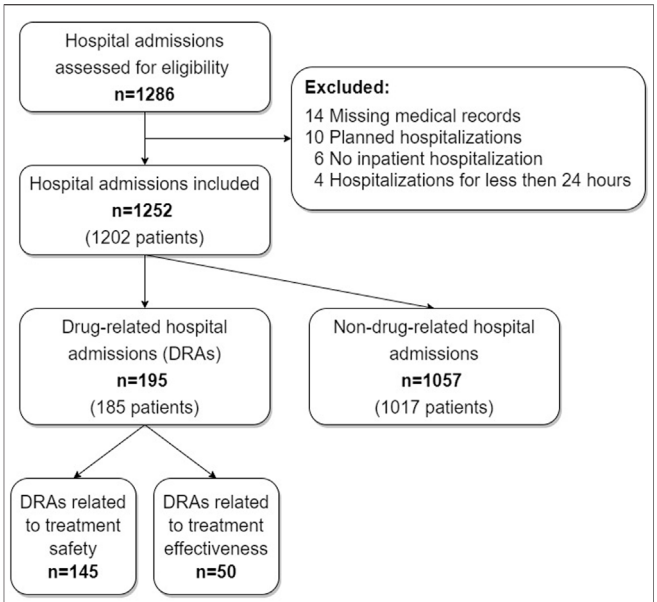

FIGURE 1 | A flow diagram depicting the number of hospital admissions at each step of the study.

The demographic and clinical characteristics of the study sample and the comparison of subgroups are shown in **Table 1**.

Table 2 shows the comorbidities of the study sample and the comparison of subgroups.

Table 3 shows the number of hospital admissions with corresponding medication classes in the patients' medication history and the comparison of subgroups.

Clinical Manifestation of Drug-Related Hospital Admissions

A total of 152 ADEs were related to treatment safety. More than one ADE was identified in 7 DRAs. **Table 4** shows the MedDRA classification of ADEs related to treatment safety.

Table 5 shows the classification of DRAs related to treatment effectiveness according to MedDRA.

Medications Involved in Drug-Related Hospital Admissions Related to Treatment Safety

Table 6 shows the ATC classification of medication classes involved in DRAs related to treatment safety. A total of 254 medications were involved in ADEs related to treatment safety. The medications classes most frequently concerned the

TABLE 1 | Demographic and clinical characteristics of the study sample and the comparison of subgroups.

Characteristic	Total N = 1252	DRAs *n* = 195	DRAs related to		Non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Age							
Median	71	75	68	77	70	82	76
IQR	58–82	66–84	59–78	70–85	56–81	71–86	69–83
Sex							
Female—No. (%)	570 (46%)	91 (47%)	19 (38%)	72 (50%)	479 (46%)	27 (54%)	45 (47%)
Male—No. (%)	682 (54%)	104 (53%)	31 (62%)	73 (50%)	578 (55%)	23 (46%)	50 (53%)
Number of medications in medication history							
Median	5	8	5	9	5	8	10
IQR	2–9	5–11	3–8	6–12	1–8	5–10	7–13
Charlson comorbidity index							
Median	4	5	5	6	4	6	6
IQR	2–6	4–7	2–6	4–7	2–6	4–7	4–7
Estimated glomerular filtration rate							
Median	66	55	65	54	69	54	54
IQR	44–88	34–81	41–90	32–74	46–89	34–76	31–74
Body mass index							
Median	26	26	26	26	26	26	26
IQR	23–31	23–29	24–29	23–31	23–31	23–28	24–31

DRA, Drug-related hospital admission; IQR, interquartile range.

Cardiovascular system (27%), Blood and blood forming organs (26%), Antineoplastic and immunomodulating agents (16%), and Nervous system (11%). More than one medication was involved in 70 (48%) DRAs related to treatment safety.

The most common medications involved in DRAs related to treatment safety included low dose acetylsalicylic acid (n = 23), warfarin (n = 22), prednisone (n = 8), hydrochlorothiazide (n = 8), clopidogrel (n = 7), furosemide (n = 7), perindopril (n = 6), insulin (n = 6), amiodarone (n = 5), bisoprolol (n = 5), ibuprofen (n = 5), nadroparin (n = 5), and spironolactone (n = 5).

Medications Involved in Drug-Related Hospital Admissions Related to Treatment Effectiveness

Table 7 shows the ATC classification of the medication classes involved in 50 DRAs related to treatment effectiveness (N = 62). There were 9 DRAs related to treatment effectiveness in which more than one medication class was involved.

Causality Assessment

Causality was assessed for every event separately. There were 7 DRAs, with more than 2 ADEs contributing to hospital admission. According to the causality assessment, 51% ADEs were probable, and 49% ADEs were possible. No ADE was certain, as no event was a recognized pharmacological phenomenon, and rechallenge was almost never performed. ADEs with probable causality were events unlikely to be attributed to disease, and the response to withdrawal (or drug initiation) was clinically reasonable, while ADEs with possible causality included events that could also be explained by disease or the information on withdrawal (or drug initiation) was lacking or unclear. **Table 8** shows the categories of causal relationships of ADEs involved in DRAs. Within DRAs related to treatment effectiveness, 46% of events had a probable causal relationship. Within DRAs related to treatment safety, 53% of events had a probable causal relationship.

Contribution to Hospital Admissions

In 55% of DRAs, ADEs only contributed to the admission, which means that ADE was one factor among others that together resulted in hospitalization. The most common other factors were heart failure decompensation and infection. **Table 9** shows the categories of contributions to hospital admissions.

Potentially Preventable Drug-Related Hospital Admissions

The overall potential preventability of DRAs was 51.3% (both definitely avoidable and possibly avoidable DRAs). We have identified 50 potentially preventable DRAs related to treatment safety and 50 potentially preventable DRAs related to treatment effectiveness. In addition, 83 (43%) DRAs were not avoidable, and 12 (6%) DRAs were unevaluable.

Table 10 shows the classification of preventable DRAs related to treatment safety. Regarding treatment safety, the most common preventability aspects included inappropriate drug selection, inappropriate monitoring, inappropriate dose selection, and inappropriate lifestyle measures.

Table 11 shows the classification of preventable DRAs related to treatment effectiveness. The most common preventability aspect of DRAs related treatment effectiveness was medication nonadherence.

Potentially preventable DRAs were also classified according to the Pharmaceutical Care Network Europe classification of DRPs (**Supplementary Tables S1, S2**).

TABLE 2 | Comorbidities of the study sample and inter-group differences.

Presence of comorbidity	Total *N* = 1252	DRAs *n* = 195	DRAs related to		Non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Arterial hypertension	60%	75%	70%	77%	57%	74%	79%
Dyslipidemia	34%	41%	28%	45%	33%	40%	47%
Diabetes	28%	38%	40%	37%	26%	34%	39%
Coronary artery disease	21%	29%	32%	28%	20%	28%	28%
Valvular heart disease	19%	33%	38%	32%	16%	22%	37%
Atrial fibrillation	17%	31%	22%	34%	15%	30%	37%
Vertebrogenic algic syndrome	17%	27%	14%	31%	16%	36%	28%
Tumors	17%	23%	6%	28%	16%	20%	33%
Heart failure	14%	26%	32%	24%	12%	24%	24%
Chronic kidney disease	13%	24%	10%	29%	11%	30%	28%
Hyperuricemia/gout	11%	13%	4%	16%	11%	16%	16%
Osteoarthrosis	11%	12%	8%	14%	11%	16%	13%
Benign prostatic hyperplasia	11%	16%	16%	16%	10%	18%	15%
Hypothyreosis	10%	13%	10%	14%	9%	16%	14%
Anemia	9%	17%	10%	19%	8%	16%	21%
Chronic venous insufficiency	9%	16%	16%	17%	8%	20%	15%
Dementia	9%	10%	6%	12%	8%	16%	9%
Venous thromboembolism	8%	13%	16%	12%	7%	16%	11%
Depression/anxiety	8%	11%	18%	9%	7%	10%	8%
Liver disease	8%	13%	18%	12%	7%	12%	12%
Peripheral artery disease	7%	11%	8%	12%	7%	14%	12%
Chronic obstructive pulmonary disease	7%	10%	14%	8%	7%	2%	12%
Osteoporosis	7%	10%	2%	13%	6%	10%	15%
Peptic ulcer	6%	9%	4%	11%	6%	20%	6%
Heart arrhythmia	6%	6%	6%	6%	6%	6%	5%
Gastroesophageal reflux disease	6%	8%	6%	9%	6%	8%	9%
Asthma	6%	6%	8%	5%	6%	4%	5%
Obesity	27%	22%	16%	24%	28%	18%	27%
Overweight	31%	35%	42%	33%	31%	32%	34%
Tobacco smoking	17%	15%	28%	11%	17%	16%	8%
Alcohol consumption	10%	11%	26%	6%	10%	8%	5%
Immobility	5%	7%	2%	9%	4%	12%	7%

DRA: Drug-related hospital admission.
Note: Comorbidities with <2% prevalence were omitted from this table for readability.

Medications Involved in Preventable Drug-Related Hospital Admissions

Medications associated with potentially preventable DRAs related to treatment safety are listed in **Table 12**.

The highest share of potential preventability in medication classes repeatedly involved in DRAs related to treatment safety was observed for Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. For detailed information, see **Table 13**.

Medications Involved in Non-preventable Drug-Related Hospital Admissions

The most common medication classes involved in non-preventable DRAs included Antithrombotic agents (24%), Antineoplastic agents (19%), Diuretics (11%), Corticosteroids for systemic use (8%), Immunosuppressants (6%), Antibacterials for systemic use (5%), Beta blocking agents (5%), and Agents acting on the renin-angiotensin system (5%).

Clinical Manifestations Associated With Potentially Preventable Drug-Related Hospital Admissions

The most common clinical manifestations associated with potentially preventable DRAs related to treatment safety were Hypoglycemia (6), Gastroduodenal hemorrhage (6), Depressed level of consciousness (5), and Bradycardia (4). The MedDRA classification is shown in **Table 14**.

DISCUSSION

The aims of the study (prevalence of DRAs, medications involved in DRAs, clinical manifestations of DRAs, preventability of DRAs, and preventability aspects) are discussed separately:

Prevalence of Drug-Related Hospital Admissions

Epidemiological studies demonstrate that the burden of ADRs in both inpatient and outpatient settings is substantial (Bouvy et al.,

TABLE 3 | Baseline medications grouped by ATC group and inter-group differences.

ATC group	Total *N* = 1252	DRAs *n* = 195	DRAs related to		non-DRAs *n* = 1057	DRAs related to safety	
			Treatment effectiveness *n* = 50	Treatment safety *n* = 145		Preventable *n* = 50	Non-preventable *n* = 95
Diuretics	58%	90%	92%	89%	52%	70%	99%
Antithrombotic agents	53%	78%	52%	88%	48%	84%	89%
Agents acting on the renin-angiotensin system	40%	43%	40%	44%	40%	44%	44%
Drugs used in diabetes	36%	51%	60%	48%	33%	46%	48%
Beta blocking agents	35%	44%	34%	48%	33%	42%	51%
Drugs for obstructive airway diseases	32%	32%	30%	32%	33%	16%	41%
Lipid modifying agents	32%	35%	28%	37%	32%	34%	39%
Drugs for acid related disorders	30%	46%	26%	52%	27%	48%	55%
Analgesics	23%	39%	8%	50%	20%	50%	51%
Calcium channel blockers	22%	25%	16%	28%	22%	32%	25%
Psychoanaleptics	22%	27%	28%	26%	21%	24%	27%
Psycholeptics	21%	27%	16%	30%	20%	44%	23%
Mineral supplements	16%	24%	10%	29%	15%	22%	33%
Antigout preparations	15%	19%	6%	24%	14%	20%	26%
Cardiac therapy	13%	26%	16%	29%	11%	16%	36%
Urologicals	13%	19%	14%	21%	11%	16%	23%
Thyroid therapy	12%	14%	4%	17%	12%	18%	17%
Vitamins	12%	18%	14%	19%	11%	12%	23%
Antiepileptics	8%	14%	6%	17%	7%	18%	16%
Vasoprotectives	7%	10%	6%	11%	7%	16%	8%
Anti-inflammatory and antirheumatic products	7%	14%	10%	16%	6%	32%	7%
Antihypertensives	6%	8%	4%	10%	5%	14%	7%
Antianemic preparations	6%	9%	10%	8%	5%	8%	8%
Drugs for functional gastrointestinal disorders	6%	11%	6%	12%	5%	10%	14%
Corticosteroids for systemic use	5%	13%	4%	16%	4%	4%	22%
Antineoplastic agents	5%	18%	0%	25%	2%	4%	36%
Antihistamines for systemic use	5%	8%	4%	9%	4%	4%	12%
Ophthalmologicals	5%	6%	0%	8%	4%	8%	7%
Laxatives	3%	4%	0%	6%	3%	6%	5%
Immunosuppressants	3%	7%	4%	8%	2%	2%	12%
Cough and cold preparations	3%	4%	0%	5%	2%	0%	7%
Anti-parkinson drugs	2%	5%	4%	6%	2%	6%	5%
Other nervous system drugs	2%	0%	0%	0%	3%	0%	0%
Antidiarrheals, intestinal antiinflammatory/ antiinfective agents	2%	6%	6%	6%	2%	4%	6%
Drugs for treatment of bone diseases	2%	2%	0%	2%	2%	4%	1%

DRA, Drug-related hospital admission; ATC: Anatomical Therapeutic Chemical.
Note: Medication classes with <2% prevalence were omitted from this table for readability.

2015). As the population is aging and multimorbidity and polypharmacy are increasing, one would expect the prevalence of DRAs to rise as well. However, at the same time, safer alternatives are being used in clinical practice, high-risk medications are being withdrawn from the market, and preventative measures are being implemented in clinical practice. The prevalence of DRAs differs due to inconsistencies in the definitions and methods of DRA identification (Leendertse et al., 2010; Linkens et al., 2020; Laatikainen et al., 2021), the selected threshold of causality assessment (Wallerstedt et al., 2021), patient population (Beijer and de Blaey, 2002; Leendertse et al., 2010; Laatikainen et al., 2021) and whether the denominator includes all admissions, only acute admissions, or specific wards (Leendertse et al., 2010). When comparing the prevalence of DRAs, one has to take all these things into account. Due to the current heterogeneity, it is practically impossible to compare the prevalences of DRAs among different studies. We found that 15.6% of acute hospital admissions were drug-related. The prevalence of DRAs related to treatment safety was found to be 11.6%. If we excluded the cases with possible causality, the prevalence would be 6%. If we limited the finding only to ADEs with a probable causal relationship which was the main reason for hospital admission related to treatment safety, the prevalence would be 3%. The results of the subgroup analysis can be found in **Supplementary Table S3**. A noteworthy difference is between different age groups. Among older patients (65 years or older), the prevalence of DRAs was 18.6% while the prevalence of DRAs among the rest of the patients was 10%. The prevalence of DRAs among patients aged 75 years or older was 20%.

This study followed the OPERAM DRA adjudication guide (Thevelin et al., 2018), which was interested in DRPs that cause harm. To differentiate between potential DRPs and manifest DRPs, the term ADEs was used for manifest DRPs. However, the term was

TABLE 4 | MedDRA classification of ADEs related to treatment safety (N = 152).

MedDRA system organ class (No., %)	MedDRA preferred term	No.
Gastrointestinal disorders (31, 20.4%)	Gastroduodenal hemorrhage	10
	Intestinal hemorrhage	7
	Diarrhea	3
	Gastric ulcer perforation	3
	Pancreatitis	1
	Gastrooesophageal reflux disease	1
	Gastritis	1
	Esophagitis	1
	Duodenal perforation	1
	Abdominal discomfort	1
	Dyspepsia	1
	Nausea	1
Metabolism and nutrition disorders (26, 17.1%)	Hyponatremia	12
	Hypoglycemia	6
	Hyperglycemia	3
	Dehydration	2
	Hyperkalemia	2
	Calciphylaxis	1
Blood and lymphatic system disorders (18, 11.8%)	Bone marrow toxicity	10
	Microcytic anemia	7
	Anemia folate deficiency	1
Nervous system disorders (17, 11.1%)	Cerebral hemorrhage	6
	Depressed level of consciousness	8
	Subdural hemorrhage	2
	Diplopia	1
Infections and infestations (14, 9.2%)	Infection susceptibility increased	10
	Clostridium difficile colitis	4
Cardiac disorders (12, 7.9%)	Bradycardia	7
	Atrioventricular block	3
	Hypertension	1
	Cardiomyopathy	1
Vascular disorders (10, 6.6%)	Hypotension	4
	Hematoma	3
	Syncope	2
	Hemorrhage	1
Renal and urinary disorders (8, 5.3%)	Hematuria	4
	Prerenal failure	4
Respiratory, thoracic, and mediastinal disorders (7, 4.6%)	Hemoptysis	3
	Pulmonary embolism	1
	Pulmonary alveolar hemorrhage	1
	Interstitial lung disease	1
	Epistaxis	1
Immune system disorders (4, 2.6%)	Drug hypersensitivity	4
Psychiatric disorders (2, 1.3%)	Confusional state	1
	Disorientation	1
Endocrine disorders (1, 0.7%)	Sec. adrenocortical insufficiency	1
General disorders and administration site conditions (1, 0.7%)	Fatigue	1
Injury, poisoning, and procedural complications (1, 0.7%)	Fall	1

ADE, Adverse Drug Event; MedDRA, Medical Dictionary for Regulatory Activities.

also applied to DRP related to treatment effectiveness. One could argue that manifest DRPs related to treatment effectiveness should not be called ADEs, since ADE is mostly defined as an injury resulting from the use of a drug, and the term ADE does not include failure to use a drug (Nebeker et al., 2004). Another confusion comes when comparing ADRs and ADEs. Some studies use the definition of ADR as a noxious and unintended response to a drug, which occurs at doses normally used, while others drop the part about normally used doses or use other definitions. Therefore, one must be cautious even when comparing studies with the same outcomes, as they might be using different definitions. There is a pressing need for further discussion and international consensus on this topic (Falconer et al., 2019).

Medications Implicated in Drug-Related Hospital Admissions

Several studies have revealed that DRAs are caused by commonly used medications. In our study, the most common medication

TABLE 5 | MedDRA classification of DRAs related to treatment effectiveness (N = 50).

MedDRA system organ class	No.	%	MedDRA preferred term	No.
Cardiac disorders	16	32	Heart failure signs and symptoms	14
			Myocardial infarction	2
Nervous system disorders	9	18	Ischemic stroke	9
Metabolism and nutrition disorders	9	18	Diabetic complication	9
Vascular disorders	6	12	Venous thrombosis	3
			Hypertension	2
			Granulomatosis with polyangiitis	1
Blood and lymphatic system disorders	3	6	Anemia	3
Infections and infestations	2	4	Infection	2
Immune system disorders	2	4	Crohn's disease	2
Psychiatric disorders	2	4	Depression	1
			Bipolar disorder	1
Endocrine disorders	1	2	Thyrotoxic crisis	1

DRA, Drug-related hospital admission; MedDRA, Medical Dictionary for Regulatory Activities.

TABLE 6 | ATC classification of medication classes involved in DRAs related to treatment safety (N = 254).

ATC code	ATC group	No.	%
B01	Antithrombotic agents	65	25.6
L01	Antineoplastic agents	30	11.8
C03	Diuretics	28	11.0
H02	Corticosteroids for systemic use	14	5.5
C07	Beta blocking agents	14	5.5
M01	Anti-inflammatory and antirheumatic products	13	5.1
C09	Agents acting on the renin-angiotensin system	13	5.1
N02	Analgesics	11	4.3
L04	Immunosuppressants	10	3.9
J01	Antibacterials for systemic use	9	3.5
A10	Drugs used in diabetes	8	3.1
C01	Cardiac therapy	8	3.1
N03	Antiepileptics	5	2.0
N06	Psychoanaleptics	5	2.0
N05	Psycholeptics	5	2.0
C08	Calcium channel blockers	3	1.2
R03	Drugs for obstructive airway diseases	2	0.8
C02	Antihypertensives	2	0.8
M03	Muscle relaxants	2	0.8
A12	Mineral supplements	1	0.4
A07	Antidiarrheals, intestinal anti-inflammatory/antiinfective agents	1	0.4
H01	Pituitary and hypothalamic hormones and analogues	1	0.4
R05	Cough and cold preparations	1	0.4
N04	Anti-parkinson drugs	1	0.4
G03	Sex hormones and modulators of the genital system	1	0.4
G04	Urologicals	1	0.4

DRA, Drug-related hospital admission; ATC, Anatomical Therapeutic Chemical.

classes involved in DRAs related to treatment safety were Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, Beta blocking agents, Anti-inflammatory and antirheumatic products, and Agents acting on the renin-angiotensin system. The OPERAM trial has found Diuretics and Antithrombotic agents to be the most frequently involved or omitted medication classes in DRAs (Blum et al., 2021). Summarizing our findings on DRAs related to treatment effectiveness and DRAs related to safety, we have found the same medication classes (Antithrombotic agents and Diuretics) to be most frequently involved in DRAs.

Regarding preventable DRAs related to treatment safety, the most common medication classes identified in our study were Anti-inflammatory and antirheumatic products, Antithrombotic agents, Drugs used in diabetes, Diuretics, Cardiac therapy, Psycholeptics, Analgesics, and Beta blocking agents. Similar findings were reported in a systematic review (Howard et al., 2007), which identified antiplatelets, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, opioid analgesics, drugs affecting the renin-angiotensin system, and beta-blockers as the medication classes most commonly involved in preventable DRAs related to ADRs and overtreatment.

TABLE 7 | ATC classification of medication classes involved in DRAs related to treatment effectiveness (N = 62).

ATC code	ATC group	No.	%
C03	Diuretics	14	22.6
B01	Antithrombotic agents	12	19.4
A10	Drugs used in diabetes	8	12.9
C09	Agents acting on the renin-angiotensin system	7	11.3
C10	Lipid modifying agents	5	8.1
C07	Beta blocking agents	3	4.8
J01	Antibacterials for systemic use	3	4.8
B03	Antianemic preparations	3	4.8
L04	Immunosuppressants	2	3.2
C08	Calcium channel blockers	1	1.6
A07	Intestinal antiinflammatory agents	1	1.6
H03	Thyroid therapy	1	1.6
N06	Psychoanaleptics	1	1.6
N05	Psycholeptics	1	1.6

DRA, Drug-related hospital admission; ATC, Anatomical Therapeutic Chemical.

Regarding preventable DRAs related to treatment effectiveness, the systematic review by Howard et al. identified diuretics, antiepileptics, drugs used in diabetes, and beta-blockers to be most commonly involved in DRAs. A systematic review of prospective observational studies (Mongkhon et al., 2018) identified medications targeting the cardiovascular system, respiratory system, central nervous system, endocrine system, and medication used to treat infections to be most commonly associated with hospital admissions due to medication nonadherence. In our study, the most common medication classes were Diuretics, Antithrombotic agents, Drugs used in diabetes, and Agents acting on the renin-angiotensin system.

Comparison With Other Countries

Compared to lower-income countries, we have observed a lower prevalence of DRAs related to Antiinfectives for systemic use. Antiinfectives for systemic use were frequently involved in DRAs in Ethiopia (Angamo et al., 2017; Demessie and Berha, 2022), South Africa (Mouton et al., 2016), Nigeria (Adedapo et al., 2021), and India (Geer et al., 2016). Antiinfectives for systemic use were also frequently implicated in DRAs in Brazil (de Paula et al., 2012) during the time when the requirement to be prescription only was not met. In higher-income countries, Antiinfectives for systemic use are among the top medication classes among the pediatric population. A review comparing ADR-related hospitalizations in developed and developing countries (Angamo et al., 2016) found that antiinfectives were more commonly reported to be associated with ADR-related admissions in developing countries than in developed countries.

Compared to certain higher-income countries, Opioids were not among the most common medication classes involved in DRAs related to treatment safety. Opioids appear to be frequently involved in the United States (Budnitz et al., 2011; Poudel et al., 2017), Australia (Zhang et al., 2019), Canada (Bayoumi et al., 2014). A possible explanation could be that strong opioids are not yet widely prescribed in the Czech Republic compared to these countries. However, hospital admissions due to tramadol were also present in our setting. Otherwise, the same medication classes continue to be involved in DRAs in different countries.

Clinical Manifestations of Drug-Related Hospital Admissions

Clinical manifestations of DRAs related to treatment safety most frequently concerned Gastrointestinal disorders (especially Gastrointestinal hemorrhage), Metabolism and nutrition disorders (especially Hyponatremia, Hypoglycemia) and Blood and lymphatic system disorders (Bone marrow toxicity, Microcytic anemia), Nervous system disorders (Depressed level of consciousness), Infections and infestations (Increased infection susceptibility) and Cardiac disorders (Bradycardia). Gastrointestinal disorders and Microcytic anemia were associated with anticoagulants, antiplatelets, and NSAIDs. Hyponatremia was associated with the use of thiazide diuretics. Hypoglycemia was associated with the use of insulin and sulfonylureas. Bone marrow toxicity was associated with the use of antineoplastic agents. A depressed level of consciousness was associated with opioid analgetics. Increased susceptibility to infection was associated with immunosuppressants. Bradycardia was associated with beta-blockers, amiodarone, and digoxin.

TABLE 8 | Causality assessment of ADEs.

Causality category	All ADEs *N* = 202	Treatment safety *n* = 152	Treatment effectiveness *n* = 50
probable	104	81	23
possible	98	71	27

ADE, Adverse drug events.

TABLE 9 | Classification of DRAs—contribution to hospital admissions.

Contribution to hospital admission	All DRAs *N* = 195	Treatment safety *n* = 145	Treatment effectiveness *n* = 50
main reason	88	55	33
contributory reason	107	90	17

DRA, Drug-related hospital admission.

TABLE 10 | Classification of potentially preventable DRAs related to treatment safety (N = 50).

Categories of preventable DRAs related to treatment safety	No.	Medication involved
OVERUSE		
Drug without an indication	4	low-dose acetylsalicylic acid (3), levodopa
UNDERUSE		
Omission of an indicated drug	3	omission of gastric acid suppressants despite prior gastritis or gastrointestinal ulcer naproxen, ibuprofen, ibuprofen (+rivaroxaban)
MISUSE		
Wrong drug	13	
• inappropriate according to guidelines		nimesulide, furosemide
• contraindication or precaution for a certain condition with increased risk of toxicity		diclofenac (2), meloxicam (2), ibuprofen (2), nimesulide, amiodarone, bisoprolol, dosulepin, doxazosin
Wrong dose	9	
• the dose was too high		glimepiride, tramadol
• the dose was not adapted to the patient characteristics (age, renal function, weight)		diclofenac, tiapride, nadroparin
• the dose was given too frequently		metoprolol
• accidentally ingesting a toxic amount of drug		tramadol + zolpidem, tiapride, insulin
Inappropriate monitoring	11	
• symptoms of bradycardia, heart rate		amiodarone (+bisoprolol), verapamil, digoxin (+nebivolol)
• symptoms of bleeding, INR		warfarin (5)
• blood glucose		insulin (2)
• blood potassium		potassium chloride
Drug-drug interactions	1	haloperidol (+morphine, fentanyl)
OTHER		
Inappropriate lifestyle measures	9	
• food intake		glimepiride, insulin
• fluid intake		furosemide (2), digoxin, amiloride (+telmisartan), perindopril
• smoking		hormonal contraceptives
• heavy episodic alcohol consumption		warfarin

DRA, Drug-related hospital admission; INR, International Normalized Ratio.

TABLE 11 | Classification of potentially preventable DRAs related to treatment effectiveness (N = 50).

Categories of preventable DRAs related to treatment effectiveness	No.	Medication classes involved
UNDERUSE		
Omission of the indicated drug	8	Antithrombotic agents (2), Antithrombotic agents + Lipid modifying agents (2), Agents acting on the renin-angiotensin system (1), Antianemic preparations (1), Thyroid therapy (1), Diuretics + Agents acting on the renin-angiotensin system (1)
The duration of therapy is too short	1	Antithrombotic agents (1)
Adherence concerns	35	Diuretics (7), Drugs used in diabetes (6), Agents acting on the renin-angiotensin system (4), Antibacterials for systemic use (3), Antithrombotic agents (3), Antianemic preparations (2), Immunosuppressants (2), Antithrombotic agents + Lipid modifying agents (1), Calcium channel blockers + Antithrombotic agents (1), Calcium channel blockers + Beta blocking agents + Diuretics + Lipid modifying agents (1), Diuretics + Agents acting on the renin-angiotensin system + Antithrombotic agents + Lipid modifying agents (1), Diuretics + Beta blocking agents (1), Intestinal antiinflammatory agents (1), Psychoanaleptics (1), Psycholeptics (1)
MISUSE		
Inappropriate monitoring	5	Drugs used in diabetes (2), Diuretics (2), Antithrombotic agents (1)
Inappropriate discontinuation or dose decrease	1	Diuretics + Beta blocking agents (1)

DRA, Drug-related hospital admission.

Clinical manifestation of DRAs related to treatment effectiveness most frequently concerned Cardiac disorders (particularly Heart failure symptoms), followed by Nervous system disorders (Ischemic stroke) and Metabolism and nutrition disorders (Diabetic complications). Heart failure symptoms were associated with the underuse of diuretics. Ischemic stroke due to cardioembolism was associated with the underuse of anticoagulants, while ischemic stroke due to atherosclerosis was associated with the underuse of antiplatelet agents, statins, and antihypertensive therapy. Diabetic complications were associated with nonadherence to antidiabetics.

TABLE 12 | Medication classes involved in potentially preventable DRAs related to treatment safety (N = 51).

Medication classes	No.	Medications
Anti-inflammatory and antirheumatic products	12	ibuprofen (4), diclofenac (3), meloxicam (2), nimesulide (2), naproxen (1)
Antithrombotic agents	10	warfarin (6), acetylsalicylic acid (3), nadroparin (1)
Drugs used in diabetes	6	insulin (4), glimepiride (2)
Cardiac therapy	4	digoxin (2), amiodarone (2)
Diuretics	4	furosemide (3), amiloride (1)
Psycholeptics	4	tiapride (2), haloperidol (1), zolpidem (1)
Analgesics	2	tramadol (2)
Beta blocking agents	2	metoprolol (1), bisoprolol (1)
Agents acting on the renin-angiotensin system	1	perindopril
Antihypertensives	1	doxazosin
Anti-parkinson drugs	1	levodopa
Calcium channel blockers	1	verapamil
Mineral supplements	1	potassium chloride
Psychoanaleptics	1	dosulepin
Sex hormones and modulators of the genital system	1	hormonal contraceptive

DRA, Drug-related hospital admission.

TABLE 13 | Medication classes and corresponding share of preventability of DRAs related to treatment safety.

Medication classes repeatedly involved in DRAs related to treatment safety	DRAs related to treatment safety (No.)	Preventable DRAs related to treatment safety (No.)	Share (%)
Anti-inflammatory and antirheumatic products	13	12	92
Psycholeptics	5	4	80
Drugs used in diabetes	8	6	75
Antihypertensives	2	1	50
Cardiac therapy	8	4	50
Calcium channel blockers	3	1	33
Psychoanaleptics	5	1	20
Analgesics	11	2	18
Antithrombotic agents	65	10	15
Diuretics	28	4	14
Beta blocking agents	14	2	14
Agents acting on the renin-angiotensin system	13	1	8

DRA, Drug-related hospital admission.
Note: Medication classes involved only once in DRAs and medication classes that were not involved in preventable DRAs related to treatment safety were excluded.

TABLE 14 | MedDRA categories of preventable DRAs related to treatment safety (N = 50).

MedDRA system organ class	No.	%	MedDRA preferred term
Gastrointestinal disorders	14	28	Gastroduodenal hemorrhage (6), Gastric ulcer perforation (2), Intestinal hemorrhage (2), Esophagitis (1), Diarrhea (1), Gastritis (1), Nausea (1)
Metabolism and nutrition disorders	10	20	Hypoglycemia (6), Hyperkalemia (2), Dehydration (2)
Nervous system disorders	9	18	Cerebral hemorrhage (2), Subdural hemorrhage (2), Depressed level of consciousness (5)
Cardiac disorders	5	10	Bradycardia (4), Atrioventricular block (1)
Vascular disorders	3	6	Hematoma (2), Syncope (1)
Respiratory, thoracic, and mediastinal disorders	3	6	Pulmonary embolism (1), Pulmonary alveolar hemorrhage (1), Hemoptysis (1)
Renal and urinary disorders	2	4	Prerenal failure (2)
Blood and lymphatic system disorders	2	4	Microcytic anemia (2)
Psychiatric disorders	1	2	Disorientation (1)
General disorders and administration site conditions	1	2	Fatigue (1)

MedDRA, Medical Dictionary for Regulatory Activities; DRA, Drug-related hospital admission.

Similarly, a study in the United Kingdom (Rogers et al., 2009) identified heart failure and stroke to be the most frequent manifestations of DRAs due to undertreatment. In a study in Belgium (Somers et al., 2010), the most common symptom associated with drug therapy failures was dyspnea. A study from Australia (Kalisch Ellett et al., 2021) identified that chronic heart failure and osteoporosis were most frequently associated with potentially suboptimal medication-related processes of care related to the underuse of medications. However, there are not many studies that focus not only on DRAs related to treatment safety but also on DRAs related to treatment effectiveness.

Preventability of Drug-Related Hospital Admissions

We have found that half of DRAs were potentially preventable. However, in the subgroup of DRAs related to treatment safety, only 34% of DRAs were found to be preventable. Meta-analysis on the preventability of ADRs (Hakkarainen et al., 2012) found that half of ADRs among adult outpatients can be prevented.

Recent studies have also observed higher preventability: 60.9% (Li et al., 2021) 42.9% (Dechanont et al., 2021), 53.5% (Maříková et al., 2021), 46% (Kalisch Ellett et al., 2021) 47% (Lombardi et al., 2020), 76.4% (Cabre et al., 2018) 69% (Giardina et al., 2018). However, most of them were limited to older patients, in whom the preventability is higher than in the general population.

Like the prevalence of DRAs, the prevalence of preventable DRAs varies according to many factors. The inclusion of indirect drug-related causes for patient morbidity (errors of omission) and average sample age is associated with a higher prevalence of preventable DRAs (Winterstein et al., 2002). Variations can also be explained by differences in study populations and data collection methods (Patel et al., 2017).

Preventability Aspects

A systematic review (Howard et al., 2007) identified problems with patient adherence to medication (33.3%) and prescribing problems (30.6%) as the most common underlying causes of preventable DRAs, followed by monitoring problems (22.2%).

Taking the results of DRAs related to treatment safety and treatment effectiveness together, our study confirms these findings. In our study, 38% of preventable DRAs concerned medication adherence problems, 35% concerned prescribing problems (drug selection, dosage selection, treatment duration) 17% inappropriate monitoring. Furthermore, 1% were related to medication reconciliation problems and 9% were related to inappropriate lifestyle measures (fluid intake, food intake, alcohol consumption, and smoking).

Similar underlying causes were also observed in a recent study on medication-related hospital readmissions (Uitvlugt et al., 2021), which found that 35% of preventable readmissions were due to prescribing errors, and 35% of preventable readmissions were due to nonadherence. Uitvlught et al. had pointed out that if patients present at the emergency department due to nonadherence, this will typically manifest itself as a worsening of their underlying disease, and only if the patient indicates that they are not adherent, this will be recognized as an ADE. Additionally, Uitvlugt et al. had found that 30% of preventable readmissions were due to transition errors. In this study, only one transition error was identified. However, our study did not assess readmissions. The explanation could be that not all transition errors have been revealed. Pharmacists could play a role in managing patient electronic medication records both in the hospital (medication reconciliation, discharge list) and in the pharmacy (over-the-counter medications) and potentially reduce the discrepancies in the medication history.

Howard et al. suggested concentrating interventions on the drug groups that accounted for more than half of the drug groups associated with preventable DRAs (antiplatelets, diuretics, NSAIDs, and anticoagulants). In our study, Anti-inflammatory and antirheumatic products, Antithrombotic agents, Drugs used in diabetes were the medication classes that accounted for more than half of the medication classes associated with preventable DRAs related to treatment safety. Diuretics, Antithrombotic agents, Drugs used in diabetes, and Agents acting on the renin-angiotensin system were the medication classes, which accounted for more than half of the medication classes associated with preventable DRAs related to treatment effectiveness.

Similarly, (Schmiedl et al., 2018), suggested regular individualized medication reviews of the most commonly implicated drugs in preventable DRAs. In this prospective multicenter, long-term study conducted in Germany (Schmiedl et al., 2018), the most frequently implicated drugs included digitoxin, low-dose acetylsalicylic acid, phenprocoumon, diclofenac, fast-acting insulin, glyburide (glibenclamide), spironolactone, torasemide, and intermediate-acting combined with fast-acting insulin. The most common preventability aspects included missing prevention strategies, relevant drug-drug interactions, and inappropriate drugs for age, body weight, and comorbidities.

In the prospective multicenter study from the Netherlands (Leendertse et al., 2008), medication classes associated most often with potentially preventable DRAs included antiplatelet drugs, oral anticoagulants, NSAIDs, and their combinations, antidiabetic drugs, and medications that act on the central nervous system. The most common medication errors associated with potentially preventable DRAs in the HARM study (Leendertse et al., 2008) included lack of a clear indication for the medication, nonadherence to the medication regimen, inadequate monitoring, and drug-drug interactions.

Epidemiological studies on preventable DRAs are constantly needed since clinical practice is changing as new preventive measures are being implemented. Compared to the past, lower target serum digoxin concentrations are recommended. Digoxin concentrations ≥1.2 ng/ml are avoided, since it has been shown to increase cardiovascular mortality (Rathore et al., 2003) and other ADEs. Lower doses of spironolactone are used in practice, and potassium levels and renal function are monitored following the publication that identified increased hyperkalemia-associated morbidity and mortality among patients treated with angiotensin-converting enzyme inhibitors and spironolactone (Juurlink et al., 2004). In the geriatric population, the goal is

not too tight glycemic control, and sulfonylureas (especially glibenclamide) are prescribed less often.

Academicians should assess potential options that exceed the obligatory demands. Additional efforts are still needed to identify evidence-based interventions during sick days. Recently, the absence of a sick day management plan was identified to be among the root causes of preventable ADEs (de Lemos et al., 2021). Similarly, in our study, DRAs were related to acute illness accompanied by dehydration. However, randomized controlled trials that access the risks and benefits of temporarily stopping angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers are still needed.

In addition, there is a need for the development of safe and effective medications for chronic pain. On the one hand, NSAIDs contribute to DRAs related to the gastrointestinal tract. On the other hand, opioids pose a risk of opioid dependence and addiction and other ADEs.

In the same way, the preventability aspects of DRAs related to treatment effectiveness will also change over time. There is still a huge burden of diseases affecting the cardiovascular system on hospital admissions. Recently, SGLT2 inhibitors (empagliflozin or dapagliflozin) have been recommended in certain patients with heart failure. Underuse of these medications could become a new DRP that contributes to hospital admissions of patients with heart failure with reduced ejection fraction. In addition, target low-density lipoprotein cholesterol levels for cardiovascular disease prevention have been modified. Last but not least, addressing medication nonadherence might get a greater awareness in the future.

Interpretation

Recently, it was suggested that the widespread use of a signal detection cut-off in descriptive prevalence studies may have contributed to the perception that harmful drug treatment is the major problem of health care (Wallerstedt et al., 2021). Therefore, it should be underlined that medications often pose a risk in certain situations and many ADEs are multifactorial in nature. The underlying causes are also related to the behavior of the patients (medication nonadherence and inappropriate lifestyle measures).

Wallerstedt et al. have another excellent point in stating that studies on DRAs in which the benefits of treatment are not captured may bring about the risk of unjustly discrediting pharmacotherapy. This view is supported by our finding that Antithrombotic agents and Diuretics were the common cause of DRAs related to treatment safety and simultaneously the most common cause of DRAs related to treatment effectiveness. Had we only included DRAs related to treatment safety, a layman not taking the benefit-risk balance into account could assume that these medications are rather harmful. On the one hand, the use of Antithrombotic agents was associated with bleeding events, but on the other hand, their underuse was associated with cases of thromboembolic stroke due to atrial fibrillation. Similarly, on the one hand, Diuretics were involved in electrolyte imbalances and prerenal failure. On the other hand, withdrawal of Diuretics was associated with decompensation of heart failure.

Wallerstedt et al. point out that an adverse event can be the consequence of a prudent benefit-risk evaluation and correct drug treatment. These observations are confirmed by our finding that only a minority of DRAs related to treatment safety were preventable. We agree with Wallerstedt's statement that medication error would probably be the primary interest from a health care perspective as these events could possibly be prevented. However, we think that the information on non-preventable ADRs might also be valuable as it could prompt pharmaceutical companies to invest in the development of safer alternatives.

Wallerstedt et al. have also emphasized that problems that may just as well have been caused by the disease may be less relevant when quantifying a health care problem for health care decision making and suggested restricting the reported events to those with at least a probable causal relationship with drug treatment. Therefore, it should be emphasized that the prevalence of DRAs identified in this study (15.6%) included events with possible causality, contributory reasons of admission, and ADRs, which were not preventable as well. Our definition of DRA covered all manifest DRPs that were the main reason or contributed to hospital admission. If we took into account only manifest DRPs that were the main reason for hospital admissions, the prevalence of DRAs would be 7%. If we took only manifest DRPs with a certain or probable causal relationship into account, the prevalence of DRAs would be 6%.

Strengths

The first strength of the study is that electronic medical records were used as a data source for DRA identification. It has been noted that spontaneous reporting or database methods of data collection underreport ADEs and ADRs compared to medical chart screening (Leendertse et al., 2010). Another advantage of using medical records is the possibility to detect some cases of DRAs related to treatment effectiveness. Electronic medical records capture important health information (e.g., presenting complaint, laboratory data, documented ADRs, previous falls, smoking status, smoking history, alcohol consumption) compared to administrative claims databases.

The second strength of the study is the method of DRA identification. Own definitions and assessments hinder the interpretation and comparison of different studies. This study followed a comprehensive guide, and both causality assessment and assessment of contribution to the hospital admissions were performed. We have not limited the identification of DRAs to the trigger list since trigger lists require constant updates whenever official guidelines are updated (Hedman, 2020). As described in the DRA adjudication guide (Thevelin et al., 2018), only manifest DRPs (DRPs that caused harm) that were the main reason or contributory reason for hospital admission were considered DRA. Drug-related laboratory deviations and ADEs that were present at admission but did not contribute to hospital admission were not included in the definition of DRA. However, they can be found in **Supplementary Tables S4, S5**.

The third strength is that the study assessed potential preventability and identified medication classes involved in potentially preventable DRAs as well as preventability aspects.

As suggested by Wallerstedt et al., preventable DRAs should be the main concern of research, as DRAs, which can potentially be avoided, are of interest for clinical practice.

The fourth strength is the generalizability of the study. Most studies focus on specific departments. In this study, no exclusion criteria related to department were applied.

Additional strength could be the categorization of DRAs on DRAs related to treatment safety and DRAs related to treatment effectiveness. Although the latest guidelines focused on manifest DRPs, they have not suggested differentiating between problems and causes. Perhaps it could be useful to classify DRAs in a hierarchical manner, separate causes from problems, as was suggested for DRPs (van Mil et al., 2004).

Limitations

The main limitation of this study is the retrospective data collection process. The gold standard method is a prospective evaluation of patient medical records, laboratory tests, and interviews with patients and care providers (Parameswaran Nair et al., 2018). The limitation related to retrospective data collection includes the absence of medication reconciliation, patient interview, medication adherence confirmation. Therefore, the finding that the prevalence of DRAs related to treatment effectiveness was not as high as the prevalence of DRAs related to treatment safety could be skewed since no patient interview was conducted, and medication nonadherence was only taken into account when explicitly stated in electronic medical records.

The second limitation is the inclusion of cases with a possible causal relationship. Recently, Wallerstedt et al. suggested restricting reported events to those with at least a probable causal relationship with drug treatment (Wallerstedt et al., 2021). Although this suggestion differs from the OPERAM DRA adjudication guide (Thevelin et al., 2018) and AT-HARM10 tool (Kempen et al., 2019), we have provided these results in **Supplementary Tables S6–S10**. The essential distinctions between probable causal relationship and possible causal relationship are that in the latter case, there may be another equally likely explanation for the event, and/or there is no information or uncertainty with regard to what has happened after stopping. Therefore, the case is classified as possible, not only when the event could also be explained by disease but also when the information on withdrawal is lacking. There are cases when a dechallenge cannot be performed (e.g., when the benefit of the medication is greater than the risks or patient death). However, with the inclusion of a possible causal relationship, there is a possibility of a non-drug-related explanation of the symptoms being classified as ADE. In our study, there were cases of hyperkalemia associated with a reduction in kidney function due to dehydration and events that were multifactorial (hyponatremia, fall, syncope). Coppes et al. (2021) have highlighted that the tools to identify DRAs have no scale to assess the medication-relatedness of hospital admission, so some cases might be identified as drug-related, but disease progression may play a larger role. Wallerstedt et al. indicated that medical doctors are more likely to attribute the hospital admission to exacerbation of disease while pharmacists tend to attribute the event to ADEs (Wallerstedt et al., 2021). Therefore, there is a possibility of over-attribution of conditions to ADEs. Several other issues arise in applying causality assessment algorithms to adverse drug events. There is a need to update the algorithmic methods to allow perfect applicability in all possible clinical scenarios accordingly or not with the terms of marketing authorization (Mascolo et al., 2017).

The third limitation is the heterogeneity of electronic medical records. Variability of the completeness of electronic medical records between departments might affect the results. In our study, the share of falls on DRAs might be underestimated as the electronic medical records from the department of surgery were insufficient to evaluate the causality of falls.

The last limitation is the assessment of inter-rater reliability. Fleiss cappa indicated slight agreement (0.09) between the raters. However, only the cases preselected by the main investigator have undergone consensus assessment, as the consensus assessment of each case would be time-consuming. However, given the fact that pharmacists tend to attribute adverse events rather to the medications than the disease, the risk of a potential miss will likely be small.

CONCLUSION

The total prevalence of DRAs to University Hospital Hradec Králové *via* the emergency department was 15.6%. Of 195 DRAs, 74% DRAs were related to treatment safety, and 26% DRAs were related to treatment effectiveness. If we took only manifest DRPs that were the main reason for hospital admissions into account, the prevalence of DRAs would be 7%.

ADEs affecting Gastrointestinal disorders and Metabolism and nutrition disorders accounted for 38% of DRAs related to treatment safety. Cardiac disorders accounted for 32% of all DRAs related to treatment effectiveness.

DRAs related to treatment safety most frequently involved Antithrombotic agents, Antineoplastic agents, Diuretics, Corticosteroids for systemic use, and Beta blocking agents, while DRAs related to treatment effectiveness most frequently involved Diuretics, Antithrombotic agents, Drugs used in diabetes, Agents acting on the renin-angiotensin system, and Lipid modifying agents.

The potential preventability of DRAs was 51%. Anti-inflammatory and antirheumatic products, Antithrombotic agents, and Drugs used in diabetes represented were most frequently associated with preventable DRAs related to treatment safety. The medication classes with the highest of preventability included Anti-inflammatory and antirheumatic products, Psycholeptics, and Drugs used in diabetes. The most common preventable ADEs included gastroduodenal hemorrhage, hypoglycemia, and a depressed level of consciousness.

The preventability aspects involved in potentially preventable DRAs related to treatment safety included primarily problems with drug selection, inappropriate monitoring and problems with dose selection, and inappropriate lifestyle measures. On the contrary, medication nonadherence was the most common preventability aspect of potentially preventable DRAs related to treatment effectiveness.

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 Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové.

AUTHOR CONTRIBUTIONS

ZO, MM, and JV conceived and designed the study. JK created the registry of patients admitted to University Hospital Hradec Králové *via* the department of emergency medicine. ZO designed a Microsoft Access database for data collection. ZO collected and analyzed the data. ZO, MM, and JV were involved in the interpretation of data. JV supervised the study and critically revised the manuscript for important intellectual content. ZO drafted the manuscript, and all co-authors contributed to and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.899151/full#supplementary-material

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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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SYSTEMATIC REVIEW
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Effect Western Medicines Combined With Nao-Xue-Shu in Patients With Hypertensive Intracerebral Hemorrhage: A Network Meta-Analysis

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Purpose: To explore the efficacy of nimodipine, nifedipine, and edaravone (EDA) combined with Nao-Xue-Shu in patients with hypertensive intracerebral hemorrhage (HICH) and to determine the best western medicine combined with Nao-Xue-Shu for treating HICH patients using a ranking method.

Methods: After a comprehensive search of the China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP information database, Chinese Biomedical Database (CBM), PubMed, Embase, and Cochrane Library database from the database establishment 31 December 2021, data extraction and quality assessment were conducted for the included articles. The primary outcome measure was the effectiveness after treatment. Secondary outcome measures were after-treatment the National Institutes of Health Stroke Scale (NIHSS) scores, hematoma volume, perihematoma edema volume, and inflammatory factor expression levels. Statistical analyses were performed using Stata 16.0 and RevMan 5.3.0 software.

Results: We included 19 randomized controlled trials (RCTs) and six non-RCTs. The effective rate after treatment was ranked from the best to the worst as follows: routine cure measure (RCM) + nifedipine + Nao-Xue-Shu, RCM + EDA + Nao-Xue-Shu, RCM + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, RCM + EDA, and RCM. The post-treatment NHISS scores from lowest to highest were as follows: RCM + EDA + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + EDA, RCM + nimodipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, RCM + Nao-Xue-Kang, and RCM. The post-treatment hematoma volume from minimum to maximum was as follows: RCM + EDA + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, RCM + Nao-Xue-Kang, and RCM. The post-treatment perihematoma edema volume from minimum to maximum was as follows: RCM + EDA + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, and RCM. For inflammatory factor expression levels after treatment, IL-6 concentration levels after treatment from lowest to highest wasas follows: RCM + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu,

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RCM + nimodipine + Nao-Xue-Shu, RCM + EDA + Nao-Xue-Shu, and RCM. TNF-α concentration levels after treatment from lowest to highest was as follow: RCM + nimodipine + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, and RCM.

Conclusion: Nao-Xue-Shu combined with nifedipine showed better effectiveness after treatment in HICH patients compared with the other combinations. Nao-Xue-Shu combined with EDA was more effective for improving neurological function and reducing both hematoma and edema volumes around the hematoma compared with the other combinations. However, Nao-Xue-Shu alone or Nao-Xue-Shu combined with nimodipine may be more effective for reducing proinflammatory factor expression.

Keywords: hypertensive intracerebral hemorrhage, edaravone, nimodipine, nifedipine, Nao-Xue-Shu, network meta-analysis

INTRODUCTION

Spontaneous intracerebral hemorrhage (SICH) is the deadliest, most disabling, and most difficult type of stroke to treat (Tapia-Pérez et al., 2014). Unlike most other stroke types, its morbidity and mortality rates have not decreased over time. It is estimated that over two million people are affected by intracerebral hemorrhage (ICH) worldwide each year. One-third of ICH patients die within 1 month, and a significant number of survivors are left with a permanent disability (Feigin et al., 2009; Steiner et al., 2011). Hypertension was also found to be the most important independent risk factor for patients with ICH, and it is present in about 50% of patients with ICH (Wityk and Caplan, 1992). Middle-aged and elderly people with untreated hypertension or uncontrolled treated hypertension are at risk of ICH, and this SICH caused by hypertension is called hypertensive ICH (HICH) (Woo et al., 2004; Xu et al., 2017).

For HICH patients, early hematoma removal may alleviate ischemia or remove toxic chemicals, thus reducing damage to the neurological tissue (Xi et al., 2006; Vespa et al., 2013). Surgery has the potential to improve neurological recovery after HICH. However, surgical treatment can only partially remove the hematoma, and completely removing the hematoma takes 3–5 days. In HICH patients, the presence of a post-operative edema band surrounding the hematoma and subsequent harm induced by the surgical procedure may limit the effectiveness of its treatment (Teernstra et al., 2003; Thompson et al., 2015). Furthermore, most prospective randomized controlled trials (RCTs) have failed to show that surgical treatment improves the prognosis in these patients (Auer et al., 1989; Batjer et al., 1990; Mendelow et al., 2005). Therefore, there is an urgent need to explore effective treatment options to improve clinical outcomes in patients with HICH.

In addition to active surgical treatment, many researchers have recently investigated the effectiveness of the conservative use of western medicine (such as antihypertensive drugs, anticoagulants, and dehydrant) and Chinese medicine (such as Nao-Xue-Kang and Nao-Xue-Shu) to replace treatment or as palliative treatment for HICH patients. Among them, Nao-Xue-Shu is a typical traditional Chinese medicine.

Nao-Xue-Shu promotes Qi, activates blood, and removes blood stasis, thereby promoting hematoma absorption, reducing brain edema around the hematoma, modulating inflammatory factor to improve the microenvironment, and reducing free radicals. Some researchers have used it alone or in combination with western medicine to treat HICH patients, and explored their effectiveness in reducing the volume of the hematoma and degree of edema around a hematoma in patients with HICH to improve nerve function damage and regulate inflammatory factors (Jiang et al., 2016). Currently, western drugs that have been explored include nimodipine, nifedipine, and edaravone (EDA), all of which had some effectiveness in improving vascular spasm, scavenging free radicals, and alleviating or preventing secondary brain injury after cerebral hemorrhage (Li et al., 2014; Zhang Z, 2017; Li, 2017; Zhang, 2019). However, there is still a lack of direct-comparison evidence between different western pharmaceuticals paired with Nao-Xue-Shu, and it is unclear which western drugs combined with Nao-Xue-Shu are best for patients with HICH. Therefore, the network meta-analysis indirect comparison principle was used to explore the efficacy of nimodipine, nifedipine, and EDA combined with Nao-Xue-Shu in patients with HICH and to analyze which western medicine combined with Nao-Xue-Shu is best for treating HICH patients using a sequencing method.

METHODS

The systematic review and network meta-analysis were performed according to the checklist of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for network meta-analysis.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this study were in accordance with the PICO (P: patient, I: intervention, C: comparison, O: outcome) principle. The inclusion criteria were as follows: patients with a history of hypertension and computed tomography scan-confirmed ICH at the time of the

first onset and at least 18 years of age. In the intervention group, patients received Nao-Xue-Shu or Nao-Xue-Shu combined with a western medicine treatment in addition to the routine cure measures (RCM). In the control group, patients RCM alone or RCM combined with a western medicine treatment. Study types included RCTs or non-RCTs that enrolled at least 25 people. The primary outcome indicator was the clinical response rate after treatment (response rate = mostly cured + significant improvement + improvement) on the basis of the National Institutes of Health Stroke Scale (NIHSS) neurological deficit scores, which was classified as follows: 1) mostly cured, where the neurological deficit score decreased by 91–100 percent, and the disability degree was grade 0; 2) significantly improved, where the neurological deficit score decreased by 46–90 percent, and the disability degree was grade 1 to 3; 3) improved, where the neurological deficit score decreased by 18–45 percent; 4) no change, where the neurological deficit score decreased by 17 percent; 5) deterioration, where the neurological deficit score decreased or increased by more than 18 percent; and 6) death. Secondary outcome indicators were the volume of cerebral hematoma and edema after treatment and the concentration levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α after treatment.

The exclusion criteria were as follows: publications including patients with cerebral hemorrhage caused by rupture of cerebral arteriovenous malformations or trauma; publications including patients with severe heart, lung, liver, kidney, or coagulation dysfunction; single-arm trials; animal trials; and case reports.

Literature Search

"Intracranial hemorrhage," "intracerebral hemorrhage," "brain hemorrhage," "Naoxueshu," "Nao-Xue-Shu," and "Nao Xue Shu" were used as MeSH search terms and keywords. A comprehensive search was conducted using the China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP information database, Chinese Biomedical Database (CBM), PubMed, Embase, and Cochrane Library database from the database establishment 31 December 2021. Relevant references, abstracts of conference papers, ongoing or unpublished trials in World Health Organization clinical registries, and relevant meta-analyses or systematic reviews published in the past 3 years were searched manually and retrieved.

Data Screening and Quality Evaluation

All the retrieved publications were independently screened by two reviewers. The included RCTs were evaluated using the six aspects of the Cochrane risk of bias tool, as follows: randomization, allocation hiding, blind application, data integrity, selective reporting, and other biases. The included non-RCTs were evaluated using the three aspects of the Newcastle–Ottawa scale, as follows: selectivity, comparability, and results. Any problems or disagreements encountered in the process of screening, including analysis articles and quality assessment, were resolved by two reviewers after consultation or by a third reviewer through consultation.

Data Extraction

The following data from all the included articles were extracted using Microsoft Excel worksheets: author, publication year, country, study type, age, intervention measures, number of participants in each intervention group, and clinical outcome indicators (primary and secondary outcome indicators). For studies with missing data, the original author was contacted to try to obtain the data.

Statistical Analysis

The RevMan 5.3 (Cochrane Collaboration, London, United Kingdom) was used for paired meta-analysis. The relative ratio (RR) and 95% confidence interval (CI) were used for dichotomous data. The mean and standard deviation (SD) were used to evaluate the efficacy of different treatment regimens for continuous data. The heterogeneity was assessed using the Cochrane Q test and I^2 statistic. $I^2<50\%$ was considered to have low heterogeneity and a fixed-effect model was used, while $I^2>50\%$ was considered to have high heterogeneity and a random-effect model was used. A funnel plot was performed when more than 10 articles were included, which was used to evaluated the potential publication bias. Statistical difference was considered when the two-sided p value was less than 0.05.

The network meta-analysis was performed using Stata 16.0 software (StataCorp, College Station, TX United States) to analyze the efficacy of different interventions. Before evaluating the direct and indirect evidence, we use the cut-off point method to verify whether there was inconsistency in the Network model. We used surface under the cumulative ranking curves (SUCRA) to rank the interventions for each outcome.

RESULTS

Literature Search

There were 1,001 articles that were retrieved. Among them, 134 duplicate articles were deleted after reading the titles and abstracts, and 808 articles were deleted on the basis of the research purpose and article type. Additionally, 20 articles were deleted on the basis of the inclusion and exclusion criteria. Finally, 25 articles were included in the network meta-analysis. The flow chart of the study selection process is shown in **Figure 1**. Nineteen RCT articles (Lu et al., 2004; Zhang and Ji, 2011; Yao, 2012; Li et al., 2014; Miao and Yan, 2014; Wang et al., 2014; Jiang et al., 2016; Wang et al., 2016; Zhang Z, 2017; Zhang T. J, 2017; Li, 2017; Wei and Ma, 2017; Yang et al., 2017; Zhu et al., 2017; Yi and Zeng, 2018; Zhou et al., 2018; Hou et al., 2019; Yang, 2019; Chen and Ma, 2020) and six non-RCT articles (Yang et al., 2015; Guo et al., 2017; Hao et al., 2018; Duan et al., 2019; Wang et al., 2019; Zhang, 2019) were included in the network meta-analysis, with a total sample size of 2,335 patients. Types of included studies, types of interventions, and other details are shown in **Supplementary Table S1**.

Quality Evaluation

Nineteen RCTs were included in the analysis, all of which used the correct randomization method and had complete data.

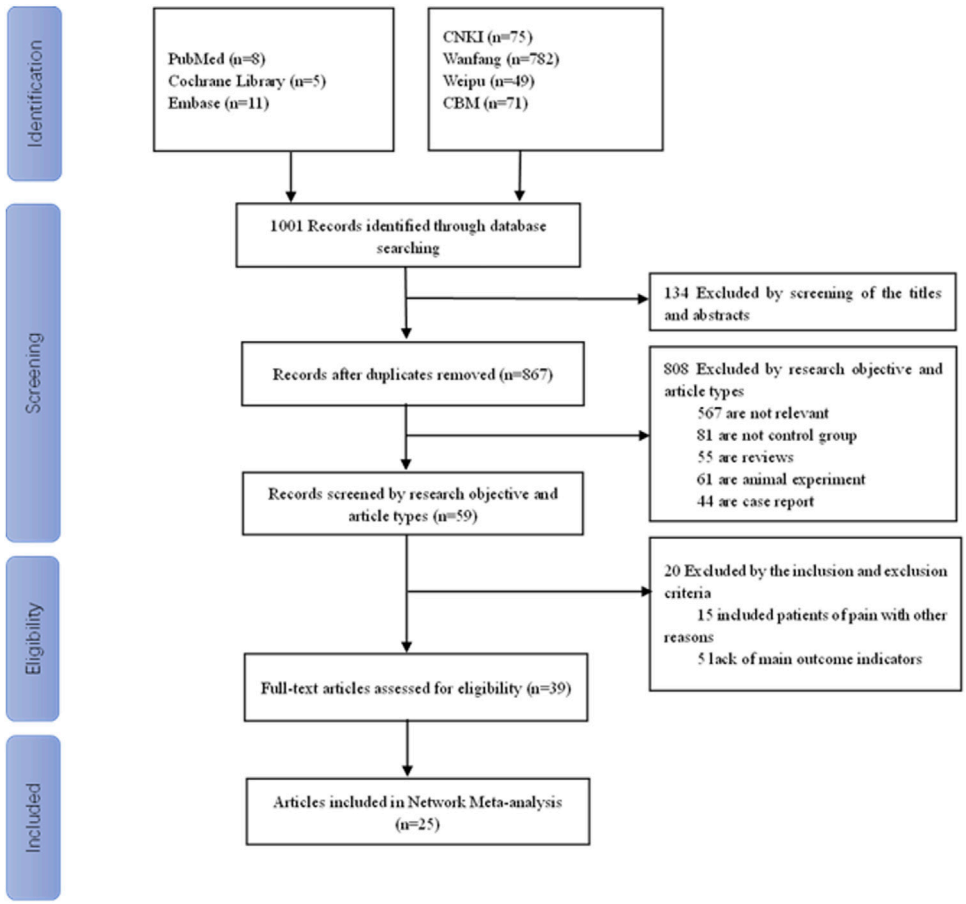

FIGURE 1 | Flow chart of the study selection process.

Except for Wang et al. (2014) (Wang et al., 2014) and Wang et al. (2016) (Wang et al., 2016), there were no selective reports. However, it is unclear whether implementation of the allocation concealment and blinding was performed correctly in most studies. Thus, the quality of the RCTs included in the analysis was moderate (**Figure 2**). The Newcastle–Ottawa Scale assessment tool was used for the six non-RCTs, which scored high in selectivity, comparability, and results (**Supplementary Table S2**), indicating that the included non-RCTs were of high quality.

Traditional Meta-Analysis and Publication Bias

Using the fixed-effect model, a subgroup analysis of the post-treatment efficiency of the different interventions revealed that there was no heterogeneity between subgroups (I^2<50%, $p > 0.1$; **Supplementary Figure S1**). This analysis revealed that, compared with RCM, RCM combined with Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, and RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with EDA and Nao-Xue-Shu had higher post-treatment efficiency. Additionally, RCM combined with EDA and Nao-Xue-Shu also had a higher post-treatment response rate than RCM combined with EDA. Using the random-effect model, subgroup analysis of the NIHSS scores after treatment with different interventions indicated that there was significant heterogeneity between the subgroups (I^2>50%, $p < 0.1$; **Supplementary Figure S2**). This analysis showed that compared with RCM, RCM combined with Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, and RCM combined with EDA and Nao-Xue-Shu had a lower NIHSS scores after treatment (the lower the NIHSS scores, the better the patient's neurological function). However, the NIHSS scores of RCM combined with nimodipine were not lower than that of RCM alone. Additionally, NIHSS scores of RCM combined with EDA and Nao-Xue-Shu were not lower than RCM combined with EDA.

A funnel plot analysis was performed on the post-treatment efficiency of the two interventions, revealed that no evidence of publication bias was observed for the comparison and the results were statistically robust (**Figure 3**).

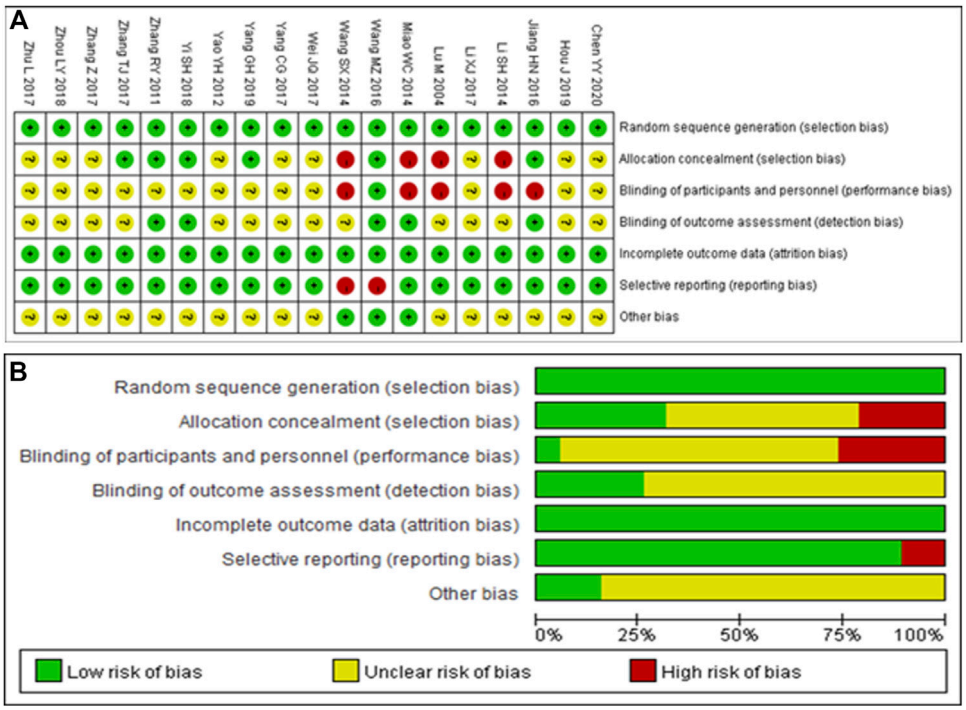

FIGURE 2 | Quality assessment of the included randomized controlled trials. **(A)** Each risk of bias item is presented as the percentages across all included studies. **(B)** Each risk of bias item for each included study. Green indicates a low risk of bias, yellow indicates an unclear risk of bias, and red indicates a high risk of bias.

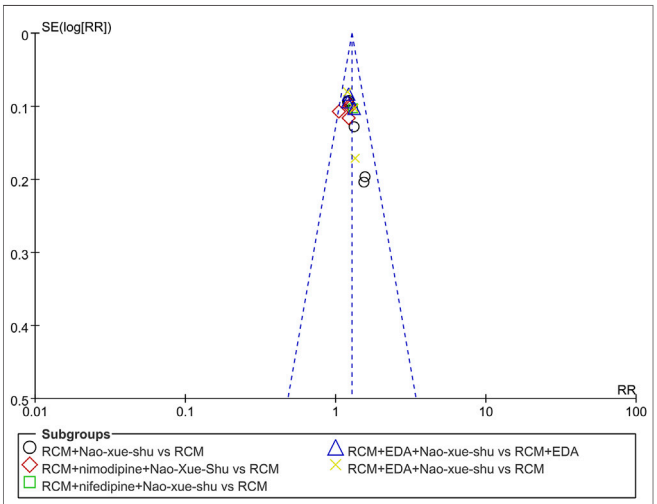

FIGURE 3 | Funnel plots for the detection of publication bias on the post-treatment efficicency.

Network Meta-Analysis

Network Diagram of Different Intervention Measures

A direct comparison is shown if there is a direct line between the two intervention groups, but if there is no line, there is no evidence of a direct comparison. The dot size in the figure represents the sample size, and the line thickness represents the number of studies. RCM was found to be the most frequent control (**Figures 4A–F**).

Inconsistency Test

There was no direct or indirect comparative evidence in the included studies, so no inconsistency test was conducted.

Sequence Diagram of Network Meta-Analysis

Among the articles included in the analysis, 17 reported post-treatment response rates, involving six different interventions, for which a network meta-analysis was performed (**Figure 5A**). This analysis revealed that RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with EDA and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, and RCM combined with EDA had higher post-treatment effective rate than RCM for treating patients with HICH. The order of post-treatment effectiveness from best to worst was as follows: RCM combined nifedipine and Nao-Xue-Shu, RCM combined EDA and Nao-Xue-Shu, RCM combined Nao-Xue-Shu, RCM combined nimodipine and Nao-Xue-Shu, RCM combined EDA, and finally RCM.

There were 15 articles that included the NIHSS scores after treatment, involving seven different interventions. The network meta-analysis (**Figure 5B**) revealed that RCM combined with EDA and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with EDA, RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, and RCM combined with Nao-Xue-Kang had lower post-treatment NIHSS scores than RCM for treating patients with HICH. The order of post-treatment NIHSS scores from lowest to highest was as follows: RCM combined with EDA and Nao-Xue-

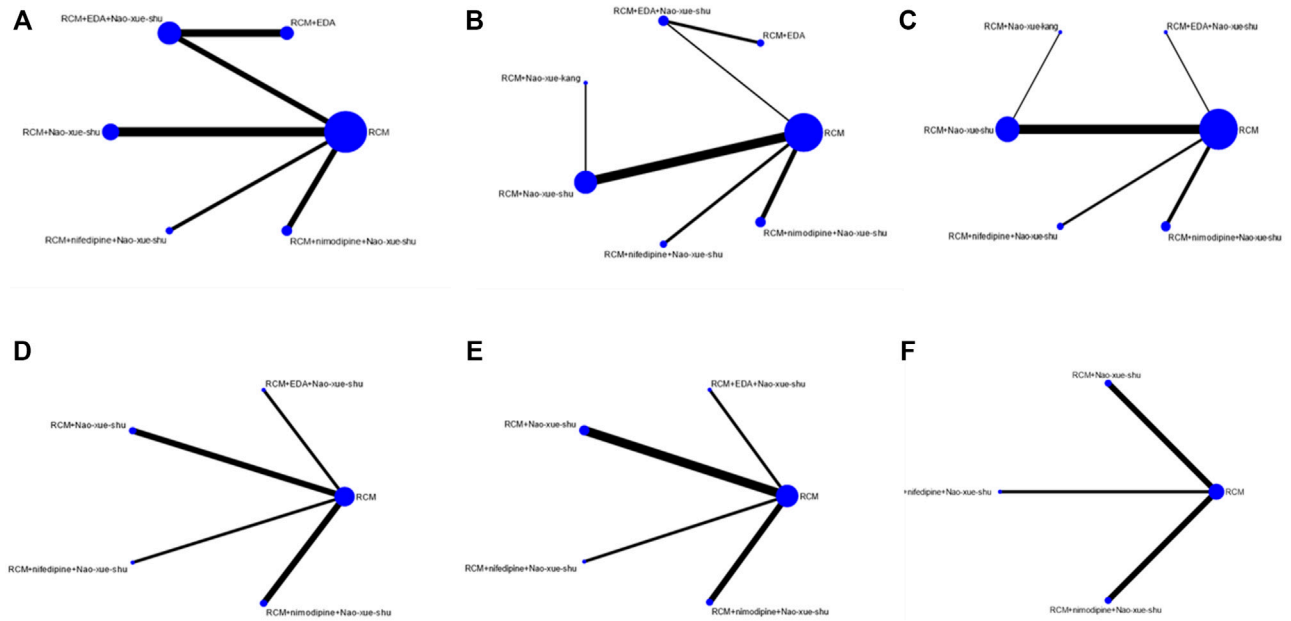

FIGURE 4 | Network charts. Network charts based on the **(A)** effectiveness of different interventions, **(B)** neurological deficit score, **(C)** hematoma volume after treatment, **(D)** edema volume after treatment, **(E)** IL-6 concentration after treatment, and **(F)** TNF-α concentration after treatment. IL, interleukin; TNF, tumor necrosis factor.

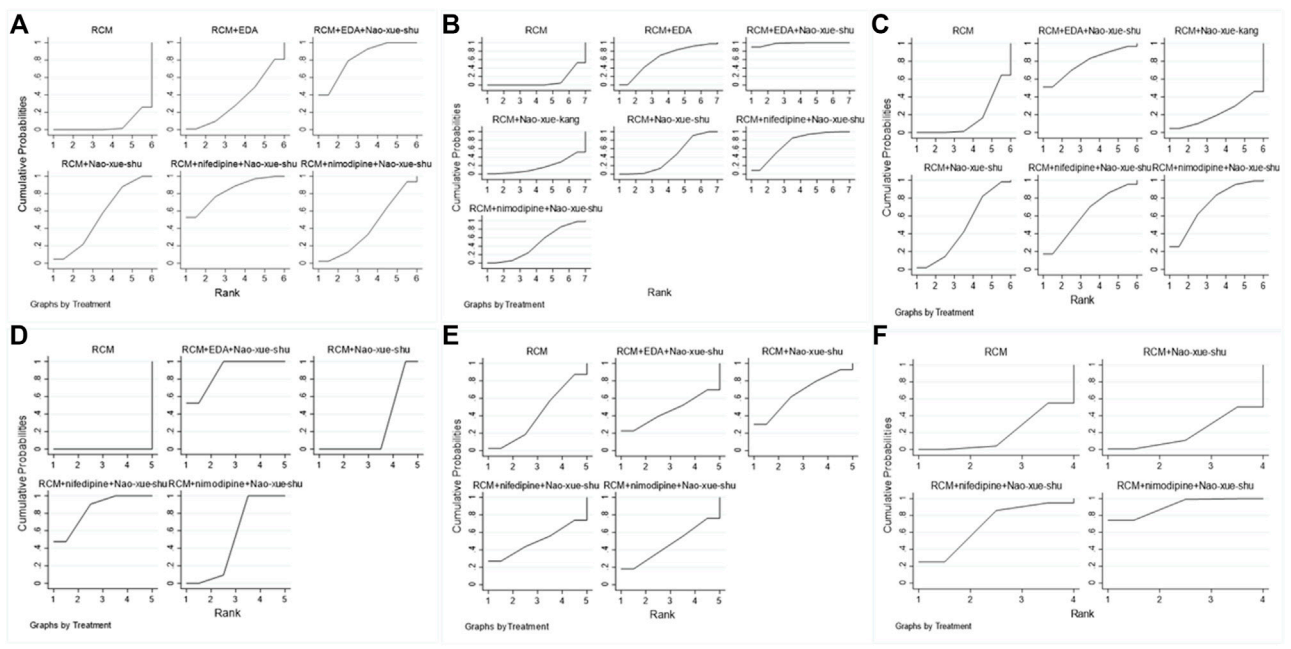

FIGURE 5 | The rank charts. Rank charts based on the **(A)** effectiveness of different interventions, **(B)** neurological deficit score, **(C)** hematoma volume after treatment, **(D)** edema volume after treatment, **(E)** IL-6 concentration after treatment, and **(F)** TNF-α concentration after treatment IL, interleukin; TNF, tumor necrosis factor.

Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with EDA, RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, RCM combined with Nao-Xue-Kang, and finally RCM.

For the post-treatment hematoma volume, 14 studies involving six different interventions were analyzed in the network meta-analysis (**Figure 5C**). This analysis revealed that RCM combined with EDA and Nao-Xue-Shu, RCM combined

with nimodipine and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, and RCM combined with Nao-Xue-Kang had a smaller post-treatment hematoma volume than that of RCM for treating patients with HICH. The order of post-treatment hematoma volume from minimum to maximum was as follows: RCM combined with EDA and Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, RCM combined with Nao-Xue-Kang, and finally RCM.

For the post-treatment perihematoma edema volume, six studies involving five different interventions were analyzed using a network meta-analysis (**Figure 5D**). This analysis revealed that RCM combined with EDA and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, and RCM combined with Nao-Xue-Shu showed a smaller post-treatment edema volume than that of RCM for treating patients with HICH. The order of post-treatment edema volume from minimum to maximum was as follows: RCM combined with EDA and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, and finally RCM.

There were seven reports that presented the IL-6 concentration levels after treatment, involving five different interventions. A network meta-analysis was performed on these seven studies (**Figure 5E**), and it revealed that RCM combined with Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, and RCM combined with EDA and Nao-Xue-Shu showed lower post-treatment IL-6 concentration levels than those of RCM when treating HICH patients. The order of post-treatment IL-6 concentration levels from lowest to highest was as follows: RCM combined with Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with EDA and Nao-Xue-Shu, and finally RCM.

Additionally, there were five reports that presented the TNF-α concentration levels after treatment, involving four different interventions. The network meta-analysis (**Figure 5F**) revealed that RCM combined with nimodipine and Nao-Xue-Shu and RCM combined with nifedipine and Nao-Xue-Shu had lower post-treatment TNF-α concentration levels than RCM combined with those of Nao-Xue-Shu and RCM when treating HICH patients. The order of post-treatment TNF-α concentration levels from lowest to highest was as follows: RCM combined with nimodipine and Nao-Xue-Shu, RCM combined with nifedipine and Nao-Xue-Shu, RCM combined with Nao-Xue-Shu, and RCM.

DISCUSSION

HICH is a common neurosurgical disease, which can be life-threatening and also cause a heavy economic burden to patients' families and to society (Zhang et al., 2014). Although adverse effects associated with HICH are well known, there have been no major advances in treatment regimens to date (Tang et al., 2018). Traditional medicine, especially Chinese medicine, is a complete medical system with thousands of years of application history, and its clinical practice mainly focuses on diagnosis and treatment. Chinese medicine has been shown to play a vital role in treating diseases such as diabetes, cancer, and rheumatoid arthritis (Wang S et al., 2021; Wang Y et al., 2021; Li et al., 2021; Xiang et al., 2021). Therefore, an increasing number of Chinese scholars began to explore the efficacy and safety of Chinese medicine therapy in patients with HICH.

Nao-Xue-Shu is a traditional Chinese patent medicine that is composed of astragalus root, leech, stone calamus, *Achyranthes*, cortex moutan, rhubarb, and Chuanxiong. Based on its beneficial effects of tonifying Qi, activating blood, and removing blood stasis, an increasing number of researchers are exploring the efficacy of this medicine alone or in combination with western medicine to treat HICH patients. However, it is unclear whether this drug is more effective when used alone or in combination with western medicine, and the best western medicine combined with Nao-Xue-Shu to treat HICH patients has not been determined.

Thus, the network meta-analysis indirect comparison principle was used to comprehensively search the existing clinical trials involving HICH treatment with Nao-Xue-Shu alone or in combination with different western medicines. Nineteen RCTs (Lu et al., 2004; Zhang and Ji, 2011; Yao, 2012; Li et al., 2014; Miao and Yan, 2014; Wang et al., 2014; Jiang et al., 2016; Wang et al., 2016; Zhang Z, 2017; Zhang T. J, 2017; Li, 2017; Wei and Ma, 2017; Yang et al., 2017; Zhu et al., 2017; Yi and Zeng, 2018; Zhou et al., 2018; Hou et al., 2019; Yang, 2019; Chen and Ma, 2020) and six non-RCTs (Yang et al., 2015; Guo et al., 2017; Hao et al., 2018; Duan et al., 2019; Wang et al., 2019; Zhang, 2019) were included. The results showed that compared with RCM, treating HICH patients with RCM + nifedipine + Nao-Xue-Shu, RCM + EDA + Nao-Xue-Shu, RCM + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, or RCM + EDA showed higher post-treatment effectiveness. HICH patients treated with RCM + EDA + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + EDA, RCM + nimodipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, or RCM + Nao-Xue-Kang showed lower post-treatment NIHSS scores compared with those of RCM. Additionally, RCM + EDA + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + Nao-Xue-Shu, or RCM + Nao-Xue-Kang treatment in HICH patients showed a smaller post-treatment hematoma volume compared with that of RCM, while RCM + EDA + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, or RCM + Nao-Xue-Shu showed a smaller post-treatment edema volume compared with RCM. Moreover, RCM + Nao-Xue-Shu, RCM + nifedipine + Nao-Xue-Shu, RCM + nimodipine + Nao-Xue-Shu, or RCM + EDA + Nao-Xue-Shu showed lower post-treatment IL-6 and TNF-α concentration levels compared with RCM.

Combined with the above analysis, Nao-Xue-Shu combined with nimodipine, nifedipine, or EDA had higher post-treatment efficiency and also significantly improved the neurological function compared with that of Nao-Xue-Shu alone.

Additionally, the above-mentioned combinations of Chinese and western drugs reduced both the hematoma and edema volumes around hematoma and the release of pro-inflammatory factors compared with Nao-Xue-Shu alone. Among these combinations, Nao-Xue-Shu combined with nifedipine improved treatment effectiveness the most, while Nao-Xue-Shu combined with EDA improved the neurological function and reduced the hematoma and edema volumes around hematoma the most compared with the other groups. Furthermore, treatment with Nao-Xue-Shu alone or Nao-Xue-Shu combined with nimodipine may be more effective in reducing the expression level of pro-inflammatory factors compared with the other groups. Thus, we found that for HICH, various western drugs combined with Nao-Xue-Shu had their own therapeutic advantages. However, it remains unclear which western drugs combined with Nao-Xue-Shu are more suitable for HICH patients.

There are some limitations in this study. First, all studies included in the analysis were research from China, and because the included studies were not from any other countries or ethnic groups, we cannot determine whether Nao-Xue-Shu combined with western medicine can be generalized to other countries and ethnicities. Second, this analysis included non-RCTs and medium-quality RCTs, so high-quality, large-scale, multi-center RCTs are still needed to further verify the efficacy and safety of Nao-Xue-Shu combined with different western drugs to treat HICH patients.

CONCLUSION

The results of this network meta-analysis suggest that Nao-Xue-Shu combined with nifedipine showed better effectiveness after treatment in HICH patients compared with the other combinations. Nao-Xue-Shu combined with EDA was more effective for improving neurological function and reducing both hematoma and edema volumes around the hematoma compared with the other combinations. However, Nao-Xue-Shu alone or Nao-Xue-Shu combined with nimodipine may be more effective for reducing proinflammatory factor expression.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

CT performed the study subject and design, data extraction, statistical analysis, interpretation of data and manuscript drafting. LM contributed to the study design, data extraction, statistical analysis and manuscript revising. MF contributed to the study design, data extraction, statistical analysis and interpretation of data. LX and WQ performed study design, statistical analysis, and critical revision of manuscript. FM and ZZ extracted the data. SD and HQ were involved in critical revision of manuscript. The final manuscript was approved by all authors.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.892904/full#supplementary-material

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SYSTEMATIC REVIEW
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Risk of Fracture With Dipeptidyl Peptidase-4 Inhibitors, Glucagon-like Peptide-1 Receptor Agonists, or Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-analysis Combining 177 Randomized Controlled Trials With a Median Follow-Up of 26 weeks

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Aim: This study aims to investigate the association between the use of dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), or sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and the risk of fracture among patients with type 2 diabetes mellitus.

Methods: Medline, Embase, Cochrane Library, and Clinical-Trials.gov databases were searched for randomized controlled trials (RCTs). Network meta-analysis was performed for total fracture and a series of secondary outcomes.

Results: A total of 177 RCTs (n = 165,081) involving the risk of fracture were identified (a median follow-up of 26 weeks). DPP-4i, GLP-1 RAs, and SGLT-2i did not increase total fracture risk compared with insulin (odds ratio: 0.86, 95% confidence interval: 0.39–1.90; 1.05, 0.54–2.04; 0.88, and 0.39–1.97, respectively), metformin (1.41, 0.48–4.19; 1.72, 0.55–5.38; 1.44, 0.48–4.30), sulfonylureas (0.77, 0.50–1.20; 0.94, 0.55–1.62; 0.79, 0.48–1.31), thiazolidinediones (0.82, 0.27–2.44; 1.00, 0.32–3.10; 0.83, 0.27–2.57), α-glucosidase inhibitor (4.92, 0.23–103.83; 5.99, 0.28–130.37; 5.01, 0.23–107.48), and placebo (1.04, 0.84–1.29; 1.27, 0.88–1.83; 1.06, 0.81–1.39).

Conclusions: The use of DPP-4i, GLP-1 RAs, or SGLT-2i is unlikely to increase the risk of fracture among type 2 diabetes mellitus patients.

Keywords: DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, fracture, diabetes mellitus

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1 INTRODUCTION

There is an increased risk of fracture observed in both female and male patients with type 2 diabetes mellitus (T2DM) compared with non-diabetic individuals (Janghorbani et al., 2007; Formiga et al., 2020). Fracture in T2DM was significantly associated with severe disability, social burden, and reduction in quality of life (Hamann et al., 2012). The risk of fracture in T2DM patients may be attributed to reduced bone strength or poor bone quality, with varied effects of hypoglycemic drugs on bone metabolism. It is particularly important to determine whether hypoglycemic drugs can increase the risk of fracture.

A lot of research in this field has been carried out, and there are studies which reported the effects of different hypoglycemic drugs on fracture risk in T2DM (Lee et al., 2019; Salari-Moghaddam et al., 2019; Qian et al., 2020; Zhang et al., 2020). Dipeptidyl peptidase-4 inhibitors (DPP-4i) and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become widely used in T2DM patients as a novel class of blood glucose–lowering drugs with improved weight loss, low risk for hypoglycemia, and reduction in glycated hemoglobin (Drucker and Nauck, 2006; Ismail-Beigi, 2012; Cefalu et al., 2014). Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are another type of novel glucose-lowering agent and have also gained increasing use in recent years, which reduce plasma glucose concentrations by inhibiting proximal tubular reabsorption of glucose in the kidney (Davis et al., 2014). Though previous studies, including meta-analyses, have investigated the impact of DPP-4i, GLP-1 RAs, and SGLT-2i on the risk of fracture in patients with T2DM, their findings are not consistent (Su et al., 2015; Gamble et al., 2018; Adimadhyam et al., 2019; Cheng et al., 2019; Hidayat et al., 2019).

This network meta-analysis was performed to investigate the association between the use of DPP-4i, GLP-1 RAs, or SGLT-2i and the risk of fracture among patients with T2DM by synthesizing the data from all available randomized controlled trials (RCTs).

2 PARTICIPANTS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) checklist.

2.1 Search Strategy

Medline, Embase, ClinicalTrials.gov, and the Cochrane Library were searched from inception to 7 September 2019. We used "Glucagon-Like Peptide-1 Receptor," "Dipeptidyl-Peptidase IV Inhibitors," and "Sodium-Glucose Cotransporter 2 Inhibitors" as keywords or MeSH terms, accompanied with relevant free words, to search these above databases. Details of search strategies are provided in **Supplementary Appendix S1**.

2.2 Study Selection

Only RCTs involving DPP-4i, GLP-1 RAs, or SGLT-2i compared with placebo or other antidiabetic agents [metformin (Met), insulin, sulfonylurea (SU), thiazolidinedione (TZD), and

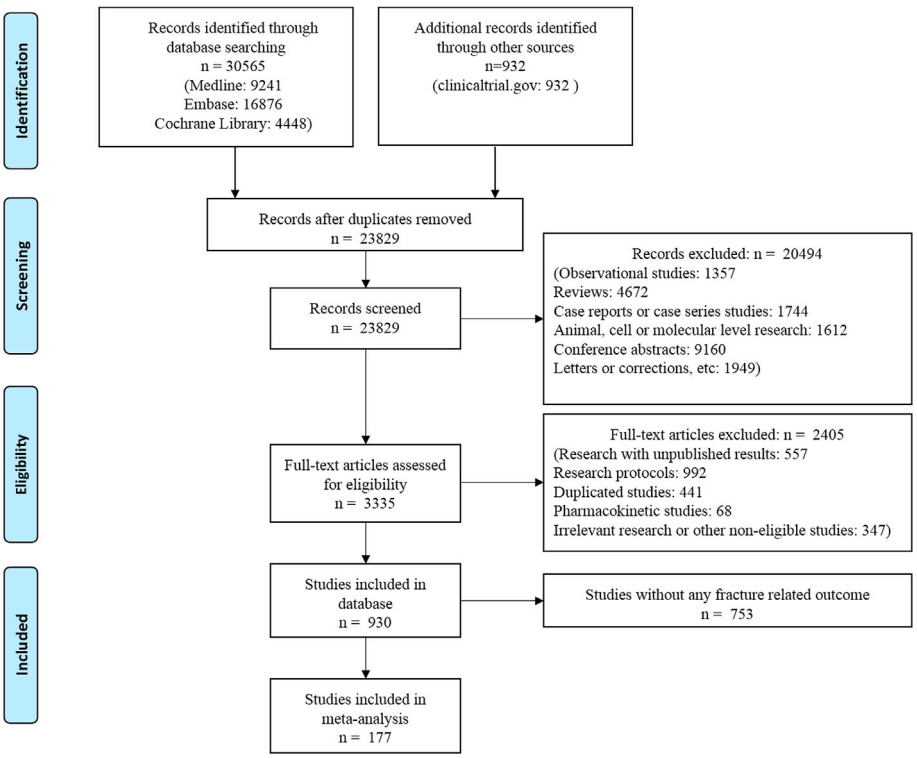

FIGURE 1 | Flow chart of studies considered for inclusion.

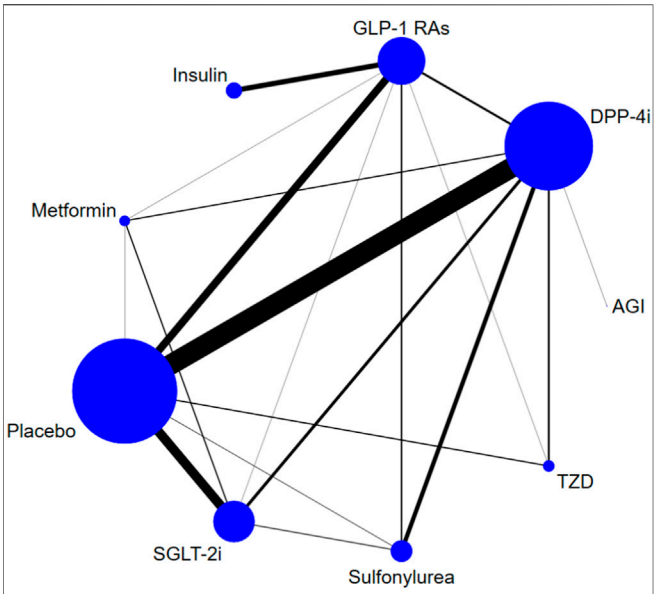

FIGURE 2 | Evidence structure of DPP-4i–, GLP-1 RA–, and SGLT-2i–based therapies on risk of fracture. Note: The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials. The width of the lines represents the cumulative number of randomized controlled trials for each pairwise comparison, and the size of every node is proportional to the number of randomized participants (sample size). DPP-4i: dipeptidyl peptidase-4 inhibitors; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; TZD: thiazolidinedione; AGI: alpha-glucosidase inhibitor; SGLT-2i: sodium-glucose cotransporter-2 inhibitors.

alpha-glucosidase inhibitor (AGI)] in patients with T2DM and reporting on any fracture as an outcome were included in this analysis (**Supplementary Appendix S2**). No other restrictions were applied to our eligibility criteria. The eligibility of studies was assessed independently by three reviewers (FL, SC, and FS), with any disagreement resolved by consensus.

2.3 Data Extraction and Quality Assessment

Data extraction was conducted by using the Aggregate Data Drug Information System (ADDIS version 1.16.5). Data extracted from eligible studies included trial information (first author, publication year, sample size, trial duration, types of interventions, and controls), baseline characteristics of patients (background therapy, duration of T2DM, age, baseline level of HbA1c, body weight, etc.), and results on bone fracture (including all fractures, upper limb fracture, lower limb fracture, hip fracture, etc.). Two investigators (FL and SC) extracted data independently, in duplicate.

The quality of studies was assessed according to the extracted information by Cochrane Collaboration's tool for assessing risk of bias [including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., company funding)] (Higgins et al., 2022). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence as high, moderate, low, or very low by taking into account the within-study limitations, imprecision, heterogeneity, indirectness, and publication bias for each outcome (University of Bern IoSaPM, 2017). We reported this study according to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) checklist (Hutton et al., 2015).

2.4 Data Analysis

2.4.1 Methods for Direct Treatment Comparisons

Traditional pairwise meta-analysis was performed by using the DerSimonian–Laird random-effects model (DerSimonian and Laird, 1986). The odds ratio (OR) and 95% confidence interval (CI) for each outcome were calculated. I^2 was used to assess the heterogeneity of direct treatment.

2.4.2 Methods for Indirect and Mixed Comparisons

The primary outcome of this study is total fracture. In all studies included, some studies have reported the events of fractures in different body parts, for instance, spinal fracture, hip fracture, upper limb fracture, lower limb fracture, and other fractures. So network meta-analysis was also performed for a series of secondary outcomes of the specific fractures of our concern, including spinal fracture, hip fracture, upper limb fracture, lower limb fracture, and other fractures. We performed a frequentist random-effects network meta-analysis. OR with 95% CI was summarized and integrated into a network evidence body for each fracture outcome. We obtained the result of any pairwise comparison in the network evidence body through direct or indirect comparison. A node-splitting model (Dias et al., 2010) and a loop-specific approach (Higgins et al., 2012) were used to assess the inconsistency between direct and indirect treatment effects. A predictive interval plot that incorporates the extent of heterogeneity was used to evaluate the extent of uncertainty in the estimated effect size for the network meta-analysis. Uncertainty affected by heterogeneity was defined as a disagreement between the CIs of relative treatment effects and their predictive intervals. A series of box plots were drawn to compare whether there were significant differences in baseline age, HbA1c, duration of T2DM, sample size, and trial duration between different comparison pairs, so as to evaluate the transitivity assumption of this network body of evidence.

2.4.3 Publication Bias

The difference between the observed effect size and the comparison-specific summary effect for each study was calculated. Publication bias was evaluated according to whether the funnel diagram was symmetrical.

All analyses were conducted by using STATA Version.14.0 (pairwise meta-analysis, network meta-analysis, estimation of inconsistency and heterogeneity, and funnel plot) and R Version.4.1.1.

3 RESULTS

3.1 Study Characteristics

The flow chart of the literature search is shown in **Figure 1**. Overall, 177 RCTs (n = 165,081 patients) met the eligibility criteria and were included in this network meta-analysis. Trial

DPP-4i	0.82 (0.53,1.27)	0.98 (0.72,1.35)	0.86 (0.39,1.90)	1.41 (0.48,4.19)	0.77 (0.50,1.20)	0.82 (0.27,2.44)	4.92 (0.23,103.83)	1.04 (0.84,1.29)
1.22 (0.79,1.88)	GLP-1 RAs	1.20 (0.75,1.91)	1.05 (0.54,2.04)	1.72 (0.55,5.38)	0.94 (0.55,1.62)	1.00 (0.32,3.10)	5.99 (0.28,130.37)	1.27 (0.88,1.83)
1.02 (0.74,1.40)	0.84 (0.52,1.33)	SGLT-2i	0.88 (0.39,1.97)	1.44 (0.48,4.30)	0.79 (0.48,1.31)	0.83 (0.27,2.57)	5.01 (0.23,107.48)	1.06 (0.81,1.39)
1.16 (0.53,2.57)	0.96 (0.49,1.86)	1.14 (0.51,2.57)	Insulin	1.65 (0.44,6.15)	0.90 (0.38,2.12)	0.95 (0.26,3.55)	5.72 (0.24,133.65)	1.21 (0.57,2.59)
0.71 (0.24,2.10)	0.58 (0.19,1.81)	0.69 (0.23,2.07)	0.61 (0.16,2.27)	Metformin	0.55 (0.17,1.75)	0.58 (0.12,2.68)	3.48 (0.14,88.55)	0.74 (0.25,2.18)
1.29 (0.84,2.00)	1.06 (0.62,1.82)	1.27 (0.77,2.10)	1.11 (0.47,2.62)	1.83 (0.57,5.83)	Sulfonylurea	1.06 (0.33,3.40)	6.35 (0.29,138.35)	1.34 (0.85,2.11)
1.22 (0.41,3.64)	1.00 (0.32,3.12)	1.20 (0.39,3.69)	1.05 (0.28,3.91)	1.73 (0.37,8.00)	0.95 (0.29,3.04)	TZD	6.00 (0.24,153.27)	1.27 (0.42,3.80)
0.20 (0.01,4.29)	0.17 (0.01,3.64)	0.20 (0.01,4.28)	0.17 (0.01,4.09)	0.29 (0.01,7.33)	0.16 (0.01,3.43)	0.17 (0.01,4.25)	AGI	0.21 (0.01,4.50)
0.96 (0.78,1.19)	0.79 (0.55,1.14)	0.94 (0.72,1.23)	0.83 (0.39,1.77)	1.36 (0.46,4.03)	0.74 (0.47,1.17)	0.79 (0.26,2.36)	4.73 (0.22,100.56)	placebo

FIGURE 3 | Odds ratio with 95% CI of network meta-analysis for risk of fracture. Note: Results of direct comparisons were listed in the upper triangle, and the estimation was calculated as the row-defining treatment compared with the column-defining treatment. Results of network meta-analysis were listed in the lower triangle, and the estimation was calculated as the column-defining treatment compared with the row-defining treatment. NA: not available. DPP-4i: dipeptidyl peptidase-4 inhibitors; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; SGLT-2i: sodium-glucose cotransporter-2 inhibitors; TZD: thiazolidinedione; AGI: alpha-glucosidase inhibitor.

duration ranged from 12 to 384 weeks, with a median follow-up of 26 weeks (IQR: 24–54 weeks). The average age of the included patients was 57.68 years (SD: 5.08). The mean diabetes duration at baseline was 8.20 years (SD: 4.45) and the mean baseline HbA1c level was 8.14% (SD: 0.53%).

3.2 Evidence Network

Eight classes of treatments were analyzed, including DPP-4i (consisting of any drug among sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, teneligliptin, etc.), GLP-1 RAs (consisting of any drug among albiglutide, exenatide, lixisenatide, liraglutide, semaglutide, etc.), SGLT-2i (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, ertugliflozin, luseogliflozin, tofogliflozin, etc.), and five other classes of active antidiabetic agents (Met, insulin, SU, TZD, and AGI) and placebo. 166 trials (93.8%) were two-arm studies, 10 trials were three-arm studies, and one trial was a four-arm study (**Figure 2**). The box plots of baseline characteristics drawn according to the comparison pairs are shown in **Supplementary Appendix S9**. The patients' baseline age (years), baseline HbA1c (%), baseline duration of T2DM (years), sample size, and trial duration (weeks) did not show significant differences among different comparison pairs, and there were few outliers, which indicated that the transitivity assumption of the network evidence body was established (**Supplementary Appendix S3**).

3.3 Risk of Bias

For the total 177 studies included in this analysis, majority of the studies were determined to be at "low risk" of bias in random sequence generation (151/177, 85.3%), blinding of participants and personnel (142/177, 80.2%), and blinding of outcome assessment (140/177, 79.1%). Some studies were judged as "low risk" of bias in allocation concealment (97/177, 54.8%), complete outcome data (65/177, 36.7%), and selective reporting (65/177, 36.7%). Only a few studies were rated as "high risk" of bias in the above items. 46.3% of the studies were funded by enterprises. Overall, the risk of bias across the evidence network was relatively low (**Supplementary Appendix S4**).

3.4 Direct Treatment Comparisons

We conducted a series of traditional paired meta-analysis on all interventions that have a direct comparison between these two for total fracture. The comparison includes placebo vs. DPP-4i, DPP-4i vs. AGI, SGLT-2i vs. GLP-1 RAs, SGLT-2i vs. metformin, SGLT-2i vs. placebo, TZD vs. DPP-4i, GLP-1 RAs vs. metformin, GLP-1 RAs vs. placebo, TZD vs. placebo, GLP-1 RAs vs. DPP-4i, GLP-1 RAs vs. insulin, GLP-1 RAs vs. sulfonylurea, GLP-1 RAs vs. TZD, sulfonylurea vs. placebo, DPP-4i vs. metformin, DPP-4i vs. SGLT-2i, DPP-4i vs. sulfonylurea, metformin vs. placebo, and SGLT-2i vs. sulfonylurea. The results of all the above comparisons show that there is no significant statistical difference between the two compared; that is, there is no significant difference in the risk of fracture in the above comparisons (**Supplementary Appendix S5**).

3.5 Network Meta-Analysis of DPP-4i, GLP-1 RAs, and SGLT-2i on Total Fracture Risk and Secondary Outcomes

Figure 3 shows the network meta-analysis results of the comparative effect of DPP-4i, GLP-1 RAs, SGLT-2i, other antidiabetic agents, and placebo on total fracture risk. DPP-4i did not increase total fracture risk compared with insulin (OR: 0.86, 95% CI: 0.39–1.90), Met (OR: 1.41, 95% CI: 0.48–4.19), SU (OR: 0.77, 95% CI: 0.50–1.20), TZD (OR: 0.82, 95% CI: 0.27–2.44), AGI (OR: 4.92, 95% CI: 0.23–103.83), and placebo (OR: 1.04, 95% CI: 0.84–1.29), respectively.

GLP-1 RAs did not increase fracture risk compared with insulin (OR: 1.05, 95% CI: 0.54–2.04), Met (OR: 1.72, 95% CI: 0.55–5.38), SU (OR: 0.94, 95% CI: 0.55–1.62), TZD (OR: 1.00, 95% CI: 0.32–3.10), AGI (OR: 5.99, 95% CI: 0.28–130.37), and placebo (OR: 1.27, 95% CI: 0.88–1.83), respectively.

SGLT-2i did not increase fracture risk compared with insulin (OR: 0.88, 95% CI: 0.39–1.97), Met (OR: 1.44, 95% CI: 0.48–4.30), SU (OR: 0.79, 95% CI: 0.48–1.31), TZD (OR: 0.83, 95% CI: 0.27–2.57), AGI (OR: 5.01, 95% CI: 0.23–107.48), and placebo (OR: 1.06, 95% CI: 0.81–1.39), respectively.

Secondary outcomes based on fracture of different parts indicated that DPP-4i, GLP-1 RAs, and SGLT-2i did not increase the risk of fracture, respectively (**Supplementary Appendix S6**).

3.6 Inconsistency and Heterogeneity Test

The result of local inconsistency about fracture risk showed that all loops were consistent according to the CIs. The test for inconsistency using the node-splitting model revealed no significant difference about the total fracture between direct and indirect comparisons (global inconsistency, $p = 0.97$). The predictive interval plot showed that there was little heterogeneity in this study. Summary estimations of network meta-analysis were relatively robust (**Supplementary Appendix S7**). The fracture outcomes in secondary outcomes were also tested for inconsistency and heterogeneity, and have not been tested for significant heterogeneities or inconsistencies either.

3.7 Publication Bias

Funnel plots were shown in **Supplementary Appendix S8**. For total fracture, scatters in the funnel plot were almost symmetrical, visually. But the linear regression line was close to horizontal, indicating that the publication bias in the result of total fracture between small and large studies was relatively high. For other five secondary outcomes, the scatters in the funnel plots were almost symmetrical, visually.

3.8 Quality of Evidence

The GRADE process was completed using CINeMA software (http://cinema. ispm.ch/). The quality of most studies was moderate. With concern of within-study bias and imprecision, the quality of evidence in the total fracture was rated as moderate (**Supplementary Appendix S9**).

4 DISCUSSION

In the study, we analyzed 177 eligible RCTs, including 165,081 patients. Our network meta-analysis showed that 1) there was no evidence to indicate an increased risk of fracture associated with DPP-4i–, GLP-1 RA–, and SGLT-2i–based therapies in patients with T2DM compared with other antidiabetic agents or placebo; 2) secondary outcomes based on fracture of different parts indicated that DPP-4i, GLP-1 RAs, and SGLT-2i did not increase the risk of fracture, respectively.

In agreement with our findings, a meta-analysis of observational studies did not support an association between the use of DPP-4i, GLP-1 RAs, or SGLT-2i and the risk of fracture (Hidayat et al., 2019). A meta-analysis of 51 RCTs reported that there was no significant association between DPP-4 inhibitor use and the incidence of fractures, when DPP-4 inhibitor is compared with placebo or an active comparator (Mamza et al., 2016). Fu et al. (2016) reported that DPP-4 inhibitor use does not modify the risk of bone fracture compared with placebo or other antidiabetic medications in patients with T2DM (RR = 0.95; 95% CI: 0.83–1.10). A population-based cohort study showed that the use of GLP-1 RAs versus other anti-hyperglycemic drugs was not associated with fracture risk (Driessen et al., 2015a). Multiple meta-analyses have indicated that SGLT-2i does not increase the risk of bone fracture compared with placebo in patients with T2DM (Ruanpeng et al., 2017; Azharuddin et al., 2018; Cheng et al., 2019). Toulis et al. (Toulis et al., 2018) conducted a retrospective cohort study by using Health Improvement Network data and reported that patients initiating dapagliflozin did not have an elevated risk for fractures compared with patients initiating any other antidiabetic medication [HR 0.89 (95% CI: 0.66–1.20)]. In this population-based new-user cohort study using data from two large US healthcare databases, canagliflozin use was not associated with an increased risk of fracture compared to GLP-1 agonists (Fralick et al., 2019).

However, contrasting evidence emerged from a meta-analysis suggesting exenatide treatment was associated with an elevated risk of incident fractures (MHOR = 2.09; 95% CI: 1.03–4.21) compared to placebo or other active drugs (Su et al., 2015). The reasons for the inconsistency of the research conclusions may be related to the low number of fracture cases in this meta-analysis and the durations of trials. There are also observational studies showing that the use of SGLT-2i can increase the risk of fracture. A retrospective cohort study using the Truven Health Market Scan (2009–2015) database observed an 82% increase in risk of fractures within the first 2 weeks of treatment with SGLT-2i, with 95% CI of 0.99–3.32 (Adimadhyam et al., 2019). In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, a significant increase in fractures was seen with canagliflozin (4.0%) vs. placebo (2.6%), and the incidence of fractures was higher with canagliflozin (2.7%) vs. noncanagliflozin (1.9%) in the overall population (Watts et al., 2016). The inconsistent results may be related to the use time of SGLT-2i and the presence or absence of TZD, which is known to have an increased risk of fractures (Meier et al., 2008; Loke et al., 2009).

As a robust predictor of fracture risk, bone mineral density (BMD) is a surrogate reflecting bone strength. While (Hidayat et al., 2019) reported that basal DPP-4 activity was not significantly associated with BMD of the hip, lumbar spine or total body, or incident hip fractures in elderly community-dwelling men and women. In a cohort of elderly community-dwelling adults, plasma DPP-4 activity was not associated with BMD or incident hip fractures (Carbone et al., 2017). Iepsen et al. (2015) showed the use of liraglutide increased bone formation and prevented bone loss after weight loss in obese women. Dapagliflozin had no effect on bone formation and resorption or BMD in both male and post-menopausal female patients (Ljunggren et al., 2012). While the relationship between hypoglycemic drugs and BMD may reflect the effects of drugs on fracture risk, our systematic review could not provide evidence on BMD as all RCTs included in this review did not conduct BMD test for diabetic patients.

Previous studies have reported fracture-prone sites in diabetic patients. A systematic review (Janghorbani et al., 2007) indicated that type 2 diabetes was associated with an increased risk of hip fracture in

both men and women, but not with fractures of the distal forearm, ankle, proximal humerus, or vertebra. A nested case-control study among patients with type 2 diabetes suggested that the use of SGLT-2i and other antidiabetic drug classes was not associated with an increased risk of fractures of the upper or lower limbs compared to use of DPP-4 inhibitors (Schmedt et al., 2019). Consistent with most of these findings, our analysis based on different parts of the body did not find that the use of DPP-4i, GLP-1 RAs, and SGLT-2i increased the risk of fracture. The results of this study suggested that TZD did not increase the risk of fracture. Because this study mainly evaluated the fracture risk of three new hypoglycemic drugs (SGLT-2 inhibitors, GLP-1 RAs, and DPP-4 inhibitors), the condition for searching the literature is that at least one arm is any one of these three drugs. The study on the comparison of TZD and other hypoglycemic drugs is not the outcome of this study, so it is not included in this study, especially the RCT study used to evaluate the safety related to the comparison of TZD and placebo. Owing to the purpose of this study and the characteristics of the included literature, the results of TZD compared with other hypoglycemic drugs are mainly indirect comparisons. CIs are generally wide, and there may be an outcome that TZD does not increase the risk of fracture.

Recently, studies on GLP-1 RAs, DPP-4i, and SGLT-2i in fracture risk of type 2 diabetes patients showed that gender differences may not be enough to play a decisive role in the increase of fracture risk in T2DM (Driessen et al., 2015b; Hou et al., 2018; Rådholm et al., 2020; Davie et al., 2021). Therefore, this study did not analyze gender factors.

Our study has several strengths. First, the predictive interval plot showed that there was little heterogeneity in this study. Second, in addition to assessing the overall risk of fractures, our study also assessed the risk of fractures in different parts of the body.

This study also has some limitations. First, none of the RCTs included were tested for BMD and bone metabolism indexes, which are closely related to the risk of fracture. Second, some CIs in results are particularly wide, for example, the result range of AGI compared with placebo. The reason is that both interventions are used as the control group in this study, and the comparison of results between AGI and placebo are based on indirect comparison. Third, this study regards all the same types of hypoglycemic drug (regardless of the dose or specific drug) as the same intervention and has not considered the effects of specific drugs and their doses on the outcomes. Fourth, most of the included RCTs were conducted in Western countries, but whether they are suitable for other regions, such as Asian populations, remains to be discussed. Fifth, the literature retrieval time of this study is up to 2019, so the results of the latest research could not be included in time.

In conclusion, our meta-analysis suggests that the use of DPP-4i, GLP-1 RAs, and SGLT-2i is not associated with an increased risk of fracture in patients with T2DM. In addition, more RCTs are required to investigate the number of fractures with the use of DPP-4i, GLP-1 RAs, and SGLT-2i, as a primary endpoint, rather than an adverse event.

CONCLUSION

Dipeptidyl peptidase-4 inhibitors (DPP-4i) and the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become widely used in T2DM patients as a novel class of blood glucose–lowering drugs with improved weight loss, low risk for hypoglycemia, and reduction in glycated hemoglobin. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are another type of novel glucose-lowering agents and have also gained increasing use in recent years, which reduce plasma glucose concentrations by inhibiting proximal tubular reabsorption of glucose in the kidney.

There are two new findings in the study. First, the use of DPP-4i, GLP-1 RAs, or SGLT-2i is unlikely to increase the overall risk of fracture among type 2 diabetes mellitus patients. Second, secondary outcomes based on fracture of different parts indicated that DPP-4i, GLP-1 RAs, and SGLT-2i did not increase the risk of fracture, respectively.

Our results offer the best available evidence of the impact of DPP-4i, GLP-1 RAs, or SGLT-2i on fracture risk based on randomized controlled trials. Therefore, more evidence is provided for the rational use of these drugs in clinical trials.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

FS designed the study and gave guidance for this work. SC and FL retrieved the document. SY, FL, SC, ZL, and QY built databases and extracted data. FL input data and conducted statistical analysis. SC input data and was a major contributor in writing the manuscript. ZY embellished and revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.825417/full#supplementary-material

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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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Drug and therapeutics committee interventions in managing irrational drug use and antimicrobial stewardship in China

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Aim: This study aimed to investigate the key points in the transformation of the functions of the Drug and Therapeutics Committee (DTC) of the Shandong Provincial Third Hospital and how to provide full authority to its role in the control of rational drug use, especially in the management of antibiotic use.

Method: A prescription review management group, antimicrobial stewardship group, and rational drug use service group were established under the DTC. From January 2016 to December 2021, each group played a role in promoting rational drug use and antimicrobial stewardship. In addition, we performed statistics on typical management cases, irrational drug use, bacterial resistance rate, and drug costs from 2015 to 2021 to evaluate the effect of management by the DTC.

Results: Intervention by the DTC led to a significant reduction in prescribing errors (71.43%, $p < 0.05$), the intervention acceptance rate increased by 16.03%, and the problem solved rate increased by 32.41% ($p < 0.05$). Resistance rates of general spectrum antibiotics were reduced remarkably after the intervention. The quality of drug treatment was improved and patient drug expenses was continuously reduced.

Conclusion: Giving full play to the functions of the DTC can significantly improve the level of drug treatment and reduce unreasonable drug use to save unnecessary drug expenses and slow the development of drug resistance.

KEYWORDS

drug and therapeutics committees, rational drug use, management measures, drug cost control, clinical pharmaceutical care

Introduction

The Drug and Treatment Committee (hereinafter referred to as the DTC) is at the top of the hierarchy of hospital pharmacy management (Tyler et al., 2008). Previously, its members were primarily pharmaceutical personnel. The Committee's main function was to guide the supply and allocation of drugs in the hospital according to the overall development plan and policies of the hospital. This function took the form of organizing regular meetings and discussions. This arrangement led to the failure of the pharmaceutical commission to play the overall decision-making function of the drug management center, especially the role of promoting rational drug use and rational use of antibiotics (Webb, 2012). The irrational use of antibiotics in China is more prominent than the rational use. First, irrational use of antibiotics increases the incidence of adverse drug reactions and drug-induced diseases. Second, it leads to increased bacterial drug resistance, resulting in the continuous reduction in effectiveness or even failure of some typically effective antibiotics. This combination not only affects the treatment of the disease, but also increases the economic burden of patients and objectively contributes to the unreasonable rise of medical expenses.

China established the national DTC in March 2022 to further strengthen the pharmaceutical administration of medical institutions, promote rational drug use, and give full play to the role of expert technical support. The main responsibilities of the Committee include: studying the development status of pharmaceutical management in medical institutions and proposing policy suggestions; providing technical support for the establishment and improvement of drug selection, procurement, use, and evaluation systems in medical institutions; promoting the implementation of clinical diagnosis and treatment guidelines related to drug treatment and guiding principles for clinical application of drugs; promoting the establishment and improvement of China's pharmaceutical care system; strengthening the instruction of pharmacists and standardizing pharmaceutical care; and investigating and manage major mass drug accidents.

Beginning in 2011, our hospital optimized the organizational structure, division of labor, management functions, and work priorities of its DTC. The main purpose of the DTC is to promote the formulation and implementation of clinical diagnosis and treatment guidelines related to drug treatment and guiding principles for clinical application of drugs, monitoring, and evaluating the use of drugs in the institution, proposing intervention and improvement measures, and guiding clinical rational drug use (Lloyd et al., 2021; Zaragoza Laura Largeau et al.). Before 2016, the DTC had no sub groups. The DTC is composed of the heads of medical, pharmaceutical, infectious diseases, clinical microbiology, nursing, hospital infection management, and other departments and personnel with relevant professional senior technical post qualifications.

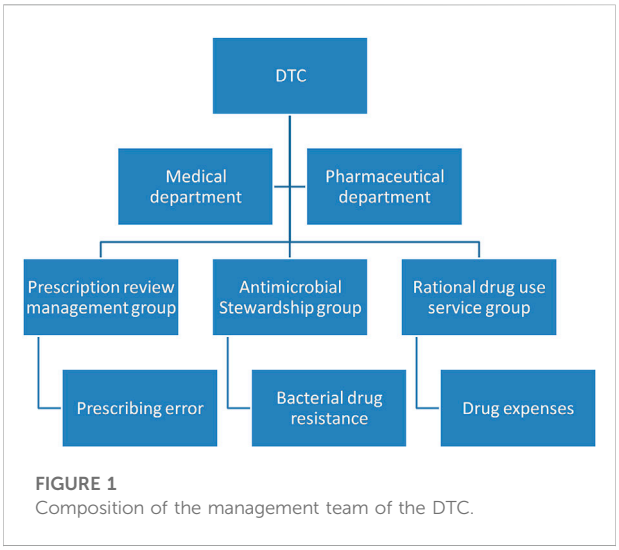

FIGURE 1
Composition of the management team of the DTC.

Medical, pharmaceutical, and other departments are jointly responsible for daily management of the duties of the DTC. The antimicrobial stewardship group was established under the DTC in 2016.

Methods

Design and setting

This study was conducted in China at the Shandong Provincial Third Hospital, Shandong University, a 1,400-bed tertiary university teaching hospital. The members of the DTC are personnel from the medical, pharmaceutical, and nursing departments and clinical medical experts. The specific work is organized and implemented by the medical and pharmaceutical departments. The primary management function of the DTC in our hospital was the control of irrational drug use and antimicrobial stewardship beginning in 2016. Typical management cases, bacterial resistance rates, irrational drug use, and drug expenditures from 2016 to 2021 were summarized. We separated the study duration into two periods according to the time of introduction of antimicrobial stewardship (beginning January 2016): Before intervention: 1 year before the introduction (from January 2015 to December 2015); after intervention: 6 years after the introduction (from January 2016 to December 2021).

Aim of the study

This study aimed to investigate the key points in the transformation of the functions of the DTC and how to provide full play to its role in the control of rational drug use, especially in the management of antibiotic use.

Organization and responsibilities of the drug and therapeutics committee

To better promote rational drug use, six working groups were established under the DTC. The main responsibilities included the following: selection of hospital drug variety, analysis and evaluation of drug risks, monitoring and analysis of drug use, and evaluation of rational drug use and antimicrobial stewardship. Among these groups, the prescription review management group, antimicrobial stewardship group, and rational drug use service group were responsible for monitoring rational drug use and antimicrobial stewardship (Figure 1).

The main tasks of the antimicrobial stewardship group were to review all antibiotic prescriptions for information related to, for example, indications, time of dose, and dosing density, duration, and route. Real-time recommendations were provided by the antimicrobial stewardship team for correcting antibiotic choice, density, duration, and route based on microbiological results and treatment protocols. Monthly multidisciplinary antibiotic rounds were undertaken in all departments. Antimicrobial stewardship team members reported inappropriate antibiotic use to hospital and department leaders monthly. Real-time information on antibiotic resistance was reported on the hospital information system.

The prescription review team evaluated prescriptions every month for the rational use of drugs and comments on cases of unreasonable use were directed to the physician. The prescription review team paid attention to the delivery of understandable information, established a preliminary prescription audit system to monitor drug use, and intervened in a timely manner in cases of unreasonable drug use.

The rational drug use service group organized clinical pharmacy-related training to improve the level of rational drug use. The DTC organized Committee members and clinical medicine and clinical pharmacy experts to conduct dynamic monitoring of prescribed medications, regularly sampling prescriptions or cases for reasonable evaluation. The evaluation results have been reported (Yang et al., 2021; Pallares et al., 2022). The types of irrational drug use, DTC interventions, and outcomes of the intervention were recorded by clinical pharmacists. In addition, the effect of rational use of antibiotics was evaluated with changes in trends of bacterial drug resistance as measured with the minimal inhibitory concentration method.

Data analysis

Statistics were performed on the rate of rational drug use and the rate of antibiotic utilization, with a focus on monitoring the proportion of drug use and drug costs to evaluate the effect of the intervention. The regression equation was obtained with SPSS Linear-by-Linear Association and linear regression. Trend analysis was performed and Student's t tests were calculated using SPSS version 22. The accepted significance level for all hypothesis contrasts was 0.05.

Results

Irrational drug use

Instances of irrational drug use and their causes and proposed interventions to counter them were categorized according to a simplified form of the Pharmaceutical Care Network Europe drug-related problem classification (PCNE-DRP), version 9.0. Serious prescribing errors that required correction related to inappropriate prescription, missing drug indications, inappropriate drug combinations, combinations with herbal medications or dietary supplements, over-prescription of drugs, and errors related to the dose, frequency, and duration of treatment. The types of irrational drug use, DTC interventions, and outcomes of the intervention are detailed in Table 1.

The DTC intervention led to a significant reduction in prescribing errors (Table 1). The prescribing errors decreased by 71.43% from 2015 (287 cases) to 2021 (82 cases) ($p < 0.05$). The regression equation of prescribing error was: $y = 33.107x + 310.57$ ($F = 1958.07$, $p < 0.05$; $t = -44.25$, $p < 0.05$; $R^2 = 0.9934$), indicating a linear downward trend. The intervention acceptance rate increased by 16.03% from 2015 (79.09%) to 2021 (95.12%) ($p < 0.05$). The regression equation of the intervention acceptance rate was: $y = 2.6975x + 76.217$ ($F = 285.31$, $p < 0.05$; $t = 16.89$, $p < 0.05$; $R^2 = 0.9908$), indicating a linear upward trend. The problem solved rate increased by 32.41% from 2015 (48.08%) to 2021 (80.49%) ($p < 0.05$). The regression equation of the problem solved rate was: $y = 5.823x + 44.16$ ($F = 43.32$, $p < 0.05$; $t = 6.58$, $p < 0.05$; $R^2 = 0.9416$), indicating a linear upward trend. Irrational drug use continuously reduced; the level of drug treatment improved.

Continuous optimization of rational drug use indicators

Goals related to the previous ones were to continuously strengthen the management of rational drug use through timely intervention by the DTC, manage clinical cases of excessive use of antibiotics or adjuvant drugs, and strengthen the optimal control of indicators. From 2016 to 2021, the scale of the hospital continued to expand (from 800 to 1,400 beds) and the number of patients with severe diseases and disorders continued to increase. However, the rate of antibiotic utilization was stably controlled, as was the proportion of drug expenses related to antibiotics (Figure 2).

TABLE 1 Types of irrational drug uses and DTC interventions.

The cause	Frequency (%)						
	2015	2016	2017	2018	2019	2020	2021
C1 Drug selection							
C1.1 Inappropriate drug according to guidelines/formulary	39 (13.59)	32 (13.28)	29 (14.36)	27 (15.34)	24 (16.44)	18 (15.93)	16 (19.51)
C1.2 Inappropriate drug (within guidelines but otherwise contra-indicated)	22 (7.67)	17 (7.05)	15 (7.43)	11 (6.25)	9 (6.16)	6 (5.31)	2 (2.44)
C1.3 No indication for drug	23 (8.01)	17 (7.05)	15 (7.43)	12 (6.82)	11 (7.53)	10 (8.85)	6 (7.32)
C1.4 Inappropriate combination of drugs, drugs and herbal medications, or drugs and dietary supplements	31 (10.8)	29 (12.03)	24 (11.88)	21 (11.93)	17 (11.64)	13 (11.5)	9 (10.98)
C1.7 Too many drugs prescribed for indication	33 (11.5)	31 (12.86)	27 (13.37)	21 (11.93)	16 (10.96)	12 (10.62)	8 (9.76)
C3 Dose selection							
C3.1 Drug dose too low	9 (3.14)	7 (2.90)	8 (3.96)	6 (3.41)	5 (3.42)	5 (4.42)	4 (4.88)
C3.2 Drug dose too high	22 (7.67)	18 (7.47)	16 (7.92)	15 (8.52)	11 (7.53)	9 (7.96)	7 (8.54)
C3.3 Dosage regimen not frequent enough	12 (4.18)	7 (2.9)	6 (2.97)	6 (3.41)	4 (2.74)	2 (1.77)	2 (2.44)
C3.4 Dosage regimen too frequent	33 (11.50)	28 (11.62)	21 (10.40)	17 (9.66)	14 (9.59)	9 (7.96)	8 (9.76)
C4 Treatment duration							
C4.1 Duration of treatment too short	22 (7.67)	16 (6.64)	9 (4.46)	8 (4.55)	6 (4.11)	6 (5.31)	6 (7.32)
C4.2 Duration of treatment too long	23 (8.01)	22 (9.13)	18 (8.91)	17 (9.66)	15 (10.27)	11 (9.73)	7 (8.54)
C9 Other							
C9.1 No or inappropriate outcome monitoring (incl. Therapeutic drug monitoring)	18 (6.27)	17 (7.05)	14 (6.93)	15 (8.52)	14 (9.59)	12 (10.62)	7 (8.54)
Total	287	241	202	176	146	113	82
DTC Interventions							
I1 At prescriber level							
I1.1 Prescriber informed only	82 (28.57)	50 (20.75)	33 (16.34)	29 (16.48)	24 (16.44)	17 (15.04)	15 (18.29)
I1.2 Prescriber asked for information	55 (19.16)	34 (14.11)	25 (12.38)	20 (11.36)	15 (10.27)	14 (12.39)	12 (14.63)
I1.3 Intervention proposed to prescriber	78 (27.18)	99 (41.08)	88 (43.56)	84 (47.73)	72 (49.32)	64 (56.64)	41 (50)
I1.4 Intervention discussed with prescriber	72 (25.09)	58 (24.07)	56 (27.72)	43 (24.43)	35 (23.97)	18 (15.93)	14 (17.07)
I3 At drug level							
I3.1 Drug changed to . . .	86 (29.97)	79 (32.78)	52 (25.74)	45 (25.57)	37 (25.34)	32 (28.32)	27 (32.93)
I3.2 Dosage changed to . . .	52 (18.12)	48 (19.92)	47 (23.27)	42 (23.86)	34 (23.29)	24 (21.24)	17 (20.73)
I3.3 Formulation changed to . . .	22 (7.67)	19 (7.88)	29 (14.36)	23 (13.07)	22 (15.07)	18 (15.93)	12 (14.63)
I3.4 Instructions for use changed to . . .	34 (11.85)	27 (11.2)	16 (7.92)	12 (6.82)	8 (5.48)	8 (7.08)	6 (7.32)
I3.5 Drug paused or stopped	49 (17.07)	38 (15.77)	30 (14.85)	28 (15.91)	21 (14.38)	17 (15.04)	10 (12.2)
I3.6 Drug started	44 (15.33)	30 (12.45)	28 (13.86)	26 (14.77)	24 (16.44)	14 (12.39)	10 (12.2)

(Continued on following page)

TABLE 1 (*Continued*) Types of irrational drug uses and DTC interventions.

The cause	Frequency (%)						
	2015	2016	2017	2018	2019	2020	2021
Intervention Acceptance							
A1 Intervention accepted	227 (79.09)	197 (81.74)	171 (84.65)	151 (85.8)	131 (89.73)	105 (92.92)	78 (95.12)
A1.1 Intervention accepted and fully implemented	121 (42.16)	113 (46.89)	110 (54.46)	115 (65.34)	119 (81.51)	92 (81.42)	72 (87.8)
A1.2 Intervention accepted, partially implemented	49 (17.07)	52 (21.58)	40 (19.80)	23 (13.07)	8 (5.48)	8 (7.08)	2 (2.44)
A1.3 Intervention accepted but not implemented	57 (19.86)	32 (13.28)	21 (10.4)	13 (7.39)	4 (2.74)	5 (4.42)	4 (4.88)
A2 Intervention not accepted	60 (20.91)	44 (18.26)	31 (15.35)	25 (14.2)	15 (10.27)	8 (7.08)	4 (4.88)
A2.1 Intervention not accepted: not feasible	31 (10.8)	26 (10.79)	22 (10.89)	17 (9.66)	10 (6.85)	6 (5.31)	3 (3.66)
A2.2 Intervention not accepted: no agreement	29 (10.10)	18 (7.47)	9 (4.46)	8 (4.55)	5 (3.42)	2 (1.77)	1 (1.22)
Status of the drug-related problem							
O1 Problem solved	138 (48.08)	133 (55.19)	125 (61.88)	118 (68.1)	115 (78.77)	90 (79.65)	66 (80.49)
O2 Problem partially solved	32 (11.15)	32 (13.28)	25 (12.38)	20 (10.43)	12 (8.22)	10 (8.85)	8 (9.76)
O3 Problem not solved	117 (40.77)	76 (31.54)	52 (25.74)	38 (21.47)	19 (13.01)	13 (11.50)	8 (9.76)

C: causes, I: interventions, A: acceptance, O: Status of the drug-related problem.

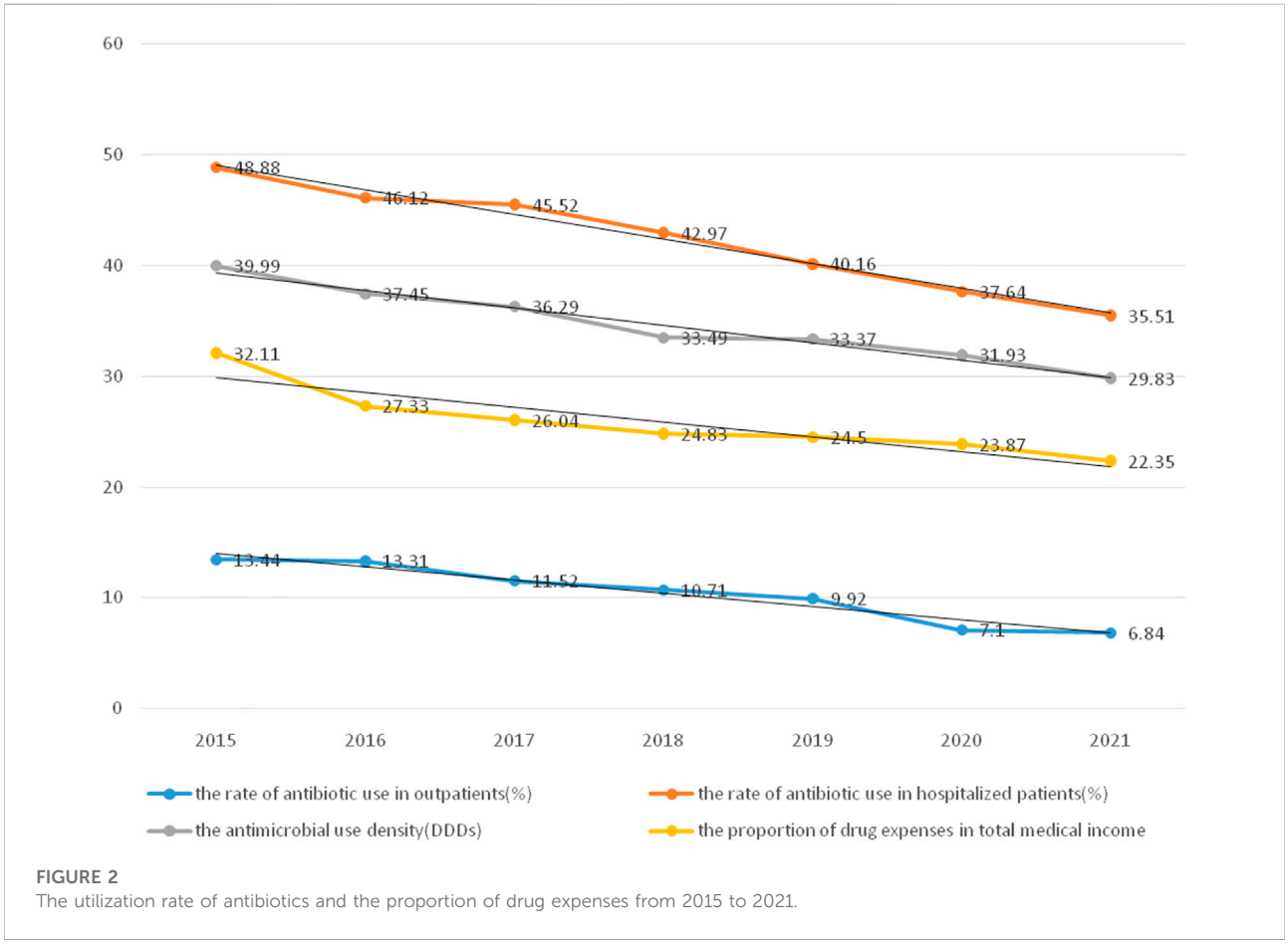

FIGURE 2
The utilization rate of antibiotics and the proportion of drug expenses from 2015 to 2021.

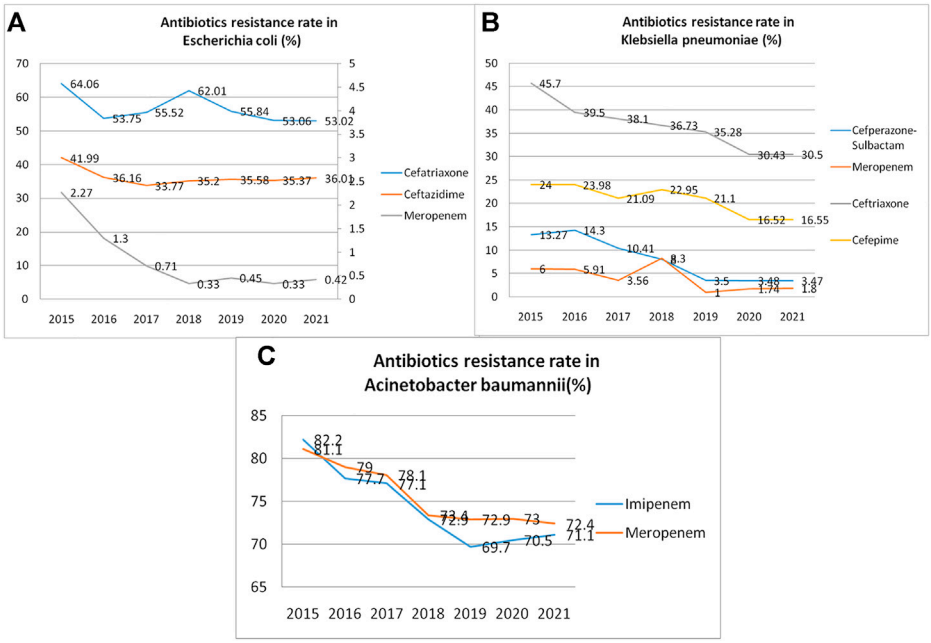

FIGURE 3
Antibiotic resistance rates (per year) reduced remarkably during the study period. **(A)**. Resistance rate of three antibiotics commonly used in *Escherichia coli* infection; **(B)**. Resistance rate of four antibiotics commonly used in *Klebsiella pneumonia* infection; **(C)**. Resistance rates of two antibiotics commonly used in *Acinetobacter baumannii* infection.

The rate of antibiotic use in hospitalized patients decreased by 13.37% from 2015 (48.88%) to 2021 (35.51%) ($p < 0.05$). The rate of antibiotic use in outpatients decreased by 6.6% from 2015 (13.34%) to 2021 (6.84%) ($p < 0.05$). The antimicrobial use density decreased by 10.16% from 2015 (39.99%) to 2021 (29.83%) ($p < 0.05$). The proportion of drug expenses in the total medical expenditures decreased by 9.76% from 2015 (32.11%) to 2021 (22.35%) ($p < 0.05$).

Antibiotics resistance rate

The resistance rate of general spectrum antibiotics reduced remarkably after intervention. Resistance rates of three commonly used antibiotics (cefatriaxone, ceftazidime, and meropenem) in *Escherichia coli* were significantly lower after intervention than those before intervention (64.06 vs. 53.02%, 41.99 vs. 36.01%, 2.27 vs. 0.42%; all $p < 0.05$) (Figure 3A). Resistance rates of commonly used antibiotics (cefepime, ceftriaxone, meropenem, and cefoperazone-sulbactam) in *Klebsiella pneumoniae* were significantly lower after intervention than those before intervention (24.00 vs. 16.55%, 45.7 vs. 30.5%, 6.00 vs. 1.8%, 13.27 vs. 3.47%; all $p < 0.05$) (Figure 3B). Resistance rates of imipenem and meropenem in *Acinetobacter baumannii* were reduced by the intervention (82.2 vs. 71.1%, 81.1 vs. 72.4%; all $p < 0.01$) (Figure 3C) (Figure 3).

Discussion

The DTC of our hospital was established in 2002 with a primary function of ensuring drug supply. However, with the transformation of pharmaceutical functions in Chinese hospitals, the focus of the hospital pharmacy should change from ensuring drug supply to strengthening rational drug use and pharmaceutical technical services. In contrast, the phenomenon of irrational drug use in hospitals and the excessive use of antibiotics are becoming more and more obvious. An effective institution is needed to control irrational drug use. Therefore, the management function of the DTC in our hospital changed beginning in 2016, focusing on monitoring the rationality of clinical medication use, especially antimicrobial stewardship (Ribeiro-Vaz et al., 2016;and Brooks, 2010).

In recent years, medical institutions have actively implemented China's policy on the rational clinical application of antibiotics and strengthened the control of nosocomial infections. Under the guidance of the DTC, with the standardized management and rational application of antibiotics in hospital, the strengthening of communication ability between laboratory and clinic, and the strengthening of awareness of prevention and control of drug-resistant bacterial infection, the spread of drug-resistant bacteria has been curbed to a certain extent (Zhang et al., 2018; Yang et al., 2020). The goals of rational drug use and antimicrobial stewardship are to reduce

improper drug use, improve drug treatment level, reduce drug expenditures, and delay bacterial drug resistance, so as to better protect the safety of patients. As the organization responsible for the management of rational drug use and antimicrobial stewardship, the DTC needs a stable management department to coordinate relevant work. The pharmacy department is not presently competent for relevant responsibilities. Thus, the cooperation of medical and other departments is needed to determine the division of labor and truly ensure the smooth development of rational drug use hospital-wide (Björkman et al., 2007; Ciccarello et al., 2021). The joint efforts and full cooperation of all members of the DTC are the basis for effective rational drug use (Alefan et al., 2019).

In terms of specific work measures, the DTC should promote the improvement of drug treatment planning through functional management and expert cooperation. In addition, the DTC should ensure the rational use of drugs through index monitoring and rational drug use evaluation (Plet et al., 2013; Religioni and Pakulska, 2020). Therefore, we should have various comprehensive management measures in addition to departmental cooperation to better realize this drug management function (Gustafsson et al., 2011; Matlala et al., 2015). Moreover, the DTC should also be supported by a convenient pharmaceutical management statistics information platform (Durán-García et al., 2011).

One role of the DTC should be to urge doctors to use drugs rationally. This is needed because although most doctors abide by the norms, there are always a few who do not fully regulate the use of drugs for various reasons. In the early stages of the DTC, our hospital continuously strengthened management and achieved good results. However, the next step should start with improving the organizational form of the pharmaceutical Committee and strengthening its monitoring, analysis, decision-making, accountability, and other responsibilities so that the use of drugs is reasonably monitored. Likewise, we will continue to track and rectify any abnormal conditions found, clarify the responsibilities of the department in the management of doctors, help them find clues to illegal drug use, help them carry out management, and continuously promote the Plan-Do-Check-Act cycle. With the continuous development of the expert autonomous pharmaceutical Committee, the spirit of self-discipline in doctors will continue to strengthen. Ultimately, drugs will be effective in the continuous improvement of medical technology.

Conclusions

Intervention by the DTC, as the guardian of safe and rational drug use, led to a significant reduction in prescribing errors. The DTC established a monitoring and long-term management mechanism for the rational use of antibiotics, improved society's understanding of the harm of antibiotic abuse, and worked hard to maintain the health of the population. In conclusion, the implementation of the DTC in our hospital reduced medical expenses, improper use and abuse of drugs, and antibiotic resistance rates. However, further efforts are needed to improve the use of antibiotics. Based on our experience, it is strongly recommended to implement a DTC in all local hospitals in China.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

JY and LZ: Research idea, study design, statistical analysis. Y-YG and Ning Ding: Data analysis and interpretation. Y-TL: Statistical analysis.

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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.

Publisher's note

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A machine learning-based risk warning platform for potentially inappropriate prescriptions for elderly patients with cardiovascular disease

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Potentially inappropriate prescribing (PIP), including potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs), is a major risk factor for adverse drug reactions (ADRs). Establishing a risk warning model for PIP to screen high-risk patients and implementing targeted interventions would significantly reduce the occurrence of PIP and adverse drug events. Elderly patients with cardiovascular disease hospitalized at the Sichuan Provincial People's Hospital were included in the study. Information about PIP, PIM, and PPO was obtained by reviewing patient prescriptions according to the STOPP/START criteria (2nd edition). Data were divided into a training set and test set at a ratio of 8:2. Five sampling methods, three feature screening methods, and eighteen machine learning algorithms were used to handle data and establish risk warning models. A 10-fold cross-validation method was employed for internal validation in the training set, and the bootstrap method was used for external validation in the test set. The performances were assessed by area under the receiver operating characteristic curve (AUC), and the risk warning platform was developed based on the best models. The contributions of features were interpreted using SHapley Additive ExPlanation (SHAP). A total of 404 patients were included in the study (318 [78.7%] with PIP; 112 [27.7%] with PIM; and 273 [67.6%] with PPO). After data sampling and feature selection, 15 datasets were obtained and 270 risk warning models were built based on them to predict PIP, PPO, and PIM, respectively. External validation showed that the AUCs of the best model for PIP, PPO, and PIM were 0.8341, 0.7007, and 0.7061, respectively. The results suggested that angina, number of medications, number of diseases, and age were the key factors in the PIP risk warning model. The risk warning platform was established to predict PIP, PIM, and PPO, which has acceptable accuracy, prediction performance, and potential clinical application perspective.

KEYWORDS

cardiovascular diseases, potentially inappropriate prescribing, potentially inappropriate medications, potential prescribing omissions, machine learning, predictive models

1 Introduction

With the rapid aging of the global population, countries around the world are currently facing a serious problem of an aging population and the health problems of the elderly. It is estimated that by 2050, the number of people aged over 60 years will reach 2.1 billion worldwide (Phillips, 2017), and the proportion will be more than 20% (Biritwum et al., 2013). The elderly have poor physical function and often suffer from comorbidities (Vermunt et al., 2017). Costs related to comorbidities are a significant economic burden to patients and healthcare systems (King and Giedrimiene, 2021). During recent years, there has been a growing interest in the study of disease associations in aging patients. Accumulated evidence has suggested that cardiovascular diseases are the most common comorbid condition in older people with multimorbidities (Manckoundia et al., 2020). In addition, cardiovascular diseases are considered a leading cause of death, and the rate reached 10%–30% in the LifeLines Cohort Study (Van der Ende et al., 2017). Importantly, this becomes even more pronounced in the elderly population (Hamilton-Craig et al., 2015; Valdés et al., 2018).

Moreover, elderly patients usually have several comorbidities that leads to polypharmacy, increasing the risk of potentially inappropriate prescribing (PIP) (Corsonello et al., 2010; Gallagher et al., 2011; D'Cruz et al., 2012; Chen et al., 2014; Hyttinen et al., 2019b), especially leading to an increase in adverse drug reactions (ADRs) (Maaroufi et al., 2021). Additionally, PIP includes potentially inappropriate medications (PIM) and potential prescribing omissions (PPO), which is a key factor influencing the occurrence of ADR in elderly patients (O'Mahony and Gallagher, 2008). PIM is very common in elderly patients with cardiovascular disease (Sheikh-Taha and Dimassi, 2017; Maaroufi et al., 2021). 98.2% of elderly patients, who were admitted to medical or cardiovascular ICUs in a large tertiary teaching hospital in Brazil, had at least one PIM (Galli et al., 2016). According to a multicenter, prospective cohort study that recruited 1,280 patients (median age of 82 years) in England, PIM contributed to ADR in 12% of elderly patients (Parekh et al., 2019).

Currently, there are various criteria for assessing PIP (Petrovic et al., 2016; Lopez-Rodriguez et al., 2020); for instance, the Beers criteria developed in the United States (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019) and the STOPP/START criteria developed in Ireland (O'Mahony et al., 2015). Although these criteria are currently in wide use for post-event evaluation, there are some shortcomings, such as the inability to provide advance warning of the risk of PIP in elderly patients. Through early warning of PIP, physicians or pharmacists will be able to identify patients at risk of PIP and adopt individualized interventions to reduce the risk of ADR.

Some studies have shown that PIP in elderly patients can be identified using the frailty index (Cullinan et al., 2016) and the new Croatian tool (Matanović and Vlahović-Palčevski, 2014). However, these approaches were not convenient enough, as they would require a lot of time and effort. In recent years, with the rise of artificial intelligence, machine learning algorithms have been increasingly applied to develop predictive models (Badet et al., 2021; Fralick et al., 2021; Hossain et al., 2021; Lin et al., 2021; Mišić et al., 2021; Pinaire et al., 2021). Multiple studies reported that machine learning algorithms could predict severe hypoglycemia in hospitals, identify genetic risk factors for the progression and survival of colorectal cancer, etc. Patel et al. used machine learning algorithms to develop predictive models to identify predictors of inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs) of PIP in elderly patients with osteoarthritis (Patel et al., 2020).

However, the following problems remain to be resolved: 1) Fewer data pre-processing methods are used. Our previous study (Wu et al., 2020) has demonstrated that different data pre-processing methods ($p < 0.05$) are important in choosing an optimal data pre-processing method. 2) Fewer machine learning algorithms are used. Our previous study (Wu et al., 2020) used 14 machine learning algorithms, and the results showed the variability between different machine learning algorithms. Each machine learning algorithm applies in different conditions. At most two machine learning algorithms in the above studies were used, which was not sufficient. 3) Fewer platforms for risk prediction. Risk warning platforms can output the risk of PIP in elderly patients with cardiovascular disease, which might alert physicians or pharmacists to review the medicines.

Thus, the present study analyzed the information on PIP, PIM. and PPO of cardiovascular disease in elderly patients, and established a prediction platform using multiple machine learning algorithms to predict the risk of PIP, PIM, and PPO in elderly patients with cardiovascular disease.

2 Materials and methods

2.1 Data sources

Participants who were discharged from the Department of Geriatric Cardiology at Sichuan Provincial People's Hospital

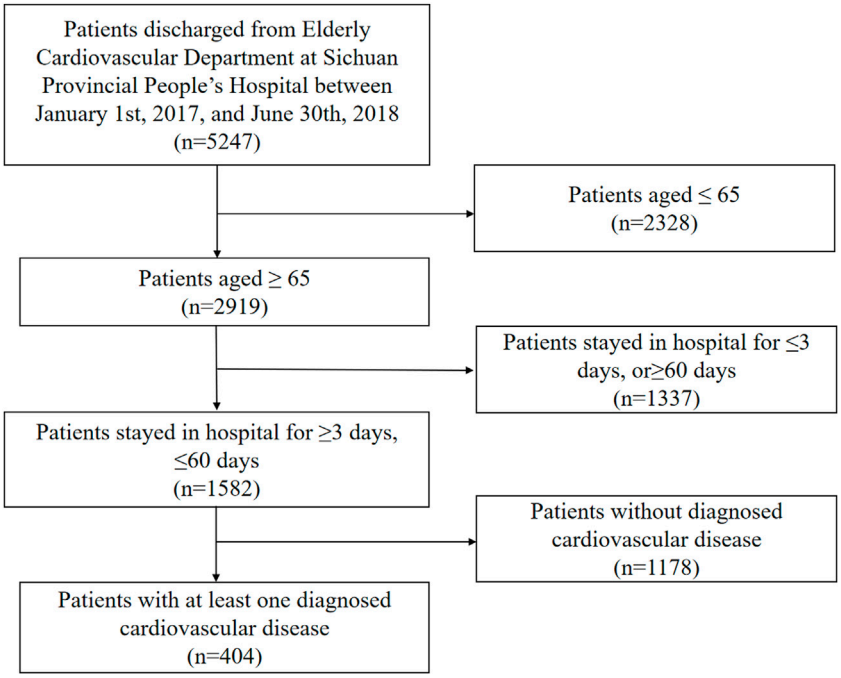


FIGURE 1
Flowchart of patient selection.

from January 2017 to June 2018 were included in this study. Their clinical information, including prescription information, medical record information, and results of laboratory tests, were collected from the electronic medical record. The following inclusion criteria were used for the selection of the study participants: 1) age ≥65 years; 2) the duration of hospitalization between 3 and 60 days; and 3) diagnosed with at least one cardiovascular disease (hypertension, myocardial infarction, angina pectoris, hyperlipidemia, peripheral vascular disease, and indication for antithrombotic therapy, which was determined by cardiovascular physicians). The patient selection flowchart is shown in Figure 1.

The STOPP/START criteria (version 2) for the cardiovascular system and antiplatelet/anticoagulant drugs were used to identify PIP prescriptions in elderly patients, including 24 PIM criteria (13 for cardiovascular system and 11 for antiplatelet/anticoagulant drugs) and 8 PPO criteria for the cardiovascular system. Each electronic medical record was independently reviewed by three pharmacists, Wu Xingwei, Zhang Jiaying, and Xiong Huan, who had received training from the chief pharmacists (Tong Rongsheng and Long Enwu) to ensure the accuracy of the results. All disagreements were resolved by consulting the chief physician of internal medicine.

The patient's ID number, name, home address, and telephone number were anonymous during the data acquisition for ethical reasons. As this is a retrospective study without intervention, the ethics committee considered it unnecessary to obtain informed consent from patients. All variables were coded (X1, X2, . . . , Xn) to allow blinded analysis of patient data.

2.2 Data pre-processing

2.2.1 Data pre-screening

Data pre-screening included three processes: 1) deleting columns with more than 90% missing data; 2) deleting columns with a single value occupying more than 90%; and 3) deleting columns with coefficient of variation less than 0.01. Variables meeting one of the abovementioned conditions would be considered less informative.

2.2.2 Data sampling

To minimize the adverse impact of data imbalance on prediction performance, the following data sampling methods were used: 1) no sampling; 2) random upsampling, which duplicates minority class samples to create additional minority class samples; 3) random undersampling, which randomly selects samples from the initial dataset to create a new smaller dataset; 4) synthetic minority oversampling technique (SMOTE), which achieves upsampling by linear interpolation between a small

number of class samples and their nearest neighbors; and 5) borderline SMOTE upsampling, which improves the SMOTE method by upsampling only the border samples of a small number of classes, thus improving the class distribution of the samples.

2.2.3 Feature screening

Three feature selection methods were used for feature screening: 1) no screening; 2) the Lasso screening method which evaluates the importance of variables and output the results by introducing a penalization parameter penalizing and discarding unimportant variables (variables with coefficients near zero); and 3) the Boruta screening method which is a feature selection algorithm to identify the minimal set of relevant variables.

2.3 Model development

Fifteen datasets were generated by five data sampling methods and three feature screening methods, and 18 machine learning algorithms were used on each dataset, respectively, to develop a total of 270 models. Machine learning algorithms in this study included logistic regression, decision tree, Gaussian naive bayes, Bernoulli naive bayes, multinomial naive bayes, passive aggressive, AdaBoost, bagging, gradient boosting, eXtreme gradient boosting (XGBoost), K-nearest neighbor (KNN), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), random forest, stochastic gradient descent (SGD), support vector machine (SVM), extra tree, and ensemble learning (Wu et al., 2020). These abovementioned algorithms were commonly used and were suitable for binary classification. In comparison to single classification algorithms, ensemble algorithms always prove to be more effective and stable in prediction models.

The whole process of model development could be described as follows:

(1) The data set was divided into a training set and a test set in a ratio of 8:2 (according to our sample size, a ratio of 8:2 would be more suitable than 9:1 or 7:3)
(2) Models were trained in the training set so that the loss function was minimized. Internal validation was performed by the ten-fold cross-validation method.
(3) Test set data were passed into the trained model for assessing model prediction performance. Bootstrapping was employed for external validation.
(4) The model with the best performance was selected.

2.4 Model evaluation

The area under the receiver operating characteristic curve (AUC), accuracy, precision, recall, and F1 score were adopted as quantitative metrics to evaluate the performance of models, and the candidate model achieving the best performance was selected as the optimal prediction model. The contribution of each variable to the predictive model was estimated with SHapley Additive exPlanation (SHAP). The modeling process is shown in Figure 2.

A total of 270 prediction models were developed based on different sampling methods and feature screening methods. On the test set, the model with the highest AUC value was selected and used to establish the prediction platform for PIP, PIM, and PPO.

2.5 Sample size validation

To train the best model, the bootstrap method was used to randomly select 10%, 20%, 30%,.....100% of the resampling data from the training set, and the test set was used to test the predictive ability of the model. The AUC values of the best models of PIP, PPO, and PIM were estimated. The above process was repeated 100 times, and the results were plotted on a line graph. We judged the contribution of the sample size to improve the prediction performance of models according to the inflection point change of the line graph.

2.6 Statistical analysis

Categorical data were described by frequency (percent), and continuous data were statistically described by mean and standard deviation (Mean ± SD). Analysis of variance (ANOVA) and rank sum test were used for univariate analysis.

Statistical analysis was performed using stats in Python 3.8, and model development was implemented using sklearn in Python 3.8. The front-end of the PIP prediction platform was written in JavaScript, and the back-end was written in Python 3.8.

3 Results

A total of 404 elderly patients with cardiovascular diseases were eligible for this study. The mean age of the patients was 79.1 years, and 59.9% were male. Participants identified as PIP, PIM, and PPO were 318 (78.7%), 112 (27.7%), and 273 (67.6%), respectively. The most frequent PIPs were antiplatelet agents simultaneously used with vitamin K antagonists, direct thrombin inhibitors, or factor inhibitors in patients (37 instances, accounting for 21.5% of total PIPs). Table 1 shows detailed patient demographic information and clinical information as the independent variables, with PIP, PIM, and PPO as the dependent variables.

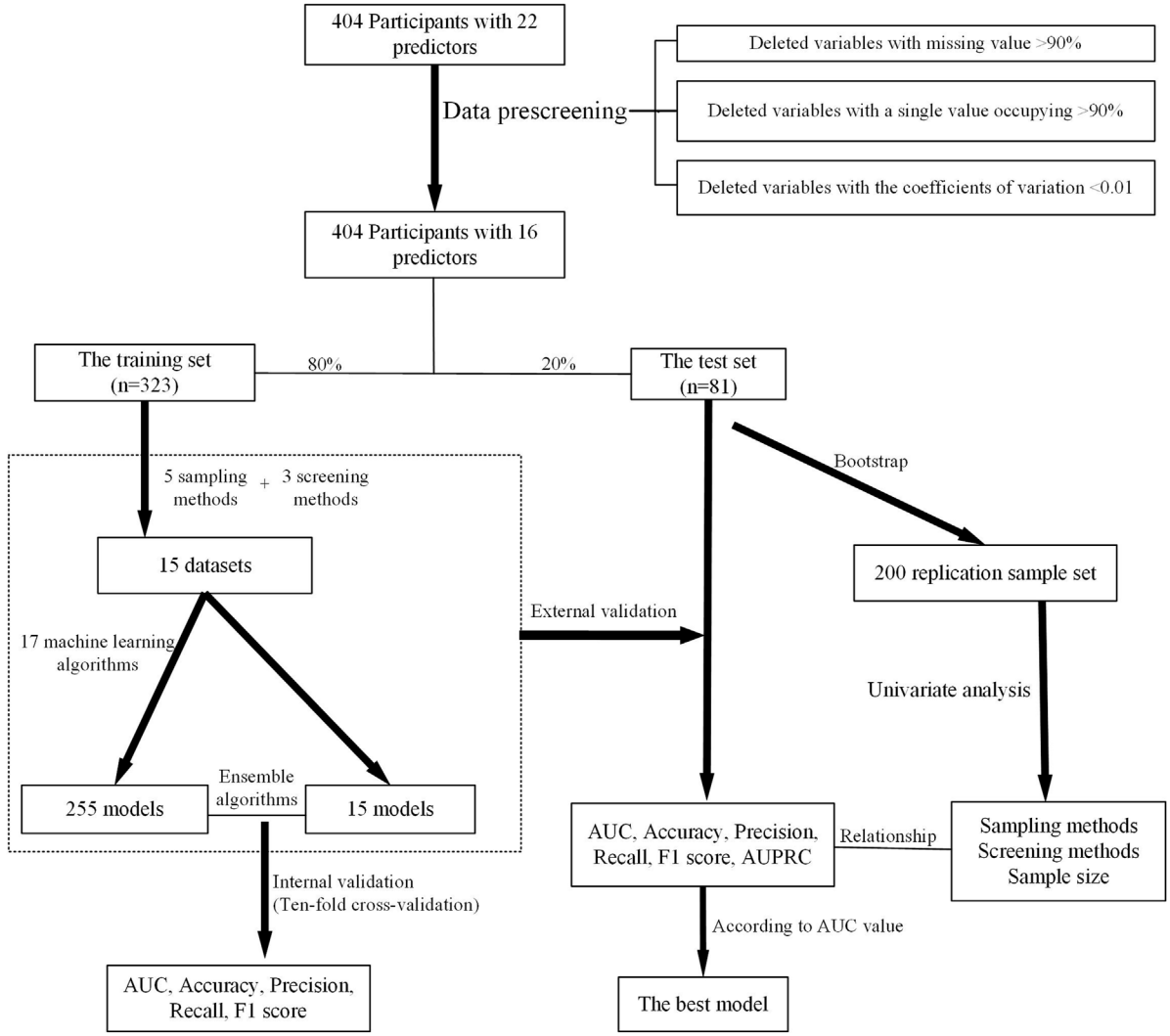


FIGURE 2
Overview of the modeling method.

3.1 Data pre-processing

3.1.1 Data pre-screening

After removing columns that met the deleting criteria, 16 variables were retained and 6 variables were deleted (X8 myocardial infarction, X11 heart block, X16 venous thromboembolism, X17 history of gout, X18 renal failure, and X21 anticoagulant therapy).

3.1.2 Feature screening

After data pre-screening and data sampling, the variables were screened using the Lasso method and the Boruta method, as shown in Supplementary Figure S1. The results showed that the five most important variables in the PIP model were angina, atherosclerosis, heart failure, diabetes, and number of medications (Supplementary Figure S1A). In the PPO model, the five most important variables were number of medications, angina, atherosclerosis, and history of cardiovascular diseases (Supplementary Figure S1B). The most important variables in the PIM model were number of medications, number of diseases, duration of hospitalization (days), age, and heart failure (Supplementary Figure S1C).

3.2 Model validation

3.2.1 Internal validation

Internal validation was performed using the 10-fold cross-validation method. Fifteen datasets were created using five data sampling methods and three feature screening methods. Two

TABLE 1 Information of PPO, PIP, PIM, and characteristics in the participants.

No.	Variable	Parameter	Value (N = 404)
	PIP	No	86 (21.3%)
		Yes	318 (78.7%)
	PPO	No	131 (32.4%)
		Yes	273 (67.6%)
	PIM	No	292 (72.3%)
		Yes	112 (27.7%)
X1	Gender	Female	242 (59.9%)
		Male	162 (40.1%)
X2	Age (years)		79.1 ± 8.18
X3	Duration of hospital stay (days)		19.5 ± 9.96
X4	Number of diseases		6.3 ± 2.45
X5	Number of medications		16.2 ± 9.74
X6	Hypertension	No	95 (23.5%)
		Yes	309 (76.5%)
X7	Cerebrovascular disease	No	215 (53.2%)
		Yes	189 (46.8%)
X8	Myocardial infarction	No	390 (96.5%)
		Yes	14 (3.5%)
X9	Angina	No	279 (69.1%)
		Yes	125 (30.9%)
X10	Heart failure	No	235 (58.2%)
		Yes	169 (41.8%)
X11	Heart block	No	370 (91.6%)
		Yes	34 (8.4%)
X12	Atrial fibrillation	No	336 (83.2%)
		Yes	68 (16.8%)
X13	Atherosclerosis	No	93 (23.0%)
		Yes	311 (77.0%)
X14	Hyperlipidemia	No	342 (84.7%)
		Yes	62 (15.3%)
X15	Diabetes	No	280 (69.3%)
		Yes	124 (30.7%)
X16	Venous thromboembolism	No	395 (97.8%)
		Yes	9 (2.2%)
X17	History of gout	No	392 (97.0%)
		Yes	12 (3.0%)
X18	Renal failure	No	367 (90.8%)
		Yes	37 (9.2%)
X19	Peptic ulcer or alimentary tract hemorrhage	No	352 (87.1%)
		Yes	52 (12.9%)
X20	History of cardiovascular disease	No	45 (11.1%)
		Yes	359 (88.9%)
X21	Anticoagulant therapy	No	30 (7.4%)
		Yes	374 (92.6%)

(Continued on following page)

TABLE 1 (*Continued*) Information of PPO, PIP, PIM, and characteristics in the participants.

No.	Variable	Parameter	Value (N = 404)
X22	Antithrombotic therapy	No	119 (29.5%)
		Yes	285 (70.5%)

hundred and fifty-five models for predicting PIP, PPO, and PIM respectively, were built using 18 machine learning algorithms. Different data sampling methods and different machine learning algorithms in the PIP model were significantly affected by the prediction performance of the PIP model ($p < 0.0001$). Details are listed in Supplementary Table S1.

As shown in Supplementary Table S2, different data sampling methods and different machine learning algorithms showed significant differences in the prediction performance of the PPO model ($p < 0.0001$), but the different feature screening methods were not significant ($p > 0.05$).

The results of the PIM prediction model were similar to those of the PPO prediction model. Significant differences between different data sampling methods and machine learning algorithms on the prediction performance of the PIM model are shown in Supplementary Table S3.

3.2.2 External validation

Applying 18 machine learning algorithms, 270 machine learning models were developed for each output. External validation of the models was performed by bootstrapping 200 samples in the test set. Different data sampling methods, different feature screening methods, and different machine learning algorithms in the PIP models had a significant effect ($p < 0.0001$) on prediction performance (list in Supplementary Table S1).

As presented in Supplementary Tables S1, S3, the results of the external validation of the PIM and PPO models were consistent with the PIP models. Data sampling methods, feature screening methods, and machine learning algorithms showed statistically significant differences in the prediction performance of the PIM and the PPO model.

3.2.3 Variable importance

The data from 200 bootstrapping samples were entered in the PIP, PIM, and PPO models. The contribution of each variable to the prediction performance in the different models is shown in Supplementary Figure S2 by the averaged AUC value when the variable was included in the prediction model. The five most important variables in the PIP model were cerebrovascular disease, history of cardiovascular disease, number of medications, duration of hospitalization (days), and age, while diabetes, gastrointestinal bleeding, hypertension, and angina were the least important (Supplementary Figure S2A). In the PPO model, the five most important variables were diabetes, hyperlipidemia, heart failure, duration of hospitalization (days), and gastrointestinal bleeding, while the five least important variables were hypertension, cerebrovascular disease, antithrombotic therapy, and atrial fibrillation (Supplementary Figure S2B). The most important variable in the PIM model were diabetes, antithrombotic therapy, duration of hospitalization (days), age, and hypertension, while gastrointestinal bleeding, hyperlipidemia, history of cardiovascular disease, and atrial fibrillation were unimportant (Supplementary Figure S2C).

3.3 Model selection

3.3.1 Model evaluation

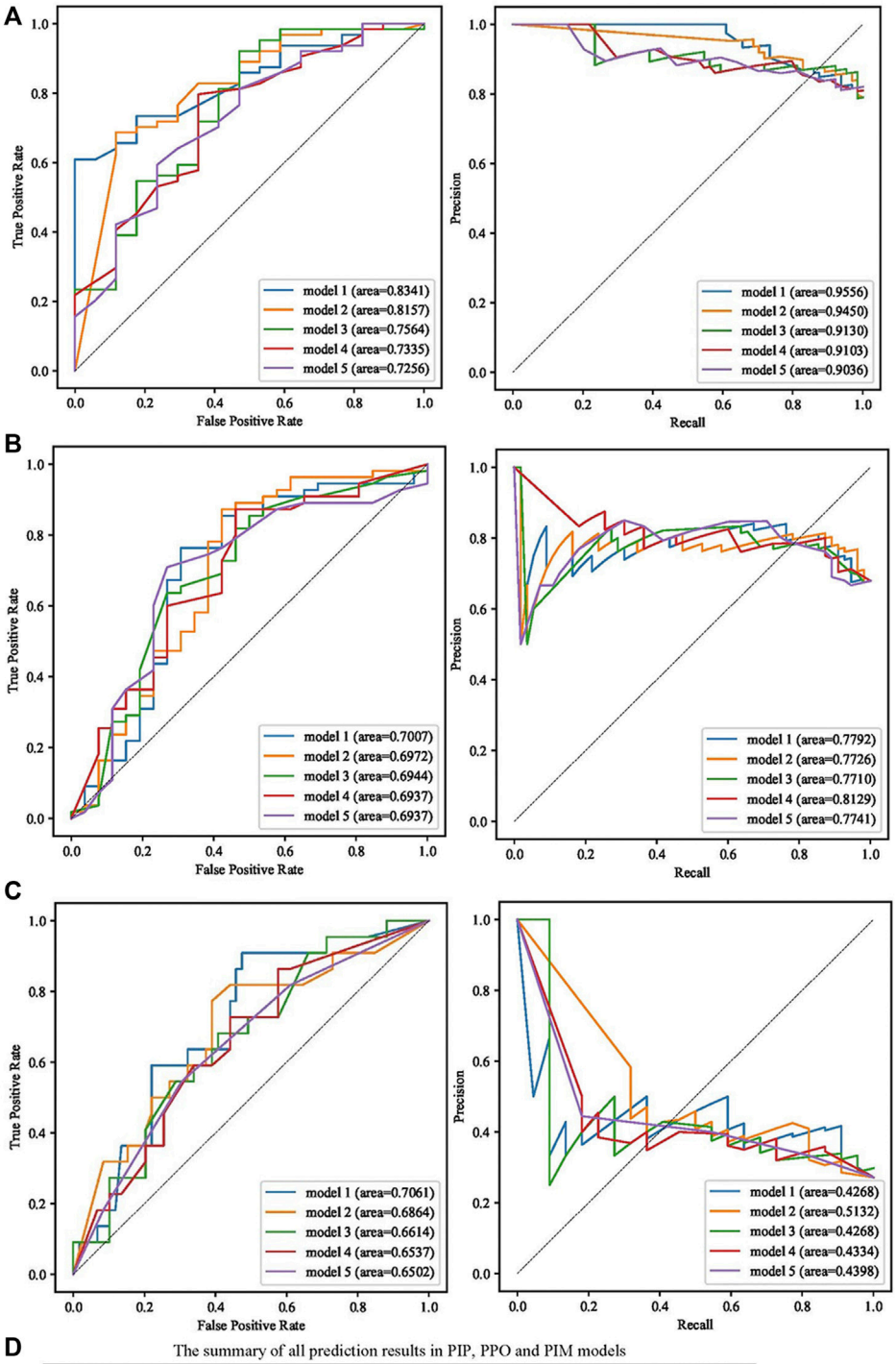
AUC, accuracy, precision, recall, F1 score, and the area under the precision-recall curve (AUPRC) were used to evaluate the predictive performance of models, and the best models according to the AUC value are presented in Figure 3. The prediction performance of the PIP model achieved an AUC of 0.8341 and an AUPRC of 0.9556 (Figure 3A). As presented in Figure 3B, the best performing PPO model had the highest AUC (0.7007) and AUPRC (0.7992). The best prediction performance of the PIM model provided an AUC of 0.7061 and an AUPRC of 0.4268 (Figure 3C). The best predictive performance metrics of PIP, PIM, and PPO are presented in Figure 3D.

3.3.2 SHapley additive explanation evaluation

SHAP can interpret the output of any machine learning model. The contribution of variables in the PIP model is explained by SHAP, and the results are shown in Figure 4. As illustrated in Figure 4A, SHAP estimated the contribution of each feature value in each sample to the prediction. Cerebrovascular disease, heart failure, age, hyperlipidemia, and hypertension provided a positive contribution to the SHAP value, while duration of hospital stay (days), myocardial infarction, and gender provided a negative contribution. Cerebrovascular disease was the most important variable.

As presented in Figure 4B, the SHAP value of each feature in each sample was calculated and plotted. Variables were ranked in descending order by summarizing the SHAP values of each sample. For example, the higher the values of duration of hospital stay (days), lower the value of SHAP.

The mean of the absolute value of the SHAP value of each variable, which was regarded as of feature importance, was plotted as shown in Figure 4C. The top five most important variables in the PIP model were angina, atherosclerosis, number of diseases, number of medications, and history of cardiovascular disease.



D

The summary of all prediction results in PIP, PPO and PIM models

Models	AUC	Accuracy	Precision	Recall	F1 Score	AUPRC
PIP	0.8341	0.716	0.9362	0.6875	0.7928	0.9556
PPO	0.7007	0.7407	0.8036	0.8182	0.8108	0.7792
PIM	0.7061	0.6543	0.4062	0.5909	0.4815	0.4268

FIGURE 3
Summary of the performance of PIP, PPO, and PIM model. **(A)** The results of AUC and AUPRC in the best five PIP model. **(B)** The results of AUC and AUPRC in the best five PPO model. **(C)** The results of AUC and AUPRC in the best five PIM model. **(D)** The summary of AUC, accuracy, precision, recall, F1 score, AUPRC in the best PIP, PPO, and PIM model.

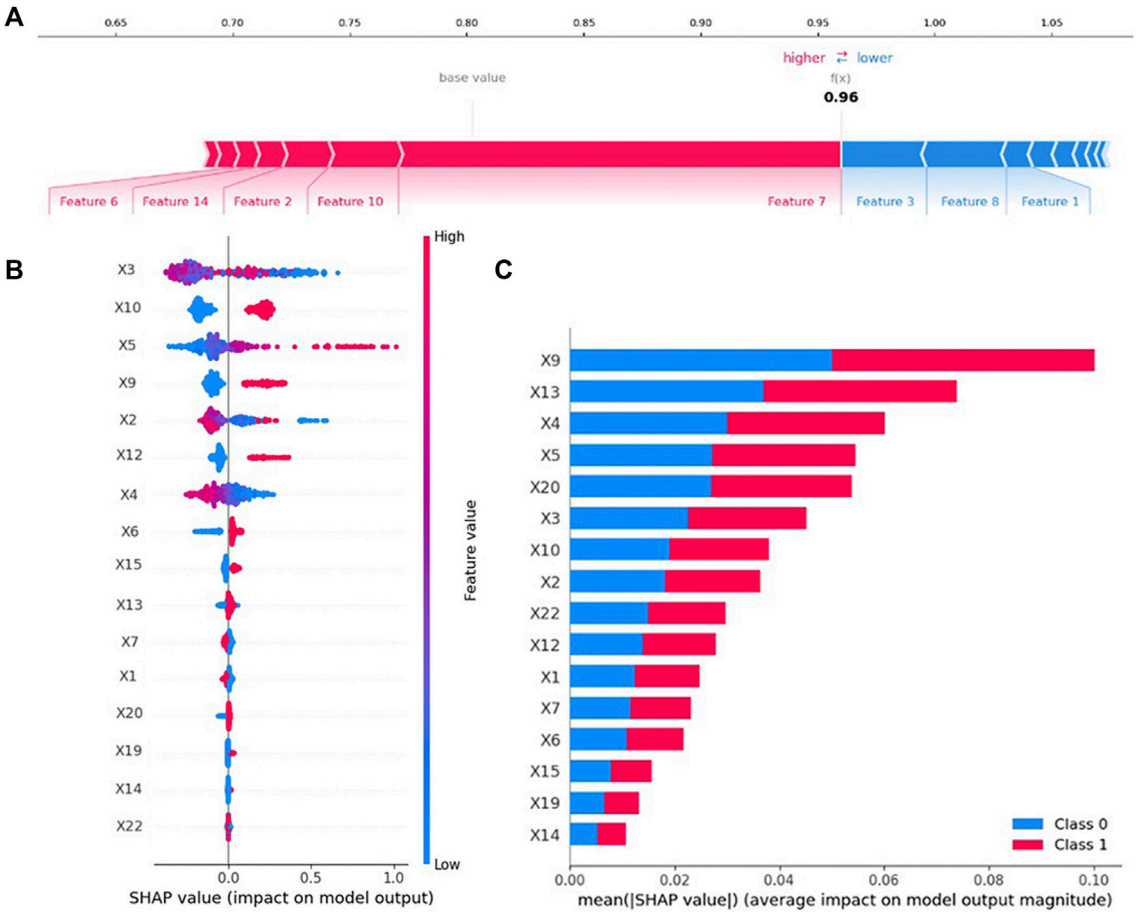


FIGURE 4
Variable contribution to the PIP model by SHAP Value. **(A)** Contribution of each feature value in one sample. **(B)** Summary of SHAP value of each variable. **(C)** Absolute average of SHAP value of each variable.

3.4 Sample size validation

The adequacy of the sample size was verified using the resampling bootstrapping method, and the results are plotted in Supplementary Figure S3. In the PIP model, the AUC gradually increased and the dispersion of the AUC value decreased as the percentage of sample size increased. When the sample size reached 70%, the curve flattened. The results indicated that the performance of the PIP model might be affected when expanding the sample size (Supplementary Figure S3A). In both the PPO model and the PIM model, both the curves showed an upward trend. These results indicate that the performance of the PPO and PIM models might be improved even further with the addition of samples (Supplementary Figures S3B,C).

3.5 Development prediction platform

Based on the parameters of the best models of PIP, PPO, and PIM, the prediction platform was established for individualized intervention. The input interface will be used to receive information on key variables in each patient (Figure 5A), and the output interface will show the risk rate of PIP, PIM, and PPO (Figure 5B). The software has obtained the Computer Software Copyright Registration Certificate (No. 7960815) received from the National Copyright Administration of the PRC (Supplementary Figure S4).

4 Discussion

In this study, a total of 404 elderly patients with cardiovascular disease who were hospitalized for 3–60 days were included. Five data sampling methods and three feature screening methods were used to construct 15 datasets, and 270 machine learning models were developed using 18 machine learning algorithms. AUC, accuracy, precision, recall, F1 Score, and AUPRC were used to evaluate the performance of the models. The PIP prediction platform was developed based on the parameters in the best model (the AUCs of the PIP, PPO, and PIM models were 0.8341, 0.7007 and 0.7061, respectively).

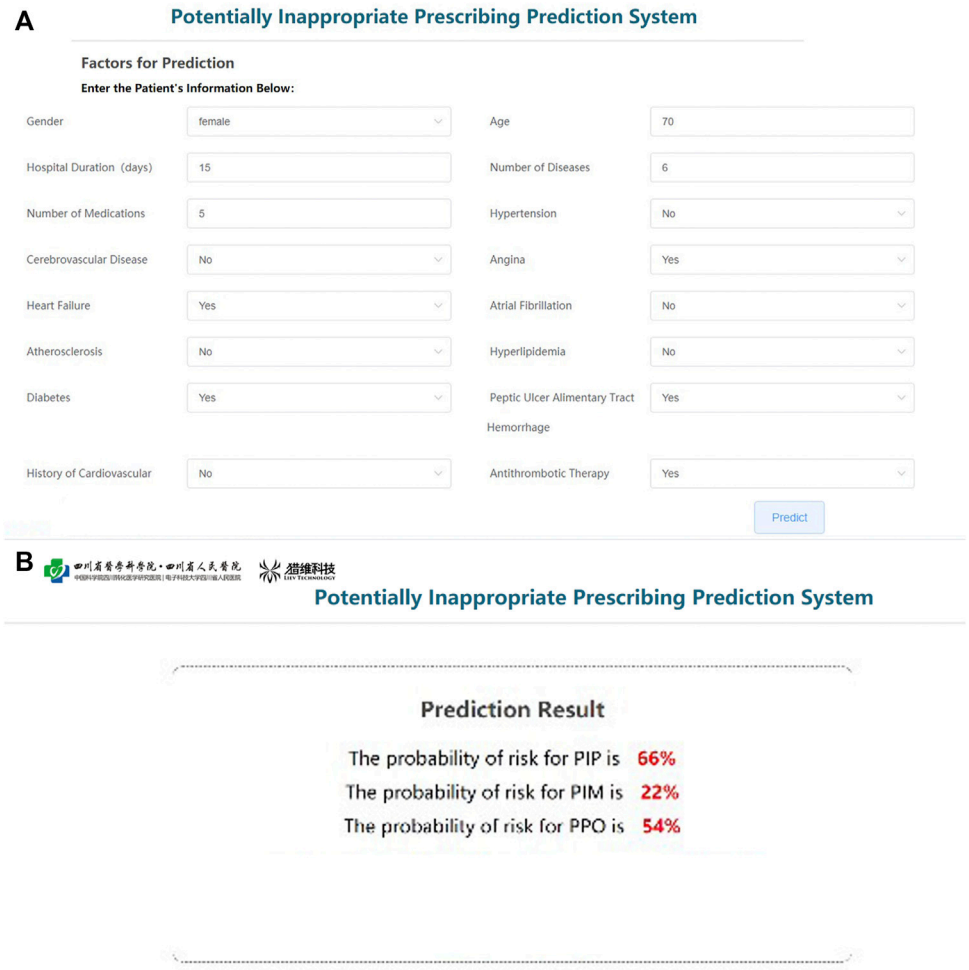


FIGURE 5
Operation interface of PIP warning platform. **(A)** User input interfaces. **(B)** User output interfaces.

One study reported that length of stay, comorbidities, and age were associated with PIP in elderly patients (Abegaz et al., 2018). Muhlack et al. (2018) found that elderly patients with multiple diseases, frailty, and cognitive impairment were more likely to have PIM. Meanwhile, the study showed that elderly patients with lower levels of education, those taking multiple medications, and unplanned hospitalization were more likely to have PIM. Previous research suggested that the number of medications prescribed was associated with the occurrence of PIM (Nieves-Pérez et al., 2018; Ma et al., 2019). Maaroufi et al. (2021) found significant correlations between PIM and the number of medications used (at home), gender, unauthorized medications, and the number and type of comorbidities, with information on the number of medications used. Multiple results showed that comorbidities and the number of medications were key risk factors for developing PIP in the elderly. Moreover, a recent study showed that the prevalence of PIP was related to the days of hospitalization (Xu et al., 2020). According to the electronic medical record in the hospital, patients whose duration of hospitalization was between 3 and 60 days were included in the study. Patients whose length of stay was less than 3 days might die following hospitalization or have a few examinations after hospitalization and should be excluded. In this study, we found that angina, atherosclerosis, heart failure, diabetes, and the number of medications used were more strictly associated with the development of PIP in elderly patients with cardiovascular disease. These results suggest that patients with the above variables need additional care and attention. Furthermore, using these variables in similar studies may be interesting in the future.

Similar to this study, Patel et al. (2020) built prediction models using cross-validated logistic regression (CVLR) and XGBoost to screen predictors of potentially inappropriate osteoarthritis in the elderly with NSAIDs. The machine learning algorithms used in this study included two machine learning algorithms used by Patel

et al. (2020). Compared to this study, Patel et al. (2020) reported a better predictive performance with an AUC of 0.8341 and an accuracy of 0.7160. However, Patel's study did not perform external validation and had poor generalization ability. In this study, external validation was performed. Additionally, the ensemble algorithms summarized the output of the five best models (assessed by AUC) among the trained models and generated output according to the voting principle, which could help to improve the prediction performance of models. The results suggested that the model in the present study had a stronger generalization ability and higher prediction accuracy.

5 Limitations

This study had a number of limitations. First, this study was based on data from a single medical center in China. We are not certain if our results can also be generalized to other hospitals with a large elderly population. Second, according to the sample size results of this study and the results of other studies (Black et al., 2018; Rose et al., 2018; Hyttinen et al., 2019a; Hyttinen et al., 2019b), a larger sample size is needed to further optimize the model in the future. Third, this study was a retrospective analysis, so there were cases of incomplete data or missing records. For example, educational status has previously been demonstrated to be associated with the development of PIP. However, we lacked such data.

6 Conclusion

In summary, we developed a risk warning platform for potentially inappropriate prescriptions in elderly patients with cardiovascular disease who are over 65 years of age and with hospitalization between 3 and 60 days. We explored various combinations of different sampling methods, feature selection methods, and algorithms. Additionally, the contribution of variables was demonstrated by several methods. The risk warning platform could conveniently inform clinicians about the risk of PIP, which is key to the development of effective and personalized treatment strategies.

Data availability statement

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

Author contributions

WX was involved in reviewing prescriptions, model design, and data analysis. CH, LM, and QL contributed to writing and approval of the final manuscript. LE assisted in reviewing prescriptions. TR and ZJ were responsible for revising the research. All authors agreed to be accountable for the content of the work.

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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.2022.804566/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Results of feature screening in different models. **(A)** In the PIP model. **(B)** In the PPO model. **(C)** In the PIM model. (The importance of each variable was summarized and shown with the mean of the 15 datasets. The variable names are shown in Supplementary Table S1).

SUPPLEMENTARY FIGURE S2
Contribution of each variable to prediction performance in different models. **(A)** In the PIP model. **(B)** In the PPO model. **(C)** In the PIM model. (The importance of each variable was summarized when the variable was included in the models. The variable names are shown in Supplementary Table S1).

SUPPLEMENTARY FIGURE S3
Results of sample size validation **(A)** In the PIP model. **(B)** In the PPO model. **(C)** In the PIM model.

SUPPLEMENTARY FIGURE S4
Computer Software Copyright Registration Certificate.

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Adverse drug reactions and correlations with drug–drug interactions: A retrospective study of reports from 2011 to 2020

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Introduction: Adverse drug reactions (ADRs) represent a public health problem worldwide that deserves attention due to the impact on mortality, morbidity, and healthcare costs. Drug–drug interactions (DDIs) are an important contributor to ADRs. Most of the studies focused only on potential DDIs (pDDIs), while the detailed data are limited regarding the ADRs associated with actual DDIs.

Methods: This retrospective study evaluated ADRs reported between 2011 and 2020 in a tertiary hospital. The causality and severity of ADRs were evaluated through the Naranjo Algorithm and Hartwig's scale, respectively. Preventability classification was based on the modified Schoumock and Thornton scale. For ADRs with at least two suspected drugs, pDDIs were identified according to the Lexi-Interact. We further checked whether the ADR description in the reports corresponded to the clinical consequences of the pDDIs.

Results: A total of 1,803 ADRs were reported, of which 36.77% ADRs were classified as mild, 43.26% as moderate, and 19.97% as severe. The assessment of causality showed that the distributions of definite, probable, and possible categories were 0.33%, 58.68%, and 40.99%, respectively. A total of 53.97% of ADRs were identified as preventable ADRs, while 46.03% were recognized as unpreventable. The severity of ADRs was significantly correlated with age, the number of suspected drugs and preventability. Antimicrobial agents were the most common implicated pharmacological group, and the most frequently affected system was the gastrointestinal system. Considering individual drugs, aspirin was the most frequently reported drug. Among 573 ADRs with at least two suspected drugs, 105 ADRs were caused by actual DDIs, of which only 59 and 6 ADRs were caused by actual DDIs in category D and X, respectively. The most frequent drugs involved in actual DDIs of category D were aspirin and heparin, with the majority of ADRs being gastrointestinal bleeding.

Conclusion: This study analyzed the pattern of ADRs in detail and obtained clinical evidence about ADRs associated with actual DDIs. These findings may be useful to compare patterns between different centers and to design

preventive strategies for ADRs. Continuous education and training should be provided for physicians regarding the knowledge and recognition of ADRs associated with DDIs.

KEYWORDS

adverse drug reactions, drug–drug interactions, causality, severity, preventability

Introduction

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is an unintended and noxious response that is detected in patients after the use of drugs for the prophylaxis, diagnosis or treatment of a disease at doses normally used (Edwards and Aronson, 2000). ADRs, as a major threat in the healthcare system, contribute significantly to mortality, morbidity, extended hospital stays, and increased healthcare costs (Khan, 2013; Angamo et al., 2016). A meta-analysis showed that the percentage of ADR-induced admissions in patients over 60 years old was accurately estimated to be 8.7% (Oscanoa et al., 2017). To minimize the consequences of ADRs, it is necessary to study ADRs in terms of their early identification and prevention and to motivate healthcare professionals to report ADRs (Arulappen et al., 2018).

According to a WHO report, 60% of ADRs are preventable (Lau et al., 2003). Drug–drug interactions (DDIs) are an important cause of preventable ADRs. The increasing number of patients with multimorbidity and the growing complexity of therapeutic agents have led to widespread polypharmacy, which could result in the rising numbers of potential DDIs (pDDIs), especially in elderly individuals (Obreli-Neto et al., 2012a; Scondotto et al., 2018). Although there are several databases available that could be used to evaluate pDDIs, the clinical relevance and actual clinical importance of majority pDDIs remain insufficiently characterized and underestimated (Roblek et al., 2015). Actual DDIs are identified on the basis of clinical evidence, such as laboratory test results or symptoms, consequently, the frequency of actual DDIs is much lower than that of pDDIs (Magro et al., 2012; Zheng et al., 2018). Over the past years, a substantial number of articles have been published about ADRs due to DDIs (Leone et al., 2010; Obreli-Neto et al., 2012a; Obreli Neto et al., 2012b; Kovacevic et al., 2019; Letinier et al., 2020; Magro et al., 2020). A 6-year retrospective study in Bengbu in China showed that among the ADRs reported between nervous system drugs in hospitalized patients, 12.14% of the ADRs were associated with potential and actual DDIs, and actual DDIs were present in 6.21% of all ADRs (Shi et al., 2014). However, the incidence of ADRs resulting from DDIs could not be accurately estimated primarily because of differences in study designs and populations (Mirosevic Skvrce et al., 2011).

In this context, the present study aimed to describe the distribution of ADRs, assess causality, preventability and severity of ADRs, and determine factors involved in the severity of ADRs in a tertiary hospital between 2011 and 2020. Additionally, we described and analyzed the most frequent drugs suspected to cause ADRs and the organ system classes affected by ADRs. Furthermore, we evaluated the pDDIs among the ADRs with more than one suspected drug, estimated the incidence of ADRs due to actual DDIs and characterized ADRs caused by actual DDIs.

Materials and methods

Data collection

In this retrospective single-center study, all the ADRs was collected from the National ADR Monitoring system in Jinshan Hospital of Fudan University, between 01 January 2011 and 31 December 2020. Jinshan Hospital is a tertiary general hospital with a 700-bed capacity in the Jinshan district of Shanghai. In 2020, there were 28,533 hospital admissions, and 1.28 million outpatient and emergency department visits. ADR reports were filled out according to a specific ADR report format and submitted in paper based or electronic way by healthcare professionals, including physicians, pharmacists, and nurses.

Once received, the reported ADRs were reviewed and evaluated by ADR surveillance unit of the pharmacy department. Only the reported ADRs followed the WHO definition (Edwards and Aronson, 2000) and without any uncertainty or mistakes were accepted after exclusion of duplicates and uploaded to ADR Monitoring system. A series of exclusion criteria were applied to ensure a robust data set for analysis. Exclusion criteria included the following: 1) ADRs with doubtful causality with Naranjo's algorithm (Naranjo et al., 1981). 2) ADR forms with insufficient information 3) ADRs symptoms similar to the original disease.

The demographic and other information relevant to ADRs were documented, including gender, age, diagnosis, admission department, suspected drugs, concomitant medications, drug details, organ system involved in the ADR, the management and outcome of the ADRs, and the type of reporter. One report could describe one or more ADRs. The incriminated drugs were classified by pharmacological group according to the WHO Anatomical Therapeutic Chemical Classification (ATC). The involved system organ classes were determined according to WHO Adverse Reaction Terminologies (WHO-ART). Two

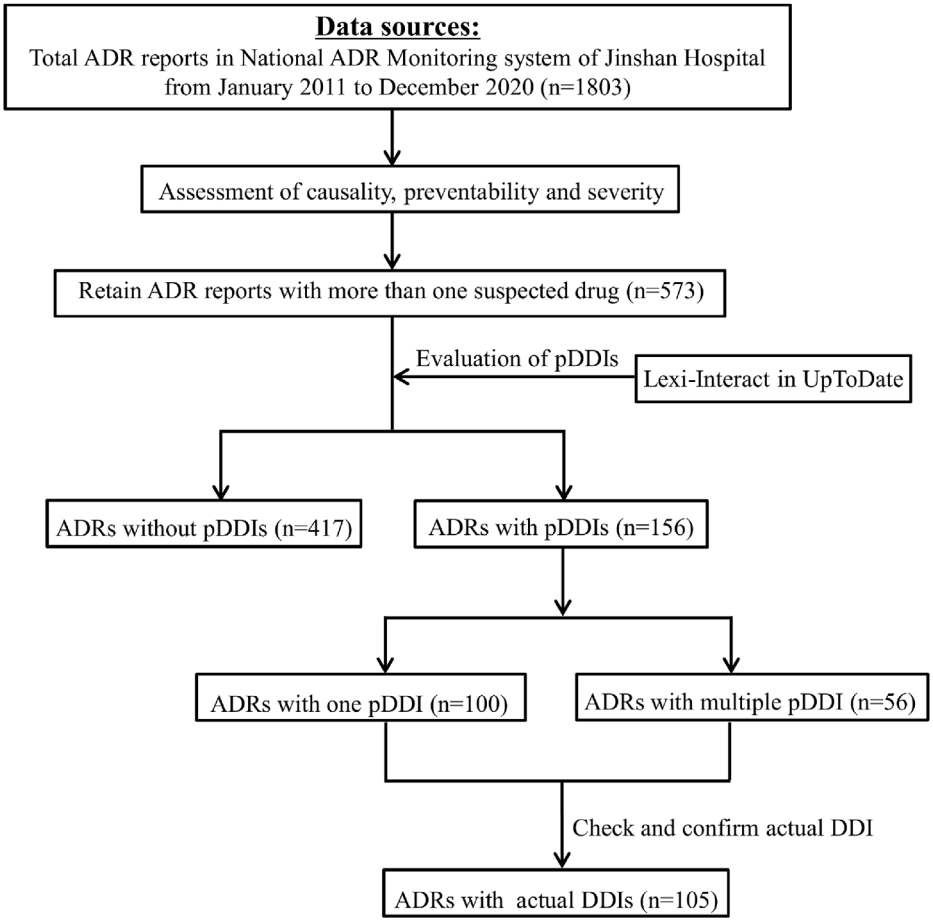

FIGURE 1
Flowchart depicting the study process.

investigators cross checked the data for accuracy. Flowchart depicting the study process was shown in Figure 1.

Causality, preventability, and severity assessment

Each ADR was further evaluated for various parameters, such as causality, severity and preventability, using previously validated and recognized approaches. The assessment of causality was performed using the Naranjo Algorithm, which consists of 10 individually scored criteria. ADRs were categorized as possible ADRs (1–4), probable ADRs (5–8) or definite ADRs (≥9) based on the total score (Naranjo et al., 1981). Severity classification was based on Hartwig's scale, which showed the criteria and matched levels used for ADR severity assessment. ADRs were considered as severe if they resulted in one of the following outcomes: the requirement for intensive medical care, permanent harm to the patient, or the death of the patient (Hartwig et al., 1992). The preventability of ADRs was assessed by the modified Schoumock and Thornton scale and classified into definitely preventable, probably preventable and not preventable reactions (Schumock and Thornton, 1992). In our study, both definitely and probably preventable ADRs were considered as one category of preventable reactions.

Evaluation of potential drug–drug interactions

For ADRs caused by two or more suspected drugs, pDDIs were identified by the software Lexi-Interact in UpToDate. The evaluation results of pDDIs were classified into five levels of risk as no known interaction (A), no action needed (B), monitor therapy (C), consider therapy modification (D), and avoid combination (X). We further verified whether the clinical consequences of pDDIs corresponded to the description of the ADR in the report, and if consistent, the pDDI was considered

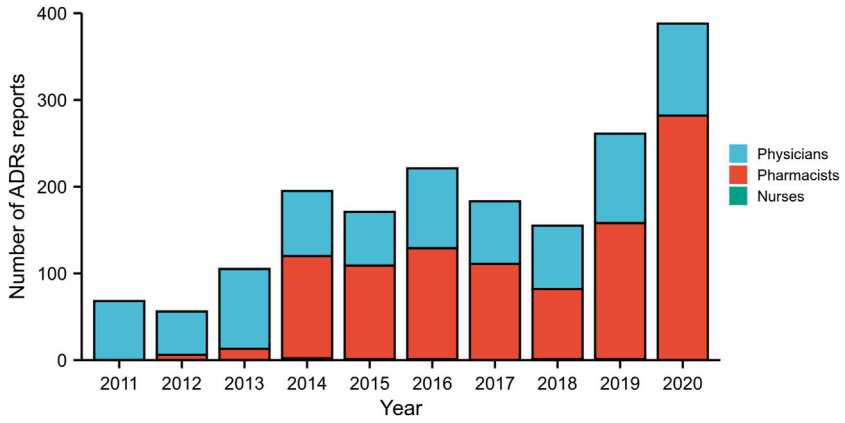

FIGURE 2
The total number of adverse drug reaction (ADR) reports and the distribution of reporters from different occupations by year during 2011–2020.

the actual DDI. Two clinical pharmacists independently assessed the probability, severity and preventability of ADRs as well as the consistency between ADRs and pDDIs. Any discrepancies were resolved by discussion.

Statistical analysis

Descriptive statistics were applied to describe the population as well as the clinical characteristics of ADRs and pDDIs. The categorical data were presented as numbers and proportions. Sankey diagrams of severity in preventable and unpreventable ADRs were plotted with the R package alluvial. The Mann–Whitney *U* test was used to evaluate the correlation between gender and the severity of ADRs. Spearman's rank tests were performed to determine the association of age, the number of suspected drugs and the category of preventability with the severity of ADRs. The Kruskal–Wallis *H* test was performed to evaluate the correlation between the route of administration and the severity of ADRs. Statistical analysis was performed using IBM SPSS Statistics version 25. A p-value < 0.05 was considered statistically significant.

Results

Department and reporter distribution of adverse drug reactions

From January 2011 to December 2020, a total of 1,803 ADRs were reported by healthcare professionals in our hospital, although the number of ADRs reported was relatively small between 2011 and 2013. During this 10-year period, pharmacists contributed 55.69% of all ADR reports, followed by physicians (43.98%). The frequency of ADRs reported by nurses was low, accounting for only 0.33%. The annual number of reports was no more than 221 during 2011–2018, however, this number subsequently increased significantly over the next 2 years, reaching 388 in 2020 (Figure 2). A small proportion of ADRs were reported by pharmacists between 2011 and 2013, however, since 2014, more than half of ADR reports have been submitted by pharmacists. Detailed data by the year and distribution of reporters were shown in Figure 2. In our study, the highest percentage of ADRs was collected from the gastroenterology department (26.8%), followed by the departments of emergency and critical care medicine (11.4%), cardiology department (7.9%), and neurology department (7.8%) (Figure 3). The proportions of ADRs collected from clinical departments were presented in Figure 3.

Causality, preventability, and severity assessment of adverse drug reactions

ADRs were further analyzed for causality, preventability and severity, as shown in Table 1. The assessment of causality according to the Naranjo Algorithm showed that the numbers of definite, probable and possible ADRs were 6 (0.33%), 1,058 (58.68%), and 739 (40.99%), respectively. According to Hartwig's Severity Assessment Scale, 663 (36.77%) ADRs were classified as mild, 780 (43.26%) as moderate, and 360 (19.97%) as severe. The evaluation of the preventability of ADRs using the modified Schumock and Thornton criteria revealed that 973 (53.97%) ADRs were identified as preventable ADRs, including 93 as definitely preventable and 880 as probably preventable, while 830 (46.03%) ADRs were recognized as unpreventable. Symptomatic or specific treatment was given for 1,045 (57.96%) ADRs. According to the records of ADR reports, the

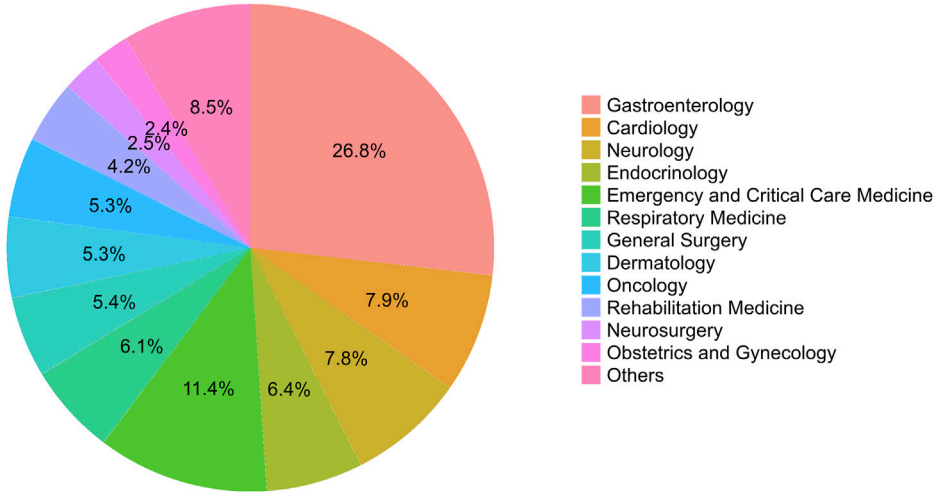

FIGURE 3
The percentage of adverse drug reactions (ADRs) from different clinical departments.

TABLE 1 Assessment and pattern of adverse drug reactions.

Variable	Number of ADRs (%)
Causality assessment	
Definite/probable	1,064 (59.01)
Possible	739 (40.99)
Severity	
Mild	663 (36.77)
Moderate	780 (43.26)
Severe	360 (19.97)
Preventability	
Definitely/probably preventable	973 (53.97)
Unpreventable	830 (46.03)
Treatment given	
Yes	1,045 (57.96)
No	758 (42.04)
Outcome of ADRs	
Recovered	238 (13.20)
Improved	1,462 (81.09)
Continuing/unclear	103 (5.71)
Fate of the suspected drug	
Drug withdrawn	1,700 (94.29)
Dose altered/rechallenge	103 (5.71)

majority of ADRs (81.09%) had improved, 238 (13.20%) patients had recovered from their ADRs, and 103 (5.71%) ADRs continued or their status was unclear. Suspected drugs were withdrawn in 1,700 (94.29%) ADR reports, but an altered dose or no change in therapy was observed in 103 (5.71%) reports. The visual design follows the principle of the Sankey diagram, which links the ADR characteristics by lines and signifies the quantities *via* line width, stratified by preventability (Figure 4).

Characteristics of adverse drug reactions according to severity assessment

The characteristics of ADRs according to severity assessment were shown in Table 2. A total of 1,803 ADRs were identified among 1,779 patients. Multiple ADRs in the same patient may be identified with different severity scale, so Table 2 depicted the distribution of mild, moderate, and severe reactions between different gender and age based on ADRs rather than patients. Concerning patient gender and ADRs, 46.87% males and 53.13% females experienced ADRs over the past 10 years. The proportion of mild ADRs was higher in females (60.33%) than in males (39.67%), however, the ratio of males to females was approximately 1:1 among those experiencing moderate and severe ADRs. The Mann–Whitney *U* test revealed significant differences in the mild, moderate, and severe ADR distributions between the males and females.

As shown in Table 2, the percentage of ADRs was highest among elderly individuals over 65 years of age (42.87%), followed by the 41–64-year (38.38%) and 18–40-year (14.03%) age groups. The minimum number of ADRs was observed in the age group under 18 years (4.71%). More than half of severe ADRs occurred in elderly individuals over 65 years of age. The majority of ADRs (67.72%) were identified with only one suspected drug, followed by 24.35% with two suspected drugs, and only 143 (7.93%) ADRs were found with ≥3 suspected drugs. According to Hartwig's scale, 46.03% of ADRs were classified as unpreventable ADRs, 48.81% as probably preventable ADRs and 5.16% as definitely preventable ADRs. The percentage of unpreventable ADRs significantly decreased with ADR

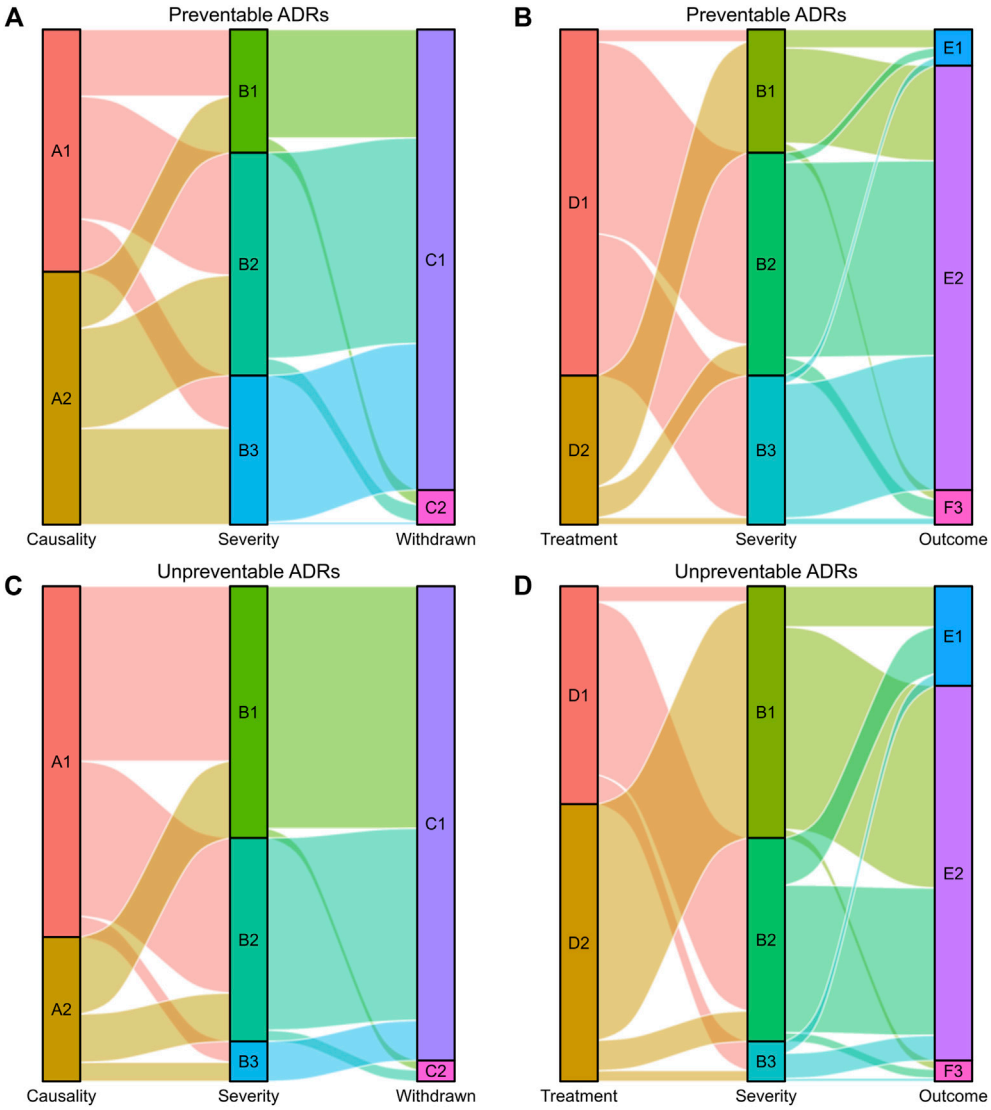

FIGURE 4
Sankey diagram of severity in preventable and unpreventable ADRs. **(A,B)** The causality assessment, fate of the suspected drug, treatment given and outcome of ADRs matched with ADR severity in preventable ADRs. **(C,D)** The causality assessment, fate of the suspected drug, treatment given and outcome of ADRs matched with ADR severity in unpreventable ADRs. The causality assessment of ADRs (A1 and A2), A1: Definite/Probable, A2: Possible. ADR severity (B1, B2, and B3), B1: Mild, B2: Moderate, B3: Severe. Fate of the suspected drug (C1 and C2), C1: Drug withdrawn, C2: Dose altered/No change. Treatment given (D1 and D2), D1: Treatment given, D2: No treatment. Outcome of ADRs (E1, E2, and E3), E1: Recovered, E2: Improved, E3: Continuing/Unclear.

severity (mild 63.65% vs. moderate 43.72% vs. severe 18.61%). The statistical results revealed significant positive correlations of ADR severity with age (Spearman's $R = 0.167$, $p < 0.001$), the number of suspected drugs (Spearman's $R = 0.136$, $p < 0.001$) and ADR preventability (Spearman's $R = 0.299$, $p < 0.001$).

The route of administration was classified according to the first suspected drug in the ADR reports. More than half of ADRs were associated with oral medicines regardless of their severity rating. Unexpectedly, the proportion of ADRs associated with intravenous drugs gradually decreased with increasing severity. The Kruskal–Wallis H test was further carried out and showed a significant association between the route of administration and the severity of ADRs (Table 2).

Drugs involved in adverse drug reactions and effects on organ systems

The pharmacological groups implicated in the ADRs were summarized in Table 3. Systemic antimicrobial agents were the

TABLE 2 Comparison of mild, moderate, and severe reactions.

Characteristics	Total, *n* (%)	Mild, *n* (%)	Moderate, *n* (%)	Severe, *n* (%)	*p*-value	*R*
Gender						
Male	845 (46.87)	263 (39.67)	399 (51.15)	183 (50.83)	<0.001[a]	—
Female	958 (53.13)	400 (60.33)	381 (48.85)	177 (49.17)		
Age (years)						
<18	85 (4.71)	18 (2.71)	66 (8.46)	1 (0.28)	<0.001[b]	0.167
18–40	253 (14.03)	130 (19.61)	104 (13.33)	19 (5.28)		
41–64	692 (38.38)	286 (43.14)	269 (34.49)	137 (38.06)		
≥65	773 (42.87)	229 (34.54)	341 (43.72)	203 (56.39)		
Number of suspected drugs						
1	1,221 (67.72)	499 (75.26)	512 (65.64)	210 (58.33)	<0.001[b]	0.136
2	439 (24.35)	126 (19.00)	202 (25.90)	111 (30.83)		
≥3	143 (7.93)	38 (5.73)	66 (8.46)	39 (10.83)		
Preventability						
Unpreventable	830 (46.03)	422 (63.65)	341 (43.72)	67 (18.61)	<0.001[b]	0.299
Probably preventable	880 (48.81)	210 (31.67)	392 (50.26)	278 (77.22)		
Definitely preventable	93 (5.16)	31 (4.68)	47 (6.03)	15 (4.17)		
Route of administration						
Oral	1,019 (56.52)	340 (51.28)	409 (52.44)	270 (75.00)	<0.001[c]	
Intravenous	683 (37.88)	281 (42.38)	321 (41.15)	81 (22.50)		
Others	101 (5.60)	42 (6.33)	50 (6.41)	9 (2.50)		

[a]Mann–Whitney *U* test.
[b]Spearman.
[c]Kruskal–Wallis H.
The *R* value represents Spearman's correlation coefficient.

most commonly implicated drugs (22.75%), with 14.53% and 39.32% of their associated ADRs being classified as severe and preventable ADRs, respectively. Cardiovascular agents were the second most frequently reported class of drugs responsible for ADRs (12.41%), followed by medications for the alimentary tract and metabolism (12.06%). Drugs acting on the blood and blood-forming organs represented 11.75% of the reports (32.45% severe and 83.11% preventable ADRs). Drugs acting on the musculoskeletal system were implicated in 10.77% of the ADRs (39.71% severe and 71.48% preventable ADRs). Traditional Chinese medicines were implicated in 10.07% of the reports (18.53% severe ADRs and 54.44% preventable ADRs).

The frequency of commonly prescribed drugs among total and severe ADRs was shown in Table 4. When individual drugs were considered, aspirin was responsible for a maximum number of both total and severe ADRs, far more than any other drugs. Among the total ADRs, levofloxacin (82) was the second most frequent causative drug, followed by compound pseudoephedrine hydrochloride (65) and clopidogrel (48). In addition to aspirin, the drugs most frequently involved in severe ADRs were clopidogrel (17), levofloxacin (16), compound pseudoephedrine hydrochloride (14), and diclofenac sodium (13).

Upon a review of the outcomes of ADRs, the most frequently affected system was the gastrointestinal system (30.83%), with the clinical symptoms of nausea, vomiting, abdominal pain, diarrhea, abdominal distention, and so on. In addition, the commonly reported reactions were skin and appendage disorders (22.44%) and liver and biliary system disorders (14.19%). A more detailed description was presented in Table 5.

Adverse drug reactions caused by drug–drug interactions

pDDIs were evaluated in 573 of 1,803 ADR reports (31.78%) involving more than one suspected drug. 156 ADRs were identified with pDDIs of category C, D, and X, of which 100 ADRs were identified with only one pDDI and 56 ADRs with multiple pDDIs. Table 6 showed that 208 pDDIs of category C were identified in 112 ADRs, 74 pDDIs of category D in 58 ADRs, and 11 pDDIs of category X in 10 ADRs. Furthermore, we checked whether the reported ADRs were consistent with the potential clinical consequences of pDDIs. The results showed 105 ADRs were caused by actual DDIs, accounting for 18.32% of the ADR reports with more than one suspected drug. Among

TABLE 3 Pharmacology groups according to the WHO-ATC code and their pattern in ADRs.

Pharmacology groups	Number of patients	ADR frequency (%)	Number of severe ADRs (%)	Number of preventable ADRs (%)
Alimentary tract and metabolism	256	310 (12.06)	65 (20.97)	51 (16.45)
Blood and blood-forming organs	230	302 (11.75)	98 (32.45)	251 (83.11)
Cardiovascular system	281	319 (12.41)	85 (26.65)	208 (65.20)
Dermatologicals	6	7 (0.27)	1 (14.29)	6 (85.71)
Genito urinary system and sex hormones	9	9 (0.35)	1 (11.11)	3 (33.33)
Systemic hormonal preparations, excl. sex hormones, and insulins	72	76 (2.96)	15 (19.74)	13 (17.11)
Anti-infectives for systemic use	503	585 (22.75)	85 (14.53)	230 (39.32)
Antineoplastic and immunomodulating agents	129	192 (7.47)	24 (12.50)	161 (83.85)
Musculo-skeletal system	253	277 (10.77)	110 (39.71)	198 (71.48)
Nervous system	153	163 (6.34)	32 (19.63)	86 (52.76)
Antiparasitic products, insecticides, and repellents	4	4 (0.16)	0	2 (50.00)
Respiratory system	39	42 (1.63)	5 (11.90)	20 (47.62)
Sensory organs	4	4 (0.16)	0	0
Traditional chinese medicine	240	259 (10.07)	48 (18.53)	141 (54.44)
Others	22	22 (0.86)	0	5 (22.73%)

[a]Each ADR may have multiple suspected drugs, therefore the total number of incriminated drugs exceeds the ADRs.
WHO-ART, WHO Adverse Reaction Terminologies; ADR, adverse drug reaction.

TABLE 4 Top 10 incriminated drugs in total and severe ADRs based on frequency.

Ranking	Total ADRs		Severe ADRs	
	Drugs	Frequency (*n*)	Drugs	Frequency (*n*)
1	[a]Aspirin	134	[a]Aspirin	52
2	Levofloxacin	82	Clopidogrel	17
3	[a]Compound pseudoephedrine hydrochloride	65	Levofloxacin	16
4	Clopidogrel	48	[a]Compound pseudoephedrine hydrochloride	14
5	Moxifloxacin	47	[a]Diclofenac sodium	13
6	[a]Diclofenac sodium	42	[a]Paracetamol, aminophenazone, caffeine, and chlorphenamine maleate	11
7	Metformin	40	[a]Analgin	10
8	Azithromycin	39	Cefoperazone sodium and sulbactam sodium, warfarin, lansoprazole, compound reserpine	8
9	Rosuvastatin	34	Valsartan, metformin, compound irbesartan, and hydrochlorothiazide	7
10	Cefuroxime	33	[a]Ibuprofen, [a]compound ibuprofen and codeine, [a]compound paracetamol, caffeine and aspirin, rosuvastatin	6

[a]These drugs belong to the category of non-steroidal anti-inflammatory drugs (NSAIDs).
ADR, adverse drug reaction.

them, 59 and 6 ADRs were caused by actual DDIs in the category D and X, respectively.

Tables 7, 8 summarized the ADRs caused by actual DDIs belonging to category X and D, respectively. Potassium chloride and promethazine were the drug–drug combination most involved in ADRs caused by actual DDIs in category X, with severe and adverse clinical consequences to the gastrointestinal system. The most frequent drugs involved in actual DDIs of category D were aspirin (n = 34) and heparin (n = 26), and the great majority of ADRs caused by DDIs were associated with gastrointestinal bleeding. Aspirin/heparin (n = 10) and heparin/clopidogrel (n = 10), followed by aspirin/warfarin (n = 6) and

TABLE 5 Organs or systems involved in ADRs according to WHO classification.

Organs/systems	Clinical manifestations/symptoms	Frequency (%)
Skin and appendages disorders	Itching, urticaria, rash, maculopapular rash, erythema, etc.,	639 (22.44)
Musculo-skeletal system disorders	Myasthenia, myalgia, muscle bleeding, arthralgia, lower limb spasm, osteoporosis	26 (0.91)
Central and peripheral nervous system disorders	Dizziness, headache, peripheral neuropathy, coma, grand mal seizure, manic-depressive psychosis, etc.,	186 (6.53)
Autonomic nervous system disorders	Red flush, erythromelalgia	3 (0.11)
Vision disorders	Ocular abnormality, conjunctival hemorrhage, ocular pain, blurred vision	6 (0.21)
Hearing and vestibular disorders	Tinnitus	5 (0.18)
Special senses other, disorders	Taste perversion	1 (0.04)
Psychiatric disorders	Circulatory psychotic reactions, insomnia, manic reactions, sleep disorders, neurosis, etc.,	28 (0.98)
Gastro-intestinal system disorders	Nausea, vomiting, abdominal pain, gastrointestinal bleeding, abdominal distention, flatulence, black feces, diarrhea, hematemesis, etc.,	878 (30.83)
Liver and biliary system disorders	Abnormal liver function, jaundice, elevated liver enzymes, cholestatic hepatitis, biliary cirrhosis	404 (14.19)
Metabolic and nutritional disorders	Electrolyte abnormality, hyperuricemia, increased blood lactic acid, hypokalemia; hyponatremia, hyperkalemia, hypoglycemia, hyperglycemia, etc.,	52 (1.83)
Endocrine disorders	Male breast pain, non-specific endocrine disease, thyroiditis, hyperparathyroidism	5 (0.18)
Cardiovascular disorders, general	Hypotension, hypertension	64 (2.25)
Heart rate and rhythm disorders	Palpitations, tachycardia, bradycardia, cardiac arrest, arrhythmias, atrioventricular block	35 (1.23)
Respiratory system disorders	Dyspnea, asthma, cough	34 (1.19)
Red blood cell disorders	Anemia	3 (0.11)
White cell and respiratory disorders	Leukopenia, leukopenia, granulocytopenia, and granulocytopenia	8 (0.28)
Platelet, bleeding, and clotting disorders	Bone marrow suppression, thrombocytopenia, coagulopathy, hematemesis, etc.,	119 (4.18)
Urinary system disorders	Hematuria, abnormal renal function, urinary retention	54 (1.90)
Reproductive disorders, female	Genital itching, breast enlargement, menstrual disorders	3 (0.11)
Body as a whole—general disorders	Fatigue, allergic reactions, chills	220 (7.72)
Application site disorders	Phlebitis, skin necrosis	70 (2.46)
Resistance mechanism disorders	Decreased IgG4, systemic lupus erythematosus syndrome	5 (0.18)
Total[a]		2,848 (100%)

[a]Some ADRs with multiple system or organ disorders.
WHO, World Health Organization; ADR, adverse drug reaction.

TABLE 6 Distribution of the potential drug–drug interactions with category C, D, and X in ADRs.

Risk rating	Type of drug-drug interaction	ADRs (*n*)	pDDIs (*n*)
C	Monitor therapy	112	208
D	Consider therapy modification	58	74
X	Avoid combination	10	11

ADR, adverse drug reaction; pDDI, potential drug–drug interaction.

aspirin/ibuprofen (n = 5), were the drug–drug combinations most involved in ADRs caused by DDIs of category D.

Discussion

In this study, physicians and pharmacists were the groups that reported the great majority of ADRs, and the frequency of ADRs reported by nursing staff was low, which may be due to their extensive workload in everyday practice, inattention and unawareness toward ADR reporting or worry about legal implications (Singh et al., 2017). The reporter distribution of ADRs varies widely in different studies because of differences in healthcare structures as well as the awareness and motivation of healthcare professionals. The number of ADRs was relatively small, especially for ADRs reported by pharmacists between

TABLE 7 ADRs caused by actual drug–drug interactions belonging to category X.

Drug pairs	*n*	Reliability of pDDIs	Potential clinical consequences	Reported ADRs	Severity of ADRs
Diclofenac-indomethacin	1	Fair	Increased the risk of gastrointestinal toxicity	Gastrointestinal bleeding, melena	Moderate
Dexamethasone-desmopressin	1	Fair	Increased the risk of hyponatremia	Electrolyte abnormalities, edema	Severe
Potassium chloride-chlorphenamine	1	Fair	Enhanced the ulcerogenic effect of potassium chloride	Gastrointestinal bleeding	Severe
Potassium chloride-Promethazine	3	Fair	Enhanced the ulcerogenic effect of potassium chloride	Gastrointestinal bleeding (1), abdominal pain and anorexia (1), gastritis, and abdominal distension (1)	Severe-3

ADR, adverse drug reaction; pDDI, potential drug–drug interaction.

2011 and 2013, indicating underreporting in pharmacovigilance. The key to improving ADR reporting rates is adequate pharmacovigilance education and training for healthcare professionals (Barzaga Arencibia et al., 2012).

In the present study, we analyzed the pattern of ADRs based on the causality, severity, and preventability in our hospital, all of which vary among different hospitals due to differences in the population characteristics and hospital specialties. Naranjo's causality assessment showed that only 0.33% of reports were definite because of limited use of dechallenge and rechallenge processes for ethical reasons as well as the retrospective study design without the ability to assess the ADR completely. The suspected drugs were withdrawn among 94.29% of ADRs, and for the remaining 5.71% of ADRs, the suspected drug doses were altered or rechallenge processes were initiated. In this study, 19.97% of ADRs were classified as severe. Severe ADRs, as major concerns for public health, are a contributing factor of hospitalizations and morbidity (Rottenkolber et al., 2011; Marques et al., 2014). The analysis indicated a preventability rate of 53.97% among ADRs, comparable with the results of studies conducted in Romania and Jordan showing that 41% and 44.7% of ADRs were preventable, respectively (Farcas et al., 2014; Al Damen and Basheti, 2019). However, the data from a study showed lower preventability for ADRs (12%) compared with our finding (Dequito et al., 2011). As described in previous studies, insufficient monitoring, inappropriate dosing, and DDIs were the most frequent factors involved in ADR preventability (Farcas et al., 2014; Al Damen and Basheti, 2019). Incriminated drugs were withdrawn in 94.29% of the reports, which is in line with a previous study in a psychiatric department of a tertiary care teaching hospital in India (Patel et al., 2015). The high proportion of withdrawal may be due to the reporting nature of ADRs that troublesome ADRs are more likely to be detected.

There may be significant difference between male and female regarding the ADR prevalence due to factors such as body mass index, fat composition, hormonal effects, drug susceptibility, or genetic differences in the levels of enzymes (Haile et al., 2013; Rukmangathen et al., 2020). However, we demonstrated that females had only slightly higher incidence of ADRs than males in the present study. The frequency of ADRs increased with age, with the highest prevalence of ADRs in elderly individuals over 65 years (42.87%), followed by individuals 41–64 years of age (38.38%), which is in concordance with the findings of a previous study (Shepherd et al., 2012). Older patients are particularly vulnerable to ADRs owing to the multiple-drug regimens used for chronic diseases and physiological changes in this population, such as reduced gastrointestinal motility and gastric blood flow, impaired repair mechanisms, and lower mucosal protection (Marusic et al., 2014). A systematic review of ADRs in elderly individuals revealed that comorbid complexity was positively associated with ADR occurrence (Alhawassi et al., 2014). In the present study, there were statistically significant differences in the incidence of severe ADRs in the different gender and age groups, and polypharmacy increased the proportion of severe ADRs.

Anti-infectives for systemic use were the most common pharmacological group, accounting for 22.75% of total ADRs in our study, which is in line with previous studies (Haile et al., 2013; Marques et al., 2014). The excessive use of antibiotics may be responsible for the increased risk of ADRs. Cardiovascular system agents (12.41%) were the second most frequently incriminated pharmacological class of ADRs in our study, among them, 65.20% were preventable ADRs. A systematic review showed that cardiovascular medicines were commonly associated with preventable drug-related admissions (Howard et al., 2007). In another study, cardiovascular agents were identified as the second most frequently responsible drugs linked to preventable ADRs (Farcas et al., 2014).

TABLE 8 ADRs caused by actual drug–drug interactions belonging to category D.

Drug pairs	*n*	Reliability of pDDIs	Potential clinical consequences	Reported ADRs	Severity of ADRs
Aspirin-loxoprofen	2	Good	Increased risk of bleeding	Gastrointestinal bleeding (2)	Severe (2)
Aspirin-warfarin	6	Excellent	Enhanced anticoagulant effect	Gastrointestinal bleeding (4), hematuria (1) and gingival bleeding (1)	Severe (2), Moderate (4)
Aspirin-heparin	10	Good	Enhanced anticoagulant effect	Gastrointestinal bleeding (3), hematuria and melena (2), hematuria (1), epistaxis (1), non-specific hemorrhage (1), coagulopathy (1), and hemorrhagic dermatitis (1)	Severe (4), Moderate (4), Mild (2)
Aspirin-ginkgo	4	Fair	Enhanced anticoagulant effect	Gastrointestinal bleeding (2), gingival and gastrointestinal bleeding (1), hematuria and melena (1)	Severe (4)
Aspirin-diclofenac	3	Good	Increased risk of bleeding	Gastrointestinal bleeding (2), hematemesis (1)	Moderate (2),Severe (1)
Aspirin-ibuprofen	5	Good	Increased risk of bleeding	Gastrointestinal bleeding (5)	Severe (3), Moderate (2)
Aspirin-celecoxib	1	Good	Enhanced adverse effect	Gastrointestinal bleeding	Severe
Aspirin-ticagrelor	1	Fair	Enhanced antiplatelet effect	Melena	Moderate
Aspirin-propyphenazone	1	Good	Increased risk of bleeding	Gastrointestinal bleeding	Moderate
Aspirin-rivaroxaban	1	Fair	Increased risk of bleeding	Gastrointestinal bleeding	Moderate
Heparin-clopidogrel	10	Good	Enhanced anticoagulant effect	Gastrointestinal bleeding (3), hematuria and melena (2), hematuria (1), epistaxis (1), non-specific hemorrhage (1), cerebral hemorrhage (1), muscle hemorrhage (1)	Severe (4), Moderate (5), Mild (1)
Heparin-dipyridamole	2	Good	Enhanced anticoagulant effect	Gingival and gastrointestinal bleeding (1), hematuria and melena (1)	Severe (2)
Heparin-tirofiban	4	Good	Enhanced anticoagulant effect	Hematuria and melena (1), non-specific hemorrhage (1), gastrointestinal bleeding (1), thrombocytopenia (1)	Severe (2), Moderate (1), Mild (1)
Docetaxel-carboplatin	2	Fair	Increased myelosuppressive effect	Thrombocytopenia (1) and leukopenia (1)	Moderate (2)
Docetaxel-epirubicin	1	Excellent	Enhanced adverse effect	Myelosuppression and fatigue	Moderate
Docetaxel-cisplatin	1	Fair	Increased myelosuppressive effect	Myelosuppression	Moderate
Digoxin-amiodarone	1	Excellent	Increased serum concentration of digoxin	Atrioventricular block and bradycardia	Severe
Dihydrocodeine-tizanidine	1	Fair	Enhanced CNS depressant effect	Somnolence	Mild
Rivaroxaban-clopidogrel	1	Fair	Increased risk of bleeding	Gastrointestinal bleeding	Moderate
Glimepiride-acarbose	1	Fair	Enhanced hypoglycemic effect	Hypoglycemia	Mild
Amikacin-vancomycin	1	Fair	Enhanced nephrotoxic effect of aminoglycosides	Abnormal renal function	Moderate

ADR, adverse drug reaction; CNS, central nervous system.

The system most frequently affected by ADRs in this study was the gastrointestinal system, accounting for 30.83%, probably due to more than half of the suspected drugs being administered orally. This was followed by skin and appendage disorders (22.44%). This observation is consistent with the findings of a prospective observational study of hospitalized pediatric patients, which reported gastrointestinal system disorders (51.56%) and skin and appendage disorders (18.75%) as the most frequent manifestations of ADRs (Kurian et al., 2016).

As DDIs are usually predictable and manageable, ADRs caused by DDIs may be prevented by monitoring the patient closely or replacing the responsible drugs with other medications. To reduce the risk of DDIs and improve patient safety, it is essential that healthcare professionals regularly review the medication regimens, recognize potentially interacting drug pairs, and withdraw unnecessary drugs (Magro et al., 2020). A prospective study showed that the number of patients with pDDIs and actual DDIs decreased by 18% and 43%, respectively, with an intervention based on a computerized

clinical decision support system containing information on drug combinations (Bertsche et al., 2010). However, reporters less frequently recognize actual DDIs due to the limited availability of DDI databases or alerting drug-interaction systems (Mirosevic Skvrce et al., 2011). Therefore, it is important to increase the knowledge of pharmacovigilance through the additional education of healthcare providers.

In a previous study, we investigated the prevalence of pDDIs and their association with characteristics in outpatient prescriptions (Ren et al., 2020). However, to assess the clinical impact of DDIs on public health, only ADRs associated with DDIs should be considered. In our study, 105 ADR reports were induced by actual DDIs, accounting for 18.32% of the ADR reports with more than one suspected drug. This percentage was close to the proportion reported by Magro et al. (2020). According to the online version of DRUGDEX® system, they verified DDI among serious ADRs containing at least two suspected or concomitant drugs in the National Pharmacovigilance database from Veneto Region, and identified 17.4% ADR reports associated with a DDI. However, the results of another study performed in an Italian spontaneous reporting database showed that regarding patients treated with at least two drugs, 6.5% of ADR reports was associated with a DDI using the DRUGDEX® system (Leone et al., 2010). Similarly, a prospective cohort study conducted in the primary public health system of the Ourinhos microregion in Brazil revealed that the incidence of DDI-related ADRs was 6% in elderly outpatients using DDI-checker programs (DrugDigest®, Drugs®, Micromedex®, and Medscape®) (Obreli-Neto et al., 2012b).

In the present study, aspirin and heparin were the drugs most frequently associated with actual DDIs of category D, with symptom of gastrointestinal bleeding. Similarly, a prospective observational study conducted in the cardiology unit of an Indian hospital showed that heparin and aspirin were the most common drugs responsible for DDIs, and bleeding was the most frequent clinical consequence (Mateti et al., 2011). Furthermore, aspirin, which is widely used for the prevention of vascular events, was reported to increase the baseline risk of gastrointestinal bleeding by approximately 60% among older persons aged over 70 years in a randomized controlled trial (Mahady et al., 2021).

Although the study had important findings regarding the pattern of ADRs and the role of actual DDIs in ADRs over the past decade along with a large sample size, several limitations should be taken into consideration. First, as a retrospective study, data were collected from the clinical records of ADRs always with incomplete information, such as information on concomitant drugs, comorbidities, lifestyle, diet, and so on. Prospective studies will be carried out to clarify and reduce this limitation in the future. Second, this study was conducted at a single institution, limiting the generalizability of its findings due to the differences in population characteristics and prescribing patterns. Last, the single source of the DDI screening database used in this study may hinder the identification of DDIs because consistent criteria for DDI identification and assessment are currently lacking.

Conclusion

This study of ADR data collected over 10 years revealed that almost all ADRs were reported by pharmacists and physicians in our hospital, and the severity of ADRs was significantly correlated with age, the number of suspected drugs and preventability. Systemic antimicrobial agents were the most frequently incriminated pharmacological group, and aspirin was responsible for the largest proportion of total and severe ADRs. The gastrointestinal system was the system most frequently affected by ADRs. As observed in this study, aspirin and heparin were the most common drugs in actual DDIs of category D, resulting in gastrointestinal bleeding.

Active pharmacovigilance programs are important to accurately identify and assess ADRs in the clinical setting, further minimize drug-induced harm and improve the quality of patient care. Our findings obtained clinical evidence about ADRs associated with actual DDIs in our hospital. It will be necessary to make clinicians aware of the possibility of DDI-related ADRs and achieve a clear understanding of drug pairs resulting in DDI-related ADRs, in order to guide the prescribing practices and minimize the harms from actual DDIs. Moreover, rigorous prescription and frequent monitoring of drug therapy are essential for reducing the risk of ADRs.

Data availability statement

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

Ethics statement

This study was approved by the Ethics Committee of Jinshan Hospital, Fudan University at Shanghai, China (approval No. JIEC 2022-S29).

Author contributions

HJ, ZF, XL, and NZ contributed to the conception and design of the study. HJ, YL, WR, YL, and XT contributed to the recording and statistical analysis of the data. HJ and XL wrote the first draft of the manuscript. XL and NZ made critical

revisions to the manuscript. All authors 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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Affecting children's knowledge about rational use of medicines using read-along videos of pictorial storybooks

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Although efforts have been taken to educate the public about medication from a very young age, there are very limited availability and accessibility of education material for children. The aim of this study is to assess the impact of read-along videos of pictorial storybooks on children's knowledge about rational use of medicines. This study compared pre and post knowledge scores in a nonrandomized, one-group pre-test-post-test experimental design. Pre-recorded read-along storytelling videos were used as intervention covering two topics on rational use of medicine -medicine storage and antibiotic resistance. The questionnaire and intervention videos were distributed using Google Forms to children aged six and seven in Malaysia *via* online social media platforms. 521 children completed the study. The mean baseline knowledge score for medication storage was 4.89 (SD = 1.12) pre-test and 5.44 (SD = 0.78) post-test while for antibiotic resistance the mean was 3.616 (SD = 1.340) pre-test and 4.820 (SD = 1.134) post-test. A Wilcoxon signed-rank test showed statistically significant changes on medication storage ($Z = -10.21$, $p < 0.001$) and antibiotic resistance ($Z = -14.869$, $p < 0.001$) related knowledge among children. Pictorial storybook read-along video interventions were shown to be effective in improving children's knowledge on rational use of medicine. Education and awareness on the use of antibiotics should be prioritized.

KEYWORDS

rational use of medicine, pictorial storybook, Children, read-along video, pretest-posttest

1 Introduction

In 2007, the World Health Organization (WHO) released a report outlining global strategies to promote rational use of medicine which include policy coordination, providing unbiased information and promoting public education on medicines (World Health Organization, 2007). In response to this, Malaysia has launched a national health campaign known as "Know Your Medicine" which aimed to promote quality use of medicine through patient education (Pharmaceutical Services Division,

2022). Since then, various initiatives and materials have been taken to educate the public including training modules, printed and digital promotional materials, talks, media appearance in television, radio, newspapers, and social media platforms (Ahli Farmasi Rakan Ubat Anda, 2021; Duta Kenali Ubat Anda, 2022; Know Your Medicine Talk at, 2021; Know Your Medicines Ambassador, 2021; Hayin and Asyikin, 2019).

Medication literacy plays a significant role in determining treatment outcomes. The ability of patients to acquire, understand and use information about their medications affects their knowledge, skills, and confidence to manage their health conditions (Yadav et al., 2019). Several studies have showed important correlation between medication literacy, patient empowerment and improvement of self-management behaviors. Interactions between patient empowerment (PE) and communicative and critical health literacy (CCHL) at baseline were found to be significantly associated with 1-year global self-management behaviors. In a prospective study among Type 2 Diabetes Mellitus (T2DM) patients, PE was reported to improve self-management behaviors in patients with high CCHL but was less effective in patients with low CCHL (Wang et al., 2016). In addition, a meta-analysis by He et al. (He et al., 2017) showed that diabetes self-management education significantly reduced all-cause mortality risk in type 2 diabetes patients.

Medicines are regularly used to treat common acute illness in children. However, as the prevalence of chronic diseases such as asthma and diabetes showed increasing pattern among children, medication use in this group is expected to be more common (Al-Rubeaan, 2015; Sha et al., 2015). A cross sectional population-based study conducted in Saudi Arabia involving 23,523 participants showed high prevalence of diabetes in children and adolescents at approximately 10.84% (Al-Rubeaan, 2015). A qualitative study conducted among pediatric patients reported that majority of them managed their medications independently despite minimal knowledge on their medications. In terms of counselling experiences, both parents and pediatric patients were receptive for medication counselling particularly during prescription changes or initiation of new medication (Abraham et al., 2017). A study among adolescents in Taiwan presented that participants with lower medication knowledge, lower self-efficacy and lower medication literacy were more likely to engage in inappropriate self-medication (Lee et al., 2017).

In order to optimize the role of medication literacy and patient empowerment in health management, those two components should be aligned to individual's cognitive, affective and behavioral abilities (Velasco et al., 2021). Childhood is a critical stage for development of fundamental cognitive, physical, and emotional processes. Intervention at early childhood will promote development of good health-related behaviors and ameliorate future health risks (Bröder et al., 2017). Although children are often considered too young to be responsible and independent of their medications, early medication education exposure will help in shaping their behavior and attitude toward medication later in life (Hampson et al., 2015). Study among pediatric patients highlighted the potential utilization of interactive and educational technologies to facilitate pharmacist's counseling and educate children about the effective and safe use of medicines (Abraham et al., 2017).

Malaysia has taken the initiative to address these issues by producing medication-related modules for children. The modules are incorporated in the primary school health curricular under the rational use of medication syllabus. Education training modules on medication were also conducted by trained pharmacists through mass lecture, workshop, or small group work. Despite the efforts, the availability and accessibility to these children education materials are still very limited. In addition, content of the existing materials is insufficient for children use. For example, the topic on rational medication use comprised of only four pages in primary 1 (children aged 7) textbook (Azhar et al., 2016). In view of the lack of medication education materials for children, Aras Mega in collaboration with Pharmaceutical Services Program has produced a series of pictorial storybooks on medication use. The series were published in 2019 under the *Siri Kenali Ubat* (Know Your Medicine Series).

To date, there are limited studies assessing the impact of these materials on medication literacy among children. Therefore, in this study we aimed to assess the impact of read-along videos of pictorial storybooks on children's knowledge about rational use of medicines. Methods and materials.

2 Methods

2.1 Study design

Following Fraenkel and Wallen (Fraenkel and Wallen, 1990), one-group pre-test-post-test experimental design was adopted for this study. Table 1 illustrates the one-group pre-test-post-test experimental design.

Siri Kenali Ubat is a medication education material tailored for children, which portrays stories using characters named *Olah* who is a child, *Emak* who is *Olah*'s mother and *Uwan* who is *Olah*'s grandmother. One of the authors of this manuscript, SB, is the main author of these books. This series has five volumes. Only two volumes (Figure 1) were used in this study: 1) *Di Mana Ubat Olah?* (Where is Olah's Medicine?), which emphasizes on proper storage of medicine by illustrating a story of *Olah* who's have had a fever and is searching for medicine all around the house. 2) *Misi Melawan Raksasa Kuman* (Mission Against Monster Germ) explains about antibiotic resistance and the importance of taking antibiotic appropriately by illustrating a war between the body's immune system army against bacteria. Using topics

TABLE 1 One group Pre-test-Post-test Design.

Pre-test	Intervention	Post-test
Children to complete a questionnaire on knowledge about rational use of medication	Participants will watch the 2 volumes of *Siri Kenali Ubat* in pre-recorded read along storytelling videos	Children to complete a questionnaire on knowledge about rational use of medication

FIGURE 1
The two volumes of *Siri Kenali Ubat* book series.

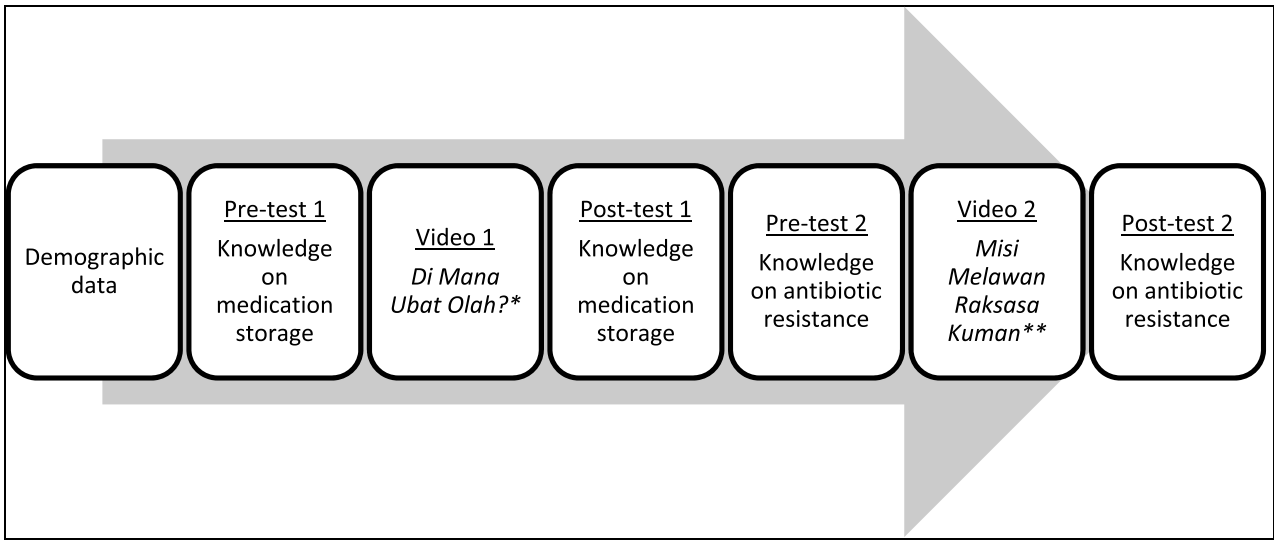

FIGURE 2
Flow of the survey.

that are related to common medication concerns, the series come with features that fit children's reading preferences such as big fonts, colorful and simplified facts in a narrative fiction together with captivating illustration and graphics.

Our initial plan was to have a face-to-face interaction with the school children at their school and allowing them to go through and read the books. However, during the study period, due the COVID-19 pandemic, all schools were closed to curb the infections. Alternatively, the research team decided to video-record one of the authors (SB) narrating the story to the children by flipping the pages one-by-one. Storytelling is a well-known practice that facilitates children's language development and learning. It has been shown that read-aloud or read-along is effective in helping young children to develop lifelong literacy skills and behaviors (Malin, 2010).

2.2 Instrument

Developing a survey questionnaire for children is challenging. However, after considering many factors (Bell, 2007) and discussion with research team member, a simple and structured questionnaire was developed in *Bahasa Melayu*, our national language, based on the topics covered in the two books. The flow of the survey is shown in Figure 2. Questionnaire was transformed into online format by using Google Form and the videos were attached in the link. Same questionnaire was used for both pre- and post-tests. A pilot test involving 5 to 10 children aged 6–7 years was conducted. Minor changes in terms and sentences were made based on the pilot test.

Parents' and children's consents were obtained prior to starting the survey. The survey instrument was administered and distributed through online social media platform such as WhatsApp, Facebook and Instagram.

Answers for pre- and post-tests were in the form of either "Yes", "No" or "Don't know". A maximum score of six for each test is possible when all the questions are answered correctly. Correct answers will be given 1 mark while answers with "Don't know" or wrong answers will be given a 0.

Each child watched the video with his/her parents. Parents could guide the participants by reading the questions and answer options. They were advised not to lead the participants to the correct answers and to encourage participants to answer based on their understanding.

Face and content validation by an expert panel consisting of academicians, pharmacists, and schoolteachers ($n = 5$) who have years of experience in related field was also conducted before the questionnaire was distributed to the participants. The knowledge section of the survey demonstrated good internal reliability and consistency with a Cronbach's alpha value of 0.70.

2.3 Sample

Children aged 6–7 years old in 2021 across Malaysia represent the population of this study. Children who have been exposed to *Siri Kenali Ubat* books were excluded from

TABLE 2 Classification of level of knowledge.

Level of knowledge	*Medication Storage/Antibiotic resistance*	*Rational use of medicine*
	Score (max = 6)	Total score (max = 12)
Low (<60%)	0–3	0–7
Moderate (60–79%)	4	8–9
High (80–100%)	5–6	10–12

TABLE 3 Socio-demographic characteristic (n = 521).

Characteristics	Number of children (%)
Age (years)	
6	357 (68.5)
7	164 (31.5)
Gender	
Male	265 (50.9)
Female	256 (49.1)
Ethnicity	
Malay	502 (96.4)
Others	9 (1.7)
Chinese	5 (1.0)
Indian	5 (1.0)

this study and this was one of the screening questions in the questionnaire.

2.4 Ethical consideration

Ethical approval was obtained from the Universiti Teknologi MARA ethical committee [REC/05/2021 (MR329)].

2.5 Data analysis

Level of knowledge was classified into three levels based on Bloom's cutoff: high level (80–100%), moderate level (60–79%), and low level (<60%) (Bloom, 1956). Thus, a high-level score was 5–6 (80–100%), moderate level was 4 (60–79%), and low level was 0–3 (<60%) for medication storage and antibiotic resistance (Table 2). Whereas for total score on rational use of medicine, low level was a score of 0–7, moderate level was 8–9 and high level was 10–12.

Descriptive analysis was used to describe sample distribution and demographic data. The data was checked for meeting analysis assumptions and data entry together with statistical analysis was carried out using SPSS version 21.0 (SPSS Inc. Chicago, IL). Despite meeting the assumption of independent, the data has heterogeneous distribution between normal and non-normal distribution. Thus, non-parametric analysis was adopted for this study. Wilcoxon Sign-Ranked test was used to assess the differences of score before and after intervention within the same group. McNemar test was used to compare categorical data. Significance level was set at $\alpha < 0.05$.

3 Results

3.1 Characteristics of the study population

During the 6 weeks of data collection from 12 July to 22 August 2021, 578 children participated in the study. Only 531 children met the inclusion criteria and 10 children were further excluded due to unavailability of consent from either the parents or children. Thus, 521 children were included for further analysis. Table 3 summarizes the demographic characteristics of participants in this study.

3.2 Knowledge on rational use of medicine

The children's baseline knowledge is generally high for medication storage and low for antibiotic resistance but was seen to be mixed in the total score as demonstrated in Table 4.

Approximately 10% of the children (n = 54) had a low level of knowledge, 18.8% (n = 98) a moderate and more than half (70.8%, n = 369) classified as having a high level of knowledge on medication storage pre-intervention. Post-intervention, only 2.1% (n = 11) had a low level of knowledge, 10.6% (n = 55) a moderate and more than three quarter (87.3%, n = 455) was classified as having a high level of knowledge. The mean baseline knowledge score for medication storage is 4.89 (SD = 1.12) for pre-test and 5.44 (SD = 0.78) for post-test. Inspection of the skewness, kurtosis and Kolmogorov-Smirnov statistics indicated that the assumption of normality for mean difference between pre and post-test was not supported. A Wilcoxon Signed Rank test (Table 5) showed that the 4 min story telling video using the book *Dimana Ubat Olah*? Elicit a statistically significant change on medication storage knowledge among children ($Z = -10.21$, $p < 0.001$).

At baseline, 43% (n = 226) of the children were classified as having a low level of knowledge on antibiotic resistance and 30% (n = 156) had a moderate level of knowledge while only 27% (n = 139) was classified of having a high level of knowledge on antibiotic resistance (Table 4). After intervention, higher scores were seen. The percentage of children with a low level of knowledge was 11.1% (n = 58), a moderate level of knowledge was 27% (n = 141) whereas 62% had a high level of knowledge (n = 322). The mean baseline knowledge score for medication storage was 3.616 (SD = 1.340) and 4.820 (SD = 1.134) for post-test. As assumption of normality for mean difference between pre and post-test was not supported, non-parametric test

TABLE 4 Level of participants' knowledge on medication storage, antibiotic resistance and rational use of medicine.

Level of knowledge	Pre-test, *n* (%)	Post-test, *n* (%)
Medication Storage		
Low	54 (10.4)	11 (2.1)
Moderate	98 (18.8)	55 (10.6)
High	369 (70.8)	455 (87.3)
Antibiotic Resistance		
Low	226 (43.4)	58 (11.1)
Moderate	156 (29.9)	141 (27.1)
High	139 (26.7)	322 (61.8)
Rational Use of Medicine (Total score of medication storage and antibiotic resistance)		
Low	154 (29.6)	29 (5.6)
Moderate	183 (35.1)	124 (23.8)
High	184 (35.3)	368 (70.6)

was used. A Wilcoxon signed-rank test showed that the 5 min story telling video using the book *Misi Melawan Raksasa Kuman* resulted in a statistically significant change on antibiotic resistance topic knowledge among children ($Z = -14.869$, $p < 0.001$) (Table 5).

The improvements were also evident and significant in each question pre- and post-intervention for both topics. Table 6 summarized the results for each given question. For the question on "Medicine can be kept on dining table", at baseline 81% (n = 422) of the children answered correctly. After intervention, 15.2% (n = 79) changed their answers to correct answer giving a total of 94%. Similar changes were seen in questions on "Medicine can be kept near the cooking hob" (97.1 vs. 99.8%), "Medicine should be kept away from children" (93.1 vs. 97.7%), "Medicine should be kept away from hot temperature and direct sunlight" (80.4 vs. 89.8%), "Medicine should be kept in a wet and damp area" (85.4 vs. 92.9%) and "All medicine should be kept in refrigerator" (51.8 vs. 69.9%).

In addition, for the question on "Antibiotic helps our body to kill bacteria", at baseline 89.3% (n = 465) of the children answered correctly (Table 6). After intervention, 10.2% (n = 53) changed their answers to the correct answer (n = 513, 98.5%). Following that, at baseline, 81% (n = 421) children believed that antibiotic helps to kill virus and post-intervention more children provided the correct answer (19 vs. 52%). Similarly, at baseline 57% (n = 296) children believed that "All disease requires antibiotic treatment" and this perception changed after intervention where more children provided the correct answer (43.2 vs. 68.5%).

4 Discussion

Video storytelling using pictorial storybooks addressing medication storage and antibiotic resistance were found to result in a significant improvement in children's knowledge. Various studies using storytelling methods found to have improved children's vocabulary, language, mathematical reasonings and scientific concepts (Hassinger-Das et al., 2015; Kalogiannakis et al., 2018; Picton and Clark, 2019). However, to date no study evaluated the use of storybooks to improve knowledge on rational use of medication among young children.

In a similar approach, effectiveness of cartoon video on knowledge and oral hygiene among students with hearing disabilities revealed that the cartoon was able to enhance knowledge even in students with hearing impairment. The study found that mean score for children's knowledge on oral health increased from 7.73 (SD ± 0.38) to 10.75 (SD ± 0.42) post 1 day and 14.23 (SD ± 0.38) post 1 week respectively (Yanti et al., 2017). Additionally, a non-randomized quasi-experimental pre-test and post-test study (Nurcahyani and Padmawati, 2019) investigated on early childhood education and reproductive health among children aged five to six. This study utilized stop-motion videos as an intervention and found substantial knowledge improvement in children's knowledge scores after intervention. In our study, although the videos were not animated compared to the two studies mentioned above, the read-along video could mimic actual reading activity in-person and the results of significant improvement in knowledge authenticate the approach. Having said that, converting the *Siri Kenali Ubat* book series into animation characters and videos could be a promising field to explore in future.

A common educational intervention such as counselling has been utilized to improve knowledge on medications across different patient populations. A multisite, stepped-wedge trial in Colorado, United States which investigated the effectiveness of counselling intervention among caregivers of youths aged 10–17 years, reported a 2-fold improvement in medication storage after the intervention

TABLE 5 Result of analysis of the effect of *Dimana Ubat Olah?* And *Misi Melawan Raksasa Kuman* video on Children's knowledge.

Topic (score range)	Mean score		Z[a]	*p*-value
	Pre-test	Post-test		
Medication storage (0–6)	4.889	5.441	−10.207	<0.001
Antibiotic resistance (0–6)	3.616	4.820	−14.869	<0.001
Rational use of medicine (0–12)	8.505	10.261	−15.261	<0.001

[a]Wilcoxon-signed ranks.

TABLE 6 Children knowledge changes based on questions.

Question	Correct answer (%)		[a]*p*-value
	Pre-test	Post-test	
Medication storage			
1. Medicine can be kept on dining table	81.0	94.0	<0.001
2. Medicine can be kept near the cooking hob	97.1	99.8	<0.001
3. Medicine should be kept away from children	93.1	97.7	<0.001
4. Medicine should be kept away from hot temperature and direct sunlight	80.4	89.8	<0.001
5. Medicine should be kept in a wet and damp area	85.4	92.9	<0.001
6. All medicine should be kept in refrigerator	51.8	69.9	<0.001
Antibiotic Resistance			
1. Antibiotic helps our body to kill bacteria	89.3	98.5	<0.001
2. Antibiotic also helps our body to kill virus	19.2	51.6	<0.001
3. Antibiotic should be finished even the patient has recovered	77.9	84.6	<0.001
4. If antibiotic is not finished, bacteria that was not killed by the antibiotic will turn to a stronger monster	58.7	88.5	<0.001
5. Germ monster is dangerous and may cause death	73.3	90.2	<0.001
6. All disease requires antibiotic treatment	43.2	68.5	<0.001

[a]McNemar test.

(Miller et al., 2020). Another study (Gregorian et al., 2020) also suggested that when compared to individuals who did not receive any educational intervention, those who did were more likely to keep their medications in a secured location. Whilst in children, the combination of verbal or written counselling with pictograms were found to be more effective in promoting proper use of medicines (Sletvold et al., 2020). This implies that the use of pictures and illustrations while educating children on rational use of medicines could amplify the transfer of knowledge.

In the United States, a 2018 National Household Medication Survey revealed that 76.7% households inappropriately stored at least one medication and 34.7% stored medication on counter tops where children could easily access them (Funk et al., 2021). In Brazil, a study revealed that households with insufficient storage conditions frequently kept medications within the reach of children (Martins et al., 2017). Majority users of high-risk medication such as opioid pain relievers were also found to have kept the medication in unsafe manner without lock or latched storage despite having children at home (McDonald et al., 2017). Our study found that at baseline, 93.1% of children agreed that medicines should be kept away from them and the percentage increased to 97.7% after the intervention. Although the children's knowledge level looks promising, it is important to note that most acute drug poisoning cases in children that result in hospitalization are due to unintentional and accidental ingestion (Bell et al., 2018; Matalová et al., 2019). Thus, we cannot emphasize enough on educating children and their parents on the importance of safe medication storage.

In this study, compared to medication storage, children seem to have a lower level of knowledge on antibiotics and antibiotic resistance at baseline. However, this improved after the intervention. 81 and 57% of children in this study believed that "antibiotics are used to kill virus" and "all diseases require antibiotics", respectively. Although there was an increase in the percentage of correct answers after intervention, only half of the children were able to correctly identify that antibiotics are not able to kill the viruses. A study in Ghana investigating the effectiveness of storytelling and picture drawing among children revealed that 81% children believed antibiotics will cure most coughs and colds (Appiah et al., 2021). This percentage reduced to 63% after intervention. Despite intervention to educate children, they seem to have a lack of understanding of the purpose of antibiotics. Children rely on parents for right information, however, even parents are misinformed regarding the use of antibiotics. In a study conducted in China, 79% of parents thought that antibiotics could cure viral infections (Yu et al., 2014).

Antibiotic resistance has been a topic of interest for many years and yet there is an incomplete understanding of and misperceptions about it (McCullough et al., 2016). Children are not exceptional (Deo et al., 2018). Misuse and overuse of antibiotics are one of the major reasons leading to antibiotic resistance (World Health Organization (WHO), 2017). Thus, it is imperative to create awareness on safer use of antibiotics. Children's involvement as active participants in health care efforts is usually underappreciated. Little is known about how to create instructional resources for children that will allow them to be the "changing agents" in their communities. Therefore, this study serves as a good example on establishing engagement with children in providing them a basic knowledge on antibiotic resistance to

empower rational use of antibiotic among the children and eventually the community. However, improvement in knowledge regarding antibiotics may need a long-term effort and education materials should include basic concepts of antibiotics, the appropriate indications and administration, and the potential hazards of antibiotics (McCullough et al., 2016).

4.1 Limitation and recommendation

We acknowledge several limitations in this study. There was a large demographic disparity which included a majority of participants from one ethnicity. This is mainly due to the use of convenience sampling method. In a multi-ethnic country, the findings from this study may not represent the whole Malaysian population. We were able to cover only two volumes from the *Siri Kenali Ubat* series instead of all five due to a concern on children's attention time span. Future studies may explore other sampling strategies to ensure the sample to be more representative of entire Malaysian children population and evaluate the other volumes in the series.

In view of COVID-19 pandemic restriction, the schools were closed for physical operation. A face-to-face read along session was impossible and to adapt to the situation, read-along videos were developed. However, future research could explore other educational approaches such as physical story telling sessions or interactive activities together with some hands-on activities.

Another limitation that might be due to the cultural specificity of the population, is the fact that children already had a high level of knowledge on the topics investigated and we did not collect data on children's medical illness and whether they are prescribed with long-term medication. Additionally, there may be a ceiling effect on learning as the survey was done in a close proximity to the videos. Thus, more studies will need to be conducted to find to what degree the positive impact found in this study will replicate for groups of children with low baseline knowledge levels and at different time span.

5 Conclusion

Pictorial storybook read-along video interventions using *Siri Kenali Ubat* series were shown to be effective in improving children's knowledge on rational use of medicine on the topic of medication storage and antibiotic resistance. It is imperative to prioritize educating children on antibiotic use and resistance. Future studies should develop and assess children's specific medication education materials in various topics to empower our future generation to be more aware and knowledgeable in rational drug use.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Universiti Teknologi MARA. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SB and MK contributed to conception and design of the study. SB organized the database and performed the statistical analysis. MK and SB wrote the first draft of the manuscript. MK and ZM supervised the study. All authors contributed to manuscript revision.

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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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Pharmacists' experiences on adverse drug reaction: 10 years later

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Adverse drug reaction (ADR) is one of the leading public health concerns associated with high mortality rate. Healthcare professionals, particularly pharmacists, have a significant role in monitoring and preventing ADRs. This study was conducted on Malaysian Pharmaceutical Society (MPS) pharmacists who worked at the hospitals, health clinics, and community pharmacies to determine if pharmacists' experiences on ADRs are still the same 10 years later. In 2010, a postal survey and in 2020, an online survey were conducted among these pharmacists. A total of 472 pharmacists and 208 participated in 2010 and 2020, respectively. About 82% and 90% of hospital/health clinic pharmacists (HCPs) observed an ADR over the last 6 months in 2010 and 2020, while 60% and 100% community pharmacists in 2010 and 2020 observed an ADR, respectively. Perindopril was the top drug (HCPs: $p = 0.657$; CPs: $p = 0.98$), and rash was the top ADR reported by the pharmacists in both years (HCPs: $p < 0.001$; CPs: $p = 0.679$). The most common actions taken by HCPs in 2010 were to report the ADR ($p = 0.343$), while in 2020, most HCPs explained to patients regarding the reaction ($p = 0.061$), which was also the same in the CP group in 2020 ($p = 0.958$). The top factor encouraging ADR reporting in both years and both pharmacist groups was the high degree of severity of the reaction (HCPs: $p < 0.001$; CPs: $p = 0.769$). While the top factors discouraging ADR reporting were a lack of information from the affected patients (HCPs: $p = 0.2$; CPs: $p = 0.656$), reaction is widely known (HCPs: $p = 0.001$; CPs: $p = 0.144$) and uncertainty of the causal relationship (HCPs: $p = 0.169$; CPs: $p = 0.609$). Majority of the pharmacists agreed that severe reactions should be reported (HCPs: $p = 0.158$; CPs: $p = 0.501$) and the main aim for reporting is to measure the incidence of ADRs (HCPs: $p = 0.148$; CPs: $p = 0.762$). Despite being able to identify ADRs during the daily practice, many pharmacists especially community pharmacists are not reporting them. There is a misconception on the purpose of reporting ADRs. An interventional program and ADR reporting training would be a useful step in improving ADR reporting practice.

KEYWORDS

adverse drug reaction, pharmacists, community pharmacists, reporting ADRs, survey

Introduction

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in patient for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (World Health Organization, 2020). ADR is one of the leading public health concerns associated with high morbidity and mortality rates, causing prolongation of hospitalization, unnecessary readmission, and increased healthcare expenditure (Sultana et al., 2013; Chan et al., 2016). Thus, post-marketing surveillance is essential to monitor the ADRs of new drugs in the market (Sultana et al., 2013).

Spontaneous ADR reporting is the mainstay of monitoring adverse drug reactions of newly marketed drugs. Since the thalidomide incident, WHO initiated the International Programme for Adverse Drug Reaction Monitoring for global drug safety monitoring (Olsson, 1998). Together with the United States Food and Drug Administration (FDA) and the European Medicines Agency, WHO advanced the regulatory practice protecting the global community (Olsson, 1998). Spontaneous reporting systems were first established in the Netherlands, United Kingdom, and Denmark in the 1960s. Many countries followed suit soon after.

In Malaysia, all suspected ADR cases are submitted to the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) which will then be submitted to the Uppsala Monitoring Centre in Sweden for inclusion into the WHO database (Aziz et al., 2007). Although an ADR reporting system has been in place since decades, underreporting of ADRs is still a nagging issue. A study among community pharmacists in Malaysia reported that the percentage of underreporting ADR is as high as 90–95% (Elkalmi et al., 2014).

Compared to other healthcare professionals, pharmacists are highly perceived for their role in implementing pharmacovigilance (PV) principles and reporting ADRs in their daily clinical practice as it is their core duties (Elkalmi et al., 2014; Bahnassi and Al-Harbi, 2018). Most pharmacists are aware of the existence of a system for reporting; however, only a few pharmacists have reported (Alsaleh et al., 2017). A study conducted in 2010 described that either these pharmacists lack knowledge on the process of reporting an ADR or lack confidence on which ADR to report. Identifying an ADR is challenging. Healthcare professionals sometimes fail to recognise that an ADR has occurred by misinterpreting patients' complaints or symptoms as minor and irrelevant, or related to the progression of their medical conditions. This may explain why many ADRs are never recognized (Dormann et al., 2003). These highlight the need for a robust education in spontaneous ADR reporting systems and pharmacovigilance for pharmacists (Elkalmi et al., 2014).

This study was conducted to identify whether pharmacists were able to identify ADRs during their daily routine and the actions taken once the ADRs were identified. This survey was conducted in 2010 and 10 years later in 2020 to compare whether there were any changes in the context of practices among pharmacists in regard to identifying ADRs. The result from this research study can be used as a hallmark for stakeholders to execute a plan to develop new strategies to further improve pharmacists' knowledge, attitude, and practices towards identifying and reporting ADRs.

Material and methods

Study design

This was a questionnaire-based study. The questionnaire on experiences of pharmacists on ADRs in Malaysia was administered in 2010 and 2020. The population involved all Malaysian Pharmaceutical Society (MPS)–registered pharmacists who were working at hospitals, health clinics, or community pharmacies. The study in 2010 involved a postal survey. A survey pack comprised a cover letter explaining the survey, the questionnaire, and a post-paid return envelope was mailed to all MPS-registered pharmacists. A second reminder with the survey pack was sent 2 months later. This survey was conducted between January 2010 and May 2010.

Meanwhile, in 2020, an online survey was conducted. A cover letter and the questionnaire were transferred to Google Forms and the link was sent out to all MPS pharmacists through emails and WhatsApp messages of MPS pharmacists with the help of MPS secretariats. Reminders were sent every month for about three times. This study was conducted between March 2020 and July 2020.

Questionnaire

A questionnaire was designed following a literature search and discussions with the research team. The questionnaire was reviewed for content and validated by an expert panel of pharmacy academic and researchers (n = 5). A pilot study was conducted on a sample of 122 pharmacists, and the questionnaire was modified accordingly. The questionnaire

was reviewed again to ensure suitability for use in 2020, and was validated by a team of experts consisting academicians and practicing pharmacists (n = 5).

There were four sections with a total of 21 items in the questionnaire. Section A gathered information on respondents' demographics. Section B consisted of a screening question to know whether the respondents had direct patient contact for the last 6 months. Those who did not have a direct contact were not included in the analysis.

Section C determined respondents' experiences on ADR:

1) whether they have observed an ADR in the last 6 months,
2) how frequently they observed an ADR in the last 6 months,
3) what type of ADRs were observed—a list of common ADRs based on reports received by the MADRAC, literature, and pilot study were created for the respondents to choose, and they could choose more than one answer. An open-ended option was also given for the respondents to fill, in case the ADR was not listed.
4) The drugs associated with the observed ADRs—a list of common drugs based on MADRAC reports, literature, and pilot study was created for respondents, and they could choose more than one answer. An open-ended option was also given for the respondents to fill, in case the drug was not listed.
5) Actions taken regarding the observed ADR—a list of actions was created based on the literature and pilot study, and the respondents could choose more than one answer. An open-ended option was also given for the respondents to fill in case the action was not listed.

Section D evaluated respondents' attitude and awareness on reporting ADRs—whether they were aware of the available system, its aims, and the types of ADRs that should be reported and factors encouraging and discouraging ADR reporting.

Sample size was calculated using the Raosoft® Sample Size Calculator. In 2010, there were approximately 2,000 MPS-registered pharmacists in Malaysia. With a confidence level of 95%, a margin of error of 5%, and response of distribution of 50%, the calculated sample size was 323. In 2020, there were a total of 5,000 MPS-registered pharmacists in Malaysia. With a confidence level of 95%, a margin of error of 5%, and response of distribution of 50%, the calculated sample size was 357.

Inclusion and exclusion criteria

Pharmacists registered with MPS and who worked at hospitals, health clinics, or community pharmacies were included in this study. Pharmacists who do not have any contact with patients for the past 6 months, for example, pharmacists who were working in a hospital pharmacy store or enforcement unit were excluded. This was identified through a screening question at the beginning of the questionnaire: "During your daily activities, do you have a direct contact with patients?"

Ethical approval

Ethical approval was obtained from the Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, United Kingdom, and permission for conducting the survey, from the President of MPS in 2010. This research also obtained an ethical approval from the Research Ethics Committee of Universiti Teknologi MARA [600-FF (PT.5/1)], and permission to conduct online survey, from the President of MPS in 2020.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics version 20.0, and the level of significance was set at $p < 0.05$. Descriptive statistics were performed on all data. To ensure the data were entered accurately and completely, frequencies of variables were computed and checked for values outside possible ranges. The Pearson chi-square test was used to compare pharmacists' experiences on ADR between the 2 years and between the pharmacist groups.

Results

Demographic data

In 2010, a total of 1,477 questionnaires were mailed to MPS-registered pharmacists. Of these, a total of 472 questionnaires were returned giving a response rate of 32%, and 438 were included in the analysis (34 were excluded because of missing data). However, the number of respondents was higher than that of the calculated sample size (n = 323). While in 2020, emails were sent to approximately 5,000 MPS pharmacists, and a total of 208 pharmacists responded to the questionnaire (58% of the calculated sample size and response rate of 4%).

Based on Table 1, a total of 257 hospital/clinic pharmacists (HCPs) and 181 community pharmacists (CPs) completed the questionnaire in 2010, whilst in 2020, 185 HCPs and 23 CPs completed the online survey. Generally, there was no significance difference in the demographics of the respondents (p = 0.17) between both years. In both years, the highest respondents were HCPs (59% and 89%) and female (74% and 76%). In 2020, 55% of the pharmacists had been in practice for 5 years and less, whereas

TABLE 1 Demographic data of pharmacists in 2010 and 2020.

Demographic/year	2010 (*N* = 438) n (%)		2020 (*N* = 208) n (%)	
Gender				
Male	112 (26)		53 (26)	
Female	326 (74)		155 (76)	
Level of education				
Bachelor's degree	380 (86)		164 (79)	
Master's degree	55 (13)		44 (21)	
Doctor of philosophy	3 (1)		-	
Work setting				
Hospital/health clinic	257 (59)		185 (89)	
Community pharmacy	181 (41)		23 (11)	
Years of work experience				
5 years or less	204 (47)		115 (55)	
More than 5 years	234 (53)		93 (45)	
	HCP *N* = 259	CP *N* = 182	HCP *N* = 185	CP *N* = 23
Had patient contact; n (%)	226 (87)	180 (99)	152 (82)	20 (87)
	HCP *N* = 226	CP *N* = 180	HCP *N* = 152	CP *N* = 20
Observed a suspected ADR last 6 months; n (%)	186 (82)	107 (60)	137 (90)	20 (100)
	HCP *N* = 186	CP *N* = 107	HCP *N* = 137	CP *N* = 20
Reported an ADR before; n (%)	163 (88)	15 (14)	110 (81)	8 (40)

in 2010, most of the pharmacists had more than 5 years of experiences (53%).

Of the 185 HCPs in 2020, 152 (82%) claimed to have direct contact with patients in the past 6 months, while 20 CPs (87%) out of 23 claimed the same. In 2010, 87% (n = 226) out of 259 HCPs, and 99% of CPs claimed to have direct contact with patients. Pharmacists who did not have any contact with patients for the past 6 months were excluded from further analysis.

Pharmacists' experiences on ADRs

Pharmacists were asked to state their experiences of observing ADRs in the last 6 months (Table 1). In 2020, 90% of 152 HCPs and 100% CPs encountered an ADR in the last 6 months. In 2010, 82% of 226 HCPs and 60% of 180 CPs reported the same. Pharmacists who did not encounter any ADR in the last 6 months were excluded from further analysis. Of the pharmacists who have encountered an ADR in the last 6 months, 88% and 81% of HCPs in 2010 and 2020 have reported an ADR before, respectively, while only 14% and 40% of CPs in 2010 and 2020 have done so, respectively.

Table 2 shows the comparison of responses between HCPs and CPs in 2010. The top five adverse drug reactions encountered by pharmacists in 2010 were rash, itchiness, dry cough, dizziness, and headache. Only dry cough showed significant difference between the two pharmacist groups. However, rash was the most reported ADRs in both groups. The top five drugs associated with the observed ADRs in 2010 were perindopril, aspirin, metformin, diclofenac, and amlodipine. There were significance differences between HCPs and CPs for all drugs except diclofenac, while perindopril was on the top of the list in both groups. Among the top five actions taken regarding the observed ADRs, only "make note in patient's chart" had no significance difference between HCPs and CPs. It is also important to note that only 1% of CPs in 2010 reported the ADRs but more than 60% asked patients to inform doctors and explained to patients regarding the reaction.

TABLE 2 Comparison between hospital/health clinic pharmacists (HCPs) and community pharmacists (CPs) in 2010.

	HCP (n = 186)	CP (%) (n = 107)	[a] (%)p-value
Types of ADRs observed (top five in 2010)			
Rash	52	60	0.175
Itchiness	44	54	0.079
Dry cough	31	46	0.012
Dizziness	32	35	0.616
Headache	31	24	0.210
Drugs associated with the observed ADRs (top five in 2010)			
Perindopril	37	42	0.011
Aspirin	17	28	<0.001
Metformin	11	34	<0.001
Diclofenac	20	15	0.869
Amlodipine	16	25	0.001
Actions taken regarding the observed ADRs (top five in 2010)			
Explain to patient regarding the reaction	48	61	<0.001
Ask patient to inform doctor	44	64	<0.001
Send report to MADRAC	52	1	<0.001
Suggest to patient to stop the medicine	20	43	<0.001
Make note in patient's chart	32	25	0.992
The type of ADRs pharmacists believe should be reported (top five in 2010)			
Severe reactions	97	75	0.816
Reactions to new drugs	95	61	<0.001
Unexpected/unusual reactions	92	63	0.011
Certain (sure, ascertained) reactions	87	58	0.005
Teratogenicity phenomenon	86	51	<0.001
Factors encouraging pharmacists to report a suspected ADR (top five in 2010)			
The high degree of severity of a clinical reaction	96	70	0.077
The involvement of a newly licensed drug	86	50	<0.001
The reaction is not widely known	82	47	<0.001
The specific typology of the reaction (unusual/unexpected)	81	45	<0.001
An obvious causal relationship with the administration of the drug	81	42	<0.001
Factors discouraging pharmacists to report an ADR (top five in 2010)			
Lack of information from the affected patient	74	55	<0.001
The uncertainty of a causal relationship with the administration of the drug	60	55	<0.001
The reaction is widely known	52	62	<0.001
The uncertainty of the type of reactions to be reported	57	52	0.004
The low degree of severity of a clinical reaction	45	53	<0.001
Pharmacists believes on the aim of monitoring the spontaneous reporting of suspected ADRs (top five in 2010)			
To measure the incidence of ADRs	94	74	0.597
To identify uncommon ADRs	97	68	0.007
To identify previously unknown ADRs	94	66	0.112
To maintain a database of ADRs	88	67	0.554
To identify factors predisposing patients to ADRs	78	58	0.072

[a]Pearson chi-square.

TABLE 3 Comparison between hospital/health clinic pharmacists (HCPs) and community pharmacists (CPs) in 2020.

	HCP (n = 137)	CP (n = 20)	[a]p-value
Types of ADRs observed (top five in 2020)			
Rash	76%	35%	0.083
Itchiness	72%	9%	0.816
Oedema periorbital	38%	5%	0.971
Dry cough	28%	40%	0.014
Headache	28%	5%	0.115
Drugs associated with the observed ADRs (top five in 2020)			
Perindopril	26%	35%	0.179
Diclofenac	23%	35%	0.101
Amoxicillin	18%	10%	0.447
Amlodipine	16%	25%	0.155
Mefenamic acid	16%	15%	0.922
Actions taken regarding the observed ADRs (top five in 2020)			
Explain to patient regarding the reaction	58%	50%	0.192
Do further evaluation	58%	45%	0.447
Send report to hospital drug information center	57%	15%	0.019
Make note in patient's chart	54%	15%	0.033
Send report to MADRAC	52%	5%	0.002
The types of ADRs pharmacists believe should be reported (top five in 2020)			
Severe reactions	93%	60%	0.877
Reactions to new drugs	93%	55%	0.304
Unexpected/unusual reactions	91%	55%	0.433
Teratogenicity phenomenon	87%	55%	0.82
Reactions to vaccines	86%	50%	0.37
Factors encouraging pharmacists to report a suspected ADR (top five in 2020)			
The high degree of severity of a clinical reaction	92%	85%	0.588
An obvious causal relationship with the administration of the drug	75%	52%	<0.001
The involvement of a newly licensed drug	70%	60%	0.218
The reaction is not widely known	68%	54%	0.021
The specific typology of the reaction (unusual/unexpected)	67%	54%	0.04
Factors discouraging pharmacists to report an ADR (top five in 2020)			
A lack of information from the affected patient	80%	50%	0.772
The uncertainty of the type of reactions to be reported	55%	45%	0.315
The uncertainty of a causal relationship with the administration of the drug	53%	50%	0.092
The low degree of severity of a clinical reaction	34%	50%	0.002
A lack of time to report reactions	29%	50%	<0.001
Pharmacists believes on the aim of monitoring the spontaneous reporting of suspected ADRs (top five in 2020)			
To measure the incidence of ADRs	97%	60%	0.36
To identify uncommon ADRs	96%	60%	0.477
To maintain a database of ADRs	94%	60%	0.788
To identify previously unknown ADRs	93%	60%	0.959
To identify factors predisposing patients to ADRs	93%	55%	0.244

[a]Pearson chi-square; MADRAC, Malaysian ADR Advisory Committee.

TABLE 4 Comparison between hospital/health clinic pharmacists (HCPs) in 2010 and 2020.

	2010 (n = 186)	2020 (n = 137)	[a]p-value
Types of ADRs observed (top five among HCPs)			
Rash	52%	76%	<0.001
Itchiness	44%	72%	<0.001
Dry cough	31%	29%	0.559
Headache	31%	28%	0.503
Dizziness	32%	25%	0.176
Drugs associated with the observed ADRs (top five among HCPs)			
Perindopril	37%	35%	0.657
Amlodipine	20%	21%	0.872
Diclofenac	11%	31%	0.001
Aspirin	17%	18%	0.841
Mefenamic acid	7%	22%	0.001
Actions taken regarding the observed ADRs (top five among HCPs)			
Send report to MADRAC	52%	57%	0.343
Explain to patient regarding the reaction	48%	58%	0.061
Send report to hospital drug information centre	43%	52%	0.117
Ask patient to inform the doctor	44%	42%	0.754
Do further evaluation	32%	58%	<0.001
The types of ADRs pharmacists believe should be reported (top five among HCPs)			
Severe reactions	97%	93%	0.158
Reactions to new drugs	95%	93%	0.353
Unexpected/unusual reactions	92%	91%	0.687
Certain (sure/ascertained) reactions	87%	91%	0.242
Reactions to vaccines	88%	86%	0.586
Factors encouraging pharmacists to report a suspected ADR (top five among HCPs)			
The high degree of severity of a clinical reaction	96%	85%	<0.001
An obvious causal relationship with the administration of the drug	81%	68%	0.009
The involvement of a newly licensed drug	86%	49%	0.001
The reaction is not widely known	82%	50%	0.001
The specific typology of the reaction (unusual/unexpected)	81%	48%	0.001
Factors discouraging pharmacists to report an ADR (top five among HCPs)			
A lack of information from the affected patient	74%	80%	0.2
The uncertainty of a causal relationship with the administration of the drug	60%	53%	0.169
The uncertainty of the type of reactions to be reported	57%	55%	0.688
The reaction is widely known	52%	28%	0.001
The low degree of severity of a clinical reaction	45%	34%	0.036
Pharmacists believes on the aims of monitoring the spontaneous reporting of suspected ADRs (top five among HCPs)			
To identify uncommon ADRs	97%	96%	0.836
To measure the incidence of ADRs	94%	97%	0.148
To identify previously unknown ADRs	94%	93%	0.765
To maintain a database of ADRs	88%	94%	0.067
To identify factors predisposing patients to ADRs	78%	93%	0.001

[a]Pearson chi-square; MADRAC, Malaysian ADR Advisory Committee.

TABLE 5 Comparison between community pharmacists (CPs) in 2010 and 2020.

	2010 (n = 107)	2020 (n = 20)	[a]p-value
Types of ADRs observed (top five among CPs)			
Rash	60%	35%	0.679
Itchiness	54%	45%	0.303
Dry cough	46%	40%	0.283
Gastritis	37%	15%	0.310
Dizziness	36%	20%	0.784
Drugs associated with the observed ADRs (top five among CPs)			
Perindopril	54%	35%	0.98
Diclofenac	43%	35%	0.457
Aspirin	36%	5%	0.043
Mefenamic acid	28%	15%	0.705
Amlodipine	20%	25%	0.12
Actions taken regarding the observed ADRs (top five among CPs)			
Ask patient to inform the doctor	81%	40%	0.097
Explain to patient regarding the reaction	78%	50%	0.958
Suggest to patient a different drug	38%	25%	0.992
Make note in patient's chart	32%	15%	0.521
Do further evaluation	25%	45%	0.001
The types of ADRs pharmacists believe should be reported (top five among CPs)			
Severe reactions	96%	60%	0.501
Unexpected/unusual reactions	80%	55%	0.714
Reactions to new drugs	79%	55%	0.608
Certain (sure/ascertained) reactions	65%	60%	0.142
Teratogenicity phenomena	65%	55%	0.163
Factors encouraging pharmacists to report a suspected ADR (top five among CPs)			
The high degree of severity of a clinical reaction	90%	60%	0.769
The involvement of a newly licensed drug	64%	40%	0.834
The reaction is not widely known	60%	20%	0.046
The specific typology of the reaction (unusual/unexpected)	58%	30%	0.418
An obvious causal relationship with the administration of the drug	54%	40%	0.616
Factors discouraging pharmacists to report an ADR (top five among CPs)			
The reaction is widely known	79%	40%	0.144
A lack of information from the affected patient	71%	50%	0.656
The uncertainty of a causal relationship with the administration of the drug	70%	50%	0.609
The low degree of severity of a clinical reaction	67%	50%	0.481
The uncertainty of the type of reactions to be reported	66%	45%	0.835
Pharmacists believes on the aims of monitoring the spontaneous reporting of suspected ADRs (top five among CPs)			
To measure the incidence of ADRs	94%	60%	0.762
To identify uncommon ADRs	87%	60%	0.579
To maintain a database of ADRs	86%	60%	0.526
To identify previously unknown ADRs	85%	60%	0.478
To identify factors predisposing patients to ADRs	75%	55%	0.433

[a]Pearson chi-square.

Table 3 shows the comparison of responses between HCPs and CPs in 2020. Of the top five ADRs encountered by pharmacists in 2020, only dry cough showed significant difference between HCPs and CPs which is similar to 2010 data. However, a new ADR, oedema periorbital, appeared in top five list, whereas dizziness was not in the top five list as in 2010. The top five drugs associated with the observed ADRs in 2020 were perindopril, diclofenac, amoxicillin, amlodipine, and mefenamic acid. This list was different from the list in 2010 where aspirin and metformin were replaced with amoxicillin and mefenamic acid. All drugs showed no significant difference between HCPs and CPs. However, it is worth noting that perindopril was the highest drug reported in both years. The action "explain to patient regarding the reaction" topped the list in 2010 and 2020. Although this action had significance difference in 2010, it was found statistically not different in 2020. Only the actions "send report to drug information center," "make note in patient's chart," and "send report to MADRAC" were statistically different in both pharmacist groups in 2020.

Table 4 shows the comparison of responses of HCPs in 2010 and 2020. The top five ADRs encountered by HCPs were rash, itchiness, dry cough, headache, and dizziness. Only ADRs involving the dermatology system, rash, and itchiness were found to be statistically different and highest in both years. Among the top five drugs associated with the observed ADRs, only diclofenac and mefenamic acid had significance difference in both years in which less than 15% of HCPs in 2010 stated these drugs. However, perindopril remained in the top. Regarding the action taken, only "do further evaluation" had significant difference in both years. "Send report to MADRAC" remained in the top of the list of HCPs in 2010, whereas "explain to patient regarding the reaction" was the top in 2020.

Table 5 shows the comparison of responses of CPs in 2010 and 2020. Rash was the highest in 2010, whereas itchiness was the highest ADR observed in 2020. However, none of the top five ADRs had significant differences in both years. In both years, perindopril remained the top reported drug which did not have a significant difference. Only aspirin had a significant difference, where 5% CPs in 2020 and 38% CPs in 2010 reported the drug. The drug list of CPs appeared to be the same as the top five drugs list of HCPs, but the ranking differed. The most action taken by CPs in 2010 was "ask patient to inform the doctor," whereas in 2020, it was "explain to patient regarding the action." However, none of the actions were found to be significantly different.

Spontaneous ADR reporting

In 2010, the top five ADRs pharmacists believed should be reported were severe reactions, reactions to new drugs, unexpected/unusual reactions, certain reactions, and reactions of teratogenicity phenomenon (Table 2). All but "severe reactions" showed significant difference between HCPs and CPs in 2010. However, severe reactions topped the list for both the groups. In 2020, four types of ADRs in the top five list remained the same as those in 2010 (Table 3). "Reactions to vaccines" was a new addition to the list. However, all ADRs in the list had no significant difference between both groups, and "severe reactions" remained in the top of the list. When the top five list was compared with the same groups of pharmacists (Tables 4 and 5), "severe reactions" remained in the top list. Both HCPs and CPs had no significance difference on the list of ADRs to be reported when compared in both years (Tables 4 and 5).

When asked about the factors that encourage and discourage ADR reporting, the degree of severity of the reaction, whether the reaction was widely known, and the causal relationship with the administration of the drug were three of the top five factors quoted (Table 2, Table 3, Table 4, and Table 5). Other factors that encourage reporting included involvement of a newly licensed drug and specific typology of the reaction. Whilst other discouraging factors included "a lack of information from the affected patient" and "uncertainty of the type of reactions to be reported." The factor "a lack of information from the affected patient" topped the list in 2010 and 2020. This had a significant difference between HCPs and CPs in 2010 but no significant difference in 2020.

Pharmacists were asked to identify the aims of monitoring spontaneous reporting of suspected ADRs, and the top five were "to measure incidence of ADRs," "to identify uncommon ADRs," "to identify previously unknown ADRs," "to maintain a database of ADRs," and "to identify factors predisposing patients to ADRs" (Table 2, Table 3, Table 4, and Table 5). "To measure incidence of ADRs" topped the list in both years and no significant difference was found between HCPs and CPs in 2010 and 2020 (Tables 2 and 3).

Discussion

In 2010, 82% of HCPs and 76% CPs observed a suspected ADR, while in 2020, 90% HCPs and 100% CPs observed a suspected ADR in the last 6 months. These findings show that most pharmacists are identifying (observing) ADRs during their daily routine as quoted in a study by Irujo et al. (2007), "almost every pharmacist had detected an ADR at least once in their professional life." Even though pharmacists are able to identify ADRs, these were not reported in most cases especially in the CP groups and similar findings were observed in another study (Alsaleh et al., 2017). Pharmacists are highly educated and have a professional responsibility in the provision of pharmaceutical care which includes the identification, prevention, and

resolution of drug-related problems (DRPs). It is one of their core jobs to ensure the safe use of medicine. Reporting ADRs is equally important.

The top two types of ADRs observed by the pharmacists in this study were mostly related to the dermatological systems—rashes and itchiness. These were the same in 2010 and 2020 as well as in both HCP and CP groups. A review and a study conducted in a tertiary care hospital in India reported that ADRs related to gastrointestinal, cardiovascular, and nervous system were the most common (Geer et al., 2016; Khalil and Huang, 2020). The report by MADRAC shows that the highest number of ADR reports received was related to skin and subcutaneous tissues, and the highest number of reports received was from pharmacists (National Pharmaceutical Control Bureau, 2019). On top of that, ADR reports related to dermatology received by MADRAC have been the highest since 2010 (National Pharmaceutical Control Bureau, 2010). Skin is the most common target for ADRs. They are manifested as skin rashes and/or eruptions. Cutaneous reactions occur in 2–3% of inpatients and in about 2% of outpatients (Farshchian et al., 2015). Pharmacists can easily identify ADRs involving skin because of their objective manifestations compared to other organ systems.

The most common drug associated with the observed ADRs by both group of pharmacists in both years was perindopril. There is an increased usage of perindopril in Malaysia (Malaysian Statistics on Medicines, 2020). A study conducted in Malaysia investigating ADR-related admissions reported perindopril as one of the drugs causing the ADR-related admissions (Karuppannan et al., 2013). In another study conducted in Singapore, the most common drug category causing the ADR-related admission was cardiovascular drugs (Chan et al., 2016). Whereas in India, anti-infectives were quoted as the most common drug causing ADRs (Geer et al., 2016).

Perindopril and other angiotensin-converting enzyme (ACE) inhibitors are mostly associated with dry cough (Pinto et al., 2020). In this study, dry cough was reported as one of the most common ADRs in both years. A MADRAC newsletter reported that perindopril is the suspected drug contributing to the highest number of ADR reports, and the top three reactions associated with the drug were cough, dry cough, and dizziness (National Pharmaceutical Control Bureau, 2009). Studies were also reporting increased incidence of cough among perindopril users (Bavanandan et al., 2005), and extensive data are available on the incidence of perindopril-induced cough (Pinto et al., 2020). All these findings could have alerted healthcare professionals to be more vigilant of any signs of cough among patients who use ACE inhibitors particularly perindopril.

In response to observing ADRs, most HCPs and CPs in 2010 and 2020 claimed that they have explained to patients regarding the reaction. Delli et al. (2022) reported that through an effective interaction with patients, pharmacists are able to provide information relating to the usage of the medications, which includes the aspect of safe use of medications in order to enhance patients' understanding and knowledge about their medications. Several studies have also reported that the most common intervention given by community pharmacists was consulting their patients regarding the drug-related problems (Schröder et al., 2011; Ylä-Rautio et al., 2020). Pharmacist and patient interactions are important to foster patient-centred care. Thus, it is a necessary skill pharmacists should acquire.

However, when comparing the actions taken between the HCP and CP groups, CPs in 2010 and 2020 were inclined to ask patients to inform their doctor regarding the ADR. This was also reported in a Spanish study of factors influencing ADR-reporting among community pharmacists, where more than 80% of CPs usually tell patients to visit their doctor when an ADR is suspected (Irujo et al., 2007). Similarly, another study conducted in Saudi Arabia claimed that approximately 77% of CPs refer patients to a doctor (Mahmoud et al., 2014). When patients report symptoms that the pharmacists attribute to potential ADRs and they think patients need to take an action, referring them to their doctor is a reasonable course of action if there is no immediate need for medical intervention.

Of the 137 CPs who claimed to have observed ADRs in 2010, only 1% have taken the action to report the ADRs to MADRAC compared to 52% out of 186 HCPs. The percentage was lower than that in a study conducted among community pharmacists in South India (12%) (Pinto et al., 2020). This is also reflected in the annual report of National Pharmaceutical Regulatory Agency (National Pharmaceutical Control Bureau, 2009). However, an increase in the number of CPs reporting was seen in 2020 (5%). Even so, this figure is still considered low compared to that of HCPs. One reason for these differences could be the types of ADRs observed by both groups of pharmacists. Minor reactions such as gastritis were more often observed by CPs and therefore, may not be reported. A few studies reported that the common reasons given by CPs for not reporting ADRs are that ADRs are not serious and already known (Irujo et al., 2007; Shaik Rahmat and Karuppannan, 2021), which is comparable to this study. Hence, pharmacists chose to solve the problem by discussing with patients (Hämmerlein et al., 2007) and most probably advise patients to stop taking the drug (Mahmoud et al., 2014).

Another reason could be that HCPs are well informed about the procedure and process of reporting ADRs (Hadi et al., 2013) compared with CPs. Previous studies have documented the lack of knowledge of CPs about ADR reporting (Hämmerlein et al., 2007; Elkalmi et al., 2014) and are mostly unsure of the types of ADRs to be reported and had insufficient knowledge on ADRs (Shaik Rahmat and Karuppannan, 2021). Thus, the CP group is prompted to refer

patients to their physicians, anticipating that the physicians themselves will be able to solve and report the ADRs (Mahmoud et al., 2014). CPs may have the wrong perception that ADR reporting is the responsibility of physicians and HCPs (Mahmoud et al., 2014). In addition to educating and training CPs, perhaps it is time to remunerate pharmacists for reporting ADRs, and a study found remuneration is one of the motivating factors to report ADRs among pharmacists (Li et al., 2018).

The type of ADRs which most pharmacists in 2020 and 2010 perceived should be reported was severe reactions. Several studies reported the same—pharmacists will report if an ADR was serious or severe (Elkalmi et al., 2014; Alsaleh et al., 2017; Bahnassi and Al-Harbi, 2018; Aldryhim et al., 2019). In the study by Aldryhim et al. (2019), about 70% of pharmacists believed serious ADRs should be reported and additionally quoted that pharmacists' therapeutic knowledge and continuous medical education were also the main factors that would encourage them to report an ADR. In Syria, 48% of the pharmacists reported seriousness of a reaction as the top in the list of factors encouraging them to report an ADR (Bahnassi and Al-Harbi, 2018).

When compared between the groups, HCPs in 2010 and 2020, "reactions to vaccines" was in the top five list. However, this was not listed in the top five list of the CP group. MADRAC, in 2015, in relation to Adverse Events Following Immunisation (AEFI), reported that there was an increment of 26.8% in the reports received relating to AEFI from the year 2014 (1,080 reports) to 2015 (1,369 reports) (Hämmerlein et al., 2007). This saw a multi-fold increase from 2020 (1,495 reports) to 2021 (28, 976 reports) presumably due to COVID-19 vaccinations (National Pharmaceutical Control Bureau, 2022). Human papillomavirus (HPV) vaccines were introduced through the HPV vaccination programme since 2010 for the prevention of cervical cancer in Malaysia (Muhamad et al., 2018). Since then, many reports relating to the vaccine were received by the MADRAC, and this accounted for a proportion as high as 87.6% (Rosli et al., 2017). This corresponds to the current findings on why the majority of pharmacists believed that reactions to vaccinations should be reported.

The WHO stated that the aims of pharmacovigilance are for early detection of previously unknown ADRs, detection of any increase in the frequency of known ADRs, identification of risk factors and possible mechanisms of ADRs, and estimation of benefit/risk analysis and dissemination of information to improve drug prescribing and regulation (World Health Organization, 2020). Based on the Malaysian Guidelines for Reporting and Monitoring (National Pharmaceutical Control Bureau, 2016), the primary purpose of reporting ADRs include an early detection of any suspected reactions, to identify uncommon drug reactions, to maintain a database for sharing ADRs information in Malaysia as well as to identify the risk factors which may predispose patients to ADRs. Most HCPs and CPs were able to identify the actual purposes. However, it was noted that at the top of the list, HCPs and CPs claimed that ADRs are reported to measure the incidence of ADRs. The incidence rate cannot be measured *via* spontaneous reporting because there is no information on the population denominator (number of people prescribed with the suspected drug). This suggests that there is a misconception in these group of pharmacists on the role of pharmacovigilance. Since reporting of ADRs is the only system which can be implemented in carrying out post-marketing surveillance in many countries including Malaysia; thus, it is crucial to improve the knowledge regarding this among pharmacists and other healthcare professional (Aziz et al., 2007; Gonzalez-Gonzalez et al., 2013) so that the significance of ADR reporting is understood and appreciated.

A lack of information from affected patients was the most cited factor discouraging reporting among HCPs in 2010. It is rather surprising since HCPs have more access to patients' record compared to CPs, and it is reasonable if this factor was cited the highest among CPs. On top of that, this factor was still one of the top five factors in 2020 among HCPs and the percentage has increased to 80%. Similar responses were noted among pharmacists in other studies (Aziz et al., 2007; Alsaleh et al., 2017). In the process of identifying and diagnosing an ADR, it is important that detailed information is gathered from affected patients. This will guide healthcare professionals to establish a causal relationship between the reaction and the suspected drug in a reliable way (Cheema et al., 2017). It is noteworthy that "uncertainty of a causal relationship with the administration of the drugs" was also cited as one of the discouraging factors which could have been led by the lack of information from patients.

Low degree of severity of a clinical reaction, uncertainty regarding the type of reactions to be reported, and uncertainty of a causal relationship with administration of the drug remain as the major factors hindering ADR reporting similar to other studies (Edwards and Aronson, 2000; Shaik Rahmat and Karuppannan, 2021). Other factors cited were lack of training and knowledge that could have resulted in the lack of confidence in reporting ADRs (Edwards and Aronson, 2000; Alsaleh et al., 2017; Shaik Rahmat and Karuppannan, 2021). This suggested the importance of continuous training and equipping with up-to-date information regarding ADRs. A study has proven that the ADR reporting rates among pharmacists have increased up to 5.9-fold after an educational training session on pharmacovigilance (Herdeiro et al., 2008) as well as an increase in reporting of serious, unexpected, high-causality, and new drug-related ADRs (Gonzalez-Gonzalez et al., 2013).

Limitations

The current study has several limitations. The pharmacist population in this survey may not be

representative of all pharmacists in Malaysia because the experiences of non-MPS members were not explored. Members of MPS may differ from other Malaysian pharmacists in that they chose to join the professional body and thus, may be more up to date with clinical or legal issues affecting the profession. However, the extent to which being members of the MPS would have affected pharmacists' responses is unknown.

The respondents were asked to recall the types of ADRs, causative drugs, and actions taken in response to the ADRs observed in the last 6 months. There are possibilities that pharmacists had difficulty recalling the ADRs, meaning that details may be recalled incorrectly. Furthermore, pharmacists in the hospitals or specific wards (such as medical wards or ICU) may have observed a higher number of ADRs compared with others, and it was not possible to identify this from the survey. A cross tab of the observed ADR and the drug which was responsible for the ADR could not be done because the respondents were given the choice to select more than one answer for both questions.

The online survey, although shared to all MPS pharmacists, did not reach the desired sample size of 377, and the results from this study may not represent all HCPs and CPs in Malaysia. Although measures were taken to send out the link multiple times, the survey was conducted during the peak of COVID-19 infections and announcement of lockdown in March 2020 somehow affected the number of respondents, as pharmacists were carrying out their duties to ensure continuous care was provided.

Conclusion

This study shows that pharmacists in Malaysia encounter patients with ADRs in their daily work activities. However, there were differences in the management of patients with ADRs by hospital and community pharmacists. The role of pharmacists is important in identifying, resolving, and preventing adverse drug reactions and can be further enhanced through education and training. It is also important to emphasise the importance of reporting an ADR especially among the community pharmacists. Pharmacists also play an important role in educating patients about their drug therapy. Although the current practice of reporting ADRs by HCPs is reassuring, they should be regularly updated and reminded of the importance of reporting ADRs to ensure that this practice is continued throughout their professional life. CPs, on the other hand, should be educated about the ADR report system and understand that reporting ADRs is the responsibility of all healthcare professionals.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, United Kingdom, and the Research Ethics Committee of Universiti Teknologi MARA. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MK contributed to conception and design of the study. MK and NR organized the database and performed the statistical analysis. MK and NR wrote the first draft of the manuscript. KW, SA, KT, and HB supervised the postal survey and contributed in the design of the study. MK supervised the online survey. All authors contributed to manuscript revision.

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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.

Publisher's note

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Primary percutaneous coronary intervention in CAD patients: A comparison of major adverse cardiovascular events of second- and third-generation drug-eluting stents

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Background: Biodegradable polymer (BP) drug-eluting stents (DES) have been introduced as a novel solution to the problems of durable polymer (DP) stents. In Pakistan, very few studies are available for the treatment intervention in post-primary percutaneous coronary intervention (PPCI) patients. Our study will compare the major adverse cardiovascular events (MACEs) and their predictors in patients with coronary artery disease (CAD) undergoing PPCI with second- or third-generation DES.

Methodology: An observational, retrospective, cohort study was carried out on CAD patients undergoing PPCI with either second- (DP-XIENCE Prime/XIENCE Xpedition) or third-generation (BP-BioMatrix NeoFlex/BioMatrix Alpha) DES. MACEs were assessed after 1 year of PPCI procedure in 341 patients and screened as per inclusion/exclusion criteria (167 in the second-generation group and 174 in the third-generation group).

Results: The number of male patients (86.2%) was more than female patients in our study population. MACEs were reported in 4.19% patients after 1 year duration, and the percentage of MACEs was more in the second-generation DES group (4.77%) than in the third-generation group (3.44%); however, statistical analysis has not found any significant difference (p = 0.534). The

Abbreviations: BES, biolimus-eluting stent; BP, biodegradable polymer; CAD, coronary artery disease; DES, drug-eluting stents; DP, durable polymer; EES, everolimus-eluting stent; HTN, hypertension; MACE, major adverse cardiovascular event; MI, myocardial infarction; PPCI, primary percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; ST, stent thrombosis; STEMI, ST-elevated myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

rate of myocardial infarction (1.19% vs. 0.57%) and stent thrombosis (1.8% vs. 1.15%) was more in the second-generation DES group. However, restenosis (1.19% vs. 1.15%) and cardiac death (0.59% vs. 0.57%) were almost same in both groups. A significant association was found between MACEs and diabetes mellitus (p = 0.025), hypertension (p = 0.035), smoking (p = 0.008), and a family history of CAD (p = 0.018).

Conclusion: BP-BioMatrix and DP-XIENCE DES have comparable clinical outcomes. Findings of the current study will assist the policy makers and healthcare providers in the rationalization of scarce resources and evidence-based patient care. However, longer follow-up studies are required for convincing results.

KEYWORDS

coronary artery disease, primary percutaneous coronary intervention, major adverse cardiovascular events, XIENCE, BioMatrix

Highlights

- Biodegradable polymer stents are a novel solution to the problems of DP-DES and leave a polymer-free stent after releasing anti-proliferative drugs.
- To improve longevity and health after PPCI, detection of MACEs and their risk factors is very crucial.
- BP-DES have comparable/superior outcomes as compared to DP stents.
- Smoking, family history of CAD, and DM are significant predictors of MACEs.

Background

Coronary artery disease (CAD) develops when the arteries of the heart are not able to supply enough oxygen-rich blood to the heart (National Heart, L AND Blood Institute, 2022). Worldwide, CAD is the second major cause of mortality, and its prevalence is equally high in South Asia. It has been estimated to affect up to 44% of the US adult population by the year 2030 (Ferreira-González, 2014; Dar et al., 2018). In Pakistan, CAD prevalence is about 11.2% in the local population (in females, it is 13.3%, and in males, 7.9%) (Dar et al., 2018). As compared to other ethnic groups, the people of South Asia are more prone to the development of atherosclerosis and thus have a high mortality rate (Nadeem et al., 2013). In the treatment of patients with CAD, major goals are to decrease the incidence of major adverse cardiac events (MACEs) that includes the composite of all-cause death, stent thrombosis (ST), myocardial infarction (MI), target lesion/vessel revascularization (TLR/TVR), and restenosis; improve symptoms, quality of life (QoL), and functional status; and to prolong life (Adnan et al., 2017; Zibaeenezhad et al., 2019).

If medical treatment for CAD is inappropriate or fails, there are two invasive procedures; one is the coronary artery bypass graft (CABG), the major cardiac surgery, and another is the balloon angioplasty or percutaneous transluminal coronary angioplasty (PTCA). PTCA involves the use of a balloon catheter for non-surgical widening of the artery. Recently, stents are being used in most of the PTCA procedures. Stents are composed of a thin wire-mesh platform which acts as a permanent prosthetic lining for keeping an artery inflated and maintaining its patency (excellence, 2003). The incidence of morbidity and mortality in patients with CAD has been reduced substantially by percutaneous coronary intervention (PCI). In the 1980s, bare metal stents (BMS) proved superior to balloon angioplasty with improved clinical outcomes and angiographic results. Later on, to decrease revascularization and neointimal hyperplasia associated with BMS, drug-eluting stents (DES) were designed in 2001 (Adnan et al., 2017; Dar et al., 2018; Lee and de la Torre Hernandez, 2018).

The coronary stent industry is growing on a rapid pace. There are many disadvantages of second-generation durable polymer drug-eluting stents (DP-DES) including the presence of a permanent polymer. The third-generation biodegradable polymer (BP) stents resolve the short-comings of DP-DES by leaving a polymer-free stent after completion of the anti-proliferative drug release process (Mehta et al., 2013; El-Hayek et al., 2017; Lee and de la Torre Hernandez, 2018; Sakamoto et al., 2018; Bangalore, 2019; Picard et al., 2019). Degradation completes in a duration of 3 to 15 months. Moreover, BP-DES are cost-effective as compared to the DP stents (Tsai et al., 2017). After PCI in patients with CAD, MACEs are the important reason of morbidity and mortality. To improve longevity and health, detection of the risk factors of MACE and their treatment is very crucial (Tsai et al., 2017). The major risk factors that have an impact on post-PCI outcomes in patients with CAD are smoking, hypertension (HTN), hyperlipidemia, and diabetes mellitus (DM) (Lin et al., 2017; Tsai et al., 2017; Wiemer et al., 2017; Kim et al., 2019).

Currently, the studies available on PCI have mainly focused on outcomes. Encouraging results have been found in the randomized controlled trials (RCTs), but longer duration follow-up studies awaited these newer generation stents (Nogic et al., 2018). Likewise in Pakistan, studies are available on the treatment intervention and assessment of therapeutic/adverse outcomes; however, there is a dearth of literature on the comparative studies of MACEs in post-PCI and post-primary-PCI (PPCI) patients. In the wake of multiplicity of options in the stent industry, decision makers need access to evidence-based information. Therefore, our study was designed to compare the MACEs in CAD patients undergoing PPCI with second- or third-generation DES and to evaluate the predictors of MACEs. This would be the first comparison-based study on BioMatrix and XIENCE stents in the Pakistani population.

Methods

Study design

An observational, cohort study was designed to assess MACEs in patients with CAD after PPCI with second-generation (Abbott's Everolimus-Eluting XIENCE Prime/XIENCE Xpedition) or third-generation (Biosensors' Biolimus-Eluting BioMatrix NeoFlex/BioMatrix Alpha) DES. The study consisted of two phases: a retrospective phase (in which data were retrieved from the hospital record) and a prospective phase (follow-up of patients at 1 year duration, post-PCI). The major adverse cardiovascular events are defined as the composite endpoints of non-fatal MI, stent thrombosis, clinically driven TVR/TLR, and cardiovascular death (Zibaeenezhad et al., 2019). The XIENCE Xpedition Everolimus-Eluting Stent (EES) having a cobalt chromium strut loaded with 100 μg/cm^2 everolimus and XIENCE Prime (Abbott) is also a 100 μg/cm^2 everolimus-coated stent (Abbott, 2013; Abbott, 2015). The BioMatrix Biolimus-Eluting Stent (BES) has a polylactic acid (PLA) biodegradable polymer (Biosensors International, Switzerland) (Separham et al., 2011). The BioMatrix NeoFlex is indicated in ST-elevated myocardial infarction (STEMI) patients, acute coronary syndrome (ACS), and diabetic patients. BioMatrix was first approved in 2015 (BIOSENSORS, 2020). The current study has been conducted at the Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi, Pakistan. AFIC-NIHD is the country's leading tertiary care cardiac center accredited with RCSEP for cardiac surgery training.

Study population and subjects

All participants complying with the inclusion and exclusion criteria were recruited in the study. Inclusion criteria: All patients undergoing PPCI procedure at the study site between July and December 2019, patients with age 18 years or older, and those who have received either the second-generation XIENCE Prime/XIENCE Xpedition or the third-generation BioMatrix NeoFlex/BioMatrix Alpha stents were included in this study. There was no restriction regarding the type or length of the lesion. Exclusion criteria: All patients under 18 years of age, who have undergone PPCI for any other disease except CAD (arrhythmic diseases, cardiomyopathies, cardiac valvulopathies, *etc.*); received BMS, first-generation DES, or second-/third-generation stents except for XIENCE or BioMatrix; have previous history of PCI/PPCI, CABG, or plain old balloon angioplasty (POBA); and those who have received multiple stents were excluded.

The sampling technique was non-probability convenience sampling. Sample size calculation was not performed, and all the participants meeting inclusion/exclusion criteria were recruited in the study [however, *a priori* power analysis was conducted, and keeping the power (1—β) value of 0.8, the calculated sample size was 169 patients in each group]. A total of 815 participants were screened according to the inclusion/exclusion criteria, who had undergone PPCI at the study site from July to December 2019. Those not fulfilling the inclusion criteria were dropped, and only 341 patients were enrolled. The participants were assigned to their respective

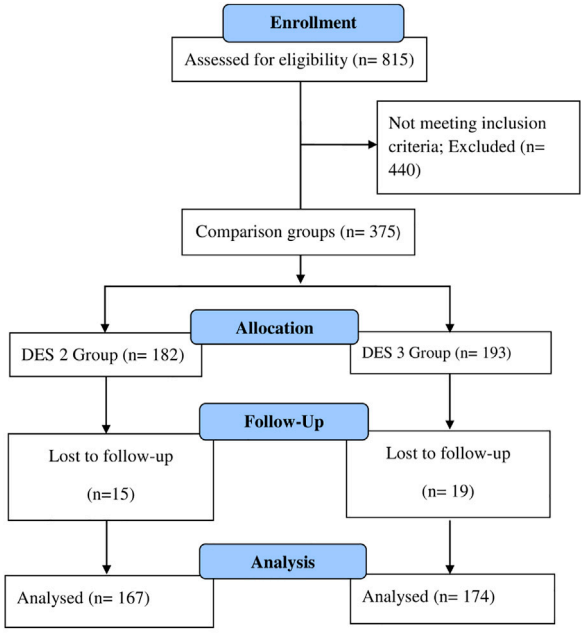

Figure 1. CONSORT Flow Diagram

FIGURE 1
CONSORT flow diagram.

groups, that is, second- or third-generation DES on the basis of the stent type they had received in the past on cardiologist discretion (167 in the second-generation XIENCE group and 174 in the third-generation BioMatrix group) (Figure 1).

Operational definitions

Primary percutaneous coronary intervention refers to the strategy of taking STEMI patients directly to the cardiac catheterization laboratory to proceed mechanical revascularization using the balloon angioplasty, aspiration thrombectomy, coronary stents, and other measures (Levine, 2014). Myocardial infarction is the increase in myocardial necrosis biomarkers above the upper range limit associated with at least one of these conditions: development of the Q-wave on electrocardiography, ischemic symptoms, and the ECG changes that indicate ischemia (El-Hayek et al., 2017). Restenosis is the reduction in the diameter of lumen post-PCI, and it usually occurs between 3 and 12 months after stenting. Stent thrombosis has been defined as the presence of a thrombus that originates in the scaffold/stent or in the 5-mm distal or proximal segment to the scaffold/stent or in the side branch that originates from the scaffold/stented segment and the presence of one of these criteria; the new electrocardiograph (ECG) changes, suggesting acute ischemia, acute onset of the ischemic symptoms at rest, or typical rise or fall in the cardiac biomarkers. TLR is the repeated percutaneous intervention or the bypass surgery procedure of target vessels performed due to restenosis or any other complication of the targeted lesion. TVR is defined as the repeat surgical bypass or PCI of any portion of the target vessel or the target lesion (Garcia-Garcia et al., 2018). Cardiovascular death was defined as the death caused by any cardiac issue (e.g., heart failure, MI, or fatal arrhythmia) and unknown or un-witnessed death (Maupas et al., 2017).

Data collection method

A data collection form was designed to obtain the patient's history and demographic details. Angiographic characteristics, stent type, and reason for PPCI were retrieved from patients' record at the hospital. At 1 year post-PPCI, all patients were interviewed during their follow-up visits to evaluate the past medical history and assessment of risk factors. Clinical outcomes were recorded by accessing MACEs in 1 year duration, that is, the incidence of MI, ST, TVR, TLR, and death. In-hospital MACEs (post-stenting procedure) were not assessed. and only after discharge, MACEs were included.

Statistical analysis

Data evaluation was carried out by using the statistical software package for social sciences (IBM SPSS statistics version 21). Numbers and percentages were calculated for categorical variables, and the chi-squared test was applied for comparison. Continuous variables' data were presented as the mean and standard deviation (SD) and the Mann–Whitney U test was used for the calculation of the p-value. MACE data were presented as frequencies and percentages. The association of MACEs with the demographic, angiographic, and risk factors was assessed by binary logistic regression analysis using the Wald test. Univariate analysis was performed first, and those variables having a p-value ‘0.25 were assessed again *via* multivariate analysis. The odds ratio and p-value were assessed, and the p-value less than 0.05 was considered statistically significant.

Results

Demographic and angiographic characteristics of the study population

Demographics of the study population (i.e., gender, age, residence, education, and occupation status) are presented as frequencies and percentages. The study population consisted of more male participants (86.2%) than female participants (13.8%); 52.2% patients were in the age group of 58–75 years (Table 1).

Angiographic characteristics of the study participants include the type of MI, culprit artery (the treated vessel), CAD diagnosis, access site, and length of the stent. Summary statistics of these categorical variables is presented as frequencies and percentages except for stent length that is calculated as the mean value and standard deviation (Table 2). The type of MI on ECG was categorized as anterior MI (67.4%) and inferior MI (32.55%). Four categories were made based upon the treated vessel which are the left anterior descending coronary artery (LAD), right coronary artery (RCA), left circumflex coronary artery (LCX), and obtuse marginal branches (OM branch). In majority of the participants, the treated vessel was the LAD (55.1%). CAD types diagnosed in the study population were the single-vessel CAD (SVCAD) 38.4%, double-vessel CAD (DVCAD) 32.4%, and triple-vessel CAD (TVCAD) 29.1% (n = 99). The stent's length range was 14–74 mm with the mean 28.86 mm (28.86 ± 8.679), for the second-generation DES, the mean value was 29.39 ± 9.825 and 28.86 ± 7.451 for the third-generation DES.

Risk factor assessment

The risk factors assessed for MACEs include a family history of CAD, smoking status, DM, HTN, and

TABLE 1 Demographic characteristics of the study participants.

Demographic variable		Second-generation DES group (n = 167)	Third-generation DES group (n = 174)	Total (n = 341)	p-value *
Gender	Male	143 (85.6%)	151 (86.8%)	294 (86.2%)	0.641
	Female	24 (14.4%)	23 (13.2%)	47 (13.8%)	
Age (years)	19–38	3 (1.8%)	4 (2.3%)	7 (2.1%)	0.056
	39–57	83 (49.7%)	63 (36.2%)	146 (42.8%)	
	58–75	75 (44.9%)	103 (59.2%)	178 (52.2%)	
	>75	6 (3.6%)	4 (2.3%)	10 (2.9%)	
Residence	Urban	132 (79%)	107 (61.5%)	239 (70.1%)	$p < 0.001$
	Rural	35 (21%	67 (38.5%)	102 (29.9%)	
Education	Illiterate	—	1 (0.6%)	1 (0.3%)	$p < 0.001$
	Primary	11 (6.6%)	28 (16.1%)	39 (11.4%)	
	Secondary	72 (43.1%)	95 (54.6%)	167 (49%)	
	Intermediate	27 (16.2%)	28 (16.1%)	55 (16.1%)	
	Graduate	57 (34.1%)	22 (12.6%)	79 (23.2%)	
Occupation	Unemployed	82 (49.1%)	79 (45.4%)	161 (47.2%)	0.494
	Employed	85 (50.9%)	95 (54.6%)	180 (52.8%)	

*The chi-squared test is used for the calculation of the p-value.

TABLE 2 Angiographic characteristics of the study participants.

Angiographic characteristic		Second-generation DES group (n = 167)	Third-generation DES group (n = 174)	Total (n = 341)	p-value*
Type of MI	ANT MI	108 (64.67%)	122 (70.11%)	230 (67.45%)	0.283
	INF MI	59 (35.33%)	52 (29.89%)	111 (32.55%)	
Culprit artery	LAD	87 (52.1%)	101 (58.04%)	188 (55.1%)	0.079
	RCA	54 (32.3%)	60 (34.4%)	114 (33.4%)	
	LCX	15 (8.9%)	10 (5.74%)	25 (7.3%)	
	OM branch	11 (6.59%)	3 (1.73%)	14 (4.1%)	
CAD diagnosis	SVCAD	62 (37.13%)	69 (39.66%)	131 (38.5%)	0.89
	DVCAD	54 (32.33%)	56 (32.2%)	110 (32.4%)	
	TVCAD	50 (29.9%)	49 (28.16%)	99 (29.1%)	
Access site	Radial	167	174	341 (100%)	**
Stent length (mm)	—	29.39 ± 9.825	28.36 ± 7.451	28.86 ± 8.679	0.274

ANT MI, anterior MI; INF MI, inferior MI; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; OM branch, obtuse marginal branch; SVCAD, single-vessel coronary artery disease; DVCAD, double-vessel coronary artery disease; TVCAD, triple-vessel coronary artery disease. * Chi-squared test is used for calculation of the p-value; for the continuous variable "stent length," the Mann–Whitney t-test was used. **no statistics as the access site is constant.

hyperlipidemia. Frequencies and percentages were calculated for these categorical variables. Summary statistics is presented in Table 3.

Summary statistics shows that about 29% people were having a previous history of CAD, more patients in the second-generation than in the third-generation DES group. About 19.1% people were ex-smokers, more in the third-generation DES group (n = 35), while 16.7% patients were also current smokers. DM^+ patients were 21.1% (n = 72), more in the third-generation DES group (n = 39), while hypertensive patients were more in the second-generation DES group (n = 59); total HTN^+ patients were 33.1%. Hyperlipidemia was found in 20.5% patients; the number was more in the third-generation DES group (n = 38).

Major adverse cardiovascular events

MACEs were categorized as MI, restenosis, stent thrombosis, TLR/TVR, and cardiac death. Frequencies and percentages are presented as follows (Table 4).

TABLE 3 Risk factors in the study participants.

Risk factor of MACEs		Second-generation DES group (n = 167)	Third-generation DES group (n = 174)	Total (n = 341)	p-value *
Family history of CAD	Yes	53 (31.7%)	46 (26.4%)	99 (29%)	0.401
	No	114 (68.3%)	128 (73.6%)	242 (71%)	
Ex-smoking history	Yes	34 (20.36%)	35 (20.11%)	69 (20.2%)	0.307
	No	133 (78.7%)	139 (79.89%)	272 (79.8%)	
Current smoking status	Yes	27 (16.2%)	36 (20.7%)	63 (18.5%)	0.282
	No	140 (83.8%)	138 (79.3%)	278 (81.5%)	
Diabetes mellitus	Yes	33 (19.8%)	39 (22.4%)	72 (21.1%)	0.548
	No	134 (80.2%)	135 (77.6%)	269 (78.9%)	
Hypertension	Yes	60 (35.92%)	53 (30.46%)	113 (33.1%)	0.284
	No	107 (64.07%)	121 (69.54%)	228 (66.9%)	
Hyperlipidemia	Yes	32 (19.2%)	38 (21.8%)	70 (20.5%)	0.629
	No	135 (8.8%)	136 (78.2%)	271 (79.5%)	

*Chi-squared test is used for the calculation of the p-value.

TABLE 4 Major adverse cardiovascular event distribution in the second- and third-generation DES.

MACE	Second-generation DES group (n = 167)	Third-generation DES group (n = 174)	Total (n = 341)
MI	2 (1.19%)	1 (0.57%)	3 (0.9%)
ST	3 (1.80%)	2 (1.15%)	5 (1.5%)
Restenosis	2 (1.19%)	2 (1.15%)	4 (1.2%)
Cardiac death	1 (0.59%)	1 (0.57%)	2 (0.59%)
Non-cardiac death	2 (1.19%)	3 (1.72%)	5 (1.5%)
No MACE reported	157 (94.01%)	165 (94.83%)	322 (94.4%)

MI: myocardial infarction, ST: stent thrombosis, TLR: target lesion revascularization, LVR: target vessel revascularization; DES: drug-eluting stents.

MACEs include adverse events in patients monitored at the follow-up after 12 months from the date of PPCI (after discharge until 1 year), and in-hospital MACEs (during the hospital stay after the procedure) were not included. One MI case was reported in the third-generation DES group and two in the second-generation group. ST occurred in five patients (1.5%); a greater number of ST cases were observed in the second-generation DES (1.79%) than in the third-generation DES (1.15%) group, and no TVR/TLR was reported. The restenosis rate and cardiac death were almost the same in both groups: restenosis 1.19% vs. 1.15% and cardiac death 0.59% vs. 0.57% in the second- and third-generation DES groups, respectively. In 94.4% study population, no MACEs were reported at 1-year follow-up. Overall, the percentage of MACE was 4.19%; in the second-generation DES, it was 4.77%, and in the third-generation DES, it was 3.44%.

Binary logistic regression analysis (Wald test) was performed to find the association of MACEs with risk factors (i.e., DM, HTN, smoking, hyperlipidemia, and family history), demographic factors (age and gender), and angiographic variables (CAD diagnosis and the type of MI). Univariate analysis was performed first; those variables having a p-value ˂0.25 were assessed again *via* multivariate analysis (Table 5). The DES type, although not significant, was included in multivariate analysis due to its importance in the model. Overall, the logistic regression model was significant χ^2 (8) = 38.211 and $p < 0.0005$. The model explained 36.6% variance (Nagelkerke R square) in the MACE and correctly classified 96.2% of cases.

No high multi-collinearity was observed among predictors as assessed through the correlation matrix; all correlation coefficient values were below 0.90. A significant association ($p < 0.05$) was found between MACE, DM, HTN, current smoking, and family history. diabetes mellitus [$p = 0.025$, 95% CI: 0.061–0.828, Exp (B) = 0.226]; odds of having MACE in DM^+ patients are 0.226 times more than non-DM patients. Hypertension [$p = 0.035$, 95% CI: 0.050–0.894, Exp (B) = 0.212]; odds of MACE in HTN^+ patients were 0.212 times more than non-hypertensive patients. The current

TABLE 5 Factors associated with the occurrence of MACEs.

Sr No	Variable	Univariate analysis			Multivariate analysis		
		Odds ratio [exp (B)]	CI [95% CI for exp (B)]	*p*-value[a]	Odds ratio [exp (B)]	CI [95% CI for exp (B)]	*p*- value[a]
1	Age (Yes)	1.0	b*	0.99	—	—	—
	(No)	Ref			—		
2	Gender (Yes)	1.795	0.481–6.694	0.384	—	—	—
	(No)	Ref			—		
3	DM (Yes)	1.456	1.181–1.796	<0.001	0.226	0.061–0.828	0.025
	(No)	Ref.			Ref		
4	HTN (Yes)	1.125	0.925–1.371	0.005	0.212	0.050–0.894	0.035
	(No)	Ref.			Ref		
5	Current smokers (Yes)	1.291	0.893–1.692	0.023	0.141	0.033–0.603	0.008
	(No)	Ref			Ref		
6	Family history (Yes)	1.312	1.043–1.649	0.006	0.209	0.057–0.762	0.018
	(No)	Ref			Ref		
7	Hyperlipidemia (Yes)	1.007	0.816–1.243	0.161	0.474	0.165–2.307	0.474
	(No)	Ref			Ref		
8	DES type (BioMatrix)	1.409	0.478–4.15	0.534	0.297	0.142–1.813	0.297
	(XIENCE)	Ref			—		
9	CAD diagnosis (SVCAD)	5.474	0.602–49.758	0.131	0.069	0.008–1.203	0.069
	(DVCAD)	0.473	0.141–1.586	0.225	2.035	0.519–7.98	0.308
	(TVCAD)	Ref			Ref		
10	Type of MI (ANT MI)	1.158	0.379–3.541	0.797	—	—	—
	(INF MI)	Ref			—	—	—
11	Stent length	0.988	0.931–0.988	0.684	—	—	—

a: $p < 0.05$ is considered significant (binary logistic regression analysis has been performed to find the association of MACE with risk factors); b*: non-computable.

smoking status [$p = 0.008$, 95% CI: 0.033–0.603, Exp (B) = 0.141] and family history [$p = 0.018$, 95% CI: 0.057–0.762, Exp (B) = 0.209]. Although a greater number of MACE cases were reported in the second-generation DES ($n = 8$) than the third-generation DES group ($n = 6$), statistical analysis has not found any significant association ($p = 0.297$).

Discussion

Newer generation BP-DES have been presented as a standard of care in PPCI. Various studies have compared the BP-DES with DP-DES; however, to the best of our knowledge, current study is the first comparative study of the third-generation BP-BioMatrix stents (BioMatrix Alpha and BioMatrix NeoFlex) and the second-generation DP-XIENCE stents (XIENCE Prime and XIENCE Xpedition) to evaluate the MACE in patients with CAD, post-PPCI, in the Pakistani population. The results of the current study found no significant difference in the rate of MACE between two stent types; however, the overall percentage of MACEs was more in XIENCE stents (4.75%) than in BioMatrix (3.44%) stents.

The number of male patients was much more than females in our sample (85.6%), and same findings were reported in several other PPCI studies [76.2% (Shah et al., 2018), 86% (Mian, 2014), and 81.8% (Mehta et al., 2013)]. The result of this study found that BP-BioMatrix stents are having similar or superior outcomes than DP-XIENCE stents at 1-year follow-up. These outcomes are in agreement with many other studies (Tsai et al., 2017; Park and Rha, 2020). Comparable results of BP-EES (XIENCE) and BP-sirolimus-eluting stents (SES) (orsiro) were obtained at 12 months follow-up in a RCT; TLR was same in both groups ($p = 0.58$) (Windecker et al., 2015). Safety and efficacy of the second-generation EES (XIENCE Prime, XIENCE V, and Promus), BES (BioMatrix, BioMatrix Flex, and Nobori), and zotarolimus-eluting stents (ZES) (resolute integrity/resolute) were compared in a study, and no significant association was found in the statistical analysis (Park et al., 2013). A prospective, randomized controlled, follow-up study found similar/comparable MACE of BP-biolimus-eluting stents (BioMatrix)

and DP-EES (XIENCE-V) at 12 months follow-up (Separham et al., 2011).

Many other studies have also evaluated same outcomes; the NEXT trial compared BES (Nobori) with EES (XIENCE/Promus), follow-up after 1 year found the non-inferiority of BES (Natsuaki et al., 2013). A multicenter grand-DES registry compared efficacy and safety of BES (BioMatrix/BioMatrix Flex/Nobori), EES (XIENCE Prime/XIENCE V/Promus), and ZES (resolute integrity/resolute) and obtained comparable outcomes (Ki et al., 2020). Another study also concluded that there is no significant difference between MACEs of DP-EES and BP-BES (2.7% vs. 2.7%: p = 0.984) (Parsa et al., 2016). The COMPARE II trial found that the overall percentage of MACEs was more in BP than DP stents; however, results were not statistically significant (Vlachojannis et al., 2017). Comparison of long-term clinical outcomes of BP and DP stents by Tsai et al. (2020) has found no significant difference in MACEs (Smith et al., 2019). Women are reported to have a higher risk of developing adverse events; however, in our study, no significant association was found between MACEs and gender (Giustino et al., 2016).

Results of some studies showed the superiority of BP-DES to DP-DES (Mattke et al., 2019). A study reported that BP-SES were associated with the lower rate of MACEs than DP-DES at 1 year follow-up (Mian, 2014). Another study was carried out to evaluate the MACE of BP-EES and reported 3.8% MACE at follow-up. In India, a multicenter trial found 0.45% MACEs in BioMatrix BES at 1 year follow-up (Mehta et al., 2013; Shah et al., 2018). The LEADERS trial is a multicenter, 5 -year follow-up study comparing outcomes of BES with SES. Results showed that BES have superior safety and efficacy than SES (Zhang et al., 2015). In French e-BioMatrix registry, the MACE percentage was lower than the LEADERS trial of sirolimus-eluting cypher stents (DP-DES). The LEADERS randomized trial concluded that BP stents were having better safety and efficacy than DP-DES (Stefanini et al., 2012; Maupas et al., 2017). Toru et al. (2018) have compared vascular response of the second- and third-generation DES, in terms of quality and quantity, and concluded that the third-generation stents might have better long-term clinical outcomes (Miyoshi et al., 2018). Major adverse cardiovascular and cerebrovascular events (MACCEs) of second-generation XIENCE and third-generation synergy were compared in a RCT; results have found 19% of MACCEs in XIENCE and 16% in synergy (Walsh, 2018).

On the contrary, in some studies, results were not comparable to the findings of the current study. SORT OUT V: a randomized non-inferiority trial concluded that biodegradable polymer stents were not associated with better outcomes than DP stents (Christiansen et al., 2013). Results of a study comparing DP-EES and BP-SES showed that the rate of TLR was more in BP stents at a follow-up of 386 days (Kakizaki et al., 2020). The significant association of MACEs has been found with many factors like hypertension, smoking, hyperlipidemia, DM, and a family history of CAD. Our study evaluated the association of MACEs with various risk factors, that is, DM, smoking status, HTN, CAD family history, and hyperlipidemia. In statistical analysis, the significant association of MACEs was obtained with DM (p-value; 0.025), HTN (p-value; 0.035), family history of CAD (p-value; 0.018), and the current smoking status (p-value; 0.008). A higher risk of restenosis, mortality, and re-vascularization has been reported in diabetic patients (Seth et al., 2013).

A prospective study compared MACEs in diabetic and non-diabetic patients in Peshawar; the ratio of MACEs was more in the diabetic group, but a statistically significant association was not obtained (Adil et al., 2021). In another study in India, MACEs associated with BES in diabetic patients were evaluated (Seth et al., 2013). Although e-BioMatrix French registry evaluated MACEs in biolimus stents, the rate of MACE was same in diabetic and non-diabetic populations (Maupas et al., 2017). BP-SES and DP-EES were compared in diabetic patients, and results concluded that BP stents were associated with more TLR than DP stents in diabetic people (Kakizaki et al., 2020). The percentage of MACE was more in DM and hypertensive patients at a follow-up of 66.5 months, and the combined effect of DM and HTN increased the incidence of MACEs further (Zibaeenezhad et al., 2019).

Another study evaluated the long-term impact of DM and HTN. Results found that mortality and MI were highest in the DM group ($p < 0.001$) as compared to HTN and HTN + DM groups (Lin et al., 2017). Evidence of smoking association with the increased rate of MACEs after implantation of DES was also found in a study carried out at Peshawar Hospital (Adnan et al., 2017). A study to evaluate the smoking impact on MACEs was conducted in Korea that concluded similar efficacy and safety in smokers vs. non-smokers (Kim et al., 2018). MACE and smoking association were accessed in a meta-analysis, which found that smoking is not associated with MACE (Hu et al., 2015). This is contradictory to the current study results, where a significant association has been found between smoking and MACEs. A retrospective study in Tehran was conducted to recognize major predictors of MACE after PCI and found that DM (p = 0.007) and CAD family history (p = 0.003) were risk factors of MACEs. The study was conducted on elderly patients (age ≥65 years) (Aghajani et al., 2018).

Study limitations

This study has been conducted at a single center, so the sample may not be the representative of the whole CAD

population. Stent selection bias may exist due to retrospective nature. Severity of disease was also not accounted in the study.

Conclusion

Newer generation BP-DES have been introduced as a novel solution to the problems of durable polymer stents. Our study has compared the safety and efficacy of BP-BioMatrix stents with the older DP-XIENCE DES and evaluated the major predictors of MACEs. Biodegradable polymer stents were found to have comparable or superior efficacy and safety than the durable polymer stents at 1 year follow-up duration. Results demonstrated non-inferiority of BP-DES. However, studies with a longer follow-up, larger sample size, and randomized trials are required to better define comparative MACEs in both groups. Significant predictors of MACEs were hypertension, diabetes mellitus, smoking, and family CAD history.

Future Perspective

Results of the current study will assist the policy makers and healthcare providers in the rationalization of scarce resources and will provide information about the new biodegradable polymer stents. However, RCTs with longer follow-up duration are required for convincing evidence.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Bioethics Committee, Quaid-i-Azam University, Islamabad (BEC-FBS-QAU2020-243), and Institutional Review Board (IRB), Armed forces Institute of Cardiology (AFIC-NIHD), Rawalpindi (vide letter No. 10/11/R&D/2020/95). The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors (SB, AK, AHK, MK, SM, and SR) conceptualized and designed the study. SB and AB collected the data. SB, AK, and MK contributed to the data acquisition and analysis. SB drafted the manuscript, and AK, AHK, SM, and SR reviewed the manuscript critically. All authors read and approved the final manuscript. The study was supervised by AK.

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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.

Publisher's note

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