SOCIAL AND ADMINISTRATIVE POLICY IN HEALTHCARE AND PHARMACY PRACTICE

EDITED BY: Kingston Rajiah, Shazia Qasim Jamshed and
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PUBLISHED IN: Frontiers in Pharmacology and Frontiers in Public Health

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88976-302-3
DOI 10.3389/978-2-88976-302-3

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SOCIAL AND ADMINISTRATIVE POLICY IN HEALTHCARE AND PHARMACY PRACTICE

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Citation: Rajiah, K., Jamshed, S. Q., Ibrahim, M. I. M., eds. (2022). Social and Administrative Policy in Healthcare and Pharmacy Practice. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-302-3

Table of Contents

05 ***Editorial: Social and Administrative Policy in Healthcare and Pharmacy Practice***
Kingston Rajiah, Shazia Qasim Jamshed and Mohamed Izham Mohamed Ibrahim

08 ***Prevalence of Polypharmacy, Hyperpolypharmacy and Potentially Inappropriate Medication Use in Older Adults in India: A Systematic Review and Meta-Analysis***
Akshaya S. Bhagavathula, Kota Vidyasagar, Manik Chhabra, Muhammed Rashid, Rishabh Sharma, Deepak K. Bandari and Daniela Fialova

23 ***"Expecting the Unexpected:" Nurses' Response and Preparedness of Terrorism-Related Disaster Events in Quetta City, Pakistan***
Fazal ur Rehman Khilji, Abdul Raziq, Maryam Shoaib, Nosheen Sikander Baloch, Shanaz Raza, Zaffar Iqbal, Rabia Ishaq, Sajjad Haider, Qaiser Iqbal, Nafees Ahmad and Fahad Saleem

33 ***Determinants of Growth in Prescription Drug Spending Using 2010–2019 Health Insurance Claims Data***
HyeYeong Lee, Dahye Park and Dong-Sook Kim

43 ***Do We Need a Specific Guideline for Assessment and Improvement of Acromegaly Patients Adherence?***
Maria Kamusheva, Alexina Parvanova, Yanitsa Rusenova, Silvia Vandeva and Atanaska Elenkova

52 ***Public–Private Mix Models of Tuberculosis Care in Pakistan: A High-Burden Country Perspective***
Waseem Ullah, Ahmad Wali, Mahboob Ul Haq, Aashifa Yaqoob, Razia Fatima and Gul Majid Khan

63 ***A Qualitative Study Exploring Community Pharmacists' Experiences and Views About Weight Management Interventions and Services in Klang Valley, Malaysia***
Rohit Kumar Verma, Wei Wen Chong, Nur Akmar Taha and Thomas Paraidathathu

72 ***A Qualitative Study on Medication Taking Behaviour Among People With Diabetes in Australia***
Akram Ahmad, Muhammad Umair Khan and Parisa Aslani

82 ***What Factors Hindered the Access to Essential Anticancer Medicine in Public Hospitals for the Local Population in Hubei Province, China***
Chaoyi Chen, Zhanchun Feng, Yufeng Ding, Ziqi Yan, Jia Wang, Ruoxi Wang and Da Feng

94 ***Does Family Migration Affect Access to Public Health Insurance? Medical Insurance Participation in the Context of Chinese Family Migration Flows***
Luchan Liu

106 ***The Establishment and Practice of Pharmacy Care Service Based on Internet Social Media: Telemedicine in Response to the COVID-19 Pandemic***
Huibo Li, Siqian Zheng, Da Li, Dechun Jiang, Fang Liu, Wei Guo, Zhenying Zhao, Yanfei Zhou, Jingting Liu and Rongsheng Zhao

115 ***Factors Associated With Hospital Readmission of Heart Failure Patients***
Maitha Abdul-Aziz Al-Tamimi, Syed Wasif Gillani, Mohamed Elhassan Abd Alhakam and Kishore Gnana Sam

124 ***Effects of Volume-Price Contracts on Pharmaceutical Prices: A Retrospective Comparative Study of Public Hospitals in Hubei of China***
Zhuoxian Li, Chaojie Liu, Keyuan Zuo, Junjie Liu and Yuqing Tang

134 ***Factors Associated With Off-Label Oncology Prescriptions: The Role of Cost and Financing in a Universal Healthcare System***
Noa Gordon, Daniel A. Goldstein, Boaz Tadmor, Salomon M. Stemmer and Dan Greenberg

142 ***The Impact of Health Care Reform Since 2009 on the Efficiency of Primary Health Services: A Provincial Panel Data Study in China***
Chaoyang Yan, Hui Liao, Ying Ma and Jing Wang

153 ***Pharmacist-Led Intervention on the Inappropriate Use of Stress Ulcer Prophylaxis Pharmacotherapy in Intensive Care Units: A Systematic review***
Peipei Xu, Qiusha Yi, Cuitong Wang, Linan Zeng, Keith M. Olsen, Rongsheng Zhao, Mingyan Jiang, Ting Xu and Lingli Zhang

165 ***Combatting Substandard and Falsified Medicines: Public Awareness and Identification of Counterfeit Medications***
Faris El-Dahiyat, Khairi M. S. Fahelelbom, Ammar Abdulrahman Jairoun and Sabaa Saleh Al-Hemyari

173 ***Cost-Effectiveness Analysis of Camrelizumab Versus Chemotherapy as Second-Line Treatment of Advanced or Metastatic Esophageal Squamous Cell Carcinoma***
Hongfu Cai, Baohua Xu, Na Li, Bin Zheng, Zhiwei Zheng and Maobai Liu

181 ***Contextualising the Perceptions of Pharmacists Practicing Clinical Pharmacy in South Africa—Do We Practice what We Preach?***
Elmien Bronkhorst, Natalie Schellack and Andries G. S. Gous

190 ***Effectiveness of Community Pharmacy Diabetes and Hypertension Care Program: An Unexplored Opportunity for Community Pharmacists in Pakistan***
Madeeha Malik, Azhar Hussain, Usman Aslam, Ayisha Hashmi, Mojtaba Vaismoradi, Khezar Hayat and Shazia Jamshed

frontiers | Frontiers in Public Health

EDITORIAL
published: 10 May 2022
doi: 10.3389/fpubh.2022.901847

Editorial: Social and Administrative Policy in Healthcare and Pharmacy Practice

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Keywords: medication adherence, outcome evaluation (health care), disease management, medication use, patient behavior

Editorial on the Research Topic

Social and Administrative Policy in Healthcare and Pharmacy Practice

Most public health policies and activities in developing and developed countries are government-funded, so new information should be open to the public (1). There is a need to focus on both strengths and weaknesses of medication use policy, medication marketing, and evaluation of theoretical models. Furthermore, these could impact practice and/or patient behavior in responses to the social, health, and environmental challenges providing both theoretical and empirical findings. Potential issues include but are not limited to medication products/programs/services, medication adherence, disease management, medication use policy, and medication marketing (2–4). Social and health issues related to delivering health care services, medical governance, medication management, and pharmaceutical management related to multilevel, multi-stakeholder, and multi-sectoral approaches to healthy and affected communities should be explored. It is noteworthy to criticize ethical issues related to medication products/programs/services, medication use policy, and medication marketing. The ideas relevant to the social policy and health policy-related concepts received contributions from health policymakers, academics, practitioners, and collaborators in other sectors whose work impacts social and administrative policy. They were the appropriate sources to discuss how policy and practice change over time, how it compares across the globe, and how it is realized at all levels, from international to local. Whilst focused on relevance to practice, it was understood that examining the theories and philosophies that underpin social and administrative policy was essential. It captured a diversity of opinions across a broad range of fields, from the traditional (medication adherence; disease management; medication use policy; medication marketing, etc.) to the new (big data, new technologies). This Research Topic provided a venue for health professionals in social and administrative policy disciplines with a specific interest in policy and practice to share their research findings and other Research Topics related to public health.

The publications under this Research Topic highlighted key components like quality use of medicines, drug utilization, pharmacy care services, Potentially Inappropriate Medication (PIM), pharmacoeconomics, and pharmaceutical policies.

A qualitative exploration of the medication-taking behavior among Indian immigrant diabetics in Australia highlighted spontaneity in initiating their treatment as prescribed. Still few postponed starting their treatment due to preconceived notions about side effects and adverse effects related to medication, while other few resorted to Ayurveda forms of treatment. Those who did not receive expected results from an alternative form of treatment switched to a conventional

OPEN ACCESS

Edited and reviewed by:
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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *22 March 2022*
Accepted: *22 April 2022*
Published: *10 May 2022*

Citation:
Rajiah K, Jamshed SQ and Mohamed Ibrahim MI (2022) Editorial: Social and Administrative Policy in Healthcare and Pharmacy Practice. Front. Public Health 10:901847. doi: 10.3389/fpubh.2022.901847

modality. Long-term discontinuation was also reported. Akram et al. executed this research in a way that the "in-depth information" extracted participants' experiences and perspectives with contemplative explications.

The systematic review cum meta-analysis by Bhagavathula et al. is a vivid account of the regional variations of the prevalence of both polypharmacy, hyper polypharmacy, and inappropriate medication use in different Indian states. The authors skillfully undertook the concept of risk of bias in all 27 included studies which were then followed by performing meta-analyses. We cannot deny a myriad of cultures and practices in different geographic regions, which in turn, are the points of limitations in the current systematic review cum meta-analyses. The conclusive remarks reported extensively high polypharmacy and hyper polypharmacy coupled with traces of inappropriate medication use.

Another systematic review by Xu et al. highlighted the issue of inappropriate medicine use for stress ulcer prophylaxis (SUP) in intensive care patients and how this has been handled by clinical pharmacists' interventions. The authors carefully tackled study selection and quality assessment of included studies but deferred meta-analyses due to the heterogeneity of participants. Interestingly, the review reported that despite clinical pharmacists' interventions the extent of inappropriate use of SUP pharmacotherapy during ICU transfer is high, and recommended to include the pharmacists' suggestions for discontinuation of SUP pharmacotherapy. Although no cost-effectiveness analysis was performed a few studies in the review reported that the intervention from clinical pharmacists generated economic benefits in strengthening and improving SUP pharmacotherapy.

The research from UAE researchers on substandard and falsified medicines and understanding of and identification of counterfeit medicines among the lay public deserve merit to be discussed. Although a descriptive cross-sectional study but as it was executed in different regions of UAE through a web-based validated tool, El-Dahiyat et al. reported a sparse understanding of the identification of counterfeit medicines and recommended the need for educational campaigns to sensitize the lay public about the efficacy and safety of medicines but also to emphasize the importance of avoiding counterfeits.

Pharmacists generally provide patient care services either solo or sometimes conjointly as active members of the patient care team and generate consolidated health outcomes and improved satisfaction rates followed by a substantial decrement in healthcare costs. One cannot deny the significant role of pharmacists as immunizers, public health specialists, organizers of health and wellness screening programs, and medication therapy managers in recent years. Few of the published articles in this Research Topic account for how pharmacists can be involved in weight management programs and exercised potential influence on diabetes and hypertension.

In a Malaysian study, Verma et al. extensively explored how community pharmacists contributed to weight management and the challenges and facilitators involved in their role extension. Fulfilling the basic criteria of executing qualitative research, they reported that community pharmacists are instrumental in exercising influence in weight management programs and expressed their readiness in imparting educational advice and lifestyle modifications coupled with medication and supplement counseling and referrals to other healthcare professionals. Also reported challenges like paucity of time and proper space allocation along with reimbursement issues, they advocated following substantial remuneration models for community pharmacists involved in weight management schemes.

Likewise in a randomized, controlled, single-blinded, pre-post intervention study from Pakistan, community pharmacists are reported to be involved in diabetes and hypertension care. Malik et al. assessed the effects of pharmacist counseling on blood pressure and glucose control among patients attending community pharmacies and reported better knowledge in diabetes and hypertension in patients enrolled in the intervention group.

Another research from South Africa within the paradigm of pharmacy care services generated a rewarding vision of the predicaments in the line of clinical pharmacy practice and envisaged the recent profile of clinical pharmacists and their roles and responsibilities. It was reported that when working in hospital wards they performed many functions which include both clinical and logistical but recommended to have certification system need to be in place which will standardize the practice of clinical pharmacy services in different facilities.

Timely research from China advocated setting up and divulge a tele pharmacy support system to execute pharmaceutical care during the COVID-19 pandemic. Under the aegis of the Beijing Pharmacists Association, a remote pharmacy service model was set up to provide medication consultation services using WeChat App. The constructed "Cloud Pharmacy Care" platform had attracted more than 1,400 viewers and 66 followers within 2 months followed by more than 35 cases of patient counseling. The forte of this interactive consultation model strengthened the medication therapy management aspect for chronically ill patients and reported superior compliance and dissemination of safe medication knowledge.

Another research from United Arab Emirates UAE promptly recommended the role of clinical pharmacists in combating readmissions and rehospitalizations in heart failure patients and explicated non-compliance with medications as the major cause of rehospitalization.

A unique study from researchers in Bulgaria also tapped the importance of adherence to medications in acromegaly and advocated instituting a national level guideline that not only has methods of assessment but also going to deal with the improvement of adherence in acromegaly patients. In this stepwise study where first the literature review was done along with an analysis of Bulgarian legislative documents, the researcher Kamusheva et al. did a pilot study for the assessment of the level of treatment adherence among hospitalized patients followed by the development of the plan for the implementation of specific guidelines BULMEDARCO Bulgarian Guideline For Medication Adherence Assessment And Improvement In Acromegaly.

The economic evaluation provided evidence for the quality of health care delivery improvement and health outcomes. The

uptake of evidence-based practices assures the efficient use of limited healthcare resources. Four studies investigated the economic aspect of medicines. A study by Cai et al. measured the cost-effectiveness of camrelizumab in treating patients with advanced or metastatic esophageal squamous cell carcinoma. It is evident that camrelizumab as a second-line therapy is cost-effective in terms of its QALY compared to chemotherapy. Economic burden and financing sources of off-label oncology treatment were assessed by Gordon et al. They discovered that the main sources of funding were private health insurance. In addition, the average monthly cost of off-label treatment was 4–5 times much higher than the net average household monthly income. Lee et al. studied the trends of pharmaceutical expenditures using Korean National Health Insurance claim data. They indicated that the increase in the number of drugs used as the driver of the increase in prescription drug spending. Li H. et al. evaluated the price effect of the volume-price contract initiative on pharmaceutical supplies to public hospitals in China. They found that the reduction of the unit price of procured cardiovascular medicines is associated with the volume-price contract initiative. The initiative worked well for cardiovascular medicines, but the impact varied for other medicines.

Potentially Inappropriate Medication (PIM) use are linked with numerous adverse effects and mortality in Geriatrics (5). In this Research Topic, a study by Bhagavathula et al. demonstrated that the prevalence of PIM use among the geriatric population is high in India. Oncology medicines give rise to many challenges for policymakers while the pricing of products due to increasing uncertainty during marketing authorization with variation in combination regimens, cost-effectiveness and budget impact. In this Research Topic, a study by Cai et al. reported that the oesophagal squamous cell carcinoma patients' quality of life could improve with camrelizumab, be cost-effective, and reduce adverse reactions. Another study by Chen et al. stated that increased price and decreased affordability as barriers to access anticancer essential medicines. Another study by Liu quoted that public medical insurance is an essential means of preventing uncertainty and avoiding health risks among the people who cannot access health. A study by Gordon et al. stated that in a comprehensive healthcare system, the financing sources of the off-label treatments may influence access to it. In most countries, expenditures on healthcare have increased after implementing the national health insurance system covering medications (6). In this Research Topic, a study by Lee et al. revealed that increased prescription drug spending was mainly due to an increase in the number of drugs used. Another study by Li Z. et al. stated that the volume-price contract initiative has the potential to bring down the price of pharmaceutical supplies. According to WHO, counterfeit pharmaceutical products are fraudulently and deliberately mislabeled similar to the source (7). A study on this Research Topic by El-Dahiyat et al. mentioned that drug counterfeiting is a menace to any nation's economy and public health. Hence, awareness among the public is essential.

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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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.

frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 19 May 2021
doi: 10.3389/fphar.2021.685518

Prevalence of Polypharmacy, Hyperpolypharmacy and Potentially Inappropriate Medication Use in Older Adults in India: A Systematic Review and Meta-Analysis

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: 25 March 2021
Accepted: 26 April 2021
Published: 19 May 2021

Citation:
Bhagavathula AS, Vidyasagar K, Chhabra M, Rashid M, Sharma R, Bandari DK and Fialova D (2021) Prevalence of Polypharmacy, Hyperpolypharmacy and Potentially Inappropriate Medication Use in Older Adults in India: A Systematic Review and Meta-Analysis. Front. Pharmacol. 12:685518. doi: 10.3389/fphar.2021.685518

Background: Older people often receive multiple medications for chronic conditions, which often result in polypharmacy (concomitant use of 5–9 medicines) and hyperpolypharmacy (concomitant use of ≥10 medicines). A limited number of studies have been performed to evaluate the prevalence of polypharmacy, hyperpolypharmacy, and potentially inappropriate medication (PIM) use in older people of developing countries. The present study aimed to investigate regional variations in the prevalence of polypharmacy, hyperpolypharmacy, and PIM use in older people (60 + years) in India.

Methods: Studies were identified using Medline/PubMed, Scopus, and Google Scholar databases published from inception (2002) to September 31, 2020. Out of the total 1890 articles, 27 were included in the study.

Results: Overall, the pooled prevalence of polypharmacy was 49% (95% confidence interval: 42–56; $p < 0.01$), hyperpolypharmacy was 31% (21–40; $p < 0.01$), and PIM use was 28% (24–32; $p < 0.01$) among older Indian adults. Polypharmacy was more prevalent in North-east India (65%, 50–79), whereas hyperpolypharmacy was prevalent in south India (33%, 17–48). Region-wize estimates for the pooled prevalence of PIM use in India were as follows: 23% (21–25) in East, 33% in West (24–42), 17.8% in North (11–23), and 32% (26–38) in South India. The prevalence of PIM use in adults aged ≥70°years was 35% (28–42), in those taking more medications (≥5.5/day) was 27% (22–31), and in adults using a high number of PIMs (≥3) was 29% (22–36). Subgroup analysis showed that cross-sectional studies had a higher pooled prevalence of polypharmacy 55% (44–65) than cohorts 45% (37–54). Hyperpolypharmacy in inpatient care settings was 37% (26–47), whereas PIM use was higher in private hospitals 31% (24–38) than government hospitals 25% (19–31).

Conclusion: Polypharmacy and hyperpolypharmacy are widely prevalent in India. About 28% of older Indian adults are affected by PIM use. Thus, appropriate steps are needed to promote rational geriatric prescribing in India.

Systematic Review Registration: https://clinicaltrials.gov, identifier [CRD42019141037].

Keywords: polypharmacy (source: MeSH, NML), India, potentially inappropriate medication (PIM), prevalence, older (diseased) population, hyperpolypharmacy

INTRODUCTION

There were 703 million people aged 65˚years or over in the world in 2019. The number of the older people is projected to double to 1.5 billion by 2050, with a more prominent increase in developing countries (He and Kinsella, 2020). According to the United Nations Population Fund's (UNFPA) 2021 flagship State of World population report, there are nearly 93 million (6.8%) older people (aged 65˚years or above) in India, and the number is projected to exceed 227 million in 2050 (United Nations Population Fund).

In general, older people often receive multiple medications for chronic conditions, which often result in polypharmacy (concomitant use of 5–9 medicines) and hyperpolypharmacy (concomitant use of ≥10 medicines) (Masnoon et al., 2017). Research shows that older adults in India frequently use multiple medications. There are wide regional variations in the prevalence ranging from 5.8% in West Bengal (west region) and 93.1% in Uttaranchal (North India) (Sharma et al., 2019). Although medications are essential to improve a patient's health status and quality of life, suboptimal prescribing and the use of multiple drugs may have adverse outcomes (Pravodelov, 2020; O'Mahony, 2020; Bala et al., 2019). Moreover, polypharmacy and hyperpolypharmacy are strongly linked to a broad range of negative health outcomes and are considered proxy indicators of potentially inappropriate medication (PIM) use (Guillot et al., 2020).

The term PIM is defined as medications that have adverse effects and, when used by older adults, may outweigh the clinical advantages of the drug, such as mental and functional decline, adverse drug events, drug interactions, unplanned hospitalization, morbidity, and mortality (Thomas and Thomas, 2019; Xing et al., 2019; de Oliveira et al., 2020; Weeda et al., 2020). Higher-income countries have taken several steps to improve rational prescribing in older adults and have developed evidence-based explicit tools to screen and prevent PIM use in older patients. Explicit tools comprise lists of drugs or drug classes (developed from literature reviews, expert opinion, and consensus techniques) that, when prescribed or underprescribed, can cause harm in older people. Beers criteria and the Screening Tool of Older Persons' prescription (STOPP) and the Screening Tool to Alert to Right Treatment (START) are the most commonly referenced tools (Topinková et al., 2008; Hill-Taylor et al., 2013; American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; Thomas and Thomas, 2019; Weeda et al., 2020).

Several systematic reviews and meta-analyses on the prevalence of polypharmacy and PIM use in the older population, using data from developed countries (Kaufmann et al., 2014; Muhlack et al., 2017; Liew et al., 2019; Thomas and Thomas, 2019; Xing et al., 2019; Davies et al., 2020; de Oliveira et al., 2020; Liew et al., 2020; Mohamed et al., 2020; Weeda et al., 2020), indicated a rising trend of inappropriate medication use in the current healthcare system. However, differences in the population, healthcare settings, and medication use process may limit the generalizability of these findings in developing countries, including India. Given the rapidly increasing older population, increasing burden of chronic diseases, and wide variations in polypharmacy use across India, the prevalence of PIM use in the Indian older population is pertinent. We hypothesized that the prevalence of polypharmacy, hyperpolypharmacy, and PIM use in India would be higher than in the western countries, and their distribution may vary across different states in India. Thus, this study aimed to perform a systematic review and meta-analysis to assess the overall prevalence and regional variations (north, east, west, and south: NEWS) of polypharmacy, hyperpolypharmacy, and PIM use in older people in India.

METHODS

The study was performed according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000). The research protocol is registered on PROSPERO, 2019 (CRD42019141037).

Search Strategy

We comprehensively searched Medline/PubMed, Scopus, Google Scholar, and bibliographic databases from inception (2002) to September 31, 2020. The search process was initiated in april 2019 and updated until September 31, 2020. We used combinations of Medical Subject Headings (MeSH) and free text words to identify the relevant studies related to the exposure (e.g., polypharmacy, hyperpolypharmacy, potentially inappropriate prescribing (PIP), PIMs, and to search terms related to outcomes (e.g., prevalence, estimates, percentage, burden). Complete details about the search terms used in various databases have been listed in **Supplementary Table S1**.

Selection Criteria and Data Extraction

The studies met the following criteria; observational (cross-sectional, case-cohort, or cohort) on the older population

(aged 60 and older), conducted in India, and reported prevalence of polypharmacy, hyperpolypharmacy, and PIM use, using any explicit criteria to assess the appropriateness of drugs prescribed. The following articles were excluded; duplicate studies, abstracts, letters, editorials, conference proceedings, review articles, meta-analyses, non-population-based studies, and interventional studies.

Selection of Studies

Three reviewers (ASB, RS and KVS) independently screened the titles and abstracts of the initially identified studies to determine whether each study met the predefined eligibility criteria. Full-text articles were retrieved for selected titles. References of the retrieved articles were also screened to identify the additional eligible articles. Any disagreements regarding selection were resolved through discussion, consensus, or consultation with other team authors (MC, MR, and SPS).

Data Extraction

Full texts of included studies were read, and three reviewers (RS, MC, and KVS) extracted the relevant data from the selected studies. The extracted data included author details, year of publication, geographic origin, study design and settings, patient sampling, participant characteristics (e.g., age range, mean age, sex, comorbidities, and number of prescribed medications), measurements (explicit criteria), and information on outcomes (type of medication use, number of patients exposed to PIM, number of PIMs identified and percentage of the older population on polypharmacy and hyperpolypharmacy). Prevalence estimates of PIM use were stratified to provide specific estimates of the subsets (mean age, gender, study duration, and the average number of medications).

Quality Assessment

The methodological quality of the included studies was evaluated using the Newcastle Ottawa Scale (NOS) for cross-sectional and cohort studies (Luchini et al., 2017). The NOS assesses the representativeness of the sample, sample size, response rate, ascertainment of exposure, control of confounding variables, assessment of preventability, and appropriate statistical analysis. The NOS scores range from 0 (lowest grade) to 9 (highest grade). Studies scoring seven or above were considered high quality, and those with scores below seven were of low quality.

Statistical Analysis

The estimates of polypharmacy, hyperpolypharmacy, and PIM use were expressed as proportions (%) with corresponding 95% confidence intervals (CI). The pooled prevalence estimates of outcome variables were calculated using regional population size weights. The magnitude of heterogeneity between the studies was assessed using the I^2 statistic (% residual variation due to heterogeneity), and Tau^2 (method of moments estimate of between-study variance) was used for each of the pooled estimates. I^2 values range between 0 and 100%, and is considered low for I^2 <25%, modest for 25–50%, and large for >50% (Higgins et al., 2003). As differences between the studies were very high (95–99% inconsistency), a random effect DerSimonian-Laird model was used in all analyses (Higgins et al., 2003). In case of substantial heterogeneity, the source of heterogeneity was investigated using stratified analyses and meta-regression analysis, based on the study-level characteristics, such as year of publication, study duration, mean age, women-to-men ratio, the mean number of drugs, number of PIM use, and quality of studies based on NOS scale. The interaction between the subgroups of each factor was assessed using Cochran's *Q* test, degree of freedom (df), and *p*-value resulting from Cochran's *Q* test. A *p*-value of <0.10 was considered statistically significant for Cochran's *Q* test (Huedo-Medina et al., 2006). The risk of publication bias was inspected by using the symmetry of funnel plots, and Egger's and Begg's tests were also used. Statistical analyses were performed using STATA software, version 16 MP (StataCorp, College Station, TX).

RESULTS

Study Selection

A total of 1890 references were initially identified through electronic databases. After removing 165 duplicates, a total of 1835 titles and abstracts were screened to determine if they met the inclusion criteria, as described in the methodology section. Full-text assessment of 119 potentially relevant articles resulted in 27 eligible studies (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Kumar et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Borah et al., 2017; Rakesh et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015; Undela et al., 2014; Dhikav et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Shah et al., 2011; Mandavi et al., 2011; Zaveri et al., 2010; Harugeri et al., 2010), as shown in **Figure 1**. The list of articles that are excluded (n = 92) due to various reasons is presented in **Supplementary Table S2**.

Characteristics of Included Studies

All the studies included in the present study were published between 2010 and 2019. Sample size varied on regional basis from 90 to 1,510, making a total of 11,649 patients. All the studies included both women and men (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Kumar et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Borah et al., 2017; Rakesh et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015; Undela et al., 2014; Dhikav et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Shah et al., 2011; Mandavi et al., 2011; Zaveri et al., 2010; Harugeri et al., 2010); however, seven studies included more women than men(Dhikav et al., 2014; Umar et al., 2015; Salwe et al., 2016; Kumar et al., 2017; Narvekar et al., 2017; Bhatt et al., 2019; Chandrasekhar et al., 2019). Among the studies, nineteen

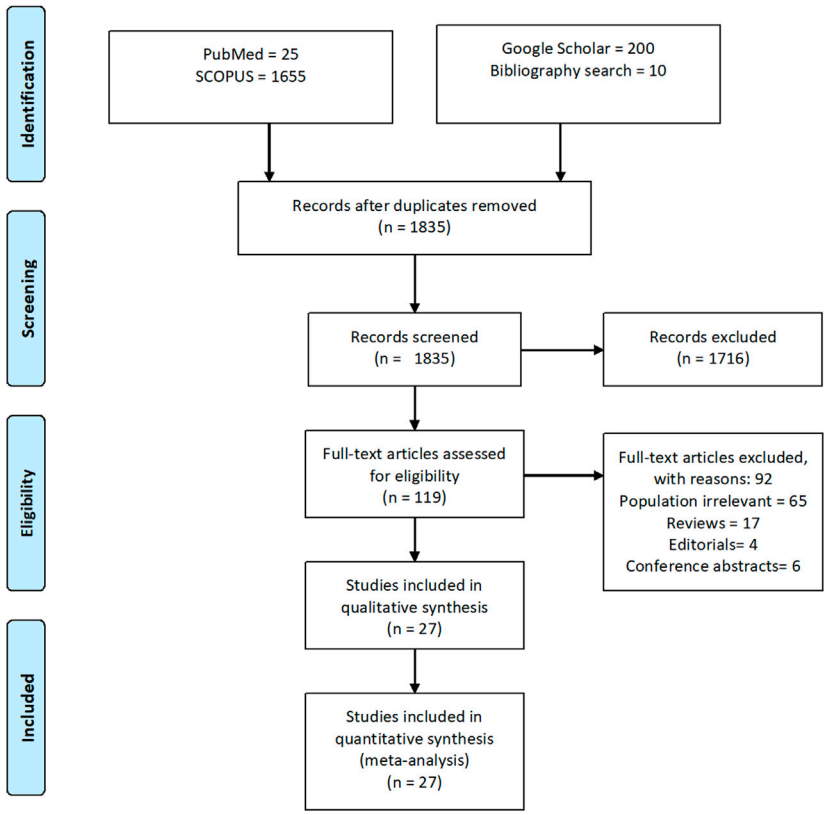

FIGURE 1 | PRISMA diagram of the literature selection in this systematic literature review and meta-analysis.

were cohort design (Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Anjum et al., 2017; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015; Undela et al., 2014; Dhikav et al., 2014; Karandikar et al., 2013; Nagendra et al., 2012; Shah et al., 2011; Harugeri et al., 2010), and eight were cross-sectional studies (Zaveri et al., 2010; Mandavi et al., 2011; Momin et al., 2013; Swathi and Bhavika, 2016; Borah et al., 2017; Kumar et al., 2017; Rakesh et al., 2017; Bhatt et al., 2019). The majority of the studies were conducted in South India (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Benjamin et al., 2018; Rakesh et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Danisha et al., 2015; Umar et al., 2015; Nagendra et al., 2012; Harugeri et al., 2010), six in North India (Mandavi et al., 2011; Karandikar et al., 2013; Dhikav et al., 2014; Undela et al., 2014; Kashyap et al., 2015; Kumar et al., 2017), three in Eastern states (Devarapalli et al., 2017; Pradhan et al., 2017; Pradhan and Panda, 2018), four in Western region (Zaveri et al., 2010; Shah et al., 2011; Momin et al., 2013; Narvekar et al., 2017) and only one study in North-east India (Borah et al., 2017). Twenty-one studies provided data on the prevalence of polypharmacy (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Pradhan et al., 2017; Borah et al., 2017; Rakesh et al., 2017; Anjum et al., 2017; Swathi & Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Umar et al., 2015; Undela et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Mandavi et al., 2011; Harugeri et al., 2010), fourteen studies reported estimates of hyperpolypharmacy (Bhatt et al., 2019; Chandrasekhar et al., 2019; Benjamin et al., 2018; Devarapalli et al., 2017; Anjum et al., 2017; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Umar et al., 2015; Undela et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Harugeri et al., 2010), whereas all the twenty-seven studies reported PIM use in the older population (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Kumar et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Borah et al., 2017; Rakesh et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015; Undela et al., 2014; Dhikav et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Shah et al., 2011; Mandavi et al., 2011; Zaveri et al., 2010; Harugeri et al., 2010). Most of the studies used 2012 Beers criteria (Bhatt et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Devarapalli et al., 2017; Kumar et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Borah et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015;

TABLE 1 | Characteristics of included studies.

Author, year	Study characteristics						Explicit criteria	Prevalence (%)		
	States	Design	Period	Setting	Sample size	Age, years (Mean/ median)	Explicit criteria	Polypharmacy[a]	Hyperpolypharmacy[b]	PIM use
Bhatt et al. (2019)	Kerala	Cross-sectional	6	Outpatient	400	73.6 ± 6.7	Beer's criteria	45.8	13.5	34
Chandrasekhar et al. (2019)	Kerala	Cohort	12	Inpatient	210	Phase 1: 72.59 ± 6.37 Phase 2: (71.99 ± 6.30	STOPP/START criteria	60	35.7	Overall: 41.9, phase 1: 43.5, phase 2: 40.2
Motallebzadeh et al., (2019)	Karnataka	Cohort	6	Inpatient	480	Unspecified	Beers criteria	36.4	Unspecified	11.6
Benjamin et al. (2018)	Karnataka	Cohort	7	Inpatient	350	92 (68)	Beers criteria, STOPP criteria	37.1	58.6	2012 Beers: 27.7, STOPP: 24.6
Pradhan et al. (2018)	Odisha	Cross-sectional	3	Outpatient	425	72.5 ± 7.6	Beers criteria	75.1	Unspecified	23.8
Devarapalli et al. (2017)	Andhra Pradesh	Cohort	Unspecified	Inpatient	135	66.9 ± 0.2	Beers criteria	38.5	35.5	25.9
Kumar et al., (2017)	Jammu & kashmir	Cohort	6	Inpatient	203	Unspecified	Beers criteria	Unspecified	Unspecified	3.7
Pradhan et al. (2017)	Odisha	Cross-sectional	4	Outpatient	800	75.8 ± 6.9	Beers criteria	41.5	Unspecified	21.8
Narvekar et al. (2017)	Goa	Cohort	5	Inpatient	150	68.88 (range: 60–87)	Beers criteria	Unspecified	Unspecified	44
Borah et al. (2017)	Assam	Cross-sectional	6	Both	150	Unspecified	Beers criteria	72	Unspecified	28.7
Rakesh et al. (2017)	Karnataka	Cross-sectional	16	Outpatient	426	71.6 ± 6.4	MAI, beers criteria, STOPP criteria, and START criteria	66.2	Unspecified	19.9
Anjum et al. (2017)	Tamil nadu	Cohort	6	Inpatient	90	Unspecified	Beers criteria	40	50	51.1
Burla et al. (2016)	Telangana	Cohort	3	Outpatient	287	Unspecified	Beers criteria	68.3	Unspecified	20.2
Salwe et al. (2016)	Puducherry	Cross-sectional	3	Inpatient	100	71.64 ± 6.51	Beers criteria	53	27	48
Chowta et al. (2016)	Karnataka	Cross-sectional	12	Outpatient	120	71.56 ± 6.61	Medication appropriateness index, STOPP/START, Beer's criteria	42.5	2.5	32.5
Kashyapa et al. (2015)	Chandigarh	Cohort	Unspecified	Inpatient	1,510	67.2 ± 0.2	Beers criteria	39	38.7	21
Pattani et al. (2015)	Kerala	Cohort	12	Inpatient	200	72.2 ± 8.04	Beers criteria	Unspecified	Unspecified	53
Umar et al. (2015)	Karnataka	Cohort	6	Inpatient	203	70 ± 2.4	Beers criteria	57.1	7.9	37.4
Undela et al. (2013)	Chandigarh	Cohort	9	Inpatient	1,215	68 ± 7.0	Beers criteria 2003 and beers criteria 2012	46	40	2003 Beers: 11 2012 Beers: 16
Dhikav et al. (2014)	New Delhi	Cohort	12	Outpatient	143	70.1 ± 10.1	Beers criteria	Unspecified	Unspecified	41.9
Karandikar et al. (2013)	Maharashtra	Cross-sectional	8	Both	600	Unspecified	Beers criteria and STOPP/START criteria	41	15	STOPP: 11.9 Beers: 7.3
Momin et al. (2013)	Gujarat	Cohort	12	Inpatient	210	69.34 ± 5.26	Beers criteria 2003 and 2012	50.9	34.7	2003 Beers: 40 2012 Beers: 28.57
Vishwas et al. (2012)	Karnataka	Cohort	9	Inpatient	540	66 (range: 60–95)	Beers criteria and STOPP	50.2	44.4	24.6

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies.

Author, year	Study characteristics						Explicit criteria	Prevalence (%)		
	States	Design	Period	Setting	Sample size	Age, years (Mean/median)	Explicit criteria	Polypharmacy[a]	Hyperpolypharmacy[b]	PIM use
Shah et al. (2011)	Gujarat	Cohort	27	Both	400	Unspecified	Beers criteria and Phadke's criteria	Unspecified	Unspecified	27.2
Mandavi et al. (2011)	Chandigarh	Cohort	5	Outpatient	1,081	68.2 ± 0.20	Beers criteria	58	Unspecified	10.8
Zaveri et al. (2010)	Gujarat	Cohort	4	Outpatient	407	Unspecified	Beers criteria	Unspecified	Unspecified	23.6
Harugeri et al. (2010)	Karnataka	Cohort	18	Inpatient	814	66 years (range: 60–95)	Beers criteria	36.6	53.7	23.5

[a]*using >5 drugs;*
[b]*using ≥10 drugs, PIM: potentially inappropriate medication; STOPP: screening tool of older persons' prescriptions; START: screening tool to alert to right treatment.*

Dhikav et al., 2014), only one study used 2015 STOPP/START criteria (Chandrasekhar et al., 2019), while the rest of the studies used a different version of the Beers criteria in combination with other PIM criteria (Shah et al., 2011; Nagendra et al., 2012; Karandikar et al., 2013; Chowta et al., 2016; Rakesh et al., 2017; Benjamin et al., 2018). The characteristics of the included studies are summarized in **Table 1**.

Quality of Included Studies

The quality assessment of included studies was assessed using NOS for the cross-sectional and cohort studies. The highest quality score was 9, and the lowest was 4. The average score of the NOS scale was 7.4, indicating high quality. In the risk of bias assessment, four studies (14.8%) were of lower quality, with a NOS score of <7. Based on NOS criteria, three studies were of lower quality based on criteria 1 (representativeness of the exposure group or sample representation), seven studies based on criteria 2 (selection of non-exposure group or sample selection), and three studies based on criteria 3 (not report the definition of the exposure); only four of eight cross-sectional studies performed appropriate statistical tests (criteria 7). Detailed results on the NOS quality assessment are presented in **Supplementary Table S3**.

Prevalence of Polypharmacy

Out of 27 publications, twenty-one studies, comprising 9,391 participants, reported a prevalence of polypharmacy among older adults. The pooled prevalence of polypharmacy in India, after weighing the regional population size, was 49% (n = 10,146, 95% CI: 42–56; I^2 = 98.2%, p < 0.01, τ^2 0.03). Region-wize data showed significant differences in the prevalence of polypharmacy between different regions of India (Q = 5.47, df = 4; p < 0.01) ranging from 39% (95% CI: 22–56; I^2 = 99.3%, p < 0.01) in Northern states to 52% (95% CI: 27–77, I^2 = 98.8%, p < 0.01) in East India. Studies from West India (51%, 95% CI: 44–58), and North-east India reported higher prevalence of polypharmacy (72%, 95% CI: 65–79). Moreover, the majority of studies were conducted in South India (Harugeri et al., 2010; Nagendra et al., 2012; Kashyap et al., 2015; Umar et al., 2015; Chowta et al., 2016; Salwe et al., 2016; Swathi and Bhavika, 2016; Devarapalli et al., 2017; Narvekar et al., 2017; Pradhan and Panda, 2018; Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019), where the prevalence of polypharmacy was 49% (95% CI: 42–57; I^2 = 95.3%, p < 0.01). The data on the prevalence of polypharmacy in other regions is summarized in **Figure 2**.

Hyperpolypharmacy

Fourteen studies investigated the prevalence of hyperpolypharmacy among the older population in India (Bhatt et al., 2019; Chandrasekhar et al., 2019; Benjamin et al., 2018; Devarapalli et al., 2017; Anjum et al., 2017; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Umar et al., 2015; Undela et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Harugeri et al., 2010). The pooled estimate of hyperpolypharmacy was 31% in India (n = 6,497, 95% CI:

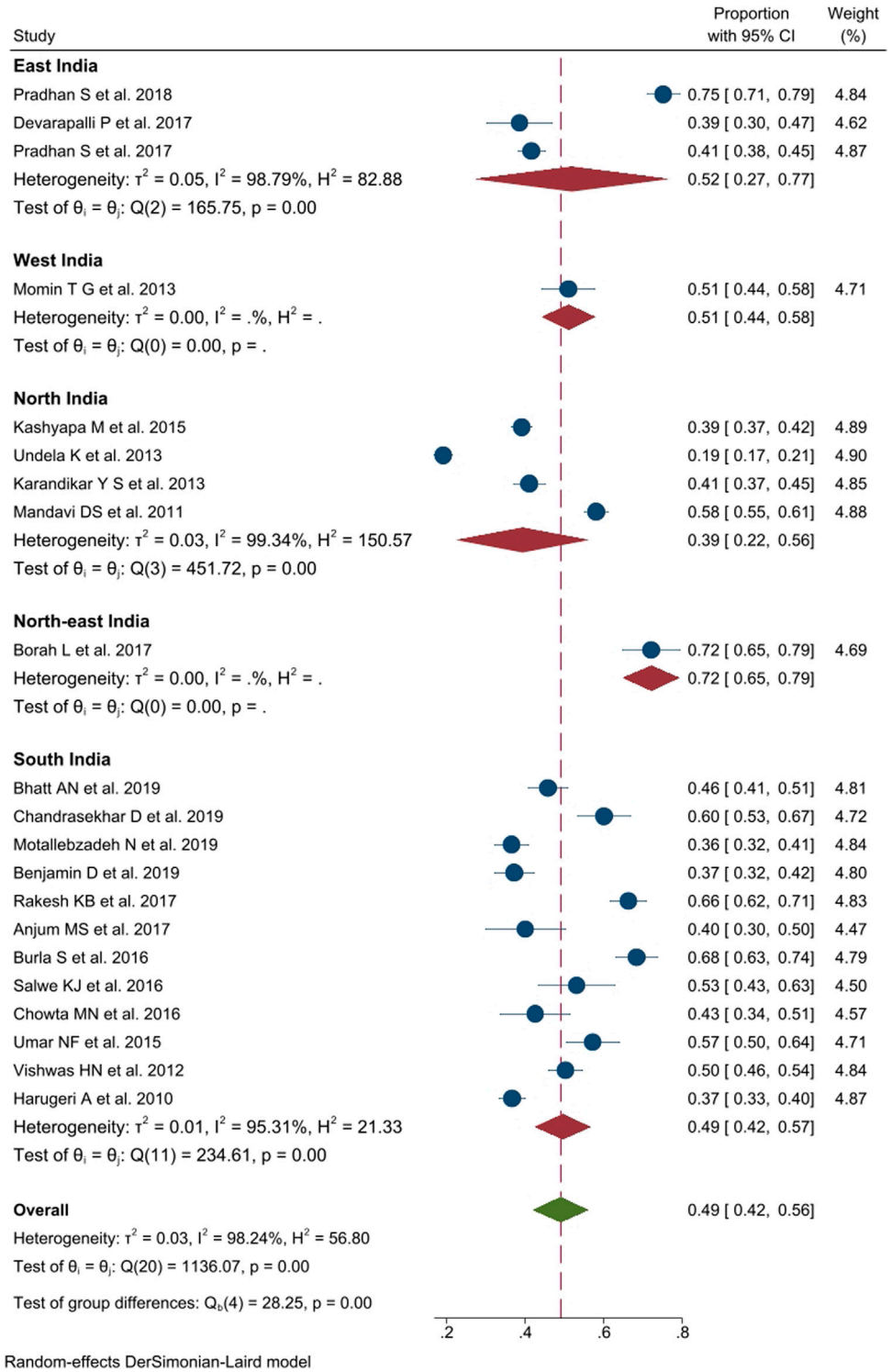

FIGURE 2 | Prevalence of polypharmacy use (5-9 medications) in older people across various geographic regions in India.

21–40; I^2 = 98.9%; $p < 0.01$; τ^2 0.0321). Region-wize data on the prevalence of hyperpolypharmacy among older adults showed considerable variations with 36% prevalence was seen in East India (95% CI: 27–44), 35% in West India (95% CI: 28–41), 23% in North India (95% CI: 8–39) and 33% (95% CI: 17–48) in South India, as shown in **Figure 3**. However, these differences between the regions were not statistically significant ($Q = 2.08$, df = 3; $p = 0.560$).

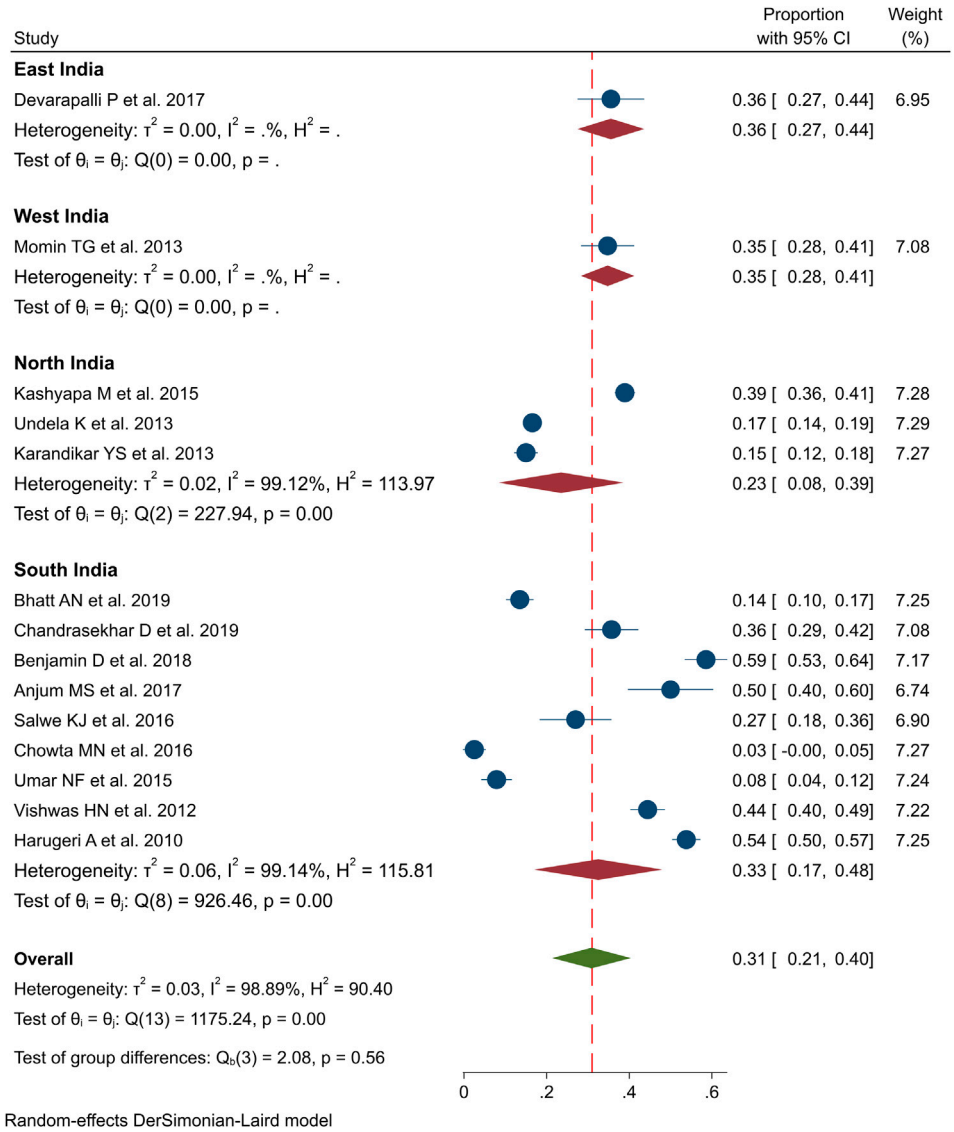

FIGURE 3 | Prevalence of hyperpolypharmacy (≥10 drugs) use in older people across various geographic regions in India.

PIM Use

All the 27 studies provided PIM estimates among the older population in India (Bhatt et al., 2019; Chandrasekhar et al., 2019; Motallebzadeh et al., 2019; Pradhan and Panda, 2018; Benjamin et al., 2018; Devarapalli et al., 2017; Kumar et al., 2017; Pradhan et al., 2017; Narvekar et al., 2017; Borah et al., 2017; Rakesh et al., 2017; Anjum et al., 2017; Swathi and Bhavika, 2016; Salwe et al., 2016; Chowta et al., 2016; Kashyap et al., 2015; Danisha et al., 2015; Umar et al., 2015; Undela et al., 2014; Dhikav et al., 2014; Karandikar et al., 2013; Momin et al., 2013; Nagendra et al., 2012; Shah et al., 2011; Mandavi et al., 2011; Zaveri et al., 2010; Harugeri et al., 2010). The pooled prevalence of PIM was found to be 28% by using random-effect model (n = 11,649, 95% CI: 24–32; I^2 = 97.3; p < 0.01; τ^2 0.0117), which indicated substantial heterogeneity, as shown in **Figure 4**. Comparison of PIM proportions in India showed significant differences among the four regions (NEWS) (Q = 18.8, df = 4; p < 0.01). West India and South India demonstrated a relatively higher pooled prevalence of 33% (95% CI: 24–42, p < 0.01) and 32% (95% CI: 26–38, p < 0.01), respectively, while North India and East India had a lower pooled prevalence of 17 and 23%, respectively. The variations in the pooled prevalence of PIM use are further illustrated in the forest plot in **Figure 4**.

Stratified Analysis

A stratified meta-analysis of the prevalence of polypharmacy, hyperpolypharmacy, and PIM use in India is summarized in **Table 2**. We stratified the studies by various baseline characteristics and interrogated the source of heterogeneity and differences between the groups. Significant heterogeneity was

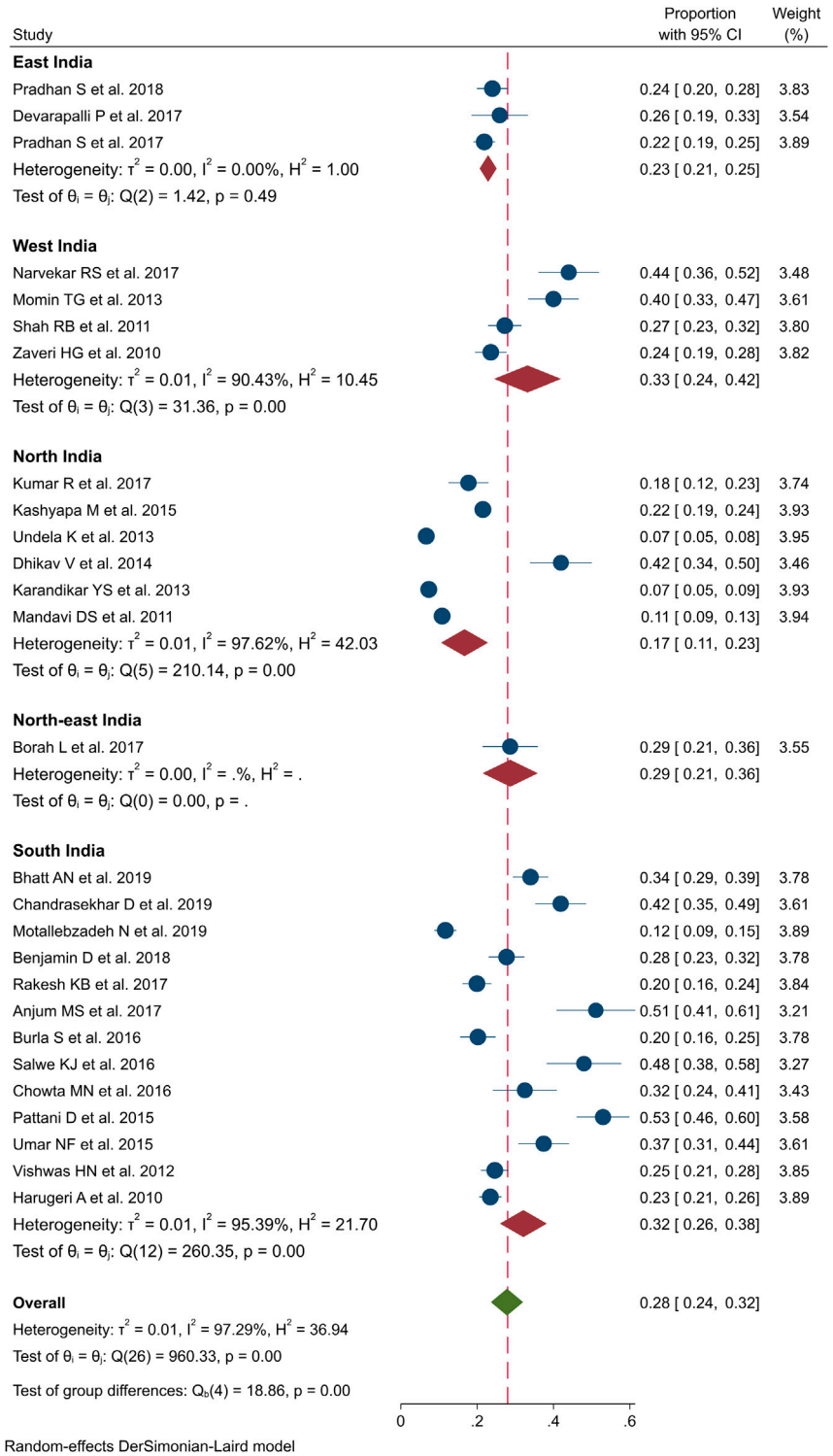

FIGURE 4 | Prevalence of potential inappropriate medication (PIM) use in older people across various geographic regions in India.

detected among all the subgroups; for instance, studies performed for less than 6°months of duration had a higher pooled prevalence of polypharmacy (59%), compared to those conducted for 6–12°months (46%) and >1 year (47%). A significant heterogeneity between the groups was observed ($Q = 26.4$, df = 3; $p < 0.01$). Regarding PIM use, studies conducted before 2013 had a lower pooled prevalence (22%) than those conducted between 2013 and 2016 (31%); however, the pooled prevalence slightly decrease for studies conducted after 2017.

TABLE 2 | Stratified meta-analysis of the prevalence of polypharmacy, hyperpolypharmacy, and potential inappropriate medication (PIM) use in India.

Characteristics	Number of studies	Pooled prevalence in percentage (95% CI)	*p* For interaction[a]	I^2 (%)	Z	Heterogeneity between groups		
1. Polypharmacy						*Q*	df	*p*
Year of publication			0.001			0.43	2	0.807
≤2012	3	48 (42–56)		-	7.08			
2013–2016	8	46 (34–58)		98.4	7.57			
≥2017	10	51 (41–61)		97.3	10.1			
Study duration			0.001			26.43	3	<0.001
<6°months	5	59 (47–72)		97.6	9.28			
6–12°months	12	46 (36–55)		97.7	9.51			
>1°year	2	47 (44–50)		-	34.6			
Mean age			0.001			0.41	2	0.81
<70	8	46 (33–59)		99.1	6.90			
≥70	8	50 (42–58)		93.9	12.36			
NA	5	52 (37–66)		97.1	6.96			
Percentage of female			0.001			0.04	1	0.84
<50%	15	49 (41–58)		98.6	11.0			
≥50%	6	48 (38–58)		93.1	9.37			
Average number of drugs			0.001			14.55	2	0.001
<5.5	2	61 (57–65)		-	30.2			
≥5.5	15	49 (41–58)		98.6	11.07			
NA	4	45 (36–54)		88.8	9.78			
Number of PIM use			0.001			0.37	1	0.54
<3	12	47 (41–53)		95.3	14.7			
≥3	9	52 (37–66)		99.0	7.2			
Quality of studies[b]			0.001			0.66	1	0.42
High (≥7)	18	48 (40–54)		98.4	12.36			
Low (<7)	3	56 (38–74)		-	6.01			
2. Hyperpolypharmacy								
Year of publication			0.001			29.81	2	0.001
≤2012	2	50 (47–53)		-	37.0			
2013–2016	7	20 (10–31)		*98.7*	3.76			
≥2017	5	39 (19–58)		*98.2*	3.79			
Study duration			0.001			72.9	3	0.001
<6°months	1	27 (19–36)		-	6.08			
6–12°months	10	28 (18–37)		98.6	5.46			
>1°year	1	54 (50–57)		-	30.79			
Mean age			0.001			8.83	2	0.012
<70	6	37 (24–51)		98.8	5.55			
≥70	6	24 (8–40)		98.8	2.99			
Na	2	17 (15–20)		-	12.45			
Percentage of female			0.001			0.82	1	0.365
<50%	10	33 (22–44)		98.8	5.99			
≥50%	4	25 (9–40)		97.9	3.07			
Average number of drugs			0.001					0.001
<5.5	1	3 (1–7)		-	1.75			
≥5.5	10	36 (26–46)		98.6	6.82			
Na	1	23 (8–37)		-	3.06			
Number of PIM use			0.001			0.70	1	0.403
<3	9	34 (21–47)		98.85	5.12			
≥3	5	25 (9–41)		98.12	3.08			
Quality of studies[b]			0.001			31.2	1	0.001
High (≥7)	12	34 (24–43)		*98.7*	6.76			
Low (<7)	2	5 (2–5)		-	3.53			
3. PIM use								
Year of publication			0.449			3.33	2	0.189
≤2012	5	22 (15–29)		93.9	5.87			
2013–2016	10	31 (24–39)		97.3	8.17			
≥2017	12	28 (23–34)		96.3	10.04			
Study duration			0.930			7.46	3	0.059
<6°months	7	27 (19–34)		96.2	7.0			
6–12°months	15	31 (24–37)		97.0	9.21			
>1°year	3	23 (20–27)		-	12.41			
Mean age			0.072			5.76	2	0.056

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TABLE 2 | (*Continued*) Stratified meta-analysis of the prevalence of polypharmacy, hyperpolypharmacy, and potential inappropriate medication (PIM) use in India.

Characteristics	Number of studies	Pooled prevalence in percentage (95% CI)	*p* For interaction[a]	I^2 (%)	Z	Heterogeneity between groups		
<70	9	24 (19–30)		96.7	8.64			
≥70	9	35 (28–42)		93.9	9.66			
Na	9	25 (19–32)		94.5	7.68			
Percentage of female			0.179			1.57	1	0.210
<50%	20	26 (22–30)		96.0	12.92			
≥50%	7	34 (22–46)		96.3	5.74			
Average number of drugs			0.548			4.08	2	0.130
<5.5	4	23 (18–27)		70.5	9.54			
≥5.5	17	27 (22–31)		96.1	12.11			
Na	6	35 (22–48)		97.5	5.31			
Number of PIM use			0.782			0.15	1	0.702
<3	17	27 (23–32)		95.7	11.57			
≥3	10	29 (22–36)		96.8	8.24			
Quality of studies[b]			0.112			5.30	1	0.021
High (≥7)	23	27 (23–30)		96.2	13.50			
Low (<7)	4	37 (29–46)		75.8	8.68			

[a]p-*value from meta-regression analyses,*
[b]*New-Castle Ottawa scale score, PIM: potential inappropriate medication.*

Grouping the studies by various subgroups did not reduce heterogeneity, and no significant difference was observed between the groups (duration of the study, mean age, percentage of females, the mean number of medications prescribed, and the number of PIM identified). However, significant differences in the heterogeneity were observed between low-quality and high-quality studies ($Q = 5.30$, df = 1; $p = 0.021$).

Subgroup Analysis

Subgroup analysis by geographic region, study design, type of hospital, and study settings did not influence the prevalence estimates of polypharmacy, hyperpolypharmacy, and PIM use, as shown in **Table 3**. However, the prevalence of hyperpolypharmacy in outpatient settings (8%) and cross-sectional studies (14%) was low. The prevalence of PIM use varied between inpatient (31%) and outpatient settings (25%); however, lower prevalence of PIM use was reported in government hospitals (25%).

Publication Bias Assessment

The Egger's and Begg's tests indicated statistically significant publication bias for the polypharmacy estimates (Egger test: $p = 0.034$) and PIM use (Egger test: $p = 0.027$ & Begg's test: $p = 0.001$). Visual examination of the funnel plots showed asymmetry and suggested publication bias, as shown in **Supplementary Figure S1**.

DISCUSSION

Overuse and misuse of medications in the older population are among the major concerns in India (Porter and Grills, 2016). The growing culture of irrational and unnecessary prescribing of medications in the older population may increase the risk of adverse outcomes. Multiple studies demonstrated that poor prescribing practices (Chaturvedi et al., 2012), inappropriate medication selection (Boralkar et al., 2011; Castelino et al., 2011), and frequent misuse of drugs to earn profits (Roy et al., 2007; Kotwani et al., 2010) are some of the factors that result in polypharmacy, hyperpolypharmacy, and PIM use in India. In particular, older people with multiple comorbidities are exposed to polypharmacy, and suboptimal prescribing may increase their likelihood of receiving PIMs (Fabbietti et al., 2018).

We assessed the prevalence of polypharmacy, hyperpolypharmacy, and PIM use among the older population through a comprehensive systematic review and reported regional differences in prevalence across four regions in India. Data from 27 studies (11,649 participants) reported a higher prevalence of polypharmacy (49%), hyperpolypharmacy (31%), and PIM use (28%) among the older population in India. Region-specific estimates showed that polypharmacy is widely prevalent in Northern India (72%), hyperpolypharmacy in the eastern and western parts of India (36%), and PIM use (33%) in Western states. Furthermore, polypharmacy is more frequently observed in outpatient settings (57%) and hyperpolypharmacy in inpatient settings (37%). Stratified analysis showed variations in PIM exposure across subsets, and governmental hospitals showed a lower prevalence of PIM use than private hospitals (25 vs. 27%). Considerable variations in polypharmacy and hyperpolypharmacy are seen among cross-sectional studies in comparison to cohort studies.

The regional differences in the prevalence of polypharmacy, hyperpolypharmacy, and PIM use among the older population noted in our study could be due to the inclusion of a limited number of studies, smaller sample size, and differences in socioeconomic conditions, risk factors, and quality of healthcare services across the four regions of India. Two-thirds of the studies were conducted in South India, where the level of awareness of geriatric care and polypharmacy prevalence was very high compared to other regions. The *Sharma et al.* study demonstrated the differences in the prevalence of polypharmacy

TABLE 3 | Subgroup analysis for the potential variables between studies of prevalence of polypharmacy, hyperpolypharmacy and potential inappropriate medication (PIM) use in older population in India.

Subgroups		No of studies	Prevalence (95%CI)	Test for heterogeneity			Between subgroup differences		
				Tau^2	p	I^2	Q	df	p
Polypharmacy									
Geographical region	South India	12	49% (42–57%)	0.0148	<0.01	99%	28.25	4	<0.001
	East India	3	52% (27–77%)	0.0472	<0.01	99%			
	North India	4	39% (22–56%)	0.0298	<0/01	99%			
	West India	1	51% (44–58%)	-	-	-			
	North east India	1	72% (65–79%)	-	-	-			
Study design	Cross-sectional	8	55% (44–65%)	0.0234	<0.01	97%	1.70	1	0.191
	Cohort	13	45% (37–54%)	0.0242	<0.01	98%			
Hospital	Government	8	53% (38–67%)	0.0428	<0.01	99%	0.65	1	0.418
	Private	13	46% (41–52%)	0.0102	<0.01	93%			
Setting	Inpatient	12	43% (35–51%)	0.0168	<0.01	97%	5.11	2	0.077
	Outpatient	7	57% (47–67%)	0.0169	<0.01	97%			
	Both in-and-outpatient	2	56% (26–87%)	0.0472	<0.01	98%			
Hyper polypharmacy									
Geographical region	South India	9	33% (17–48%)	0.0551	<0.01	99%	2.08	3	0.555
	East India	1	36% (27–44%)	-	-	-			
	North India	3	23% (8–39%)	0.0176	<0.01	99%			
	West India	1	35% (28–41%)	-	-	-			
Study design	Cross-sectional	4	14% (6–22%)	0.0059	<0.01	95%	11.65	1	<0.001
	Cohort	10	38% (26–49%)	0.0313	<0.01	99%			
Hospital	Government	3	30% (13–47%)	0.0218	<0.01	99%	0.01	1	0.916
	Private	11	31% (19–44%)	0.0444	<0.01	99%			
Setting	Inpatient	11	37% (26–47%)	0.0305	<0.01	99%	17.44	2	<0.001
	Outpatient	2	8% (0–19%)	0.0058	<0.01	96%			
	Both in-and-outpatient	1	15% (12–18%)	-	-	-			
PIM use									
Geographical region	South India	13	32% (26–38%)	0.0118	<0.01	95%	18.86	4	0.001
	East India	3	23% (21–25%)	0	0.49	0%			
	North India	6	17% (11–23%)	0.0055	<0.01	98%			
	West India	4	33% (24–42%)	0.0071	<0.01	90%			
	North east India	1	29% (21–36%)	-	-	-			
Study design	Cross-sectional	8	27% (18–35%)	0.0127	<0.01	97%	0.16	1	0.693
	Cohort	19	28% (23–34%)	0.0127	<0.01	98%			
Hospital	Government	13	25% (19–30%)	0.0095	<0.01	97%	1.82	1	0.176
	Private	14	31% (24–38%)	0.0166	<0.01	97%			
Setting	Inpatient	15	31% (24–38%)	0.0169	<0.01	98%	2.47	2	0.290
	Outpatient	9	25% (19–31%)	0.0075	<0.01	95%			
	Both in-and-outpatient	3	21% (5–37%)	0.0190	<0.01	98%			

in the Indian states and reported that Uttaranchal (93.1%) from North India and Southern states, such as Telangana (82.8%) and Karnataka (84.6%), had the highest prevalence of polypharmacy compared to Northeast -West Bengal (5.8%), Tripura (East India) (6.8%), Madhya Pradesh (central India) (8.3%) and Goa (West India) (13.8%) (Pravodelov, 2020). While the underlying reasons for the increasing prevalence of polypharmacy are still unknown, our findings highlight the need to develop strategies to reduce polypharmacy in clinical practice and motivate physicians to adopt more judicious prescribing to reduce the number of medications among the older population in India.

Polypharmacy and hyperpolypharmacy are proxy indicators for PIM use in older populations, leading to adverse clinical outcomes. The findings of the current study revealed an increasing incidence of hyperpolypharmacy. The pooled estimates showed a much higher prevalence of hyperpolypharmacy (31%) in India than the developed countries like the United States of America (1%) (Assari et al., 2019), New Zealand (2.1%) (Nishtala and Salahudeen, 2015), Australia (8%) (Wylie et al., 2020), Sweden (18%) (Hovstadius et al., 2010), and Finland (28%) (Jyrkkä et al., 2009). Several review articles suggest that the application of clinical guidelines in the older population may contribute to hyperpolypharmacy (Hilmer and Gazarian, 2008; Scott and Guyatt, 2010; Kojima et al., 2020). However, it is widely recognized that the evidence-based guidelines are derived from clinical trials that generally exclude older patients with comorbidity (Sheridan and Julian, 2016; Guthrie and Boyd, 2018). This research provides vital information to alert clinicians and researchers about the dire need to reduce the medication burden in older people.

Our findings on the pooled prevalence of PIM use showed that 28% of older patients in India are affected by PIM; a similar trend was observed over the years in high-income countries (33.3%) (Liew et al., 2019). This study did not identify potential variations across different

regions ranging from 33 to 36%, except North India (23%). In a recent meta-analysis of studies conducted among older patients in primary care settings, the pooled prevalence of PIM use was 33.3% in high-income countries, varying from 24.8% in North America to 59.2% in Australasians (Liew et al., 2019). In the same study, the prevalence of PIM use in middle-income countries was 23.2%. With the increase in the older population, our pooled results suggest a need for multi-pronged approaches to address PIM use in India. Some approaches include medication reviews by clinical pharmacists and the implementation of a computerized clinical decision support system. Moreover, there is a need to plan broader interprofessional interventions to motivate clinicians to reduce polypharmacy and improve the optimal use of medications in older people. The World Health Organization suggested monitoring and rectifying potential PIM prescribing regularly and prioritizing medication safety at the national level to reduce PIM use in the older population (World Health Organization, 2017).

Findings from this study demonstrate the prevalence of polypharmacy, hyperpolypharmacy, and PIM use in Indian states and highlight the urgency to address inappropriate medication use in the older population. Therefore, future studies with a multi-pronged approach should be conducted, focusing on comprehensive geriatric medication reviews by clinical pharmacists, computerized clinical decision support systems, and prioritizing rational geriatric prescribing at the national level. Moreover, multifaceted randomized controlled trials are needed to evaluate the effects of the intervention on clinically relevant outcomes such as hospitalization, medication costs, and health-related quality of life.

Strengths and Limitations

This is the first systematic review and meta-analyses to consolidate the quantitative evidence on the wide-ranging impact of polypharmacy, hyperpolypharmacy, PIM use in various states of India. We also thoroughly assessed the risk of bias in each of the 27 observational studies. We further conducted meta-analyses stratified according to the suspected potential source of heterogeneity between the studies and subgroups.

The study findings are subject to some limitations. First, factors like geographic areas, cultures, and practices vary widely across the states in India, which may influence the results. Second, higher heterogeneity in the outcomes may be due to differences in sample size (ranging from a few hundred to a few thousand). Low power and precision may produce higher Cochran Q (heterogeneity x^2 test statistics) and I^2. More studies were conducted in South India than in any other region. Third, publication bias was present in the selected studies and has been known to affect heterogeneity. We performed a more stratified subgroup analysis to explore the source of heterogeneity and differences within the subsets.

CONCLUSION

The prevalence of polypharmacy and hyperpolypharmacy among older Indian adults is relatively high. Almost a quarter of the older people are affected by PIM use in India. Significant regional differences exist in the prevalence of polypharmacy, hyperpolypharmacy, and PIM use. These findings highlight the need for urgent steps to promote rational geriatric prescribing and prioritize pharmacist-led comprehensive medication reviews to reduce medication-related problems among older people in India.

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

Conception and design: ASB, RS, KV. Acquisition of data: all authors. Analysis and interpretation of data: ASB, KV, MC, RS, DKB. Drafting the article: ASB, MC, MR. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: ASB. Statistical analysis: ASB, KV, MC, RS. Administrative/technical/material support: DKB. Study supervision: DF.

FUNDING

Research works have been funded by SVV260551 grant of the Faculty of Pharmacy in Hradec Králové, Charles University, Czech Republic (supervisor: Assoc. Prof. D. Fialová). Research works of D. Fialová has been financially supported also by the project InoMed NO.CZ.02.1.01/0.0/0.0/18_069/0010046 "Pre-application research into innovative medicines and medical technologies (InoMed)" co-funded by the European Union; the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant No. 764632; PROGRESS Q42 program at the Faculty of Pharmacy, Charles University, Czech Republic (KSKF-2 scientific group) and I-CARE4OLD Horizon 2020 project ID: 965341.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.685518/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.

frontiers in Public Health

ORIGINAL RESEARCH
published: 25 May 2021
doi: 10.3389/fpubh.2021.695143

"Expecting the Unexpected:" Nurses' Response and Preparedness of Terrorism-Related Disaster Events in Quetta City, Pakistan

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OPEN ACCESS

Edited by:
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Naeem Mubarak, Lahore Medical and Dental College, Pakistan
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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: 14 April 2021
Accepted: 22 April 2021
Published: 25 May 2021

Citation:
Khilji FR, Raziq A, Shoaib M, Baloch NS, Raza S, Iqbal Z, Ishaq R, Haider S, Iqbal Q, Ahmad N and Saleem F (2021) "Expecting the Unexpected:" Nurses' Response and Preparedness of Terrorism-Related Disaster Events in Quetta City, Pakistan. Front. Public Health 9:695143. doi: 10.3389/fpubh.2021.695143

Background: In addition to the psychiatric and societal misery, terrorism places an exceptional burden while delivering healthcare services. Accordingly, a responsive and well-prepared healthcare system ensures effective management of terrorism-related events. Within this context, with a strong historic grounding in addressing situations of societal crisis nurses are well-placed in contributing to the global arena of humanitarian policy and social research. Therefore, assessing their response and preparedness is vital in effective management of a terrorism-related disaster. For that very reason, we aimed to evaluate nurses' preparedness and response toward terrorism-related disaster events in Quetta city, Pakistan.

Methods: A qualitative design was adopted to explore nurses' response and preparedness of terrorism-related disaster events. By using a semi-structured interview guide through the phenomenology-based approach, in-depth, face-to-face interviews were conducted. Nurses practicing at the Trauma Center of Sandeman Provincial Hospital (SPH), Quetta, were approached for the study. All interviews were audio-taped, transcribed verbatim, and were then analyzed for thematic contents by the standard content analysis framework.

Results: Fifteen nurses were interviewed and thematic content analysis revealed five themes. All nurses have experienced, responded to, and managed terrorism-related disaster events. They were prepared both professionally and psychologically in dealing with a terrorism-related disaster. Among limitations, space and workforce were highlighted by almost all the respondents. Lack of disaster-related curricula, absence of a protocol, recurrence of the disaster, and hostile behavior of victim's attendants during an emergency were highlighted as a key barrier toward terrorism-related disaster management.

Conclusion: The skills and expertise needed to address a terrorism-related disaster are well-understood by the nurses but are lacking for various reasons. In addition to the review and adaption of the nursing curriculum specifically for terrorism-related disaster management, collaboration and dialogue between various stakeholders is required to efficiently manage terrorism-related disaster events.

Keywords: medication services, terrorism, disaster, preparedness and response, nurses

INTRODUCTION

Defined as "*an occurrence disrupting the normal conditions of existence and causing a level of suffering that exceeds the capacity of adjustment of the affected community*" (1), disasters are a complex global problem (2). Throughout history, disasters have produced adversative consequences (3) and literature reveals that the prevalence of disasters has risen during the past decades (4). Disasters vary from localized events to large-scale urgencies that cause mass casualties with devastating results and adversely influence the health of a population (5).

Parallel to the natural disasters and emergencies, terrorism-related or man-made disasters have fueled since the 1970s (6). Arise in terrorist-related events throughout the previous decades is reported (4). Although the Global Terrorism Index (7) described a decline of terrorism-related events in recent years, 15,952 global deaths were still reported in 2019. Furthermore, the number of countries affected by terrorism remained high as 71 countries recorded at least one death from terrorism in 2018, the second highest number of countries since 2002 (7). In term of regions, South Asia has had the highest impact from terrorism since 2002, while Central America and the Caribbean region have had the lowest impact. Lastly, the global economic impact of terrorism in 2018 was US $33 billion in constant purchasing power parity, a decline of 38 percent from its 2017 level (7). It should be remembered that the figure is conservative and does not include indirect impacts on business, investment and the costs associated with security agencies in countering terrorism. In addition, there are wide-ranging economic consequences that have the potential to spread quickly through the global economy with significant social ramifications.

Terrorism-related disasters not only cause catastrophic destruction of life and public infrastructures, but also, disrupt normal healthcare delivery and, to a great extent, the ability to cope at all levels with disaster victims. Becker and Middleton highlighted that along with first responders, healthcare institutes and professionals play a central role in addressing the health impacts of terrorism-related events (8). They provide immediate and critical care during emergencies, respond to disasters and preserve the safety of the community (9, 10). As terrorism-related disasters creates chaos and muddle in the society, an effective disaster management plan is needed that can help to alleviate some of the pandemonium wrought by the unexpected event. Correlating terrorism-related events and healthcare system, it is critical that the institutes and professionals are professionally prepared and trained to manage the unfortunate events. Accordingly, disaster management and preparedness of the healthcare system is widely studied in literature (11–13). Since the September 11 terrorist attacks, government agencies and professional societies around the globe have focused greater attention on the importance of healthcare professionals' preparedness and response toward terrorism-related events (14). Within this context, although the Institute of Medicine (IMS) reported improved preparedness and response of emergency departments toward terrorist-related event in the USA, major hurdles and challenges were also highlighted (15). On the contrary, information about the response and preparedness toward a terrorism-related disaster is scarce from the developing world but based on the developed world example (15), we can hypothesize that it is far below satisfaction.

Shifting our concerns to terrorism-related events in a developing country like Pakistan, the country was identified as one of the seriously high overwhelmed states being affected by terrorism-related disasters (16, 17). From 2002 to 2009, Pakistan was considered viable of a 12 percent rise in terrorism across the globe (16). Concerning the Pakistan Institute of Peace Studies (PIPS) security description, the terrorist violence resulted in 19,165 killings of individuals during the years 2003 and 2009 including civilians, officials of law enforcement agencies as well as the terrorists. Additionally, countrywide 2,113 (highest among all) terrorist attacks were acknowledged in the year 2010, which resulted in 2,913 deaths of individuals, and additionally 5,824 were wounded (18). In addition to the economical and societal obliteration, the terrorism-related events always place an additional burden on the already weakened healthcare system of the country. With deprived infrastructure, constraint of human resources and financial limitations (19, 20), healthcare system of Pakistan face additional burden once a terrorism-related event occurs. Under such conditions, it is vital that healthcare institutes and professionals are prepared and trained to manage a terrorism-related event under limited resources and financial constraints otherwise the results can be devastative. Also, understanding the preparedness and management is important in order to effectively handle the disaster in future. However, to the best of our knowledge and through extensive literature review, the information on healthcare professional's preparedness and response to a terrorism-related disaster in Pakistan is not reported in literature. Considering the high incidence of terrorism-related events in Pakistan and scarcity of information on its management, we designed this study to evaluate the response and preparedness of healthcare professionals (nurses) toward terrorism-related events in Quetta city, Pakistan.

METHODS

Study Design and Settings

We adopted a qualitative study design (in-depth, face-to-face interviews). This method is flexible and consents to detailed exploration of respondents' attitudes, experiences, and intentions (21, 22). Also, qualitative studies generate a wide range of ideas and opinions that individuals carry about issues, as well as divulge viewpoint and differences among groups (23, 24). But most importantly, qualitative methods fill the gaps that are left unexposed by survey-based research specifically when it comes to under-discovered research areas (25). Therefore, inline to the objectives of this study, a qualitative design was a unmatched choice for inductive approaches aimed at generating concepts and hypothesis which have far more potential for research than any other models (26).

The study site was the Trauma Center Quetta (TC). Established in 2016 and located within the premises of Sandeman Provincial Hospital (SPH) Quetta, the TC is well-equipped and deals with emergent situations and provides prompt health care facilities 24/7 to the victims of terrorism-related as well as general trauma events (27). Prior to the establishment of TC, the causality department of SPH managed emergencies including the victims of terrorism. The TC is a 30-bedded facility with 24 physicians, 33 nurses, and 7 pharmacists stationed to offer healthcare services.

Study Participants, Criteria, and Sampling

Registered nurses with minimum nursing diploma, stationed and practicing at the TC and consenting to participate in the study were approached for data collection. Based on our objective (nurses involved in managing terrorism-related disaster event), it was apparent to adopt the purposive sampling method (28). Nurses on rotations, stationed in the TC as part-timers and not willing to participate were excluded.

The Interview Guide (Validation, Reliability, and Pilot Study)

The research team constructed a semi-structured interview guide after an extensive literature review (29–33), through expert panel discussion, and experience sharing (34–36). The guide was established with widely framed, open-ended questions that gave enough opportunities to the respondents. Parallel, nurses were also encouraged to provide their own narratives and to share further information relevant to terrorism-related disaster management.

The guide was constructed in the English language and was translated into Urdu (National language of Pakistan) by an independent linguistic expert. The translated guide was back-translated into English to avoid discrepancies by another independent translator (37). With little amendments in translation, the guide was subjected to face and content validity through a panel of experts (senior nurses and physicians) having experience in terrorism-related disaster management. Once the validity was ensured, the guide was piloted with four nurses to ensure that topics to be discussed were at the level that respondents would comprehend with ease. The preliminary data and conclusion confirmed that the discussion topics were enough and appropriately phrased to answer research questions and to minimize validity and reliability threats. As the validity and reliability of the discussion guide was ensured, it was made available for the main study. Data and participants of the pilot study were not included in the final analysis.

We used the triangulation and member checks to establish credibility that contributed to trustworthiness. The data was audited to determine if the research situation applies to the similar circumstances. It was made sure that analysis conducted in a precise, consistent, and exhaustive manner through recording, systematizing, and disclosing the methods of analysis with enough detail to ensure that process is credible.

Interview Procedure, Data Collection, and Analysis

The first author conducted the interviews at the TC. The interviewer carries a Masters degree in practice research and was professionally trained and ensured before the interviews were conducted. Keeping the nature of the study and the ease of the respondents into consideration, the interviews were conducted in Urdu. All participants were briefed about the study objectives before the interviews. A debriefing session was again conducted at the end of the discussion. The interviews started with an ice-breaking session. Probing questions were asked in between conversations to clarify the meanings of responses and to gain insight of the topic being discussed.

Each interview was audio-recorded that lasted for ∼45 min to 1 h. To draw in-depth views, the freedom to express additional reviews and comments was given to the nurses. The second author acted as an observer while the third author assisted in monitoring the field notes, facial expressions and body language that complemented the audio recordings. Interviews were conducted until thematic saturation was reached and no new information was discovered. This redundancy signals to researchers that data collection may cease (38, 39). The interviews were conducted and transcribed the next day in order to ensure that saturation goes parallel. The research team analyzed the recordings (verbatim) and later arranged an informal gathering where nurses were presented with the finalized interview scripts (40). They were asked for confirmation of precision and accuracy of words, ideas, and jargon used during the script analysis. Once confirmed, the transcripts were translated into English by another independent translator for thematic content analysis (41, 42). NVivo® was used for coding and analysis through iterations (43) and inconsistencies were resolved through mutual consensus. All emerging themes and subthemes were discussed among the research team for accuracy and were presented for data inference and interpretation.

Ethical Approval

Institutional review board at the Faculty of Pharmacy and Health Sciences, University of Baluchistan approved the study protocol (UoB/Reg:/GSO/67). Written consent was taken from the respondents before the interviews. The nurses were introduced to the nature of the research prior to the beginning of the interviews, were made secure of the confidentiality of their responses and their right to withdraw from the study.

RESULTS

Demographic Data

Fifteen nurses took part in the interview process out of which 9 (60%) were females. All respondents were practicing as a staff nurse and had a diploma in nursing. Thirteen (86.7%) respondents had an overall nursing experience of fewer than 10 years (median = 8). While talking specifically about working at the TC, 8 (53.3%) had an experience of more than 18 months. None of the respondents was trained precisely in terms of managing disasters as shown in **Table 1**.

Thematic content analysis resulted in five major themes (**Table 2**). The themes and sub-themes are discussed as under.

Theme 1: Terrorism-Related Disaster Event (Experience, Information Source, and Call-Up Mechanism)

Subtheme 1a: Experience of Terrorism-Related Disaster Event(s)

Improvised explosive devices (IEDs) and suicidal attempts on security forces and law enforcing agencies were the most common terrorism-related disasters experienced and reported by the nurses. The incidence of mass shooting at the Bethel Memorial Methodist Church in the city was also mentioned. Summarizing, all respondents had experienced, responded to and managed a terrorism-related disaster at the TC.

TABLE 1 | Demographic characteristics of the respondents.

Characteristics	Frequency	Percentage
Age (years)		
18-27	7	46.7
28-37	8	53.3
Gender		
Male	6	40.0
Female	9	60.0
Education		
Nursing diploma	15	100
Nursing experience (years)		
1-10	13	86.7
>10	2	13.3
Experience at Trauma center (months)		
6-12	5	33.3
13-18	2	13.3
>18	8	53.3
Current position		
Staff nurse	15	100
Specialization		
None	12	80.0
Cardiac	2	13.3
Psychiatry	1	6.6
Specialization in Disaster Management		
None	15	100

> *"I was at routine work at the TC when a suicidal attack was reported. I also experienced the bomb blast in the heart of the city. God! (holding the head in grief) both unfortunate and tragic events resulted in multiple casualties." (Nurse 2, Male)*

Another female nurse (Nurse 4) added that:

> *"I still remember August 2016 where a suicide bombing killed more than 50 people (majority of them were lawyers). The injured list was separate. It was a horrifying condition for all of us."*

Subtheme 1b: Disaster-Related Information Sources and Call-Up Mechanism

Imperatively speaking, as soon as a disaster occurs, healthcare practitioners should be informed promptly so they can respond efficiently and effectively. Therefore, a sound and responsive information management system plays a vital role across the hospitals as well as other affiliating institutes. This allows in reducing economic losses and mitigates the number of injuries or deaths that may result from a disaster. For that reason, the nurses were inquired about their information sources and call-up mechanism once a terrorism-related disaster has occurred.

> *"We have our institutional/departmental WhatsApp groups where updated news and events are shared repeatedly. Additionally, social media and the National News Network is also a prompt source of disaster-related events. Besides, Quetta is a small city and once an unfortunate incidence occurs, the news is spread in no time." (Nurse 1, Female)*

The respondents were also inquired about the call-up mechanism in case of disaster-related emergencies. All off-duty nurses of the TC receive a phone call from the hospital administration in case of a terrorism-related event. Moreover, it is acknowledged that they must report the TC as soon as possible once they have received the unfortunate news through any mean necessary. In short, the information sources and call-up mechanism adopted by the hospital in contacting nurses during an emergency was well-appreciated by the study respondents.

> *"We (nurses of the TC) reside in the hospital premises that is within 5 minutes walking distance when compared to the TC. Normally we will receive a phone call in case of emergencies. Other than that, it is one of our job descriptions to rush and report at the TC as soon as possible. The reporting mechanism is simple, straightforward and effective." (Nurse 8, Female)*

Theme 2: Response Toward the Terrorism-Based Disaster Event

Subtheme 2a: Professional Response

Response includes events and activities that address the short- and long-term effects of a disaster. A prompt and effective response provides immediate support to maintain life improves health and helps in reducing the overall impact of the disaster. Consequently, it is important to understand the response of the healthcare professionals during the time of a disaster. Associating to the responses we received, nurses were confident

TABLE 2 | Schematic presentation of themes and sub themes identified during data analysis.

Theme 1: Terrorism-related disaster event (experience, information source and call-up mechanism)		
Sub theme 1(a): Experience of terrorism-related disaster event(s)		**Sub theme 1(b):** Disaster-related information sources and call-up mechanism
⇩		
Theme 2: Response toward the terrorism-based disaster event		
Sub theme 2(a): Professional response	**Sub theme 2(b):** Personal response	**Sub theme 2(c):** Inclusive response
⇩		
Theme 3: Preparedness of terrorism-related disaster management		
Sub theme 3(a): Current level of knowledge and familiarity of terrorism-related disaster management	**Sub theme 3(b):** Workforce, infrastructure, and supplies	**Sub theme 3(c):** Triage, communication and coordination
⇩		
Theme 4: Barriers toward terrorism-related disaster management		
Sub theme 4(a): Safety concerns and issues	**Sub theme 4(b):** Lack of disaster management content	**Sub theme 4(c):** Lack of drills and hands-on trainings
⇩		
Theme 5: Suggestions and recommendations		

in responding to such terrorism-related disasters in a professional and proficient manner. Based on their disaster management experience and the number of encounters faced, our respondents assured that they are always prepared to respond to an emergency in a timely and specialized manner.

> *"As soon as we are informed about an emergency (or we know it by any means), we arrange and organize essential equipment and supplies at the TC. This includes preparation of the operation theaters, ward beds and availability of the medicine trolleys. We make sure that everything is prepared and ready before the arrival of the victims." (Nurse 4, Female).*

Subtheme 2b: Personal Response

While responding to a disaster, healthcare professionals are also exposed to trauma and may develop post-traumatic anxiety, stress, and depression. This development of adversative conditions can negatively affect their psychosocial well-being. Therefore, it is equally vital to understand the psychological response of healthcare professionals in a hostile condition. Inline to what is being described, nurses of the current study reported a positive response and strong determination while responding and managing victims that are brought to the TC. Also, our respondents stated that they are physically and mentally ready to face any unfortunate condition that may happen at any time.

> *"Once the victims are brought to the TC, the circumstances and environment is beyond explanation. Therefore, we must support the healthcare professionals, victims and their attendees both professionally and generally. We have to overcome the stressful and panic conditions and for that we are always mentally and physically ready." (Nurse 6, Female)*

Subtheme 2c: Inclusive Response

Although our respondents were prepared (both professionally and psychosocially) in dealing a terrorism-related disaster, certain deficiencies were also noted during the interviews. As in other developing nations, healthcare institutes of Pakistan are faced with a non-existence of disaster management response mechanism and system. Hence nurses' response to the

emergencies is based on their past experiences and encounters. Terrorism-related disasters are not predictable by any means, and healthcare institutes can get additional benefit in dealing such disasters if a real-time supporting tool for disaster response is introduced and implemented.

> *"I have read about the emergency response checklists and smart response systems. In my views, implementation of a system at the TC while responding to a disaster can help us to a great extent. Now we are handling the situations based on our experiences and no operating guideline is available." (Nurse 9, Male)*

Theme 3: Preparedness of Terrorism-Related Disaster Management

Subtheme 3a: Current Level of Knowledge and Familiarity of Terrorism-Related Disaster Management

Preparedness is related to the measures taken to prepare for and reduce the effects of disasters. It provides a platform that helps in designing procedures and eventually results in saving lives. Within this context, effective disaster management requires adequate knowledge of the events that is critical for risk reduction. Therefore, assessing disaster management knowledge among healthcare professionals is vital in addressing disaster-related issues. For that very reason, we inquired about the level of knowledge and familiarity of terrorism-related disaster management among our study respondents. Nurses of the current study expressed strong reservations regarding their knowledge and familiarity of terrorism-related disaster management. In continuation, all respondents agreed that there are no training opportunities, nor any seminars/workshops offered that can help in improving their understanding of terrorism-related disaster management.

> *"It is my second year at the TC. Since then I have received no formal training regarding terrorism-related disaster management. There is no information module or written material that can help in improving our knowledge. What we are doing is purely based on our experience gained from handing terrorism-related emergencies." (Nurse 11, Female)*

Subtheme 3b: Workforce, Infrastructure, and Supplies

Another important component while discussing disaster preparedness is the availability of a management framework. However, developing countries are faced with lack of management framework because of limited health budgets, shortage of healthcare professionals, and overburdened healthcare system. The same was explained by the respondents when they were asked about the availability of workforce and infrastructure at the TC. However, the respondents were satisfied with the medicines and supplies that are available at the TC.

> *"We are facing shortage of workforce at the TC. Same goes to the space as it is also limited. In case of a mass disaster we utilize other sections of the hospital. We do not mind going for an extra stretch and to overload ourselves because saving lives is our priority. (Nurse 1, Male)*

While discussing about the medicine and supplies, Nurse 9 (female) explained that:

> *The medicine and supply trolleys are well-prepared by the pharmacists. Normally it is enough to handle 80-90 victims prior to any terrorism-related event."*

Subtheme 3c: Triage, Communication, and Coordination

Triage refers to the order of treatment during a mass disaster. An effectual triage needs an operative and active coordination and communication system that can identify the treatment priorities while managing a mass disaster. Unexpectedly, our responders were unaware of this term and had little or poor knowledge of order of treatment. This is because of their poor knowledge of disaster management (as discussed above) and lack of coordination among different institutes.

> *"Order of treatment! (Confused). As soon as the victims arrive, we manage them according to their needs and severity. We do not have a protocol in determining the order of the patients and frankly we do not have this idea of triage." (Nurse 6, Female)*

Some issues related to lack of coordination and communication was also reported by the respondents. Within the TC, the coordination and communication were satisfactory, however; nurses had some reservation toward other departments of the hospital.

> *"In routine days (other than a disaster event) patients are also referred to TC from causality department. If we can good coordination and communication, it would be much better to manage the patients and to prepare in advance." (Nurse 3, Female)*

Theme 4: Barriers Toward Terrorism-Related Disaster Management

Subtheme 4a: Safety Concerns and Issues

Recurrence of the disaster as well as people' (attendees of the victims) hostile behavior during an emergency was mentioned as a key barrier toward terrorism-related disaster management. Our respondent had serious concerns and displayed major uncertainties as they had experience multiple encounters of the same kind. Such hostile behaviors and actions of the people placed the safety of the healthcare professionals at risk and resulted in the destruction of institutional assets.

> *"Once a terrorism-related event occurs (especially suicidal attack), there are chances of another attack because people will rush to the TC, crowd will gather, so will be an easy target for the terrorists. At the same time, people start agitation and clamoring because of their loved ones is in critical condition. It is very hard to concentrate on job when you have the thought of another suicidal attack on mind and angry crowd here and there." (Nurse 11, Male)*

Subtheme 4b: Lack of Disaster Management Content

Another barrier that was cited by the nurses was absence of subjects related to disaster management in the nursing curriculum as well as during the training period. Practically speaking, the respondents reported to have no idea of disaster management once they start nursing practice at the healthcare institutes. Therefore, the only choice is to follow the practice and to perform what is being practiced at the hospital.

> *"There is nothing about disaster management in the nursing course. We are also not taught about disaster management at the hospital during our residency or regular practice. This is an important subject and we must know about it." (Nurse 14, Female)*

Subtheme 4c: Lack of Drills and Hands-On Trainings

Lastly, absence of disaster drills and hands-on trainings were emphasized as a potential barrier toward disaster management. Openly, there is no concept of disaster drill at the institute nor the nurses have attended any hands-on training or workshop that was aimed to improve their disaster management skills. Drill and hands-on sessions are important as in addition to skill development, it improves the confidence that results in an increased efficiency and efficacy during emergencies and crisis.

> *"The hospital has never arranged training(s) related to disaster management. Unlike other institutes, we never had a mock exercise or drill to improve our response and skills in course of an emergency. It is simple; continue doing what we are doing every day." (Nurse 8, Male)*

Theme 5: Suggestions and Recommendations

Summarizing the replies, all respondents were of the same opinion when they were asked about their suggestion while managing a disaster. Expansion of TC (human resource, space, and supplies), provision of line of instructions, plans and protocols to the employees, training sessions and exercises, and periodical revision and assessment to assure its readiness and preparedness of the TC were key recommendations of the study respondents.

> *"We have long way to go. We need space, healthcare professionals and enough supplies. Besides, the administration must build our skills through continuous training sessions and assure time by time that we are ready to face a disaster in an efficient manner." (Nurse 15, Male)*

DISCUSSION

Terrorism is never meant to kill as many people as possible. Terrorism-related events are planned to instill fear among people, dislocate social function, and perturb the general well-being of societies (44). Manifestations of terrorism-related events at a societal level result in community dysfunction that further reshapes as indiscriminate insecurity hence rupturing of the social fabric (45). While reconstructing infrastructure is relatively easy, the rejuvenation of societies and societal trust is often intricate and uncertain (46). In line with what is being discussed, healthcare system is not exempted from heightened concern when terrorism strikes at a community level. In the nutshell, terrorism impacts individuals, communities, and society on multiple levels and the consequences are devastating in both short and long term.

The current study was aimed to assess the response and preparedness of nurses toward terrorism-related disaster management. We believe that the interviews extracted enough information that was able to answer the questions that were established earlier. Shifting our concerns to terrorism-related events in Pakistan, majority of the terrorism-related activities are reported from the province of Baluchistan (47). For decades, Baluchistan is in continuous unrest and is facing tremendous economic and social harm because of these terrorism-related events. Since the 9/11, Baluchistan remained the worst victim of terrorist attacks in Pakistan as more than 1,000 individuals were killed and 1,570 were injured in 52 major terrorist attacks in the past 12 years (48). Even though a 33% reduction of terrorist-related events was reported in 2019, 145 people still lost their lives and 528 were injured in attacks including bombings, target killings, and landmine blasts (49). The upsurge of terrorism resulted in the establishment of the National Disaster Management Authority (NDMA) in 2005 and subsequently Provincial Disaster Management Authorities (PDMA) in all provinces. Since then, substantial progress has been made in advancing emergency planning and preparedness for terrorism-related events at national and provincial levels. Along with the efforts of NDMA and PDMA, healthcare system of the country has also played a crucial role when providing care and rehabilitation services to the victims. Nevertheless, with all the progress, the state of preparedness and assessment of professional response of healthcare system while dealing with a terrorism-related disaster is unknown. Keeping this limitation of information in mind, the current research aimed to ascertain how responsive and prepared the healthcare professionals (nurses) while managing a man-made disaster are.

Nurses of the current study identified financial constraints, lack of human resource, and deprived healthcare infrastructure as a major barrier while managing a terrorism-related disaster. Because of terrorism, Pakistan's economy has suffered a direct and indirect cost of almost US $126.79 billion (50). Local business and international trade are also adversely affected and resulted in increased inflation and loss of business market share. Furthermore, terrorism also increased government expenditure on security to maintain law and order in the country. This reallocation of government resources decreased expenditure on social sector development and decreased economic growth (50). Although the Government of Pakistan is winning the war against terrorism (51), the country is still facing economical and financial issues that are playing a major role in providing ample facilities to the healthcare system. Nevertheless, the development of a highly equipped TC, appointment of specialized healthcare professionals, and continuous monitoring of the hospitals do reveal the sincerity of efforts while responding and preparing for a terrorism-related event.

Nurses form the backbone of a healthcare system, especially when there is war, conflicts, and disasters (52). Nurses play important roles throughout the therapeutic cycle and are among the first professionals to provide care for people affected by a terrorist attack (53). Therefore, nurses in active war zones, emergencies and dealing with terrorism-related event needs professional training and unique skill set (54). This need is also evident from our study whereby the respondents agreed that without adequate training and protection, they are placing their health as well as the safety of the patients in jeopardy. Correlating the training and development, nursing education is of paramount importance while managing a disaster. Consequently, the nursing curriculum should be sufficiently rationalized with the updated knowledge to effectively respond to terrorism-related disasters (55) which is also reported by the respondents of the current study.

Disasters and other health emergencies such as suicidal attacks, road-side bombings, and other forms of IEDs require tangible plans for management. The International Council of Nurses (ICN) Disaster Management Continuum Model suggests four main components: mitigation, preparedness, response, and recovery (56). The main purpose of this model is to lessen the negative impact on lives and infrastructure, improve recovery, and construct community pliability to disasters (56). Parallel to the ICN, The International Nursing Coalition for Mass Casualty Education (INCMCE) has also developed competencies for all nurses, as well as online modules for meeting competencies while managing a disaster (57). Regrettably, such guidelines or protocol were not known to the respondents of the current study. Our discussion with the senior nurses revealed that as conventional education is provided in the classrooms, nurses are often unaware of such reported guidelines. Additionally, as the job description requires attending the patients' need, least attention is given by the nurses in inquiring new information. As discussed above, a thorough revision of the nursing curriculum and provision of continuous medical education is one way to improve the deficiency and to update the knowledge level of the nurses. It is evident that appropriate education and training of nurses for disasters is important for optimizing the safe functioning and minimizing emotional and psychological damage (18). Competency-based education provides an international infrastructure for nurses to learn about emergency preparedness and response which is seemed to be lacking in the current healthcare system of Pakistan.

Although our respondents agreed that disaster preparedness is highly needed to handle unpredictable calamitous situations effectively, lack of training to work efficiently in disaster management was reported. Our findings are supported by Pourvakhshoori and colleagues whereby the authors also reported poor training of Iranian nurses while managing a disaster (18). It is vital that nurses are aware of effective triage, emergency treatment, evacuation, and reintegrating the victims back to their routine. In addition, nurses should also be trained to take care of the amputations and undertake a life and limb-saving treatment. In the nutshell, basic knowledge and skill set to address terrorism-related emergencies or events is highly important (58). Unfortunately, nurses of the current study were unaware of triage, reintegration, and recuperation that clearly reflect the urgent need of training and development of nurses especially in the context of terrorism-based disaster management.

Healthcare system is an ever-evolving profession and nursing is not an exception. For that reason, regular curricular review and renewal is compulsory in nursing education (59). Continuing education assures continued competence (60) and leads the nurses to combat the chaotic situations. Our qualitative analysis clearly reflected that emergency management should be included in the regular training curriculum of nursing schools in Pakistan and is also backed by the World Health Organization.

CONCLUSION

Nurses are an integral part of healthcare system and play a vital role in responding to and managing terrorism-related disasters. The skills and expertise needed to address a terrorism-related disaster are well-understood but are lacking for various reasons. Interpreting nurses' views through the extracted themes exposed review and adaption of the nursing curriculum specific for terrorism-related disaster management. Furthermore, continuous on-job training and education was also highlighted that will aid in responding and managing the disasters in an efficient manner. Lastly, in-house programs for nurses to learn more about terrorism-related disaster management are needed that will be helpful in preparing them for possible encounters in the future.

LIMITATIONS

Qualitative research is not statistically representative as well as it is difficult to investigate causality. Furthermore, as we targeted nurses of the trauma center, recruiting nurses from other department may provide different results. This is achievable with a mixed methodological study in near future.

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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional review board, Faculty of Pharmacy and Health Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FK, AR, MS, and NB conducted the literature review and developed the interview protocol and the guide. FK

conducted the interviews while RI and SR monitored the process as observers. SH and ZI analyzed and drafted the manuscript, which was subject to critical revision by NA and FS. The study was supervised by FS and NA. All authors read and approved the final manuscript. All authors contributed equally.

ACKNOWLEDGMENTS

The authors would like to acknowledge the nurses for their contribution to the work described in this manuscript. We would also like to thank the hospital administration for their continuous support during the interview process.

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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.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 31 May 2021
doi: 10.3389/fphar.2021.681492

Determinants of Growth in Prescription Drug Spending Using 2010–2019 Health Insurance Claims Data

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Background: Despite policies to manage prescription drug spending and ensure accessibility, prescription drug spending has continued to increase in South Korea. Using nationwide claims data, this study analyzed trends in total pharmaceutical expenditures and pharmaceutical expenditures by drug classification.

Methods: We conducted a retrospective population-based study using the Korean National Health Insurance claims database from January 2010 through December 2019. Pharmaceuticals were categorized as new drugs, continued drugs, and abandoned drugs. Prescription drug spending was calculated using the components of price and quantity for individual products in successive two-year periods, to obviate the need to consider changes over time.

Results: Total pharmaceutical expenditures increased by 54.2% from 2010 to 2019 (from USD 11.3 billion to USD 17.4 billion). The average annual growth rate was 4.9% overall (the 4% rate for continued drugs was decomposed into –3.5% for the price of drugs, 8.0% for the quantity of drugs, and –0.5% for mixed effects, a measure of changes in drug treatment patterns). The trends were generally consistent. Particularly sharp increases in expenditures were found for groups L (antineoplastic and immunomodulating agents), C (cardiovascular system drugs), and A (alimentary tract and metabolism drugs).

Conclusions: Since increased prescription drug spending was primarily driven by an increase in the quantity of drugs used, consumer-focused policies to reduce drug use are necessary.

Keywords: drug spending, price, quantity, determinants, claims database

OPEN ACCESS

Edited by:
Kingston Rajiah, International Medical University, Malaysia

Reviewed by:
Natasa Duborija-Kovacevic, University of Montenegro, Montenegro
Tanja Mueller, University of Strathclyde, United Kingdom

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *17 March 2021*
Accepted: *27 April 2021*
Published: *31 May 2021*

Citation:
Lee H, Park D and Kim D-S (2021) Determinants of Growth in Prescription Drug Spending Using 2010–2019 Health Insurance Claims Data. Front. Pharmacol. 12:681492. doi: 10.3389/fphar.2021.681492

INTRODUCTION

In many countries, healthcare expenditures after the national health insurance system implemented medication coverage have increased faster than GDP and total public expenditures (OECD, 2020). In particular, with the introduction of direct acting antiviral agents for hepatitis C, expensive medications for rare diseases, expensive anticancer drugs, and individualized medications, the financial sustainability of health systems is being threatened (OECD, 2019). Therefore, in most countries, policies have been implemented to curb prescription drug spending, but prescription drug spending remains a challenging issue (Belloni et al., 2016).

South Korea became an aging society in 2000 and an aged society in 2018. It is expected that in 2025, Korea will become a super-aged society, with 20% of the population exceeding 65 years of age (KOSIS, 2019). The Korean government introduced the National Health Insurance (NHI) system in 1989. The NHI currently covers 97% of the population, while the remaining 3% are covered by the Medical Aid Program. Korea has achieved universal health insurance with a fee-for-service system. The list of medicines reimbursable under the NHI is uniformly applied nationwide. The Ministry of Health and Welfare (MOHW) and Health Insurance Review and Assessment Service (HIRA) determine pharmaceutical reimbursements based on a value assessment (health technology assessment, HTA) considering clinical usefulness and an economic evaluation. After unifying several payers into a single payer in 2000, the health insurance system faced issues with fiscal deficits in the early 2000s. Thus, many policies aiming to limit medical and prescription drug spending have been implemented. On the supply side, the positive listing system was implemented in 2007, drug price reduction from 2012 to 2013, price–volume agreement in January 2014, and drug price reduction based on market transaction survey results in March 2016 (Kwon et al., 2015). On the demand side, reviews of doctors' prescription patterns, incentives to reduce prescription drug spending, alternative preparations by pharmacists, patient out-of-pocket payments, and diagnosis-related groups in hospitals were implemented. Simultaneously, in order to improve patients' access to medicines, policies were implemented to expand health insurance coverage. The Korean government reduced patients' co-payments of total healthcare expenditures for four major diseases (cancer, rare diseases, cardiovascular diseases, and cerebrovascular diseases) in 2013 and all diseases in 2018, alleviated decision-making of reimbursement for new medicines, and expanded the scope of benefits, such as other indications of already listed drugs. To increase access to new medicines and reduce the financial burden of health insurance, risk-sharing arrangements between government and pharmaceutical companies have also been introduced since 2013 (Kwon and Godman, 2017).

Rising prescription drug spending has remained a constant issue in South Korea. As a benchmark for comparison, the rate of increase in prescription drug spending in Organization for Economic Co-operation and Development (OECD) countries was 1.6% from 2013 to 2017, but the rate of increase in expenditures was 4.2% for retail pharmaceuticals and 7.9% for hospital pharmaceuticals in 2017 (OECD, 2020). Due to reduced insurance premium income from an aging population and expected economic difficulties from the expansion of health insurance coverage, the financial burden on South Korea's national insurance system is concerning.

It is expected that expensive new drugs will continue to be introduced, so it is necessary for policy-makers to understand factors that drive growth in prescription drug spending and promote efficiency in financial expenditures. Several studies have classified the drivers of increasing drug spending into price, quantity (number of prescriptions), and mixed effects (Gerdtham, 1993; Gerdtham et al., 1998; Dubois et al., 2000; Chernew et al., 2001; Aitken et al., 2009). Mixed effects refer to changes in the types of drugs used for the same injury or disease in the same treatment class (OECD, 2019). However, few studies have examined changes in price and quantity by drug therapeutic classification. Therefore, this study aimed to measure the effects of price and quantity on prescription drug spending from 2010 to 2019 in South Korea.

METHODS

Data Source and Categories

We conducted a retrospective population-based study using the Korean National Health Insurance claims database from January 2010 through December 2019. This database contained information on both in-hospital and outpatient visits from a population of 51.8 million as of 2020. The database includes demographic characteristics, diagnosis, healthcare utilization (visit date, test, procedures, length, and spending), and medicine use (product name, ingredient name, dose, days of therapy, and spending). All claims have been submitted electronically since 2007, and all data files (e.g., type of medical facilities and patients' demographic files) could be linked by unique patient identification numbers.

The analytical unit of this study was medication (different active ingredients and doses). Prescription drug spending referred to total spending, including patient out-of-pocket fees and value-added tax (VAT); this was calculated from the medications listed in the healthcare claims data from the entire population.

We analyzed changes in prescription drug spending according to each dimension using the health insurance database. The analytical dimensions were inpatient/outpatient, type of medical institution, and drug classification. The therapeutic classification followed the World Health Organization Anatomical Therapeutic Chemical (ATC) system (WHOCC, 2020).

Pharmaceuticals were categorized into new drugs, continued drugs, and abandoned drugs. New chemical entities were defined as products manufactured by a single company with an active ingredient that was newly listed in the cumulative health insurance reimbursement list of medicines that year and not claimed in any previous years. Continued drugs were drugs that were included in the reimbursement list and used in a given year and the previous year, and abandoned drugs were drugs that were not used after a given year.

Trend of Healthcare Spending

Trend analysis was conducted using prescription spending, macroscopic indicators such as economic and demographic changes, and the number of listed medicines in health insurance benefit coverage. We collected data on GDP per capita, medical expenditures as a proportion of GDP, and pharmaceutical expenditures as a proportion of medical expenditures from the OECD, and gathered data on the total population and the population above 65 years of age from the Korean Statistical Information Service (KOSIS) for each year.

We analyzed the number of drugs (new drugs, continued drugs, and abandoned drugs), total pharmaceutical expenditures, and pharmaceutical spending per patient by year. We also determined total monthly pharmaceutical spending overall and by sector.

Determinants of Pharmaceutical Spending and Analysis

We analyzed the categories of new drugs, continued drugs, and abandoned drugs. During the 10-year study period, the increase from previous years was calculated using two-year intervals. Prescription drug spending was calculated using the components of price and quantity by individual products. The decomposition equation was as follows. The mixed effect was analyzed by the composition ratio of the main components.

$$\text{Expenditure } (E) = \text{Price } (p) \times \text{Mixed effect} \times \text{Quantity } (Q), \quad (1)$$

$$\frac{E_{T^1}}{E_{T^0}} - 1 = \left\{ \theta^{E_C} \times \left(\frac{E_{C^1}}{E_{C^0}} - 1 \right) \right\} + \left\{ \theta^{E_A} \times (-1) \right\} + \frac{E_{N^1}}{E_{T^0}} \quad (2)$$

where E_{T^0} is the total prescription drug spending in the previous year, E_{T^1} is the total prescription drug spending in the given year, E_{C^0} is the continued drug spending in the previous year, E_{C^1} is the continued drug spending in the given year, E_{N^1} is the new drug spending in the given year, E_{A^0} is the abandoned drug spending in the previous year, θ^{E_C}, (E_{C^0}/E_{T^0}) is the share of continued drug spending in the previous year, and θ^{E_A}, (E_{A^0}/E_{T^0}) is the share of discontinued or abandoned drug spending in the previous year.

Newly listed drugs were chemical substances/doses that were utilized for the first time in a given year and not listed until that year. Although no information was available for quantity in the previous year for new drugs and in the next year for abandoned drugs, we calculated both the price and quantity for continued drugs. In order to examine changes in the price and quantity in continued drugs, a price index and a quantity index for each time period were calculated for continued drug spending. Quantity was defined as the length of prescription. Quantity was subdivided into quantity by the main ingredient and quantity by drug classification (ATC level 3).

To calculate the indices, the Fisher index, which allocates the same weight to the reference time point and the comparison time point, was used (Fisher, 1922). The Fisher ideal index ($I^F = \sqrt{I^I \times I^P}$) is the geometric mean of the Laspeyres index and the Paasche index (Hoekstra et al., 2003), defined as follows:

$$I^P(\text{Price index}) = \sqrt{\frac{\sum_i^m \sum_j^{n_i} p_{1ij} \times u_{0ij} \times q_{0i\cdot}}{\sum_i^m \sum_j^{n_i} p_{0ij} \times u_{0ij} \times q_{0i\cdot}} \times \frac{\sum_i^m \sum_j^{n_i} p_{1ij} \times u_{1ij} \times q_{1i\cdot}}{\sum_i^m \sum_j^{n_i} p_{0ij} \times u_{1ij} \times q_{1i\cdot}}}, \quad (3)$$

$$I^U(\text{Composition index}) = \sqrt{\frac{\sum_i^m \sum_j^{n_i} p_{0ij} \times u_{1ij} \times q_{0i\cdot}}{\sum_i^m \sum_j^{n_i} p_{0ij} \times u_{0ij} \times q_{0i\cdot}} \times \frac{\sum_i^m \sum_j^{n_i} p_{1ij} \times u_{1ij} \times q_{1i\cdot}}{\sum_i^m \sum_j^{n_i} p_{1ij} \times u_{0ij} \times q_{1i\cdot}}}, \quad (4)$$

$$I^Q(\text{Quantity index}) = \left(\frac{E_{C^1}/E_{C^0}}{I^P \times I^U} \right) \quad (5)$$

where p_{0ij} is the price of the jth item in the ith main ingredient group in the previous year, p_{1ij} is the price of the jth item in the ith main ingredient group in the given year, u_{0ij} is the share of the jth item in the ith main ingredient group in the previous year, u_{1ij} is the share of the jth item in the ith main ingredient group in the given year (=share by item), q_{0i} is the total quantity of n_i items that have the ith main ingredient in the previous year, and q_{1i} is the total quantity of n_i items that have the ith main ingredient in the previous year (=total quantity by main ingredient).

The price factor used in the price index was the price per day of the prescription, and the corresponding quantity factor was the length of the prescription. When the composition ratio used to calculate the price index, quantity index, and composition index in the Fisher index was set as the composition within the same main ingredient group, the quantity factor was calculated as quantity by the main ingredient. The list and real prices are almost the same in Korea, and we used the real price from the given year. Although 10 years is quite a long time, we compared expenditures for successive two-year periods to obviate the need to consider inflation. The price index measured the effect of price changes on the increase in prescription drug spending, as the quantity and share in the main ingredient group were fixed at the comparison time point. The composition ratio measured the shift from low-price pharmaceuticals to high-price pharmaceuticals. The impact of the composition ratio on the increase in prescription drug spending was measured by fixing the price and quantity while changing the weight within the main ingredient group.

$$\begin{aligned}&\text{Prescription drug spending } (E_C) = \text{Price per drug (p)} \\ &\times \text{Composition ratio within the main ingredient group (MIX)}, \\ &\times \text{Quantity by main ingredient } (Q) \\ &= \sum_{i=1}^m \sum_{j=1}^{n_i} \left[p_{ij} \times \frac{q_{ij}}{\sum_j^{n_i} q_{ij}} \times \sum_j^{n_i} q_{ij} \right] \end{aligned} \quad (5)$$

where n_i is the number of items in the ith main ingredient group, p_{ij} is the price of the jth item in the ith main ingredient group (= price per day of prescription), $\frac{q_{ij}}{\sum_j^{n_i} q_{ij}}$ is the share of the jth item in the ith main ingredient group, and $\sum_j^{n_i} q_{ij}$ is the total quantity of n_i items that contain the ith main ingredient (= total length of prescription).

RESULTS

Pharmaceutical Expenditures Overall and by Sector

The total population and the population above 65 years of age increased. The proportion of elderly adults increased from 10.7% in 2010 to 15.1% in 2019. GDP per capita, as an economic indicator, increased steadily. Medical expenditures as a proportion of GDP also increased steadily from 5.9% in 2010

to 8.0% in 2019. In contrast, pharmaceutical expenditures as a proportion of medical expenditures decreased steadily from 24.7% in 2010 to 20.0% in 2019.

Total pharmaceutical expenditures increased from USD 11.3 billion in 2010 to USD 17.4 billion in 2019, representing a 54.2% increase. Total healthcare expenditures increased significantly with the introduction of new healthcare diagnostic technology; as a result, pharmaceutical expenditures as a proportion of medical expenditure decreased. The absolute amount of pharmaceutical expenditures decreased until April 2012 and increased thereafter. The average increase per year was 4.9%. Pharmaceutical expenditures decreased due to the drug price reduction policy from 2012 to 2013, but steadily increased since 2014. After the expansion policy of health insurance coverage in 2016, total pharmaceutical expenditures increased. Pharmaceutical expenditures per person older than 65 years increased from USD 0.77 thousand in 2010 to USD 0.96 thousand in 2019, corresponding to an average annual growth rate per year of 2.51%. In contrast, the average annual growth rate of pharmaceutical expenditures per person under 65 years was 3.65% (**Table 1**).

Figure 1 presents the monthly pharmaceutical expenditures, overall, and by sector, between 2010 and 2019. In certain months, expenditures decreased when fewer outpatient visits were made due to holidays. There were major increases in expenditures in the outpatient sector in 2016, 2018, and 2019. Pharmaceutical expenditures jumped in secondary and tertiary hospitals in 2016, 2018, and 2019.

Determinants of Pharmaceutical Expenditures

Table 2 examines the components of total pharmaceutical expenditures (price, quantity, and mixed effects) by categories of drugs (new, continued, and abandoned) and type of healthcare utilization (inpatient or outpatient).

The average rate of increase per year was 4.9%, and it was divided into 1% for new drugs, 4% for continued drugs, and -0.1% for abandoned drugs. For continued drugs, we decomposed the trend into –3.5% for price, 8.0% for quantity, and –0.5% for mixed effects. The contribution of product price steadily showed the effect of reducing drug costs for continued drugs. The only decrease in pharmaceutical expenditures was observed after the reduction in all drug prices in 2012, and the magnitude of the reduction was slight. Although drug prices continued to decrease, the quantity of high-price drugs used steadily increased since 2014, eventually accounting for the largest proportion among the components of pharmaceutical expenditures.

Contribution by Drug Classification

Table 3 shows changes in and contributions to pharmaceutical expenditures (divided into continued, new, and other drugs) by drug classification. Among continued drugs, changes in and contributions to pharmaceutical expenditures increased for most drug groups. Classified using ATC level 1, a large increase was seen for continued and new drugs in groups L (antineoplastic and immunomodulating agents), C (cardiovascular system), and A (alimentary tract and metabolism). When drugs were classified using ATC level 2, the highest increase in total average pharmaceutical expenditures per year was found for C10 (lipid modifying agents), followed by L01 (antineoplastic agents). In ATC level 3, the highest expenditures were found for L01X (other antineoplastic agents), C10 A (lipid modifying agents, plain), and L04 A (immunosuppressants), in a descending order. Among new drugs, the highest annual average increases, and changes were found for groups L (antineoplastic and immunomodulating agents) and J (anti-infective for systemic use) in the ATC level 1 classification. Using ATC level 2, the highest values were found for L04 (immunosuppressants), and using ATC level 3, the highest values were found for J05 A (direct acting antivirals), L01X (other antineoplastic agents), and A10 B (blood glucose lowering drugs, excluding insulins) in a descending order (**Figure 2**). The ingredients with the largest annual growth rate among the continued products were rosuvastatin and ezetimibe (8%), followed by osimertinib (5%), atorvastatin (4%), rosuvastatin (4%), pembrolizumab (4%), and choline alfoscerate (4%). For new drugs, the highest annual growth rate was found for sofosbuvir (2%).

Table 4 demonstrates the continued drugs that had the largest impact on the rate of increase in pharmaceutical expenditures (divided into the components of price, quantity, and mixed effects) by drug classification. Similar to **Table 3**, anomalous trends were only observed from 2012 to 2013, when the drug price reduction policy was implemented, and the trend was similar in other years. ATC 1-level L (antineoplastic and immunomodulating agents) showed a large increase in price. While the prices of groups A (alimentary tract and metabolism) and J (anti-infective for systemic use) were relatively low, the increase in the quantity used was high.

DISCUSSION

This study measured the effects of price and quantity on prescription drug spending from 2010 to 2019 in South Korea by dimension and drug classification. Using the average rate of increase in total prescription drug spending over the 10 years of 4.9% as a reference value (100%), the relative increase was 81% for continued drugs, 21% for new drugs, and –2% for abandoned drugs. The relative change in the price factor was –71% on average, that of the mixed factor of price and quantity was –10%, and that of the quantity factor was 162%.

We found a decreasing trend in price and an increasing trend in quantity, and this result is similar to that of the previous research that the change of prices had a decreasing effect on drug expenditures (Kwon et al., 2015; Jo et al., 2016). This finding appears to be the result of continued policy efforts to reduce drug prices. The use of newer and more expensive products has also been identified in previous studies as a significant cost driver in many drug classes (Gerdtham and Lundin, 2004; Morgan et al., 2004; Soppi et al., 2018). Our

TABLE 1 | Trends in pharmaceutical expenditures and economic and demographic changes by year.

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Change (CAGR) (%)
Demographic changes[a]											
Total population (1,000 population)	49,554	49,937	50,200	50,429	50,747	51,015	51,218	51,362	51,607	51,709	0.47
Population above 65 years of age (1,000 population 65+)	5,288	5,516	5,795	6,057	6,319	6,566	6,790	7,148	7,459	7,826	4.45
Proportion of elderly	10.7%	11.0%	11.5%	12.0%	12.5%	12.9%	13.3%	13.9%	14.5%	15.1%	3.90
Expenditures											
Gross domestic product (GDP) per capita (USD)[b]	23,083	25,100	25,458	27,178	29,242	28,724	29,287	31,605	33,429	31,838	3.64
Total medical expenditures as a proportion of GDP[b]	5.9%	6.0%	6.1%	6.2%	6.5%	6.7%	6.9%	7.1%	7.6%	8.0%	3.44
Total medical expenditures (billion USD)[c]	65	70	74	78	84	92	100	109	119	128	7.82
Total pharmaceutical expenditures (billion USD)	11.3	11.8	11.4	11.6	12.1	12.7	14.0	14.8	16.1	17.4	4.91
Total pharmaceutical expenditures per person (thousand USD, under 65)	0.16	0.17	0.16	0.16	0.17	0.17	0.19	0.20	0.21	0.22	3.65
Total pharmaceutical expenditures per person (thousand USD, 65+)	0.77	0.79	0.74	0.74	0.75	0.77	0.83	0.86	0.91	0.96	2.51
Pharmaceutical expenditures as a proportion of medical expenditures	24.7%	24.2%	23.3%	22.2%	21.4%	20.8%	20.8%	20.4%	20.0%	20.0%	–2.32
Number of medicines											
Total number of products	14,169	13,663	13,580	14,568	15,656	17,361	19,817	20,636	21,134	21,160	4.56
Number of new drugs	–	198	238	259	254	488	395	324	275	232	2.00
Number of continued drugs	13,921	14,715	14,163	14,784	15,860	17,256	19,830	21,054	21,651	22,659	5.56
Number of abandoned drugs	248	248	271	329	228	229	186	372	266	399	5.43

[a]*Korean Statistical Information Service (KOSIS) census data.*
[b]*OECD.*
[c]*Korean Statistical Information Service, update 09-08-2020 (MDY).*
CAGR, compound annual growth rate.

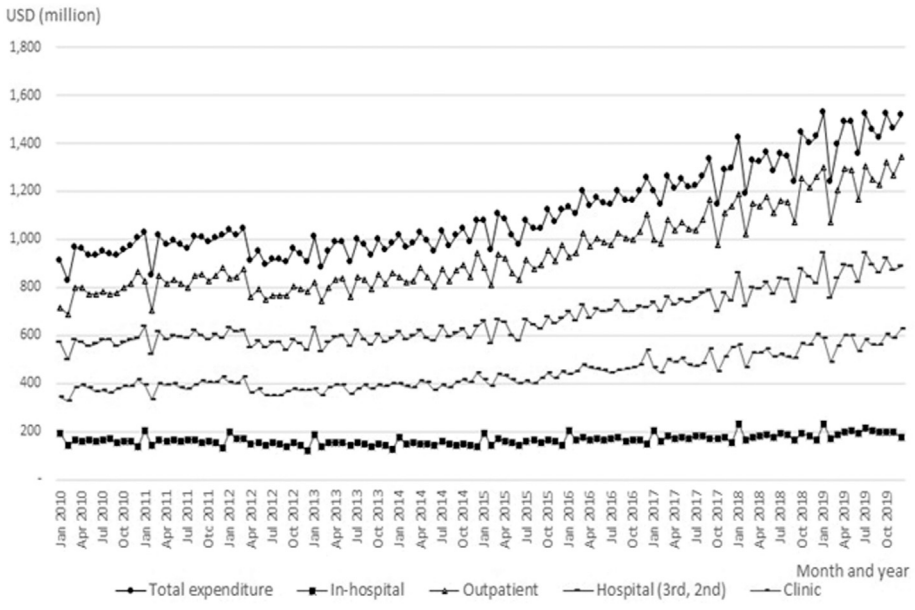

FIGURE 1 | Monthly pharmaceutical expenditures (total and by sector).

TABLE 2 | Contributions to changes in pharmaceutical spending by 2-year periods, overall and by sector (%).

	2010–2011 vs. 2012–2013	2012–2013 vs. 2014–2015	2014–2015 vs. 2016–2017	2016–2017 vs. 2018–2019	Annual average	(Change)
Total Relative increment	−0.74	7.82	16.40	16.09	4.9	(100)
New drugs	1.58	2.19	2.69	1.70	1.0	(21)
Continued drugs	−2.22	5.81	13.77	14.67	4.0	(81)
Price (P)	−16.34	−6.51	−2.19	−3.04	−3.5	(−71)
Mixed effect in the main active ingredient	−1.36	−1.24	−1.09	−0.22	−0.5	(−10)
Quantity (Q)	15.48	13.56	17.05	17.92	8	(162)
Abandoned drugs	−0.10	−0.17	−0.06	−0.27	−0.1	(−2)
Inpatient relative increment	−6.05	1.92	10.77	10.89	2.2	(100)
New drugs	0.62	3.27	1.68	2.64	1.0	(47)
Continued drugs	−6.48	−1.16	9.21	8.48	1.3	(57)
Price (P)	−15.62	−7.45	−4.14	−3.58	−3.8	(−176)
Mixed effect in the main active ingredient	−0.67	−0.45	−0.93	0.01	−0.3	(−12)
Quantity (Q)	9.81	6.74	14.28	12.05	5.4	(245)
Abandoned drugs	−0.19	−0.19	−0.12	−0.23	−0.1	(−4)
Outpatient Relative increment	0.31	8.91	17.38	16.94	5.4	(100)
New drugs	2.09	2.01	4.61	1.56	1.3	(24)
Continued drugs	−1.58	7.10	12.82	15.69	4.3	(78)
Price (P)	−16.80	−6.31	−1.58	−2.94	−3.5	(−63)
Mixed effect in the main active ingredient	−1.50	−1.40	−1.19	−0.24	−0.5	(−10)
Quantity (Q)	16.72	14.81	15.59	18.87	8.2	(152)
Abandoned drugs	−0.20	−0.21	−0.05	−0.31	−0.1	(−2)

Changes were calculated as the annual average.

TABLE 3 | Contributions to changes in pharmaceutical spending by two-year periods for ATC level 1 groups of medicines (%).

	2010–2011 vs. 2012–2013			2012–2013 vs. 2014–2015			2014–2015 vs. 2016–2017			2016–2017 vs. 2018–2019			Annual average			(Change)		
	N	C	A	N	C	A	N	C	A	N	C	A	N	C	A	N	C	A
Total	1.58	−2.22	−0.10	2.19	5.81	−0.17	2.69	13.77	−0.06	1.70	14.67	−0.27	1.0	4.0	−0.1	(21)	(81)	(−2)
A	0.44	−1.27	−0.03	0.43	1.20	−0.13	0.37	2.37	0.00	0.19	2.14	−0.01	0.2	0.6	−0.02	(4)	(11)	(−0.4)
B	0.12	0.09	0.00	0.17	1.02	0.00	0.37	1.55	−0.03	0.10	1.55	−0.09	0.1	0.5	−0.02	(2)	(11)	(−0.3)
C	0.12	0.06	−0.01	0.14	0.73	0.00	0.15	2.59	0.00	0.07	3.11	0.00	0.1	0.8	0.00	(1)	(16)	(0.0)
D	0.01	−0.07	0.00	0.01	−0.11	0.00	0.04	0.43	0.00	0.01	−0.09	−0.02	0.0	0.0	0.00	(0)	(0)	(−0.1)
G	0.06	0.05	0.00	0.03	0.52	0.00	0.07	0.35	0.00	0.02	0.63	0.00	0.0	0.2	0.00	(0)	(4)	(0.0)
H	0.00	0.09	0.00	0.01	0.01	0.00	0.01	0.11	0.00	0.06	0.12	0.00	0.0	0.0	0.00	(0)	(1)	(0.0)
J	0.27	−1.21	0.00	0.18	0.45	0.00	1.14	0.57	0.00	0.41	−0.46	−0.03	0.3	−0.1	0.00	(5)	(−2)	(−0.1)
L	0.25	0.75	0.00	0.86	0.64	0.00	0.35	2.09	0.00	0.60	3.28	−0.05	0.3	0.8	−0.01	(5)	(17)	(−0.1)
M	0.09	−0.62	0.00	0.07	0.25	−0.01	0.03	0.64	0.00	0.11	0.84	0.00	0.0	0.1	0.00	(1)	(3)	(0.0)
N	0.02	0.24	−0.01	0.04	0.76	0.00	0.03	1.37	0.00	0.06	1.90	0.00	0.0	0.5	0.00	(0)	(11)	(0.0)
P	0.00	−0.02	0.00	0.00	0.00	0.00		0.00			0.00	0.00	0.0	0.0	0.00	(0)	(0)	(0.0)
R	0.05	−0.22	0.00	0.09	0.26	0.00	0.04	0.50	0.00	0.02	0.53	−0.02	0.0	0.1	0.00	(1)	(3)	(−0.1)
S	0.12	−0.09	0.00	0.15	0.22	0.00	0.07	0.77	0.00	0.05	0.86	−0.01	0.0	0.2	0.00	(1)	(5)	(0.0)
V	0.02	0.33	0.00	0.02	0.03	0.00	0.02	0.43	0.00	0.01	0.26	−0.03	0.0	0.1	0.00	(0)	(3)	(−0.1)

Changes were calculated as the annual average (based on 7 decimal points).
N, new drugs; C, continued drugs; A, abandoned drugs.
A, Alimentary Tract and Metabolism.
B, blood and blood-forming organs.
C, cardiovascular system.
G, dermatologicals.
H, genitourinary system and sex hormones.
J, systemic hormonal preparations, Excl. sex hormones, and insulins.
M, anti-infectives for systemic use.
N, antineoplastic and immunomodulating agents.
R, musculoskeletal system.
D, nervous system.
L, antiparasitic products, insecticides, and repellents.
p, *respiratory system.*
S, sensory organs.
V, various.

study showed that continued drugs had the largest impact on the growth in pharmaceutical expenditures, followed by new drugs and abandoned drugs, in a descending order.

Among the continued products, mixed effects were found due to changes in treatment trends. This finding is in accordance with results reported in previous studies. The mixed effects had diverging trends in inpatient and outpatient settings. For inpatients, the rate of change was −12%, indicating a shift to lower-price drugs, and for outpatients, the rate was 10%, indicating a shift to higher-price drugs. Previous research found that the quantity of drugs contributed to increased prescription drug spending (Jo et al., 2016; Kwon, Kim, et al., 2015). Jo et al. analyzed data from June 2012 to 2018 and reported that mixed effects accounted for 40–60% within the drug classification category and 30–40% within ingredients (Jo et al., 2016). According to this study, the total mixed effect increased by 21%, while it decreased for inpatients. The contributors to increased prescription drug spending were found to be different by sector. However, quantity increased sharply for both inpatients and outpatients.

By drug classification, the greatest increase was found in groups L, C, and A of ATC level 1. Due to the influx of new medications, spending for antineoplastic and immunomodulating agents (L) such as anticancer medications, anti-infectives for systemic use (J) such as antivirus drugs, and alimentary tract and metabolism (A) such as diabetes medication increased. Among continued medications, spending for antineoplastic and immunomodulating agents (L) such as anticancer medications and cardiovascular system (C) such as antilipidemic drugs increased. However, the prices of alimentary tract and metabolism (A) such as diabetes medication and anti-infectives for systemic use (J) such as antibiotics decreased, but the quantity increased. The mixed effect showed that treatment trends shifted to expensive antineoplastic and immunomodulating agents (L) such as anticancer medications.

Although the absolute amount of pharmaceutical expenditures increased, pharmaceutical expenditures as a proportion of total medical expenditures decreased because total medical spending increased more significantly with the introduction of new diagnostic technology. Moreover, it seems that the ongoing implementation of cost containment policies for pharmaceutical expenditures has stabilized pharmaceutical spending. We hypothesized that aging might drive growth in the quantity of drugs; however, the increase in pharmaceutical expenditures in individuals over the age of 65 years was lower than that in under-65 individuals. This means that the increase in prescription drug quantity and spending was due to changes in treatment patterns or diagnostic technology rather than aging. According to the OECD report "Tackling wasteful spending on

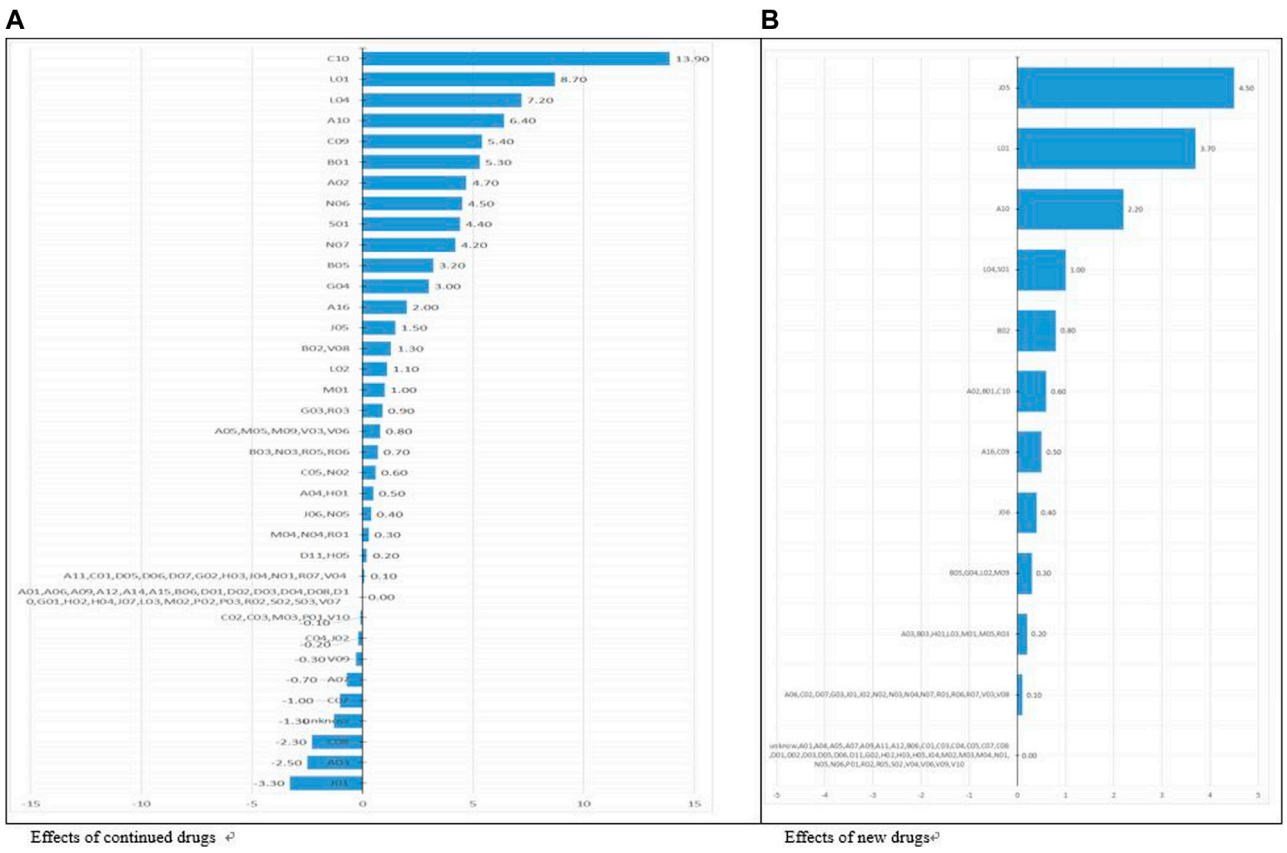

FIGURE 2 | Effects of drugs by categories (continued, new) categorized by ATC level 2 (%).

TABLE 4 | Pharmaceutical expenditures of continued drugs by 12 ATC 1-level groups during the period 2010–2019 (%).

	2010–2011 vs. 2012–2013			2012–2013 vs. 2014–2015			2014–2015 vs. 2016–2017			2016–2017 vs. 2018–2019			Annual average			(Change)		
	Price	**Quantity**	**Mixed**	**Price**	**Quantity**	**Mixed**	**Price**	**Quantity**	**Mixed**	**Price**	**Quantity**	**Mixed**	**Price**	**Quantity**	**Mixed**	**Price**	**Quantity**	**Mixed**
Total	–16.34	21.66	–7.55	–6.51	10.69	1.63	–2.19	8.21	7.74	–3.04	11.22	6.48	–3.5	6.5	1.0	(–71)	(131)	(21)
A	–9.30	–1.35	–0.38	–0.44	8.81	2.81	2.93	2.61	–0.78	–0.26	–0.19	–0.03	–1.4	2.1	–0.2	–29	43	–3
B	0.67	–1.14	–0.25	–0.32	–0.64	2.38	1.92	1.89	0.06	–0.22	–0.12	–0.02	–0.1	0.7	0.0	–3	14	–1
C	0.44	–0.82	–0.41	–0.64	–0.41	1.72	3.20	3.80	0.04	–0.16	–0.20	–0.05	–0.2	1.0	0.0	–4	21	–1
D	–0.51	0.12	–0.07	0.02	0.48	–0.25	0.54	–0.11	–0.04	0.02	–0.03	0.00	–0.1	0.1	0.0	–1	2	0
G	0.34	–0.58	–0.06	–0.13	–0.32	1.21	0.44	0.77	0.03	–0.11	–0.03	–0.01	–0.1	0.3	0.0	–1	5	0
H	0.66	–0.02	–0.02	–0.02	–0.63	0.03	0.14	0.14	0.06	0.00	–0.01	0.00	0.1	0.0	0.0	2	–1	0
J	–8.89	–0.50	–0.09	0.10	8.42	1.05	0.71	–0.56	–0.74	–0.10	–0.05	0.01	–1.2	1.2	–0.1	–24	24	–2
L	5.51	–0.72	–0.33	–0.68	–5.22	1.50	2.58	4.00	0.46	–0.14	–0.17	–0.05	0.5	0.4	0.0	10	7	0
M	–4.59	–0.28	–0.10	–0.17	4.34	0.58	0.79	1.03	–0.38	–0.05	–0.05	–0.01	–0.6	0.8	–0.1	–13	17	–1
N	1.77	–0.86	–0.22	–0.39	–1.67	1.79	1.69	2.32	0.15	–0.16	–0.11	–0.03	0.0	0.5	0.0	1	10	0
P	–0.12	0.00	0.00	0.00	0.11	–0.01	0.00	0.00	–0.01	0.00	0.00	0.00	0.0	0.0	0.0	0	0	0
R	–1.65	–0.29	–0.08	–0.11	1.56	0.60	0.62	0.65	–0.14	–0.06	–0.04	–0.01	–0.3	0.4	0.0	–5	9	–1
S	–0.68	–0.25	–0.12	–0.18	0.65	0.52	0.96	1.05	–0.06	–0.05	–0.06	–0.01	–0.2	0.4	0.0	–3	8	–1
V	2.40	–0.03	–0.07	–0.05	–2.27	0.07	0.53	0.32	0.20	–0.01	–0.03	0.00	0.3	–0.2	0.0	6	–3	0

Notes: Changes were calculated as the annual average (based on 7 decimal points).

A, Alimentary Tract and Metabolism.

B, blood and blood-forming organs.

C, cardiovascular system.

G, dermatologicals.

H, genitourinary system and sex hormones.

J, systemic hormonal preparations, excl. sex hormones, and insulins.

M, anti-infectives for systemic use.

N, antineoplastic and immunomodulating agents.

R, musculoskeletal system.

D, nervous system.

L, antiparasitic products, insecticides, and repellents.

p, *respiratory system.*

S, sensory organs.

V, various.

health," nearly 20–33% of total health expenditures could be deemed wasteful (OECD, 2017). The OECD report stated that low-value care includes over-testing, unnecessary surgical interventions, and the inappropriate use of antimicrobials. To reduce inappropriate use and waste, the OECD suggested that interventions such as performance- and value-based payments, and patient co-payments for low-value care should be introduced (OECD, 2017).

To our knowledge, this is the first study that analyzed the contributors to increased prescription drug spending in the past 10 years in a representative manner. Thus, the results are generalizable. Second, considering that the total study duration (10 years) is a long period, it is meaningful that new, continued, and abandoned drugs were analyzed at two-year intervals, resulting in analytic units of two-year periods, to analyze the effect of each type on increased prescription drug spending. Third, differences in price, quantity, and mixed effects within the drug classification categories were observed. Fourth, the analysis by institution type (inpatient and outpatient) was also a strength. Last, most existing studies discussed contributors to prescription drug spending in terms of price, quantity, and mixed effects, but only one study examined the drug classification. This study explored contributions to recent increases in prescription drug spending by drug classification. However, this study did not consider the daily dose when calculating quantity, since price was defined as the price per day of the prescription and quantity was defined as the length of the prescription. Policy-makers and national insurance administrators should focus more on managing quantity and mixed effects when managing prescription drug spending.

Our study also has several limitations. First, our analysis examined trends due to population aging, but did not correct for this factor by adjusting for patient composition. The increase in the number of elderly population and individuals with chronic diseases is likely to have affected spending significantly. Second, changes in the economy, policies, and system beyond supply and demand aspects may have had a considerable influence on prescription drug spending. The reduction in drug prices that occurred from 2012 to 2014 may have had a major effect on the drop in prescription drug expenditures during that period. The analysis took this timing into consideration, but it was not possible to account for all other policy changes. Third, when calculating prescription drug spending, preparation fees were not included in this study.

In conclusion, after decomposing the increase in prescription drug spending, it was found that the increase was primarily driven by the quantity of continued drugs, so policies to address this issue should be prepared. These are important concerns for a policy when establishing the pharmaceutical policies for rational volume control of continued drugs and deliberate decision-making for the reimbursement of new medicines. Further study is also needed on strategies to reduce the volume of inappropriate use of low-value care.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because access to the dataset is limited. Request to access the datasets should be directed to our institution.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board by Health Insurance Review and Assessment Service (HIRA). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HL: data management, analysis, and writing the draft paper; DP: revising draft; D-SK: design of study, writing, and revising 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.

frontiers in Public Health

ORIGINAL RESEARCH
published: 14 July 2021
doi: 10.3389/fpubh.2021.693409

Do We Need a Specific Guideline for Assessment and Improvement of Acromegaly Patients Adherence?

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OPEN ACCESS

Edited by:
Kingston Rajiah, International Medical University, Malaysia

Reviewed by:
Leandro Kasuki, Instituto Estadual do Cérebro Paulo Niemeyer (IECPN), Brazil
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *10 April 2021*
Accepted: *14 June 2021*
Published: *14 July 2021*

Citation:
Kamusheva M, Parvanova A, Rusenova Y, Vandeva S and Elenkova A (2021) Do We Need a Specific Guideline for Assessment and Improvement of Acromegaly Patients Adherence? Front. Public Health 9:693409. doi: 10.3389/fpubh.2021.693409

Background: Adherence to therapy is one of the most important elements during the therapeutic process ensuring the predefined therapeutic outcomes. The aim is to analyze the need and importance of treatment adherence guideline for acromegaly patients and the possibilities for its development and implementation in Bulgaria.

Methods: A set of methods was applied: (1) a literature review in the electronic database for identification of articles and guidelines related to adherence and acromegaly; (2) analysis of Bulgarian legislative documents; (3) a pilot study for assessment of the level of treatment adherence among hospitalized Bulgarian acromegaly patients in 2018; (4) a plan for development and implementation of specific guideline was created entitled BULMEDACRO - BULgarian guideline for MEdication aDherence assessment and improvement in ACROmegaly.

Results: No specific guidelines for evaluation, monitoring, reporting and/or improving adherence in acromegaly patients has been found in the literature. Requirements for regular assessment of the level of adherence, application of appropriate methods for improvement and monitoring are not sufficiently formulated and mandatory. The pilot study confirmed that therapy adherence among Bulgarian patients with acromegaly is relatively high as almost 90% of patients report that they strictly comply with their prescribed treatment regimen. It is necessary, however, a specific guideline focused on the methods for assessment and improvement of adherence, in order to ensure monitoring and follow-up of acromegaly patients.

Conclusions: Patients with acromegaly should be the focus of specially designed national programs, initiatives and/or guidelines for regular evaluation and improvement of the adherence level. Despite the difficulties and the lack of an adequate legal basis, successive steps initiated by different stakeholder are needed.

Keywords: acromegaly, adherence, Bulgaria, guideline, health policy

INTRODUCTION

Timely and long-term use of prescribed therapy as recommended by the medical specialists is the key to effective control, especially in chronic diseases. A number of studies show that medicines are often not used as prescribed, leading to poor clinical outcomes and higher health care costs. According to published data, ∼50% of patients do not take their medications as per their physicians' instructions (1). In certain potentially asymptomatic diseases, such as hypertension, the incidence of non-adherence might reach 80% (2). Addressing the problems with non-adherence to therapy can improve the quality of health care, support better control of chronic diseases, improve therapeutic outcomes and generally reduce the social and economic burden of disease. Non-adherence is one of the most significant challenges facing healthcare professionals, healthcare decision-makers and researchers. Moreover, a recent study pointed out the need for a specific instruments to assure the medication adherence among patients with non-communicable and other chronic diseases during COVID-19 outbreaks (3).

Critical predictors of adherence are trust, understanding, and effective patient - medical specialist relationship. Adherence is the extent to which the patient's behavior matches agreed recommendations from the prescriber (4). Therefore, achieving optimal behavior is a joint process of communication and understanding between the participants in the therapeutic process. Healthcare professionals can improve their patients' behavior when taking medication on an individual and systemic level using variety of methods and approaches and identifying the factors influencing the level of adherence. Following a specific guideline or algorithm can enhance the level of adherence and prevent the consequences of non-adherence. Patients should be actively involved in decisions related to their therapy and be fully consented and informed of the therapeutic process and procedures (5). Being between treatment and outcomes adherence is a crucial element and factor for achieving the desired therapeutic results (1). As it was stated in a Cochrane review "Interventions for enhancing medication adherence" improving therapy adherence might lead to a greater impact on the outcomes than an improvement in treatments (6).

Acromegaly is a rare endocrine disease affecting 2–11 people per million annually and characterized by oversecretion of growth hormone from benign adenoma of the pituitary gland in more than 95% of all cases (7). Early diagnosis, proper treatment, adherence to prescribed therapy and regular monitoring increase the chances of therapeutic success and reduce the risk of disability. According to an epidemiological study (2010), the estimated prevalence in Bulgaria is around 49 cases/million as the annual number of health insured patients with acromegaly or pituitary gigantism is around 200 (8). According to studies, the most common causes of long-term active disease are the patient's refusal to escalate the therapeutic strategy and non-compliance with prescriptions. In a previous study, we identified that the number of studies assessing the level of adherence, consent and persistence to the therapeutic regimen among patients with acromegaly is limited (9). Moreover, there is a lack of systematically conducted real-life studies assessing the level of adherence among acromegaly patients (10). Considering the lack of awareness, training among healthcare professionals and limited resources for adapting suitable practices for improvement and regular assessment of medication adherence especially during pandemic, relevant and urgent activities in this direction are needed (3, 11). Therefore, our aim is to analyze the need of treatment adherence guideline focused on acromegaly patients, give initial pilot results for the level of treatment adherence among Bulgarian acromegaly patients and present initial statements for further development of such guideline for the Bulgarian healthcare system.

METHODS

A literature review limited to English- and Bulgarian-language guidelines and articles published in PubMed and the electronic database of Central Medicine Library, Medical University of Sofia, Bulgaria between January 2000 and January 2021 using the following key words: acromegaly AND adherence AND guidelines.

Several documents adopted in Bulgaria were analyzed for requirements related to adherence assessment and tools for adherence improvement: Good Pharmacy Practice (2020) (12), Good Healthcare Professionals Practice (2020) (13), Good Medical Practice (2013) (14), National Health Strategy 2020 (15), project of National Health Strategy 2021–2030 (16), Pharmacotherapeutic guideline for treatment of endocrinology diseases approved by National Council on Pricing and reimbursement of medicinal products, annex of Regulation No 16 21.11.2019, Ordinance on the terms, rules and procedure for regulation and registration of prices for medicinal products, 2013 (17), Law on the medicinal products in human medicine, 2007 (18) and National Health Insurance Fund requirements for treatment of acromegaly in ambulatory settings (19).

Based on the current adherence policy, education and practice in Bulgaria and the results from the literature search, a plan for development and implementation of specific guideline was created entitled BULMEDACRO - BULgarian guideline for MEdication aDherence assessment and improvement in ACROmegaly. The content of the guideline was developed on the basis of similar guides already published and implemented in the practice.

A pilot study for assessment the level of treatment adherence among hospitalized Bulgarian acromegaly patients at the University Specialized Hospital for Active Treatment in Endocrinology "Acad. Ivan Penchev," Sofia was conducted in 2018 using patients reports. Patients' records on the regular consumption of prescribed therapy and the reasons for non-adherence were analyzed. Descriptive statistics were used to identify the number of patients adhering to the therapy, their prescribed therapy and demographic characteristics. All patients with acromegaly were asked to take part in the study. They provided signed written informed consent at their admission authorizing the use of their pseudonymized data for scientific purposes. The local hospital ethics committee approved the study (4/09.08.2019).

RESULTS

Literature Review

Adherence is an objective of some researchers or non-governmental organization in Bulgaria but they are focused mainly on socially significant diseases such as diabetes, hypertension, asthma, HIV and chronic obstructive pulmonary disease (20–37). We have not identified any study aimed at analyzing the specifics of adherence among patients with rare diseases. Our previous systematic review (SR) of the scientific literature examined the level of adherence, compliance and persistence and the determinants of non-adherence in acromegaly patients in general (9). Eleven studies, which strengths and weaknesses were assessed through STROBE checklist, were included in this SR based on screening of 165 identified studies in the databases. Study sample sizes range from 1 to 1308 as the adherence rates vary between 60.7 and 92.1% for pegvisomant, 87% for lanreotide depot, and 89% for octreotide LAR. The main factors for non-adherence and loss of follow-up are side effects (100%), lack of symptoms (70.6%), financial problems (5.9%; 89%), medication discomfort (56%) and lack of motivation (23.3%). Acromegaly patients treated with long-acting SSA or pegvisomant have high level of adherence due to convenience of administration, the facilitated treatment regimen and achieving a satisfactory response. The systematic review have not identified any studies on Bulgarian acromegaly patients level of adherence and emphasizes the need for more adherence studies among heterogeneous subgroups of patients on different therapeutic regimens - mono- or combination therapy, as well as in more detail exploring the possibilities of using interventions to optimize adherence (9, 38–48).

A consensus on issues regarding therapy of acromegaly is developed in Spain in 2018. The experts agreed on that acromegaly patients should be informed about the therapy costs for the purposes of assuring treatment adherence. It is emphasized that education is one of the main factors for achieving successful treatment and provision of high level of adherence to treatment (49). Clinical guideline on "*Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence*" was developed by National Institute for Health and Care Excellence (NICE) and published in 2009. It is not focused on specific disease but gives the main principles and methods for patients involvement in the therapy and limiting the risk for non-adherence (4, 50). However, no separated guidelines for evaluation, monitoring, reporting and/or improving adherence in acromegaly patients has been found in the literature. Plunkett and Barkan developed a dialogue map involving patients, nurses, and physicians for the purposes of optimization and improvement of treatment initiation, adherence, and persistence in acromegaly patients (51). The authors highlighted the importance of education programs and communication for achieving the therapeutic goals (51).

Bulgarian Policy and Adherence Guidelines

Adherence issues are not in the focus of most of policy or legislative documents in Bulgaria. Requirements for regular assessment of adherence level and application of appropriate methods for improvement and monitoring are not sufficiently formulated and mandatory. The issues related to treatment adherence are mentioned at different level in several documents (**Table 1**):

1. The Ordinance on the terms, rules and procedure for regulation and registration of prices for medicinal products from 2013 requires data for adherence improvement only for the purposes of Health Technology Assessment for any new medicinal product-candidate for reimbursement.
2. According to the National Health Insurance Fund (NHIF) requirements for treatment (initiating and continued) of acromegaly in ambulatory settings adopted in 2020, acromegaly patients should declare and sign written informed consent that they will follow the prescriber recommendations and not change arbitrarily the prescribed therapy paid by the NHIF.
3. Good Pharmacy Practice define the role of the pharmacists in the process of treatment but without giving any algorithms and without providing the best practices for assessment and improvement of adherence. In case of initiation of therapy the pharmacists should check whether the patient understands the type of prescribed therapy and how to take it. During the follow-up period the pharmacists should monitor whether the patient takes the therapy as it was prescribed by the physician. Moreover, the pharmacist ensures adequate education and information and assist for solving of various drug-related problems.
4. Good Medical Practice states the physicians' responsibilities to inform their patients about all risk and benefits associated with the prescribed therapy, to inform patients in a way they understand and make sure that the patient understands the benefits and risks of the treatment as well as to ensure effective communication with their patients for achieving efficient care and for establishing a relationship of trust.
5. According to Good Healthcare Professionals Practice, all health care specialists (nurses, midwives etc.) should participate in collection, storage and analysis of information, which is the basis for periodically evaluate the quality of health care and use the analysis to improve their practice.

Adherence Among Bulgarian Patients With Acromegaly

The study included all patients with acromegaly ($n = 130$) treated at the University Hospital "Acad. Ivan Penchev", Sofia in 2018, and to whom pharmacotherapy was applied. Patient characteristics are presented depending on adherence to therapy. 89% ($n = 116$) adhere to and regularly take their prescribed therapy. Only 14 patients (11%) reported irregular drug therapy for various reasons, the main of which were administrative barriers (lack of therapy on the market, most likely due to export issues) (**Figure 1**). Financial difficulties and pregnancy have been cited as causes by two patients. For half of the patients, the cause of non-adherence was not identified. Half of those who do not adhere to drug therapy were men with a mean age of 50.43 years and 50% - women with a mean age of 52 years. The average duration of the disease in the two groups (adherent and non-adherent) was

TABLE 1 | Analyzed policy documents.

Document	Objectives	Adherence issues
Good medical practice, 2020	A set of rules for diagnostic and therapeutic activities in making diagnostic and treatment decisions by physicians.	✓ The term "adherence" is not mentioned; ✓ Effective communication with patients related to prescribed therapies.
Good healthcare professionals* Practice, 2020	Based on the ethical aspects and the professional behavior of healthcare professionals	✓ The term "adherence" is not mentioned; ✓ Nurses inform patients for the procedures and treatment and provide education for patients and their relatives ✓ Include patients in making decision for the provided health care activities.
Good pharmacy practice, 2020	Provision of high standards for pharmaceutical care. Contains rules for professional attitude of pharmacists to patients, self-control etc.	✓ The term "adherence" is not mentioned; ✓ Initiation of therapy - The pharmacists should check whether the patient understands what therapy is prescribed and how to take it; ✓ Continued therapy - The pharmacists should monitor whether the patient takes the therapy as it was prescribed. ✓ The pharmacist ensures adequate education and information. ✓ The pharmacist assist for solving of drug related problems.
National health strategy, 2020	Strategic document that specifies the goals for healthcare system development (till 2020)	✓ The term "adherence" is not mentioned; ✓ Centers for prevention, diagnosis, treatment, follow - up and rehabilitation of patients with specific diseases. ✓ Goal is to implement the concepts of pharmaceutical care, consulting patients for prescribed medications. ✓ Programs for rational medicines use.
National health strategy, 2021–2030 (project)	Strategic document that specifies the goals for healthcare system development (2021–2030)	✓ The term "adherence" is not mentioned; ✓ M-Health and e-Health are priorities stated in the National Drug Policy. ✓ Improving access and sharing treatment data for statistical, research or treatment purposes and encouraging patient feedback on the quality of healthcare services.
Pharmacotherapeutic guideline for treatment of endocrinology diseases, 2019	Evidence-based algorithm for treatment of endocrinology diseases (incl. acromegaly)	✓ The term "adherence" is not mentioned;
Law on the medicinal products in human medicine, 2007	Legislative framework for the pharmaceutical sector	✓ The term "adherence" is not mentioned; ✓ The pharmacy is defined as a health establishment for giving consultation.
Ordinance on the terms, rules and procedure for regulation and registration of prices for medicinal products, 2013	Rules for pricing of medicines, procedure for inclusion of medicines in the Positive Drug List, monitoring the effect of therapies, requirements for HTA	Mentioned in Annex 6 to Article 35, paragraphs 3 and 6 "Guidance on requirements for the contents of the Health Technology Assessment analysis:" *"The added value of the therapy with the new health technology, such as improved safety,* ***improved adherence to the therapy*** *compared to alternatives, as measured using specific clinical indicators against existing alternatives, must be clearly justified."* *"All adverse events of clinical or economic relevance (e.g., affecting patients' quality of life, mortality,* ***adherence to therapy****) should be included in the analysis…"*
National health insurance fund requirements for treatment of acromegaly in ambulatory settings, 2020	Includes criteria for initiating therapy with Octreotide, monitoring and continued treatment with Octreotide, Pegvisomant or combination therapies	✓ Declaration signed by patients for following the therapy plan and not changing the therapy; ✓ No defined tools/strategies for assessing adherence.

**Nurses, midwives, pharmacy assistants, etc.*

comparable: 10 and 8.5 years. The number of comorbidities and the type of therapy was also comparable between the two groups – respectively, 3 and 2 concomitant diseases; 68% of adherent patients and 79% of non-adherent were on monotherapy; 32 and 21%, respectively, were on combination therapy (**Table 2**).

Logically, statistically significant more patients who followed the prescribed therapy achieved complete remission compared to non-adherent patients: 93.18 vs. 6.82% ($p = 0.001$). Similar results were observed for remission rate and retention level, as adherence to therapy logically provided a higher response rate ($p = 0.0005$).

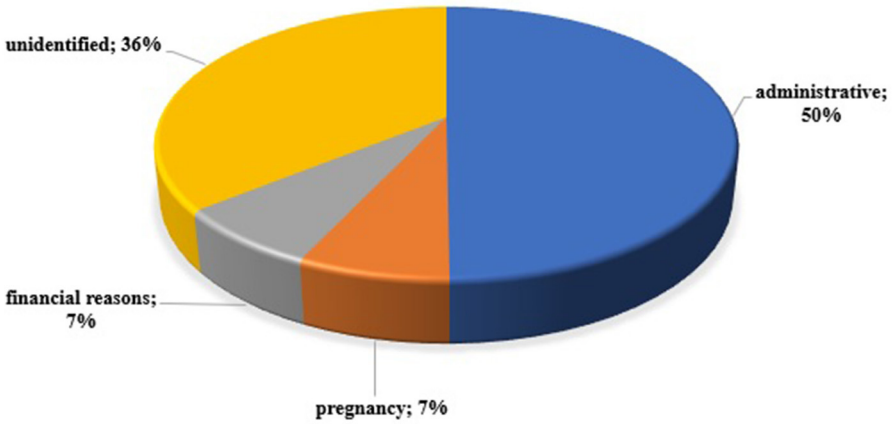

FIGURE 1 | Reasons for non-adherence in the pilot study among acromegaly patients.

TABLE 2 | Patients' characteristics.

	Patients (%)	Men	Average age - men (years)	Women	Average age – women (years)	Disease duration (years)	Concomitant diseases - average number	Patients on monotherapy	Patients on combination therapy
Adherence	89%	35%	48.7	65%	55.76	10	3	68%	32%
Non-adherence	11%	50%	50.43	50%	52	8.5	2	79%	21%

Structure and Content of Bulmedacro - Bulgarian Guideline for Medication Adherence Assessment and Improvement in Acromegaly. Draft Version

The Guideline is intended for healthcare professionals (physicians endocrinologists, pharmacists, nurses) and should be created on the basis of wide consensus of all involved stakeholders - patients organizations and professional organizations representatives (physicians, pharmacists, and nurses). The final content of the guideline should be based on studies specifically designed for the Bulgarian population and addressing the beliefs, attitudes of patients and healthcare professionals about the best possible adherence assessment and improvement instruments and tools suitable for the heterogenous acromegaly patients' groups. The guideline should include more details on the nature and importance of adherence measurement and improvement and should define each specific role of the healthcare professional in the process. Collecting and reporting the level of adherence should be in compliance with good practices for documenting and publishing of results of real-life studies involving patients (**Table 3**).

DISCUSSION

The documents identified in the results section give very briefly some legislative basis for provision of regular assessment and improvement of the adherence level among different patients groups. This fact is in contrast with NICE practice where detailed guidelines on medicines adherence and medicines optimization have been implemented with recommendations on the best practice among all patient populations and healthcare settings (52). However, NICE's guidelines do not include specific recommendations on strategies applicable for adherence assessment and improvement for any specific diseases or conditions. Marie-Schneider highlighted the increased need of continuing development and adoption of national policies which support medication adherence considering the important role of the pharmacists in delivering a service to the patients. Moreover, in countries such as Australia, Spain, Denmark, Finland, US, Switzerland and England a number of diseases-specific or generic programs for supporting medication adherence exists. In England, USA and Switzerland, programs related to medication adherence motivation and consultation with the active role of pharmacists have been adopted (53). Some states of the USA have implemented policies and requirements for reimbursement of adherence activities performed by pharmacists (54). The need for further development of more tools and algorithms for adherence assessment and improvement with the active participation of community pharmacists has been recognized by Rickles et al. (55). In Bulgaria, no specific adherence policy documents have been developed, published or adopted in the practice which determines the importance of further discussions, conferences and expert debates. Focusing on the issues of adherence is crucial

TABLE 3 | Draft version of BULMEDACRO content.

Parts of the guideline	Content
Introduction and scope of the guideline	Who is it for? Why do we need a guideline? What is the scope?
Adherence - essence and basic principles and characteristics	What is adherence? Which are the main components of adherence (initiation, persistence, and discontinuation)?
Other terms - compliance, concordance	Definitions and characteristics of the other terms used in the literature
Acromegaly	Clinical manifestation, epidemiology in Bulgaria
Acromegaly treatment	Main therapeutic approaches and their specifics
Systematic review of adherence studies among acromegaly patients	Identification and analyzing the studies published in the literature
Methods for adherence assessment among general population	- Indirect methods - Direct methods
Preferred methods for adherence assessment among acromegaly population	Which methods for assessment are the most suitable for acromegaly patients?
Approaches for improvement patients adherence among general population	- Education; - Dosing aids: calendar blister packages, pill boxes, Webster-packs; medication calendars, reminder charts; - Regimen simplification; - Direct communication with health providers; - Adherence reminder aids such as modern technology devices etc.
Approaches for improvement patients adherence among acromegaly population	Which methods for improvement are the most suitable for acromegaly patients? How to involve patients in the process?
Algorithm for healthcare professionals (physicians, pharmacists, nurses) behavior for regularly adherence assessment and improvement in different groups of acromegaly patients	- Newly diagnosed patients on monotherapy - Patients on combination therapy - Patients who switched their therapy
Collecting and reporting the results	Following the GDPR rules
Annexes	Schemes, tables etc. of applicable methods for assessment and improvement of adherence

in order to avoid future complications and to achieve the desired outcomes with minimum additional public resource. According to data from a cross-sectional survey among 24,000 adults with chronic illness, more than half of them forgot to take medications and almost 40% had stop treatment within a year (56). Having in consideration these data and the fact that no detailed information for the adherence level among Bulgarian population exists, the need for adequate national disease-oriented adherence policy could be defined.

Undoubtedly, the initiation of procedure for development and implementation of BULMEDACRO - BULgarian guideline for MEdication aDherence assessment and improvement in ACROmegaly is crucial. Despite the available texts in the identified legislative documents, not clearly defined tools or instruments for regular assessment and improvement of medication adherence are described. Draft documents based on consensus among patients representatives groups (patients organizations), medical specialists (general practitioners, endocrinologists, nurses, pharmacists) and academia should be prepared and published in order to create a basis for initiating a process of medication adherence guidelines, national programs or initiatives development by the responsible legislative bodies. Further studies for the level of adherence of various patients groups, existing barriers or challenges experienced by the patients for actively involvement in the therapeutic process, the physicians' attitude to the adherence issues and the best possible approaches for adherence levels improvement among acromegaly patients in Bulgaria should be conducted. Based on the studies results, more comprehensive analysis could be done and after discussions, round tables and shared experience, a comprehensive guideline could be developed. The legislative issues for adopting the guideline are complex and related mainly with the lack of specific normative texts stating the obligation of developing and adopting of such guidelines. Moreover, broader perspective for development of national adherence policy covering the whole health system should be considered by identifying the current level of adherence among different patients groups, the barriers for optimal adherence and the approaches for improvement. Having the main direction for adherence assessment and improvement, a disease-specific approaches could be developed, discussed and implemented by experts (11).

To the best of our knowledge, no similar studies among Bulgarian patients with acromegaly have been conducted. Moreover, the Bulgarian society awareness about medication adherence issues is still very poor. Therefore, our study emphasized the importance of adherence and the need for implementation of policy and national guidelines. This pilot study showed that acromegaly patients adherence to therapy is relatively high. Almost 90% of the patients reported that they strictly follow the prescribed treatment regimen. The main barrier to adherence in the study period was the

lack of medicines. Most likely, this was due to the parallel export of somatostatin analogs, which makes it difficult for patients to access, and hence the possibility of adequate adherence to therapy. Our previously conducted systematic review based on a systematic search in the Internet-based scientific databases PubMed, Google Scholar, Bioseek, aimed at assessment the level of adherence, compliance or persistence with therapy or therapeutic regimen in acromegaly patients, concluded that treatment with long - acting SSA or with pegvisomant leads to high level of adherence. The main reasons for the high level of adherence is due to the ease of administration, facilitated treatment regimen, and satisfactory response (9). A follow-up nationally-based study among acromegaly patients using more specific tools to assess the level of adherence is needed. Following-up the level of adherence should be defined as a significant part of the whole therapeutic process.

The main limitation is the pilot character of the adherence assessment study and not applying more specific instrument for adherence assessment. Moreover, some patients might be lost to follow-up and therefore the total number of patients with low or no adherence could be higher. Further detailed study on adherence among acromegaly patients using specific instruments is required. The structure of BULMEDACRO guideline gives only brief overview of the possible elements included inside the document. Wider discussions and involvement of more experts in the field would lead to improvement of the guideline structure and its future content. However, our study is the first Bulgarian one focused on the adherence issues among specific patients groups with rare condition. Therefore, the study could be used as an initial step for further investigations and improvements in the field of adherence assessment and management.

CONCLUSIONS

Adherence to therapy is one of the most important elements of the therapeutic process ensuring desired therapeutic outcomes. Neglecting its importance for the individual patients and for the whole society, could lead to additional costs for complications, hospitalization, decreased quality of life and lack of clinical improvement despite the innovative and expensive therapies for which the society pays billion euro annually through its public funds. Patients with rare diseases should be also in the focus of specifically developed national programs, initiatives and/or guidelines for regularly assessment and improvement of adherence level. Despite the difficulties and lack of adequate legal basis, successive steps initiated by different stakeholder are required.

DATA AVAILABILITY STATEMENT

Data are available from the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee in USHATE Acad. Ivan Penchev, Medical University-Sofia, Bulgaria (approval number 4/09.08.2019). Written informed consent for study participation was obtained from the patients/participants. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK, YR, SV, AE, and AP carried out the research. MK and YR drafted the manuscript. MK, YR, and AP entered the patients' data in a database. MK, AE, and SV participated in the study design and reviewed the paper. All the authors have provided valuable contributions to the manuscript, read, and approved the final manuscript.

FUNDING

This work was supported by the Bulgarian Ministry of Education and Science under the National Program for Research Young Scientists and Postdoctoral Students.

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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.

frontiers in Public Health

ORIGINAL RESEARCH
published: 10 August 2021
doi: 10.3389/fpubh.2021.703631

Public–Private Mix Models of Tuberculosis Care in Pakistan: A High-Burden Country Perspective

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Introduction: Pakistan ranks fifth in the globally estimated burden of tuberculosis (TB) case incidence. Annually, a gap of 241,688 patients with TB exists between estimated TB incidence and actual TB case notification in Pakistan. These undetected/missed TB cases initiate TB care from providers in the private healthcare system who are less motivated to notify patients to the national database that leads to significant underdetection of actual TB cases in the Pakistani community. To engage these private providers in reaching out to missing TB cases, a national implementation trial of the Public–Private Mix (PPM) model was cohesively launched by National TB Control Program (NTP) Pakistan in 2014. The study aims to assess the implementation, contribution, and relative treatment outcomes of cohesively implemented PPM model in comparison to the non-PPM model.

Methods: A retrospective record review of all forms (new and relapse) patients with TB notified from July 2015 to June 2016 was conducted both for PPM- and non-PPM models.

Results: The PPM model was implemented in 92 districts in total through four different approaches and contributed 25% (81,016 TB cases) to the national TB case notification. The PPM and non-PPM case notification showed a strong statistical difference in proportions among compared variables related to gender ($p < 0.001$), age group ($p < 0.000$), and province ($p < 0.000$). Among PPM approaches, general practitioners and non-governmental-organization facilities achieve a treatment success of 94–95%; private hospitals achieve 82% success, whereas Parastatals are unable to follow more than half of their notified TB cases.

Discussion: The PPM model findings in Pakistan are considerably consistent with countries that have prioritized PPM for an increasing trend in the TB case notification to their national TB control programs. Different PPM approaches need to be scaled up in terms of PPM implemented districts, PPM coverage, PPM coverage efficiency, and PPM coverage outcome in the Pakistani healthcare system in the future.

Keywords: infectious disease control, healthcare system, lower middle income countries, health policy & practice, global health, public health

OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Babar Tasneem Shaikh, JSI Research & Training Institute, Pakistan
Lawrence Ulu Ogbonnaya, Ebonyi State University, Nigeria

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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *30 April 2021*
Accepted: *09 July 2021*
Published: *10 August 2021*

Citation:
Ullah W, Wali A, Haq MU, Yaqoob A, Fatima R and Khan GM (2021) Public–Private Mix Models of Tuberculosis Care in Pakistan: A High-Burden Country Perspective. Front. Public Health 9:703631. doi: 10.3389/fpubh.2021.703631

INTRODUCTION

Despite management advances in the 21st century, tuberculosis (TB) remains the leading cause of death from curable infection worldwide (1). The world population is 7.7 billion, and one-fourth (1.7 billion) of the global community is estimated to be latently infected with TB (2), which makes it the 10th leading cause of death worldwide (3). Among the infected population, Pakistan ranks fifth in the global TB burden (4). In 2019, there was an estimated number of 570,000 incident cases, an actual number of 328,312 notified cases who started treatment under national TB management guidelines, and 241,688 missed TB cases in the Pakistani community (4).

To narrow the gap between estimated and notified TB cases in high-burden countries including Pakistan, the WHO has recommended a model of TB care, which is termed as Public–Private Mix (PPM) intervention. PPM refers to engagement by the National Tuberculosis Control Program (NTP) of different countries with private sector providers of TB care in those countries (5). However, NTP Pakistan in 2005 achieved 100% coverage of WHO-recommended Directly Observed Treatment Short Course Therapy (DOTS) in all health facilities within the public sector (6). But, the PPM model was launched on a pilot scale in 2004, and this initiative was area-specific only (7).

After almost a decade of pilot-scale engagement of the PPM model in Pakistan, WHO reported that a gap of 3.3 million TB cases exists between estimated incidence and notified cases across the globe and Pakistan alone, was contributing 7% to this globally estimated gap. This was evident because the Pakistan TB case detection rate in 2013 was standing at 58% and it was missing 42% of the estimated number of incident cases (8). Viewing the undiagnosed cases with active TB that can transmit the disease into 30–50% of their extended contacts (9), missing cases burden was a public health challenge for NTP stakeholders.

To address this challenge of the under-detection of TB cases, NTP in 2014 mobilized exploratory research studies on improving the case detection rate in Pakistan. National TB prevalence survey and capture–recapture study of private-sector TB facilities in Pakistan indicated under-reporting of detected TB cases and under-diagnosis (10, 11). It was also documented that the treatment of diagnosed TB cases in the private sector may be non-adherent to NTP guidelines (12). Since the motivation of private providers to manage TB in clinics varies, so treatment attrition rates are high, and intermittent TB case management practices can lead to the emergence of drug-resistant TB cases in the Pakistani healthcare system (13). Finally, analysis of area-specific PPM implemented projects between 2004 and 2009 suggested that sustained, extended involvement of PPM approaches is required in the country followed by large-scale quantitative and qualitative studies for assessing the efficacy and cost-effectiveness of these implemented models (14).

During the ongoing exploratory research, the NTP annual report 2014 also indicated that the involvement of a private stakeholder in TB care in Pakistan is quite large and diverse. They are not only limited to formal providers like private general practitioners but also include informal providers like pharmacists, nurses, chemists, and philanthropists. This list also adds up semigovernment and large private hospitals, non-governmental organizations (NGOs), insurance agencies, community and religious leaders, researchers, and industries involved in mineral resource extraction (15).

The above list of private stakeholders and exploratory research findings triggered NTP to intensify collaboration with private providers in TB care. This led to extending the *ad hoc*-scale functioning of PPM toward the cohesive, large-scale implementation of the PPM model in 2014. The NTP team then defined the following four approaches for implementing the PPM model at the national level: solo general practitioner (GP) model, run TB care facility model of NGOs, private hospital models, and other public sector (Parastatal) models. All four approaches of PPM were categorized shortly as PPM-1, PPM-2, PPM-3, and PPM-4, respectively (15).

Once adopted in 2014, overall, the contribution of PPM intervention to TB case notifications and outcomes is known; however, the individual contribution of different PPM approaches at a large scale is not documented. Given the varied TB stakeholders in the Pakistani arena, testing which PPM models contribute the most and which models work in particular geographic settings is important; these data can help in national TB-related program planning. Based on this rationale, we designed a study to assess the contribution of four approaches of the cohesively implemented PPM model toward the national TB case notification. The objectives were specifically to explore the implementation mechanism of different PPM approaches in all four Pakistani provinces, to determine the proportion of TB cases notified by the implemented PPM approaches (private sector) in comparison to the non-PPM model (public sector) in program data of NTP, and to compare the relative treatment outcomes of PPM-notified cases to non-PPM TB cases.

MATERIALS AND METHODS

Study Design

A descriptive cross-sectional study based on the retrospective review of routinely collected NTP data from July 2015 to June 2016.

Study Context

All four provinces (i.e., Punjab, Sindh, Khyber Pakhtunkhwa, and Balochistan) of Pakistan. A total of 122 districts (36 in Punjab, 29 in Sindh, 25 in Khyber Pakhtunkhwa, and 32 in Balochistan) are included in these four provinces (16), and almost 97% of the Pakistani population resides in this geographical area (17). The PPM model has been cohesively implemented in these four provinces since 2014.

Study Population

All forms of patients (new and relapse cases) with TB are notified in PPM- and non-PPM-implemented districts.

Ethical Approval

Ethical approval for conducting this project was obtained from the Advanced Studies and Research Board, Quaid-i-Azam University Islamabad, and the Institutional Review Board

(IRB) Ethics Committee, Research Unit, NTP, Ministry of National Services, Regulations, and Coordination, Islamabad, Pakistan (F.1-7/MISC-2017/151).

Data Collection

The PPM implementation mechanism and PPM participating facilities in the operational districts were abstracted from the NTP database. The NTP support mechanism (material supply, financial support, and technical support) for the PPM model implementation was also checked during the study period.

Aggregate data of notified TB cases and their relative treatment outcomes were extracted from the quarterly case notification report form (TB-07) and quarterly outcome report form (TB-09), respectively, for PPM and non-PPM models. The data of the patient reported to NTP by the participating TB facilities are compiled in the TB-07 and TB-09 forms. All patients with TB-07 form have a TB-09 one. TB-07 categorizes the patient demographics like gender, age, province, type of patient, and disease classification, whereas TB-09 records the outcome of the patient notified on TB-07. These two forms are updated quarter-wise, and a report is generated in the form of Microsoft Excel spreadsheets (Microsoft Corp., WA, USA) in each NTP implemented district (district level). These quarterly reports are then compiled at the provincial level and finally at the national level. So, data were compiled for all four quarterly national spreadsheets from mid-2015 to mid-2016.

Data collection was performed on different time periods, both for TB case notification and treatment outcomes of the notified cases. This is because a TB case (PPM and non-PPM) once notified at TB facility on TB-07 form, then the treatment outcome of that notified case is recorded on TB-09 after 6–9 months of initiating drug-susceptible TB treatment (i.e., by the end or after third NTP quarterly review meeting from the date of notifying TB case), which is then finally updated into the NTP program data. So, we took all TB-07 forms of the study population (notified TB cases from July 2015 to June 2016) and during May and June 2017, we compiled data of all TB-09 forms available in the NTP database for the study period.

Data Analysis

The collected data was imported, organized, and cleaned into Excel (Microsoft Excel 2016 edition). The cleaned data were checked for accuracy of entry and then analyzed descriptively for the study period for the following process indicators reported in **Table 1**. Viewing descriptive (statistical) analysis, the categorical variables were presented as counts and proportions (%), and the significance of the statistical test (chi-square) was taken at a p-value of < 0.05.

RESULTS

PPM Implementation Mechanism

The PPM model was operating through a common agreement [memorandum of understanding, (MOU)] between NTP (public arm) and participating private health facility owners (private arm) with relevance to the national TB guidelines. The NTP support mechanism (material supply, financial support, and technical support) to the private provider was also the same and equally distributed in all TB facilities operating through the PPM model (PPM-1, 2, 3, and 4). The NTP support mechanism in all these PPM approaches was provided by the Provincial TB control program (NTP provincial wing) through the district TB control program (NTP district wing). However, the PPM registered cases were notified by private providers to the district TB control program (DTB), then to the Provincial TB control program (PTP), and finally updated into the NTP database.

The four PPM approaches were following a particular set of patient examination, diagnostic, and follow-up procedures. The detailed procedure of the initial presentation of presumptive patients with TB at the aforementioned PPM facilities until their final diagnosis and follow-up plan has been mentioned in **Table 2**.

PPM Implemented Districts and Participating Facilities

Viewing the PPM implementation throughout all four provinces, the PPM model was operationalized in 92 districts in total during the study period (see **Supplementary Figure**), ranging from 11 districts engagement for the Private Hostel model (PPM-3) to 80 districts implementation in solo GP model (PPM-1). The number of participating PPM facilities within the PPM-implemented district (PPM coverage) showed a varying pattern among all four PPM approaches. The PPM coverage outcome of private hospital facilities was the highest (325 TB cases notified per PPM participating facility) among PPM approaches. The breakup of PPM implemented districts, PPM coverage, and PPM coverage outcome in four provinces is further described in **Figure 1**.

PPM TB Case Notification

A total of 327,002 TB cases were notified to NTP from four provinces of Pakistan from mid-2015 to mid-2016. Out of them, 81,016 (25%) cases were contributed by the PPM model. The female-to-male ratio of TB cases is slightly higher among PPM notified cases when compared to non-PPM cases. **Table 3** depicts that the PPM TB case notification was considerably higher to non-PPM model in patients aged <15 years (19.4 vs. 8.1%) and >54 years (33.0 vs. 16.5%), respectively but lower in notifying TB cases aging 15–34 years (21.0 vs. 46.6%) and >54 years of age (26.6 vs. 28.8%). The PPM contribution is high (22.5%) when compared to the non-PPM contribution (18.5%) in Sindh province. Chi-square tests for PPM and non-PPM case notification show that a very strong significant difference exists in proportions among compared variables related to gender ($p < 0.001$), age group ($p < 0.000$), and province ($p < 0.000$) involved for the study period.

Table 4 shows that out of the total PPM contribution (81,016), a majority (45.8%) of the PPM cases were contributed by solo GP approach, and only (4.8%) cases by Parastatal approach. Province-wise, solo GP clinics notified the highest proportion of patients with TB in Baluchistan (79.4%), Khyber Pakhtunkhwa (68.7%), and Punjab (42.8%), whereas NGOs stood with a maximum (42.1%) PPM contribution in Sindh province. **Table 5** indicates that pulmonary cases (79.2%) were notified more than extrapulmonary (20.8%) and clinically diagnosed

TABLE 1 | Key definitions of Public–Private Mix (PPM) intervention.

Indicator	Definition	Source
Incident cases	The estimated number of new and relapse cases of Tuberculosis (TB) arising in a given year.	Obtained from the annual WHO global TB report figures of incident TB cases in Pakistan for a given year.
Case notification	The actual number of new and relapsed TB cases reported to WHO for a given year.	Obtained from the annual WHO global TB report figures of notified TB cases in Pakistan for a given year.
Case detection rate	The ratio of the number of reported cases to the number of estimated TB cases in a given year.	Obtained from the annual WHO global TB report figures of TB case detection rate in Pakistan for a given year. Calculated as the number of cases notified divided by the number of estimated cases for that year, expressed as a percentage.
PPM implemented district	The administrative locality/subset unit of a province where the PPM model is being implemented.	Obtained by looking at quarterly case notification report form (TB-07) of a province and noting the names of PPM implemented districts in that province.
PPM coverage	The number of all healthcare facilities that were part of PPM within a PPM implemented district.	By counting and confirming the names of operating PPM facilities in PPM districts mentioned in quarterly case notification report forms (TB-07) from July 2015 to June 2016.
PPM coverage efficiency	The percentage of PPM facilities engaged among the available range of private TB facilities that were not a part of PPM within a PPM implemented district.	By matching the number of PPM TB facilities (NTP Umbrella) with TB facilities operating other than the PPM model (outside NTP Umbrella) in a particular district.
PPM coverage outcome	The mean number of patients with TB notified per PPM TB facility.	Calculated by dividing the PPM-notified cases in total by a total number of participating facilities for a respective PPM model.

TABLE 2 | Operational procedure of Public–Private Mix (PPM) models of Tuberculosis (TB) care in Pakistan.

PPM model	Stakeholders involved	Operation/patient flow
Solo general practitioner (GP) model (PPM-1)	There is a formal agreement between a GP preferably a TB specialist (private provider) operating in his private clinic, a district TB coordinator (public sector), and an intermediary NGO responsible for the coordination of public and private providers.	• Presumptive TB patient visits the trained private GP clinics for a regular check-up. • Paramedic staff supporting the GP maintains the patient's record on NTP-provided TB register and provides him with a voucher for performing the diagnostic tests. • The private laboratories on PPM-1 panel perform the tests free of cost on receiving the voucher from visiting patients. • The patient after getting results of all the diagnostic results re-visits the GP for final diagnosis.
Non-Governmental-Organization (NGO) run TB care facility model (PPM-2)	There is a formal agreement between NTP and NGO head along with the willing physician, practicing in NGO clinic	• NGOs' manage TB presumptive and patients through their small hospitals and outpatient clinics with laboratories, providing TB care services. • Paramedic staff supporting the GP in NGO clinics performs the TB case notification and its treatment outcomes on NTP provided recording and reporting (R&R) tool.
Private hospital model (PPM-3)	Medical superintendents of the hospital usually sign the agreement with the NTP team for following the national TB management guidelines.	• PPM-3 facilities operate through trust and large private tertiary care (non-profit) hospitals equipped with TB diagnostic and treatment services and operated by trained staff. • These hospitals offer free-of-charge services to visiting TB patients for TB diagnosis and treatment but charge the patients for non-TB treatment.
Other public sector (Parastatal) model (PPM-4)	Medical superintendents of the parastatal facility are signing authority involved with the NTP team	• PPM-4 model comprises semi-government (autonomous) hospitals with independent administration authorities who provide TB care facilities under one roof essentially to their employees. • It covers healthcare institutions established by organizations working under the administration of the Federal government who do not report to Provincial TB Control Programs (PTP).

(43.5%) than bacteriologically diagnosed (32.5%) cases. The run TB care facilities of NGOs were slightly better (81.8%) at diagnosing pulmonary TB. However, the private hospital approach was the only PPM approach that contributed more to bacteriologically confirmed cases than the clinically diagnosed cases (39.9 vs. 32.5%) along with an increased number of relapse cases (5.9%).

Treatment Outcomes of PPM-Notified Cases

Referring to **Table 6**, the overall treatment success rate was recorded (90.6%) for PPM-notified TB cases; ranging from just 46.7% successful treatment in Parastatal facilities to 94.9% success in NGO facilities. The PPM model was more likely to record "treatment completed" than the non-PPM model (69.4 vs. 64.5%)

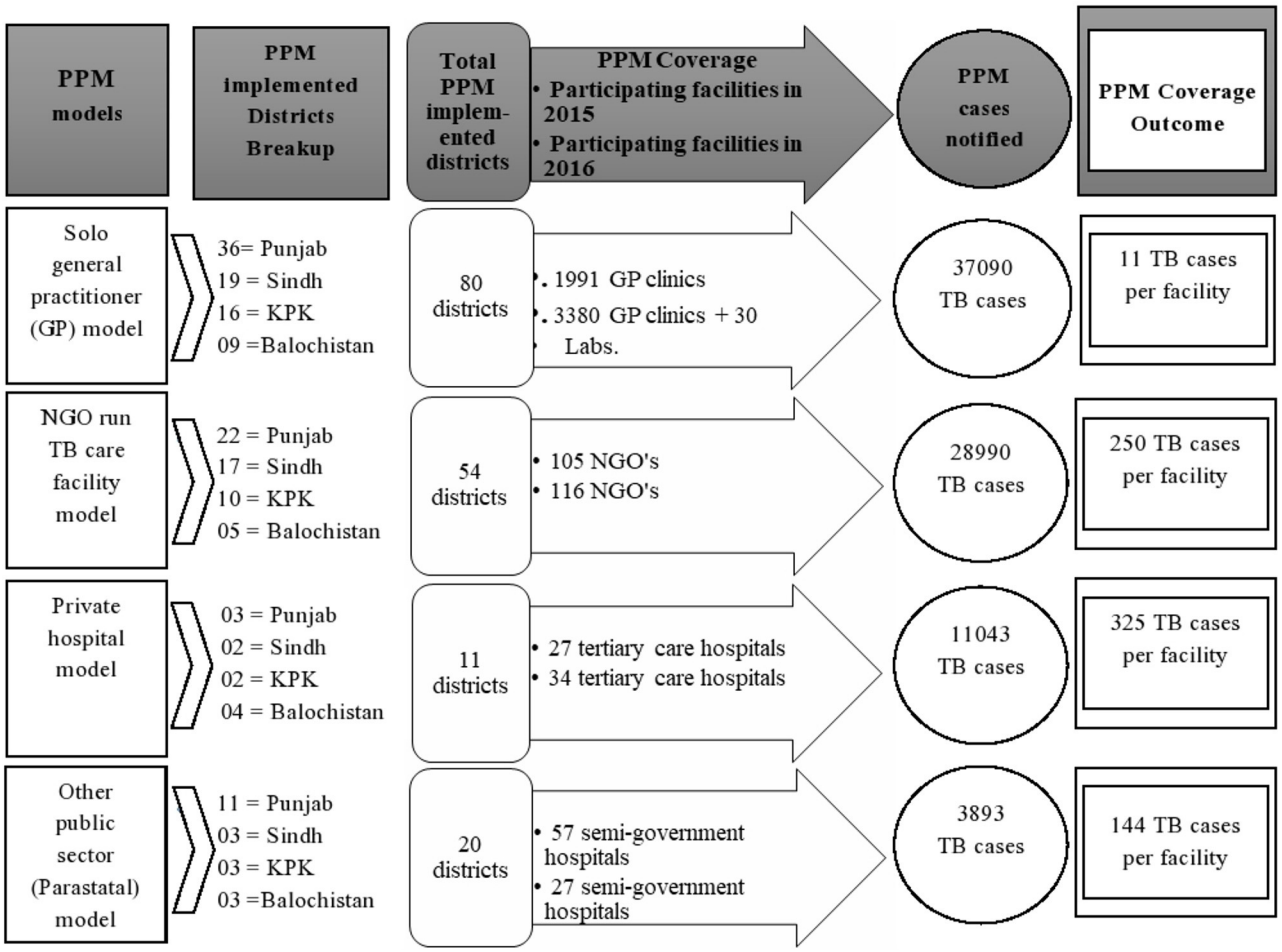

FIGURE 1 | Overview of Public-Private Mix (PPM) model implementation in four provinces of Pakistan from July 2015–June 2016.

TABLE 3 | Sociodemographic characteristics of patients with tuberculosis (TB) notified by total, non-PPM, and PPM models in Pakistan.

Variables	TB Notification (all forms) *n* (%)	Contribution to notification by non-PPM (all forms) *n* (%)	Contribution to notification by PPM (all forms) *n* (%)	*p*-value (PPM vs. non-PPM)
Total	32,7002 (100)	245,986 (75)	81,016 (25)	
Gender				
Male	164,355 (50.2)	124,030 (50.4)	40,325 (49.8)	<0.001
Female	162,647 (49.8)	121,956 (49.6)	40,691 (50.2)	
Age in years				
<15	35,670 (11.0)	19,958 (8.1)	15,712 (19.4)	<0.000
15–34	131,595 (40.0)	114,605 (46.6)	16,990 (21.0)	
35–54	92,327 (28.0)	70,783 (28.8)	21,544 (26.6)	
>54	67,410 (21.0)	40,640 (16.5)	26,770 (33.0)	
Province				
Punjab	210,773 (64.5)	158,837 (64.6)	51,936 (64.1)	<0.000
Sindh	63,648 (19.5)	45,407 (18.5)	18,241 (22.5)	
KPK	43,464 (13.0)	33,350 (13.5)	10,114 (12.5)	
Baluchistan	9,117 (3.0)	8,392 (3.4)	725 (0.9)	

KPK, khyber pakhtunkhwa; PPM, public–private mix.

TABLE 4 | Contribution to national Tuberculosis (TB) case notification by different Public–Private Mix approaches from July 2015 to June 2016.

Variables	Total PPM *n* (%)	PPM-I[a] *n* (%)	PPM-2[b] *n* (%)	PPM-3[c] *n* (%)	PPM-4[d] *n* (%)
Total	81,016 (100)	37,090 (45.8)	28,990 (35.8)	11,043 (13.6)	3,893 (4.8)
Province					
Baluchistan	725 (100)	576 (79.4)	79 (10.9)	47 (6.5)	23 (3.2)
KPK	10,114 (100)	6,952 (68.7)	2,509 (24.8)	601 (6.0)	52 (0.5)
Punjab	5,1936 (100)	22,249 (42.8)	18,666 (35.9)	7,461 (14.4)	3,560 (6.9)
Sindh	18,241 (100)	7,313 (40.4)	7,736 (42.1)	2,934 (16.1)	258 (1.4)

[a]*General practitioner model,* [b]*NGO run TB. care facility model,* [c]*Private hospital model,* [d]*Other public sector (Parastatal) model, KPK, khyber pakhtunkhwa.*

TABLE 5 | Disease classification of Tuberculosis (TB) cases notified by different Public–Private Mix approaches from July 2015 to June 2016.

Variables	Total PPM *n* (%)	PPM-I[a] *n* (%)	PPM-2[b] *n* (%)	PPM-3[c] *n* (%)	PPM-4[d] *n* (%)
Total	81,016 (100)	37,090 (100)	28,990 (100)	11,043 (100)	3,893 (100)
Disease classification					
Pulmonary	64,193 (79.2)	28,845 (77.7)	23,729 (81.8)	8,653 (78.3)	2,986 (76.6)
Extra Pulmonary	16,823 (20.8)	8,245 (22.3)	5,261 (18.2)	2,390 (21.7)	907 (23.4)
Type of patients (Pulmonary)					
Bacteriologically positive	26,332 (32.5)	11,367 (30.6)	9,346 (32.2)	4,402 (39.9)	1,217 (31.2)
Clinically Diagnosed	35,295 (43.5)	16,721 (45.1)	13,356 (46.1)	3,593 (32.5)	1,625 (41.7)
Relapse	2,566 (3.2)	757 (2.0)	1,007 (3.5)	658 (5.9)	144 (3.7)

[a]*General practitioner model,* [b]*NGO run TB. care facility model,* [c]*Private hospital model,* [d]*Other public sector (Parastatal) model.*

among the favorable outcomes. The unfavorable outcomes (see **Table 6**) were recorded more for PPM as compared to non-PPM-notified TB cases (9.4 vs. 6%), mostly attributed to Parastatal facilities; this is evident as 53.3% of PPM-4 notified cases were not successfully treated during the study period.

DISCUSSION

This study was the first large-scale study to assess the individual contribution of different approaches of the PPM model in Pakistan after its cohesive implementation at the national level. Overall, the PPM model contributed to the TB case notification (by 25%) in program data of NTP between July 2015 and June 2016, suggesting that more TB cases can be notified utilizing PPM intervention in Pakistan. This finding is considerably consistent with countries that have prioritized the PPM model for an increasing trend in TB case notification to their national TB control programs (5). Of the WHO-reported countries contributing between 5 and 56% to TB notification through PPM (18), our study was of value with a 25% contribution to the national database.

Disaggregating TB case notification by gender shows that PPM notified more TB cases in females than males, which is contrary to the non-PPM proportion of male TB cases exceeding female cases. PPM and non-PPM gender patterns in the notification are, respectively, in accord with previous study trends in sex-specific TB case notification in western and eastern provinces of Pakistan over 10 years (19). In terms of individual age groups involved, the PPM model is most likely to identify pediatric and elderly aged TB cases in comparison to the non-PPM model. The enhanced contribution of PPM to the pediatric age group may be attributed to the decision of NTP to engage PPM as one of the five key initiatives to detect missed childhood TB cases and minimize delayed diagnosis of these TB cases (20). Elderly aged patients with TB may prefer PPM facilities because of more access, response, and individualized option in comparison to non-PPM facilities (21), which might not be the case for the preference of adult-age patients with TB for initiating TB care at these facilities. Hence, the PPM model was contributing to a smaller number of young adult and middle-age TB cases. So, this varying pattern of health-seeking among all four patient age groups involved in this study reveals that different age group patients with TB tend to seek and initiate TB care differently (i.e., some prefer PPM, whereas others non-PPM) in the Pakistani community.

From the province viewpoint, the PPM model is more likely to identify TB cases in Sindh when compared to the non-PPM model. This might well be due to the low utilization of public sector health services by the population due to the non-availability of staff and medicines and thus seeking TB care more from private providers in Sindh (22). PPM findings of less contribution in Khyber Pakhtunkhwa and Baluchistan might be attributed to population preference in these two provinces to access public (government) sector hospitals more than private hospitals due to their financial constraints (23). However, qualitative studies can be performed in the

TABLE 6 | Accumulated treatment outcomes of Tuberculosis (TB) cases notified to national TB program in Pakistan from July 2015 to June 2016.

Outcome	Total *n* (%)	Non-PPM *n* (%)	PPM *n* (%)	PPM-1 *n* (%)	PPM-2 *n* (%)	PPM-3 *n* (%)	PPM-4 *n* (%)
Total	327,002 (100)	245,986 (100)	81,016 (100)	37,090 (100)	28,990 (100)	11,043 (100)	3,893 (100)
Cure	89,808 (27.5)	72,655 (29.5)	17,153 (21.2)	8,134 (21.9)	6,531 (22.5)	2,309 (20.9)	179 (4.6)
Tx* Complete	214,851 (65.7)	158,642 (64.5)	56,209 (69.4)	26,854 (72.4)	20,990 (72.4)	6,725 (60.9)	1,640 (42.1)
Subtotal Success	304,659 (93.2)	231,297 (94.0)	73,362 (90.6)	34,988 (94.3)	27,521 (94.9)	9,034 (81.8)	1,819 (46.7)
Failed	1,414 (0.4)	820 (0.3)	594 (0.7)	203 (0.5)	236 (0.8)	153 (1.4)	2 (0.0)
Died	4,313 (1.3)	3,069 (1.2)	1,244 (1.5)	646 (1.8)	219 (0.8)	360 (3.2)	19 (0.5)
LTFU	9,571 (2.9)	7,697 (3.1)	1,874 (2.3)	426 (1.1)	350 (1.2)	993 (9.0)	105 (2.7)
Not evaluated	4,148 (1.3)	3,014 (1.2)	1,134 (1.4)	343 (1.0)	275 (1.0)	474 (4.3)	42 (1.1)
Record not found	2,897 (0.9)	89 (0.0)	2,808 (3.5)	484 (1.3)	389 (1.3)	29 (0.3)	1,906 (49.0)
Subtotal unfavorable	22,343 (6.8)	14,689 (6.0)	7,654 (9.4)	2,102 (5.7)	1,469 (5.1)	2,009 (18.2)	2,074 (53.3)
LTFU/NE/ RNF	16,616 (5.0)	10,800 (4.4)	5,816 (7.1)	1,253 (3.4)	1,014 (3.5)	1,496 (13.5)	2,053 (53.0)
Failed/died	5,727 (1.8)	3,889 (1.6)	1,838 (2.3)	849 (2.3)	455 (1.6)	513 (4.6)	21 (0.3)

[a]General practitioner model, [b]NGO run TB care facility model, [c]Private hospital model, [d]Other public sector (Parastatal) model; Tx, treatment; LTFU, loss to follow up; NE, not evaluated; RNF, record not found.*

future to explore the reasons for less contribution of PPM in the province of Punjab in comparison to non-PPM TB case notification.

Among PPM approaches, the solo GP model contributed the highest percentage of total PPM cases in Punjab, Khyber Pakhtunkhwa, and Baluchistan (see **Table 2**). This might well be due to the GP model engagement in an extensive number of PPM implemented districts (80 out of total 92 districts), and improved PPM coverage: as 1991 GP clinics in 2015 were almost doubled to 3,380 GP clinics and 33 private laboratories in 2016, whereas the number of health facilities for the remaining PPM approaches remained nearly constant or dropped throughout the study period (see **Figure 1**). The total solo GP model contribution of 46% in this study is in contrast with the previous study in 2009, which documents only 5% PPM-1 contribution to total PPM cases mainly due to PPM-1 operational issues and limited health facilities implementation (14), that seems to be largely resolved during our study. However, the lowest treatment coverage outcome of GP facilities (11 TB cases per facility) in comparison to the remaining PPM approaches indicates that only a few GPs might have been actively involved in enrolling patients with TB at their clinics. Despite the hugely engaged network of GP clinics in four provinces, this low level of GP commitment in TB patient enrolment is consistent with experiences learned from PPM implemented GP clinics in six towns of Karachi (24).

The PPM-implemented districts and PPM coverage may not be the sole indicators for improved PPM TB case notification when we compare PPM-notified cases of GP and NGO facilities in Sindh province. That is, with a slightly different number of PPM-implemented districts for both GP and NGO approaches in Sindh (19 vs. 17 districts), and an overall reduced range of coverage of NGOs in comparison to the latter (116 vs. 3,380 facilities), the approach of NGOs still was the marginally largest PPM contributor in Sindh. First, this might be due to the enhancement in PPM coverage efficiency of the NGO model in the province, as 61 out of 62 available NGO facilities offering TB services in Sindh were working under the umbrella of NTP during the study period. The second possible reason might be the improvement in PPM coverage outcome of NGO facilities in comparison to GP facilities (250 cases vs. 11 cases notified per participating facility). This enhanced NGO cases per facility finding (PPM coverage outcome) were also consistent with large-scale partnerships between NGO-led model and NTP for improving TB services for the high-risk population in India (25). Hence, the improved PPM coverage outcome of NGO facilities in comparison to GP facilities in Sindh points out another important PPM indicator, that is, among two PPM models that have nearly the same implementation in districts, the model having improved PPM coverage outcome can likely contribute more PPM cases than the second model with reduced PPM coverage outcome.

Moving away from the concept of comparing PPM approaches with an almost equal number of PPM-implemented districts but having different PPM coverage outcomes toward PPM approaches with an unequal distribution of PPM-implemented districts and different PPM coverage provides another important PPM insight. The private hospital approach (PPM-3) is adopted with the least number of PPM-implemented districts in the study period (i.e., 11 out of 92 PPM districts), but its contribution in terms of PPM coverage outcome is highest (325 cases notified per participating facility) in comparison to the remaining PPM approaches (PPM-1 = 11, PPM-2 = 250, PPM-4 = 144 cases per facility). This shows that a PPM approach even with the lowest implementation in a district (such as PPM-3) can have an improved rank in contributing PPM cases per facility in comparison to the PPM coverage outcome of other models with a much higher number of PPM-implemented districts involved. This finding also indicates that Private hospital facilities might be a useful resource in terms of the number of PPM cases initiating TB care per PPM facility but needs to be scaled up for overall improvement in the remaining PPM indicators for the enrolled patients. This whole discussion of different PPM indicators (PPM-implemented district, PPM coverage, PPM coverage efficiency, and PPM coverage outcome) is reflective of their importance at various steps of scaling up the PPM model in future studies in Pakistan.

Viewing the remaining socio-demographics of PPM-notified cases, among the pulmonary cases, clinically diagnosed patients were notified more than bacteriologically confirmed ones; mostly attributed by NGOs, closely followed by GPs. This indicates that both NGOs and GP facilities were associated with over-reliance on radiography, suggestive disease histology, and the under-use of sputum smear microscopy for diagnosis. This diagnosis pattern of GP clinics is consistent with clinicians in other countries (26), suggesting a careful review of recruiting and training private practitioners in PPM-DOTS in Pakistan (27). While for NGO-run TB care facilities, future research can be conducted to explore the possible reasons for over-reliance. However, the private hospital approach remains the sole PPM approach that was not only good in detecting bacteriologically confirmed among pulmonary cases but also slightly better in notifying patients previously treated, and now diagnosed with a recurrent episode of TB.

Among notified patients who started treatment in PPM facilities, the treatment success rate (90.6%) was considerably higher than the WHO-recommended target of 85% (28). This finding also supported previous PPM studies in Pakistan showing that the PPM model is not limited to contributing to TB case findings but also maintains a good treatment success (24, 27). Among PPM approaches, GP and NGO facilities achieve the same outcomes as non-PPM, with treatment success of 94–95% and only 3–4% not evaluated or lost; private hospitals achieve 82% success because of a total of 14% not evaluated or lost; Parastatals are unable to follow more than half of cases, and therefore achieve a success rate of just 47%, the number of participating facilities fell from 57 in 2015 to 31 in 2016, and they contributed only 1.1% of case notifications in these four provinces from mid-2015 to mid-2016. Private hospital facilities may have slightly higher rates of failure/death (4.65 vs. 1.8% overall) but this may well be due to more complicated cases presenting to hospitals. "Loss to follow-up" and "Not evaluated" were also recorded more in private hospitals. This default for the hospital was consistent with PPM findings in Indonesia (29).

Out of 81,016 patients with TB, the outcome record of 2,808 PPM cases was found missing; these cases were notified (on TB-07) but their outcome record (on TB-09) was not available, mostly attributed to Parastatals. This was considerably high as compared to non-PPM contribution (3.5 vs. 0.0%) and reflects a gap between notification and recording treatment outcome in the PPM model particularly, within Parastatal facilities. This gap can be covered by developing PPM mechanisms for better documentation and patient follow-up (30). Combining the percentage contribution of notified TB patient's outcomes with "loss to follow-up," "not evaluated," and "record not found" PPM contribution is still high than non-PPM (7.1 vs. 4.4%) (see **Table 6**). This finding can be reflective of the need to think beyond PPM-DOTS expansion and start focusing on the quality of TB care provided in PPM facilities (31). The enhancement in quality of TB care in the PPM model can involve implementing PPM approaches based on socio-cultural dynamics and processes (32), introducing national electronic-case-based surveillance for TB in PPM facilities (5), and involving and training remaining TB stakeholders who often serve as the first point of contact for TB care such as pharmacists (33–37), nurses (38, 39), and traditional healers (40), which are largely neglected as a part of the healthcare team within PPM model in Pakistan.

Strengths

The first strength of the PPM intervention study (different approaches of conventional PPM model), is that the data was collected from routinely maintained program data, so the findings are likely to reflect the program realities. Second, the study population has a large sample size, our estimate is likely to be precise. Third, the STROBE guidelines were followed for study design, methodology, and reporting of outcomes which minimizes the risk of methodological biases (41). Fourth, the study provides evidence and a descriptive overview of total TB case notification (PPM and non-PPM) from all TB treatment facilities available for 97% Pakistani DOTS population residing in four provinces in the study period.

Limitations

First: the PPM intervention study was limited to the quantitative assessment of different PPM approaches. Qualitatively, it could not explore the reasons either for performance perspectives of the model's stakeholders and patients undergoing treatment in PPM facilities or variation of PPM contractual arrangements in different provinces and areas of Pakistan. Second: a record review was done and the reliability of routinely collected data

cannot be assured. Third: the figures were extracted using aggregate data which is expected to have minor fluctuations as compared to individual facility data. Fourth: the study could not include the PPM case notification of the remaining 3% Pakistani population due to ethical approval constraints by NTP. Lastly, the aggregate PPM data lacks the segregation of participating GPs' working either in Government as well-private TB facilities during morning and evening timings or practicing solely in the private health sector.

CONCLUSIONS

The PPM intervention is contributing substantially to the national TB case notification in possibly all the age groups, gender, and provinces, so the PPM model implementation is requisite to detect missing cases and end the TB epidemic in the Pakistani healthcare system. Based on the evidence presented for different approaches of the cohesively implemented PPM model in this study, we conclude that GPs, NGOs, and Private hospital facilities should be scaled up, but Parastatal facilities need to be substantially reformed.

RECOMMENDATIONS

Among PPM approaches (PPM-1,-2,-3, and−4), GP facilities scale-up should be focused more toward their PPM coverage outcome as well as revising the PPM-1 strategies for inclusion of GPs' exclusively practicing TB care in the private sector, while NGO facilities for an increase in their PPM coverage, and Private hospitals in terms of enhancement in PPM coverage efficiency, PPM implemented districts, along with extending the treatment success rate up to 85%. Reforms in Parastatal facilities should not only be aimed at upgrading the Parastatal contribution toward PPM TB case notification but also improving their follow-up mechanisms to avoid the default of Parastatal notified TB cases as well as retaining the number of Parastatal facilities offering TB services.

Moreover, a strong PPM infrastructure for TB control is vital for a country where the private sector in its current state (i.e., cohesively implemented PPM model), contributes considerably to the notification of missing TB cases. To reach out the missing TB cases further though PPM model, the mobile, robust, and systematic inclusion of the remaining nine private TB providers (such as pharmacists, nurses, philanthropists, chemists, community leaders, religious leaders, researchers, insurance agencies, and mineral industries) in the Pakistani PPM program are needed. This can be achieved either through their recognized participation as a part of the national TB healthcare team, legislating the mandatory TB case notification act in the remaining provinces of KPK, Sindh, and Balochistan, or incentivizing their TB referral services according to national TB guidelines in the form of an MOU. In the future, the engagement of all private providers of TB care will not only provide equity of access to an extended number of the patients seeking care for TB treatment in Pakistan but can also extend the current PPM contribution (from 25 to 56%) to the national TB database.

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 ethical approval for the conduct of this project was obtained from the Advanced Studies and Research Board, Quaid-i-Azam University Islamabad, and Research Unit, NTP Pakistan. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WU conceived and designed the study, collected, interpreted, and analyzed the data, drafted the first version of the paper, and revised the final manuscript. MH coordinated for data collection and provided input into the data interpretation. AW coordinated for data collection, provided input into the data interpretation, and assisted in revising the manuscript. AY provided advice on data analysis and interpretation. RF assisted in the conceptual phase and study design, reviewed the first draft, and assisted in revising the final manuscript. GK assisted in the conceptual phase and study design, reviewed the first draft, and provided approval to the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by the Special Program for Research and Training in Tropical Diseases at the WHO/TDR. The training model is based on a course developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union, Paris, France) and Médecins Sans Frontières (MSF, Geneva, Switzerland). The specific SORT IT program that resulted in this publication was implemented by the National Tuberculosis Control Program of Pakistan, through the support of WHO-TDR. However, no funding has been granted for covering the Article Processing Fee.

ACKNOWLEDGMENTS

The authors wish to thank the staff at Data Surveillance Team, National Tuberculosis Control Program, Pakistan for assisting with data verification from routine program data (national database).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.703631/full#supplementary-material

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frontiers in Public Health

ORIGINAL RESEARCH
published: 01 September 2021
doi: 10.3389/fpubh.2021.720928

A Qualitative Study Exploring Community Pharmacists' Experiences and Views About Weight Management Interventions and Services in Klang Valley, Malaysia

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OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Mohammed Tahir Ansari, University of Nottingham Malaysia, Malaysia
Naveel Atif, Xi'an Jiaotong University, China

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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: 12 June 2021
Accepted: 09 August 2021
Published: 01 September 2021

Citation:
Verma RK, Chong WW, Taha NA and Paraidathathu T (2021) A Qualitative Study Exploring Community Pharmacists' Experiences and Views About Weight Management Interventions and Services in Klang Valley, Malaysia. Front. Public Health 9:720928. doi: 10.3389/fpubh.2021.720928

Objective: To qualitatively explore the perspectives of community pharmacists in Malaysia on their roles in weight management, and the barriers and facilitators in the expansion of these roles.

Methods: A purposive sampling method was used to recruit community pharmacists in Klang Valley, Malaysia. Semi-structured individual interviews were conducted with community pharmacists, with an interview guide, from May 2018 to January 2019. The interviews were conducted in person (face-to-face). All interviews were audio-recorded with consent and transcribed verbatim. The interview transcripts were analyzed thematically, whereby emerging themes were coded and grouped into categories.

Results: Twenty-four community pharmacists were recruited, with years of experience in pharmacy practice ranging from 2 to 40 years. Participants described their perceptions on the different weight management interventions where they emphasized the importance of a comprehensive lifestyle intervention and viewed that it should be the first-line intervention. Participants regarded their weight management service as easily accessible or approachable since community pharmacies are often the first point of call for patients seeking advice for their conditions before consulting doctors. Barriers identified by community pharmacists were mainly organizational in nature, which included lack of private consultation rooms, lack of time, and lack of qualified staff. Participants also described the need for training in weight management.

Conclusion: Community pharmacists in Malaysia believed that they can positively contribute to the area of weight management. They cited multiple roles that they could play in weight management interventions and services. The roles cited include provision of education and advice, including on lifestyle modifications, drug therapy,

weight loss products and supplements, and monitoring and providing referrals to other healthcare professionals. However, barriers would need to be addressed, including through pharmacist training, to strengthen and improve community pharmacists' roles and contributions in weight management service.

Keywords: weight management, community pharmacist, community pharmacy, obesity, overweight, intervention and views, qualitative exploration

INTRODUCTION

Obesity is globally recognized as a public health concern. Obesity is defined as excessive fat accumulation to the extent that it presents a risk to health. Global age-standardized estimates from World Health Organization show that in 2016, over 650 million adults (aged 18 years and older) were obese, which corresponds to about 13% of the world's adult population (1). Worldwide obesity among adults has nearly tripled since 1975, increasing from a prevalence of 4.7% in 1975 to a prevalence of 13.1% in 2016 (1). In Malaysia, a sharp increment in the prevalence of obesity over the last four decades has been documented. In 1975, about 1.4% of the Malaysian adult population was obese, but the figure has since risen to 15.6% in 2016, with more than 10 times increase in the prevalence (1). In this regard, Budgujar et al. (2) highlighted that complications associated with obesity were known to obese Malaysians; however, awareness programs are still needed to control the intensity of obesity in Malaysia.

There has been a transformation in the professional skills of the pharmacy profession over the last decades. Pharmacists, especially in the community settings, have been acknowledged for their capability to extend their role in assisting public health activities such as weight management, in addition to the traditional role of promoting quality use of medicines. Like other parts of the world, Malaysian community pharmacists are one of the most accessible health care professionals, and hence should be ideally placed to be professional advocates for public health on the front line of health care, which includes weight management.

Previous empirical research has been conducted in Australia and New Zealand to investigate the role of community pharmacists in weight management. Community pharmacists generally expressed positive views on their role in weight management. They believed that as trained health care professionals, they held a unique position compared to other community-based healthcare providers and therefore had a definite role to play in weight management (3, 4). They viewed themselves to be approachable by virtue of their ability to have regular contact with patients due to prescription dispensing, and patients are more comfortable talking to pharmacists than to general practitioners (4, 5). This feature facilitates their active role in the delivery of weight management services since they considered that such services build on the existing trust and good rapport between patients and pharmacists (4, 5).

According to previous surveys conducted, about 75–90% of the community pharmacists in Malaysia participated in the delivery of weight management services (WMS) (6, 7). Most of the community pharmacists in Malaysia in a previous study (8) reported providing extended services related to weight management, including anthropometric and physiological measurements. Such findings are encouraging, as they indicate that community pharmacists in Malaysia may have a positive perception of their roles in weight management, and thus represents a potential opportunity to further explore their role in WMS. Although a previous qualitative study has explored the provision of professional pharmacy services among community pharmacists in Sarawak (9), no research to date has qualitatively explored the views and perspectives of the community pharmacists in Malaysia regarding their role in weight management specifically.

Therefore, this qualitative study aims to explore in-depth the experiences and views of community pharmacists in Malaysia on weight management interventions and WMS. This study also aims to qualitatively explore the perspectives of community pharmacists in Malaysia on their roles in weight management, and the barriers and facilitators in the expansion of these roles.

METHODS

Study Design

A qualitative approach was utilized to explore community pharmacists' views on weight management and their roles or involvement in weight management interventions and WMS. Data were collected *via* face-to-face semi-structured interviews, as they provided participants with an opportunity to develop and express their views. This study utilized a phenomenological approach, which is a philosophical approach that seeks to gain a description of the phenomenon from the participants' point of view (10).

Sampling Process

A purposive sampling method was used to identify community pharmacists with different demographic variables, including the type and location of community pharmacies in which they worked. Community pharmacists who owned and/or worked in community pharmacies in the Klang Valley, Malaysia, had a minimum of 2 years' experience in the community pharmacy setting, and had previous experience in the management of overweight and obese patients, were deemed eligible. Those who were not willing to sign the consent form, had <2 years of working experience and did not provide WMS from their pharmacy were excluded. Community pharmacists who had previously registered for a weight management training program conducted by the Malaysian Pharmacists Society (MPS) were contacted and asked about their interest in participating in the

study. A participant information sheet was provided for further details. Community pharmacists who expressed their interest in participating in the interview were then contacted over the phone to schedule an appointment for the interview.

The sampling process stopped when thematic saturation was reached and no additional data was obtained from the last six participants.

Interview Guide

The interview guide was adapted from a similar study that was conducted among community pharmacists in New Zealand (4). Permission to adapt the interview guide for the study was requested from and granted by the authors. The original interview guide was modified according to the Malaysian context, in which a few questions on demographic characteristics, use of clinical practice guidelines in weight management, and requirement of training programs were either added or modified. The interview guide contained open-ended questions on perspectives of obesity, weight management interventions in community pharmacy, use of clinical practice guidelines in weight management, barriers and facilitators to expanding the role of CPs in weight management, and training needs in the area of weight management. Prior to the use in the field, the interview guide was further assessed for validity by three academic experts with experience in qualitative research and the area of community pharmacy. The interview guide was further piloted on three community pharmacists. No major changes were made after the pilot study, apart from items on demographic characteristics where the option "manager" was added under the employment section.

Interview Process

Semi-structured interviews with the community pharmacists were conducted in person (face-to-face) after individual appointments. Prior to the interviews, the interviewer explained the study objectives and obtained written informed consent from the participants. Participants were assured of the confidentiality of their responses and their right to withdraw from the study. The interviews were conducted between May 2018 to January 2019 at the participants' workplace, specifically in the consultation room of their community pharmacies, for confidentiality purposes and to avoid any distractions. The interviews were conducted in English and were audio-recorded with additional field notes taken during the interviews. The interviews averaged 35 min in length (range: 27–42 min).

Data Analysis

All interviews were audio-recorded with consent and transcribed verbatim. The researcher (RKV) read each transcript repeatedly while listening to the recorded data and made notations directly onto the transcripts. The interview transcripts were analyzed thematically, whereby emerging themes were coded and grouped into categories. The other researchers (CWW, NAT, and TP) verified the emerging themes and contents. The findings from the study are presented thematically.

RESULTS

Twenty-four community pharmacists were recruited, with 15 female pharmacists and nine male pharmacists. The age of participants ranged from 28 years to over 50 years. Their length of time in pharmacy practice ranged from 2 to 40 years. There were nine participants who worked in independent pharmacies and 15 participants who worked in chain pharmacies, respectively (**Table 1**).

Five key themes emerged from the qualitative analysis of the data. These included:

1. Identification of overweight and obese clients in community pharmacy.
2. Weight management interventions in community pharmacy.
3. Perceived roles of community pharmacists in weight management.
4. Barriers to community pharmacists' involvement in weight management.
5. Training needs in weight management for community pharmacists.

Descriptions of the key themes identified, supported by illustrative quotes, are as follows.

TABLE 1 | Sociodemographic and practice characteristics of participants ($n = 24$).

Gender distribution	
Gender frequency (n)	
Male	9
Female	15
Age distribution	
Age range frequency	
20–29	6
30–39	9
40–49	4
50–59	5
Highest qualification	
Bachelor of Pharmacy	20
Master of Pharmacy	4
Years of experience in community pharmacy	
Year range frequency	
2–5 years	8
6–10 years	5
11–15 years	2
16–20 years	4
21–25 years	3
25 years and above	2
Type of pharmacies	
Type frequency	
Chain pharmacy	15
Independent pharmacy	9
Employment status	
Type frequency	
Full time employees (includes 7 managers and 1 owner)	21
Part time employees	3

Theme 1: Identification of Overweight and Obese Clients in Community Pharmacy

All participants considered body mass index (BMI) an acceptable measure to classify their clients as overweight or obese. Nevertheless, some participants would judge their clients based on physical appearance before calculating BMI. Some participants believed that BMI alone was inaccurate, and thus would also consider body composition, i.e., amount of muscle and fat in the body. Participants estimated that the proportion of overweight or obese clients encountered in their community pharmacy, as judged based on physical appearance, ranged from 10% to over 50%. Most participants believed overweight and obesity were topics that require sensitivity in how they were introduced and addressed to their clients.

Box 1 provides a selection of participant quotations related to this theme.

BOX 1 | Selected quotes related to the identification of overweight and obese clients in community pharmacy.

Defining overweight and obesity

"The most common one would be using BMI, with two things into consideration: weight and height of the person" [Interview 7].

"At first, I will actually look at the shape of the body. After that, I will calculate the BMI" [Interview 5].

"…I would not define my customers as obese or overweight just based on BMI alone. I will consider also the proportion of muscle and fats in the body" [Interview 7].

Weight as a sensitive topic

"Weight is a sensitive issue, and a lot of times we do not initiate the topic because we do not know how comfortable they are with discussing the topic" [Interview 8].

"…Not everyone is open to discuss this issue aloud. Usually we will wait for them to ask, then we intervene" [Interview 9].

Theme 2: Weight Management Interventions in Community Pharmacy

Participants described their perceptions on the different weight management interventions in the context of community pharmacy setting. Only a few participants were aware and had read the Clinical Practice Guidelines on Management of Obesity by the Ministry of Health Malaysia (12), although none depended on the guidelines for their weight management practices. Overall, participants viewed that overweight or obese clients would benefit from a comprehensive lifestyle intervention comprising a combination of dietary and physical activity modification. Participants emphasized the importance of a comprehensive lifestyle intervention and viewed that it should be the first-line intervention.

Participants were well aware of the legal restrictions on the dispensing of drug therapy for weight management, in which they could only recommend non-prescription drugs such as orlistat as part of their weight management interventions, while a doctor's prescription is required before they could dispense prescription drugs such as phentermine. Drug therapy was mostly perceived as a last resort for participants if other weight management interventions have failed, and participants would usually refer their clients to obtain a doctor's advice before initiation of drug therapy for weight management. A few participants were mindful of the side effects of orlistat and the associated patient counseling tips to address these side effects.

All participants were familiar with the commercial weight loss products and supplements commonly sold in the pharmacy. Almost all of them would recommend these products to their clients, as they believed that the weight loss products and supplements could help their clients to achieve weight loss. Nevertheless, some participants raised potential issues surrounding the sales of these products, including the weight loss that could be of short-term due to loss of water instead of fats, as well as habit-forming potential associated with some commercial products containing laxatives. Other related problems such as overclaims of product effectiveness were also cited.

Generally, participants believed that there was a behavioral element to weight loss, in which a change of mindset was necessary for lifestyle interventions to be successful. One participant described the application of transtheoretical model as a basis to determine the client's readiness for behavioral change. Nonetheless, only one participant formally utilized cognitive behavioral therapy as part of her weight management practices.

Box 2 provides a selection of participant quotations on this theme.

BOX 2 | Selected quotes related to weight management interventions in community pharmacy.

Dietary and physical activity modification

"I think it's about guiding them to a proper lifestyle. Even if you're selling the best product, it won't be working without exercise and dietary intervention" [Interview 3].

"Exercise and maintain a healthy diet, those will be the core of the weight loss intervention" [Interview 8].

"First of all, counseling on lifestyle changes, because I believe this is the one that works among all other interventions" [Interview 9].

Drug therapy

"We don't involve so much in drug therapy. Pharmacists cannot dispense Duromine® without a prescription. It's under Group B. What we can dispense without a prescription is orlistat, a group C drug" [Interview 4].

"…I can give them drugs; drugs will be the last option if others failed. Lifestyle changes should be the first option" [Interview 2].

"…For instance, the fat absorption blocker orlistat, I find it hard to use because of the side effects" [Interview 7].

Weight loss products and supplements

"Products such as slimming tea give only temporary effect, you only lose water. It's not a true reflection of weight loss in terms of losing fat mass" [Interview 22].

"A lot of slimming teas contain senna, which is habit forming. Some customers lose weight rapidly after taking slimming teas in the first two weeks, but in longer term their body weight will bounce back because they are losing water, not losing fats" [Interview 8].

Behavioral modification

"Their mindset or how they think is very important. You intervene through the way they think and how it affects their lifestyle" [Interview 4].

"We need to do it step by step. Using the transtheoretical model, I try to find out in what stage that this person is willing to change, to see whether he is in the preparation stage, or he is in the action stage" [Interview 7].

Theme 3: Perceived Roles of Community Pharmacists in Weight Management

Participants regarded their WMS as easily accessible since community pharmacies are often the first point of call for patients seeking advice for their conditions before consulting doctors. Participants also expressed moderate to high confidence in providing WMS in general.

Participants were unanimous of the opinion that the provision of education and advice was a vital part of their role in weight management. Apart from clients who requested WMS themselves, participants also reported routinely addressing weight issues among clients with non-communicable diseases, especially those with cardiovascular disease, diabetes, hypertension, and osteoarthritis. While all participants would like to engage in modifying the physical activity and dietary behaviors of their overweight or obese clients, some would also create awareness among their clients regarding the health risks associated with overweight or obesity as well as the importance and benefits of losing weight. Almost all participants believed they play a part in promoting weight loss products or supplements to complement their weight management advices.

Participants also saw a monitoring role in themselves, whereby some would go a step further to follow up with their clients' progress to check if they have implemented the suggested lifestyle modification. Participants generally would like to be able to refer their clients to other health care professionals such as physicians, dieticians, nutritionists, and exercise trainers as part of the multidisciplinary approach to weight management. A few participants reported referring their clients to in-house nutritionists and dietitians to receive dietary counseling. Some participants also referred clients with co-existing diseases or class 3 obesity to the physicians.

Box 3 provides a selection of participant quotations on this theme.

BOX 3 | Selected quotes related to the perceived roles of community pharmacists in weight management.

Accessible and approachable

"Because we are in the primary care, we are easily accessible, so a lot of clients like to come to us first" [Interview 7].

"We are easily approachable and most probably be the first line where people will come to seek help rather than going to a doctor" [Interview 9].

Providing education and advice

"I think the main thing that we can do for the patients is actually providing information, especially in terms of diet and exercise" [Interview 11].

"We educate people about different options and different methods of losing weight healthily" [Interview 22].

Raising awareness

"…We also need to educate customers a lot about the importance of losing weight because obesity is related to a lot of chronic diseases, like diabetes, hypertension, and even Alzheimer's disease" [Interview 8].

"We can actually deliver the message: the risk of obesity and the benefit if you lose your weight" [Interview 1].

Weight loss product or supplement selling

"So product-wise, we recommend them something to burn fats like garcinia" [Interview 6].

"Product selling will help them, because advice alone will not be enough" [Interview 21].

Monitoring and follow up

"…Follow up with customers to know how much they are progressing. If you just give them advice and not following up with them, you won't know if they have changed their diet, or if they have changed their lifestyle. So, follow up is the best way to know whether the customers have successfully lost weight, or whether they find your ways are helping them" [Interview 23].

Referral to other healthcare professionals

"If we can have access to other healthcare professionals like dietitians or fitness coaches, it will definitely be useful. It's part of the holistic approach" [Interview 16].

"In our counseling process, we do let our nutritionists teach them how to manage their diet" [Interview 8].

"If they have other comorbidities or if they haven't been undergoing their blood test, then we will refer them to a doctor" [Interview 17].

Theme 4: Barriers to Community Pharmacists' Involvement in Weight Management

Participants identified several barriers to the effective delivery of WMS in the community pharmacy. Almost all participants revealed difficulty to introduce the potentially sensitive issue of weight due to their fear of offending their clients. They would hence normally wait for their clients to take the initiative, or bring out the topic in the context of other health conditions, especially diabetes, hypertension, or osteoarthritis. Some participants would utilize health biomarkers such as blood pressure or blood glucose rather than weight or BMI, as a way to open the discussion about weight indirectly. Relatedly, a few participants identified a lack of consultation room in the pharmacy to discuss the topic privately as a barrier to WMS involvement.

Another barrier perceived by participants was a lack of financial reimbursement. Participants would like to be remunerated appropriately, either from the clients or the employers, for their time taken to provide WMS. Participants believed that it would be time-consuming to provide proper weight counseling and therefore would forego some sales revenues if they provided WMS. Participants also perceived that their effort would be more appreciated if a fee is incurred for their WMS.

A lack of time also posed a barrier to the administration of WMS among some participants. This was especially true for community pharmacies that are always crowded with customers or those that are operated with only one or two pharmacists. A lack of qualified staff in the pharmacy was also cited as a barrier since quality time may not be devoted to their clients, with pharmacists having many tasks to handle.

Other barriers identified by participants included a lack of training on weight management, especially training programs with content adapted in the local context, and a lack of public awareness on their ability to deliver WMS, possibly due to a lack of formal weight management programs introduced by the pharmacy.

Box 4 provides a selection of participant quotations on this theme.

Theme 5: Training Needs in Weight Management for Community Pharmacists

Participants also described the need for training in weight management. More than half of the participants had completed

BOX 4 | Selected quotes related to the barriers to community pharmacists' involvement in weight management.

Introducing weight topic

"…Not everyone is open to discuss this issue aloud. Usually we will wait for them to ask, then we intervene" [Interview 9].

"[If] they have other comorbidities, like diabetes, [high] blood pressure, then perhaps we will recommend weight reduction. Or else, we won't interrupt" [Interview 10].

"If the customer [is] coming [for a] blood pressure or blood sugar check, and we find the reading is high, then as part of the counseling, we tell them to exercise and lose weight. From there we can start the conversation on how they can lose weight" [Interview 15].

Lack of private consultation room

"Having a private counseling room is a good thing. Because it is not very good to discuss weight issues in front of everyone especially when it is so crowded in the pharmacy" [Interview 5].

Lack of remuneration

"When we perform counseling, we may end up not doing any sales. We're actually spending time with this patient. We need to let other customers wait for our service. So I think it'll be better with a little remuneration" [Interview 3].

"Some people will be more appreciative if they actually need to pay for the service. It is something that we need to look into, and it is actually quite a good initiative. Most of the time we are not going to charge a lot, even like overseas, if they charge, it is at a minimal amount, just a little appreciation of what the pharmacists can do" [Interview 18].

Lack of time

"Sometimes time limitation is our challenge as well, because at one time you have to serve multiple clients. There's usually one to two pharmacists only in a retail pharmacy, so during peak hours, it might be a little bit difficult for us to sit down and talk to them privately" [Interview 6].

Lack of qualified staff

"...The pharmacy assistant may not be really equipped with this kind of knowledge" [Interview 3].

Lack of training

"I think it's good to have this kind of training workshop. Because I only read from the overseas websites. We don't really know whether it works for our community or not. The way we select our food, it's actually different from European countries" [Interview 3].

Lack of public awareness

"If you have something more structured like the smoking cessation program, then people will be more aware of it as well, so the proactive ones will come and seek advice, and we can monitor them in a more structured way" [Interview 21].

some previous training on how to manage overweight or obese clients. All participants who had previous training on weight management agreed that this sort of training was effective, and improved their confidence in the management of overweight or obese clients. They opined that the weight management training not only refreshed their previously acquired knowledge and skills, but also provided some new insights on weight management, for instance, on the efficacy of drug therapy for weight loss and the latest commercial weight loss products and supplements in the market. Participants who had never attended any training on weight management also considered such training to be beneficial in expanding knowledge on this topic.

In terms of training needs and preferences, participants desired to have a multi-day training program to adequately cover related aspects on weight management. They would like the training session to be conducted more than once a year to share how well they have integrated the knowledge and skills learnt during previous sessions into their daily practices. Training topics deemed necessary by the participants included cognitive behavioral therapy, exercise, and dietary counseling, particularly calorie counting, as well as communication skills to initiate potentially sensitive weight topics with clients, convince overweight or obese clients to lose weight, and build rapport with clients. Most participants would like to have experience sharing sessions or case studies as part of the weight management training, especially those that involved actual clients. In addition, some participants would like the involvement of other health care professionals in weight management training, either as participants during group discussions, or as providers of the training. A few participants would like more exposure on commercial weight loss products or supplements.

Box 5 provides a selection of participant quotations on this theme.

BOX 5 | Selected quotes related to pharmacists' training needs in weight management.

Training duration

"Maybe they can have [a] multi-day training program for us to cover more aspects and criteria, because the previous training was too short" [Interview 20].

Training frequency

"Maybe they can have more sessions instead of once a year. After the first session, we would go back and implement the knowledge and skills learnt, and we share on the next session whether they are effective" [Interview 5].

Training topics

"…Learn about dietary counseling, communication skills, exercise regimen, and products available" [Interview 13].

"We want to know more about how to control the diet and what is the calculation for calories intake" [Interview 23].

"…Communication skills, in terms of convincing the patients into weight management" [Interview 10].

"…Include a lot of case studies, so that we can learn how to practice" [Interview 22].

"It would probably help if actual patients can come and share their experiences, and that would further tell us the achievability of whatever regimen we have set up for the patients" [Interview 11].

"I would say if there is a nutritionist or dietitian or weight management specialist in hospital who can give us training, it would give us better insight" [Interview 17].

DISCUSSION

To the best of authors' knowledge, this is the first qualitative study to explore community pharmacists' views on overweight and obesity, and their potential roles in weight management in Malaysia. The findings from this study support and further explain results from the previous quantitative study that aimed to assess the attitudes, practices, and perceived barriers of Malaysian community pharmacists in the delivery of WMS. In the previous quantitative study, while many of the community pharmacists were reported to actively provide WMS, they also perceived the presence of multiple barriers (8).

Findings from the current study indicated that community pharmacists were interested to play an active role when it comes to providing WMS. The community pharmacists considered themselves to be in a favorable position to provide WMS since they believed they are accessible and approachable. Beyond lifestyle modification counseling, community pharmacists also took part in the education of their clients in creating awareness regarding the health risks associated with overweight and obesity as well as the importance of shedding extra weight. In addition, with some community pharmacists providing follow up to their clients, it indicates that they would tailor their WMS according to individual needs. These findings align with global evidence for the public health roles that community pharmacists play, where they were shown to be capable of providing both population-based and individual-level public health services such as weight management (11). Moreover, despite having trouble in raising the potentially sensitive issues of weight with their clients, community pharmacists would utilize some communication techniques to overcome the difficulty, such as raising the topic in the context of other health conditions or deranged health biomarkers. The findings reciprocated with a study in New Zealand, whereby the community pharmacists would also employ similar techniques to overcome sensitivity about raising weight topics (4). With the communication techniques they employed, it is not surprising to observe that community pharmacists would routinely address weight issues among clients with comorbidities, especially cardiovascular disease, diabetes, hypertension, and osteoarthritis.

Most community pharmacists in our study would classify their clients as being overweight or obese by calculating their BMI, which is in line with the recommendations in the Clinical Practice Guidelines on Management of Obesity by the Ministry of Health Malaysia (12). However, from an anatomical and metabolic point of view, obesity is defined as excessive accumulation of body fat, and upon these grounds, the accuracy of the BMI as a determinant of body fat mass has been frequently questioned within the literature, since it has some limitations in this regard (13, 14). Therefore, it is indeed beneficial for some community pharmacists in our study to also consider the body composition, i.e., amount of body fat and muscle of their clients in addition to BMI. Nevertheless, the Clinical Practice Guidelines on Management of Obesity by the Ministry of Health Malaysia (12) was last updated in 2004, and thus it may be not surprising that none of the community pharmacists in our study depended on the guidelines for their weight management practices. This highlighted the need to update the guidelines according to contemporary evidence to serve as a reference for community pharmacists and other health care professionals to standardize their weight management practice.

It is encouraging to observe that community pharmacists in our study placed the highest importance on comprehensive lifestyle interventions, comprising of a combination of dietary and physical activity modification, among all other weight management interventions. Beneficial effects of comprehensive lifestyle interventions have long been documented within the literature, and one such example would be the Diabetes Prevention Program, which adopted a comprehensive lifestyle intervention and reported superior outcomes in diabetes prevention with lifestyle intervention compared to pharmacologic intervention with metformin (15). While community pharmacists did acknowledge the behavioral elements of weight loss, it would be ideal if they could provide a structured behavioral program that includes cognitive behavioral therapy alongside comprehensive lifestyle interventions. Behavioral-based treatment programs improve weight loss results and are associated with improvements in obesity-associated morbidity (16).

Community pharmacists in our study would carefully screen for the suitability for the initiation of drug therapy, in which they would reserve for clients who have failed other weight management interventions, and thus was in accordance with drug manufacturers' recommendations. Nevertheless, it is noteworthy to observe that almost all community pharmacists in our study engaged in the sales of weight loss products or supplements. To date, evidence to support the efficacy and most importantly, the safety of over-the-counter weight loss products and supplements is still limited (17, 18). Moreover, within the literature, community pharmacists have been subjected to close scrutiny, where criticism from consumers emerged in the social media with regards to the perceived conflicts of interest of community pharmacists selling weight loss products to increase their net revenue (5, 19). Consumers opined that community pharmacists' advice on weight management may be biased in order to profit from selling a product (19, 20). While it is understandable that community pharmacists need to maintain a viable business, and therefore stand to gain from the sales of weight loss products or supplements, this role conflict must be addressed, and a balance achieved so that pharmacists do not allow business objectives to undermine their positive public professional image.

Baseline knowledge regarding various aspects of the evidence-based obesity management such as dietary approach, physical activity recommendation, and pharmacological therapy, as well as associated health risks, would be expected for community pharmacists providing WMS. Similar to our findings, lack of training related to obesity management was occasionally singled out as a barrier to pharmacist-led interventions within the literature (21). Community pharmacists in our study deemed training in weight management to be effective and beneficial. Perceived training needs in weight management identified by community pharmacists in our study, such as behavioral therapy, exercise, dietary counseling, and communication skills, were similar to those reported in other studies (5, 22, 23). Additionally, the desire of community pharmacists for the involvement of other health care professionals in weight management training indicated the willingness of pharmacists to understand their role and thus adopt a multidisciplinary team approach to weight management.

Barriers identified by community pharmacists in our study were mainly organizational in nature, which included lack of private consultation rooms, lack of time, and lack of qualified staff. It is good for community pharmacists to acknowledge the lack of private consultation rooms as a barrier. From patients' perspective, there is a lack of sensitivity about privacy

requirements for discussions of sensitive issues such as obesity in community pharmacy (24). The issue of privacy was also raised in the findings of the previous quantitative study (8), in which it was one of the factors influencing the acceptability of community pharmacist-led WMS. In addition, the availability of a consultation room for discussion and consultation of all health issues to take place was one of the patient's considerations when choosing a pharmacy in the United Kingdom (25). The Community Pharmacy Benchmarking Guideline of Malaysia, which serves as a set of standards that are required to be complied with for the purpose of community pharmacy practice set up in Malaysia, has recommended the installation of properly designated, private, and comfortable counseling areas (26).

On the other hand, previous studies aimed to evaluate pharmacist workload in community pharmacy indicated that pharmacists spent most of their time in dispensing medications, with little time allocated for patient counseling and interaction. For example, a study aimed to quantify the proportion of time the community pharmacists spent on various work activities noted that more than half (56%) of the community pharmacists' working time was dedicated to medication dispensing responsibilities, while patient counseling activities only constituted about one-fifth (19%) of pharmacists' working time (27). Therefore, it is not surprising to observe that a lack of time posed a major barrier to the administration of WMS in community pharmacy, from the perspectives of community pharmacists in this study. It has been proposed that by increasingly involving trained pharmacy assistants in the dispensatory role, it would free up some time of community pharmacists to involve more actively in patient counseling activities. Nevertheless, it remains to be determined if such an approach would undermine patient safety and be beneficial for the implementation of WMS in the community pharmacy.

Community pharmacists also cited lack of remuneration or reimbursement as one of the barriers to the delivery of WMS in community pharmacies. Similar qualitative studies in Australia and New Zealand had also unanimously highlighted the issue of lack of remuneration for time spent to administer WMS, and the difficulties to effectively administer WMS without remuneration (4). Remuneration is associated with clients' acknowledgment of the value of WMS provided by the pharmacist. There is therefore a need to demonstrate the value of community pharmacy-based WMS and evaluate the service economically by linking the aggregated clinical outcomes to the financial resources required to achieve these outcomes to demonstrate the cost-effectiveness of the service. Demonstrating the value of WMS would be instrumental in marketing the value of the service that our community pharmacists are providing and thus attract remuneration from stakeholders.

This was an in-depth qualitative study conducted with community pharmacists in Malaysia. To our knowledge, this is the first study to explore Malaysian community pharmacists' role in weight management. However, there are limitations to our study. Our findings may be limited in that the sample was confined to community pharmacists working in the Klang Valley area of Malaysia. While we expect that the findings apply to community pharmacies elsewhere in Malaysia, we do not rule out any possibility that some highlighted issues are specific to the geographical location in which it was conducted. Another possible limitation is that participants may have given professionally desirable responses. In addition, the views of community pharmacists in this study were limited to those who had experience in weight management or those who had attended prior training programs in this area. It may be possible that pharmacists with no experience in weight management may have different views than the ones reported here.

CONCLUSION

In general, community pharmacists in this study believed that they can positively contribute to the area of weight management. They cited multiple roles that they could play in weight management interventions and services, including provision of education and advice, selection of weight loss products and supplements, monitoring, and providing referrals to other healthcare professionals. However, practical barriers such as the lack of space, time, and reimbursement, were acknowledged. These barriers would need to be addressed to strengthen and improve community pharmacists' roles and contributions in WMS. This may include reviewing current training programs in weight management for pharmacists, and appropriate remuneration models for community pharmacy-based WMS.

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/s.

ETHICS STATEMENT

Ethical approval for this study was obtained from National University of Malaysia, Malaysia (UKM PPI/111/8/JEP-2018-664). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RV and WC conceived the study. RV carried out the interviews, analyzed the data, and drafted the manuscript. WC, NT, and TP assisted with data analysis and manuscript revision. All authors have read and approved the final manuscript.

FUNDING

This research was funded by the Institute for Research, Development, and Innovation (IRDI) of International Medical University, Kuala Lumpur, Malaysia

ACKNOWLEDGMENTS

The authors would like to acknowledge all the participants for spending their valuable time for the interviews.

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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.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 20 September 2021
doi: 10.3389/fphar.2021.693748

A Qualitative Study on Medication Taking Behaviour Among People With Diabetes in Australia

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Background: Australia has a high proportion of migrants with an increasing migration rate from India. Type II diabetes is a long-term condition common amongst the Indian population.

Aims: To investigate patients' medication-taking behaviour and factors that influence adherence at the three phases of adherence.

Methods: Semi-structured interviews were conducted with a convenience sample of 23 Indian migrants living in Sydney. All interviews were audio-recorded, transcribed verbatim and thematically analysed.

Results: ***1) Initiation:*** The majority of participants were initially prescribed oral antidiabetic medicine and only two were started on insulin. Most started taking their medicine immediately while some delayed initiating therapy due to fear of side-effects. ***2) Implementation*:** Most participants reported taking their medicine as prescribed. However, some reported forgetting their medicine especially when they were in a hurry for work or were out for social events. ***3) Discontinuation:*** A few participants discontinued taking their medicine. Those who discontinued did so to try Ayurvedic medicine. Their trial continued for a few weeks to a few years. Those who did not receive expected results from the Ayurvedic medicine restarted their prescribed conventional medicine.

Conclusion: A range of medication-taking behaviours were observed, ranging from delays in initiation to long-term discontinuation, and swapping of prescribed medicine with Ayurvedic medicine. This study highlights the need for tailored interventions, including education, that focus on factors that impact medication adherence from initiation to discontinuation of therapy.

Keywords: medication taking behaviour, medication adherence, type 2 diabetes, indian migrants, factors, three phases of adherence

OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Fahad Saleem, University of Balochistan, Pakistan
Kate McBride, Western Sydney University, Australia

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *11 April 2021*
Accepted: *24 August 2021*
Published: *20 September 2021*

Citation:
Ahmad A, Khan MU and Aslani P (2021) A Qualitative Study on Medication Taking Behaviour Among People With Diabetes in Australia. Front. Pharmacol. 12:693748. doi: 10.3389/fphar.2021.693748

INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic disorders characterised by hyperglycaemia, caused by a lack of insulin release as well as its activity (Diabetes Australia, 2018). There are several types of diabetes, with the two most prevalent types being type 1 (T1D) and type 2 diabetes (T2D) (Diabetes Australia, 2018). T1D (also known as insulin dependent or juvenile diabetes) is characterised by lack of insulin production by the pancreas and accounts for 5–10% of total cases (American Diabetes

Association, 2014; Diabetes Australia, 2018; IDF Diabetes Atlas, 2019). T2D (also called non-insulin-dependent diabetes) occurs due to inadequacy of the body to effectively utilize insulin (IDF Diabetes Atlas, 2019). T2D accounts for the majority of cases (85–90%) around the globe (Diabetes Australia, 2018). As the research presented in this article explores understanding of T2D management in Indian migrants in Australia, only issues related to T2D have been presented.

Diabetes is a long-term, progressive medical condition that requires continuous monitoring and management (Low et al., 2016). The main goals of diabetes management are to reduce symptoms, prevent associated complications and improve quality of life (Low et al., 2016). Patients can achieve these goals by adhering to their medicine (Krapek et al., 2004), lifestyle modifications such as a healthy diet, and regular exercise to maintain optimal blood sugar levels and body weight (Chang et al., 2007; Naja et al., 2014). However, poor medication adherence in T2D is well documented to be very common, and the clinical burden of non-adherence to antidiabetic medication is associated with inadequate glycemic control; increased morbidity and mortality; and increased costs of outpatient care, emergency room visits, hospitalization, and managing complications of diabetes (Polonsky and Henry, 2016). The incidence of anti-diabetic medication adherence has been reported to range between 38 and 93% (Polonsky and Henry, 2016). For example, in the United Arab Emirates, Ethiopia, Uganda, Switzerland, Botswana, and India medication adherence has been reported as 84% (Arifulla et al., 2014), 85.1% (Abebaw et al., 2016), 83.3% (Bagonza et al., 2015), 40% (Huber and Reich, 2016), 52% (Rwegerera et al., 2018) and 82.4% (Basu et al., 2018), respectively. Dhippayom et al. (2015) conducted a study among Australian patients with type 2 diabetes and found that adherence to anti-diabetic medicines was suboptimal at 64.6% (Dhippayom and Krass, 2015).

In Australia, T2D is a leading cause of morbidity and mortality and approximately 1.2 million people have been diagnosed with T2D (Diabetes in Australia, 2020). According to the Australian Bureau of Statistics as of June 2019, approximately 2.6% of the total Australian population are migrants from India (Australian Bureau of Statistics, 2020). There is a very high prevalence of diabetes among Indian-born migrants (14.8%) compared with the Australian-born population (7.1%) (Centre for Epidemiology and Research, 2006), with a higher rate of hospitalisation due to diabetes and its complications (New South Wales Health, 2008). Indian migrants may face unique healthcare challenges. Maintaining normal blood sugar levels may not be easy among Indian migrants because of several other factors affecting their health. For example, an unhealthy diet (Wells et al., 2016), poor physical activity (Venkatesan et al., 2018), poor medication adherence (Venkatesan et al., 2018), poor awareness about the health system (Straiton and Myhre, 2017), high costs of treatment (Grattan Institute, 2021), stress related to migration (Chiarenza et al., 2019), finding a job, and other family related issues (Worthington and Gogne, 2011). Furthermore, their cultural and religious beliefs may also affect their medication-taking behaviour (Worthington and Gogne, 2011).

Vrijens et al. (2012), categorised adherence into three phases, initiation, implementation, and discontinuation. "*Initiation*" was defined as "*when a patient takes the first dose of prescribed medication*". Initiation is followed by "*implementation*", and this relates to "*the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen*". "*Discontinuation*" is "*when the next dose to be taken is omitted and no more doses are taken thereafter*" (Vrijens et al., 2012). Understanding each phase is important in identifying and exploring effective ways of improving adherence.

While previous research indicates that many contributing factors have yet to be identified (Krass et al., 2015), this could be due to factors affecting different populations and factors influencing the three stages of adherence. The majority of studies in the literature either have not disclosed the phase of adherence studied (Hugtenburg et al., 2013; Sapkota et al., 2017) or did not investigate adherence at a specific phase. Moreover, the studies mentioned above which have reported adherence rates, have not necessarily reported rates according to the three phases of adherence.

While adherence to anti-diabetic medicines in the Australian community was found to be suboptimal (Dhippayom and Krass, 2015), there are limited studies on adherence and medication-taking behaviour among the migrant population in Australia. To date, no study has attempted to understand anti-diabetic medication-taking behaviour among Indian migrants with diabetes in Australia. Therefore, this in-depth qualitative study aimed to investigate patients' medication-taking behaviour and factors that influence adherence, particularly at its three phases.

METHODS

Qualitative Research

Qualitative studies provide a rich exploration of individuals' experiences and perspectives (Holloway, 1997). Qualitative methodology is valuable in developing a deeper understanding of the behaviour of patients taking anti-diabetic medicines and the factors that influence their medication taking, as quantifying the findings does not fully capture individuals' experiences. This study was part of a larger research project that investigated the medication taking behaviour of Indian migrants with type 2 diabetes living in Sydney, Australia. This paper only reports on the findings of the questions about participants' medication-taking behaviour and factors that influence adherence.

Research Questionnaire

The semi-structured interview questionnaire addressed the research aim of investigating Indian migrants' (with type 2 diabetes) understanding of the Australian healthcare system, their medication-taking behaviour, and disease management. The questions were developed based on previous research (Ching et al., 2013; Ahmad et al., 2015; Namageyo-Funa et al., 2015; Zainudin et al., 2017; Sapkota et al., 2018; Garad and Waycott, 2015). In-depth, face-to-face interviews were conducted with eligible participants at public places in Sydney, Australia. The semi-structured questionnaire was tested for its content and face validity with four participants, consisting of two qualitative methods researchers acting as pseudopatients, one member of the public (Indian migrant) and one Indian migrant

with type 2 diabetes. Only minor wording changes were made before the actual interviews were conducted. At the beginning of the interview, the participants were provided with the Participant Information Statement to ensure that they had had the opportunity to read the information and ask questions, in addition to when they received the PIS at recruitment. Participants were also asked to complete a brief questionnaire on demographic details, and the Summary of Diabetes Self-Care Activities (SDSCA) (for adherence data).

Ethical Approval and Participant Recruitment

This study was approved by the Human Research Ethics Committee (2018/415) of The University of Sydney. Participants were recruited within Greater Sydney and its surrounding suburbs, using three approaches. Firstly, advertising was conducted *via* Facebook, Gumtree, and Indian news media e.g., Indian Link. Secondly, Indian organisations and associations were approached to post the study flyer on their social media channels and distribute among their members. Thirdly, passive snowballing was used *via* the participants. Interested participants contacted the researcher directly. The researcher then provided further information about the study (a copy of the Participant Information Statement (PIS) which included detailed information about the study, and other issues such as anonymity, confidentiality and voluntary nature of participation in the study), and if the person enquiring was interested in participating, assessed them for eligibility before discussing an interview time and location. All participants were provided with study information in an unbiased manner so that no coercion was perceived by the potential participants.

Participants were included in the study if they were:

- 18 years or above
- diagnosed with type 2 diabetes and using at least one anti-diabetic medicine
- Indian born migrant living in Sydney as an Australian citizen or as a permanent resident
- not dependent on others to administer their medicine
- fluent in English or Hindi.

Written consent was obtained from each participant before the interview was started. The interviews lasted for about 40–45 min. The interviews were audio-recorded. All interviews, except one (conducted in Hindi), were conducted in English directed by the PhD student (AA) who is a registered pharmacist in India and trained in qualitative research techniques. The data saturation point was defined as the point after which no new data was acquired. Saturation was accomplished by the 18th participant and a further five interviews were conducted to ensure confirmation of identified themes. Each participant was reimbursed AUD 30 for their time and travel expense.

Data Analysis

The interview recordings were transcribed verbatim and thematically analysed by AA using a framework for thematic analysis (Spencer et al., 2003). The first four interview recordings were transcribed and analysed by AA and reviewed by PA. The remainder of the interview recordings were transcribed through a NAATI (National Accreditation Authority for Translators and Interpreters) certified transcription company. Each transcript was rechecked by AA and inconsistencies were identified and corrected. All transcripts were de-identified, and the process was completed by removing all personal information from the participants' transcripts. Data analysis was performed manually and recorded manually using Microsoft Word. Initially, the two researchers (AA and PA) independently went through some of the transcripts to gain meaning from the discussions, generated codes and derived themes. The process began as AA read the transcripts line by line and listened to the audio recordings multiple times to become familiar with the data. The initial codes were generated by AA through inductive coding. For transcript coding, a latent technique was used to capture the logical and underlying meaning of the findings. Then, important statements were identified related to the beliefs, decision-making process and experiences of the participants. After that, meanings were formulated from selected statements. Every meaning was coded and the process of combining the codes into a concept resulted in a number of themes. Finally, we combined themes to reflect the study objectives. The research team met regularly to discuss the nodes, codes, and themes generated from the transcripts.

The consolidated criteria for reporting qualitative research (COREQ) was used to provide transparency in data reporting to improve rigour, comprehensiveness and trustworthiness of the study (Tong et al., 2007).

Adherence was assessed using the Summary of Diabetes Self-Care Activities (SDSCA) was calculated based on the following formula (Toobert et al., 2000). "*% Adherence Score = Sum of adherence score for each anti-diabetic medication/(7*number of medications)*100%. Adherence score for each anti-diabetic medication = (7 − number of days medications were missed).*"

RESULTS

Demographics

Twenty-three participants were interviewed. The majority of participants were male (n = 18). Eight participants were diagnosed within the last 5 years. Sixteen participants were taking at least one oral anti-diabetic medicine and two participants were on insulin (**Table 1**).

Assessment of Medication Adherence Using Summary of Diabetes Self-Care Activities

Five of the 23 participants reported having missed at least one dose of their anti-diabetic medicine in the past 7 days. The average adherence score (%) calculated using the SDSCA questionnaire was 97.2% (**Table 2**).

Qualitative Findings

The interview findings were categorised into three broad themes, focusing on medication-taking behaviour and factors that

TABLE 1 | Demographic information of participants.

Characteristics	Variables	Data
Age (years)	Median	39
	Range	33–72
Gender	Male	*n* = 18
	Female	*n* = 5
Duration of living in Australia	<5 years	*n* = 8
	≥5–10 years	*n* = 7
	>10 years	*n* = 8
Duration since diagnosis	Median	5 years
	Range	4 months—40 years
Types of antidiabetic medicines	Oral	*n* = 16
	Oral + insulin	*n* = 0
	Insulin	*n* = 2
	Oral + Ayurvedic medicine	*n* = 3
	Ayurvedic medicine	*n* = 2

TABLE 2 | Assessment of medication adherence using SDSCA (*n* = 23).

Data on anti-diabetic medicines	Data
Minimum number of medicines	1
Maximum number of medicines	4
Median	2
Average	1.60
Adherence assessment SDSCA	—
Minimum score (%)	71.4
Maximum score (%)	97.2
Average score (%)	92.9

influence adherence at the three phases of adherence: initiation, implementation, and discontinuation. The factors influencing adherence were separated for each phase and grouped into facilitators and barriers.

Participants reported that they were diagnosed with diabetes either as a result of a routine health check-up ($n = 6$); when they suspected to have a diabetes-related symptom(s) and proceeded to self-test in India ($n = 8$); or when they went to see their doctor for non-diabetes-related complaints/symptoms ($n = 12$), or a combination of the above ($n = 3$). They initiated prescribed medicine alongside self-medication such as with Ayurvedic medicine (AM) and/or supported by religion and spirituality. The findings on AM and the impact of religion and spirituality have been presented elsewhere (Ahmad, 2021).

Medication Taking Behaviour and Practices

The majority of participants initiated their therapy soon after their diagnosis while some participants tried Ayurvedic medicines that were brought from India, initially with or without conventional medicine. If no benefits were seen in their blood sugar levels after using the AM, participants went back to the prescribed regimen. Once patients made their decision to adhere to the prescribed medicines, they felt and reported that there was no difficulty in adhering to the medicine.

Initiation

The majority of participants were initially prescribed an oral antidiabetic medicine and only two were started on insulin. Five participants were first advised of using non-pharmacological approaches such as physical exercise and a restricted diet before they were prescribed an oral antidiabetic medicine. The majority of the participants started taking their prescribed medicine, while some were in a dilemma whether to start because of various concerns such as long-term use and side-effects.

Facilitators for Initiating Prescribed Medicines

Desire to Improve Diabetes Outcome. Most of the participants reported that the key facilitator for initiating medicines was that they understood the importance of medicines in improving diabetes outcomes. They wanted to control their blood sugar level and knew that if they did not start, their blood sugar level could increase further and create problems. Importantly, they reported that starting their medicine reduced the chances of future diabetes-related complications.

> "I know very well about diabetes, it's a very dangerous disease, it will affect my organs like my kidney, eye etc, so you need to control it and it can only be managed with medications" [PD 9]

GPs Recommendations and Being Informed About Medicines

Most of the participants reported that GP consultations and their advice was an important factor in motivating them to initiate medicines as soon as they were diagnosed with diabetes. There was a clear disparity in participants' awareness of diabetes and its pharmacological and non-pharmacological treatment options, as well as the information they had received from their GPs. Those diagnosed in Australia tended to receive information from their GPs to increase their knowledge about diabetes and its treatments, and to reduce their fear and misconceptions about the medicine. This supported the participants to initiate medication taking. Additionally, these participants reported that they received very good diabetes-related services in Australia, which they reported were as a result of their visit to the GP. These services included a health plan, dietician and eye testing, which they felt better supported their diabetes treatment and care. In contrast, the experience of those who were diagnosed in India was regarded as far from optimum. Participants reported that the doctors only prescribed the medicine, and they had to pay for all other services themselves or through private insurance. They felt that they were not educated about their condition or medicine. Participants reported that they at first did not agree to use the medicine as a result of lack of understanding, but that they later decided to initiate the prescribed medicine after they had been informed either by receiving information or having searched for information themselves.

> *"In my opinion, you need to trust your doctor and follow their advice, that's what I've learned from my experience."* [PD 3]

"I'm lucky to [be] diagnosed in Australia, when I got diagnosed with diabetes, I got a healthcare plan . . . I got four sessions with a dietitian and eye check up to plan out my wellbeing, that kind of thing, so yeah it's good...but in case of India, its totally opposite, I have to pay for everything and public healthcare system totally bad over there, I never use it, I always go to my private doctor" [PD 7]

"I was diagnosed with blood donation camp in India, but my sugar was high later on when I was prescribed [Brand X] [metformin], no other information provided... I wasn't ready to start medication, I wasn't comfortable with a lack of understanding about diabetes and medications, but I started looking for diabetes, videos on Youtube, I did my own research, and my knowledge grew and was more comfortable." [PD 17]

Negative Beliefs About Medicines

Negative beliefs about medications was an important barrier to initiating therapy. The fear of side effects and medication dependence were the main factors mentioned by the participants.

However a few, despite the prescription issued by their GP, had delayed their initiation. The period of the delay ranged from a few months to a few years. They opted to start with some alternative therapies, such as home remedies, ayurvedic medicine or herbs.

"My colleague in Australia said allopathic medications [conventional medicines] have lots of side effects, you need to use it [for a] lifetime, she insisted to take ayurvedic medication because her mother using it and benefitted in India, . . . , so I decide to initiate ayurvedic medication instead of metformin as prescribed by my GP, I give try to use it, and found it effective with no side effects . . . I check the glucose level time to time . . . the name Sakkarai Kolli." [PD 22]

Fear of Injection, Discomfort and Pain

Three patients had used insulin in the past and two were currently using insulin. One patient was initiated with insulin due to high blood sugar levels. Another participant started using oral medicine and then moved to insulin, but the patient initially did not want to use insulin because of the need to inject regularly, the fear of pain, and injection scars. This resulted in a delayed use of insulin but the patient eventually started using insulin when their diabetes was not controlled with oral medication alone.

"Initially my doctor prescribe metformin but later consultant want to change it to start insulin due to my sugar level high but I do not want to use Insulin because it is injection, right, I need to use it daily, it gives 'dard' [pain] and if use injection daily scars will appear . . . I'm afraid of injection from my childhood" [PD 23]

Implementation

The majority of participants reported that they adhered to their prescribed medicines, however, they were unintentionally non-adherent through forgetting to take their medicine, especially when they were in a hurry to get to the office or when they were out at family dinners or parties.

Benefits of Antidiabetic Medication

Most reported having experienced the benefits of taking antidiabetic medicine which strengthened their confidence in the importance and need to take the medicine. Participants stated that they were more likely to continue using medicines that they have benefited from. However, what they considered as advantages of the medicine differed between the participants. For example, improved blood glucose levels and health fitness, were two positive outcomes reported by the participants.

"My GP prescribed metformin initially and [I] start taking medication and it control my sugar. . ..improves blood glucose level and also feel physically fit" [PD 1]

Intentional and Non-intentional Missed Doses

The majority of participants said that medication-taking had become a habit for them and they did not tend to forget to take their medicine. There were some who mentioned that they sometimes forgot to take their medicines because medication-taking was not an established part of their daily routine as yet. They were sometimes reminded by their family members or they used their mobile phone alarm as a reminder. Some participants did take their medicines as soon as they were reminded, while others skipped the dose and decided to continue with the next dose. Some participants also reported that they did not completely adhere to the prescribed regimen as they may miss a dose or there may be delays in their meal times due to religious and cultural rituals, festivals, etc. Sometimes unplanned social gatherings also influenced the timing of their meals and affected the timing of medication use, and sometimes this resulted in a missed dose.

Participants' behaviour indicated that adherence to prescribed medications was intentionally and non-intentionally non-adherent.

"Initially I may have been forgotten, but now it's in my everyday work routine. Usually 99% [of the time I] don't forget to take medication, but sometimes forgot about it because of some weird scheduling, you have to do something else, or you've gone out or you're out of town, xyz." [PD 9]

Some participants reported to have not adhered to their prescribed medicine because they did not want to take medicine or felt that they were careless about looking after their diabetes due to a lack of knowledge and motivation to adhere.

"First few periods, I was very reluctant, forget. My problem was I was quite rebellious to take it in precise. Nothing's going to happen to my body, I'm fit and fine, actually I was careless. I was not fully aware about diabetes and its future consequences. Over the period I read, study about diabetes

and also my wife remind and motivate me, taking these medications." [PD 11]

Some participants said they used a pillbox (e.g.,Webster pack) to help them take their medicine on time. One of the participants said that she kept her pillbox next to the bottle of water as a reminder for her to take her medications whenever she went to drink water.

"Nowadays I am using medication box, I keep for one week or one month some times, ... If you see the box is empty . . . So it's a way to remind you." [PD 5]

Some participants shared their strategy of dealing with forgetfulness, especially if going out. To avoid forgetting to take their medicines, they ensured that they always carried their medicines with them, especially when going to social gatherings. One female participant noted that it was challenging to remember to take medicines when at social gatherings. She mentioned that she always carries her bag with necessary medicines, jelly beans and some fruits.

"Whenever I got invited [to] any social or religious gatherings, first thing is I will ask, 'What time you will give dinner?'. . .they reply 'We will give you food at 7.30'. . . I will have my medication planning, . . . I need to take my insulin, jellies and some fruits, so if needed or late so I can take accordingly . . . if they delay I will go straight to the kitchen and I will ask, "Who is responsible for this food." [PD 21]

Fear of Side Effects and Medication Dependency

Once they started taking medication, the key concerns were around side effects and addiction which negatively influenced medication use and adherence. The majority of participants held the belief that conventional medicines have side effects and once they started taking medicines they would not be able to stop, which led them to continue and remain dependent on their medicine. Participants' reported that diabetes is a long-term condition and that patients have to rely on taking medicines for all of their lives.

"Taking medication . . . want control my sugar as soon as possible, My plan is that I am going to be on this medication only for 1–2 years. Want to be away from all these strong drugs [because of side effects] and make addicted, do not want dependency on the medication, need to avoid as much as can . . . going to start natural method such as ayurvedic medication" [PD 19]

Stigma Related to Diabetes

Many participants, however, delayed taking their medicines when they were out as they were not comfortable letting others know that they were diabetic. This feeling of discomfort also extended to their diet and showing anything different that would identify that they may be diabetic. For example, when taking tea or coffee, they did not inform people that they did not take sugar because of their diabetes. Participants mentioned that they made up for skipping a dose by increasing the next dose of their medicine.

"A lot of Indian Diabetic patients and in social or religious getherings, nobody will open their mouth for example they need tea without sugar. . ...in Indian culture after food provide sweets. If someone offer tea, sweets, or anything no one refuse, even myself initially for few years, use the same and its put extra calorie in their diet . . . they always said "Oh! I will take one more tablet now I did not take and straight away say to them, I am diabetic" [PD 21]

Participants raised concerns about the social stigma associated with diabetes, especially young patients with diabetes who did not disclose to others about their condition. They believed that the stigma negatively affected their dietary habits, scheduling appointments with a physician, and medication-taking behaviour (delayed or postponed medication use).

"Initially I met my GP in Australia and [was] diagnosed with type 2 diabetes and started with metformin but I did not inform my wife, and even to my parents that I am diabetic, So I do not take medicine in front of her [wife]. . .I am young, just 36 year old. . .. later inform only wife and father . . . my mother doesn't know, untill later and any of relatives or my friends, colleagues . . . wherever we go in social or religious gatherings, I used to take same food as no one knew that I am diabetic . . . the problem in Indian community they will show pity, "OMG you are 'beemar' [ill person]"..they will give advice take this and that to cure diabetes that's why I do not want let others know I have diabetes. For my wife, initially, did not inform, because it would put fear in her. . .. I feel guilty of not seeing a regular GP and not taking medicine on time." [PD 7]

Discontinuation

This theme provides an overview of why participants discontinued their medicines.

Fear of Medication Side-effects

Fear of side effects was also identified as a common barrier to persistence with medication use, and therefore, a key facilitator of medication discontinuation. Only three participants had discontinued their conventional medicine because of the fear of experiencing side effects. They had commenced ayurvedic medicine instead as they believed it was made up of natural herbs, and hence, free of any side-effects.

It was noticed that participants discontinued and then restarted the medicine a few times in their medication-taking journey. For example, one participant discontinued his medicine a few times due to fear of side effects and started taking ayurvedic medicine. When he visited India (usually on vacation every year), he stopped his prescribed conventional medicines and sought some ayurvedic medicine as suggested by his brother/relatives as they believed that it would be effective to regulate his blood sugar levels and was free from side effects.

> *"Initially insulin start (sugar was high) . . .. continued . . .. When it was normal after 4–5 months and few times went to India as it was suggested by my brother to take ayurvedic medication, he told that its really effective and no side effects."* [PD 2]

Another participant reported he discontinued his prescribed medicine for a month to try ayurvedic medicine, but resumed taking the prescribed medicine when he did not experience any benefits with the ayurvedic medicine.

> *"Immediately start metformin, later it was under control . . . my friend brought from India ayurvedic medication he was a diabetic and using it . . . said like its very effective, its made with all-natural ingredients, but no I didn't see much benefit out of it, I used it for 1 month... my friend told me that if we used this ayurvedic medication on a regular basis, diabetes would be gone completely. My sugar level was still high so again back to my medication that was prescribed by my GP."* [PD 14]

One other participant reported that he discontinued his medication for 1 year and managed his diabetes through his lifestyle changes such as restricted diet, exercise, and meditation.

> *"I was diagnosed in 2002, since then using prescribed medications but later stop taking medication because I know predicted bad consequences in later life. I believe diabetes is a condition due to bad lifestyle and need to change it . . . no need to take medication . . . 1 year no medication taking and manage well with his healthy diet, exercise and meditation with some herbs."* [PD 4]

DISCUSSION

To the best of our knowledge, this is the first study conducted among Indian migrants with type 2 diabetes in Australia that explored their medication-taking behaviour and factors affecting their adherence to prescribed anti-diabetic medicine. The findings of this study provide insight into the participants' medication-taking behaviour. The findings revealed that once a patient understood the need for a medicine to control their diabetes, they adhered better to their medicine; however, some discontinued and restarted their medicine due to fear of side-effects, medication dependency, and also to try ayurvedic medicine to manage their diabetes.

The qualitative nature of this study allowed for the exploration of participants' medication-taking behaviour and how it changed from the initiation to discontinuation phase. Initiation of medicine occurred after the participants were diagnosed with diabetes and prescribed their medicine. At the initiation phase, most participants recognised that there were some health problems related to diabetes which needed to be resolved by medicines. Once they were diagnosed and prescribed a medicine by the physician, most participants initiated their therapy. Participants' decision to initiate medicines was motivated by their belief in antidiabetic medicines and their desire to improve their health outcomes of diabetes.

An interesting finding of our study was the disparity reported by the participants who were diagnosed in India and Australia about awareness of diabetes and its management (pharmacological and non-pharmacological). Those diagnosed in Australia, showed a good understanding of diabetes and its medicines as they received information from their GPs when they were diagnosed to increase their knowledge about diabetes and its treatments, and reduce their fear and misconceptions about the medicines. These were the key facilitators for the initiation and continuity of anti-diabetic medicines. On the other hand, those diagnosed in India reported that they were only given a medicine by the doctor, and no other information was provided to them, and they thought that they had not been informed about their condition or medicine, which meant that their knowledge about diabetes and its therapy was sub-optimal in their opinions. Because of their poor understanding, they did not agree to initiate therapy and postponed medication taking for some time. Knowledge was therefore important in medication taking decision making. Similar findings have been reported in the literature, where those diagnosed with diabetes in India, have shown poor knowledge of diabetes, medicines and its prevention methods (Murugesan et al., 2007). Due to this lack of knowledge, they were reluctant to screen for further complications related to diabetes (Agarwal et al., 2005). Further, another study demonstrated poor awareness and hesitancy among newly diagnosed people with diabetes to screen for the retinopathy (11.6%) (Agarwal et al., 2005). These findings indicate a lack of adequate education regarding diabetes among the general public and also in diabetic patients especially those diagnosed in India. Therefore, serious efforts are required to educate patients about prevention and complications related to diabetes especially when they are first seen in an Australian GP clinic after arriving in Australia, or when first diagnosed in Australia.

The negative beliefs about medications (barriers) were reported by participants e.g., side effects, insulin use related discomfort, which delayed consultation with a doctor or delayed initiating prescribed conventional medicines regardless of their high blood sugar. During this period (when delaying or not taking their conventional medicine), participants tried some ayurvedic medicines and/or lifestyle modification and evaluated those strategies for any harmful or beneficial effect on their condition. Delay in seeking help from the healthcare providers or the initiation of their treatment was also reported by (Sapkota et al., 2017). Lack of knowledge about the actual side effects of diabetes medications may have contributed to the negative beliefs (Sapkota et al., 2017). Previous research has also identified that a lack of knowledge about diabetes medicines can lead to misconceptions about the medicines. Some participants who believed that the medication would harm them, delayed initiation of therapy. This finding was also reported by Polonsky and Henry, (2016). Some participants used insulin and initially did not want to initiate insulin use because they needed to inject regularly, and this caused anxiety and fear about the pain and discomfort caused by the needle. Studies have revealed that anxiety and fear of injection-associated pain have

been reported to affect approximately 30–50% of patients initiating insulin (Kruger et al., 2015).

The physician-patient relationship was also identified as an important factor impacting medication adherence, especially in the transition from initiation to the implementation phase. In this study, those who were diagnosed in Australia showed a good physician-patient relationship and communication which led to a better understanding of diabetes and medications. Previous research indicates that a good relationship with a GP (physician) may have a positive effect on a person's decision to initiate therapy (Chipidza et al., 2015). Where diet and exercise have not been effective in controlling a person's blood glucose levels within the target range, early initiation of antidiabetic medicines is important for effective diabetes control (Diabetes Australia, 2018). Delaying initiation of therapy can affect the general control of blood sugar levels. GPs must identify those patients that may delay medication taking and help them make informed decisions about initiating medicines to improve their health outcomes.

Implementation and Discontinuation Phase

In this study, once patients decided to initiate the medicine, they tended to continue with their medication, and continuation appeared to be influenced by their experience with medication use and the benefits gained. The findings indicate that patients were actively weighing their benefits (positive experience) against their concerns (negative experiences) in deciding to continue with the medicine. Positive experiences were primarily affected by medication benefits such as improved blood sugar levels, and overall well-being, and the negative experience was attributed to fear of side effects, drug dependence and also stigma related to diabetes. Such results indicate that participants whose positive experience with medicines out-weighs the fear of possible negative experience, are more likely to continue and adhere to medicines during the implementation phase. At the implementation phase, further adherence to medications can be increased by reducing their diabetes-related stigma by physicians educating their patients on diabetes and medications. An example of the extent of stigma experienced was not letting anyone in the Indian community know about a person's diabetes, which then led to non-adherence, in the form of skipping medications or delaying medication-taking when around other Indians in the community. This delay in medication-taking due to social community stigma appears to be an important factor among Indian migrants. They also did not seem to share information that they were diagnosed with diabetes even with their close relatives as they believed that people will pity them and start advising on controlling their diabetes. A review conducted on stigma related to diabetes in India showed that a person with diabetes is considered or branded as a sick person (Thanushiya et al., 2019). Social stigma towards people with diabetes affects several aspects of a person's life and affects overall outcome (Capistrant et al., 2019). Therefore, there is a need to create awareness and educate people about diabetes and its medication, and related stigmas.

This study found that fear of side effects was the principal cause of medication discontinuation. The findings are similar to those reported by Thanushiya et al. (2019) in Sri Lanka which showed that 68% of patients were skipping their medicine due to fear of side effects (Gunathilake et al., 2017). Another study conducted among Indian and Pakistani migrants with diabetes in the United Kingdom reported poor adherence due to safety concerns (fear of side effects) (Lawton et al., 2005). Indians generally believe and/or think that conventional medications are required to be used for long-term which may be associated with side-effects. Once the blood sugar level is under control, it is common among patients to discontinue their prescribed medication and start self-medication with alternative treatment such as ayurvedic medicines. This behaviour may be due to a lack of understanding about diabetes and the importance of adhering to prescribed medication even when they feel better (Porqueddu, 2017).

Participants who decide to adhere to medicines usually trade-off between benefits and adverse effects (concerns) based on their belief and experience, demonstrating the supremacy of intentional non-adherence in the implementation to discontinuation phase (Horne et al., 2013). Addressing the perceptual barriers, such as effective management of side effects, can improve the overall experience of patients with their medication, which can help in preventing intentional non-adherence.

The present research supports previous results and incorporates other factors such as medication dependency, self-medication and available alternative medicines (such as ayurvedic medicine) as factors that affect medication cessation (discontinuation) (Sapkota et al., 2017). Participants reported that their concerns about medication dependency affected their decision to avoid taking medicines. There is little evidence on patients with diabetes and their beliefs about being dependent on their antidiabetic medicine. Participants became worried about their dependence that could lead to early medication discontinuation. Several approaches may be used for resolving patients' fears about reliance on medicines and therefoe improving adherence, such as education about anti-diabetic medicines.

LIMITATIONS

This study has some limitations such as a low number of women, and the fact that the findings of a qualitative study, by its very nature, cannot be generalised. Also, the study was in a population of Indian migrants in Australia, who were on at least one antidiabetic medication, and reported high adherence rates. The findings therefore may not be applicable to other Indian populations elsewhere.

CONCLUSION

Medication-taking behaviour among Indian migrants changed, and was influenced by different factors, at the different phases of medication-taking. At the initiation phase, most started their conventional medicine as soon as prescribed by GPs, while some postponed treatment initiation. The decision to initiate and continue with medication taking was based on a balance between concerns and needs. The key

motivation was the desire to improve diabetes outcome (control blood glucose level), and some participants were motivated by advice/recommendations from GPs and the information they received about the medicine to initiate treatment. Medication benefits continued to influence adherence during the implementation phase. Negative factors such as stigma and fear of side effects and drug dependence were barriers to adherence during the implementation phase. Potential side effects were a common barrier to medication at all three phases. A few participants discontinued taking conventional medicines once they started experiencing the benefits and moved to Ayurvedic medicines; however, they restarted conventional medicines if the desired results were not achieved with the Ayurvedic medicine. The existence of adherence phase-specific factors underlines the dynamic nature of medication adherence and indicates that adherence factors may change during the medication-taking journey. Therefore it is important to recognise phase-specific factors that can be the basis for effective and lasting interventions to enhance medication adherence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will not be made available by the authors as the authors do not have approval from the Human Research Ethics Committee of The University of Sydney to release such data. Only de-identified group data is available.

ETHICS STATEMENT

This study was approved by the Human Research Ethics Committee (2018/415) of The University of Sydney. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AA and PA designed the research study. AA collected and analysed all the data, and wrote the first draft of the manuscript. PA contributed to data analysis. MU and PA contributed significantly to all drafts of the manuscript and its final version. All authors have read and agreed with the final manuscript.

ACKNOWLEDGMENTS

Sincere gratitude to all study participants for taking part in the study; and Indian associations/organizations/newspapers for their assistance in advertising this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.693748/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.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 21 September 2021
doi: 10.3389/fphar.2021.734637

What Factors Hindered the Access to Essential Anticancer Medicine in Public Hospitals for the Local Population in Hubei Province, China

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Background: *Cancer* poses a serious threat to one's health, which caused significant economic burden on the family and society. Poor availability and affordability resulted in some essential medicines failing to meet the basic health needs of this group of patients. The objective of this study was to evaluate the availability, prices and affordability of 32 anticancer essential medicines in Hubei Province, China.

Methods: Data on the availability and price related information of 32 essential anticancer medicines in the capital and five other cities of Hubei Province were collected. A total of 28 hospitals were sampled, which included 13 tertiary hospitals and 15 secondary hospitals. We used the standard methods developed by the World Health Organization and Health Action International to compare the differences in drug price, availability and affordability between secondary hospitals and tertiary hospitals.

Results: Overall, the availability of medicine was higher in tertiary hospitals. The average availability of originator brand (OBs) was 13.70% (tertiary hospitals) VS 6.67% (secondary hospitals), and lowest-priced generic (LPGs) was 62.83% (tertiary hospitals) VS 42.92% (secondary hospitals). The MPR value of most sampled medicines in secondary hospitals were less than 1. In contrast, the MPR of Cytarabine (17.15), Oxaliplatin (12.73) were significantly higher than the international reference price. The top three OBs' total expenses for 30-days treatment were Irinotecan, Oxaliplatin, Bicalutamide. Further, their affordability was relative low, as the costs for one course using these medicines were much higher than 20% of the minimum family monthly income.

Conclusion: Though the "Zero Mark-Up" and "Centralized procurement policy of anti-tumor drugs" policies have been implemented in China, the availability issue yet to be addressed. High price and low affordability were the major barriers to the access of

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Edited by:
Mohamed Izham Mohamed Ibrahim, Qatar University, Qatar

Reviewed by:
Ali Qais Blebil, Monash University Malaysia, Malaysia
Farida Islahudin, Universiti Kebangsaan Malaysia, Malaysia

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *01 July 2021*
Accepted: *30 August 2021*
Published: *21 September 2021*

Citation:
Chen C, Feng Z, Ding Y, Yan Z, Wang J, Wang R and Feng D (2021) What Factors Hindered the Access to Essential Anticancer Medicine in Public Hospitals for the Local Population in Hubei Province, China. Front. Pharmacol. 12:734637. doi: 10.3389/fphar.2021.734637

Abbreviations: HAI, Health Action International; WHO, World Health Organization; EML, Essential Medicine List; OB, Originator Brand; LPG, Lowest Priced Generic; NEML, National Essential Medicine List.

essential anticancer medicines. Measures should be taken to provide sufficient, available and affordable medicines to patients in need.

Keywords: essential anti-cancer medicine, availability, affordability, price, cancer

INTRODUCTION

Cancer has become a serious health problem, which contributed to severe burden of disease and even death (Zhu et al., 2019). A total of 9.6 million deaths due to cancer diseases were reported worldwide in 2018 (Erratum, 2020). China accounts for 21.0% of the worldwide new cancer cases, and total of 22.96 million Chinese residents died of cancer (Shaoqing, 2019). At present, anticancer medicine is a core component of treatment, but barriers to receiving cancer therapy such as high price of anticancer medicines and poor availability were yet to be solved (Smith et al., 2014). These problems may be related to medical information asymmetry and the distribution of responsibilities between the drug purchasing sector and the patients who bear the cost restrict competition in the market (Hasan et al., 2019).

Essential medicines are the indispensable drugs that satisfy the priority health care needs of the population. Meanwhile, they are selected with due regard to rational use and equitable access on their efficacy, safety and comparative cost-effectiveness (Beran et al., 2018). To better meet the necessary treatment needs, the Chinese government attaches great importance to the development and implementation of the Essential Medicine List (EML) (Khanal et al., 2019). In 2018, China re-adjusted the national EML, and increased the growth rate of oncology drugs by 35%. In terms of cancer treatment, the 2018 edition of the "National Essential Medicine List" added five kinds of non-targeted drugs, including Ifosfamide, Gemcitabine, Pingyangmycin, Capecitabine, and Letrozole (Dong et al., 2020). The supplementary medicines can greatly alleviate the burden of cancer treatment.

In addition, the price of 14 anticancer drugs fell by an average of 14.95% in China, as the National Medical Security Bureau issued centralized drug purchase measures and accelerated the pace of medical insurance drug-price negotiation (Chinese, Government, 2018; Kaiyue et al., 2021). Despite medical insurance policy system was improved, dozens of targeted anticancer drugs have been included in category B (local medical expense settlement institutions could bear approximate 55–70% of the patients' cost of anticancer drug) (Kunhe et al., 2017), due to the unbalanced distribution of medical resources and the per capita financing guarantee level of China's medical insurance is still relatively weak, the total amount of medical insurance controlled by provinces and hospitals has limited funds allocated for health care, as a result, many cancer drugs still have high treatment costs even after medical insurance promotion policies are implemented (Yf).

Recently, most of domestic studies on essential medicines focused on antibacterial drugs and medications for chronic diseases (Wu et al., 2018; Dong et al., 2020; Liang et al., 2020). Their study can reflect the common problems in the availability and affordability of essential drugs in China, however, the question regarding whether it is the same case for anticancer still awaits further investigation. Therefore, we investigated the price, availability and affordability of anticancer drugs in 28 public hospitals in Hubei Province, in order to explore the factors influencing the shortage of medicines and rapidly increasing health expenditure, and accordingly, propose corresponding strategies to the government and pharmaceutical management institutes.

METHODS

A cross sectional survey was conducted from November 2018 to January 2019. Data were collected on medicine price, availability and affordability information from tertiary hospitals and secondary hospitals in six cities of Hubei Province following WHO/HAI standardized approach and Health Action International (HAI) (Khuluza and Heide, 2017).

Study Design/Sampling

Area Selection

We selected six cities as survey regions in Hubei Province by referring to the Gross Domestic Product (GDP) in 2018, according to which, we selected three cities in high-income (Wuhan, Yichang, Xiangyang) and low-income (Huanggang, Xianning, Suizhou) areas, respectively (China YearBooks, 2019). Hospitals were selected using a multistage clustered approach. Firstly, we chose the best tertiary hospital as the survey anchor (it ranked the first in this area) in each city (for instance, Tongji affiliated hospital of Tongji medical college was selected in Wuhan city). After identifying the survey anchor, we selected at least one secondary hospital pharmacy, which was closest to the anchor hospital. Since Baidu maps was used to select secondary hospital pharmacies from a list of all facilities within a 3-h drive from each survey anchor hospital. But if back-up outlet was less than 50% of the medicines on the Medicine Price Data Collection form, then we would select another secondary hospital pharmacy in the sample list. Last, a total of 13 tertiary hospitals and 15 secondary hospitals in the public sector were selected from six cities in Hubei Province. As anticancer drugs belong to the category of key controlled drugs in China, hence, they are mainly available in secondary and tertiary hospitals of China. So we don't include retail pharmacies in our investigation.

Medicine Selection

A total of 32 medicines were included in this survey, referring to 2017 WHO Essential Medicine List (WEML) and 2018 National Essential Medicine List (NEML). Considering the common acute and medication conditions in tertiary and secondary hospitals of Hubei Province, we divided the selected medicines into two parts

TABLE 1 | List of 32 anticancer medicines surveyed in the Hubei Province.

Name	Strength	Dosage Form	Volume	WHO EML	NEML
Calcium Folinate	100 mg/10 ml	VIAL	1	no	yes
Capecitabine	500 mg	TAB-CAP	12	yes	yes
Carboplatin	100 mg/10 ml	VIAL	1	no	no
Ciclosporin	25 mg	TAB-CAP	50	yes	yes
Cisplatin	20 mg	VIAL	1	no	yes
Cyclophosphamide	200 mg	VIAL	1	no	yes
Cytarabine	100 mg	VIAL	1	yes	yes
Daunorubicin	10 mg	VIAL	1	no	no
Docetaxel Trihydrate	20 mg/ml	VIAL	1	yes	no
Doxorubicin	10 mg	VIAL	1	yes	yes
Etoposide	20 mg/ml	VIAL	1	yes	no
Fluorouracil	0.25 g/10 ml	VIAL	1	no	yes
Gemcitabine	200 mg	VIAL	1	yes	yes
Ifosfamide	500 mg	VIAL	1	yes	yes
Imatinib	100 mg	TAB-CAP	60	yes	yes
Irinotecan	40 mg/2 ml	VIAL	1	yes	no
Mercaptopurine	50 mg	TAB-CAP	50	yes	yes
Mesna	0.4 g/4 ml	AMPOULE	1	yes	yes
Methotrexate Sodium	100 mg/ml	VIAL	1	no	no
Methylprednisolone	500 mg	VIAL	1	no	no
Mycophenolate Mofetil	250 mg	TAB-CAP	40	no	yes
Oxaliplatin	50 mg	VIAL	1	yes	yes
Paclitaxel	30 mg/5 ml	VIAL	1	yes	yes
Tamoxifen Citrate	10 mg	TAB-CAP	60	yes	yes
Vincristine	1 mg	VIAL	1	yes	yes
Letrozole	2.5 mg	TAB-CAP	10	no	yes
Gefitinib	250 mg	TAB-CAP	10	no	yes
Bicalutamide	50 mg	TAB-CAP	28	yes	no
Hydroxycarbamide	500 mg	TAB-CAP	100	yes	yes
Vinorelbine	10 mg/ml	VIAL	1	yes	no
Tacrolimus	1 mg	TAB-CAP	10	no	no
Ondansetron	4 mg	TAB-CAP	10	yes	yes

according to the available data collected from the sample hospitals. Firstly, the intersection area of anticancer drugs were from the WHO Essential Medicine List and National Essential Medicine List, which included 20 core essential medicines. Then, additional 12 sample drugs were also included in this survey list as supplementary according to oncologist's recommendation and the actual needs of local hospitals. For each medicine in the survey, data were collected for two medicine types: the originator brand (OBs), and the lowest-priced generic (LPGs) equivalent found at each hospital.

Data Collection

With the aid of skilled pharmacy present, trained investigators visited the pharmacy department of the sampled tertiary and secondary hospitals. They collected information regarding the cost and availability using a standardized data collection form. At the end of each day, two students would enter the data into a designed MS Excel Workbook provided as a part of the WHO/HAI methodology (Eden et al., 2019; Saeed et al., 2019). The items included in the standardized form were as follows: basic information of the facility (hospital name, hospital level, survey date), information of the medicine (medicine in stock in the hospital on the day of data collection, yes or no), dosage, strength, medicine type (OB/LPG), and the retail price at the time of survey (**Table 1**).

Patient and Public Involvement

It was not possible or appropriate to involve patients or the public in the design, data collection, reporting or dissemination plans of this analysis.

Assessment of Availability

The availability of anticancer medicines was reported as the percentage (%) of medicine outlets in which the information was documented by surveyed facilities on the day of data collection. Availability was classified as 4°; **Absent**: 0 of facilities, suggested that we could not find these medicines in the facility; **Low**: < 50%, these medicines were rarely purchased; **Fairly high**: 50–80%, these medicines were found in several facilities; **High**: > 80%, most institutions sold these medicines. In addition, mean percentage availability of OBs and LPGs were calculated for the investigations (Zhu et al., 2019).

Price Assessment

In order to make standard comparisons, price was evaluated by median price ratio (MPR) according to WHO/HAI approach,

TABLE 2 | Availability of anticancer medicines in Tertiary and Secondary hospitals.

Medicine name	OBs(%)		LPGs (%)		Total (%)	
	Tertiary hospital	Secondary hospital	Tertiary hospital	Secondary hospital	OBs	LPGs
Calcium Folinate	0.00	0.00	47.62	60.00	0.00	53.81
Capecitabine	23.81	40.00	52.38	66.67	31.90	59.52
Carboplatin	0.00	0.00	52.38	33.33	0.00	42.86
Ciclosporin	23.08	6.67	38.10	13.33	10.48	25.71
Cisplatin	0.00	0.00	42.86	53.33	0.00	48.10
Cyclophosphamide	15.38	0.00	52.38	93.33	4.76	72.86
Cytarabine	7.69	0.00	28.57	13.33	2.38	20.95
Daunorubicin	0.00	0.00	28.57	26.67	0.00	27.62
Docetaxel Trihydrate	7.69	0.00	47.62	73.33	2.38	60.48
Doxorubicin	0.00	0.00	23.81	33.33	0.00	28.57
Etoposide	0.00	0.00	57.14	80.00	0.00	68.57
Fluorouracil	7.69	0.00	33.33	46.67	2.38	40.00
Gemcitabine	7.69	0.00	61.90	73.33	2.38	67.62
Ifosfamide	23.08	0.00	33.33	13.33	7.14	23.33
Imatinib	7.69	6.67	38.10	20.00	5.71	29.05
Irinotecan	7.69	6.67	47.62	46.67	5.71	47.14
Mercaptopurine	0.00	0.00	4.76	0.00	0.00	2.38
Mesna	7.69	0.00	38.10	20.00	2.38	29.05
Methotrexate Sodium	0.00	0.00	52.38	66.67	0.00	59.52
Methylprednisolone	38.10	40.00	9.52	26.67	39.05	18.10
Mycophenolate Mofetil	7.69	13.33	28.57	13.33	9.05	20.95
Oxaliplatin	15.38	6.67	61.90	93.33	8.10	77.62
Paclitaxel	23.08	0.00	42.86	40.00	7.14	41.43
Tamoxifen Citrate	0.00	0.00	52.38	80.00	0.00	66.19
Vincristine	0.00	6.67	28.57	46.67	3.33	37.62
Letrozole	23.08	20.00	52.38	66.67	17.14	59.52
Gefitinib	28.57	13.33	28.57	20.00	23.33	24.29
Bicalutamide	47.62	40.00	23.81	20.00	43.81	21.90
Hydroxycarbamide	0.00	0.00	38.10	40.00	0.00	39.05
Vinorelbine	7.69	0.00	42.86	53.33	2.38	48.10
Tacrolimus	15.38	13.33	28.57	20.00	11.43	24.29
Ondansetron	0.00	0.00	23.81	20.00	0.00	21.90
Mean Percent	13.70	6.67	38.84	42.92	7.57	40.88

which is the ratio of median price of individual medicine obtained during the survey (Dong et al., 2020). Moreover, we used Management Sciences for Health (MSH 2015) International Drug Price Indicator Guide as the source of reference prices. MPR was calculated using the formula given below: Median Price Ratio (MPR) = Median local unit price/International reference unit price. It can provide a more intuitive data presentation for drug price monitoring: when the value of MPR is less than 1, it indicates that the price of the drug under investigation is lower than the international average standard. In other words, the price control is efficient. The value of MPR between 1 and 2 indicates that the drug price is acceptable; if MPR>2, this means that the drug price level is high and needs to be contained (Guan et al., 2018).

Affordability

In general, the total cost of the unit treatment for chronic diseases with the standard dose of the drug is equivalent to 1 month's working days (daily wages) of the lowest paid non-technical government employee that enables him/her to purchase the standard course of cancer treatment. However, the duration of anticancer therapy may be longer. Moreover, the price of many anticancer drugs is too expensive, which causes heavy economic burden for cancer patients. Thus, with the aim to precisely assess the affordability, we used the approach proposed by Khatib and Sarwar (Khatib et al., 2015; Sarwar et al., 2018): if the total expenditure of medicine in 30 days accounted for 20% or less of the minimum family monthly income, it was regarded as affordable (Eden et al., 2019). The calculation formula was:

$$\text{Affordability} = \frac{\text{Total cost of drugs in 30 days}}{\text{20\% of the minimum monthly household income}}$$

RESULTS

We calculated the availability of originator brands (OBs) and lowest priced generics (LPGs) across the 32 anticancer medicines. In this survey, 92.43% OB was unavailable overall, and 10 OBs of 32 medicines were not available in tertiary hospitals nor secondary hospitals. The top three percentage availability of OBs in tertiary hospitals included Bicalutamide (47.62%), Methylprednisolone (38.10%) and gefitinib (28.57%). In tertiary hospitals, the average availability of OBs was 13.70%. In contrast, the mean availability of OBs was 6.67% in secondary hospitals (**Table 2**).

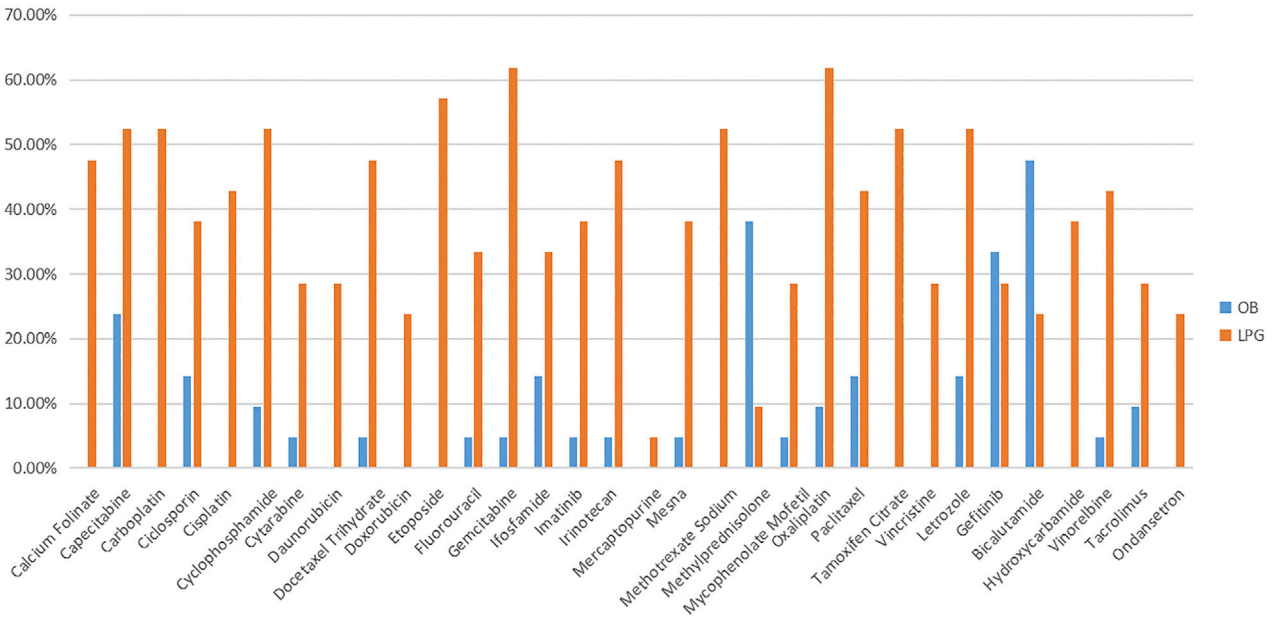

FIGURE 1 | The availability of LPG and OB medicines in tertiary hospital.

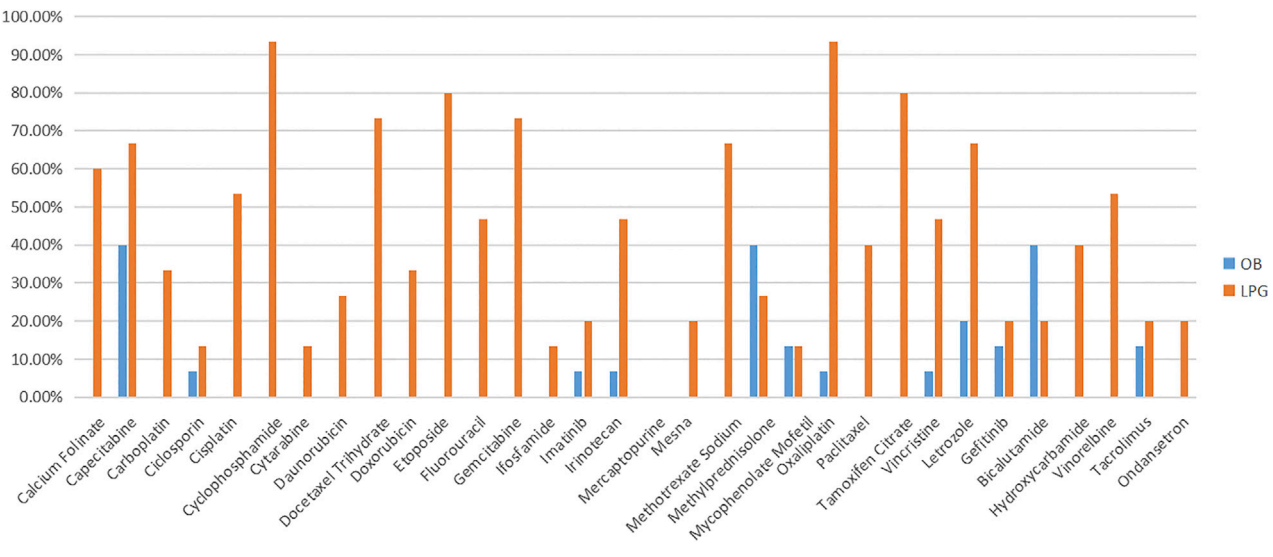

FIGURE 2 | The availability of LPG and OB medicines in secondary hospital.

For LPGs, overall, the mean availability of surveyed medicines was 40.88%, and the mean availability of LPGs was 38.84% in tertiary hospitals, and 42.92% in secondary hospitals (**Table 2**). Besides, Oxaliplatin and Gemcitabine were maximal for 61.90% in tertiary hospitals (**Figure 1**). Two medicines with the highest availability in the secondary hospitals were Cyclophosphamide (93.33%) and Oxaliplatin (93.33%). Nevertheless, most LPGs were available in secondary hospitals (**Figure 2**). In general, the availability of the selected medicines in tertiary hospitals was higher than that in secondary hospitals.

Table 3 illustrates the median price patients paid and MPR in tertiary and secondary hospitals for 32 anticancer medicines in Hubei Province. The results showed that the overall price of medicines varied from RMB0.49 to RMB2290.12. In total, the median patient prices of 4 OBs were over double the IRP. The median patient prices of OB for Oxaliplatin (RMB2290.12) ranked first. Especially, its MPR was 12.73 times higher than the international reference price (IRP)from MSH. Furthermore, the MPR of 3 OBs were **more than double** that of IRP in tertiary hospital:

TABLE 3 | The median patient price and MPR of anticancer medicines in tertiary and secondary hospitals in Hubei Province.

Medicine name	Medicine type	Tertiary hospital (*n* = 13)		Secondary hospital (*n* = 15)	
		Median price	MPR	Median price	MPR
Calcium Folinate	OB	NA	NA	NA	NA
	LPG	16.18	1.00	16.18	1.00
Capecitabine	OB	30.72	1.00	30.72	1.00
	LPG	8.16	0.27	11.14	0.36
Carboplatin	OB	NA	NA	NA	NA
	LPG	53.90	1.00	53.90	1.00
Ciclosporin	OB	9.15	1.00	NA	NA
	LPG	5.18	0.57	5.36	0.59
Cisplatin	OB	NA	NA	NA	NA
	LPG	7.57	1.04	7.30	1.00
Cyclophosphamide	OB	NA	NA	NA	NA
	LPG	25.20	1.00	25.20	1.00
Cytarabine	OB	140.49	17.15	NA	NA
	LPG	8.19	1.00	8.09	0.99
Daunorubicin	OB	NA	NA	NA	NA
	LPG	27.15	1.00	27.15	1.00
Docetaxel	OB	NA	NA	NA	NA
	LPG	204.84	0.66	123.00	0.40
Doxorubicin	OB	NA	NA	NA	NA
	LPG	23.28	1.00	23.28	1.00
Etoposide	OB	NA	NA	NA	NA
	LPG	7.79	0.78	9.28	0.93
Fluorouracil	OB	NA	NA	NA	NA
	LPG	9.80	1.98	5.10	1.03
Gemcitabine	OB	NA	NA	NA	NA
	LPG	150.99	1.00	79.75	0.53
Ifosfamide	OB	107.88	2.30	NA	NA
	LPG	47.00	1.00	42.21	0.90
Imatinib	OB	NA	NA	NA	NA
	LPG	14.05	0.70	14.05	0.70
Irinotecan	OB	385.87	1.66	NA	NA
	LPG	252.44	1.08	252.44	1.08
Mercaptopurine	OB	NA	NA	NA	NA
	LPG	0.62	0.26	NA	NA
Mesna	OB	NA	NA	NA	NA
	LPG	8.80	1.00	8.80	1.00
Methotrexate Sodium	OB	NA	NA	NA	NA
	LPG	19.60	1.00	19.60	1.16
Methylprednisolone	OB	123.96	1.00	125.83	1.02
	LPG	165.72	1.34	169.10	1.36
Mycophenolate Mofetil	OB	14.85	1.85	14.87	1.85
	LPG	8.04	1.00	8.31	1.03
Oxaliplatin	OB	2,290.12	12.73	NA	NA
	LPG	179.88	1.00	73.10	0.41
Paclitaxel	OB	94.19	2.81	NA	NA
	LPG	33.55	1.00	15.99	0.48
Tamoxifen Citrate	OB	NA	1.09	NA	NA
	LPG	0.58	NA	0.56	1.06
Vincristine	OB	NA	NA	NA	NA
	LPG	43.47	3.25	9.49	1.00
Letrozole	OB	37.55	1.00	37.73	3.26
	LPG	10.51	1.00	11.56	1.00
Gefitinib	OB	228	0.69	231.90	1.02
	LPG	158.4	1.32	158.50	0.70
Bicalutamide	OB	40.83	0.90	40.83	1.32
	LPG	27.88	NA	40.83	1.32
Hydroxycarbamide	OB	NA	1.00	NA	NA
	LPG	0.49	NA	0.49	1.00
Vinorelbine	OB	NA	NA	NA	NA
	LPG	134.82	1.00	134.82	1.00
Tacrolimus	OB	23.11	1.98	23.21	1.99
	LPG	10.51	0.90	16.32	1.40
Ondansetron	OB	NA	NA	NA	NA
	LPG	13.89	1.16	22.24	1.86

[a]*The unit of measurement of Median Price is RMB.*

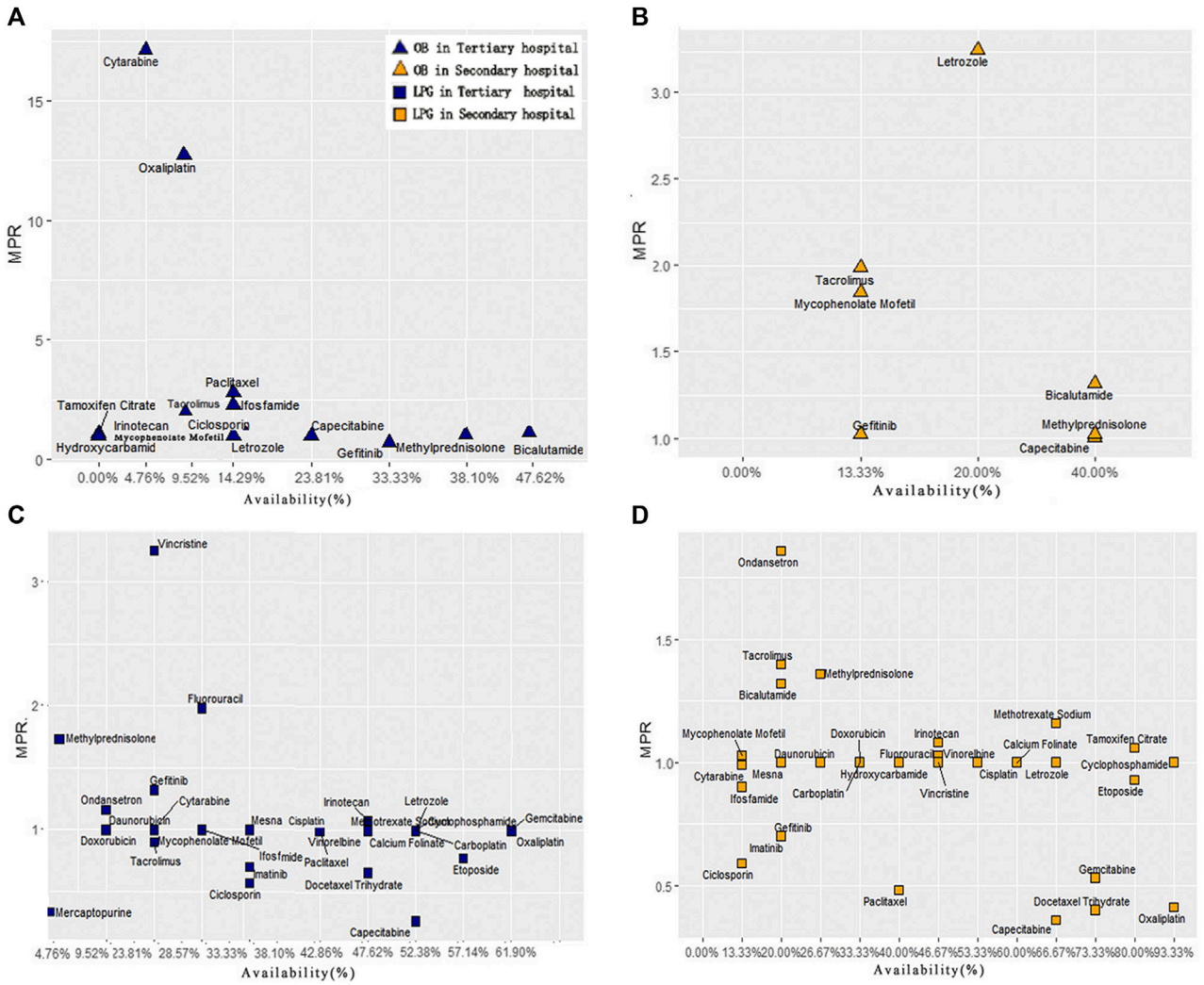

FIGURE 3 | Comprehensive analysis of anticancer medicine availability and MPR in Hubei Province. **(A)** Scatter plot of OBs availability and MPR in tertiary hospitals. **(B)** Scatter plot of OBs availability and MPR in secondary hospitals. **(C)** Scatter plot of LPGs availability and MPR in tertiary hospitals. **(D)** Scatter plot of LPGs availability and MPR in secondary hospitals.

Cytarabine (MPR = 17.15), Ifosfamide (MPR = 2.30), Paclitaxel (MPR = 2.81), respectively. The MPR value of sample medicines in **secondary hospitals** were less than 2, except Letrozole (MPR = 3.26). Additionally, the median patient prices of most LPGs were in line with IRP standards.

In order to compare the difference of drug availability and MPR value between secondary and tertiary hospitals, we made 4 scatter plots of the availability and MPR value of 32 anticancer drugs (**Figure 3**). In tertiary hospitals, for OBs, two points located in the upper left area of the graph, which were cytarabine and oxaliplatin, whose MPR was more than 10 times. However, their availability was quite low. The medicines with higher availability of OBs were gefitinib, Bicalutamide and Methylprednisolone with low MPR. For LPGs, Vincristine had the highest MPR value (3.25), and its availability was low. Eight medicines had fairly high availability with acceptable MPR value (MPR of 1 or less is interpreted as efficient procurement in the public sector) (Mendis et al., 2007; Kasonde et al., 2019).

In secondary hospitals, for OBs, only seven drugs with MPR value could be obtained. **Figure 3** indicates Letrozole with high availability and MPR. Only Capecitabine's MPR is acceptable. For LPGs, 11 medicines were highly available. Moreover, 21 drugs with MPR value were included. The result also showed that these eight medicines: Irinotecan, Methotrexate Sodium, Methylprednisolone, Mycophenolate Mofetil, Tamoxifen Citrate, Bicalutamide, Tacrolimus, Ondansetron were out of the acceptable range (MPR of 1 or less).

Table 4 shows the affordability of the anticancer medicines based on the duration of treatment. Overall, the mean affordability of the studied medicines was 2.89. For 31 LPGs, the mean affordability value was 1.79, which was

TABLE 4 | Affordability of anticancer medicines based on 20% of the minimum household monthly income in Hubei Province.

Medicine name	Medicine type	Dosage	Strength	Total course of treatment	Median patient price	Affordability
Calcium Folinate	OB	VIAL	100 mg/10 ml	NA	NA	0.00
	LPG	VIAL	100 mg/10 ml	10	16.18	0.32
Capecitabine	OB	TAB-CAP	500 mg	105	30.72	6.45
	LPG	TAB-CAP	500 mg	105	8.16	1.71
Carboplatin	OB	VIAL	100 mg/10 ml	6	NA	0.00
	LPG	VIAL	100 mg/10 ml	6	53.90	0.65
Ciclosporin	OB	TAB-CAP	25 mg	30	9.15	0.55
	LPG	TAB-CAP	25 mg	30	5.18	0.31
Cisplatin	OB	VIAL	20 mg	10	NA	0.00
	LPG	VIAL	20 mg	10	7.57	0.15
Cyclophosphamide	OB	VIAL	200 mg	20	NA	0.00
	LPG	VIAL	200 mg	20	25.20	1.01
Cytarabine	OB	VIAL	100 mg	20	140.49	5.62
	LPG	VIAL	100 mg	20	8.19	0.33
Daunorubicin	OB	VIAL	10 mg	6	NA	0.00
	LPG	VIAL	10 mg	6	27.15	0.33
Docetaxel	OB	VIAL	20 mg/ml	3.75	NA	0.00
	LPG	VIAL	20 mg/ml	3.75	204.84	1.54
Doxorubicin	OB	VIAL	10 mg	6	NA	0.00
	LPG	VIAL	10 mg	6	23.28	0.28
Etoposide	OB	VIAL	20 mg/ml	30	NA	0.00
	LPG	VIAL	20 mg/ml	30	7.79	0.47
Fluorouracil	OB	VIAL	0.25 g/10ml	300	NA	0.00
	LPG	VIAL	0.25 g/10ml	300	9.80	5.88
Gemcitabine	OB	VIAL	200 mg	15	NA	0.00
	LPG	VIAL	200 mg	15	150.99	4.53
Ifosfamide	OB	VIAL	500 mg	15	107.88	3.24
	LPG	VIAL	500 mg	15	47.00	1.41
Imatinib	OB	TAB-CAP	100 mg	112	NA	0.00
	LPG	TAB-CAP	100 mg	112	14.05	3.15
Irinotecan	OB	VIAL	40 mg/2 ml	18	385.87	13.89
	LPG	VIAL	40 mg/2 ml	18	252.44	9.09
Mercaptopurine	OB	TAB-CAP	50 mg	240	NA	0.00
	LPG	TAB-CAP	50 mg	240	0.62	0.30
Mesna	OB	VIAL	0.4 g/4 ml	10	NA	0.00
	LPG	VIAL	0.4 g/4 ml	10	8.80	0.18
Methotrexate Sodium	OB	VIAL	100 mg/ml	32	NA	0.00
	LPG	VIAL	100 mg/ml	32	9.80	0.63
Methylprednisolone	OB	VIAL	500 mg	20	123.96	4.96
	LPG	VIAL	500 mg	20	161.72	6.47
Mycophenolate Mofetil	OB	TAB-CAP	250 mg	240	14.85	7.13
	LPG	TAB-CAP	250 mg	240	8.04	3.86
Oxaliplatin	OB	VIAL	50 mg	2.6	2290.12	11.91
	LPG	VIAL	50 mg	2.6	179.88	0.94
Paclitaxel	OB	VIAL	30 mg/5 ml	30	94.19	5.65
	LPG	VIAL	30 mg/5 ml	30	33.55	2.01
Tamoxifen Citrate	OB	TAB-CAP	10 mg	30	NA	0.00
	LPG	TAB-CAP	10 mg	30	0.58	0.03
Vincristine	OB	VIAL	1 mg	4	NA	0.00
	LPG	VIAL	1 mg	4	134.82	1.08
Letrozole	OB	TAB-CAP	2.5 mg	75	23.11	3.47
	LPG	TAB-CAP	2.5 mg	75	10.51	1.58
Gefitinib	OB	TAB-CAP	250 mg	30	NA	0.00
	LPG	TAB-CAP	250 mg	30	13.89	0.83
Bicalutamide	OB	TAB-CAP	50 mg	30	134.82	8.09
	LPG	TAB-CAP	50 mg	7	23.11	0.32
Hydroxycarbamide	OB	TAB-CAP	500 mg	7	10.51	0.15
	LPG	TAB-CAP	500 mg	7	NA	0.00
Vinorelbine	OB	VIAL	10 mg/ml	7	13.89	0.19
	LPG	VIAL	10 mg/ml	7	134.82	1.89
Tacrolimus	OB	TAB-CAP	1 mg	6	23.11	2.77

(Continued on following page)

TABLE 4 | (*Continued*) Affordability of anticancer medicines based on 20% of the minimum household monthly income in Hubei Province.

Medicine name	Medicine type	Dosage	Strength	Total course of treatment	Median patient price	Affordability
	LPG	TAB-CAP	1 mg	6	10.51	0.13
Ondansetron	OB	TAB-CAP	4 mg	80	NA	0.00
	LPG	TAB-CAP	4 mg	80	13.89	2.22
Mean affordability	OB	5.29	LPG	1.79	Total	2.89

[a]*Total course of treatment is calculated as 30 days' dose of anticancer medicines.*

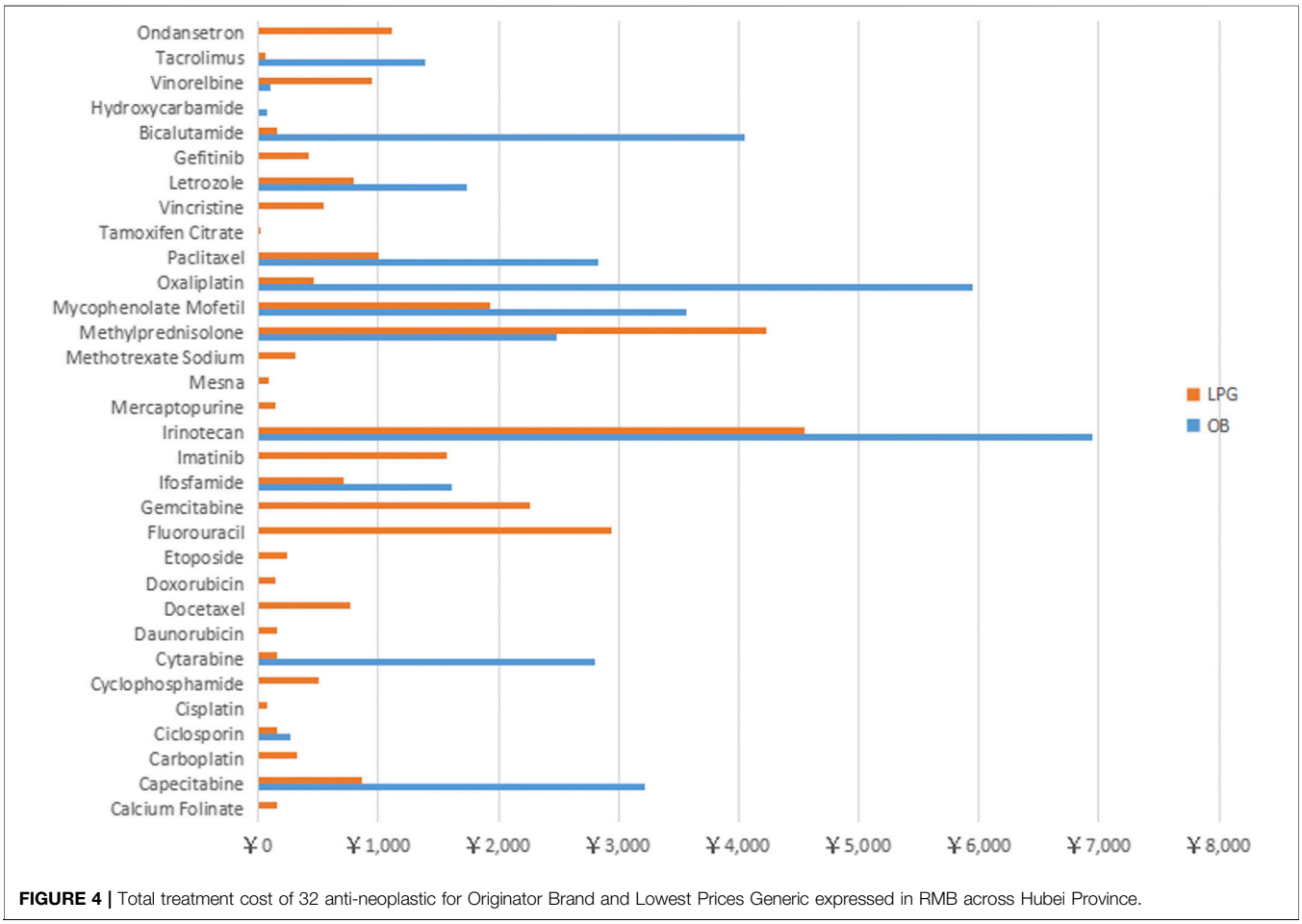

FIGURE 4 | Total treatment cost of 32 anti-neoplastic for Originator Brand and Lowest Prices Generic expressed in RMB across Hubei Province.

within normal range. However, for 14 OBs, the mean value of affordability was 5.29. Further, irinotecan (13.89) and oxaliplatin (11.91) induced large payment burden, as the cost of 30 days dosage was higher than 10 times of 20% household minimum monthly income. In the surveyed hospitals, the affordability of 50% (7/14) of the OBs exceeded the mean affordability value (5.29), and 22.58% (7/31) of LPGs was over the average affordability.

Figure 4 shows that the monthly medicine expenditure of 3 OBs (Irinotecan, Bicalutamide, Oxaliplatin) exceeded 4000 RMB, and the cost of five medicines (Paclitaxel, Methylprednisolone, Mycophenolate Mofetil, Cytarabine and Capecitabine) were within 2000–4000 RMB. For LPGs, the 30 days treatment expenditure of four medicines (Irinotecan, Methylprednisolone, Gemcitabine, Fluorouracil) were over 2000 RMB, and the cost of most of the rest medicines were around 1000 RMB.

DISCUSSION

Availability of Surveyed Medicines

The study evaluated the availability, price and affordability of 32 anticancer medicines in Hubei Province by using the WHO and HAI standard methodology. After investigating 13 tertiary hospitals and 15 secondary hospitals' essential drugs, overall, we

found that 7.57% of OB and 40.88% of LPGs were available in Hubei Province, China. The findings are similar with prior surveys in developing countries (Khuluza and Haefele-Abah, 2019; Saeed et al., 2019; Lambojon et al., 2020). Amna Saeed found that the overall availability of surveyed medicines in public sector was 6.8% only for OBs and 35.3% for the LPGs in Pakistan. In Philippines, the mean availability of surveyed medicines in the public sector was 1.3% for OBs and 25.0% for LPGs (Rui et al., 2019). They also found that most of the OB medicines were produced by large international manufacturers. Due to the lack of effective external supervision and approval for the OB medicines, price leading and brand premiums led to the relatively higher price.

Compared with secondary hospitals, the availability of surveyed medicines were higher in tertiary hospitals. Since radiotherapy and chemotherapy of tumor are very professional and expensive, they are mostly concentrated in large specialized hospitals or departments of tertiary hospitals, which contributed to the higher availability (Rui et al., 2019).

In general, the price of the OBs was high because of its core patent right of drugs, which endowed the original drug enterprises with a monopoly position (Babar et al., 2019; Zhu et al., 2019). However, LPG can be used as a competitive product to make up for its lack of accessibility (Abdel Rida et al., 2019). Especially in low and middle-income countries, hospitals will take into account the actual purchasing power of patients, and appropriately reduce the inventory proportion of OBs in hospitals (Dorj et al., 2018; Guan et al., 2018). The findings of our study showed that the availability of some medicines was relatively high, including Gemcitabine, Etoposide, Oxaliplatin, Cyclophosphamide, Tamoxifen, the underlying reason may be that these medicines could achieve better survival time in the treatment of advanced cancer and adverse reactions can be tolerated (Juxiang et al., 2015; Teng et al., 2018). Other reasons maybe they were included early in the list of national essential medicines, and widely used in the treatment of some high incidence and mortality cancers, such as lung cancer, gastric cancer, colon cancer in China (Yahong, 2019).

Price Comparison

As presented in **Figure 3**, most of the LPGs for anticancer could be acquired with acceptable price. Meanwhile, for OBs, the MPR value of **Cytarabine, Oxaliplatin and Paclitaxel** were much higher than the international reference price from MSH. Compared with LPGs, the relatively retail prices for OBs were much higher. This may be explained by the large patient's rigid demand for the above three categories of medicines. In addition, the particularity of pharmaceutical production technical and core-patient barriers made it difficult for many domestic generic drugs to reach the ideal level and curative effect of the originator brand drugs (Cameron et al., 2009).

The government has been very concerned about the field of medicine prices. In recent years, it has also issued relevant policies to curb the disordered competition in pharmaceutical market. Launching the new direction of "purchasing with quantity, linking quantity with price and combining bidding and purchasing" has pushed the price of national essential drugs back to a reasonable level (Mao et al., 2019; Dong et al., 2020). Especially, after the conformity evaluation, generic drugs gradually occupy the share of originator brand drugs and expand the OBs' substitution in favour of lowering public health expenditure in hospitals (Faruqui et al., 2019). Diversified and fair competitions between OBs and LPGs may bring more preferential benefits to patients.

Affordability

For the patients from low-income families in Hubei Province, they are still unable to afford course of treatment. Economic burden of disease becomes the major barrier that affects their access to effective targeted anticancer medicines (Mengyuan et al., 2017). In this study, the measurement affordability based on the total cost of treatment and the estimation of household income. The top five medicines with poor affordability were: *Irinotecan, Oxaliplatin, Bicalutamide and Mycophenolate Mofetil, Methylprednisolone*, which were more than 6 times of the 20% minimal monthly household income. The heavy payment burden may be caused by different dosages of 30 days treatment course and the unit price of each medicine. Meanwhile, in Mexico, most cancer medicines are also unaffordable for patients, the median affordability of patented medicines was 30.17 days' wages needed to buy 1 day of one medicine's supply (Moye-Holz et al., 2020). Hence, our government should establish special funds to support low-income household, and improve the efficiency of national medical insurance (Sarwar et al., 2018). Potential strategies worth consideration include: simplifing the approval process of new drugs at home and abroad, improving their access to the market, reducing the innovation cost, and attracking more high-quality anticancer generic drugs to enter the market (Eden et al., 2019). Importantly, in terms of the bidding and procurement process, National Health-care Security Administration negotiates with pharmaceutical manufacturers for reducing the OBs price and ensuring that the patients can afford the essential anticancer medicines (Jiao et al., 2018).

Limitations

In this survey, private hospitals and pharmacies were not included in the survey because only few designated pharmacies were licensed to operate special drugs (such as anti-cancer drugs) in China. Hence, the use of target anticancer drugs in designated pharmacies is of particular concern in subsequent studies. Second, during data collection, some "out-of-stock" medicines were not included in the calculation. Thus, the findings may not be generalizable to the whole availability of anticancer medicines. Lastly, for the convenience in comparing the affordability indicators, but lack of accounting for detailed cancer treatment protocols, all medicines charges were calculated according to the course of 30 days. In fact, the patient's cancer type and risk stratum are different, which could lead to some biases in the accuracy of affordability.

CONCLUSION

Compared with secondary hospitals, it is obvious that the availability of essential anticancer medicines was found to be much higher in tertiary hospitals. Overall, LPGs was prior to OBs in terms of availability. "Drug addition cost" is a policy adopted by the government to compensate hospital income in a specific

period of time. However, with the implementation of the "Zero Mark-up of Drugs" policy from 2009, for getting rid of compensation effect of drug income on public hospitals, the price of anticancer medicines returned to a reasonable level (Mao et al., 2019), apart from some special Originator Brand medicines' price were still much higher than the international reference price. This study also identified several types of drugs that patients could hardly afford during the treatment. Policymakers should pay more attention to the possibility of poverty caused by expenditure on major cancer diseases. More actions should be adopted to regulate and restrict the pharmaceutical industry, drug circulation, patients and doctors, and improve the availability of essential anticancer medicines in Hubei Province.

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 was approved by the Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology, and the approval number is 2020(S223). The Surveyed hospitals were informed by sending research letter prior to data collection, and all hospitals agreed to participant in this survey.

AUTHOR CONTRIBUTIONS

CC participate in study design and conception, data acquisition, data analysis, manuscript drafting. We thank ZF and YD for guiding this study, and DF design the whole investigation and attend to collect data, ZY and JW help us to input and check data, RW is responsible for proposing the revising suggestions of the manuscript draft.

FUNDING

This work was supported by National Natural Science Youth Fund (Grant Number: 71,804,052).

ACKNOWLEDGMENTS

The authors were thankful for Professor Rui Huang and their stuff who support their available time for coordination and arrangement of investigation, in addition, we also would like to all the participants who attended in this study.

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frontiers in Public Health

ORIGINAL RESEARCH
published: 30 September 2021
doi: 10.3389/fpubh.2021.724185

Does Family Migration Affect Access to Public Health Insurance? Medical Insurance Participation in the Context of Chinese Family Migration Flows

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Using 2017 Migrant Dynamic Survey (CMDS) data, logistic regression models were developed to explore the family migration rate on health care participation of floating population. The analysis reveals that 68.69% of the floating population in China moves with at least one family member, but the local health insurance participation rate of them are relative low. However, family migration rate has a significant positive correlation with the health insurance participation of the floating population at the destination, which explains by family support and social integration mechanisms. The higher the degree of family migration, the higher the likelihood of participating in local health insurance system. Age, labor contract types, migration range and cities numbers, health records, and the accessibility of health resources have a significant negative correlation with health care participation of the floating population at the destination; gender, health, marriage, education, hukou types, monthly income, migration history, and move duration have a significant positive correlation. The effect of family migration rate on health care participation is weaker in group in which people are low-educated and signs non-fixed-term contract or gets bottom 50% monthly income or under the no-kids family structure. Potential policies informed by these findings are also explored.

Keywords: public health insurance, family migrants, social welfare, floating population, public health policy

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *12 June 2021*
Accepted: *02 September 2021*
Published: *30 September 2021*

Citation:
Liu L (2021) Does Family Migration Affect Access to Public Health Insurance? Medical Insurance Participation in the Context of Chinese Family Migration Flows. Front. Public Health 9:724185. doi: 10.3389/fpubh.2021.724185

INTRODUCTION

The health and social welfare of migrants has always been a central issue in migration research. Since the 1980s, a large number of rural residents in China have poured into cities to participate in economic and social development actively. The large floating population faces great risks from its mobility while driving China's modernization. Affected by subjective factors such as insufficient health awareness and objective factors such as high health costs, relatively poor living and working environment, the migrant population often faces health problems, including infectious diseases, reproductive system diseases, occupational hazards, and mental health issues (1). Therefore, the overall health of the migrant population in China is poor, and there is a need for improved basic health services and medical security.

Under China's current urban-rural dual structure, the medical security of the floating population is in a precarious state. Although there are institutional arrangements, they are difficult to implement, and migrants cannot enjoy the same social welfare and social rights as urban residents. From 2011 to 2012, data from the China Migrants Dynamic Survey showed that the migrant population's overall medical insurance participation rate was about 69%, while the rate of urban medical insurance participation was about 26%, producing an obvious Matthew Effect (2). From 2013 to 2017, the number of migrant workers participating in social medical insurance was only 82.88%, most of whom participated in their original place of household registration. They mainly participated in the new rural cooperative medical insurance, and there was repeated participation (3). In recent years, it has been found that the medical insurance participation rate of the floating population has significantly increased and the phenomenon of repeated insurance has improved, but 10.9% of the floating population still lack any medical insurance (4).

In response, the 19th National Congress of the Communist Party of China plans to establish a multi-tiered social security system covering all the people. Public medical insurance, an important part of this system, is an essential means of preventing uncertainty and avoiding health risks among the floating population. Improving their participation in extensive and appropriate medical insurance and improving the fairness of basic medical care services will be one of the focal points and challenges in the development and construction of China's social security system in the future.

After a long period of rapid growth, the scale of China's migrant population has begun to enter a period of adjustment. Migration flow has shifted from the initial individual migration to family migration. Although the scientific measurement of family migration remains to explored, the increasing proportion of female, married, or family migrants among the floating population directly reflects this trend (5). The floating population's desire to settle with their spouses, children, or parents and work in cities is bound to bring greater demand for public services and social security at the destination. Under this conflict of demand and supply, it is urgent to explore whether family migration will affect the participation of the floating population in public medical insurance at the destination.

LITERATURE REVIEW

Public Health Insurance for Migrants

Many scholars have discussed the participation of migrant populations in medical insurance programs. Studies show that the factors affecting this participation are complicated, including three main aspects: personal, socioeconomic, and migration characteristics.

Most previous studies have stated that age is an important factor affecting the participation of migrants in medical insurance. The older the migrants or the worse their physical condition, the higher the probability they participate in medical insurance (6). However, some studies have shown that age has no significant effect (7). Relevant personal characteristics include gender, marriage, and health status (8–10). In terms of socioeconomic characteristics, having an employment contract has a greater impact than *hukou* (household registration) status in determining whether Beijing's floating population accesses social insurance (11). Having a stable contract and high job stability are also important factors (12). Regarding migration characteristics, the reasons for migration, frequency of returning home, willingness to settle long-term, and destination area characteristics are the main factors affecting the medical insurance participation rate (13, 14).

Family Migration in China

Family migration is the main trend in China's current and future population mobility. Family migration could explains in two senses: first, the process of family members from the same nuclear family moving from the countryside to the city; second, the rising proportion of the total floating population moving with family members (15). The main migration mode at present is that the husband and wife move with their children or unmarried grown-up children move with their parents; frequently, three generations of family members stay together at the destination (16). In detail, migration patterns could be distinguished for four types: all family members migrate together, husband and wife migrate together, husband or wife and children migrate together, and individuals migrate alone (17). For most migrants, "laddering migration" is the most common form, that is, family members gradually reunite at the destination, finally forming a complete family (18).

The impact of family migration mainly affects employment income, social integration, children's education, and other aspects. Family migration has an impact on the employment of the floating population. The impact of female floating population is more significant for the lower employment rate and more unstable employment (19, 20). Family migration also promotes migrant workers' participation in community activities, which can enhance their psychological and economic integration, but may reduce their willingness to reside in urban areas (21). However, some scholars have drawn the opposite conclusion, arguing that compared with individual migration, some family members who move together or move with their whole family are more inclined to stay for a long time or even settle permanently at the destination (22). The education problem of migrant children are strengthen by the increasing family migration trend. Children either live with their parents in the city or stay behind in their hometown and trapped in a dilemma of separation (23). In addition, some scholars have noticed a connection between family-centered migration and the family welfare of the floating population, but only at the level of policy analysis, it is suggested that the overall welfare of migrant families should be paid attention to when making policy, but there is a lack of empirical evidence (24, 25).

Current Study

Although the medical insurance participation of the floating population and family migration have received increasing

TABLE 1 | Definitions and assignment of variables ($N = 71,979$).

	Variable	Definitions of variable	Assignment of variables
Dependent variable	Health care	Whether to participate in medical insurance at destination in NCMS/R&NURMNI/NURBMI/UEBMI	Participated = 1 Not participated = 0
Independent variable	Family migration rate	The proportion of local member number of the total family number	Local member number/total family number
Control variables (individual characteristics)	Age	Age	2017 minus the year of birth
	Gender	Gender	Female = 0 Male = 1
	Health	Subjective health	Healthy = 1 Basically healthy = 2 Unhealthy = 3
	Marriage	The status of marriage	Single = 1 First married = 2 Remarried = 3 Divorce = 4 Widowed = 5 Cohabit = 6
	Education	Education	Primary school or below = 1 Junior high school = 2 Senior high school = 3 Junior college = 4 Bachelor degree or above = 5
	Hukou types	The type of Hukou	Agriculture = 1 Non-agriculture = 2
	Labor contract types	The type of labor contract	Non-fixed-term contract = 1 Fixed-term contract = 2 Not sign contract = 3 Not Applicable = 4
	Monthly income	The monthly salary	Take the logarithm of salary
Control variables (migration characteristics)	Migration history	Years calculated from the earliest migration year	2017 minus the first year of migration
	Move range	The range of migration	Across the province = 1 Across the city in the province = 2 Across the county in the city = 3
	Move duration	The length of time since the latest move (months)	(2017 minus the year of entry current destination)* 12
	Move cities	The number of cities he/she moved	Total number of cities
Control variables (characteristics of current health resources)	Health records	Whether to establish a health record at current destination	Established = 1 Unestablished and never heard = 2 Unestablished but heard = 3 Not clear = 4
	Accessibility of health resources	The time used to get access to the nearest health institution	Under 15 min = 1 15–30 min = 2 30–60 min = 3 60 min above = 4

NCMS, New Cooperative Medical Scheme; R&NURMNI, Rural & Non-Working Urban Residents' Basic Medical Insurance; NURBMI, Non-Working Urban Residents' Basic Medical Insurance; UEBMI, Urban Employees' Basic Medical Insurance.

academic attention, there are still relatively few empirical studies on the relationship between these two factors. Current research on this topic still has the following deficiencies. First, when discussing the factors affecting the floating population's participation in medical insurance, the trend of family migration have not been analyzed, even though it has become a consensus among scholars that China's current population mobility shows a family migration trend. Second, existing studies pay more attention to the overall health insurance coverage of China's floating population and less attention to health insurance coverage at the destination. Third, in terms of the measurement of family migration, scholars have not yet unified its definition and there are different measurement standards. Some measurements have been overly simple, and have been unable to reflect family-oriented migration flow fully.

TABLE 2 | Descriptive statistics of variables ($N = 71,979$).

Variable	Mean	SD	Min	Max	Assignment	Percent (%)
Health care	0.41	0.49	0	1	Participated	40.54
					Not participated	59.46
Family migration rate	0.83	0.26	0.10	1		
Age	38.86	9.72	19	88		
Gender	1.44	0.50	1	2	Male	55.76
					Female	44.34
Health	1.16	0.39	1	3	Healthy	85.21
					Basically healthy	13.58
					Unhealthy	1.21
Marriage	1.90	0.70	1	6	Single	20.93
					First married	73.80
					Remarried	1.82
					Divorce	2.09
					Widowed	0.52
					Cohabit	0.84
Education	2.72	1.19	1	5	Primary school or below	12.81
					Junior high school	39.00
					Senior high school	22.90
					Junior college	14.25
					Bachelor degree or above	11.04
Hukou types	1.25	0.43	1	2	Agriculture	74.89
					Non-agriculture	25.11
Labor contract types	2.26	0.72	1	4	Non-fixed-term contract	12.15
					Fixed-term contract	52.76
					Not sign contract	31.36
					Not applicable	3.74
Monthly income	8.17	0.54	0	11.70		
Migration history	10.66	7.31	1	73		
Move range	1.67	0.74	1	3	Across the province	49.75
					Across the city in the province	33.48
					Across the county in the city	16.78
Move duration	74.17	66.95	7	685		
Move cities	1.92	1.67	1	80		
Health records	2.27	1.05	1	4	Established	29.18
					Unestablished and never heard	31.32
					Unestablished but heard	22.77
					Not clear	16.73
Accessibility of health resources	1.19	0.44	1	4	Under 15 min	83.37
					15–30 min	14.92
					30–60 min	1.53
					60 min above	0.18

Therefore, this paper will measure both the existence and degree of family migration. It also discusses the impact of family migration on medical insurance participation at the destination, and attempts to provide relevant explanations, in order to provide empirical evidence for the improvement of relevant policies on family mobility and family welfare, and improve the basic well-being and anti-risk capability of migrant families.

METHOD

Data

The data used in this study come from the 2017 Migrant Dynamic Survey (CMDS). These data are from a national sample survey of the floating population, run by the National Health Commission of China. The survey were conducted annually since 2009, covering 31 provinces (regions, municipalities) and

Xinjiang Production and Construction Corps, enabling it to fully reflect the status of China's floating population. The survey questionnaire includes data variables relevant to this study, including basic information about the floating population and their family members; mobility range and trend; employment and social security; income, expenditure and residence; basic public health services; and other specific information. Jiangsu province, which contains a large number of immigrants, is a typical area to observe the family migration phenomenon. In 2017, the sample size of Chinese floating population was 169,989. After screening and converting relevant variables and removing missing values, 71,979 valid samples were analyzed.

Variables

Dependent Variable

Table 1 show the definitions and assignment of variables. We investigated whether the floating population participates in medical insurance at the destination. The relevant survey question is "Which of the following social medical insurance programs are you currently enrolled in?," with four possible types: New Cooperative Medical Scheme, Rural & Non-Working Urban Residents' Basic Medical Insurance, Non-Working Urban Residents' Basic Medical Insurance, and Urban Employees' Basic Medical Insurance. Those who participated in at least one type of medical insurance in their local area (where they currently lived) were defined as those who participated in medical insurance at the destination, while those who answered in the "household registration area" or "other places" were defined as those who did not participate in medical insurance at the destination.

Independent Variable

In previous studies, some scholars described family migration as the family size at the destination and measured it according to the number of family migrants (26). However, these studies only defined migration of couples as family migration, and did not consider whether the children followed (20). Other scholars have taken the nuclear family as the definition (19, 22). This study holds that as long as one family member (including immediate and collateral relatives) moves with the interviewee, this situation could be regard as family migration. On the contrary, if the interviewee moves alone, he/she could be regard as a non-family migration. Therefore, this paper calculates the proportion of local member number of the total family number, and use this proportion which named family migration rate to reflect the degree of family migration.

In addition, most studies consider the nuclear family or husband-wife family and tend to ignore other relatives. This study considered all relatives, but with a slight emphasis. That is, by taking the nuclear family as the benchmark and taking individual migration as the starting point, and focusing on marital relationships, we finally divided family migration into five levels. They are: (a) individual migration, (b) parents or other collateral relatives migrating with the individual, (c) children migrating with the individual, (d) spouse migrating with the individual, and (e) spouse and children migration with the individual, with scores of 1, 2, 3, 4, and 5, respectively. The higher the score, the higher the degree of family migration, which reflects the gradual completeness of the number of nuclear family members and the gradual thickening of blood relationships in the process of family migration.

Covariate

The first category is the individual characteristics of the migrant population, including age, gender, subjective health, marriage, education, type of hukou, type of labor contract, and monthly income; the second category is their characteristics of migration, including the migration history, move range, move duration and the amounts of cities' they moved in; the third category is factors of current health resources, including health records and the accessibility of these health resources.

RESULTS AND DISCUSSION

Descriptive Analysis

Current Family Migration Situation

Table 2 show the descriptive statistics of variables. In 2017, among the floating population in China, 31.31% moved to current destination alone, and the remaining 68.69% were migrants accompanied by at least one other person, further verifying that the current population flow in China no longer mainly comprises individuals. In terms of the model of family migration, only 8.5% of the migrant population migrated with their parents or other collateral relatives, 1.44% of the migrant population migrated only with their children, spousal migration accounted for 29.5%, and nuclear family migration accounted for 29.25%, indicating the nuclearization of migrating families. In terms of the family migration rate, the mean is 82.98%, the standard deviation is 0.26, the smallest and largest are relatively 0.1 and 1, means that the proportion of local member of the total family number is relatively high.

Table 3 show the heterogeneity of family migration rate among the floating population in China. According to the results, the differences on family migration rate are influenced by age, gender, marriage, hukou type, move range. The male who under 40, well-educated, in marriage status, holding agriculture hukou are more likely to have a higher family migration rate. What is more, people move within province, other than move across provinces, are more willing to relocate with their family member.

Health Insurance Participation of Floating Population

Table 4 show the relationships between personal characteristics and medical insurance participation among the floating population in China. First, in terms of individual characteristics, age, gender, health status, marriage status, education, hukou types, and labor contract types will influence the participation of health insurance of floating population. Second, the characteristics of migration such as move range will also influence the participation of health insurance. Third, the health resources characteristics have effect on participation as well, whether establish health records at destination and the distance of the nearest health institution may intervene in decisions.

Table 5 shows the health insurance participation of migrant families in China of 2017. There are 29,181 samples participated in medical insurance at the destination, accounting for 40.54%

TABLE 3 | Heterogeneity of Family migration rate by migrants' characteristics (N = 71,979).

		Family migration rate	
		Mean %	SD
Age group	<40	85.64***	0.249
	≥40	79.16***	0.270
Gender	Male	83.25**	0.260
	Female	82.64**	0.260
Health	Healthy	83.00	0.249
	Unhealthy	82.98	0.260
Marriage	In marriage	79.23***	0.273
	Not in marriage	94.61***	0.173
Education	Senior high school or below	82.64***	0.258
	Senior high school above	83.39***	0.265
Hukou types	Agriculture	83.19***	0.257
	Non-agriculture	82.35***	0.269
Labor contract types	Non-fixed-term contract	83.42	0.260
	Other contract types	82.92	0.260
Move range	Across the province	80.77***	0.265
	Move within the province	85.17***	0.253
Health records	Established	82.88	0.263
	Unestablished	83.02	0.259
Accessibility of health resources	Under 15 min	82.96	0.260
	15 min above	83.07	0.261

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
*p means p-value, *means significance level.*

TABLE 4 | Health insurance coverage by migrants' characteristics (N = 71,979).

		Health care	
		No	Yes
Age	<40	23,520	18,940
	≥40	19,278	10,239
	$\chi^2 = 710.966$, $P = 0.000$		
Gender	Male	24,200	15,938
	Female	18,598	13,243
	$\chi^2 = 26.118$, $P = 0.000$		
Health	Healthy	42,167	28,938
	Unhealthy	629	242
	$\chi^2 = 59.52$, $P = 0.000$		
Marriage	In marriage	31,841	22,588
	Not in marriage	10,957	6,593
	$\chi^2 = 85.159$, $P = 0.000$		
Education	Senior high school or below	37,136	16,643
	Senior high school above	5,662	12,538
	$\chi^2 = 8{,}100$, $P = 0.000$		
Hukou types	Agriculture	35,336	188,568
	Non-agriculture	7,462	10,613
	$\chi^2 = 33{,}000$, $P = 0.000$		
Labor contract types	Non-fixed-term contract	5,608	3,136
	Other contract types	37,190	26,045
	$\chi^2 = 90.296$, $P = 0.000$		
Move range	Across the province	20,346	15,461
	Move within the province	22,452	13,720
	$\chi^2 = 205.658$, $P = 0.000$		
Health records	Established	11,081	9,920
	Unestablished	31,717	19,261
	$\chi^2 = 551.358$, $P = 0.000$		
Accessibility of health resources	Under 15 min	35,473	24,537
	15 min above	7,325	4,644
	$\chi^2 = 18.047$, $P = 0.000$		

of the total. Therefore, the enthusiasm of the floating population for participating in insurance at the destination is not very high. This will seriously affect their medical treatment at the destination and make it difficult to address health risks in the migration process. However, only 32.18% of the people who participate in health insurance at the destination are individuals; the vast majority are family migrants. This further indicates that as the floating population gradually completes family migration and achieves family reunification in the destination, they are also seeking opportunities to improve the development capacity and welfare level of their families, including employment, old-age care, medical care, housing, and education, increasing the demand for public services.

Binary Logistic Regression Analysis

This paper analyzed whether the current family migration trend in China has an impact on the floating population's health insurance participation at the destination. The dependent variable "participation in health insurance at destination" is binary, which could be divide into either participation or non-participation. Thus, we used binary logistic regression model, which constructed as follows:

$$\ln\left(\frac{P}{1-P}\right) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_i \quad (1)$$

The variables were submitted into Stata 16.0 and the binary logistic regression models were established. Model 1 is a benchmark model that only considers personal characteristics control variables; Model 2 considered migration variables and Model 3 considered both migration variables and health resources variables. The regression analysis results show in **Table 6**.

Effects of Variables on Participation in Medical Insurance at the Destination

From Model 1 to Model 3, all of the results reveal that the current family migration trend in China has an impact on the floating population's health insurance participation at the destination. To floating population, their family migration rate is higher, the

TABLE 5 | Health insurance coverage of family migrants in China ($N = 71,979$).

		Health care		
		Yes	**No**	**Total%**
Family migrant	Yes	19,790	29,654	68.69
	No	9,391	13,144	31.31
	Total %	40.54	59.46	100.00

NCMS, New Cooperative Medical Scheme; R&NURMNI, Rural & Non-Working Urban Residents' Basic Medical Insurance; NURBMI, Non-Working Urban Residents' Basic Medical Insurance; UEBMI, Urban Employees' Basic Medical Insurance.

probability of them to take part in public health care system is higher.

Specially, Model 1 reflects the influence of individual characteristic variables on the floating population's participation in health insurance at the destination. The results show that, in addition to partial health and marriage status factors, other factors have a significant impact on the floating population's medical insurance participation. Then Model 2 considers migration variables based on Model 1, and finds that these migration factors also have great influences on the health care participation. Finally, Model 3 considers both individual, migration and health resources characteristic, it reflects the influence of family migration variables on the participation of the floating population in medical insurance at the destination after controlling for individual, migration and health resources variables.

The statistical results show that family migration rate, the degree of family migration, has a significant positive impact on the insurance participation of the floating population at the destination areas at a significance level of 5%. Exp (B) of family migration rate is 1.481, means that comparing with people with a lower family migration rate, probability of participating in local medical insurance of the people with a higher family migration rate increased by 48.1%.

In terms of individual characteristics, age and labor contract types have a significant negative correlation with participation of the floating population in medical insurance at the destination; gender, health, marriage, education, hukou types, and monthly income have a significant positive correlation. The health care participation rate of people increases 0.987 times as the age increase one unit. Generally speaking, the elderly migrant population tends to be insured. However, the results are inconsistent, which may be due to the new generation of the floating population, comparing to the older generation, have more formal work, and are more eager to settle in cities. They are therefore more willing to participate in health insurance at migration destinations, while the elderly floating population is more mobile and dependent on their hometown. What is more, comparing with floating population who signs a non-fixed or fixed-term labor contract, the people not sign a labor contract has lower probability to participate in public health care system, due to the labor law ask employers to take part in social security system for their signatory employees.

The male migrant population is more inclined to participate in medical insurance, which is 1.139 times the probability of female participation. It may be that the male migrant population faces greater health risks at work and hope to avoid these risks by participating in insurance. Worse health status has a positive effect on health care participation, for the people with terrible body health will take insurance system as a way to keep away from health risks. To marriage status, comparing with single ones, people stay in marriage status, such as first married and remarried, are more possible to take part in health care system. The one who had marriage history also willing to purchase a health care product. Also, the years the floating population has been educated indicates that if people have received good education, they will have higher health literacy and self-protection awareness, so can fully understand medical insurance and are more likely to participate in this security system. Comparing with people who just finished Primary School or Below, the probability of participating in local medical insurance will increased by 42.9, 125, 305, and 548% if people attended Junior high school, Senior high school, Junior college, and even obtained a bachelor degree or above. To those who hold an agriculture type of hukou, they are less possible to take part in health care system at destination because it is complicated for them to trans their health care records from hometown to destination. To economic status, people with relatively high incomes are likely to choose medical insurance to prevent the uncertain risks that the family may encounter. Therefore, the higher the monthly income, the more insurance fee the floating population can afford.

As for migration characteristics, there was a significant correlation between the history, range, duration, cities numbers of migration, and the participation in medical insurance at the destination. The participation rate of floating people whose first move happened many years ago is higher than those whose migration started recently. Move history increases 1 month, the participation rate will increase 2.7%. Maybe the migration history reflects the adapt ability, the longer people move, the more they will adapt to new environment, and then will adjust to current life system. It is the same for the move duration, means the length of the last time move increases 1 month, the participation rate will increase 0.4%. The longer the migration duration, the longer the floating population has been living at the destination, so it is more convenient to participate in and use medical insurance there. In terms of move range, people move across within a province are less likely to participate in health care system at destination. The health care participation rate of people who move across cities in the province and across counties in the city are 0.947 and 0.625 times of people who move across a province, respectively. It may be due to that the longer the distance traveled, the higher the cost of returning to the hometown, so they are more likely to change their institutional welfare status in their place of household registration. However, the more cities people move, the participation rate of floating people is lower. The health care participation rate of people increases 0.94 times as the number of cities they move increase 1 unit.

As for health resources characteristics, members of the floating population who have not established health records are less inclined to participate in medical insurance in the places they migrate to, which is 0.688 times that

TABLE 6 | Logistic regression results of family migration rate on access to health insurance of floating population in China ($N = 71,979$).

Variable	Model 1		Model 2		Model 3	
	B	Exp (B)	B	Exp (B)	B	Exp (B)
Family migration rate	0.435***	1.545	0.388***	1.475	0.393***	1.481
Age	0.004**	1.004	−0.013***	0.988	−0.013***	0.987
Gender (female)						
Male	0.139***	1.149	0.131***	1.140	0.130***	1.139
Health (healthy)						
Basically healthy	0.039	1.040	0.027	1.027	0.042	1.043
Unhealthy	0.426***	1.531	0.363***	1.438	0.385***	1.470
Marriage (Single)						
First married	0.485***	1.624	0.430***	1.538	0.417***	1.517
Remarried	0.663***	1.941	0.621***	1.860	0.603***	1.828
Divorce	0.255***	1.290	0.310***	1.363	0.301***	1.352
Widowed	0.337**	1.401	0.425**	1.530	0.411**	1.509
Cohabit	0.056	1.058	0.035	1.036	0.042	1.043
Education (primary school or below)						
Junior high school	0.333***	1.396	0.367***	1.443	0.357***	1.429
Senior high school	0.766***	2.151	0.830***	2.294	0.811***	2.250
Junior college	1.332***	3.790	1.414***	4.114	1.400***	4.054
Bachelor degree or above	1.779***	5.921	1.879***	6.548	1.869***	6.482
Hukou types (Agriculture)						
Non-agriculture	0.324***	1.382	0.344***	1.410	0.336***	1.399
Labor contract types (Non-fixed-term contract)						
Fixed-term contract	0.992***	2.696	1.037***	2.821	1.033***	2.811
Not sign contract	−1.179***	0.308	−1.173***	0.310	−1.156***	0.315
Not applicable	−0.780***	0.459	−0.788***	0.455	−0.782***	0.458
Monthly income	0.270***	1.310	0.195***	1.216	0.206***	1.228
Migration history			0.026***	1.027	0.026***	1.027
Move range (Across the province)						
Across the city in the province			−0.027***	0.973	−0.054**	0.947
Across the county in the city			−0.430***	0.651	−0.470***	0.625
Move duration			0.004***	1.004	0.004***	1.004
Move cities			−0.061***	0.941	−0.062***	0.940
Health records (established)						
Unestablished and never heard					−0.373***	0.688
Unestablished but heard					−0.323***	0.724
Not clear					−0.207***	0.813
Accessibility of health resources (under 15 min)						
15–30 min					−0.087**	0.916
30–60 min					−0.089	0.915
60 min above					0.260	1.296
Constant	0.000***	0.010	−3.741***	0.024	−3.55	0.029
Pesudo R^2	0.229		0.248		0.251	
Log Pseudo Likelihood	−37,438.156		−36,540.233		−36,387.426	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
*p means p-value, *means significance level.*

of people who have established health records, because there is no comprehensive health record management model for the floating population. Also, the accessibility of health resources has a negative effect on health care participation. People will more likely to take part in the public health care system if they can reach the nearest health institution under 15 min, but the health care participation rate will be 0.916 times of the former if people will reach the nearest health institution in 15–30 min.

TABLE 7 | Effect of family migration rate on health care participation by education, labor contract types, and income.

	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
	Senior high school or below	Senior high school above	Non-fixed-term contract	Other contract types	Top 50% of monthly income	Bottom 50% of monthly income
Family migration rate	0.409***	0.280***	0.278**	0.417***	0.224***	0.501***
	(1.505)	(1.323)	(1.321)	(1.517)	(1.251)	(1.650)
Control variables	Yes	Yes	Yes	Yes	Yes	Yes
N	53,779	18,199	8,743	63,235	33,642	38,336
Wald chi^2	9,237.75	2,585.44	1,474.00	14,252.45	6,215.54	8,394.43
Log pseudo likelihood	−26,755.979	−9,513.8101	−4,661.9372	−31,634.9	−16,595.99	−1,9637.989

$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, Exp (B) display in parentheses.
*p means p-value, *means significance level.*

TABLE 8 | Effect of family migration rate on health care participation by family structure.

	Model 10	Model 11	Model 12	Model 13
	Families without both young and old	Families without old but young	Families without young but old	Families with both young and old
Family migration rate	0.407***	0.389***	0.388	0.589**
	(1.502)	(1.475)	(1.474)	(1.803)
Control variables	Yes	Yes	Yes	Yes
N	24,894	44,084	1,136	1,864
Wald chi^2	5,376.86	9,641.22	212.64	425.85
Log pseudo likelihood	−12,688.507	−22,037.021	−535.183	−958.202

$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, Exp (B) display in parentheses.
*p means p-value, *means significance level.*

Heterogeneity Analysis

Table 7 show the results of heterogeneity analysis. According to the results, in the low-educated group, the effect of family migration rate on health care participation is similar to the effect reflected in total sample, while the effect in high-educated group is proved to be less. To the well-educated floating people, there are much more approaches for them to get access to health resources. In comparison, not well-educated floating people have no more choices than rely on family to collect information at a new environment. When comparing groups by labor contract types, it is obvious that the effect of family migration rate on health care participation is lower in group in which people signs non-fixed-term contract. Maybe the stable and lasting employment status means their health care participation are influenced more by their employers. In terms of income, higher monthly income will help floating people, so the effect of family migration rate on health care participation in the top 50% income group is not as great as in the bottom group.

Table 8 show the heterogeneity of health care participation among floating families with different family structure. Through calculating the number of family member who under 18 and old who above 59, family structure is divided into 4 types: families without both young and old, families without old but young, families without young but old and families with both young and old. Family migration rate has a significant positive impact on the insurance participation of the floating population at the destination areas at a significance level of 5% in three structure types except for the "families without young but old" structure.

Comparing with Model 10 and 11, the family migration rate in Model 13 has the strongest effect on health care participation, which means that if a family both have old and young family member, the more family members move to the destination, the more likely for them to take part in local health care system. To some extent, the young and the old are so vulnerable that their family have to make a stronger security network, in order to escape from potential disease risks. When the old or young family member come to the new place, the degree of fragile of whole family would increase, so it is a sensible choice to take use of local health care system, especially for families with infants or elderly members.

Explanatory Mechanism

The logit regression results show that family migration promotes the floating population's participation in medical insurance at the destination. This effect can explained by the mechanisms of family support and social integration.

Firstly, the family support mechanism works because, compared with individual migration, when multiple family members migrate together it is easier to achieve expected income targets, and the burden of medical insurance payments can

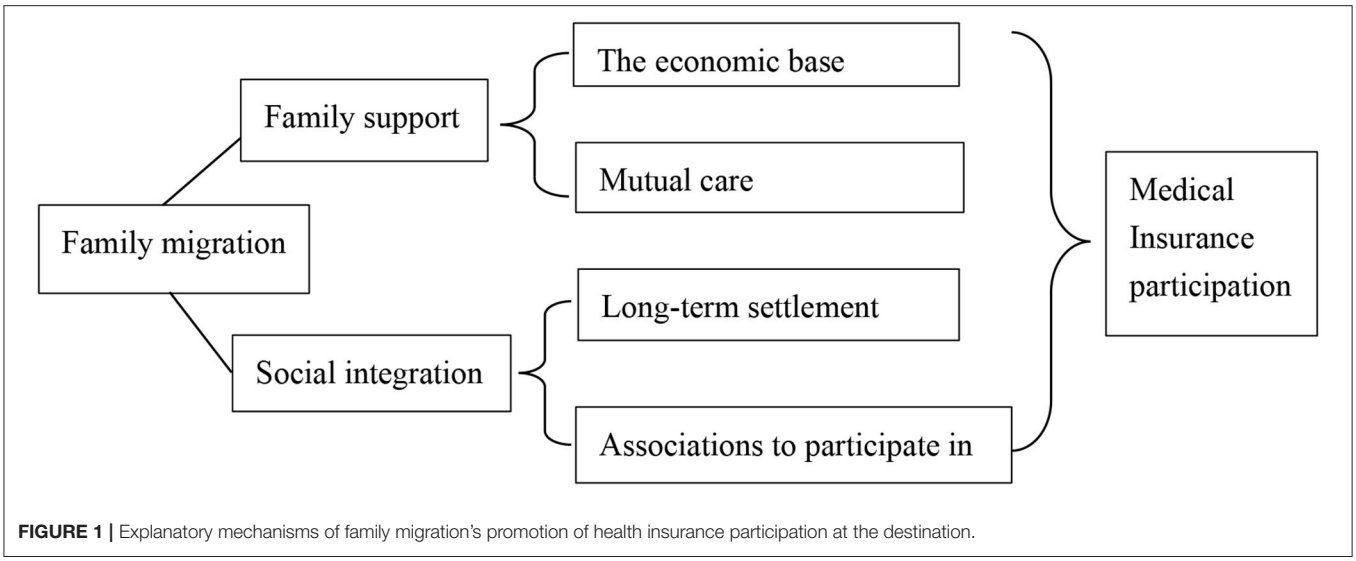

FIGURE 1 | Explanatory mechanisms of family migration's promotion of health insurance participation at the destination.

reduced. Subsequently, the family decides to participate in medical insurance at the destination, which aims to minimize, through diversified family resources, the risk caused by the lack of effective protection at the destination. It is part of the family's risk diversification strategy, which links migration decisions with the maximization of family benefits. In addition, the physical health of the elderly and children may be weaker in general, so the migration of the elderly and children increases the health risks and medical needs of the floating population to a certain extent. Family migrants also facilitate mutual care during treatment, which enhances their willingness to participate in the insurance in the destination.

The second is the social integration mechanism. With a relatively high degree of family migration, especially when all family members migrate, maintaining the welfare system attached to their *hukou* seriously weakens their protection. Family migrants' connection to their hometowns gradually reduces, and they become more closely connected to their destination. They may even wish to settle permanently in cities, which will generate a stronger demand for public services and social welfare there. The floating population no longer intends to return to their hometown, and through family migration, they expand their social network at the destination, enhance their community participation, and facilitate their use of local medical and health services.

In summary, the influence mechanism of family migration on the migrant population's participation in medical insurance at the destination concluded below (as shown in **Figure 1**).

CONCLUSIONS

Population flows in China are shifting from individual migration to partial or complete family migration. This is not only a simple gathering of people in geographic displacement, but also a profound adjustment of family lives and demands of the migrant population. Due to the *hukou* system and regional separation, the floating population in China stay on the margins of the social welfare system and trap in the dilemma of not being able to enjoy basic medical security. In this context, based on the 2017 Migrant Dynamic Survey data, this study used a binary logistic regression method to discuss the family migration rate on health care participation and the influence mechanisms. The final research conclusions are as follows:

First, in 2017, 68.69% of the floating population in China were migrants accompanied by at least one other person, which means that the current population flow in China no longer mainly comprises individuals. In terms of health care participation status, our results shows that the majority of the floating population still chooses to participate in medical insurance in their place of *hukou* registration, and they are in a vulnerable state at the destination, unable to enjoy the same public services as local people.

Second, family migration has a significant positive correlation with the health insurance participation of the floating population at the destination, which explains by family support and social integration mechanisms. The current family migration trend in China has an impact on the floating population's health insurance participation at the destination. Comparing with people with a lower family migration rate, probability of participating in local medical insurance of the people with a higher family migration rate increased by 48.1%. Family migrants have, on the one hand, good family support, including economic foundations and mutual care; and on the other, a relatively high degree of social integration, with a willingness to settle down and enthusiasm to be involved in community life at the destination, which encourages them to participate in medical insurance at the destination.

Third, the participation of the floating population in medical insurance at the destination shows differences according to various characteristics. Age, labor contract types, migration range and cities numbers, health records, and the accessibility of health resources have a significant negative correlation with

participation of the floating population in medical insurance at the destination; gender, health, marriage, education, hukou types, monthly income, migration history, and move duration have a significant positive correlation.

Fourth, the heterogeneity of health care participation among different groups within the floating population shows that the effect of family migration rate on health care participation is weaker in group in which people are low-educated and signs non-fixed-term contract or gets bottom 50% monthly income. Also, except for the "families without young but old" structure, the family migration rate of families under other three family structures, especially the "families with both young and old" structure, have stronger effect on health care participation.

Under this trend of family migration, policy-making and institutional arrangements of social welfare face with new challenges. Combined with the results of the empirical analysis and main conclusions, we have following suggestions:

First, we should establish and improve the welfare policies for migrant families to enhance their development ability. As the floating population gradually realizes the migration of complete families, they are no longer isolated. Instead of facing the loss of individual basic rights and interests, they face the loss of the overall interests of their family. Subsequently, the floating population demands basic public services such as employment, education, social security, and public health at the destination. Therefore, relevant social policies should shift from focusing on the floating population to the construction of a public service system centered on family migration. The government will improve the welfare level and expand the welfare coverage of floating population families, in order to respond to their real needs, effectively guarantee their basic welfare, and improve the overall development and security capacity of floating population families.

Second, China should speed up the coordination of medical insurance between the urban and rural areas and expand the coverage of medical insurance. In the development of China's basic medical insurance, regional differences, urban-rural divisions, administrative barriers, and other problems exist, and the portability of medical insurance is inadequate, which makes it difficult for the floating population to participate in and use medical insurance equally. On the one hand, it is necessary to establish the connecting mechanism of basic medical insurance transfer, making full use of information technology; establish multi-level medical security information networks; and simplify the reimbursement procedures in different places. On the other hand, we should strengthen the top-level design, standardize convergence processes and implementation rules, and coordinate procedures among different regions and departments to make convergence policies effective, standardized, and practical.

Finally, we should pay attention to the differences in the characteristics of the floating population and improve their enthusiasm to participate in insurance. Among the floating population, the participation rate of the older generation and female floating population at the destination is low, self-employed workers do not actively participate in insurance, and the Informal employment floating population is often excluded from welfare policy at the destination. Therefore, we should focus on particular groups among the floating population, encourage them to participate in medical insurance, and increase compulsory participation. At the same time, the higher the education level, the more likely the floating population is to participate in insurance. Therefore, education and training of the floating population should strengthen to improve their human capital and health literacy and enhance their participation awareness.

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/s.

AUTHOR CONTRIBUTIONS

LL contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

FUNDING

This research was supported by Nanjing University of Posts and Telecommunications (NYY216005), Jiangsu Provincial Social Science Fund (17SHC006), and Jiangsu Provincial University Philosophy and Social Science Research Fund (2017SJB0079).

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

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 01 October 2021
doi: 10.3389/fphar.2021.707442

The Establishment and Practice of Pharmacy Care Service Based on Internet Social Media: Telemedicine in Response to the COVID-19 Pandemic

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OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Anthony Bokolo Jnr., Norwegian University of Science and Technology, Norway
Kurt Neumann, Independent researcher, Budapest, Hungary

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *10 May 2021*
Accepted: *28 June 2021*
Published: *01 October 2021*

Citation:
Li H, Zheng S, Li D, Jiang D, Liu F, Guo W, Zhao Z, Zhou Y, Liu J and Zhao R (2021) The Establishment and Practice of Pharmacy Care Service Based on Internet Social Media: Telemedicine in Response to the COVID-19 Pandemic. Front. Pharmacol. 12:707442. doi: 10.3389/fphar.2021.707442

Objective: For patients with chronic diseases requiring long-term use of medications who are quarantined at home, the management of medication therapy during the COVID-19 pandemic is a problem that pharmacists urgently need to discuss and solve. The study aims to establish and launch a telepharmacy framework to implement pharmaceutical care during the COVID-19 pandemic.

Methods: To establish a remote pharmacy service model based on a medication consultation service platform under the official account of the "Beijing Pharmacists Association" on the social software WeChat app, obtain the medication consultation records from February 28 to April 27, 2020, during the worst period of the epidemic in China, and to perform a statistical analysis of the information about the patients seeking consultation, consultation process, content and follow-up results.

Results: The medication consultation service system and telepharmacy service model based on social software were established in February 2020. The "Cloud Pharmacy Care" platform had 1,432 views and 66 followers and completed 39 counseling cases in 2 months. Counseling was available for patients of all ages. Of the 39 cases, 82.05% of patients were young and middle-aged. During the COVID-19 pandemic, the long-term medication usage problems of patients with chronic disease were effectively addressed using "Cloud Pharmacy Care". In the consultation, 35 cases (89.7%) were related to the use of medicines or health products, and 4 cases (10.3%) involved disease state management and the use of supplements. The top five drug-related issues included the selection of medications, the dosage and usage of drugs, medications for special populations, medication therapy management of chronic diseases, and adverse drug reactions. All consultations were completed within 4 h, with a positive review rate of 97.4%.

Conclusion: During the COVID-19 pandemic, a remote pharmacy service "Cloud Pharmacy Care" based on the social software WeChat app was quickly constructed

and applied to solve the medication-related problems of patients and the public during home quarantining. The significance of the study lies in the timely and interactive consultation model helps to carry out medication therapy management for chronically ill patients and improves patients' medication compliance, improves medical quality, and plays a positive role in promoting the popularization of safe medication knowledge.

Keywords: COVID-19, medication therapy management (MTM), remote pharmacy service, innovative service model, telepharmacy

INTRODUCTION

In December 2019, a cluster of cases of acute respiratory illness caused by respiratory syndrome coronavirus 2 (SARS-CoV-2) were detected and then spread rapidly worldwide (Chen et al., 2020; Li et al., 2020; Zhu et al., 2020). The World Health Organization (WHO) declared that the 2019 coronavirus disease (COVID-19) outbreak was the sixth Public Health Emergency of International Concern (Lai et al., 2020; Patel and Jernigan., 2020). At present, it has been found that the infection spread of severe acute SARS-CoV-2 is mainly via respiratory droplets and contact transmission from person to person (Lai et al., 2020; Li et al., 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). The Chinese government has taken a series of effective administrative measures to interrupt the spread of the epidemic (Lau et al., 2020; Wu and McGoogan, 2020), including early diagnosis, patient isolation, symptomatic monitoring of contacts with suspected and confirmed cases, social distancing and community-based isolation, which played a pivotal role in limiting the COVID-19 outbreak (Wilder-Smith and Freedman, 2020; World Health Organization, 2020).

The hospital is not only the primary battlefield for pandemic prevention and treatment but also a high-risk place for epidemic transmission. During the COVID-19 pandemic, the risk of cross-infection in the hospital can be minimized by reducing hospital visits and exposure opportunities (Currie et al., 2016), strategies that have been widely adopted during the pandemic of various infectious diseases (Currie et al., 2016). Due to the pandemic, numerous non-emergency outpatient departments in Chinese hospitals were closed, causing most offline clinics to be unavailable to the public. While this crisis has presented the medical care delivery system with unparalleled challenges, COVID-19 has catalyzed rapid use of information and communications technology (ICT), such as telemedicine to deliver healthcare at a distance, offers an affordable, effective, and attractive option. Telemedicine including counseling, supervision, training, and psychoeducation in response to the pandemic, has been promoted and scaled up to reduce the risk of transmission (Li et al., 2021). Within this umbrella of telemedicine falls telepharmacy, the provision of pharmacist care by registered pharmacists and pharmacies through the use of telecommunications to patients located at a distance (Alexander et al., 2017; Win, 2017). Telepharmacy operations and services may include, but are not limited to, drug review and monitoring, dispensing, sterile and nonsterile compounding verification, medication therapy management (MTM), patient assessment, patient counseling, clinical consultation, outcomes assessment, decision support, and drug information (Alexander et al., 2017). Others are diagnostic and disease prevention services, therapeutic drug monitoring, and assessment of clinical outcomes (Hedima and Okoro, 2021).

During the pandemic, masses of patients in COVID-19-designated hospitals need therapy guidance from a pharmacist (Baldoni et al., 2019), and home-quarantined patients with chronic diseases requiring the long-term use of medications also need consultation from professionals (Li et al., 2021). Helping them manage home medicines is a problem that pharmacists urgently need to discuss and solve (Li et al., 2021). The current pharmaceutical care crisis and the need for social distancing have necessitated the need to adopt new initiatives for the treatment of patients (Anthony Jnr., 2021). Telepharmacy is expected to deliver timely pharmaceutical care while minimizing exposure to protect medical practitioners and patients and has been suggested as a method to maintain a continuum of pharmaceutical care for patients (Jnr, 2020).

As the world's first country to respond quickly to COVID-19, the Beijing Pharmacists Association (BPA) screened 27 pharmacist volunteers with rich clinical experience and medication therapy management (MTM) qualifications from tertiary hospitals quickly establish an online voluntary pharmacy service team of "Cloud Pharmacy Care" (Li et al., 2021). To reduce the burden on the front-line medical teams, out of necessity, "Cloud Pharmacy Care" remote pharmacy service provides an interpretation of treatment plans from the medical teams and solutions for medication-related issues for patients and the public (Li et al., 2021). The BPA used Delphi's method to develop an innovative remote pharmaceutical care framework in response to the current needs of epidemic prevention and control. Different from the telepharmacy provided by a traditional pharmacy, clinic, or medical institution, such as support to clinical services, remote education and handling of "special pharmacies" on medication dispensing safety, and prescription and reconciliation of drug therapies (Baldoni et al., 2019; Le et al., 2020; Pathak et al., 2020; Zhou et al., 2020), this study describes and analyses the framework, the results, and effects of internet-based remote pharmacy services supported by multidisciplinary professional pharmacists with MTM certification quickly response to the COVID-19 epidemic, with social software on smartphones for patients' medication management and remote

education. The innovative telepharmacy service aiming to provide a reference for international pharmacists.

METHODS

In response to the lack of medical resources in the epidemic area and the special situation of some home-quarantined patients requiring pharmacist guidance, in February 2020, the BPA quickly formulated an emergency remote pharmacy service framework through the Delphi method. The "Beijing Pharmacists Association" official account and medication consultation platform were built on the social software "WeChat" app. Patients can fill in personal information and health records to help pharmacists understand their overall health status. The service platform ensures patient privacy and information security.

Establish a Remote Pharmacy Service Model

The BPA screened 27 pharmacists with rich clinical experience and MTM qualifications who work in the tertiary hospitals of the Beijing and Tianjin region quickly establish the voluntary team of "Cloud Pharmacy Care", providing online free medication consultations. The professional major of pharmacists covers western medicine and traditional Chinese medicine, including cardiovascular, endocrinology, respiratory, gastroenterology, neurology, psychiatry, obstetrics and gynecology, and other specialties.

Consultation Procedure

Patients can consult the individual pharmacist or the pharmacist team about medication-related issues in the form of texts, pictures, or voice messages from 8 a.m. to 8 p.m. each day. The content of the consultation includes treatment, medication reconciliation, chronic disease MTM, lifestyle guidance, and psychological counseling. The scope of services does not involve diagnosis, medical insurance reimbursement, medical expenses, or referrals.

Implementation and Promotion of the Platform

After the service plan of the "Cloud Pharmacy Care" was approved by the Fangcang shelter hospitals, "A Letter to Fangcang Patients" was sent to the current patients by the pharmacist there. After the Fangcang shelter hospitals closed sequentially, the BPA issued service introductions to designated hospitals receiving COVID-19 patients, community health centers, and retail pharmacies in Beijing. Some medical institutions posted these service introductions in the outpatient pharmacy of the hospital for advertising.

Service Quality Control

All licensed pharmacists received standardized and unified training before starting their consultations and have learned about the updated findings regarding COVID-19 in real-time. The pharmacists needed to fill in the consultation records of each patient, and the senior pharmacists (LD and JDC) reviewed the consultation questions and answers. For complicated problems, pharmacists discussed these issues with the other pharmacists to ensure the correctness of the answers. All the questions were analyzed descriptively, and the chi-square test was used for classification statistics and comparative analysis. The consulting system prompts those receiving consultations to rate the satisfaction of the service. The number of stars (1–5) represents satisfaction from low to high. A rating above four stars indicates a favorable experience.

RESULTS

Establishment of the "Cloud Pharmacy Care" Remote Pharmacy Service

After patients log in WeChat app and follow the "Beijing Pharmacist Association" official account, they then click "I need consultation" in the "Cloud Pharmacy Care" section of the public account interface to start a consultation. The "Cloud Pharmacy Care" pharmacy service framework is shown in **Figure 1**.

The Work Mode of Medication Consultation

After receiving the patient's consulting request, the on-duty pharmacist selects "I will answer" or recommends another specialized pharmacist on the team to answer. To protect patient privacy, patient information and consultation records during the consultation process can only be seen by the patient and the responding pharmacist. Patients can also choose to follow pharmacists according to their specialty and initiate a one-on-one consultation with the pharmacist. All consultations need to be completed within 4 h of an online request.

Patient Management

Each pharmacist has a dedicated homepage, which can display personal basic information, time of visit, patient impression, patient education articles, answered consultations, and other information, from which patients can learn more about the pharmacist's information. The pharmacist's homepage also displays a QR code unique to the pharmacist. The patient can follow the pharmacist by scanning the QR code, which is convenient for secondary transmissions. Pharmacists can manage patients who follow them, view their health information, add diagnosis and treatment files to patients' records, and add tags in the settings.

Patient Education

Promoting the knowledge of rational drug use to the public is another important task of the "Cloud Pharmacy Care" service, and this is consistent with the push function of the WeChat platform. Pharmacists can compose original messages or reprint popular science articles, graphic illustrations, animations, or videos. Patient education materials are published and can be

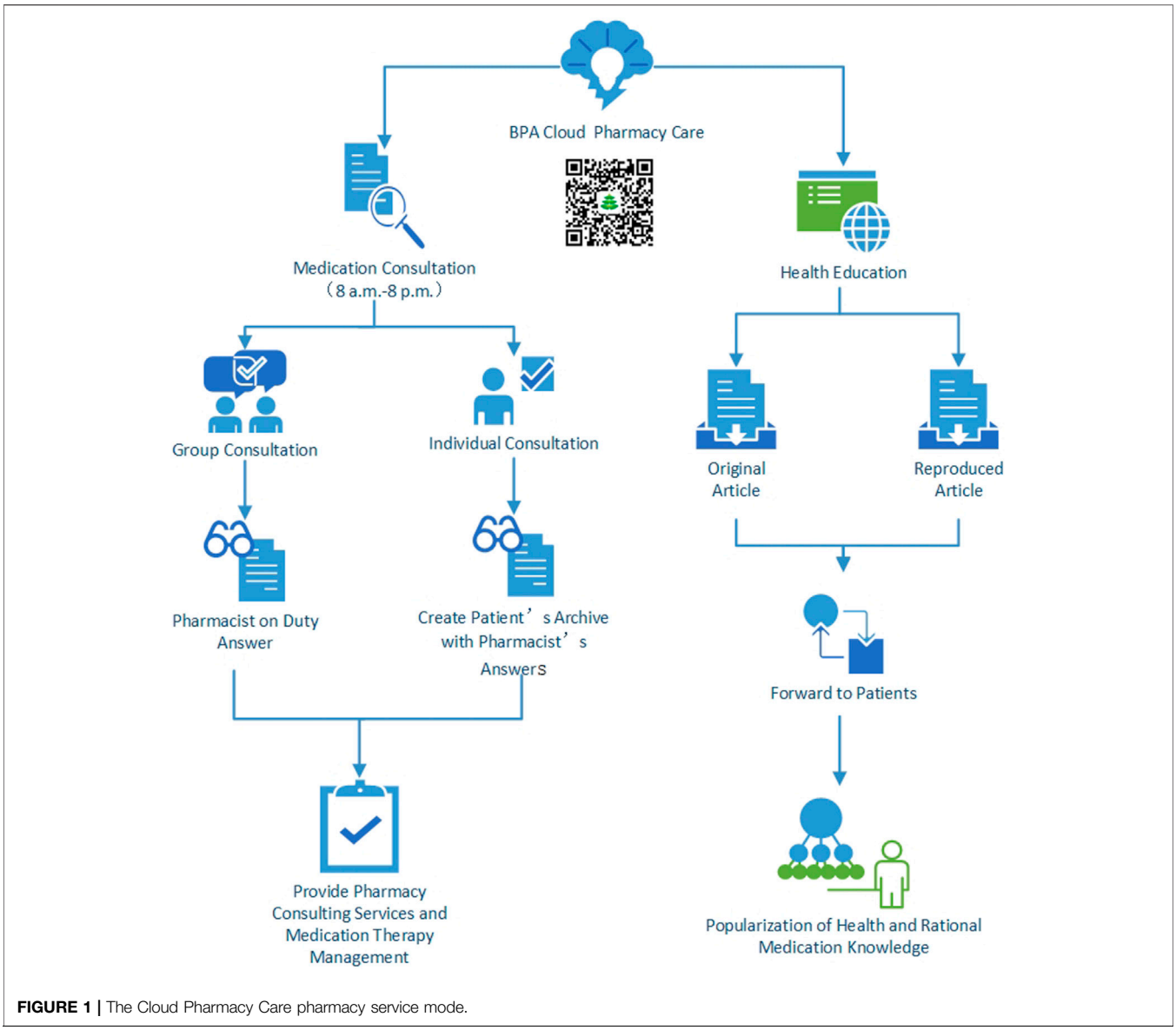

FIGURE 1 | The Cloud Pharmacy Care pharmacy service mode.

TABLE 1 | The basic characteristics of the consultant.

		Number of consultations	No. (%)
Gender			
	Male	15	38
	Female	24	62
Age	Years		
	<18	3	8
	18–40	18	46
	41–65	14	36
	>65	4	10
Consultant			
	Patient	33	85
	Replacer	4	10
	Medical personnel	2	5

sent directly to patients to facilitate education regarding rational medication use.

Tele-Consultation Results

Consulting Object

From February 28 to April 27, 2020, during the worst period of the epidemic in China, “Cloud Pharmacy Care” had 1,432 views, 66 followers, and received 39 counseling cases in the two previous months. The basic characteristics of the consultant are shown in **Table 1**. The average age of the patients was 42 years old, where the youngest was 2 years and 7 months old, and the oldest was 85 years old. Counseling was available for patients of all ages; 82.05% were young and middle-aged. Four people requested consultations on behalf of others, among which 2 were adults seeking consultations for their parents, and two were parents seeking consultations for minors.

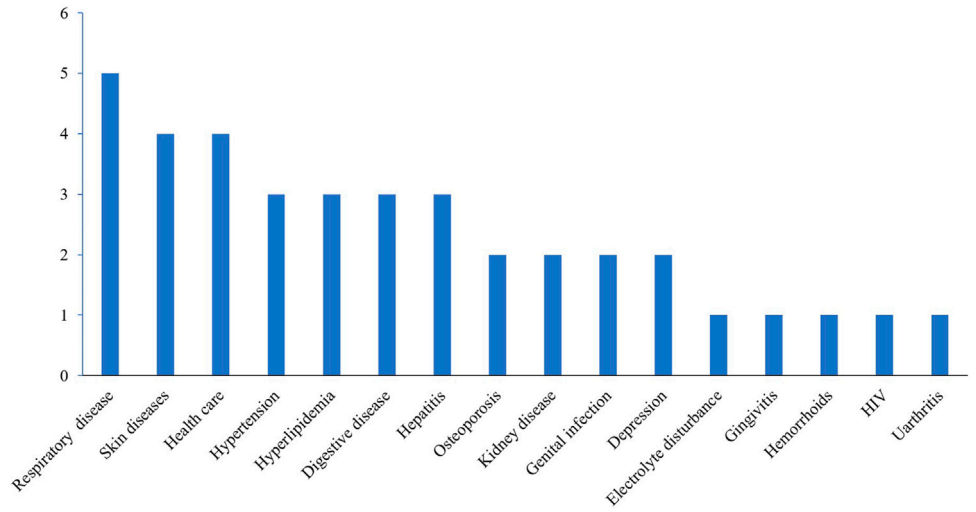

FIGURE 2 | Disease distribution involved in the consultation content.

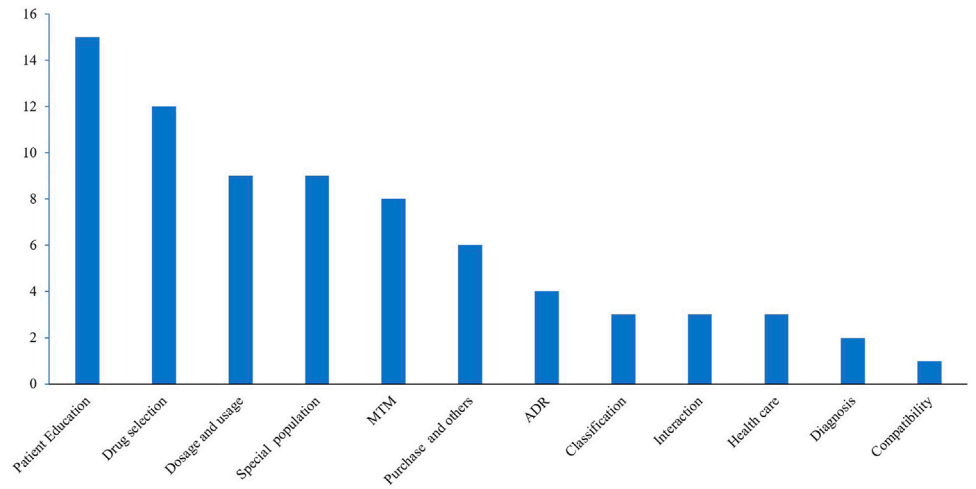

FIGURE 3 | The classification distribution involved in the consultation content.

Consulting Content

In a single consultation, there were a maximum of 13 items and a minimum of two items. On average, each consultant needed to answer four to five items. In the consultations, 35 cases (89.7%) were related to the use of medicines or health products, and 4 cases (10.3%) involved disease management and the use of supplements. The diseases and classification distribution involved in the consultation content are shown in **Figure 2** and **Figure 3**. The chi-square test showed that the classification of consultation questions does not correlate with age and gender. Three representative examples of

The pharmacist's solution and analysis of patients' medication problems were given in **Table 2**.

Service Quality Evaluation

All consultations were completed within 4 h, and the completion rate was 100%.

All those receiving consultations rated the teleconsultation service of the pharmacists: 38 people gave a rating of five stars and one person rated the consultation three stars, yielding a positive rate of 97.4%. There were no complaints from consultants, and no doctor-patient disputes occurred. The patients generally commented that the pharmacist responded in a timely, earnest, professional, patient-caring and enthusiastic manner, e.g., "During the epidemic, the guidance of the pharmacist is very valuable", "Thank you for this lovely platform."

For acute and severe patients, the pharmacists would follow up on the patient's illness and medication status after the

TABLE 2 | Representative examples of the consultations on "Cloud Pharmacy Care".

Content	Case 1	Case 2	Case 3
Chief complain	Stomach ache that affected sleep, anxiety	Swelling of the left foot and ankle	Eyelid edema
Subjective/ objective	Male, 39 years old **Gastric ulcers**: stomachache affected sleep, gastroscopy could not be done during the epidemic, need painkillers to improve the sleep **Anxiety:** Patient experiencing recurring symptoms **HIV:** take medications regularly	Female, 60 years old **Hypertension:** blood pressure approximately 140/80 mmHg **Gout:** sudden swelling of the left foot and ankle recently, consider gout recurrence	Male, 2 years and 7 months Eyelid edema for 2 days, the 3rd times onset in the last month Urine protein 4+, urine occult blood 2+, urine red blood cells 660.80/μl, urine white blood cells 29.4/μl
Past medical history	Anxiety (was on escitalopram 10 mg QD)	Gout (was on colchicine)	None
Current Medications	Atripla (tenofovir + lamivudine + efavirenz) 1 tablet p.o. QD; omeprazole capsule 20 mg p.o. QD; ibuprofen sustained-release 0.3 g p.o. BID	Indapamide 2.5 mg p.o. QD; aspirin 100 mg p.oQD.	Loratadine 5 mg p.o. QD
Drug therapy problems	**Gastric ulcers:** effectiveness-frequency inappropriate **Anxiety:** indication-untreated condition **HIV:** safety-undesirable effect	**Hypertension:** safety-undesirable effect; effectiveness-more effective drug available **Gout:** safety-undesirable effect, indication-untreated condition	Eyelid edema: indication-untreated condition, need a definite diagnosis Loratadine: effectiveness-not effective for the condition
Assessment	**Gastric ulcers:** omeprazole dosage too low, and not recommended to take NSAIDs **Anxiety:** needs additional drug therapy **HIV:** adverse drug reaction, Efavirenz may cause drug-induced anxiety	**Hypertension:** adverse drug reaction, hyperuricemia may be associated with indapamide; blood pressure poorly controlled, need different drug product **Gout:** needs additional drug therapy	Suspected to be nephritis or nephrotic syndrome
Plan	Taking omeprazole 20 mg p.o. BID, withdrawal ibuprofen Re-start escitalopram 10 mg p.o. QD	Start amlodipine 5 mg p.o. QD, aspirin 100 mg p.o. QD, colchicine 1 mg p.o. QD	Recommended to go to the hospital
Follow-up	Stomachache relieved 1 week later, and the anxiety state was well controlled 1 month later	Gout relieved, blood pressure approximately 130/80 mmHg 1 month later	Diagnosed with "nephrotic syndrome", treatment with methylprednisolone 10 mg tid, 3 days later

consultation. Examples of follow-up records are shown in **Table 2**. The senior pharmacists commented on the records of all questions and answers, and these comments were all scientific and appropriate. The telepharmacy service during the epidemic is an emerging service. We are still exploring the working framework and have been constantly improving the process of plan, do, check and act (PDCA).

DISCUSSION

Disasters and pandemics pose unique challenges to healthcare delivery. The current COVID-19 pandemic reminds us of the importance of using telemedicine to deliver care, especially in reducing the risk of cross-contamination caused by close contact during infectious public health emergency responses (Feng et al., 2020; Hollander and Carr, 2020; Smith et al., 2020; Zhou et al., 2020). Although innovative telepharmacy services will not solve all patient needs, they are well suited for scenarios in which infrastructure remains intact and pharmacists are available to reduce the public panic and address the patients' medication problems as a supplement to a remote assessment in primary care (Greenhalgh et al., 2020; Ibrahim et al., 2020) and mental health services (Yang et al., 2020; Zhou et al., 2020). In addition to the "Online Pharmaceutical Monitoring" service launched by the Tongji Medical College of Huazhong University of Science and Technology for the patients in the Fangcang shelter hospital, "Cloud Pharmacy Care" is the first online pharmacy consulting service platform organized by a professional society and composed of MTM-qualified pharmacists in China, providing free pharmaceutical care for the public during the COVID-19 pandemic (Li et al., 2021).

Construction of Telepharmacy Services

Telepharmacy models have been implemented in various countries of the world despite variations in healthcare systems. In China, "Mobile Internet + Medical Care" oriented by the big data value chain is gradually changing medical practices and processes (Wang et al., 2017). During the outbreak of the COVID-19 pandemic, the long-term medication-use problems of patients with chronic disease were effectively solved by "Cloud Pharmacy Care", such as respiratory disease, skin diseases, hypertension, hyperlipidemia, osteoporosis, etc. The top five drug-related issues include the choice of medications, the dosage and usage of drugs, medications for special populations, MTM of chronic diseases, and adverse drug reactions. In particular, through remote consultation by the pharmacists, a patient's disease could be discovered and diagnosed in time (such as the child's parents mistakenly thinking the nephrotic syndrome was allergic edema). If

discomfort or adverse drug reactions occurred (such as increased uric acid caused by indapamide), treatment was adjusted promptly.

Telepharmacy can alleviate the queuing problem and reduce the cost of transportation for patients. One of the advantages is that healthcare professionals can efficiently monitor patients' indicators and provide suggestions at any time. This is a low-cost, convenient and stable pharmacy service model that is not only suitable for emergencies but can also extend to unhealthy people, patients with chronic diseases, and healthy people who need pharmacy consultation in daily life. However, due to the short establishment time and insufficient publicity, the public's attention and the number of consultations was not very high in the first 2 months of the establishment of "Cloud Pharmacy Care". In non-pandemic times, this type of telepharmacy can facilitate patient communication when patients have barriers such as living in a rural/remote location, mobility challenges, poor access to transportation, or inflexible work or caregiving schedules.

Advantages and Value Based on Social Software

Traditional ways of communication are inefficient and painfully slow. Healthcare providers are currently experiencing transformational change and turning to social media to network, connect, engage, educate, and learn (Toney et al., 2015; Benetoli et al., 2017). As an instant messaging tool, the multifunctional WeChat official account consulting platform has many natural advantages. First, as the most widely used social software in China with nearly 1.2 billion active users, the operation is simple and not subject to excessive restrictions on age and cognitive behavior, providing a convenient method for medication consultation. Second, the "Cloud Pharmacy Care" medication consultation platform has multiple interactive forms available, such as text, voice, picture, and video. Patients can upload medical records, test and examination results, and all consultation records can be archived. At the same time, pharmacists can edit the patient's file, which is convenient for pharmacists to classify and manage patients. Third, WeChat's exclusive account login mode protects the privacy of patients, and patients can confidentially consult with pharmacists about personalized medication use. Last but not the least, from the perspective of technical implementation, with the advent of COVID-19, remote pharmacy care based on WeChat is easier to realize and apply than to establish a new APP.

Risk Management

Telemedicine adoption requires a whole-system strategy. Embedding telemedicine into routine service delivery by all healthcare providers is the most effective way of ensuring telemedicine can be readily used during emergencies, and it requires operational networks, telemedicine policies and procedures, and technology infrastructure that can be scaled up during times of epidemic. Accordingly, there are social, organizational, and technological factors that impact the widespread adoption of telepharmacy platforms by patients and medical practitioners (Bokolo, 2021). Among others, ethical considerations must be taken into account (Shokri and Lighthall, 2020). Telepharmacy services require professional knowledge, communication skills, empathy, and medical risk awareness of pharmacists. In 2018, the Chinese Pharmacist Association, Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee, and four other associations jointly issued the "Expert Consensus for Pharmacists to Provide Internet Science Popularization and Consulting Services", encouraging pharmacists to actively explore new models of Internet pharmacy services with a rigorous and scientific attitude (Chinese Pharmacists Association, Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee et al., 2020). This expert consensus highlights that pharmacists' professional activities on the internet platform must follow basic principles, ethics, and professional responsibility standards and include conducting risk management (Chinese Pharmacists Association, Chinese Pharmaceutical Association Hospital Pharmacy Professional Committee et al., 2020). In the Spanish Society of Hospital Pharmacy position statement (Morillo-Verdugo et al., 2020), the ASHP statement on telepharmacy (Alexander et al., 2017), and practice advancement initiative 2030 (ASHP Practice Advancement Initiative, 2020), the guidances also recommend that pharmacists use health information technologies to advance their role in patient care and population health.

The limitation of this paper is that the sample size of free online pharmacy consultation provided in this paper is small, because it only happened in the 2 months when the COVID-19 pandemic was the most severe in China, and also the 2 months when people in the whole country were quarantined at home. After that, the Chinese people resumed their normal life and were free to go out to the hospital. However, the framework of online pharmaceutical consultation has been successfully established, and then gradually transferred to paid pharmaceutical care.

CONCLUSION

Under the COVID-19 pandemic, a remote pharmacy service platform "Cloud Pharmacy Care" based on social software was quickly constructed and applied to help patients solve medication-related problems. In general, patients of all ages use the telepharmacy service for both acute and chronic conditions under the COVID-19 epidemic. Most patients asked questions related to their health or medications, and females preferred online consultation. Patients were more likely to ask questions related to prescription and OTC medications than questions about botanical and dietary supplements, and they are primarily interested in drug efficacy, adverse effects, and chronic disease management. Through telepharmacy services, the patients can keep in touch with their pharmacists. The study implies that the timely and interactive consultation platform helps to carry out medication management for chronically ill patients, improve patients' medication adherence, and improve medical quality, and it can play a positive role in promoting the popularization of

safe medication knowledge. Findings from this study highlight that telepharmacy is important and can be adapted to support the treatment of patients during and after the pandemic. Because the COVID-19 epidemic was effectively controlled in China, the free remote pharmaceutical care was carried out for a short time, and the sample size recorded was small. However, the remote pharmacy service framework we established is scientific and feasible. In non-pandemic times, this type of telepharmacy can facilitate patient communication. Future research should be directed at increasing the accuracy of collected patient information, documenting pharmacists' interventions, and measuring patient outcomes using an interactive model through the telepharmacy service.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

HL was responsible for study conception and design, analytic oversight, and drafting of this article. DL, DJ contributed for the construction of the pharmacy service model and manuscript development. WG, ZZ, and YZ contributed to the three consultations. SZ and FL contributed to the interpretation of results and manuscript development. RZ provided input on study design, analytic decisions, interpretation of results, and manuscript development. All authors reviewed and approved the final manuscript draft and declared that they have no conflicts of interest.

FUNDING

This study was supported by the National Science and Technology Major Special Project for New Drug Development funding (No. 2018ZX09201016). In addition, my organization, the Third Hospital of Peking University, will also cover the editing and publishing costs of this manuscript.

ACKNOWLEDGMENTS

We thank the Beijing Pharmacists Association for building the "Cloud Pharmacy Care" pharmacist volunteer team to provide pharmaceutical services to the public during the COVID-19 outbreak. We thank Hailian Wang, YZ, ZZ, Hongyan Gu, Zhizhou Wang, WG, Zhihui Tang, and JL for volunteering to solve the medication-related problems for participants in this article in their spare time.

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frontiers in Pharmacology

ORIGINAL RESEARCH
published: 11 October 2021
doi: 10.3389/fphar.2021.732760

Factors Associated With Hospital Readmission of Heart Failure Patients

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Background: Heart failure (HF) is a significant cause of mortality, morbidity and impaired quality of life and is the leading cause of readmissions and hospitalization. This study aims to identify the factors contributing to readmission in patients with HF.

Methods: A prospective-observational single-centre study was conducted in Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates. A total of 146 patients with HF are included in the study. Patient's demographics, patient medical characteristics, lab values, medications were collected for each patient, and the factors associated with readmission are identified. The primary outcome is to identify the factors contributing to readmission and reduce readmission rate. SPSS software for windows version 26 is used for data analysis.

Results: The number of patients with heart failure admitted to hospital is higher with males (73.3%) than females. 42.1% were readmitted and were not compliant, whereas patients who are not readmitted and were compliant shows a lower percentage. Noncompliance was the most significant factor associated with readmission (p = 0.02, OR = 3.6, 95%CI: 1.57 - 8.28). Other factors that are associated with readmission were low haemoglobin (p = 0.001, OR = 0.96, 95%CI: 0.94 - 0.98), and NYHA class of HF (p = 0.023, OR = 2.22, 95% CI: 1.12 - 4.43). In addition, there are other factors that are linked with the disease but were not associated with readmission in our findings such as hypertension, coronary artery disease, gender, systolic blood pressure on admission, and age. Majority of the readmitted patients were NYHA Class IV 32/57 (56.1%) against 20/89 (22.7%) in non-readmission group. Length of stay is (Median ± IQR, 6 ± 8.5).

Conclusion: The study has revealed that noncompliance, low haemoglobin and NYHA Class IV of HF were the main factors associated with readmission. Clinical pharmacist as a team member could help to improve adherence in order to reduce the rate of admission.

Keywords: heart failure, factors, readmission, non-compliance, non-adherence, financial

OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Prince Kasongo Mwila, Potchefstroom Hospital, South Africa
Muhammad Eid Akkawi, International Islamic University Malaysia, Malaysia

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *29 June 2021*
Accepted: *20 September 2021*
Published: *11 October 2021*

Citation:
Al-Tamimi MA-A, Gillani SW, Abd Alhakam ME and Sam KG (2021) Factors Associated With Hospital Readmission of Heart Failure Patients. Front. Pharmacol. 12:732760. doi: 10.3389/fphar.2021.732760

INTRODUCTION

Heart failure (HF) is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood. It is characterized by a significant clinical impact for high morbidity and mortality rates, impaired quality of life and relevant demand for health care systems. (Belfiore et al., 2020). In addition, it is the leading

cause of readmissions and frequent and re-hospitalization, which places a significant financial burden on healthcare systems worldwide. (Komajda et al., 2019)

HF is a global health issue, and it is a considerable burden to the healthcare system, responsible for costs of more than $39 billion annually in the United States alone and high rates of hospitalizations and readmissions. (Bui et al., 2011) The incidence of heart failure increases with age. The entire plateau in heart failure incidence in younger individuals may reflect decreasing incidence but increasing in older persons. (Bui et al., 2011) In the US, heart failure-related hospitalizations have increased from 2001 to 2009, surpassing four million per year, with a high percentage due to secondary hospitalizations (Belfiore et al., 2020). The increasing prevalence is paralleled by the rising costs of managing heart failure, which is projected to grow from $30.7 billion in 2012 to $69.8 billion in 2030. (Ziaeian and Fonarow, 2016) In Italy, chronic HF is the most frequent cause of hospitalization in elderly patients. (Belfiore et al., 2020). In 2014, almost 190,000 hospital admissions for HF occurred in patients older than 65 years. (Belfiore et al., 2020) According to the America Heart Association (AHA), in Asia-Pacific regions, patients with heart failure are younger and present with more severe signs and symptoms than those of Western countries. (Rajadurai et al., 2017). The Current rates of heart failure prevalence in the Asia-Pacific region range from 1.26 to 6.7%. For example, in China alone, approximately 4.2 million people have HF, whereas in India, prevalence estimates vary widely between 1.3 and 23 million, and in Southeast Asia, nine million people are estimated to have HF. (Rajadurai et al., 2017).

The estimated population in this region is 250 million, and the global prevalence of HF is 1–2%, so we estimate 3.75 million patients with HF in this region. (Elasfar et al., 2020). Data has shown that the average age of individuals with HF is at least 10 years younger than their Western counterparts, so this is a sign that heart failure is known to be a disease of the elderly, but when the mean age of incidence is in the late fifties to early sixties, then it is not a disease of the elderly in the Middle East; it is instead a disease of middle to old age population. (Elasfar et al., 2020). This age information was consistent in all registries done for heart failure in Arab countries. (Elasfar et al., 2020) The early incidence of coronary artery diseases was demonstrated in many registries, which is the primary cause of heart failure in these countries. In addition, the high incidence of diabetes mellitus in these countries is a significant risk factor for CAD and, subsequently, heart failure; in some reports, for example, diabetes mellitus affects up to 25% of adults in the Gulf countries. (Elasfar et al., 2020). Hypertension is also among the highest prevalent diseases in the Arab population, as 40–70% of heart failure patients have a history of hypertension. (Elasfar et al., 2020). Females constitute less than one-third of the HF patients presented to the hospitals, and this can be explained by less prevalence of CAD in females before menopause and the reduced access of females to medical services compared to males in many countries of this region. (Elasfar et al., 2020).

Elderly patients with HF have frequent disease exacerbations, which are often associated with precipitating factors such as poor drug compliance, inadequate treatment, drugs side effects, comorbidities, and lack of social support and indigence and without continuous monitoring system. (Khan et al., 2015). Renal failure interferes with the application of many therapeutic strategies and lifesaving medical regimens. (Elasfar et al., 2020) Various aggravating risk factors are known to induce HF decompensation. Risk factors include concomitant diseases leading to structural heart disease, including hypertension, diabetes, metabolic syndrome, and atherosclerotic disease. (Lee et al., 2019) Risk factors of Acute HF comprise coronary artery disease, hypertension, myocarditis, cardiomyopathy, valvular heart diseases, pericardial diseases, endocarditis, congenital heart disease, arrhythmia, conduction disturbance, high cardiac output state (anaemia, sepsis, arteriovenous fistula), and right HF. (Lee et al., 2019)

Non-cardiovascular conditions are common in the HF population and may contribute to the progression of heart disease and multi-organ failure, which might increase hospitalization rates. According to a Medicare analysis reported by Aranda et al., 2009, HF accounted for 28% of all hospital readmissions in the 6–9 months following the initial HF hospitalization, followed by pneumonia and chronic obstructive pulmonary disease. (Zaya et al., 2012a). Patients who were readmitted more had diabetes, peripheral vascular disease, and stroke when compared to HF patients who were not readmitted after their index hospitalization. (Zaya et al., 2012a) Diabetes mellitus is exceedingly prevalent among HF patients. (Zaya et al., 2012b) Hyperkalemia, though found to be a significant parameter in the readmission group. It is attributed to the adverse effects of ACE inhibitors, and potassium-sparing diuretics could be a potential confounder due to their presence in both groups, which could also be neutralized by loop diuretics. (Akkineni et al., 2020)

A significant portion of these costs relates to readmission after an index heart failure hospitalization. Financial barriers may result in cost-related non-adherence to medical therapies and recommendations, impacting patient health outcomes, which can worsen the patient health and lead to hospitalization and readmission, financially affecting the healthcare system. (Hobbs et al., 2010) Repeat hospitalization contributes significantly to the hospitalization expenditure as HF patients are re-hospitalized at a high rate, with approximately 50% of patients requiring readmission 6 months after initial hospitalization. (Zaya et al., 2012a) Both lengths of hospital stay and repeat hospitalization worsened prognosis and increased risk of mortality. (Zaya et al., 2012a)

Usage of GDMT in HF patients has been shown to reduce HF hospitalization, morbidity and mortality. GDMT is the mainstay of pharmacologic therapy for patients with HF who have reduced ejection fraction (HFrEF). In HFrEF, GDMT includes angiotensin-converting enzyme inhibitors (ACEI) (or angiotensin-receptor blockers (ARB) in ACEI-intolerant patients), Angiotensin Receptor Neprilysin Inhibitor (ARNi) and β blockers (BB) in all patients, as well as aldosterone-receptor antagonists (ARA), digoxin, nitrates, and hydralazine in select patients. (Tran et al., 2018). Unfortunately, no therapy has shown a mortality benefit in patients with HF with preserved ejection fraction (HFpEF). (Tran et al., 2018) Adherence has been

defined as the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider. Poor medication adherence is a common problem among HF patients leading to increased HF exacerbations, reduced physical function, higher readmission rate and mortality. (Akkineni et al., 2020) Medication adherence should be addressed in regular follow-up visits and evidenced-based interventions to improve adherence, prevent adverse outcomes and reduce the readmissions rate. (Akkineni et al., 2020) Compliance is defined as the extent to which the patient's behaviour matches the prescriber's recommendations. Though compliance has been frequently employed to describe medication-taking behaviour, it has proved problematic because it refers to a process where the clinician decides on a suitable treatment, which the patient is expected to comply with unquestioningly. (Chakrabarti, 2014).

Continuing patient and caregiver education about the importance of therapeutic compliance could play a vital role in disease progression. (Akkineni et al., 2020) Studies have shown that patients' adherence to their prescribed HF medications had fewer HF symptoms and resulted in cardiac event-free survival. (Akkineni et al., 2020) There are multiple factors that can affect the readmission of heart failure patients that still need to be assessed.

TABLE 1 | Sociodemographic distribution.

Sociodemographic		*N*	%
Gender	Male	107	73.3
	Female	39	26.7
Age (years)	Mean/±S.D	61.9 ± 14.1	
Age group	45 or less	23	15.8
	46 or more	123	84.2
Weight (Kg)	Mean/±S.D	77.2 ± 22.2	
Weight group	65 or less	45	30.8
	66–90	70	47.9
	more than 90	27	18.5
Length of stay (days)	Median ± IQR	6 ± 8.5	
Number of readmissions	Once	16/57	11
	Twice	23/57	15.8
	More than twice	18/57	12.4
Non-compliance		67/146	45.9
Poor adherence to medication		38/146	26
Not on HF medications		26/146	17.8
No history of medications		12/146	8.2
Reason of non-compliance			
Financial		47/67	72.3
Irregular to medication		12/67	18.5
Unknown		8/67	11.2

MATERIALS AND METHODS

Research Design

This study is a prospective observational single-centre study.

Sample Size

A total of 146 patients encountered with heart failure were admitted to Sheikh Shakhbout Medical City hospital from November 2020 to May 2021. The sampling technique was used Convenience Sampling technique.

Study Population

Inclusion Criteria

- All heart failure (HF) patients were admitted to the hospital.
- Patients of all stages of HF were included in the study.
- HF patients aged above 18 years old.

Exclusion Criteria

- Patients below 18 years of age.
- The patient was not diagnosed with heart failure.
- Pregnant women.

Study Settings

The study was conducted on heart failure patients in Cardiac Intensive Unit of Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates.

Duration of Study

The duration of study was 7 months. The investigator reviewed the medical profile of each patient from the date of admission till the date of discharge.

Data Collection

A patient profile form was used to collect patient demographic data, medical history and stage of heart failure according to NYHA guidelines, vital signs, laboratory data; NT-proBNP, iron status, HbA1c, radiology results; ejection fraction, and medications before admission and on discharge. Data on the cause of readmission and the contributing factors to frequent admission and readmission are obtained from the patient medical record.

Method of Data Collection

Data is collected by identifying each patient, reviewing their medical record, and collecting the data required according to the data collection form. Patients are selected based on inclusion and exclusion criteria. After data collection, the data of 146 patients are analyzed using the SPSS software. The system used for reviewing each patient medical record and data collection is the Salamatak system (electronic medical record system). Compliance and adherence are identified from the physician report after a direct communication with the patient and from the pharmacy record which indicates if the patient is adherent to medication or not.

Statistical Analysis

Descriptive statistics for the data were presented in frequencies and percentages for categorical variables, while descriptive statistics for numeric variables are presented as mean with standard deviation or median with Interquartile range. Comparison of the variables between those who were

TABLE 2 | Clinical characteristics.

	Presenting symptoms	*N* = 146	%
1	Shortness of breath	133	91.1
—	Orthopnea	59	40.4
—	Chest pain	56	38.4
—	Cough	58	39.7
—	Oedema	81	55.6
—	Tachycardia	43	29.5
—	Palpitation	20	13.7
—	Others	59	40.41
2	Types of HF	—	—
—	HFrEF	123	84.2
—	HFpEF	23	15.8
3	Associated diagnosis	—	—
—	AKI	27	18.5
—	Dementia	11	7.5
—	COPD	31	21.2

HFrEF: heart failure reduced ejection fraction, HFpEF: heart failure preserved ejection fraction, COPD: chronic obstructive pulmonary disease, AKI: Acute Kidney Injury.

TABLE 3 | Patient medical characteristics.

	Medical characteristics	*N* = 146	%
1	Smoker	—	—
—	Yes	26	17.8
—	No	103	70.5
—	Ex-smoker	17	11.6
2	Known allergies	10	7
3	Past Medical History		
—	COVID-19	15	10.3
—	STEMI	38	26.0
—	Atrial Fibrillation	55	37.7
—	CAD	88	60.3
4	Co-morbidities		
—	Anemia	63	43.2
—	Hypertension	127	87.0
—	GERD	48	32.9
—	Diabetes	96	65.8
—	CKD	85	58.2
—	Hyperlipidemia	108	74.0

GERD: Gastroesophageal reflux disease, CAD: coronary artery disease, STEMI: ST-Elevation Myocardial Infarction, CKD: chronic kidney disease.

readmitted and those who were not is made using independent *t*-test for numeric variables, while the comparison of the categorical variables was made using Chi-Square test or Fisher's exact test. Mann Whitney *U* test was used to compare the length of stay between the two groups, while multiple logistic regression was used to study the predictors of readmission. The backward stepwise method was used for creating the final model. A p value <0.05 was considered statistically significant, and SPSS software for windows version 26 was used for the analysis.

RESULTS

The number of patients with heart failure admitted to hospital was significantly higher in males (73.3%) than females. Readmission was significantly higher in patients who were admitted twice and more than twice. (**Table 1**). Of 146 patients, 91.1% admitted with shortness of breath associated with a high percentage of orthopnea and oedema. A higher percentage of patients with HFrEF as compared to HFpEF were identified. Around 37% of HF patients had multiple comorbidities (**Table 2**). Only 15 patients out of 146 had a history of covid-19. Higher percentages of patients are hypertensive and with hyperlipidemia. (**Table 3**). The mean iron value was 9.6 with SD of ±9.8. HbA1c of the majority of patients was high, which indicates a higher number of diabetic patients. The mean of NT-proBNP of patients with HF was high during admission; this indicates an essential parameter in patients with HF. (**Table 4**). A higher percentage with diastolic dysfunction is between grade II and grade III. 48.6% had both systolic and diastolic heart failure, and a lower percentage with others. The majority of patients admitted to hospital with HF were classified with class III HF according to NYHA guidelines. (**Table 5**). A total of 146 patients, 78.8%, were discharged with furosemide and a lower percentage with other diuretics. 60% were discharged with spironolactone, associated with a higher percentage of patients taking beta-blockers. (**Table 6**). Readmission is significantly higher in males than females. 42.1% were readmitted with HF and were not compliant to medications, whereas patients who are not readmitted and were compliant to medications shows a low percentage. 44% were readmitted due to multiple co-morbidities that induced HF. Most of the readmitted patients were NYHA Class IV 32/57 (56.1%) against 20/89 (22.7%) in non-readmission group. *p*-Value was significant for the compliance factor in readmission group, therefore it has a major role in readmission. (**Table 7**). The mean iron value among patients readmitted with HF was 10.7, and SD was ±12.4. The mean of HbA1c of readmitted patients was high. However, there was no significant difference in HbA1c value between readmitted and non-readmitted patients. A low level of haemoglobin was a significant factor of readmission. The *p*-value of haemoglobin was significant; this indicates that as the haemoglobin level decreases, the rate of readmission increases. In addition, the *p*-value of NT-proBNP is significant. A high level of NT-proBNP was a contributed factor for readmission. (**Table 8**). In readmitted patients, the percentage of patients on a diuretic was significantly higher than in patients who are not admitted. 96.4% of readmitted patients were on diuretics, and 77.5% were on diuretics in patients who were not readmitted. The percentage of patients who were on beta-blockers readmission rate was low. 92.1% on beta-blockers were not readmitted whereas no significant difference between patients readmission on potassium-sparing. Low iron level in HF patients was an important factor for readmission (*p*-Value; 0.009). (**Table 9**). Multiple logistic regression was applied to study the predictors of readmission. The backward stepwise method was applied for final model. The final model included eight variables but only three significant variables were associated with readmission (noncompliance, low haemoglobin and NYHA class). Noncompliance was the most significant factor associated with readmission ($p = 0.02$, OR = 3.6, 95%CI: 1.57-8.28). It's associated with higher odds of being readmitted. The other factors associated

TABLE 4 | Lab values, radiology and vital signs distribution pattern.

	—	*N* = 146	Minimum	Maximum	Mean	SD
1	Lab Values					
—	Iron micromol/L	50	3	72	9.6	±9.8
—	Haemoglobin g/l	146	8	178	119.7	±25.0
—	Transferrin saturation	49	0.03	2.64	0.2	±0.4
—	NT-proBNP admission	142	29	35,000	7,402.2	±8,451.6
—	NT-proBNP discharge	79	276	35,000	6,556.9	±7,920.2
—	HbA1c %	129	4.4	13.9	7.0	±1.9
2	Vital Signs					
—	BP at admission systolic	146	82	246	140.5	±35.1
—	BP at admission diastolic	146	40	144	80.4	±18.5
—	BP at discharge systolic	133	70	179	114.0	±18.8
—	BP at discharge diastolic	133	40	111	66.2	±12.8
3	Radiology					
—	Ejection fraction %	146	15	70	33.9	±14.6

TABLE 5 | Cardiac profiling.

Characteristic	*N* = 146	%
Diastolic dysfunction	—	—
Grade I	18	12.4
Grade II	24	16.6
Grade III	35	24.1
Grade IV	1	0.7
Unknown Grade	68	46.2
Systolic and diastolic HF	71	48.6
Systolic HF	56	38.4
Diastolic HF	19	13.0
NYHA class	—	—
I	5	3.4
II	13	9.0
III	75	51.7
IV	52	35.9

NYHA: New York Heart Association, HF: Heart Failure.

TABLE 6 | Medications on discharge.

Drug class	*N* = 146	%
ACE inhibitors	39	26.8
ARBs	19	13.1
Dyslipidemia drugs	114	78.1
Anti-platelet drugs	89	60.9
Anti-coagulant drugs	21	14.4
Calcium channelblocker drugs	36	24.7
ARNi	27	18.5
Diuretic drugs	122	83.6
Beta blocker drugs	131	89.8
Proton pump inhibitors	85	58.3
Potassium-sparing drugs	125	85.7
NOACs	33	22.6
Iron drugs	16	11.0
Bronchodilator drugs	24	16.5
Insulin	51	35.1
Anti-diabetic drugs	47	32.4
Analgesic drugs	40	27.4
Steroid drugs	21	14.4
Anti-arrhythmic drugs	23	15.7
Nitrates	27	18.5
Anti-constipation drugs	46	31.5
Other drugs	63	43.6
Non-pharmacological	40	20.6

ACEi: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers, ARNi: Angiotensin-receptor neprilysin inhibitor, NOACs: Novel Oral Anticoagulants.

with readmission were low haemoglobin (p = 0.001, OR = 0.96, 95%CI: 0.94-0.98), and NYHA class of HF (p = 0.023, OR = 2.22, 95%CI: 1.12-4.43). There are other factors that are linked with the disease but were not associated with readmission in our findings such as hypertension, coronary artery disease, gender, systolic blood pressure on admission, and age. (**Table 10**). Of 146 patients with HF, 37% of patients had multiple comorbidities that induce HF, whereas only 5.5% were deceased. (**Figure 1**). Furosemide was the most prescribing drug; bisoprolol was the next most prescribing drug. (**Figure 2**).

DISCUSSION

HF is characterized by periodic exacerbations that require treatment intensification most often in the hospital, and it is the single most frequent cause of hospitalization in person 65 years and above and a known predictor of mortality and morbidity. (Hobbs et al., 2010). Repeated hospital readmissions are frequent and increasing over time in patients with heart failure. Therefore, the factors in the present study that contribute to readmission and frequent hospitalization after being discharged are non-compliance poor adherence to medication due to financial issues, multiple co-morbidities-induced HF.

In the analysis of demographic data, it is found that patients aged 46 years or older accounted for 84.2% of the patient population, and 73.3% of patients were males. Majority of patients that are readmitted with HF are males, the incidence and prevalence of heart failure is lower in women than in men. 84.2% aged 46 and older were readmitted with the same condition. Similar findings with Huang et al., 2017, he reported that patients aged 65 years or older accounted for 69% of the patient population, and 50.8% were males. (Huang et al., 2017). Jackevicius et al., 2015, shows that according to the demographic data, patients were primarily male (98%) and elderly, with a mean age of 69 years. (Jackevicius et al., 2015). In the present study, the length of stay is (Median ± IQR, 6 ± 8.5).

TABLE 7 | Factors associated with readmission.

Characteristics	90 days readmission		*p*-value
	Yes	No	
Gender Male Female	44(77.2%) 13 (22.8%)	63 (70.8%) 26 (29.2%)	0.393
Age 45 or less 46 or more	9 (15.8%) 48 (84.2%)	14 (15.7%) 75 (84.3%)	0.992
Obesity Yes No	12 (21.8%) 43 (78.2%)	22 (25%) 66 (75%)	0.664
Smoker Yes No Ex-smoker	10 (17.5%) 42 (73.7%) 5 (8.8%)	16 (18%) 61 (68.5%) 12 (13.5%)	0.672
Allergies NKA Yes	51 (89.5%) 6 (10.5%)	85 (95.5%) 4 (4.5%)	0.189
Compliance Yes No	33 (57.9%) 24 (42.1%)	34 (38.2%) 55 (61.8%)	0.020
Adherent to medication Yes No	22 (25%) 66 (75%)	16 (28.1%) 41 (71.9%)	0.681
Multiple comorbidities induced-HF Yes No	25 (43.9%) 3 2(56.1%)	29 (32.6%) 60 (76.4%)	0.169
Diastolic dysfunction Grade I Grade II Grade III Grade IV Unknown	4 (7.1%) 8 (14.3%) 17 (30.4%) 1 (1.8%) 26 (46.4%)	14 (15.7%) 16 (18.0%) 18 (20.2%) –41 (46.1%)	0.236
NYHA class Class I Class II Class III Class IV	–3 (5.3%) 22 (38.6%) 32 (56.1%)	5 (5.7%) 10 (11.4%) 53 (60.2%) 20 (22.7%)	<0.001
LOS, Median ± IQR	7 (7.5)	6 (9)	0.112

LOS: length of stay, IQR: Interquartile Range.

TABLE 8 | Lab values, radiology and vital signs among readmission and non-readmission.

	Group	90 days readmission			No readmission			—
		N	Mean	SD	N	Mean	SD	*p*-value
1	Lab Values							
	Iron micromol/L	30	10.7	12.4	20	7.9	3.4	0.336
	Haemoglobin g/l	57	107.9	23.1	89	127.3	23.3	**<0.001**
	Transferrin saturation	29	0.3	0.5	20	0.2	0.1	0.279
	NT-proBNP admission	56	9,138.9	9,238.9	86	6,271.3	7,744.5	**0.048**
	NT-proBNP discharge	33	7,736.6	7,835.5	46	5,710.6	7,957.3	0.265
	HbA1c	50	7.1	2.0	79	7.0	1.8	0.661
2	Vital Signs							
	BP at admission Systolic	57	131.5	32.6	89	146.2	35.7	**0.013**
	BP at admission Diastolic	57	75.7	16.1	89	83.3	19.4	**0.015**
	BP at discharge Systolic	49	109.6	20.1	84	116.5	17.7	**0.041**
	BP at discharge Diastolic	49	62.8	11.9	84	68.1	12.9	**0.019**
3	Radiology							
	Ejection fraction %	57	34.2	14.6	89	33.8	14.8	0.885

TABLE 9 | Medications among readmission.

Drug class		90 days readmission		*p*-value
		Yes	No	
ACE inhibitors	N	14	25	0.730
	%	25.5%	28.1%	
ARBs	N	6	13	0.499
	%	10.7%	14.6%	
Dyslipidemia drugs	N	44	70	0.847
	%	80.0%	78.7%	
Anti-platelet drugs	N	38	51	0.157
	%	69.1%	57.3%	
Anti-coagulant drugs	N	9	12	0.602
	%	16.7%	13.5%	
Calcium channel blocker drugs	N	14	22	0.921
	%	25.5%	24.7%	
ARNi	N	10	17	0.906
	%	18.5%	19.3%	
Diuretic drugs	N	53	69	0.002
	%	96.4%	77.5%	
Beta-blocker drugs	N	49	82	0.560
	%	89.1%	92.1%	
Proton pump inhibitors	N	32	53	0.774
	%	57.1%	59.6%	
Potassium-sparing drugs	N	34	55	0.998
	%	61.8%	61.8%	
Hydralazine	N	18	18	0.092
	%	32.7%	20.2%	
NOACs	N	19	14	0.009
	%	34.5%	15.7%	
Iron drugs	N	11	5	0.009
	%	19.6%	5.6%	
Bronchodilator drugs	N	11	13	0.494
	%	19.6%	14.6%	
Insulins	N	22	29	0.439
	%	39.3%	33.0%	
Anti-diabetic drugs	N	20	27	0.454
	%	36.4%	30.3%	
Analgesic drugs	N	15	25	0.832
	%	26.8%	28.4%	
Steroid drugs	N	8	13	0.957
	%	14.3%	14.6%	
Anti-arrhythmic drugs	N	9	14	0.956
	%	16.1%	15.7%	
Nitrates	N	16	11	0.012
	%	29.1%	12.4%	
Anti-constipation drugs	N	18	28	0.874
	%	32.7%	31.5%	

(Continued in next column)

TABLE 9 | (*Continued*) Medications among readmission.

A percentage of 10.3% had a history of Covid-19, patients with previous medical histories or comorbidities such as HF are at high risk of morbidity and mortality associated with the viral infection. Zhou, Fei, et al., 2020, reported that 23% of 191 covid-19 patients were diagnosed with HF, including new or worsening HF. (Zhou et al., 2020). The virus causes kidney impairment in acute kidney injury, which may lead to volume overload that may exacerbate a pre-existing chronic HF. (Zhou et al., 2020). Anemia was demonstrated in about 20% of heart failure patients; it commonly occurs in patients with chronic HF and patients with low ejection fraction. (Elasfar et al., 2020). In previous studies, the prevalence of anaemia in hospitalized patients ranged from 15 to 61% in clinical trials, and HF registries ranged from 14 to 70%. (Belziti, 2009). Anaemia and iron deficiency badly affect the quality of life of heart failure patients and are essential therapeutic targets according to the recent studies and guidelines of HF. (Belziti, 2009).

42.1% who were readmitted with HF were non-compliant, 72.3% were having financial issues. Other reasons could be due to not taking medications regularly and multiple comorbidities induced HF. In the present study, 43.9% were readmitted and were having multiple comorbidities induced HF. Tun, H, et al., 2021, has reported common reasons for readmission are lack of counselling 200 (40%), non-compliance medication, under dose 75 (15%), non-compliance 60 (12%). (Tun, 2021).

The primary goal in HF patients is to reduce and control the rate of readmission and hospitalization. It is essential to decrease the rate of readmissions of this chronic condition to benefit the institution financially and enhance the institution efficiency. Practical strategies that should be in consideration to improve patient outcomes regarding financial issues have to be taken with higher authorities to give special consideration for such patients: proper education to be offered to patients verbally and written instructions. In addition, continuous medical education for service providers increases awareness on prescribing optimal guided-medical therapy for HF patients to reduce rate of readmission. Finally, we suggest clinical pharmacists should be a part of multidisciplinary team that

TABLE 10 | Multiple logistic regression for the factors associated within 90 days readmission.

	OR	*p*-value	95% CI for OR	
Haemoglobin	0.96	0.001	0.94	0.98
BP admission Systolic	0.98	0.009	0.97	1.00
Non-compliance	3.60	0.003	1.57	8.28
Gender (Male)	1.85	0.226	0.68	4.98
Age	0.95	0.016	0.91	0.99
NYHA class	2.22	0.023	1.12	4.43
Coronary artery disease	2.25	0.083	0.89	5.64
Hypertension	5.98	0.052	0.99	36.31

OR: odds ratio, CI: confidence interval.

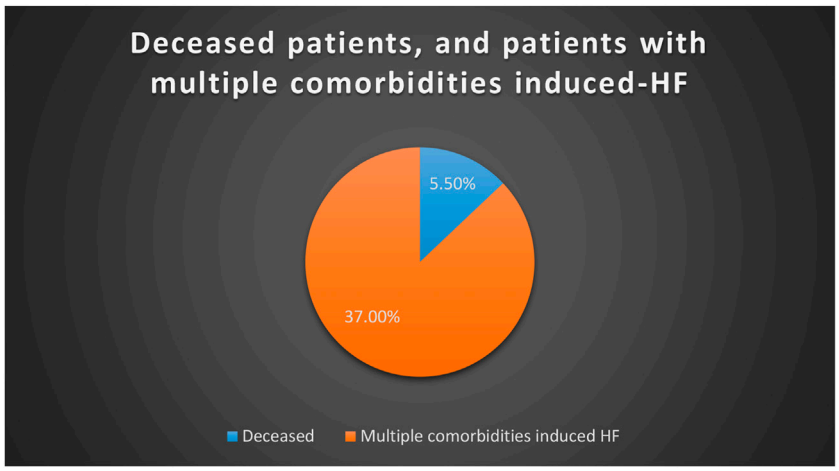

FIGURE 1 | Pie chart for deceased patients, and patients with multiple comorbidities induced-HF.

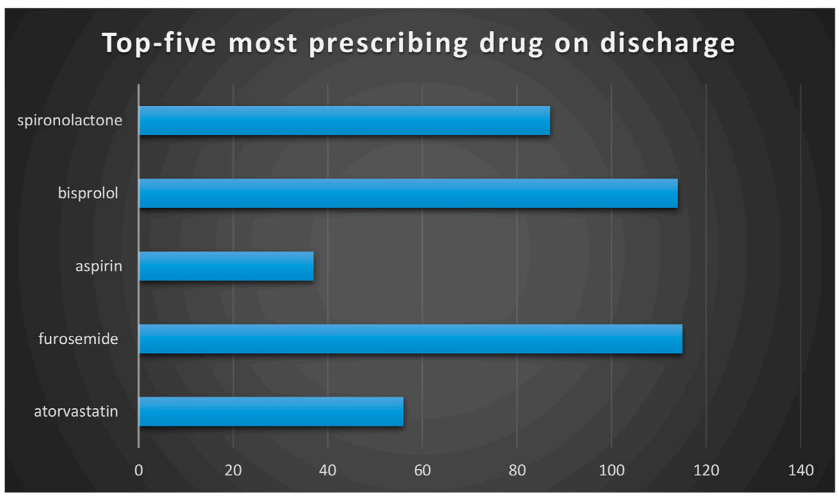

FIGURE 2 | bar graph for top-five most prescribing drugs on discharge.Furosemide/bisprolol/spironolactone/aspirin/atorvastatin.

can help to improve compliance, adherence and hence decrease the rate of readmission.

CONCLUSION

The study has revealed that noncompliance, low haemoglobin and NYHA Class IV of HF were the main factors associated with readmission. Clinical pharmacist as a team member could help to improve adherence in order to reduce the rate of admission.

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

This study is approved by the Research Ethics Committee of Sheikh Shakhbout Medical City in partnership with Mayo clinic. Reference number: MAFREC-213. The patients/participants provided their written informed consent. This study is approved by to participate in this study.

AUTHOR CONTRIBUTIONS

MAT: Principle investigator, data collection, data analysis. SWG: Main supervisor, research methodology, draft editing. MEA: draft editing, content validity, data analysis. KGS: Content validity, draft writing, data analysis.

ACKNOWLEDGMENTS

We want to express our sincere gratitude to Sheikh Shakhbout Medical City for conducting this study and acknowledging everyone who played a role in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.732760/full#supplementary-material

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frontiers in Pharmacology

ORIGINAL RESEARCH
published: 14 October 2021
doi: 10.3389/fphar.2021.741671

Effects of Volume-Price Contracts on Pharmaceutical Prices: A Retrospective Comparative Study of Public Hospitals in Hubei of China

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Background: Pharmaceutical expenditure has been increasing worldwide. Many countries have attempted to contain the increase through collective bargaining, including in China. In 2015, the Chinese government introduced a new policy to empower regional governments to reduce pharmaceutical prices through its existing tendering system which enables a lower price for products with higher procurement volumes. Xiangyang municipality in Hubei province took a lead in piloting this initiative.

Objectives: This study aimed to evaluate the effects of the volume-price contract initiative on pharmaceutical price procured by the public hospitals in Xiangyang.

Methods: A retrospective comparative design was adopted. The price of cardiovascular medicines (349 products under 164 International Nonproprietary Names) procured by the public hospitals in Xiangyang was compared with those procured in Yichang municipality in Hubei. A total of 15,921 procurement records over the period from January 2017 to December 2018 were examined (Xiangyang started the volume-price contract initiative in January 2018). Generalized linear regression models with a difference-in-differences approach which could reflect the differences between the two cities between January 2018 and December 2018 were established to test the effects of the volume-price contract initiative on pharmaceutical prices.

Results: On average, the procurement price for cardiovascular medicines adjusted by defined daily dosage in Xiangyang dropped by 41.51%, compared with a 0.22% decrease in Yichang. The difference-in-differences results showed that the volume-price contract initiative resulted in a 36.24% drop ($p = 0.006$) in the price (30.23% for the original brands, $p = 0.008$), in addition to the therapeutic competition effect (31.61% reduction in the price, $p = 0.002$). The top 100 domestic suppliers were highly responsive to the initiative (82.80% drop in the price, $p = 0.001$).

Conclusion: The volume-price contract initiative has the potential to bring down the price of pharmaceutical supplies. Higher responses from the domestic suppliers are evident.

Keywords: volume-price contract, collective procurement, competition, pharmaceutical, China, price

OPEN ACCESS

Edited by:
Kingston Rajiah, International Medical University, Malaysia

Reviewed by:
Brian Godman, University of Strathclyde, United Kingdom
Andrew Lofts Gray, University of KwaZulu-Natal, South Africa

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *15 July 2021*
Accepted: *30 September 2021*
Published: *14 October 2021*

Citation:
Li Z, Liu C, Zuo K, Liu J and Tang Y (2021) Effects of Volume-Price Contracts on Pharmaceutical Prices: A Retrospective Comparative Study of Public Hospitals in Hubei of China. Front. Pharmacol. 12:741671. doi: 10.3389/fphar.2021.741671

INTRODUCTION

Pharmaceuticals account for a profound share of total health expenditure, ranging from an average of 19.7% in high-income countries to 30.4% in low-income countries (Ye et al., 2011). This proportion was around 14.17% in European countries in 2018 (Eurostat, 2021). A rapid growth in pharmaceutical spending is a worldwide concern. The Intercontinental Medical Statistics (IMS) estimated that pharmaceutical expenditure has been increasing at a speed significantly higher than that of global economic growth. From 2010 to 2015, there was an annual growth of 6.2% in global spending on medicines, rising from $US887 billion to $US1069 billion (IMS, 2015). It is projected to exceed $US1.1 trillion in 2024 (IQVIA, 2020).

Soaring pharmaceutical expenditure imposes a great burden on government budgets, which has triggered a range of policy, regulatory and managerial interventions. Collective purchasing has been used as a tool worldwide to lower the price of pharmaceutical supplies (Dylst et al., 2011; Maniadakis et al., 2018). It forces suppliers to compete for the right to become a dominant supplier in certain markets in line with some strictly predefined criteria (Maniadakis et al., 2018). A purchaser can increase its bargaining power by widening the network of collective purchasing. South Africa, for example, introduced a national tendering system for pharmaceuticals in 1982. Empirical evidence showed that the price of pharmaceutical supplies covered by the tendering system dropped by an average of 40% or more between 2003 and 2016 (Wouters et al., 2019). In Mexico, a commission to purchase antiretrovirals and other medicines achieved a cost saving of $US52.1–121.8 million in its first 4 years since inception in 2008 (Gomez-Dantes et al., 2012; Adesina et al., 2013). Cost savings were also found through collective purchasing at the subnational levels, such as the Intermunicipal Health Consortium in Brazil (de Amaral and Blatt, 2011) and the hospital networks in Serbia (Milovanovic et al., 2004) and Brazil (Sigulem and Zucchi, 2009). Collective tendering in European countries has been proved to enhance competition, resulting in reduced prices in pharmaceutical supplies (Dylst et al., 2011; van Woerkom et al., 2012; Vogler et al., 2017; Jensen et al., 2020). In China, rising pharmaceutical expenditure has attracted a great deal of policy attention over the past decade. From 2010 to 2017, pharmaceutical expenses as a proportion of health expenditure in China declined from 41.6% to 34.4% (National Health Commission, 2019). However, it remained at a high level in comparison with OECD (Organization for Economic Cooperation and Development) countries (18.2% in 2010 and 16.1% in 2017) (OECD, 2020). The actual pharmaceutical spending over the same period increased from 883.59 billion yuan ($US129.45 billion) to 1820.30 billion yuan ($US266.67 billion) (National Health Commission, 2019).

Traditionally, pharmaceutical policy debates in China were centered around caps in pharmaceutical prices and mark-up margins allowed for health providers (Hasan et al., 2019; Liu et al., 2019). The Chinese government categorized pharmaceutical products into two groups. Group A are mainly prescription medicines while Group B are mainly over-the-counter medicines (National Development and Reform Commission, 2005). The National Development and Reform Commission (NDRC) imposed a price cap for Group A medicines based on the declared costs from the manufacturers. The provincial governments imposed a price cap for Group B medicines under the guiding prices developed by the NDRC (National Development and Reform Commission, 2005; Hasan et al., 2019). Between 1997 and 2013, over 30 mandatory regulations mostly related to price caps on medicines were announced. Empirical studies showed that these policies were not as effective as anticipated. Pharmaceutical manufacturers could easily evade price caps by registering their products as innovative new drugs through some minor modifications such as dosage forms (Wu et al., 2015; Hu and Mossialos, 2016). This is not unique to China (Vernaz et al., 2013). Meanwhile, the 15% mark-up rule for health institutions provided perverse incentives for medical doctors to prescribe more expensive medicines such as injections and traditional Chinese medicines (Meng et al., 2005; Zeng et al., 2014; Zeng et al., 2015; Hu and Mossialos, 2016). Eventually, the NDRC abolished the price cap policy in 2015 (Hu and Mossialos, 2016). Markups for health institutions on sales of medicines have been officially removed since 2017 throughout the country (Tang et al., 2018). As a result, there are high expectations that centralized tendering and collective purchasing which is gradually developing towards volume-price contract initiative will play a significant role in curtailing the pricing inflation of pharmaceutical products (Hu and Mossialos, 2016).

The exploration of centralized tendering and collective procurement of medicines in China dates back to the 1990s. But it was not until 2009 that it became a nationwide province-based governmental practice. The centralized procurement arrangements started with essential medicines for primary care and were gradually extended to pharmaceutical procurements for public hospitals. Each provincial government has its own online platform, supporting tendering, contracting, purchasing, and distribution of pharmaceutical products (Cai, 2017). Since 2010, each tender has been required to submit two separate bidding documents ("two-envelope") demonstrating its bidding price and quality of products and services, respectively (Hu and Mossialos, 2016). The winners were supposed to go with the suppliers with the highest composite score of the two envelopes (although usually the lowest price won) (Hu et al., 2019). In some provinces, only one supplier would be contracted to supply certain medicines, while in other provinces, two or more suppliers could be contracted (Hu and Mossialos, 2016). It was estimated that the price of essential medicines for primary care decreased by an average of 25% and even over 50% in some provinces between 2009 and 2010 (Hu, 2013).

Despite the overall drop in prices, the procurement system was criticized for its lack of capacity to link price with volumes of purchased medicines (Fu et al., 2015). The tendering systems overseen by the provincial governments were only responsible for identifying contracted suppliers and settling the prices of pharmaceutical products. No procurement volumes were announced specifically in the tendering. It was up to each individual health institution to make monthly purchase orders

and to settle on delivered prices through a "second bargaining" with the suppliers. In addition, there was a lack of supervision over the procurement contracts signed between the health institutions and the suppliers. As a result, pharmaceutical suppliers were placed in a financial dilemma since they could not properly establish an offer based on an accurate estimation of the market share (Tang et al., 2017). Some awarded suppliers would simply not deliver purchase orders if their bidding price was deemed too low to cover the costs. This was particularly common for the lowest-priced generic medicines (Dylst et al., 2013; Fang et al., 2013). Meanwhile, suppliers were likely to manage the risk of market uncertainty through inflating prices, especially for high-priced products (Jiang et al., 2014).

In 2015, the central government issued two policy documents, instructing provincial governments to rationalize procurement prices by attaching procurement volumes to prices in procurement contracts (General Office of the State Council, 2015; National Health and Family Planning Commission, 2015). In practice, it is up to each provincial government to decide the scope for the volume-price contract initiative. Provincial governments continue to set up the highest prices allowed for the included pharmaceutical products. However, health institutions are grouped (selected or all-inclusive at a municipal level or across several municipalities) to bargain for further lower prices for a collective volume of purchase orders. The procurement procedures have to be carried out on the provincial online procurement platform (Li et al., 2018).

Hubei started to pilot the volume-price contract initiative in 2016 in three municipalities: Wuhan, Xiangyang and Ezhou. The municipal governments were authorized to develop their own pharmaceutical catalogues covered in the initiative. However, the procurement volume of each pharmaceutical product had to be justified with reference to its consumption in the previous year (Government of Hubei Province, 2016). For each pharmaceutical product defined by molecule structure, formulation and strength, no more than two suppliers could be awarded. The government used this strategy to make the tendering more attractive (less suppliers and less competition) to those who were willing to reduce price (Government of Hubei Province, 2016). In 2017, the Hubei government issued policy instructions on the volume-based procurement procedure as a condition to sign volume-price contracts (Health Commission of Hubei Province, 2017). This study aimed to evaluate the price effect of the volume-price contract initiative on pharmaceutical supplies to public hospitals in Xiangyang municipality of Hubei province. The findings would be helpful for both researchers and policy makers since such empirical evidence is still lacking as far as we know.

METHODS

Study Setting

A retrospective comparative study was conducted in Hubei province. The volume-price contract initiative implemented in Xiangyang municipality was evaluated, with Yichang municipality serving as the control.

Hubei covers an area of 185,900 km^2 and has about 59.02 million residents. Its per capita annual disposable income reached 31,889 yuan ($US4672) for urban and 13,812 yuan ($US 2023) for rural residents in 2017, 87.62% and 102.83% of the national average, respectively (Bureau of Statistics of Hubei Province, 2018a). About 5.89% of GDP (gross domestic product) was spent on health (192.472 billion yuan, or $US28.200 billion) in 2016. There were approximately 2.50 registered physicians, 3.10 nurses, and 6.37 hospital beds per 1,000 people across 36,357 health care institutions in the province in 2017 (National Health Commission of China, 2018).

Xiangyang occupies a comparable land size (19,728 km^2) as Yichang (21,084 km^2), but with more dense dwelling. The GDP in Xiangyang ranked second among all municipalities in Hubei in 2017, while Yichang ranked third (Bureau of Statistics of Hubei Province, 2018a). However, the disposable income per capita of all residents in Xiangyang ($US3520) was slightly lower than that of Yichang ($US3543) in 2017. Xiangyang had more health resources and spent more on health compared with Yichang (**Table 1**) (Bureau of Statistics of Hubei Province, 2018c; b).

Yichang was selected as a control group through a comprehensive assessment of all 17 municipalities in Hubei using an unweighted TOPSIS (technique for order performance by similarity to ideal solution) method (Tang et al., 2016) (**Table 1** in the **Supplementary Material**). Yichang had the closest match (TOPSIS score) with Xiangyang considering eight matching variables: GDP, per capita GDP, population size, per capita disposable income, number of health institutions, number of hospital beds, number of licensed (assistant) doctors, and number of skilled health workers (**Table 1**). These indicators can reflect the level of economic and health system development (Bureau of Statistics of Hubei Province, 2018a; c; b).

Supplementary material Table S1 Results of (unweighted) TOPSIS ranking.

Study Design and Data Sources

A retrospective comparative with a difference-in-differences approach was adopted. A total of 15,921 procurement records for cardiovascular medicines over the period from January 2017 to December 2018 were examined. Cardiovascular medicines were chosen in this study since it is a key area with the growing prevalence of cardiovascular diseases and multiple medicines relevant to the treatment of cardiovascular diseases (Mirsafaei et al., 2020; Wei et al., 2020). In addition, they accounted for a large proportion of procurements for specialized medicines, and the volume-price contract initiative for cardiovascular medicines was mature and had a clear cut implementation in January 2018 (Centralized Pharmaceuticals Tendering and Procurement Center of Xiangyang, 2017). In contrast, Yichang, the control group, had not introduced the volume-price contract system over the entire study period. This enabled us to compare the procurement records in the two municipalities before and after the new initiative.

Data came from the Hubei Medical Procurement Administrative Procurement System (HMPAPS). Eligible records were identified using the anatomical therapeutic

TABLE 1 | Socioeconomic characteristics of the two study municipalities in 2017.

Socioeconomic indicator	Xiangyang (intervention)	Yichang (control)
Gross Domestic Product (GDP, 100 million CNY)	4,064.90	3,857.17
Per capita GDP (CNY)	71,990	93,331
Population size (Million)	5.654	4.136
Per capita disposable income (CNY)	24,030	24,182
Number of health institutions	3,731	3,013
Number of hospital beds	36,507	28,180
Number of licensed (assistant) doctors	13,934	10,919
Number of skilled health workers	39,591	38,275
TOPSIS score	0.378043889	0.341987109

Note: CNY - *Chinese Yuan,* TOPSIS - *technique for order performance by similarity to ideal solution.*

chemical (ATC) classification and coding system. We restricted the study sample to cardiovascular medicines with an ATC code C. A total of 15,921 procurement records over the study period for cardiovascular medicines were extracted, covering 164 International Nonproprietary Names (INN) and 349 products. These medicines were procured for the 35 public hospitals in the two municipalities: 21 in Xiangyang and 14 in Yichang. Medication needs depended on the local population and their health profiles. The local governments and medical institutions were delegated with the power to select the medicines in line with their local clinical needs. Data items extracted included: procurement serial number, hospital name, time of procurement, INN, formulations, strength, package size, procurement price per package (CNY, Chinese Yuan), procurement volume (packages), procurement cost (CNY), and suppliers of different medicines. We further classified the pharmaceutical products into subgroups according to their brand (original brand and generic) and administration routes (injectable and oral). The suppliers were categorized by ownership (domestic, joint venture, foreign-owned) and ranking of financial outputs (Southern Medicine Economic Research Institute of National Medical Products Administration, 2018; 2019).

Intervention Measures

The Xiangyang municipality (intervention group) introduced the volume-price contract initiative through a staggered approach, starting with several proton pump inhibitors (digestive medicines) at the beginning of 2017, followed by antimicrobial medicines and patent Chinese medicines in August 2017. Lessons learnt from the two stages of implementation were fed into the final stage of implementation in January 2018, targeting a broad range of specialized medicines including cardiovascular medicines. Procurement of the relevant medicines from all of the 21 public hospitals in Xiangyang were pooled for a better bargaining price based on the large pooled volume. Tendering was organized with a promised volume for each procured medicine calculated based on the clinical needs for six or more months (Health Commission of Hubei Province, 2017). The price of each procured medicine (with specified INN, dosage form, strength, pack size) under the volume-price contract was fixed for all of the covered local health institutions, which lasted for 1 year. In the volume-price contract system, the tendering and procurement procedures were integrated.

Over the study period, the Yichang municipality (control group) maintained its existing procurement system similar to that of Xiangyang prior to the introduction of the volume-price contract system. The provincial government organized the tendering and determined the awarded suppliers without guaranteed procurement volumes. Each individual hospital then conducted its own "second bargaining" for the price of purchase orders (Health and Family Planning Commission of Hubei Province, 2014). Under such a system, the governments were only responsible for identifying suppliers through tendering, leaving the actual procurements in the hands of individual health institutions.

Statistical Analysis

Price change was the primary interest of this study, which was the major policy goal of the volume-price contract initiative. The unit price of each procured medicine was calculated based on its defined daily dosage (DDD) defined by World Health Organization in 2018 (WHO Collaborating Centre for Drug Statistics Methodology, 2018) in absolute monetary terms (CNY).

Generalized linear regression models with a difference-in-differences approach were established to determine price (non-normal distribution) changes associated with the volume-price contract initiative:

$$Y_{ijt} = \alpha_0 + \beta \times Policy_{ijt} + \gamma \times X_{ijt} + \alpha_j + \delta_t + \varepsilon_{ijt}$$

where Y indicates the unit price of procured medicines, i indicates a specific cardiovascular product, j represents the public hospital, and t indicates the month (24-month periods). α_j and δ_t are fixed effects of hospitals and months, respectively. ε_{ijt} refers to the random error term. The difference-in-differences effect of the volume-price contract initiative was measured by the regression coefficient β for $Policy_{ijt}$, an interaction term between the study group (1 = Xiangyang, 0 = Yichang) and the time (1 = 2018, 0 = 2017).

Several indicators were calculated to measure competition (X_{ijt}), a dominant force for price setting in a market system. These included generic competition (the number of different products that had the same molecule defined by the ATC fifth-level code) and therapeutic competition (the number of different

TABLE 2 | Estimation of link function (Park tests) and family distribution (Box–Cox tests) of unit price of pharmaceutical products.

Study sample	Modified park test for family distribution		Box-cox test for link function	
Total	1.77	Gamma	–0.13	Log
Subsample by ownership				
Domestic suppliers outside of top 100	1.98	Gamma	–0.07	Log
Top 100 domestic suppliers	2.02	Gamma	–0.20	Log
Suppliers with joint venture	2.09	Gamma	–0.24	Log
Foreign-owned suppliers	3.53	Inverse gaussian	–0.33	Log
Subsample by medicines				
Original brand	3.53	Inverse gaussian	–0.25	Log
Generic	1.84	Gamma	–0.10	Log
Subsample by administration routes				
Injectable	2.00	Gamma	0.03	Log
Oral	1.72	Gamma	0.42	Square root

Note: Coefficients excerpted from modified Park tests: 0 = Gaussian distribution (variance unrelated to the mean); 1 = Poisson distribution (variance equal to the mean); 2 = Gamma distribution (variance exceeding the mean); 3 = Inverse Gaussian distribution (or Wald distribution). Coefficients excerpted from Box–Cox tests: 0 = log link; 0.5 = square root link; 1 = identity link.

TABLE 3 | Supply of cardiovascular medicines in the participating municipalities over the study period (2017–2018).

Characteristics of supply	Xiangyang (intervention)		Yichang (control)	
	2017	2018	2017	2018
Number of INNs	126	92	132	130
Type of procured products	229	140	233	236
Generic competitors per product per month (Mean ± SD)	1.86 (±1.56)	1.09 (±1.19)	2.29 (±2.11)	2.41 (±2.01)
Therapeutic competitors per product per month (Mean ± SD)	6.63 (±5.19)	3.84 (±3.65)	7.99 (±5.64)	8.71 (±6.14)
Number (%) of products supplied by:				
Domestic suppliers outside of top 100	141 (61.57)	78 (55.71)	139 (59.66)	128 (54.24)
Top 100 domestic suppliers	13 (5.68)	18 (12.86)	8 (3.43)	26 (11.02)
Suppliers with joint venture	47 (20.52)	26 (18.57)	54 (23.18)	53 (22.46)
Foreign-owned suppliers	28 (12.23)	18 (12.86)	32 (13.73)	29 (12.29)
Number (%) of products with:				
Original brand	43 (18.78)	26 (18.57)	43 (18.45)	40 (16.95)
Generic	186 (81.22)	114 (81.43)	190 (81.55)	196 (83.05)
Number (%) of products administered through:				
Oral	141 (61.57)	89 (63.57)	151 (64.81)	162 (68.64)
Injectable	88 (38.43)	51 (36.43)	82 (35.19)	74 (31.36)

Note: INN - *International Nonproprietary Name;* SD—*standard deviation.*

products that were in the same therapeutic subgroup defined by the ATC fourth-level code) (Zhao and Wu, 2017). Given the possibility of the nonlinear effects of competition (Spinks et al., 2013; Liu et al., 2017), a squared term of each competition indicator was added to the regression models.

We established modelling for the entire sample, as well as modelling for the subsamples categorized by ownership of suppliers and characteristics of medicines in line with the Hedonic model (Rosen, 1974). The estimation of standard errors in the modeling for the sample were clustered at the level of cardiovascular products (procurement serial numbers).

Modified Park tests and Box-Cox tests were used to estimate family distribution and link function of the outcome indicator (unit price), respectively. Log link and Gamma distribution were applied in the modelling for the entire sample and most subsamples, except for the subsample containing foreign-owned suppliers only and the subsample containing original brands only, for which log link and inverse Gaussian distribution were applied. In addition, square root link and Gamma distribution were applied in the modelling for the subsample containing oral medicines only (**Table 2**).

RESULTS

Supply of Cardiovascular Medicines

Table 3 shows changes to the procured cardiovascular medicines before and after the new initiative in the intervention group (Xiangyang) and the control group (Yichang). There were no obvious changes in the number of INNs and type of products in the control group. But the type of products dropped by 38.86%, from 229 before the initiative to 140 after the initiative; and the number of INNs dropped by 26.98%, from 126 down to 92 in the intervention group. Meanwhile, the monthly average number of both generic (changing from 1.86 to 1.09) and therapeutic (changing from 6.63 to 3.84) competitors per product also declined in the intervention group, compared with an increase in the control group (changing from 2.29 to 2.41 for generic competitors and from 7.99 to 8.71 for therapeutic competitors). Overall, the share of different medicines (generic vs original brands; oral vs injectable) and suppliers (by ownership and financial outputs) remained unchanged: the vast majority of the market was occupied by generic and oral medicines and domestic suppliers.

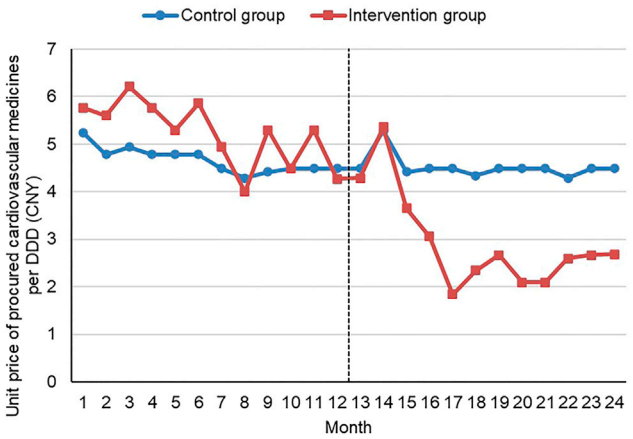

FIGURE 1 | Median unit price per DDD of procured cardiovascular medicines by month Note: CNY—Chinese Yuan; DDD—defined daily dosage

TABLE 4 | Generalized linear regression model on unit price of all procured cardiovascular medicines with difference-in-differences analyses.

Variables	β coefficient	Robust product clustered standard error	z	*p*>|z|	95% confidence interval
Intervention effect (difference-in-differences)	**−0.45**	0.16	−2.73	**0.006**	−0.77 to -0.13
Generic competition (X1)	0.17	0.20	0.87	0.385	−0.22 to 0.57
$(X1)^2$	−0.02	0.02	−0.63	0.526	−0.06 to 0.03
Therapeutic competition (X2)	**−0.38**	0.13	−3.03	**0.002**	−0.63 to -0.13
$(X2)^2$	0.01	0.01	1.35	0.176	−0.00 to 0.02
Goodness-of-fit tests					
Akaike Information Criterion (AIC) = 10.67					
Bayesian Information Criterion (BIC) = -79,081.63					

Note: Bold values indicate regression coefficients with statistical significance (p < 0.05).

Changes in Unit Price of Medicines

The median price (DDD adjusted) of procured cardiovascular medicines decreased by 41.51% in the intervention group (Xiangyang) after the initiative, down from 5.30 Yuan in 2017 to 3.10 Yuan in 2018, compared with a 0.22% decrease (from 4.49 Yuan to 4.48 Yuan) in the control group (Yichang). The median unit price hovered at a high level prior to the introduction of the volume-price contract system in the intervention group. The new initiative resulted in a dramatic drop in the unit price from the third month to the fifth month after the introduction of the volume-price contract system, followed by a levelling off of around two and three Yuan. Over the study period, no significant changes in the median unit price were observed in the control group. The median unit price in the control group was lower prior to the new initiative but higher post the new initiative in comparison with the intervention group (**Figure 1**).

Factors Associated With Changes in the Unit Price of Procured Cardiovascular Medicines

Considering the log link applied in the modelling, we made some transformations of the coefficients (Zhang et al., 2017).

The results of the difference-in-differences regression analyses showed that the volume-price contract initiative was associated with a 36.24% reduction (p = 0.006) in the unit price (DDD adjusted) of the procured cardiovascular medicines after adjustment for variations in other variables. In addition, therapeutic competition was associated with a 31.61% reduction (p = 0.002) in the unit price. No significant effects of generic competition were found (**Table 4**).

Subgroup Analyses on Intervention Effects

The subgroup difference-in-differences analyses revealed that the intervention effects on the unit price of procured cardiovascular medicines were statistically significant for those with an original brand and those supplied by the top 100 domestic suppliers. The unit price from the top 100 domestic suppliers dropped by 82.80% (p = 0.001), while the unit price of those with an original brand dropped by 30.23% (p = 0.008) as a result of the volume-price contract arrangements. No significant intervention effects were observed for the generic medicines and other suppliers. No significant intervention effects were observed in subgroups of medicines categorized by administration routes (**Table 5**).

TABLE 5 | Subgroup difference-in-differences analyses (generalized linear regression) on unit price of procured cardiovascular medicines.

Subgroup	N	Intervention effect					Goodness-of-fit tests	
		Coefficient	SE	Z	*p*>|z|	95%CI	AIC	BIC
Suppliers								
Domestic suppliers outside of top 100	7,278	0.21	0.23	0.91	0.363	–0.25 to 0.67	10.83	–32,420.92
Top 100 domestic suppliers	1,157	**–1.76**	0.52	–3.42	**0.001**	–2.78 to -0.75	8.39	–5,462.00
Suppliers with joint venture	3,561	–0.51	0.60	–0.85	0.393	–1.69 to 0.66	10.99	–10,200.43
Foreign-owned suppliers	3,925	–0.08	0.06	–1.25	0.210	–0.20 to 0.04	6.84	–31,932.43
Medicines								
Original brand	5,488	**–0.36**	0.13	-2.63	**0.008**	–0.62 to -0.09	6.59	-45,988.30
Generic	10,433	–0.28	0.18	–1.51	0.130	–0.64 to 0.08	11.32	-45,641.75
Administration route								
Injectable	4,366	0.17	0.19	0.87	0.382	–0.21 to 0.54	14.29	–23,176.32
Oral	11,555	–0.08	0.06	–1.40	0.162	–0.19 to 0.03	4.63	–100,023.10

Note: Bold values indicate regression coefficients with statistical significance (p < 0.05). AIC - *Akaike information criterion;* BIC - *Bayesian information criterion;* CI - *confidence interval;* SE - *product clustered standard error.*

DISCUSSION

Our study examined the impact of the volume-price contract initiative on the unit price of procured cardiovascular medicines through a natural experimental design involving 15,921 procurement records for 35 hospitals over a 2-year period. The generalized linear regression model with a difference-in-differences approach revealed that the volume-price contract arrangements contributed to a 36.24% drop in the unit price of procured cardiovascular medicines and a 31.61% drop in the unit price resulting from therapeutic competition after adjustment for variations in other variables. The medicines with an original brand and those supplied by the top 100 domestic suppliers were particularly sensitive to the new initiative, with a 30.23% and 82.80% drop in unit pricing, respectively.

The results indicate that the volume-price contract initiative offers an additional tool to reduce the unit price of medicines on top of the competition mechanism. Collective tendering and purchasing has been a common practice in most countries worldwide to source affordable medicines. The rationale lies in the theory of economies of scale (Li and Bai, 2019). With a large volume, the marginal cost for increasing production drops, which can result in a lowered average unit cost. Furthermore, a promised purchase volume brings certainty, which can help suppliers avoid or reduce some administrative and transaction costs. In the past, the awarded tenderers had to conduct market research, negotiate with individual health institutions, and promote their products in competition with other suppliers to win a purchase order. These costs, in particular the marketing costs, could be very high and had to be factored into consideration in the price setting (Ge, 2020; Huang and Tao, 2020). The new procurement arrangement now offered the awarded tenderers assurance of a large pooled purchase volume, giving them costing advantages in manufacturing and distributing the contracted products. This may even generate a flow-over effect on the surrounding regions through intensified price competition (Li and Bai, 2019), although we did not observe such a phenomenon in our study.

It is important to note that the impact of the volume-price contract initiative varies by supplier. The foreign-owned and joint ventures and the smaller domestic suppliers in this study were found to be less responsive to the new initiative in price setting than the top 100 domestic suppliers. The underlying reasons are not very clear. For small suppliers, their production capacity is limited, which may prevent them from participating in the large volume-based tendering. Unlikely their large counterparts, small suppliers do not have the advantage of economies of scale and may have limited space to cut costs. In addition, small domestic suppliers are most likely to be local. There may be a lack of incentives for them to reduce price under the protectionism of local governments (Wu et al., 2014).

Another interesting finding of this study is that generic medicines are less responsive in price setting to the volume-price contract system than those with an original brand. Generic medicines are always priced lower than their original-brand counterparts in the pharmaceutical retail market. The price gap between generic medicines and original brands, including cardiovascular medicines, is quite big in China (Zeng, 2013), which gives the original brands more room for price reduction. Indeed, most generic medicines are produced by small manufacturers in China. They tend to enter the retail market with low prices. The availability of lower-priced competitors can drive down the price of the original brands (Chapman et al., 2019). However, the original brands do not always engage in price competition with the generic medicines in China. They have occupied a large market share and are able to maintain higher prices due to longstanding concerns from the public about the quality of generic medicines. The perceived difference in the quality of medicines has weakened the competition effect between generic medicines and original brands (Chen and Rao, 2019).

The findings of this study have several policy implications. First, the effect of the volume-price contract initiative is effective in bringing down price only when the procurement volume is large enough. This imposes a serious challenge to the procurement of generic medicines as there are large numbers of suppliers but each occupies a small market share. The municipality-wide procurement volume may not be big

enough to incentivize suppliers to cut the price of already lower-priced generic medicines. A higher (provincial or even national) level of pooled procurement arrangement can increase the procurement volume and create a competitive market. This may also encourage large manufacturers to produce generic medicines. In recent years, the national government in China has encouraged 11 provinces/regions to organize volume-based procurement for some generic medicines (Tang et al., 2019). Second, the medicines with a brand name are very responsive in price setting to the volume-price contract system, which can bring benefits in driving the quality improvement of generic medicines as their price gaps are shrinking. In 2016, the State Council of China released policy guidelines for establishing efficacy equivalence of generic medicines with an aim to resume consumer confidence in generic medicines through strengthened quality assurance mechanisms (The State Council of the People's Republic of China, 2016).

To our knowledge, this is the first study of its kind in China to examine the impact of the volume-price contract system on the unit price of procured cardiovascular medicines. It provides additional evidence to the existing literature that advocates for collective tendering and purchasing of medicines based on volume and price. Data used in this study were extracted from the tendering platform, which had a large sample size and avoided sampling bias.

There are some limitations in this study. First, we could not exclude the potential impact of heterogeneity of medicines although the study was limited to cardiovascular medicines. The quality and efficacy information of the procured medicines was absent, preventing us from assessing the impacts of the new procurement system comprehensively apart from the unit price. The potential impact of the new supply arrangement on clinical services and patient care outcomes is unknown. However, this may not be an issue since the quality gap between generic medicines and originator brands is being gradually narrowed as seen in countries including China (Davit et al., 2009; Corrao et al., 2014; Jackevicius et al., 2016; The State Council of the People's Republic of China, 2016). In addition, there is little difference in effectiveness or safety of different medicines for cardiovascular diseases (Wei et al., 2020). Future studies should take a patient perspective and cover a wider range of medicines as the new supply arrangement may have differing effects on the supply of different medicines. Second, each individual transaction was treated as a unit of analysis without consideration of the duration of contract (because of the lack of variations) and how previous contracts informed subsequent procurement from the same supplier (because of data unavailability). Third, although China's pharmaceutical supply system has been improved substantially by the strong regulations from the government (Yan et al., 2018), there is still problem of fragmentation in the regulatory, which exacerbates the lack of transparency in the pharmaceutical system (Hu and Mossialos, 2016). In addition, China's pharmaceutical market has been characterized by dispersion and low concentration, which leads to uneven pricing problems of pharmaceuticals (Hu and Mossialos, 2016). Thus, the generalization of the conclusions to other settings should be conducted with caution.

CONCLUSION

In conclusion, the volume-price contract initiative is effective in reducing the unit price of procured cardiovascular medicines. The effect remained significant after adjustment for the competition effects. However, the impacts of the new initiative vary by medicine and supplier. The cardiovascular medicines with an original brand and the top 100 domestic suppliers were more responsive to the new initiative than others. Increasing procurement volumes may further enhance the impact of the volume-price contract system. But local protectionism can create a great barrier for cross-region collaborations.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conception and design: ZL, CL, KZ, and YT. Collection and assembly of data: ZL, KZ, and YT. Statistical analysis: ZL, CL, and YT. Interpretation: ZL, CL, KZ, JL, and YT. Manuscript preparation: ZL, CL and YT. Manuscript review: ZL, CL, KZ, JL, and YT.

FUNDING

This study was supported by the National Natural Science Foundation of China, Grant number 71704058. The funding body played no role in the study design; the collection, analysis, and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China, Grant number 71704058. The authors are also grateful to the staff in Hubei Public Resource Trading Center for their kind help in data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.741671/full#supplementary-material

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frontiers in Pharmacology

BRIEF RESEARCH REPORT
published: 19 October 2021
doi: 10.3389/fphar.2021.754390

Factors Associated With Off-Label Oncology Prescriptions: The Role of Cost and Financing in a Universal Healthcare System

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Edited by:
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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: 06 August 2021
Accepted: 22 September 2021
Published: 19 October 2021

Citation:
Gordon N, Goldstein DA, Tadmor B, Stemmer SM and Greenberg D (2021) Factors Associated With Off-Label Oncology Prescriptions: The Role of Cost and Financing in a Universal Healthcare System. Front. Pharmacol. 12:754390. doi: 10.3389/fphar.2021.754390

Purpose: Various solutions have been put forward for prescribing and reimbursing treatments outside their registered indications within universal healthcare systems. However, most off-label oncology prescriptions are not reimbursed by health funds. This study characterized the financing sources of off-label oncology use and the predictors of the decision to forego treatment.

Materials and Methods: All 708 off-label oncology requests submitted for approval in a large tertiary cancer center in Israel between 2016 and 2018 were examined for disease and patient sociodemographic characteristics, costs and financing sources, and the factors predicting actual off-label drug administration using multivariate logistic regression analysis.

Results: The mean monthly cost of a planned off-label treatment was ILS54,703 (SD = ILS61,487, median = ILS39,928) (approximately US$ 15,500). The main sources of funding were private health insurance (25%) and expanded access pharma company plans (30%). Approximately one third (31%) of the requests did not have a financing source at the time of approval. Of the 708 requests, 583 (or 82%) were filled and treatment was initiated. Predictors for forgoing treatment were the impossibility of out-of-pocket payments or the lack of a financing solution (OR = 0.407; p = 0.005 and OR = 0.400; $p < 0.0005$).

Conclusion: Although off-label recommendations are widespread and institutional approval is often granted, a large proportion of these prescriptions are not filled. In a universal healthcare system, the financing sources for off-label treatments are likely to influence access.

Keywords: cancer, off-label, cost, reimbursement, universal healthcare system

INTRODUCTION

Regulatory registration and approval are mandatory for new drugs to be marketed and for public and private health insurance reimbursement. *Off-label drug use* is defined as the prescription of an approved drug for a purpose not indicated in the marketing authorization. This includes its use to treat other conditions, age groups, dosages, or routes of administration (Saiyed et al., 2017; Wittich et al., 2012).

Off-label drug use in oncology is widespread, with estimates of up to 75% (Conti et al., 2013; Joerger et al., 2014; Hamel et al., 2015; Kalis et al., 2015; Eaton et al., 2016). There are several reasons for its growing prevalence in recent years. The first is that the regulatory approval process is expensive and lengthy. If a drug is unauthorized but used *de facto*, pharmaceutical companies have no major incentive to expand its registration and marketing authorization. This is especially germane to off-patent drugs and to rare indications where Phase III randomized controlled trials may not be feasible or economically viable (ASCO, 2006). Second, even if a drug is in clinical development, aiming for registration for a new indication, the process until final authorization is granted is lengthy. In the interim, new evidence supporting off-label use might emerge and even be included in clinical practice guidelines. Third, with life-threatening and terminal illnesses such as cancer, patients and physicians look to unapproved treatments with limited supporting evidence after standard therapies have been exhausted. This "off-evidence" use may benefit patients, based on the reasoning that different cancer indications share the same genetic or molecular characterizations. Thus, in recent years, with the increasing incorporation of personalized or tailored medicine into clinical practice, off-label use prevalence has also grown. Finally, off-label drug use may provide real hope for effective treatments that might emerge in the future. This is defined as its "option value" (Garrison et al., 2017).

New treatments revolutionized cancer care in recent years, including targeted therapies and immunotherapy. Although many have high prospects, others will be proved to have limited value in the long term (Goldstein et al., 2016). At the same time, cancer drug prices at product launch are steadily increasing (Bach, 2009; Elkin and Bach, 2010), and continue to rise after market entry, regardless of competition and market volume (Bennette et al., 2016; Gordon et al., 2017). Hence, reimbursement of new oncology treatments with questionable value is a key issue, both in market-based and universal healthcare systems (Garrison et al., 2018). In the United States for example, the Centers for Medicare and Medicaid Services (CMS) limit coverage for off-label indications to those listed in specified compendia (ASCO, 2006; Abernethy et al., 2009; Green et al., 2016) while private insurers provide off-label reimbursement, depending on the indication and supporting evidence.

In universal healthcare systems, new treatments usually compete for a share in limited budgets. Including reimbursement for off-label drugs further complicates decision-making in that public reimbursement is usually more restrictive and depends on the national health insurance legislation. In Ontario (Canada), for instance, off-label treatments are only reimbursed for severe conditions where there are no alternative treatments (Rawson and Chhabra, 2018). In European countries, coverage policies vary (Weda et al., 2017). For example. in France reimbursement is approved when there is no authorized alternative (Natz and Campion, 2012; Weda et al., 2017). In Italy, off-label prescription is legal if there is adequate evidence for safety and efficacy, however public reimbursement is available only for certain drugs included in specific lists, updated as clinical evidence accumulate (Gozzo et al., 2020). In Germany and in Japan, expert commissions are established to approve specific off-label treatments use and reimbursement (Weda et al., 2017; Bun et al., 2020).

In Israel, drugs can only be legally prescribed for their registered indications. However, regulation 29 of the Pharmacist's Regulations (1986) notes several exceptions concerning the use of unlicensed medical products and the unapproved indications of licensed medical products, including off-label use. The Institutional Drug Committees (IDCs), which are established within medical centers, provide approval if the use of the drug has been shown to be imperative and there are no other viable alternatives. As for reimbursement, the Israeli National List of Health Services (NLHS) specifies the drugs and other health technologies and services to which all residents are entitled. New treatments are recommended by a public national advisory committee and reviewed in a comprehensive process that includes clinical, economic, social and ethical factors (Shani et al., 2000). The NLHS stipulates a mandatory basic "basket" of health services that Health Maintenance Organizations (HMOs) in Israel are obligated to provide. Each HMO may add services to the basic basket. HMO exception committees discuss reimbursement of individual treatment requests that are not included in the NLHS. New health technologies are rapidly reviewed for inclusion each year, with a very good coverage of new drugs (Greenberg et al., 2009; Ribalov et al., 2016). However, since one prerequisite is approval by a major regulatory agency (e.g., the U.S. FDA) and registration in Israel, off-label use is generally not publicly reimbursed (Hammerman et al., 2011). Instead, off-label drug use is largely financed through commercial health insurances, charitable organizations, expanded access plans that are offered by pharmaceutical companies, or paid out-of-pocket by patients and their families.

Research has examined the frequency of off-label use, toxicity, and outcomes (Conti et al., 2013; Eaton et al., 2016; Herrero Fernandez et al., 2019). However, to the best of our knowledge, no study to date has assessed the economic burden and financing sources of these treatments. The current study was conducted in a large, tertiary cancer center in Israel. The objective was to describe the costs and range of financing strategies of off-label treatments in oncology and to identify the reasons why approved off-label treatments are not initiated.

METHODS

All consecutive off-label requests approved between January 2016 and December 2018 by the Institutional Drug Committee (IDC)

at Rabin Medical Center (RMC; Petah Tikva, Israel) were examined. The RMC is a 1,100-bed academic tertiary hospital and one of the largest referral centers in the country, treating approximately 20% of all cancer patients in Israel. The RMC is owned by Clalit Health Services, the largest public health insurer in Israel that provides coverage to approximately 52% of the Israeli population. The IDC reviews each request based on the available evidence to weigh the risks and potential benefits. All records are retained by the hospital pharmacy. Only injectable, oncology off-label drug requests were included, since these are reviewed by the IDC and administered in the hospital's outpatient clinic. We excluded requests for patients who died less than 60 days after request approval to minimize the bias of performance status and life expectancy on off-label treatment initiation.

For each off-label request, we collected the drug and indication information, disease characteristics, and intended financing source for the treatment. Supporting evidence was assessed for each off-label treatment according to the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) version 1.1 (Cherny et al., 2017) and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) (Mateo et al., 2018). The data were then categorized into three groups: sufficient evidence (ESMO-MCBS grade A-B, 5-4), limited evidence (ESMO-MCBS grade C, 3-1; ESCAT tier II-IIIA) and inadequate evidence (no supporting clinical trials; ESCAT tier IIIB-IV). Patient sociodemographic characteristics and in-depth disease information were collected from electronic medical records. The distance from the medical center and the socioeconomic status (SES, ranging from 1 to 10 by deciles) were calculated according to the patient's home address. We extracted off-label drug dispensing dates and dosages from the pharmacy dispensing database. We then calculated the monthly cost based on drug price lists published by the Ministry of Health (Ministry of Health, 2016). Costs are presented in Israeli Shekels (ILS), at an exchange rate of ILS3.50 to $1.00US.

The patient, disease, costs, and financing variables were subjected to descriptive statistics. A one-way ANOVA was used to compare the mean monthly costs between different groups. Univariate logistic regression analysis was performed to estimate the relationship between the independent variables and treatment initiation. Multivariate regression was used to identify factors predicting actual treatment initiation. Age, gender, and all variables that were found to be significantly distributed differentially across groups were entered into the multivariate logistic regression in one step. Statistical significance was set a-priori at $p \leq 0.05$. The data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., United States). This study was approved by the RMC ethics committee (0068-16-RMC); participant's consent was not required.

RESULTS

Off-Label Requests and Patient's Characteristics

The IDC approved 1,216 requests between January 2016 and December 2018. Of these requests, 814 were for injectable oncology off-label drugs 106 requests were for patients who died less than 60 days after approval and were excluded from the analysis, leaving 708 requests for 618 patients. The mean patient age was 62 years (range 19–95); 58% were female. The median SES decile was 7 (range 1–9). Most patients lived in the center of Israel with a mean distance of 30 km from the RMC (range 3–344 km). Most patients (76%) were insured by Clalit Health Services; 68% had public supplementary insurance.

The patients were diagnosed with lung (33%), breast (29%), gastric (9%) and pancreatic cancer (8%), with 39% defined as orphan diseases. The majority of the off-label requests were for patients with metastatic diseases (69%), who had received at least one prior treatment that had failed (53%); 25% had a molecular marker or mutation correlated with a biological plausibility for response. Off-label request were for chemotherapies (20%), targeted therapies (39%) and immunotherapies (41%). Only 48% of the requests had sufficient supporting evidence. The full description of the requests, patient diseases and socio-demographic characteristics are presented in **Tables 1**, **2**.

Off-Label Treatments Cost and Financing Sources

The mean monthly cost of the planned treatment was ILS54,703 (SD = ILS61,487, median = ILS39,928) for all requests and ILS64,436 (SD = ILS58,066, median = ILS49,157) for metastatic diseases. The main planned sources for financing were private health insurance (25%) and expanded access pharma company plans (30%). However, a large proportion (31%) of the patients did not specify a source of reimbursement at the time of the off-label request.

Of the 708 approved prescription requests, only 583 (82%) were initiated. The mean monthly costs were higher for treatments that were initiated compared to those that were not (ILS56,274 vs. ILS47,313); however, this trend was not statistically significant (**Figure 1A**). In the metastatic setting, the opposite trend was observed, with slightly, albeit not significantly, higher mean costs of treatments that were not initiated (ILS63,558 vs. ILS69,451) (**Figure 1B**). This trend persisted when further exploring metastatic setting requests by planned financing source. Treatments that were not initiated had higher mean monthly costs for private health insurance (ILS76,002 vs. ILS87,287) and when the financing source was unknown at the time of request submission (ILS43,222 vs. ILS63,290). Nevertheless, none of the trends were statistically significant (**Figure 1B**).

Factors Associated With Off-Label Treatment Initiation

To identify the patient and request characteristics that influenced the likelihood that an approved off-label request would eventually be initiated, a univariate logistic regression analysis was conducted (**Tables 1**, **2**). None of the patient characteristics were found to be predictive of treatment initiation. The disease and treatment characteristics that were significantly predictive of treatment initiation were metastatic disease (OR = 1.731; 95% CI, 1.161 to 2.581; $p = 0.007$) and the existence of a molecular marker or a targetable mutation

TABLE 1 | Off-label request patient characteristics and univariate logistic regression analysis for treatment initiation (n = 708).

Characteristic	Total *n* (%)	Treatment initiated *n* = 583 *n* (%)	Treatment not initiated *n* = 125 *n* (%)	Odds ratio	95% CI for odds ratio lower upper	*p*-value
Age (years) Median, Mean (range)	64, 62 (19–95)	64, 62 (19–95)	65, 64 (27–89)	1.012	0.997–1.028	0.114
Gender						
Male	297 (42)	243 (42)	54 (43)	1.064	0.720–1.572	0.755
Female	411 (58)	340 (58)	71 (57)			
Children	532 (75)	433 (74)	99 (79)	1.319	0.824–2.111	0.248
Health insurer						
Clalit	539 (76)	439 (75)	100 (80)	0.762	0.473–1.228	0.264
Maccabi	99 (14)	85 (14.4)	14 (11)	1.353	0.742–2.470	0.324
Meuhedet	39 (5.5)	30 (5)	9 (7)	0.699	0.323–1.512	0.363
Leumit	27 (4)	25 (5)	2 (2)	2.755	0.644–11.787	0.172
Tourist/Not insured	4 (0.5)	4 (0.5)	0 (0)	NA	NA	NA
Supplementary public insurance						
None	228 (32)	195 (33)	33 (26)	1.401	0.908–2.161	0.127
Basic	226 (32)	183 (32)	43 (34)	0.872	0.508–1.312	0.513
Premium	254 (36)	205 (35)	49 (40)	0.841	0.565–1.251	0.393
SES Median Decile	7	7	7	1.078	0.961–1.210	0.198
Decile 1–3	59 (8)	50 (9)	9 (7)			
Decile 8–10	264 (37)	217 (37)	47 (38)			
Distanceto RMC (km) Median, Mean (range)	18.5, 30 (3–344)	18.5, 30 (3–344)	15, 29 (3–344)	0.999	0.994–1.004	0.779

SES, Socioeconomic status; RMC, Rabin Medical Center; km, kilometers.
Gender is for Males compared to Females.

TABLE 2 | Off-label request characteristics and univariate logistic regression analysis for treatment initiation (n = 708).

Characteristic	Total *n* (%)	Treatment initiated *n* = 583 *n* (%)	Treatment not initiated *n* = 125 *n* (%)	Odds ratio	95% CI for odds ratio lower upper	*p*-value
Drug type						
Chemotherapy	144 (20)	122 (21)	22 (18)	1.239	0.750–2.046	0.402
Targeted therapy	272 (39)	208 (36)	64 (51)	0.529	0.358–0.780	0.001
Immunotherapy	292 (41)	253 (43)	39 (31)	1.691	1.119–2.553	0.013
Metastatic disease	491 (69)	417 (72)	74 (59)	1.731	1.161–2.581	0.007
Orphan disease	276 (39)	227 (39)	49 (39)	0.989	0.666–1.469	0.956
Marker or targetable mutation	179 (25)	157 (27)	22 (18)	1.725	1.051–2.832	0.031
Treatment line						
≥2	377 (53)	318 (55)	59 (47)	1.342	0.911–1.977	0.136
≥3	109 (15)	90 (15)	19 (15)	1.018	0.595–1.743	0.947
Supporting evidence						
Sufficient	338 (48)	226 (45)	72 (58)	1.619	1.096–2.392	0.016
Limited	322 (45)	278 (48)	44 (35)	0.596	0.399–0.899	0.012
Inadequate	48 (7)	39 (7)	9 (7)	1.082	0.510–2.296	0.837
Financing						
Expanded access	210 (30)	187 (32)	23 (18)	2.094	1.290–3.400	0.003
Charity	17 (2)	16 (3)	1 (1)	3.499	0.440–26.632	0.226
Out-of-pocket	84 (12)	71 (12)	13 (10)	1.195	0.639–2.233	0.557
Private insurance	178 (25)	152 (26)	21 (21)	1.343	0.839–2.148	0.219
No planned source	219 (31)	157 (27)	62 (50)	0.374	0.252–0.556	<0.0005
Cost per month (ILS), Mean	54,703	56,274	47,313	1	1–1	0.125

ILS, New Israeli Shekels.

which was related to a response to the treatment (OR = 1.725; 95% CI, 1.051 to 2.832; p = 0.031). Immunotherapy was predictive of treatment initiation (OR = 1.691; 95% CI, 1.119 to 2.553; p = 0.013), whereas targeted therapy was less likely to be initiated (OR = 0.529; 95% CI, 0.358 to 0.780; p = 0.001). A treatment was more likely to be initiated if it was planned to be sponsored by the pharma company through expanded access plans (OR = 2.094; 95% CI, 1.290 to 3.400; p = 0.003). By contrast, treatment initiation was less likely if no financing source was in place (OR = 0.374; 95% CI, 0.252 to 0.556; $p < 0.0005$).

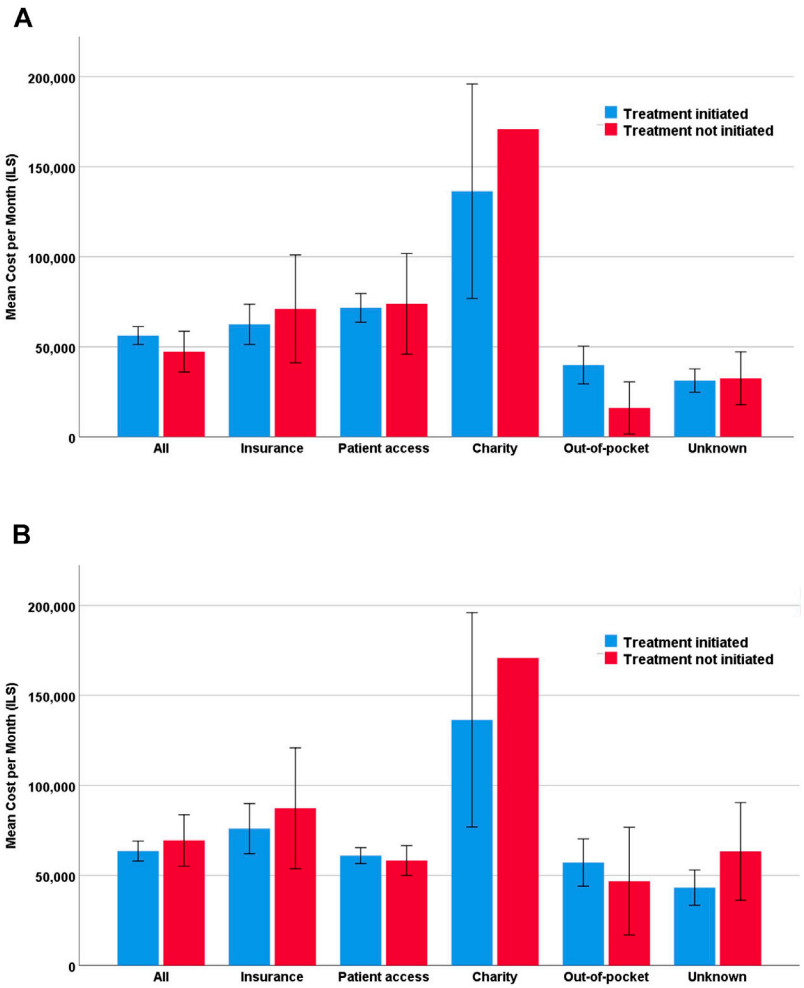

FIGURE 1 | Mean monthly cost by financing source. **(A)** All off-label requests (n = 708) **(B)** Metastatic disease off-label requests (n = 491).

A multivariate logistic regression was performed to ascertain the independent effects of age, gender, drug type, metastatic disease, marker or targetable mutation, supporting evidence level, and planned financing source on the likelihood that an approved off-label request would eventually be initiated. The model explained 12% (Nagelkerke R^2) of the variance in treatment initiation and correctly classified 82.1% of the cases. Of the potential predictor variables, only two were statistically significant: targeted therapy (OR = 0.407; p = 0.005) and unknown financing source (OR = 0.400; p < 0.0005) (**Table 3**). If the treatment was a targeted therapy or if no financing plan was in place at the time of treatment request, there was a 2.5-fold higher likelihood of not receiving treatment.

DISCUSSION

This is the first study to evaluate the range of financing sources of oncology off-label drug usage within the context of a universal healthcare system. We found that the average monthly cost of off-label treatment was ILS54,703 and ILS64,436 in the metastatic setting. These costs were 4-5-fold higher than the net average (ILS15,751) household monthly income in Israel in 2016 (Central Bureau of Statistics, 2018).

The monthly cost was not found to predict treatment initiation but the results strongly suggest that cost plays a role in the approval process of commercial insurances, since treatments that were not initiated through this financing route were more expensive, although this result was not significant. Furthermore, treatments that did not have a planned financing source upfront and were not initiated eventually tended to be more expensive, implying that cost plays an important role in treatment initiation considerations.

A significant determinant that was found to predict whether a prescription was filled or not was external funding. If the treatment had no planned financing source at the time of approval, there was a 60% lower likelihood that the prescription would be filled. On the other hand, if the drug was provided through an expanded access plan, the odds that the prescription would be filled rose by 67%.

TABLE 3 | Multivariate logistic regression predicting the likelihood of treatment initiation based on age, gender, drug type, metastatic disease, marker or targetable mutation, supporting evidence and planned financing source (n = 708).

	B	SE	Wald	df	*p*-value	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Age	0.013	0.009	2.285	1	0.131	1.013	0.966	1.031
Gender								
Male	0.458	0.252	3.292	1	0.700	1.580	0.964	2.591
Drug type								
Targeted therapy	−0.898	0.320	7.882	1	0.005	0.407	0.218	0.762
Immunotherapy	−0.221	0.378	0.340	1	0.560	0.802	0.382	1.683
Metastatic disease	0.092	0.322	0.082	1	0.775	0.912	0.485	1.715
Marker	0.275	0.277	0.991	1	0.320	1.317	0.766	2.265
Supporting evidence								
Sufficient	−0.086	0.458	0.035	1	0.852	0.918	0.374	2.252
Limited	0.659	0.444	2.203	1	0.138	1.933	0.810	4.617
Planned Financing Source								
Expanded access	0.511	0.304	2.829	1	0.093	1.668	0.919	3.026
No source	−0.916	0.262	12.252	1	<0.0005	0.400	0.240	0.668

Gender is for Males compared to Females.

Several studies have estimated the prevalence of off-label prescriptions in oncology and examined patient, disease, and clinician predictors of off-label use and outcomes. These studies, however, have only analyzed off-label usage through drug dispensing records (Joerger et al., 2014; Hamel et al., 2015; Herrero Fernandez et al., 2019) or insurance claims (Conti et al., 2013; Eaton et al., 2016). Other studies have focused on supporting evidence of off-label use to identify hurdles to drug development for rare diseases (Bun et al., 2020). By contrast, this study focused on the costs and financing of treatments and examined requests for committee approval which also included information about the planned financing source. By comparing each off-label approval to the drug dispensing data, we were able to identify approved treatments that were not initiated. This enabled us to examine how funding influences the decision to initiate or forgo off-label treatment.

In Israel, there are various solutions for prescribing drugs outside their registered indications and for reimbursement within universal healthcare systems. Since 2008, supplementary health insurance plans in Israel, which are offered by the four public health insurers, are not allowed to cover "life-saving" or "life-extending" treatments but several alternatives are still available. For example, if the off-label treatment is in the process of registration, many pharmaceutical companies will fund an expanded access plan (Fountzilas et al., 2018). Moreover, despite universal healthcare with wide coverage, 35% of Israeli adults also have private commercial health insurance (Central Bureau of Statistics, 2019). These insurance plans may cover off-label treatments if registered in another country or accepted in clinical guidelines. Some patients and families are able to pay for off-label treatments out-of-pocket, but this creates great financial hardship, since costs in oncology are high and treatment duration can be long. Charities and aid organizations offer assistance for drug supply and financial support. Nevertheless, in many instances, no financing is available and patients forgo treatment.

A cross-sectional survey conducted in 2011 examined public experiences with financing therapies outside the National List of Health Services in Israel (Sperling, 2014). The requests for reimbursement from commercial insurance (23.3 vs. 25% in this study) and aid organizations (5.2 vs. 2%) were similar. However, in the current study only 12% of the requests were financed out-of-pocket, whereas the 2011 survey reported that 56.9% of all patients relied on private purchase. It is possible that during the time between the two studies, pharmaceutical companies expanded their early access plans and a higher proportion of the population acquired private commercial health insurance covering the costs of these drugs. In this study, 31% of the requests had no planned financing source. These patients eventually pay for their therapy privately (out-of-pocket), turn to charity organizations, or forgo treatment. In fact, patients in the current study were found to be four times more likely to forgo treatment than previously reported (17.7 vs. 4.3%). This study focused solely on oncology, where drugs are more expensive, out-of-pocket payments are less feasible, and forgoing treatment is more common. Furthermore, 69% of the patients were metastatic, and many of them turned to off-label use after exhausting all the available options. Forgoing active cancer treatment might be more common in the case of a terminal diagnosis.

This study has several limitations. First, it only dealt with injectable agents administered at the outpatient clinic in the oncology center. According to Israeli regulations, oral off-label therapies are handled at the regional Ministry of Health level and approved by the district pharmacist. Prescriptions are filled by private pharmacies that specialize in off-label treatments, including importing unlicensed drugs. Thus, the findings here may not be generalizable to other types of off-label therapies. Further research is needed to determine whether different costs and payment sources, disease or sociodemographic characteristics affect prescription filling in these settings.

Second, the analysis was restricted to anticipated or intended financing sources specified by the patient when the off-label request for approval was submitted. This explains the high percentage of patients who did not know how the treatment would be financed. Actual financing may have differed from expected financing due to treatment costs or duration of treatment. Moreover, treatment can

be funded from more than one source. Capturing the patient's intention and the actual prescription filling separately could shed light on this issue.

Finally, in Israel, which has a universal healthcare system, there is a mechanism of public reimbursement of off-label treatments through special exception committees within each of the four public health insurance plans. If an off-label therapy is determined to be effective for an individual patient, payment for ongoing treatment may be authorized regardless of how it was initially financed. To prove effectiveness and obtain reimbursement, the patient must have an initial financing source for the treatment. If this initial funding is unfeasible, many patients decide not to initiate a treatment that could have been effective. Unlike other studies, both delivered and undelivered off-label treatments and associated costs were identified here. However, data confirming that the expected funding source did in fact cover the cost of treatment were not analyzed. Further research is needed on complete financing and payment information over the entire course of the off-label treatment to draw conclusions.

Although novel mechanisms are authorized by regulatory agencies to facilitate scientific and clinical innovation in the development of new personalized therapies (Mullins et al., 2010), oncologists have even more rapid technology adoption patterns. Physicians want to give hope to their patients, and patients and families want to do everything in their fight against cancer. These unmet needs increase the demand for new treatments even if there is limited value. Once an off-label treatment is prescribed, patients and their family engage in a race to obtain funding for the therapy. Little is known about the financial burden patients and families undergo in this fight to get approval and secure funding for off-label treatments. This study described the costs of off-label drug use in oncology and sources of financing. The insights from this study with respect to identifying the hurdles to access off-label treatments may be utilized in further studies focusing on the feasibility and workability of financing solutions.

DATA AVAILABILITY STATEMENT

Data are not publicly available according to the Rabin Medical Center strict institutional policy with regards to public availability of unidentified patient data. However, data that are minimally required to replicate the outcomes of this study will be made available upon request. Further inquiries can be directed to the corresponding author NG, noagordon@gmail.com.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

NG, SMS, and DGr have made a contribution to the design of the work, acquisition and data analysis; all the listed authors contributed substantially to the interpretation of the data and manuscript drafting; all the listed authors revised the submitted manuscript and approved its final version before submission.

ACKNOWLEDGMENTS

The authors wish to thank Vered Almog and Tzipi Greenwald from the pharmacy services and Shiri Kushnir from the research and development unit at the Rabin Medical Center for their collaboration. The authors also thank Norm O'Rourke, PhD, for his valuable comments on this manuscript.

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frontiers in Public Health

ORIGINAL RESEARCH
published: 22 October 2021
doi: 10.3389/fpubh.2021.735654

The Impact of Health Care Reform Since 2009 on the Efficiency of Primary Health Services: A Provincial Panel Data Study in China

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Background: Primary health care (PHC) is an important part of health systems in the world and in China. To improve the efficiency of PHC institutions (PHCIs), many countries have implemented reforms, including China's health care reform since 2009. This study aims to evaluate the impact of this reform on the efficiency of PHCIs from the perspective of the whole health system.

Methods: Data were collected from China Health Statistical Yearbooks and China Statistical Yearbooks published from 2005 to 2019. By taking the number of beds, health technicians and PHCIs as inputs and the proportion of diagnosis, treatment and admission in PHCIs as outputs, Malmquist DEA was used to evaluate the efficiency change of PHCIs, and panel data regression was performed to analyze the impact of the reform and other factors on such efficiency. The interaction between reform and economic level was also estimated.

Results: The MPI in Beijing, Tianjin, Shanghai, Hunan, and Guangdong improved after the reform. The efficiency improvement in Beijing, Tianjin and Shanghai is mainly reflected in the growth of TC, whereas the efficiency improvement in Guangdong and Hunan is mainly reflected in the growth of EC. Meanwhile, the EC and TC in Hebei, Heilongjiang, Shandong, and other provinces deteriorated. The deterioration of MPI in Shanxi, Inner Mongolia and Jilin was mainly attributed to EC. while the deterioration of MPI in Liaoning, Anhui, and Fujian provinces is mainly attributed to TC. Since 2009, the reform exerted a negative impact on MPI ($\beta = -0.06$; $P < 0.01$), TC ($\beta = -0.048$; $P < 0.01$) and EC ($\beta = -0.03$; $P < 0.01$). And such negative impact was weaker in economically developed areas ($\beta = 0.076$; $P < 0.01$).

Conclusions: Attention should be paid to future reforms: China should continue investing in PHCIs, establish a structurally integrated and functionally complementary delivery system and promote the coordination of reform policies to avoid the adverse impacts of other reform policies on PHCIs.

Keywords: primary health care, efficiency, reform, panel data study, health system

OPEN ACCESS

Edited by:
Kingston Rajiah, International Medical University, Malaysia

Reviewed by:
Rongyu Wang, Hospital of Chengdu University of Traditional Chinese Medicine, China
Yudong Miao, Zhengzhou University, China

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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *03 July 2021*
Accepted: *23 September 2021*
Published: *22 October 2021*

Citation:
Yan C, Liao H, Ma Y and Wang J (2021) The Impact of Health Care Reform Since 2009 on the Efficiency of Primary Health Services: A Provincial Panel Data Study in China. Front. Public Health 9:735654. doi: 10.3389/fpubh.2021.735654

BACKGROUND

Role of PHC in Health System

Primary health care (PHC) has been widely recognized as a crucial part of the overall health service system, and continuously improving its efficiency is essential to achieve universal health coverage. In terms of population health outcomes, a comprehensive and high-quality PHC can meet the majority of the health service needs of people throughout their lifetime (1–3). Maximizing PHC efficiency does not only reduce the wastage of health resources and realize a sustainable development of the health system but also guarantees positive and long-term health outcomes (4, 5).

Previous studies have mostly measured the efficiency of PHCIs from the input–output perspective and analyzed external factors. On the one hand, the relationship between input and output is studied quantitatively. The improvement in health outcomes is related to increased inputs from PHCIs (6–8). On the other hand, data envelopment analysis (DEA) is commonly used to measure the efficiency of PHCIs. The selected input variables mainly include operating costs and the number of administrative and technical personnel and beds, whereas the output variables mainly include the number of outpatients, referrals, hospitalizations, family services, and preventive health services (9–12). Results of these studies revealed a generally low PHCIs efficiency and large efficiency differences across regions. Many studies have pointed out that the population size within the jurisdiction of a health institution serves as the main basis for the allocation and utilization of health resources in PHCIs (13, 14). The aging population trend accelerates the transformation of the service mode of PHCIs to enhance their service efficiency (15, 16). In the process of urbanization, the changes in health service demand and the construction of a health system may affect the utilization of primary health services (17). Macroeconomic development promotes investment in PHCIs, alleviates the economic burden of residents and implements innovative reform measures to promote efficiency (18).

Many countries and regions around the world have implemented reforms aimed at improving the service efficiency of PHCIs. For instance, Singapore implemented a regional health system that aims to promote the integration of different levels of medical systems (19). Meanwhile, the State of Maryland in the US implemented a patient-centered medical home model aimed at improving the efficiency of PHCIs and reducing costs and later proved that this model can improve health outcomes and increase cost savings (20). Moreover, Reforming PHCIs has always been an important goal of China's health system reform.

Reform of PHC in China

China's health system mainly consists of three-level health service networks in rural areas (village clinics, township hospitals, and county-level hospitals) and two-level health service networks in urban areas (community health service centers and hospitals). In the 1960s and 1970s, relying on the rural collective economy, cooperative medical care, barefoot doctors and the three-level health service network constituted the principle of primary health service (21). It actively promoted people's health and was even praised by the WHO (22–24). In 2003, China implemented a new rural cooperative medical system that consolidates its disintegrating cooperative medical system by expanding its financing scale. However, relevant studies have pointed out that this new system has not fundamentally solved the challenge being faced by China's existing health systems (25).

In 2009, China implemented a comprehensive and relatively thorough health care reform that initially had five priorities, namely, to expand the coverage of medical insurance, to establish an essential drug system, to improve the ability of PHCIs, to promote public health services and to strengthen the reform of public hospitals (26). Among these priorities, strengthening PHC to achieve a universal coverage of basic medical services is an important goal of the reform. During the first 3 years of the reform, the government invested $230 billion, of which about 44% was allocated to PHCIs to provide primary health services (27).

Some studies have analyzed the impact of China's medical reform since 2009 on the efficiency of PHCIs. For instance, Kaili Zhong et al. pointed out that the health resources in the rural PHCIs of Hunan Province increased after the implementation of this reform, but the PHCIs in most counties remained ineffective (5). Yao Leng et al. found that the quantity of health resources and the service efficiency of PHCIs significantly increased after the reform, but the change in management was not obvious (28).

However, the indicators used in these studies were the absolute level of service, and no research has examined the longitudinal changes in the level of service counts of PHCIs relative to that of the entire health service delivery system. Moreover, the differences in the economic development across Chinese provinces are relatively large. Whether the 2009 reform has significantly different effects on the efficiency of PHCIs in regions with varying levels of economic development has not yet been empirically analyzed.

The relative proportion of service counts in PHCIs can objectively and accurately reflect the changes in the capacity and status of PHCIs in the entire health service system. Data from 2005 to 2017 show that the absolute number of outpatients and inpatients in China's PHCIs is growing, but their proportion in the health system exhibits a downward trend compared with tertiary hospitals (29). In addition, the utilization of health services will naturally increase along with improvements of people's ability to pay and their health care awareness. Therefore, this relatively natural service growth may overstate the efficiency of PHCIs and the impact of the reform.

The purpose of this study was (1) to evaluate the changes in the efficiency of PHCIs across various provinces of China before and after the reform since 2009 and to determine the impact of the reform on such efficiency and (2) to analyze whether the relationship between reform and efficiency is significantly differs across provinces with varying economic development levels.

METHODS

Data Sources

The data used in the study were collected from the China Statistical Yearbooks and China Health Statistical Yearbooks

published between 2006 and 2019. These yearbooks provide statistical data on the national and provincial economic, social and health services of China over the past 20 years. These data can be downloaded from public official websites. Under a strict statistical system, the data collection for each province or county is compulsory and is performed by statistical bureaus at all levels. Therefore, no missing data were reported for all variables, provinces and counties. The data used in this study were from the longitudinal data of 2006–2019 of the above two databases.

Variables and Definitions

In terms of inputs, the main variables selected in the study were the number of beds, health technicians (HTs), and PHCIs per thousand population. These indicators have always been the focus of the policy-making agencies, thereby validating the appropriateness and policy significance of the selected indicators. Previous studies have also used these indicators to evaluate service efficiency (13).

As for the outputs, the number of outpatients and inpatients represent the ability of health institutions to diagnose and treat common and relatively complex diseases. These indicators have also been the focus of policies. The ratio of output in PHCIs to the entire health system was used as another output in this study given its ability to reflect changes in the capabilities of PHCIs in the entire health system. This ratio was selected in line with the objective of increasing the PHC utilization rate in China as emphasized by the 2009 reform. The number of diagnosis and treatments in township hospitals (DToTH), community health service centers (stations) (DToCHC) and hospitals (DToH) and the number of admissions in township hospitals (AoTH), community health service centers (stations) (AoCHC), and hospitals (AoH) were also treated as outputs. The proportion of diagnosis and treatments (PoDT) and the proportion of inpatients (PoIs) in PHCIs were computed as:

$$\mathrm{PoDT} = \frac{\mathrm{DToTH} + \mathrm{DToCHC}}{\mathrm{DToTH} + \mathrm{DToCHC} + \mathrm{DToH}}$$

$$\mathrm{PoIs} = \frac{\mathrm{AoTH} + \mathrm{AoCHC}}{\mathrm{AoTH} + \mathrm{AoCHC} + \mathrm{AoH}}$$

In the covariates, per capita GDP, population, old dependency ratio (ODR), and urbanization rate were used as continuous variables that represent the economic level, total population, aging degree, and urbanization level of a region, respectively. GDP per capita and population were treated logarithmically to alleviate the heteroscedasticity. The reform was included as a binary variable according to time. **Table 1** shows the names, definitions, and codes of variables.

Statistical Method

First, the input–output and external factors of the whole country were calculated as the mean and extremum, respectively, to observe the overall changes. Furthermore, the graphic method was used to directly describe the specific changes in the input and output variables within and between provinces.

Second, Malmquist DEA was used to calculate the efficiency of PHCIs in each province. Malmquist productivity index (MPI), which belongs to the framework of non-parametric DEA, is commonly used to evaluate the vertical productivity of decision-making units. The output orientation was adopted in this work because the input is relatively fixed in a short time. This orientation is also in line with the objective of improving the ability of the health system to use existing health resources. Malmquist productivity index (MPI) was used to calculate the changes in the productivity of PHCIs across various provinces over time, which was further decomposed into efficiency change (EC) and potential technology change (TC). TC indicates that the use of new technologies promotes the movement of efficiency boundaries, hence highlighting the role of innovation (30, 31). EC refers to the "catch-up" effect, which is often related to the influence of the management level (32, 33). A value of MPI or any of its components that is greater than (less than) 1 indicates an improvement (deterioration) in performance over the analysis interval (34).

Finally, the regression method of panel data was performed to analyze the impact of the reform and other factors on the efficiency of PHCIs. A series of tests of panel data modeling was applied to identify the appropriate models to analyze the impact of reform on the efficiency of PHCIs. First, an F-test was used to check the appropriateness of using the pool effect least square method. Under the condition of rejecting the null hypothesis ($p < 0.05$), the Hausmann test was conducted to choose fixed and random effects. Results of the Hausmann test showed that the fixed effect model was more suitable when the null hypothesis is rejected; otherwise, the random effect model was more suitable. In addition, the interaction term of reform and per capita GDP was also added to the appropriate model to check for any significant difference in the impact of the reform on provinces with different economic development levels.

RStudio software was used to draw pictures. DEAP2.1 software was used to calculate MPI, EC, and TC in PHCIs. STATA software 13 was used to manipulate panel data models. Statistical significance was set at $p < 0.05$.

Ethical Approval

Given that all the data used are publicly available, ethical approval was not required for this study.

RESULTS

Table 2 shows the changes in the national input–output indicators and external factors from 2005 to 2018. On average, HTs, beds, and PHCIs increased from 2005 to 2018. PoIs increased before the reform but decreased after the reform. The same trend was observed for PoDT, but the change in proportion was smaller than that of PoIs. As far as the range of input–output changes were concerned, the beds and HTs were on the rise, among which beds exhibited a larger fluctuation range. By contrast, the PoDT and PoIs showed a downward trend. In terms of external factors, per capita GDP still rose after adjusting for CPI, and the same trend was observed for population, ODR, and urbanization rate.

Figure 1 shows the changes in the input–output of each province from 2005 to 2018. Amongst them, Guangxi, Hebei,

TABLE 1 | Definition of input–output and control variables.

	Variables	Definition
Input	Beds	Number of primary health service beds per 1,000 population
	HTs	Number of health technicians in primary health services per 1,000 population
	PHCIs	Number of primary health facilities [including township hospitals and community health service centers (stations)] per 1,000 population
Output	PoDT	The proportion of number of diagnosis and treatment of PHCIs in the total number of the province
	PoIs	The proportion of inpatients in PHCIs in the total number of inpatients in the province
Control variables	GDP	Per capita GDP (adjusted according to CPI)
	Urbanization rate	Proportion of urban population
	Population	Provincial total population
	ODR	The ratio of the population over 65 to the population between 15 and 64
	Reform	Prior to 2008–2009 (excluding 2008–2009), it was assigned a value of 0, and other years were assigned a value of 1.

Gansu, Guizhou, Inner Mongolia, Qinghai, Jiangxi, Shaanxi, Sichuan, Hunan, Jilin, and Chongqing demonstrated a relatively obvious trend of increasing input and decreasing output. Meanwhile, the input in Anhui, Fujian, Hainan, Henan, Heilongjiang, Liaoning, Tibet, and Yunnan increased, their PoDT did not change significantly, and their PoIs decreased. Hubei, Jiangsu, Ningxia, and Shandong showed an increase in input but no obvious change in output. In Beijing and Zhejiang, only the input HTs increased, whereas the other indicators showed no significant change. In Tianjin and Shanghai, the input beds decreased, while the output PoDT did not change and the PoIs obviously decreased. Differences were observed in the trends for economically developed regions and for those regions with lower economic levels, thereby suggesting that the reform may have an interactive effect with per capita GDP.

Figure 2 shows a horizontal comparison of each input–output indicator across various provinces. Zhejiang, Shandong, Hubei, Jiangsu, and Hunan always maintained high HTs, whilst the HTs in Yunnan, Ningxia, Heilongjiang, Guizhou, Tibet, Qinghai, Beijing, Inner Mongolia, Shaanxi, Guangxi, and Gansu rapidly increased. Beds in Beijing, Shanghai, Zhejiang, Tianjin, and Guangdong were low, whereas those in Sichuan, Hubei, Hunan, Chongqing, Xinjiang, Guangxi, Guizhou, Gansu, Yunnan, and Qinghai grew rapidly. The number of primary health institutions did not change remarkably. Regarding PoDT, Tianjin, Beijing, and Liaoning were always low but showed an upward trend, while the rest of the provinces gradually declined. Amongst these provinces, Sichuan, Chongqing, Guizhou, and Guangxi reported larger declines. With respect to PoIs, Hunan, Guizhou, Guangxi, Chongqing, Jiangxi, Sichuan, Anhui, Fujian, Gansu, Shandong, and Yunnan rose before the reform but declined after the reform, whereas Tianjin, Ningxia, Beijing, Shanghai, and Zhejiang were low. The input–output indicators varied greatly in regions with different economic conditions, which also suggested that the impact of reforms may be affected by economic levels.

Table 3 describes the efficiency in PHCIs in various provinces before and after the reform. At the national level, the EC, TC, and MPI all decreased after the reform, with EC reporting the largest reduction. On average, MPI in Beijing, Tianjin, Shanghai, Hunan, and Guangdong improved after the reform but showed a trend of deterioration in other provinces. The efficiency improvement of Beijing, Tianjin, and Shanghai was mainly the growth of TC, while that of Guangdong and Hunan was mainly the growth of EC. Hebei, Heilongjiang, Shandong, Henan, Chongqing, Guizhou, Yunnan, Tibet, Gansu, and Qinghai showed a deterioration in EC and TC. The deterioration of MPI in Shanxi, Inner Mongolia, Jilin, Jiangsu, Zhejiang, Hainan, and Ningxia was mainly due to EC, whereas the deterioration of MPI in Liaoning, Anhui, Fujian, Jiangxi, Hubei, Guangxi, Sichuan, and Xinjiang was mainly due to TC.

Table 4 shows the relationship amongst MPI, TC, EC, and the reform and external factors in PHCIs. Models (1)–(3) show the impact of the reform on primary health service efficiency in MPI, TC, and EC, respectively. Models (4)–(5) show the interaction of reform and GDP per capita on the efficiency of primary health services in MPI, TC, and EC, respectively. The reform had a significant negative effect on MPI, TC, and EC of PHCIs. The population had a significant positive effect on MPI and TC. It was also found that per capita GDP had a significant interaction between the reform and MPI and TC of efficiency of PHCIs, that is, the adverse impact of reform on MPI and TC in relatively developed areas was less than that in economically underdeveloped areas.

DISCUSSION

This study measured the efficiency of PHCIs at the provincial level in China and analyzed the impact of the reform since 2009 and potential external factors. Results show that the reform had not achieved the expected goal of promoting the efficiency of PHCIs. Furthermore, there were significant differences among regions with different levels of economic development, and the population size could significantly improve MPI and TC in PHCIs. The relative insufficiency of government investment, the fragmentation of health service delivery system, and the lack of reform coordination could be the factors for these results.

Compared with hospitals, the government's investment in PHCIs is relatively insufficient, which may have contributed to

TABLE 2 | Changes in input–output and external factors of PHC in China before and after the reform in 2009.

Period		Inputs			Outputs			Other external factors		
		HTs	Beds	PHCIs	PoDT	PoIs	GDP	Population	ODR	Urbanization rate
2005	Mean	0.669	0.524	0.052	0.361	0.219	14364.8	4139.5	12.23	45.41
	Max	1.123	1.056	0.246	0.513	0.404	46331.2	9380	16.24	89.09
	Min	0.344	0.214	0.013	0.120	0.053	4526.8	277	8.64	26.65
2006	Mean	0.680	0.568	0.057	0.382	0.235	16450.9	4165.5	12.4	46.42
	Max	1.073	1.095	0.242	0.663	0.414	51513.4	9392	18.6	88.7
	Min	0.394	0.258	0.013	0.125	0.049	5185.5	281	8.51	27.46
2007	Mean	0.751	0.611	0.059	0.375	0.268	19216.2	4190.9	12.57	47.35
	Max	1.163	1.015	0.239	0.523	0.475	58063.9	9449	18.32	88.7
	Min	0.489	0.262	0.020	0.186	0.033	6081.8	284	8.88	28.24
2008	Mean	0.811	0.694	0.060	0.395	0.279	20142.9	4220.2	12.76	48.20
	Max	1.198	1.054	0.234	0.526	0.501	58318.6	9544	17.33	88.6
	Min	0.503	0.252	0.025	0.216	0.027	7042.4	287	9.16	22.61
2009	Mean	0.886	0.772	0.061	0.387	0.278	20083.6	4247.1	12.82	49.11
	Max	1.230	1.207	0.229	0.498	0.506	58221.9	9638	17.97	88.6
	Min	0.537	0.268	0.030	0.249	0.028	7385.7	290	9.23	23.8
2010	Mean	0.938	0.827	0.064	0.389	0.252	20602.1	4302.7	11.41	50.95
	Max	1.242	1.320	0.227	0.496	0.466	50837.4	10441	16.17	89.3
	Min	0.566	0.219	0.031	0.246	0.021	8332.3	300	7.22	22.7
2011	Mean	0.971	0.853	0.062	0.374	0.224	21674.6	4323.9	11.52	52.17
	Max	1.292	1.406	0.225	0.467	0.418	50990.2	10505	17.36	89.3
	Min	0.591	0.219	0.033	0.241	0.019	9064.7	303	6.71	22.7
2012	Mean	1.005	0.906	0.062	0.372	0.212	21762.3	4348.0	12.05	53.43
	Max	1.406	1.511	0.221	0.492	0.404	51388.1	10594	18.26	89.3
	Min	0.609	0.229	0.033	0.245	0.017	9590.8	308	7.5	22.75
2013	Mean	1.036	0.926	0.062	0.367	0.197	21725.6	4371.5	12.49	54.45
	Max	1.481	1.544	0.220	0.477	0.415	52052.3	10644	18.62	89.6
	Min	0.667	0.215	0.033	0.231	0.014	9967.5	312	7.23	23.71
2014	Mean	1.056	0.945	0.061	0.355	0.176	21819.8	4395.0	12.95	55.55
	Max	1.408	1.572	0.216	0.477	0.371	53079.4	10724	20.04	89.6
	Min	0.687	0.210	0.032	0.226	0.009	10413.2	318	7.86	25.75
2015	Mean	1.079	0.958	0.061	0.350	0.166	21341.1	4422.2	13.67	56.64
	Max	1.456	1.584	0.213	0.464	0.342	53583.7	10849	18.69	87.6
	Min	0.714	0.203	0.032	0.218	0.008	10534.3	324	8.07	27.74
2016	Mean	1.108	0.967	0.061	0.341	0.160	21397.5	4451.1	14.22	57.85
	Max	1.506	1.601	0.208	0.451	0.325	55946.4	10999	19.79	87.9
	Min	0.727	0.203	0.032	0.211	0.008	10381.8	331	7.01	29.56
2017	Mean	1.152	1.020	0.061	0.340	0.158	21591.9	4478.5	15.08	58.98
	Max	1.521	1.670	0.205	0.445	0.314	57222.5	11169	20.6	87.7
	Min	0.778	0.202	0.032	0.216	0.008	10390.8	337	8.22	30.89
2018	Mean	1.188	1.047	0.061	0.330	0.147	21813.3	4504.9	15.69	59.99
	Max	1.572	1.717	0.201	0.422	0.292	58075.1	11346	22.69	88.1
	Min	0.791	0.222	0.032	0.191	0.008	10799.6	344	8.04	31.14

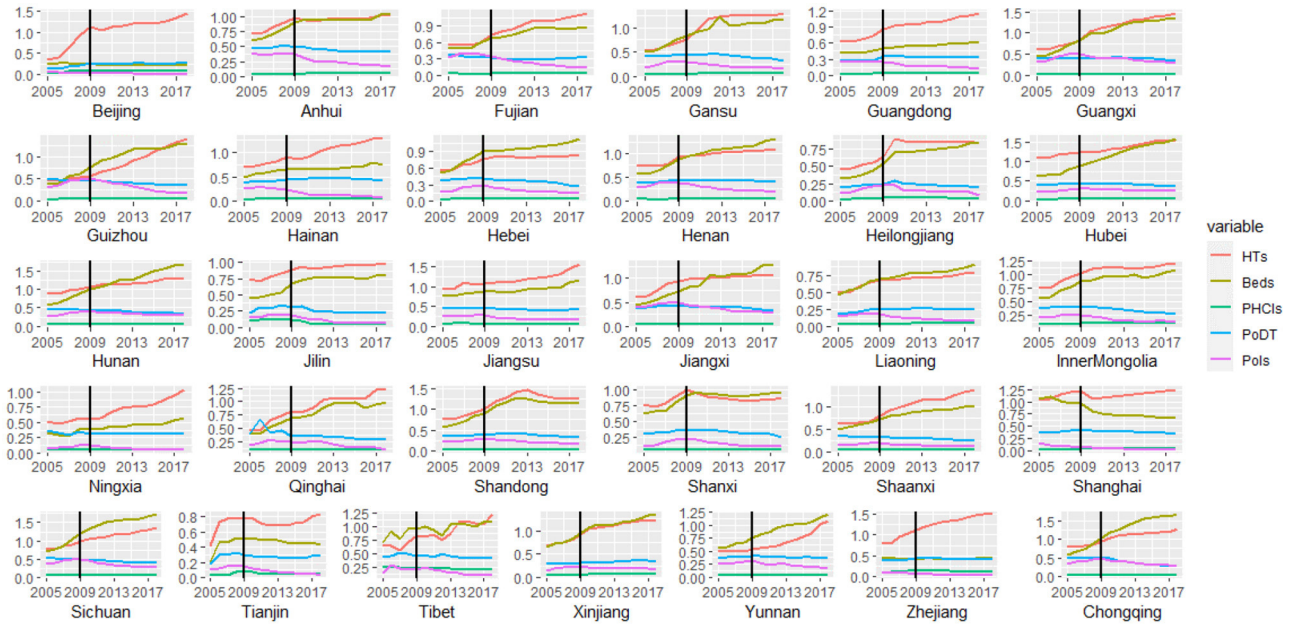

FIGURE 1 | Changes in input and output of China's provinces in 2005–2018.

the decline in the efficiency of PHCIs. In terms of infrastructure, from 2010 to 2018 after the reform, the number of primary medical institutions, the number of beds per thousand and the number of health technicians per thousand increased by 4.65, 57.8, and 21% respectively, whereas the indicators of hospitals in the same period increased by 25.3, 77.15, and 38.1% respectively (29). Regarding the growth rate, hospitals were much higher than PHCIs. These gaps in health infrastructure investment indicate that government investment in China remains focused on hospitals. Previous studies showed that township and village clinics provide the correct treatment time for only 38% and 28% patients with TB, respectively (35). And village doctors failed to ask the recommended questions for the diagnosis of the disease 82% of the time for patients with unstable angina (36). Another study pointed out that 26% of patients do not trust community health service centers, which is higher than 6% of hospitals (37). Thus, this poor quality of service and distrust may enforce patients to seek medical services in hospitals.

The fragmented service system may lead to a competition between hospitals and PHCIs for patients, which may prompt the former to offer a larger number of service relative to PHCIs due to their stronger competitiveness. In the early stage of the reform, PHCIs and hospitals were independent institutions. In terms of finance, 90% of the income of hospitals depends on the services they provided (38). The financial income of the hospitals is not affected by PHCIs but is related to patients. Therefore, hospitals have stronger motivation to compete for patients, and their competitiveness is stronger than PHCIs. In addition, in the early stage of the reform, the medical insurance payment system of PHCIs and hospitals was based on fee for service, which triggered a to the impetus of competition amongst institutions for patients. For financial gain, medical institutions tried to retain their patients rather than transfer them to the appropriate institutions. The government introduced new payment methods such as payment by disease type and global budget. However, these payments are mainly based on specific institutions rather than population (38). Thus, a corresponding coordination mechanism is lacking. Recently, the government launched the "Medical Association" of rural three-level service network and "Medical Community" of the urban two-level service network and implemented the global budget within the organization (39, 40). The effect of such implementation still needs a long time to be observed and evaluated accurately.

The fragmented health delivery system is also reflected in the duplication of its functions, which may lead to a homogenization competition amongst different levels of medical institutions. At present, the subsidy for public health services is directly paid by the central and local governments to PHCIs according to the per capita standard (41). As the economic incentives generated by the provision of public health services in PHCIs depend on the number of permanent residents in the jurisdiction, such provision cannot generate additional economic incentives. Moreover, public health services require a longer time to improve the health outcomes of the population. However, on the basis of the number of services provided by PHCIs, it could generate direct benefits and improve the health outcome of patients immediately. Therefore, PHCIs generally pay more attention to medical treatment than prevention and health management.

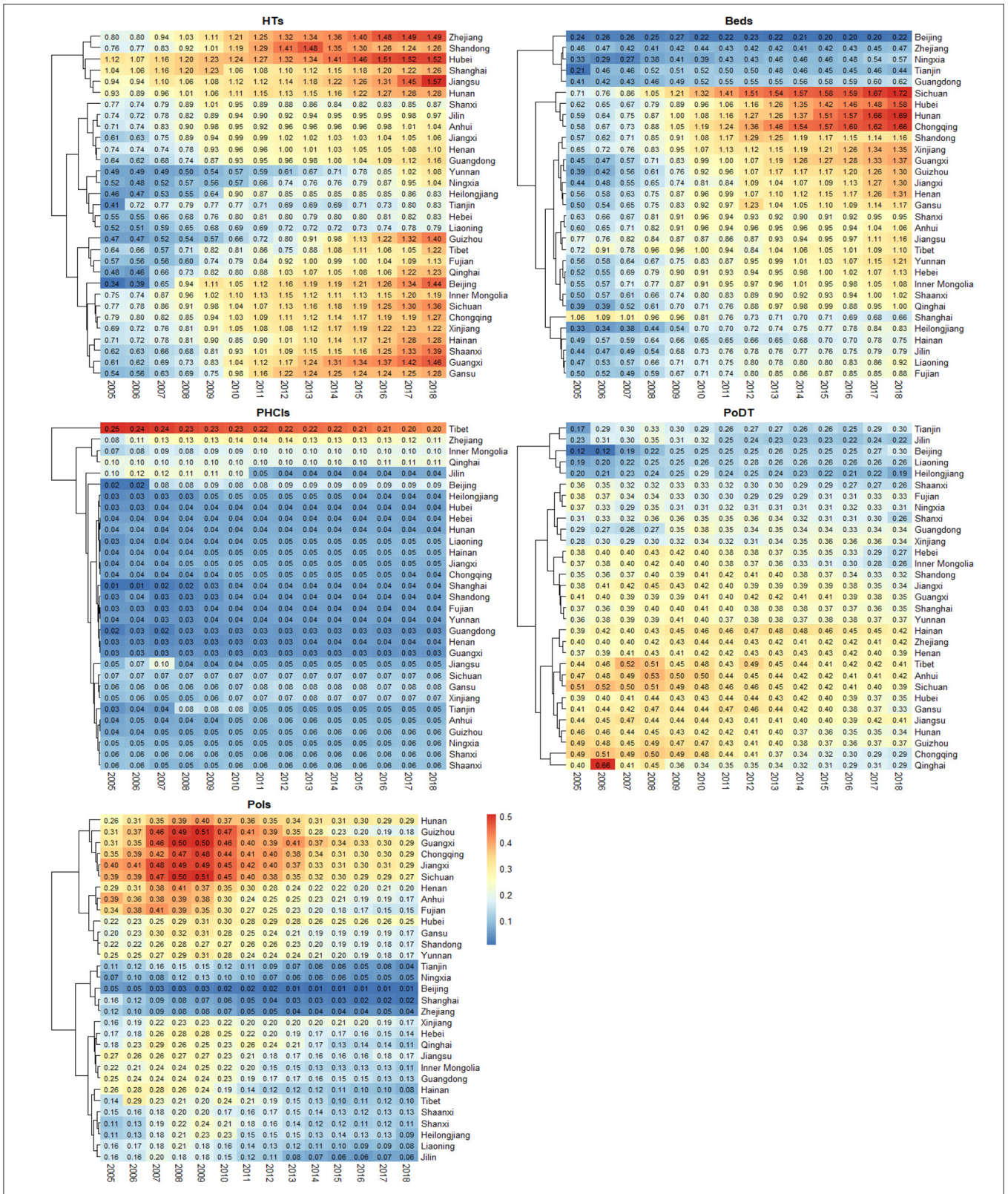

FIGURE 2 | Provincial comparison of input–output indicators in 2005–2018.

TABLE 3 | Efficiency of PHCIs in provinces before and after the reform in 2009.

Province	Before the reform			After the reform			Difference		
	EC	TC	MPI	EC	TC	MPI	EC	TC	MPI
Beijing	1.155	0.879	1.020	1.017	1.019	1.036	−0.138	0.14	0.016
Tianjin	1.042	0.933	0.967	1.037	0.945	0.979	−0.005	0.012	0.012
Hebei	1.006	0.977	0.983	1.002	0.941	0.943	−0.004	−0.036	−0.04
Shanxi	1.061	0.933	0.985	1.032	0.938	0.966	−0.029	0.005	−0.019
Inner Mongolia	1.058	0.894	0.937	0.995	0.925	0.920	−0.063	0.031	−0.017
Liaoning	1.008	1.012	1.016	1.047	0.936	0.979	0.039	−0.076	−0.037
Jilin	1.186	0.909	1.056	0.991	0.945	0.938	−0.195	0.036	−0.118
Heilongjiang	1.036	0.928	0.953	0.994	0.913	0.908	−0.042	−0.015	−0.045
Shanghai	1.000	0.860	0.860	0.992	0.967	0.960	−0.008	0.107	0.1
Jiangsu	1.097	0.894	0.978	1.003	0.961	0.963	−0.094	0.067	−0.015
Zhejiang	1.189	0.919	1.007	1.000	0.984	0.984	−0.189	0.065	−0.023
Anhui	1.000	0.967	0.964	1.006	0.939	0.944	0.006	−0.028	−0.02
Fujian	0.980	1.041	1.022	1.000	0.925	0.924	0.02	−0.116	−0.098
Jiangxi	0.976	0.971	0.948	1.008	0.905	0.911	0.032	−0.066	−0.037
Shandong	1.054	0.972	1.026	0.988	0.959	0.947	−0.066	−0.013	−0.079
Henan	1.018	1.024	1.044	1.000	0.954	0.954	−0.018	−0.07	−0.09
Hubei	0.997	0.966	0.962	1.000	0.958	0.958	0.003	−0.008	−0.004
Hunan	0.980	0.949	0.930	1.018	0.933	0.949	0.038	−0.016	0.019
Guangdong	0.931	0.974	0.913	1.028	0.955	0.981	0.097	−0.019	0.068
Guangxi	1.000	1.017	1.017	1.000	0.938	0.938	0	−0.079	−0.079
Hainan	1.038	0.946	0.980	1.012	0.960	0.971	−0.026	0.014	−0.009
Chongqing	1.005	0.974	0.978	1.001	0.924	0.925	−0.004	−0.05	−0.053
Sichuan	0.967	1.022	0.983	1.022	0.909	0.928	0.055	−0.113	−0.055
Guizhou	1.000	1.000	1.000	0.974	0.894	0.870	−0.026	−0.106	−0.13
Yunnan	1.047	0.981	1.026	0.996	0.931	0.927	−0.051	−0.05	−0.099
Tibet	1.110	0.991	1.051	1.014	0.930	0.944	−0.096	−0.061	−0.107
Shaanxi	1.027	0.923	0.940	0.999	0.931	0.929	−0.028	0.008	−0.011
Gansu	1.021	0.940	0.954	0.999	0.921	0.920	−0.022	−0.019	−0.034
Qinghai	1.035	0.959	1.033	0.976	0.917	0.895	−0.059	−0.042	−0.138
Ningxia	1.051	0.914	0.944	0.984	0.957	0.941	−0.067	0.043	−0.003
Xinjiang	1.035	0.966	0.997	1.040	0.925	0.962	0.005	−0.041	−0.035
China	1.036	0.956	0.983	1.006	0.940	0.945	−0.03	−0.016	−0.038

Previous studies showed that the hospital admission rate of hypertension in China is the highest in all OECD countries (42–44). These results indicate that the PHCIs did not achieve the expected goal in delivering basic public health services. These factors aggravated the adverse effects of fragmentation of the health delivery system and the imbalanced resource allocation on PHCIs.

The poor coordination between the reform policies also impedes efficiency improvements in PHCIs. As one of the five priorities of the reform in 2009, the essential drug system aims to reduce the price and promote the accessibility of drugs by publishing a list of commonly used drugs, bidding for the drugs in the list, allocating them to PHCIs, and selling them to patients in accordance with zero mark-up. However, this system brought more adverse effects on PHCIs. Before the implementation of this system, the drug income of PHCIs accounted for more than 50% of its total income, and the zero mark-up for drugs led to a greater decline in the income of institutions and PHCIs physicians (45). In a study of three provinces, the reported income of doctors in Tianjin township hospitals decreased by 15%, whereas that of doctors in Ningxia township hospitals and village clinics decreased by 17% and 22%, respectively (46). Furthermore, after the implementation, those pharmaceutical enterprises with the lowest quotation were often selected for bidding procurement, which also reduced the profits of these pharmaceutical enterprises and limited the stable production capacity of pharmaceutical manufacturers, thereby preventing a timely and effective supply of medicines in PHCIs (46). A study in Beijing pointed out that only 59.7% of traditional Chinese medicine and 49.1% of western medicine in the essential medicine list were stored in community health service centers due to the shortage of drugs (47). The adverse effects of the essential drug system on PHCIs have prompted patients to seek treatment in hospitals.

TABLE 4 | The impact of reform and external factors on the efficiency of PHCIs.

	Model (1) MPI	Model (2) TC	Model (3) EC	Model (4) MPI	Model (5) TC	Model (6) EC
lnGDP	−0.094	−0.044	0.032	−0.016	−0.049**	0.046*
	(0.063)	(0.040)	(0.023)	(0.025)	(0.020)	(0.026)
lnpopulation	0.261*	0.393***	−0.003	−0.000	0.002	−0.002
	(0.128)	(0.090)	(0.006)	(0.005)	(0.004)	(0.006)
Urbanization rate	0.003	0.002	−0.001	−0.000	−0.000	−0.000
	(0.002)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
ODR	−0.002	0.000	−0.001	−0.000	0.001	−0.001
	(0.002)	(0.002)	(0.002)	(0.002)	(0.001)	(0.002)
Reform(ref:0)	−0.060***	−0.048***	−0.030***	−0.764***	−0.894***	0.193
	(0.012)	(0.013)	(0.010)	(0.186)	(0.148)	(0.193)
Reform interact				0.076***	0.092***	−0.023
With lnGDP				(0.020)	(0.016)	(0.020)
_cons	−0.332	−1.894**	0.789***	1.152***	1.390***	0.651***
	(1.322)	(0.833)	(0.192)	(0.218)	(0.173)	(0.226)
Obs.	403	403	403	403	403	403

Standard errors are in parenthesis.
Fixed effect models are used in models 1 and 2 because both the F test and the Hausmann test reject the null hypothesis. Pooled ordinary least squares was applied to models 3–6 because the F test could not reject the null hypothesis.
****p < 0.01, **p < 0.05, *p < 0.1.*

The more effective reform practices and innovation measures in economically developed areas may explain the regional imbalance of the reform effect. Provinces in China have varying economic development levels and show obvious differences in their PHCIs. Specifically, economically developed areas tend to face less resistance to reform given their excellent health infrastructures. Therefore, these areas are more likely to adopt a series of innovative measures compared with their counterparts. For example, Zhejiang Province has established a full-cycle health management and referral service model for hypertension and diabetes patients. Beijing initiated a comprehensive reform of the separation of medical treatment and medicine, focusing on improving the content and quality of PHC. Shanghai launched diversified care services and cognitive impairment care services for its deeply aging population structure. These measures have a better implementation basis in areas with relatively rich primary health resources and promote the efficiency boundary of PHCIs to move forward to a certain extent, thereby alleviating the adverse impact of the medical reform on the technical efficiency of PHCIs in 2009.

Given that areas with larger populations have greater demand for basic health services, so the continuous accumulation of experience may promote a continuous improvement in the technical level of primary health institutions. Given that PHCIs mainly provide basic medical services for common and frequently-occurring diseases, these services are less difficult than the medical services provided in hospitals. Therefore, relatively more basic medical needs in areas with larger populations may accumulate more experience, and related studies have also pointed out that "learning by doing" is an important way of technological progress. Accumulating long-term experience may promote the advancement of basic medical technology in PHCIs.

To estimate and improve the efficiency of PHCIs, research on the perspective of health service delivery systems by using relative indicators can propose systematic and holistic suggestions for improving the efficiency of the primary health service system. Such work has implications for other developing countries and regions. Moreover, the analysis of the impact of economic level on the relationship between reform and the efficiency of PHCIs can provide insights for different regions to develop highly more accurate intervention measures, which can be used as reference by countries and regions with unbalanced economic development level.

Limitations

Firstly, village clinics, outpatient departments and school hospitals were excluded from this study. Whilst these institutions are parts of the PHC network, before the reform, the health service data of these institutions were missing from the China Health Statistics Yearbook. To ensure that the data before and after the reform are consistent, this study decided to exclude these institutions from the analysis. Given that previous studies have also pointed out that township hospitals and community health service centers are the main components of PHCIs, excluding these institutions only had little impact on the findings of this work.

Secondly, to calculate the relative value, this study added the hospital service number into the denominator but could not use the service number of the whole PHCIs. Before the reform, there was no service number and summary data about the whole PHC, so this study included the service number of hospitals in the denominator to ensure the comparability of data before and after the reform. Given that hospitals in China are the most important part of both the urban two- and rural three-level health

service networks, so this calculation method can accurately reveal relative changes.

Finally, this study did not consider public health indicators as input–output indicators. PHCIs in China provide basic medical and public health services. However, given the unavailability of public health data in various provinces, this study only included medical service indicators.

Conclusions

The reform since 2009 did not achieve the expected goal of improving the efficiency of PHCIs. In the follow-up reforms, the following measures are necessary: (1) to continue to increase the investment in PHCIs to narrow the gap with hospitals, (2) establish a structurally integrated and functionally complementary delivery system, and (3) avoid the adverse impacts of other policies on the efficiency of primary health services. It should be noted that in terms of the selection of output indicators or the use of methods, the efficiency value calculated in our study is relative efficiency.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://data.cnki.net/area/yearbook/single/n2012090077?z=d09; http://www.stats.gov.cn/tjsj/ndsj/.

AUTHOR CONTRIBUTIONS

CY conceived the idea and wrote framework and manuscript of the paper. HL and YM collected and sorted the data. JW critically revised the paper. All authors have read and approved the final manuscript.

FUNDING

This research was supported by National Natural Science Foundation of China (72074086 and 71673093). The publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

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frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 25 October 2021
doi: 10.3389/fphar.2021.741724

Pharmacist-Led Intervention on the Inappropriate Use of Stress Ulcer Prophylaxis Pharmacotherapy in Intensive Care Units: A Systematic review

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OPEN ACCESS

Edited by:
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Reviewed by:
Haitham Jahrami, Arabian Gulf University, Bahrain
Ali Ahmed, Monash University Malaysia, Malaysia

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *15 July 2021*
Accepted: *08 October 2021*
Published: *25 October 2021*

Citation:
Xu P, Yi Q, Wang C, Zeng L, Olsen KM, Zhao R, Jiang M, Xu T and Zhang L (2021) Pharmacist-Led Intervention on the Inappropriate Use of Stress Ulcer Prophylaxis Pharmacotherapy in Intensive Care Units: A Systematic review Front. Pharmacol. 12:741724. doi: 10.3389/fphar.2021.741724

Background: Pharmacist's direct intervention or participation in multidisciplinary management teams can improve the clinical outcome and quality of life of patients. We aimed to determine the effectiveness of pharmacist-led interventions on the inappropriate use of stress ulcer prophylaxis (SUP) pharmacotherapy in intensive care units (ICUs).

Methods: A systematic review was performed for relevant studies using searched PubMed, EMBASE (Ovid), the Cochrane Library, Cochrane Central Register of Controlled Trials (CENTRAL), and four Chinese databases from the establishment of databases to 12 March 2020. We conducted a descriptive analysis of participants, the intervention content and delivery, and the effects on inappropriate medication rates.

Results: From 529 records, 8 studies from 9 articles were included in the systematic review. The time of appropriateness judgment and the criteria of "appropriate" varied from included studies. Pharmacist interventions mainly included clarifying indications for SUP pharmacotherapy, education and awareness campaign, reviewed patients on SUP pharmacotherapy during rounds, and adjustments of drug use. Five (62.5%) studies found a significant intervention effect during hospitalization, while 2 (25%) studies at ICU transfer and 2 (25%) studies at hospital discharge. 4 (50%) studies identified the complications related to SUP pharmacotherapy and found no significant difference. 4 (50%) studies declared the pharmacist-led interventions were associated with cost savings.

Conclusion: Pharmacist-led intervention is associated with a decrease in inappropriate use of SUP pharmacotherapy during hospitalization, at ICU transferred and hospital discharged, and a lot of medical cost savings. Further research is needed to determine whether pharmacist-led intervention is cost-effective.

Keywords: pharmacist-led, stress ulcer prophylaxis, intensive care unit, systematic review, quality improvement

INTRODUCTION

With the advancement of pharmacy directed patient care, the role of pharmacists has expanded from the traditional task of distributing medications and providing basic drug information to a team-based clinical role providing patient-centered medication therapy management (Albanese et al., 2010). Many studies have confirmed that pharmacist's direct intervention or participation in multidisciplinary management teams can improve the clinical outcome and quality of life of patients by optimizing the use of drugs in different disease processes (Thomas et al., 2014; Dixon et al., 2016; Greer et al., 2016; van Eikenhorst et al., 2017; De Barra et al., 2018; McNab et al., 2018; Mes et al., 2018; Alshehri et al., 2020).

As a member of a multidisciplinary management team, pharmacists make full use of their professional knowledge and clinical experience to perform an important role in the care of intensive care unit (ICU) patients (Preslaski et al., 2013). A previous systematic review sufficiently dissected the impact on patient outcomes of pharmacist participation in multidisciplinary critical care teams (Lee et al., 2019). This paper clarified pharmacist's participation improved patient outcomes including mortality, ICU length of stay in mixed ICUs, and preventable/nonpreventable adverse drug events (Lee et al., 2019).

Patients admitted to the intensive care unit (ICU) have a risk of stress-related mucosal damage (SRMD) that may evolve into ulcers and hemorrhage (Marik et al., 2010). SRMD is apparent in 75–100% of critically ill patients within 24 h after admission to an ICU(Metz, 2000; Fennerty, 2002). And the prevalence of gastrointestinal bleeding (GIB) ranges from 5.6 to 9.0% in recent reports (Selvanderan et al., 2016; Alhazzani et al., 2017; Krag et al., 2018) and has been associated with an increased risk of death and ICU length of stay (Krag et al., 2015). Preventing potential progression from SRMD to GI bleeding, acid suppression therapies (AST) are often overused for stress ulcer prophylaxis (SUP) (Farrell et al., 2010; Frandah et al., 2014; Buckley et al., 2015; Hammond et al., 2017; Masood et al., 2018). Inconsistent recommendations on the initiation of SUP in existing guidelines, including mechanical ventilation, chronic liver disease, coagulopathy, head injury, thermal injury, and multiple trauma, *etc* (Therapeutic Guidelin, 1999; Madsen et al., 2014)). Previous studies on the prescription behaviors showed that approximate 75% of the patients received SUP during ICU stay, 14.4–42% of whom had no identifiable risk of stress ulcer (Farrell et al., 2010; Frandah et al., 2014; Buckley et al., 2015; Hammond et al., 2017; Masood et al., 2018). Although SUP has been proved effective in decreasing the incidence of gastrointestinal bleeding (Krag et al., 2014; Barbateskovic et al., 2019), it also leads to increased myocardial ischemia, Clostridium (C.) difficile infection, hospital-acquired pneumonia, increased hospitalization and prescription costs (Driks et al., 1987; Heidelbaugh and Inadomi, 2006; Grube and May, 2007; Lin et al., 2010; Marik et al., 2010; Alhazzani et al., 2013). The overuse of SUP may lead to increased adverse events, drug-drug interactions, and increased hospital and prescription costs.

Although several studies had examined the impact of pharmacist-led de-escalating SUP pharmacotherapy, they had not been reviewed. Our systematic review aimed to determine the effectiveness of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in ICUs.

METHODS

This systematic review conformed to the PRISMA statement and Synthesis without meta-analysis (SWiM) reporting guideline and was registered on PROSPERO (CRD42021239821) (Liberati et al., 2009; Campbell et al., 2020).

Eligibility Criteria

We included studies evaluating the impact of pharmacist-led interventions on the use of stress ulcer prophylaxis in patients or in the intensive care unit. We included randomized controlled trials (RCTs), cohort studies, and case-control studies. There were no restrictions on language and publication time.

Inclusion criteria followed the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework (Higgins, 2011). Participants were patients in intensive care units who were critically ill or a short stay for observation. We excluded studies that focused on all departments but did not separately provide data from ICU departments. The intervention content could be provided in part or whole by the pharmacist (i.e., the pharmacist-led). The interprofessional approaches were included only when pharmacists as part of a shared-care approach and as the primary decision makers. We included studies of any design with a comparator group of usual care or other healthcare's intervention. We included studies with the incidence pharmacotherapeutic intervention in SUP as a primary or secondary outcome. We did not limit the observation time of outcome indicators, whenever during hospitalization, at ICU discharge, or hospital discharge.

Search and Information Sources

We searched Chinese Biomedical Literature (Chinese), Cochrane Central Register of Controlled Trials (English), the Cochrane Library (English), China National Knowledge Infrastructure (Chinese), EMBASE (Ovid, English), PubMed (English), VIP (Chinese) and Wanfang (Chinese) from the establishment of databases to March 12, 2020. We obtained additional articles by hand-searching reference lists of systematic reviews and other articles and from peer-reviewers.

Our search strategy used database-specific vocabulary (e.g., Medical Subject Headings) and free-text terms text expanding from "stress ulcer", "pharmacist", and "critically ill". For "stress ulcer prophylaxis", in addition to the original expanded vocabulary, we searched clinical symptoms (such as gastrointestinal bleeding and gastric mucosal lesion) and

specific preventive drugs (including H-2 receptor antagonist, proton pump inhibitors, and sucralfate).

The search strategy was developed specifically for each database (**Supplementary Table S1**).

Study Selection

We used EndNote (version X8) reference manager for records management and duplicates removal. Two investigators (WCT and XPP) screened all titles and abstracts. Once relevant articles were screened in, two investigators (WCT and XPP) independently screened full-text articles. All inconsistent inclusion decisions were resolved through consensus with a third reviewer (YQS).

Data Collection and Quality Assessment

Study data were extracted by one investigator (WCT) using specifically developed data extraction forms and checked by another investigator (XPP). Extracted data contained: (Albanese et al., 2010): author's name, year, the country of study origin and study purpose; (De Barra et al., 2018); method (study design and information of study quality according to quality assessment criteria of different types of studies); (Mes et al., 2018); participant and setting (sample size, age, inclusion and exclusion criteria, indications for the use and cessation of SUP pharmacotherapy, the definition of rational use, and setting); (Greer et al., 2016); intervention (composition, implementer, and formation method); (Alshehri et al., 2020); outcomes (the incidence of the inappropriate use of SUP pharmacotherapy, cost of medications used for SUP, and complications of SUP pharmacotherapy; and (McNab et al., 2018) confirmation of eligibility for review.

We used the Newcastle-Ottawa Scale for assessing the risk of bias of cohort studies (Peterson et al., 2011).

Data Synthesis and Analysis

The primary outcome was the incidence of inappropriate use of SUP pharmacotherapy. Secondary outcomes included complications related to SUP pharmacotherapy and economic outcomes.

As the heterogeneity of the research inclusion criteria, the denominator was inconsistent when calculating the inappropriate rate. Some studies use all patients in the ICU as the denominator, while others use the patients receiving SUP pharmacotherapy during ICU hospitalization. Therefore, we recalculated the rate using the SUP pharmacotherapy population during ICU hospitalization as the denominator to get the standardized metric. We excluded patients with chronic AST prior to admission if there was no reconsideration of the appropriateness of chronic AST.

Due to the expected heterogeneity of participants, interventions, and the definition of inappropriate, it was hard to group studies for synthesis and undertake a meta-analysis. Instead, we conducted a descriptive analysis of participants, the intervention content and delivery, and the effects on inappropriate medication rates. And as recommended by the Cochrane handbook for systematic reviews of interventions, we used vote counting, in which the number of favorable studies is counted and compared with the number of unfavorable studies (Cumpston et al., 2019). Specifically, studies were assessed according to whether or not they found statistically significant evidence supporting the appropriate use of SUP pharmacotherapy: effectiveness (the inappropriate rate at initiation, ICU transfer and hospital discharge), safety (not increase the incidence of complications), and economy. The balance of positive vs. negative studies was used to determine the answer to the review questions.

As we we adjusted the denominator to recalculate the rate, we didn't rely on *p*-values reported by the authors of the primary studies. Chi-square tests were used for categorical group comparisons based on pre- and post-intervention groups. Data were analyzed using IBM SPSS Statistics for Windows v22.0 (IBMCorp., Armonk, NY). p-values<0.05 were considered statistically significant. For economic outcomes, we unified the monetary unit to the United States dollar (1 Australischer Dollar = 0.778 US Dollar; 1 Canadian dollar = 0.7891 United States Dollar).

RESULTS

Study Selection

A total of 529 studies were retrieved from the databases. From the total, 478 studies were excluded based on titles and abstracts and 12 studies were excluded based on full-text articles (**Figure 1**). Primary reasons for exclusion were non-ICU, non-pharmacist-led intervention, non-SUP-related medications, cannot extract ICU data separately, reviews, case reports, and duplicate literature (**Figure 1**). We included 8 studies from 9 articles in the narrative synthesis (Coursol and Sanzari, 2005; Wohlt et al., 2007; Hatch et al., 2010; Tasaka et al., 2014; Buckley et al., 2015; Guobin et al., 2015; Hammond et al., 2017; Masood et al., 2018; Anstey et al., 2019). All studies were cohort studies, of which 6 (75.0%) were retrospective and the other 2 (25.0%) were prospective. Observation periods ranged from 2 weeks to 6 months. All studies assessed appropriateness during ICU hospitalization. In addition, 4 (50.0%) studies assessed appropriateness at ICU transfer and hospital discharge at the same time (**Table 1**).

Participant Characteristics

Most studies included adult patients (6, 75.0%) and the other 2 (25.0%) did not specify the study population (**Table 2**). Regarding the type of ICU, 2 (25.0%) studies included patients in medical and surgical ICUs, 2 (25.0%) studies only included patients in medical ICU, and the other 4 (50.0%) studies did not specify the ICU category. 5 (62.5%) studies included all patients admitted to the ICU, while 3 (37.5%) studies only focused on patients who received AST. Inclusion criteria varied between studies but most of them (5, 62.5%) excluded patients having an additional indication for AST (e.g., active GIB, active peptic ulcer disease, and Zöllinger-Ellison syndrome) or they were not indicated for SUP pharmacotherapy regardless of risk factors (e.g., total gastrectomy) (Coursol and Sanzari, 2005; Hatch et al., 2010; Tasaka et al., 2014; Buckley et al., 2015; Hammond et al., 2017).

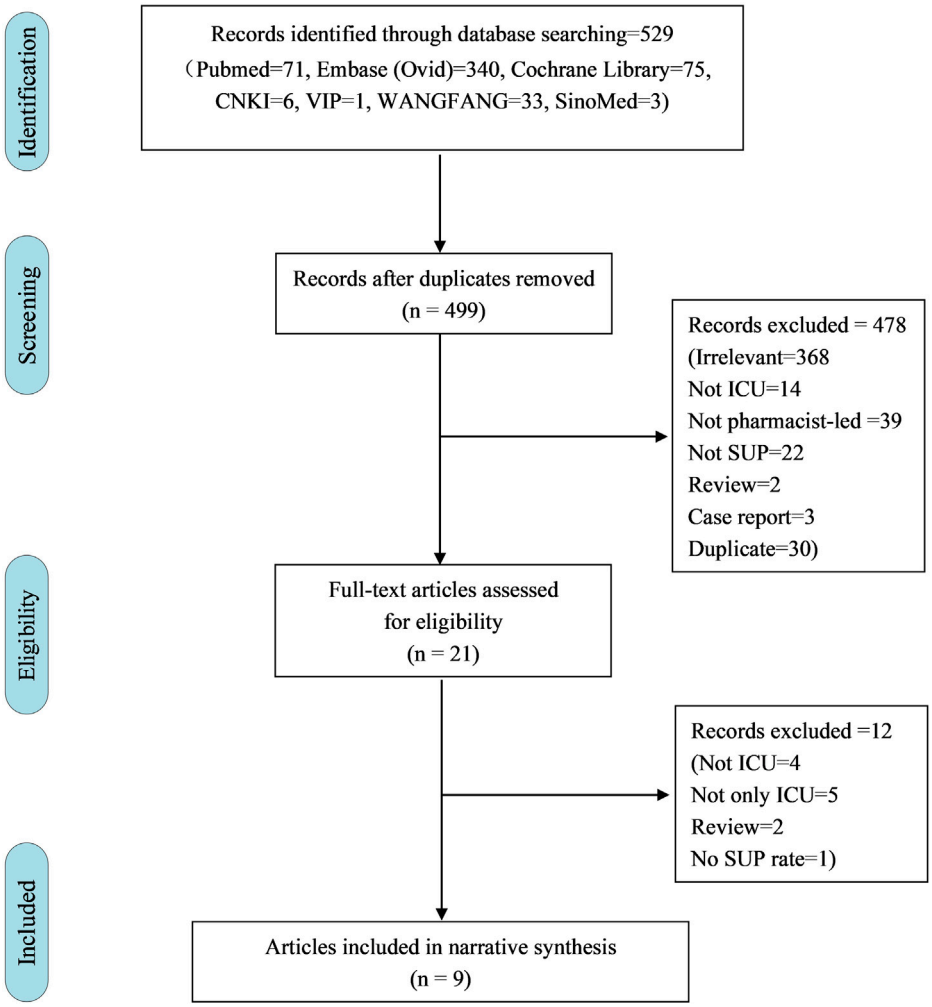

FIGURE 1 | Flow chart for screened articles.

Risk of Bias in the Included Studies

The NOS quality stars ranged between 5 and 7, and the average score was 5.88 for cohort studies (**Table 3**). Six studies had an overall fair quality, which indicated a low risk of bias. Two studies were determined as poor quality, indicating the risk of bias. 7 (87.5%) studie's exposed cohort were from single center which is not representative. All studies had no quantitative description of exposure, which means the exposure was uncertain.

Intervention Content and Delivery

Pharmacist interventions mainly included 4 aspects: 1) clarify indications for SUP pharmacotherapy; 2) education and awareness campaign; 3) reviewed patients on SUP pharmacotherapy during rounds; 4) adjustments of drug use (**Table 4**).

4 (50%) studies clarified the indication for the initiation and discontinuation of SUP pharmacotherapy by developing locally SUP pharmacotherapy guidelines/protocol or algorithm (Coursol and Sanzari, 2005; Tasaka et al., 2014; Buckley et al., 2015; Anstey et al., 2019). 4 (50%) studies provided the medical staff with an educational intervention and/or supplied a pocket card of SUP pharmacotherapy indications for reference (Hatch et al., 2010; Tasaka et al., 2014; Hammond et al., 2017; Masood et al., 2018).

In 3 (37.5%) studies, pharmacists reviewed each patient on SUP pharmacotherapy during medical ICU rounds (Hatch et al., 2010; Hammond et al., 2017; Masood et al., 2018). In 5 (62.5%) studies, pharmacists made appropriate changes on SUP pharmacotherapy, in which 2 (25.0%) studies gave the pharmacist prescriptive authority to make such changes (i.e., initiate, continue, discontinue, or modify the route of medication administration) for SUP pharmacotherapy only (Hatch et al., 2010; Tasaka et al., 2014; Buckley et al., 2015; Masood et al., 2018; Anstey et al., 2019).

Synthesis of Results

Effects on Inappropriate Use of SUP Pharmacotherapy

To clarify the definition of "inappropriate", we first clarified the indication of SUP pharmacotherapy in all studies. Based on the most recent published guidelines and the latest evidence at the time of the study's initiation, the indications for and cessation of

TABLE 1 | Characteristics of included studies.

Study ID	Country	Study design	Center	Sample size		Observation periods (months)	Outcome measurement time point	Significant intervention effect?
				Pre-	Post-			
Anstey et al. (2019)	Australia	Prospective cohort study	5	531	393	5	ICU hospitalization	No
							Hospital discharge	Yes
Masood et al. (2018)	United States	Retrospective cohort study	1	162	202	1	ICU hospitalization	Yes
Hammond et al. (2017)	United States	Retrospective cohort study	1	101	118	6	ICU hospitalization	Yes
							ICU transfer	No
							Hospital discharge	No
Buckley et al. (2015)	United States	Retrospective cohort study	1	174	167	1	ICU hospitalization	Yes
							ICU transfer	Yes
							Hospital discharge	Yes
Guobin et al. (2015)	China	Retrospective cohort study	1	20	20	1	ICU hospitalization	No
Tasaka et al. (2014)	United States	Retrospective cohort study	1	75	56	0.5	ICU hospitalization	Yes
							ICU transfer	No
							Hospital discharge	No
Wohlt et al. (2007) (pre-) Hatch et al. (2010) (post-)	United States	Retrospective cohort study	1	494	458	1	ICU transfer	Yes
							Hospital discharge	Yes
Coursol and Sanzari (2005)	Canada	Prospective cohort study	1	303	252	1	ICU hospitalization	Yes

SUP pharmacotherapy were different in each study (**Supplementary Tables S2, 3**). For the initiation of SUP pharmacotherapy, it involved 12 major risk factors (to meet one) and 14 minor risk factors (to meet two or more). The most common major risk factors were mechanical ventilation for >48 h and coagulopathy which were used by 7 (87.5%) studies. The common minor risk factors were high-dose glucocorticoid use and severe sepsis or septic shock which were used by 5 (62.5%) studies and 4 (50.0%) studies. For the cessation of SUP pharmacotherapy, 4 (50.0%) studies specified that SUP pharmacotherapy should be ceased when there is no ongoing indication (Tasaka et al., 2014; Buckley et al., 2015; Hammond et al., 2017; Anstey et al., 2019). 2 (25.0%) studies specified that SUP pharmacotherapy should be ceased when patients are discharged from ICU(Tasaka et al., 2014; Masood et al., 2018). 1 (12.5%) study specified that SUP pharmacotherapy should be ceased when patients received enteral feeding (Anstey et al., 2019). 3 (37.5%) studies did not specify the cessation of SUP pharmacotherapy (Coursol and Sanzari, 2005; Hatch et al., 2010; Guobin et al., 2015).

Between pre- and post-intervention groups, the assessment time of appropriateness varied from studies (**Figure 2**; **Table 5**). Seven studies comprised the incidence of inappropriate SUP initiation during ICU hospitalization, of which 5 (71.4%) studies found a significant intervention effect (Coursol and Sanzari, 2005; Tasaka et al., 2014; Buckley et al., 2015; Hammond et al., 2017; Masood et al., 2018). Four studies comprised the incidence of inappropriate continuation of SUP pharmacotherapy at ICU transfer, of which 2 (50.0%) studies found a significant intervention effect (Hatch et al., 2010; Buckley et al., 2015). Five studies included the incidence of inappropriate continuation of SUP pharmacotherapy at hospital discharge, of which 3 (60.0%) studies found a significant intervention effect (Hatch et al., 2010; Buckley et al., 2015; Anstey et al., 2019).

Effects on Complications and Economic Outcomes

Four studies identified the complications related to SUP pharmacotherapy (**Figure 2**; **Table 6**). There was no significant difference in the incidence of Clostridioides difficile-associated disease, pneumonia or hospital-acquired pneumonia, gastrointestinal bleeding, and thrombocytopenia between pre- and post-intervention groups.

4 (50%) studies explored the economic benefits of pharmacist-led interventions improving SUP pharmacotherapy (**Figure 2**; **Table 7**) (Coursol and Sanzari, 2005; Buckley et al., 2015; Masood et al., 2018; Anstey et al., 2019). Anstey 2019 determined the extrapolated direct savings to all Australian intensive care units from reduced SUP pharmacotherapy were $1.61 million/year, and indirect savings from the reduction in complications were $12.86 million/year nationally (Anstey et al., 2019). Masood 2018 clarified the pharmacist-led interventions could reduce the cost of medications for inappropriate SUP pharmacotherapy during the study period from $2,433.00 to $239.80 (Masood et al. (2018)). Buckley 2015 and Coursol 2005 identified the cost of the drugs for SUP per patient and clarified that the pharmacist-led intervention reduced it from $30.52±51.45 to $8.91±11.03 and $8.74 to $6.68 (Coursol and Sanzari, 2005; Buckley et al., 2015).

DISCUSSION

Summary of Evidence

This study was a systematic review of pharmacist-led interventions on the inappropriate use of SUP

TABLE 2 | Participant characteristics of included studies.*△

Study ID	Age (years)	Male sex	Department	Inclusion criteria	Exclusion criteria
Anstey et al. (2019)	T: 59 (40–71) C: 60 (42–71)[a]	T: 230 (58.5%) C: 301 (56.7%)	ICU	All adult (≥18 years) hospitalized patients	Patients aged<18 years· Cases with missing AST data
Masood et al. (2018)	NR	NR	Medical ICU	·All patients admitted to the ICU	Patients had acute GI bleeding
Hammond et al. (2017)	T: 56.24±18.35 C: 51.07±4.52	NR	Medical ICU	·All adult (≥18 years) hospitalized patients·Patients with an order for AST	Patients possessed a current diagnosis of GIB Patients on AST prior to admission to the ICU Patients with a history of Zöllinger-Ellison syndrome
Buckley et al. (2015)	T: 55.5±18.8 C: 58.3±17.1	T: 110 (65.9%) C: 90 (51.7%)	ICU	·All adult (≥18 years) hospitalized patients Patients received either an H2RA or PPI	Patients had GI diseases Patients receiving AST prior to admission to the ICU
Guobin et al. (2015)	NR	NR	ICU	·All patients admitted to the ICU Patients with an order for AST	—
Tasaka et al. (2014)	≥18	NR	Medical and surgical ICU	·All adult (≥18 years) hospitalized patients	Patients had: Active GIB Active peptic ulcer disease Total gastrectomy Solid organ transplant Dual antiplatelet therapy Concurrent antiplatelet and anticoagulation therapy Nonenteric coated pancrelipase *via* gastric feeding tube
Wohlt et al. (2007) **(pre-)** Hatch et al. (2010) **(post-)**	T: 55±19 C: 54±19	T: 269 (58.7%) C: 287 (58.1%)	Medical and surgical ICU	All adult (≥18 years) hospitalized patients	Patients had a current diagnosis of gastrointestinal bleeding, Zöllinger-Ellison syndrome, prisoner status Patients died while in the hospital
Coursol and Sanzari (2005)	18–90	T: 157 (62.3%) C: 191 (63.0%)	ICU	All adult (≥18 years) hospitalized patients	Patients refused treatment Patients died <24 h after admission Patients who pregnant Patients with gastrointestinal bleeding, or an active ulcer, or Zöllinger–Ellison syndrome

[a]*T: post-intervention group; C: pre-intervention group.*
[b]*NR: not reported.*

pharmacotherapy in intensive care units. Although the meta-analysis was not appliable for this review as the heterogeneous of judgment standards for the inappropriate use, we could speculate on the impact of pharmacist-led intervention through narrative synthesis. During hospitalization (7 related studies), the majority (71.4%, 5/7) indicated that pharmacist-led interventions were associated with a decrease in inappropriate SUP pharmacotherapy rates (Coursol and Sanzari, 2005; Tasaka et al., 2014; Buckley et al., 2015; Hammond et al., 2017; Masood et al., 2018). This ratio was 50% (4 related studies) at ICU transfer (Hatch et al., 2010; Buckley et al., 2015) and 60% (5 related studies) at hospital discharged (Hatch et al., 2010; Buckley et al., 2015; Anstey et al., 2019). No studies (4 related studies) found an increased risk of complications related to SUP pharmacotherapy (Coursol and Sanzari, 2005; Buckley et al., 2015; Hammond et al., 2017; Anstey et al., 2019). All studies (100%, 4 related studies) indicated that pharmacist-led intervention was associated with significant costs-savings (Coursol and Sanzari, 2005; Buckley et al., 2015; Masood et al., 2018; Anstey et al., 2019).

Although several SUP guidelines had been published (Armstrong et al., 1999; Vanderbilt University Medical Center, 2005; Guillamondegui et al., 2008; OrlandoRegionalMedicalCenter, 2011; Madsen et al., 2014; Ye et al., 2020), many answers to SUP questions still remain nebulous and need clarification, such as what the relevant anticipated and unanticipated adverse effects of SUP pharmacotherapy are, duration of therapy, and is there a target gastric pH goal for SUP, *etc*. Due to the different implementation time, the indication of SUP pharmacotherapy of the included studies was quite different based on the latest evidence at that time. This also increased the heterogeneity between the included studies. On January 06, 2020, the BMJRapid Recommendation published a new guideline on SUP in ICU patients (Ye et al., 2020). The guideline grouped patients into four categories according to the risk of clinically important GIB and suggested using acid suppression prophylaxis for people with higher risk (4% or higher) and for patients near this threshold, individual values and preferences become more important (Ye et al., 2020). There is currently no studies based on this latest guideline.

Pharmacist interventions varied among the identified studies and included several cointerventions. In general, for identified studies, the pharmacist-led interventions included clarifying indications for SUP pharmacotherapy, education

TABLE 3 | Risk of bias of included studies

		Anstey et al. (2019)	Masood et al., 2018	Hammond et al. (2017)	Buckley et al. (2015)	Tasaka et al. (2014)	Guobin et al. (2015)	Wohlt et al. (2007) (pre-)	Hatch et al. (2010) (post-)	Coursol and Sanzari (2005)
SELECTION	Representativeness of the Exposed Cohort	★	0	0	0	0	0	—	0	0
	Selection of the Non-Exposed Cohort	★	★	★	★	★	★	—	★	★
	Ascertainment of Exposure	0	0	0	0	0	0	—	0	0
	Demonstration That Outcome of Interest Was Not Present at Start of Study	★	★	★	★	★	★	—	★	★
COMPARABILITY	Comparability of Cohorts on the Basis of the Design or Analysis	★	0	★	★	0	★	—	★	★
OUTCOME	Assessment of Outcome	★	★	★	★	★	★	—	★	★
	Was Follow-Up Long Enough for Outcomes to Occur	★	★	★	★	★	★	—	★	★
	Adequacy of Follow Up of Cohorts	★	★	★	★	★	★	—	★	★
TOTAL	—	7	5	6	6	5	6	—	6	6
OVERALL QUALITY	—	**Fair**	**Poor**	**Fair**	**Fair**	**Poor**	**Fair**	—	**Fair**	**Fair**

and awareness campaign, review of patients on SUP during rounds and adjustments of drug use. A key role for health-system pharmacists is in the development and implementation of protocols, guidelines, and formularies for directing safe and effective use of medications that focus on patient safety and improved healthcare outcomes (Albanese et al., 2010). In the case of conflicting recommendations in the existing guidelines, only 4 identified studies (50%) had formulated the institution's protocol. Furthermore, even after the pharmacist's interventions, the rate of inappropriate use of SUP pharmacotherapy was still high at ICU transfer (3.57–53.39%), which suggests that pharmacists in future studies and clinical practice should focus on the discontinuation of SUP pharmacotherapy. Targeting specific diseases, the pharmacists could stratify patients based on the risk of clinically important GIB and implement different interventions, rather than regarded critically ill patients as a broad target group.

One proposed benefit of pharmacist-led intervention for use of SUP pharmacotherapy is decreased medical expenses. Only 4 studies reported the economic benefits of pharmacist-led interventions improving SUP pharmacotherapy and there was no cost-effectiveness analysis. Further research is needed with economic impact and cost-effectiveness analysis of pharmacist-led intervention.

Only one study was deemed to be of high quality, and most of studies (87.5%) have selection bias, including representativeness of the exposed cohort (87.5%) and ascertainment of exposure (100%). All studies only described the content and deliverer of intervention, but no process outcome being reported, such as the number of a modification proposal made, and the number of suggestions adopted by physicians. In addition, no studies have considered the cost of pharmacist intervention, which is not conducive to stakeholder's decision-making. Since almost all studies were single center with poorly representative of the community, the conclusions may not extrapolate to other institutions or country.

Strength and Limitations

Compared with published reviews (Singh-Franco et al., 2020; Orelio et al., 2021), we standardized the calculation process of the inappropriate rate so that the results of the studies were comparable. We also discussed the primary outcome at different time points including during ICU hospitalization, at ICU transfer and hospital discharge. In addition, we fully discussed the heterogeneity between the studies, and have a more correct explanation of the synthesis of the evidence in this review.

Due to the heterogeneity of identified studies, not only the studie's results, but also the design of studies including the definition of "inappropriate", the pharmacist's interventions, and the time of the judgment of appropriateness, it was difficult to precisely identify the impact of pharmacist-led interventions on the inappropriate use of SUP pharmacotherapy in intensive care units and which intervention was more efficient. We excluded several studies because of lacking key data. We were unable to contact the original author for more detailed information, which adds to the bias of this review. Besides, during the recalculation, the rate of inappropriate use of SUP pharmacotherapy at ICU transfer and hospital discharge may be underestimated as we used the SUP pharmacotherapy population during ICU hospitalization as the denominator.

Implication for Future Study and Practice

This study summarized the current evidence on pharmacist's role on the management of stress ulcer prophylaxis pharmacotherapy in intensive care units and pointed out

TABLE 4 | Intervention content and delivery of included studies

Study ID	Intervention							Details	
	Indication		Education		Rounds	Adjustments of drug use	Design	Content	Primary implementor
	Local SUP guidelines/ protocol	Algorithm	Medical staff	Materials					
Anstey et al. (2019)	●	—	—	—	—	●	NR	(a) A site-based dissemination of locally produced SUP prescription guidelines	NR
								(b) ICU pharmacist-led discontinuation of SUP prior to ICU discharge	Pharmacists
Masood et al. (2018)	—	—	●	●	●	● (prescribe authority)	NR	(a) Pharmacists reviewed patients on SUP during medical ICU rounds	Pharmacists
								(b) Pharmacists made appropriate changes (prescriptive authority) according to the guidelines	Pharmacists
								(c) Residents and fellows were educated and house staff were provided with printed copies of SUP indications	Pharmacists
Hammond et al. (2017)	—	—	●	●	●	—	NR	(a) A pharmacist provided medical residents and pulmonary/critical care fellows with an educational intervention	Pharmacists
								(b) Supplied a pocket card on SUP initiation and choice of agent	Multidisciplinary team
								(c) A pharmacist rounded with the medical ICU treatment team	Pharmacists
Buckley et al. (2015)	●	—	—	—	—	● (prescribe authority)	NR	(a) An institutional SUP prescription protocol	Pharmacists
								(b) Clinical pharmacists to initiate, modify, or discontinue stress ulcer prophylaxis	Pharmacists
Guobin et al. (2015)	—	—	—	—	—	—	NR	NR	pharmacists
Tasaka et al. (2014)	●	—	●	—	—	●	NR	(a) An institution SUP guideline	NR
								(b) An education and awareness campaign	NR
								(c) A pharmacist-led intervention	Pharmacists
Wohlt et al. (2007) (pre-) Hatch et al. (2010) (post-)	—	—	—	●	●	●	NR	(a) A memorandum and a pocket card	Pharmacists
								(b) Pharmacists also conducted medication reconciliation during daily patient care rounds and at discharge	Pharmacists
Coursol and Sanzari (2005)	—	●	—	—	—	—	NR	Stress Ulcer Prophylaxis Algorithm	pharmacists
Amount	**4**	—	—	**4**	**3**	**5**	—	—	—

TABLE 5 | The rate of inappropriate use of SUP pharmacotherapy.

Study ID	Rate of inappropriate use of SUP pharmacotherapy								
	Initiation of SUP			Continuation of SUP at ICU transfer			Continuation of SUP at hospital discharge		
	Pre-	Post-	*p*	Pre-	Post-	*p*	Pre-	Post-	*p*
Anstey et al. (2019)	19.81%	25.49%	0.198	—	—	—	36.79%	7.19%	< 0.001
Masood et al. (2018) [a] [b]	26.75%	7.14%	< 0.001	—	—	—	—	—	—
Hammond et al. (2017)	23.76%	12.71%	0.033	60.40%	53.39%	0.297	17.82%	13.56%	0.385
Buckley et al. (2015)	14.38%[a]	6.03%[a]	< 0.001	67.82%	38.92%	< 0.001	29.89%	3.59%	< 0.001
Guobin et al. (2015)	0.00%	0.00%	—	—	—	—	—	—	—
Tasaka et al. (2014)	21.26%[a]	9.09%[a]	0.004	8.00%	3.57%	0.498	6.67%	0.00%	0.131
Wohlt et al. (2007) (pre-) Hatch et al. (2010) (post-)	—	—	—	52.94%	27.27%	< 0.001	26.89%	15.74%	0.003
Coursol and Sanzari (2005)	95.74%	88.24%	0.033	—	—	—	—	—	—

[a]*The rate was calculated based on patient-day.*

[b]*Only one study (Masood 2018) included inappropriate use of SUP on patients who changed oral chronic AST use into intravenous route.*

TABLE 6 | Complications related to SUP.

Study ID	Event	Pre-		Post-		*p*
		n	N	n	N	
Anstey et al. (2019) [a]	*C. difficile*-associated disease	7	531	1	393	0.172
Hammond et al. (2017)	*C. difficile*	0	101	0	118	—
	Pneumonia	5	101	6	118	0.964
	Stress-related mucosal bleeding	1	101	0	118	0.938
Buckley et al. (2015)	Hospital-acquired pneumonia	29	174	25	167	0.668
	C. difficile-associated diarrhea	15	174	18	167	0.500
	Thrombocytopenia	11	174	5	167	0.146
	Gastrointestinal bleed	8	174	4	167	0.270
Coursol and Sanzari (2005) [a]	Significant bleeding	2	303	3	252	0.836

[a]*The incident is based on all ICU populations, not just SUP populations.*

TABLE 7 | Economical outcomes related to SUP.

Study ID	Outcome	Pre-	Post-	Other
Anstey et al. (2019)	Direct savings to all Australian intensive care units	—	—	$1.61 million/year
	Indirect savings from the reduction in complications to all Australian intensive care units	—	—	$12.86 million/year
Masood et al. (2018)	Cost of drugs for inappropriate SUP during study period	$2,433.00	$239.80	—
Buckley et al. (2015)	Cost of drugs for SUP per patient	$30.52±51.45	$8.91±11.03	—
Coursol and Sanzari (2005)	Cost of drugs for SUP per patient	$8.74	$6.68	—

the deficiencies in study design that need to be addressed in future studies, thereby contributing to clinical practice. The primary stakeholders of this study are consumers, healthcare professionals, local administrators, national policy makers and other researchers. At present, the participation of pharmacists in a multidisciplinary team is conducive to improving the effectiveness, safety, and economical outcome of patient treatment. However, for specific problems, pharmacists still need more flexible intervention methods and high-quality research to prove the cost-effectiveness of pharmacist interventions. Our research provides reference for pharmacists to participate in SUP drug management and provides methodological reference for future studies.

CONCLUSION

Pharmacist-led intervention is associated with a decrease in inappropriate use of SUP pharmacotherapy during hospitalization, at ICU transferred and hospital discharged, and a lot of medical cost savings. Further research is needed to determine whether pharmacist-led intervention is cost-effective.

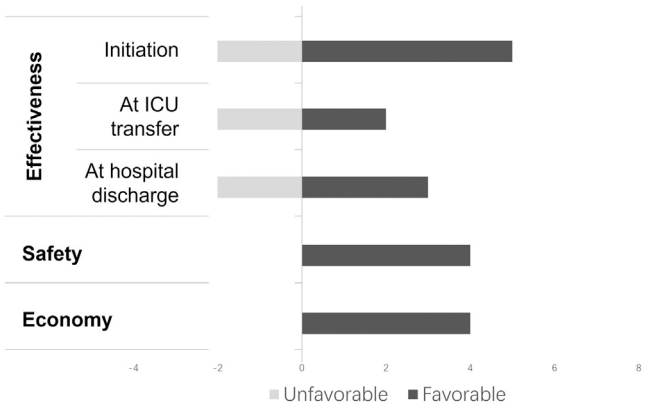

FIGURE 2 | Synthesis of finding fromthe included studies (vote counting).

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

PX contributed to study concept and design, study selection, acquisition of data, data analysis, and drafting the article. QY contributed to literature search, study selection and acquisition of data. CW contributed to study selection and quality assessment. LZ, KO, RZ, MJ, TX contributed to study concept and design and critical revision. LZ contributed to critical revision and submitted the report for publication. All authors read and approved the final manuscript.

FUNDING

Sichuan Province Science and Technology Planning Project (Key R&D Project): Research on Key Technologies of Pediatric Safety Drugs (No. 2020YFS0035) (2020.1–2021.12).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.741724/full#supplementary-material

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frontiers in Public Health

ORIGINAL RESEARCH
published: 26 October 2021
doi: 10.3389/fpubh.2021.754279

Combatting Substandard and Falsified Medicines: Public Awareness and Identification of Counterfeit Medications

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Objectives: The objective of this study was to determine the identification rate of substandard and falsified medications and its association with knowledge among public.

Methods: This descriptive cross-sectional study was conducted in different geographic areas among a convenient sample of people aged 18 or older. A validated web-based electronic questionnaire was used for data collection tool. The questionnaire contained three sections assessing the following: (1) Sociodemographic data; (2) Knowledge regarding counterfeit medicines; and (3) Ability to identify counterfeit medicines, according to 12 questions rated on a five-point Likert scale. Univariate and multivariate logistic regression analyses were used to assess the association between sociodemographic factors and counterfeit medication identification rate.

Results: A total of 320 people participated in the study. Only 98 participants (30.6%, 95% CI 25.6–35.7%) identified the counterfeit medications. Ability to correctly identify counterfeit medications was significantly higher in participants who were older ($p = 0.016$), single ($p = 0.001$), Asian ($p = 0.001$), or American ($p = 0.019$), as well as those who indicated that they would check the certification of the medications ($p = 0.015$) and report counterfeit medications to the authorities ($p < 0.0001$).

Conclusions: These results underscore the need for greater public awareness of the hazards associated with counterfeit medicines.

Keywords: falsified mediation, counterfeit medications, knowledge–attitude–behavior, identification, public awareness

OPEN ACCESS

Edited by:
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

Reviewed by:
Abdallah Y. Naser, Isra University, Jordan
Mudassir Anwar, University of Otago, New Zealand

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Specialty section:
This article was submitted to Public Health Policy, a section of the journal Frontiers in Public Health

Received: *06 August 2021*
Accepted: *30 September 2021*
Published: *26 October 2021*

Citation:
El-Dahiyat F, Fahelelbom KMS, Jairoun AA and Al-Hemyari SS (2021) Combatting Substandard and Falsified Medicines: Public Awareness and Identification of Counterfeit Medications. Front. Public Health 9:754279. doi: 10.3389/fpubh.2021.754279

INTRODUCTION

The World Health Organization (WHO) defined counterfeit pharmaceutical products as those that are deliberately and fraudulently mislabelled with respect to identity and/or source (1). Recently, WHO has introduced the more specific term "substandard and falsified (SF) medical products." Substandard medical products—also called "out of specification" products—are authorized medical products that fail to meet necessary quality standards or specifications. Unregistered or unlicensed medical products that have not undergone evaluation or approval by the National or Regional

Regulatory Authority (NRRA) for the market in which they are marketed or distributed are subject to permitted conditions under national or regional regulations and legislation. On the other hand, falsified medical products are ones that deliberately or fraudulently misrepresent their identity and composition or source (2, 3).

WHO has determined that counterfeit products could comprise about 50% of the drug market worldwide; many of these products arise from developing countries (4). According to reports sent to WHO from 20 different countries, most falsified drugs fell into one the following three categories: (1) products containing no active ingredient: about 30%; (2) products containing an incorrect quantity of the active ingredient: about 20%; and (3) products containing wrong contents: about 20% (5). According to an estimate, one in 10 pharmaceutical products are substandard or even falsified in low- and middle-income countries. Antimalarial medications are the most taking place counterfeit drugs, exhibiting about 20 per cent of the total counterfeit products and drugs reported in the year 2017 (6). The predominance of counterfeit products is highest in developing countries in Africa, Asia, and Latin America, comprising about 30–60% of all drugs in the market (2, 7–14). Worldwide, it is estimated that 10–15% of drugs are counterfeit (2, 7). Approximately 35–75% of the fake or counterfeit products that arise globally are made in India (11, 12).

Stricter methodological standards are required to determine the scale of this problem in order to raise awareness and ultimately address it. Global collaborative actions are required to enhance the management and surveillance of pharmaceutical supply-chains and regulatory agencies in low- and middle-income countries to minimize the threat of poor-quality drugs (15).

Counterfeit products are hazardous to health as well as the economy, and this is a dilemma for almost all developed and developing countries around the world. Besides. they are a major cause of treatment failure, adverse events, mortality, economic strain, development of drug resistance, and loss of confidence in medicine and various health services (3, 9, 13). The economic burden of counterfeit medicines is considerable in many developing countries, as illustrated by lost sales revenues, lost tax profit, job loss, increasing spending to fight and root out counterfeit products, money spent on ineffective counterfeit products, and expenses associated with recurrent hospitalizations due to counterfeit drugs (16–18).

Factors that increase a country's susceptibility to counterfeit medicines include healthcare infrastructure collapse, inadequate or improper regulatory procedures, and excessive costliness of essential medicines (18). According to a study in Nigeria, factors that contribute to the use of counterfeit medicines include illiteracy, ignorance, and weak law enforcement (19). According to this study, the main reasons for the prevalence of counterfeit medicine were the high cost of drugs and the greed of regulatory officials (19). From a public health perspective, counterfeit drugs threaten to deplete resources and result in poor patient outcomes, drug toxicity, disability, and even mortality. Moreover, from a commercial perspective, counterfeit drugs raise the issue of patent law violations (20).

WHO and other organizations have argued for increased public awareness of the flourishing counterfeit drugs trade and its associated public health risks (21, 22). There is limited data regarding people's awareness of counterfeit drugs and their ability to identify them.

A counterfeit drug might look similar to the original product, and, unfortunately, the only way to conclusively verify whether a product is fake is through chemical testing in an officially licensed laboratory. That said, physical evaluation of a drug's label and package design can provide clues into its counterfeit status. At a minimum, the label of any drug product (including even dietary supplements) is mandated to include: the brand name of the product, the drug's generic name, indications, size/weight, warnings/cautions, usage instructions, manufacturing details, country of origin, batch number, and a clear barcode. The absence of any of these items is a crucial indicator of counterfeit products. Awareness programs about these drug labeling requirements would be a vital step in combatting counterfeit products and limiting their use. The prevalence of low-quality drugs is a vital but poorly studied issue.

Hence this study aims to determine the identification rate of substandard and falsified medications and its association with knowledge among public.

MATERIALS AND METHODS

Study Population

This cross-sectional study was conducted using online survey in different geographic areas Europe, Asia, Africa, America and Middle East through a convenience sample of participants with different educational levels (e.g., high school, Bachelor's degree and Post graduate who were willing to participate in the study). Data was collected between May and November 2019.

Ethical Consideration

The study was approved by the Institutional Ethical Review Committee of Al Ain University (COP/2019/33) and conducted in accordance with the Declaration of Helsinki (23). The nature and purpose of the study was explained on first page of the online survey, where the participation in the survey and the individual responses will be strictly confidential to the research team and will not be divulged to any outside party. The informed consent was obtained by a participant's choice to continue to the next page and was considered their consent to participate in the study.

Data Collection

An online link to our survey was sent by email to valid and active professional LinkedIn accounts and universities websites within and outside the UAE. Accounts were retrieved from the web browser Google and recorded in a spreadsheet. Accounts were subsequently classified as personal or belonging to university institutions, private institutions, or government institutions. This online data collection method considered convenient and was used to reduce survey bias from "interviewer effect," to ease of allowing only the targeted demographics to participate, and ease of screening participants.

Sample Size Calculation

Since the estimated awareness of counterfeit medicines ranges from 50 to 93% (24–27), we assume 50% prevalence of public awareness about counterfeit medicines. Using an alpha level of 5% and a 95% confidence interval, we determined that a sample size of 550 participants is necessary for this study, assuming a non-response rate of 30%. The response rate was calculated from the pilot study. The survey link questionnaire was sent to 30 participants, from which 21 returned the filled questionnaire (response rate 70%). The following sample equation was used:

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

Research Instrument Development

The study questionnaire was developed based on items used in previous questionnaires (24–27). The questionnaire was subsequently validated and examined for the relevance and appropriateness of its contents by two clinical pharmacy lecturers from Al Ain University. In addition, Lawshe's method of assessing content validity was used to assess the instrument's quantitative content validity. Only the items with a content validity ratio (CVR) score $\geq$ 0.78 were included in the instrument. The instrument's calculated Cronbach's α value (0.72) demonstrated that it has an acceptable degree of internal consistency. The validated version of the questionnaire was then piloted with 30 subjects to ensure relevance and clarity. Responses from the pilot stage were not included in the final study results.

Research Instrument Sections

The questionnaire contained three sections assessing the following: (1) Sociodemographic data (e.g., sex, age, marital status, geographic area, education level, employment status, chronic disease diagnoses, and medication history); (2) Knowledge regarding counterfeit medicines; and (3) Ability to identify counterfeit medicines. The third section was comprised of 12 questions in which participants were asked to indicate how often they check the different pieces of information on a drug's label when purchasing medication. This was rated on a five-point Likert scale (1 = "never," 2 = "rarely," 3 = "sometimes," 4 = "often," 5 = "always").

Statistical Analysis

The analysis was performed using SPSS version 24. Qualitative variables were summarized using frequencies (percentages) as appropriate, while quantitative variables were summarized using means and standard deviations (SDs). 12 Questions addressing the counterfeit mediation identification could be answered by "always," "often," "sometimes," "rarely," or "never." A counterfeit mediation identification score was created to measure the awareness and ability of participants in identifying counterfeit medication. This score was dichotomized into two categories (e.g., yes and no). Correct response (yes) scored 1 and wrong answer (no) scored "0." The participant considered has awareness about counterfeit identification if he correctly identified all the 12 items.

Chi-square and fisher exact tests were used to determine the difference in the identification rate of substandard and falsified medications according to demographics. Univariate and multivariate logistic regression analyses were used to assess the association between sociodemographic factors and counterfeit medication identification rate. *P*-values < 0.05 were considered statistically significant.

TABLE 1 | Frequency table for demographic characteristics ($n = 320$).

Variable	Groups	Frequency	Percentage
Sex	Male	176	55%
	Female	144	45%
Age	18–24	36	11.3%
	25–34	70	21.9%
	35–44	66	20.6%
	45–54	102	31.9%
	≥55	46	14.4%
Marital status	Single	70	21.9%
	Married	250	78.1%
Regions	Europe	24	7.5%
	Asia	22	6.9%
	Africa	76	23.8%
	America	10	3.1%
	Middle East	188	58.8%
Education	Post graduate	8	2.5%
	Bachelor's degree	100	31.3%
	High school	212	66.3%
Employment status	Employed	240	75%
	Unemployed	80	25%
Chronic disease	Yes	70	21.9%
	No	250	78.1%
Take Medication in case of acute disorders	Yes	266	83.1%
	No	54	16.9%

RESULTS

Demographic Characteristics of the Study Population

A total of 320 subjects participated in the study and completed the whole questionnaire. Among these 55% ($n = 176$) were male and 45% ($n = 144$) were female. Of the total participants, 11.3% ($n = 36$) were ages 18–24, 21.9% ($n = 70$) were ages 25–34, 20.6% ($n = 66$) were ages 35–44, 31.9% ($n = 102$) were ages 45–54, and 14.4% ($n = 46$) were ages ≥55. A majority of the participants were married ($n = 250$, 78.1%). A majority of the participants were from the Middle East (58.8%), followed by Africa (23.8%), Europe (7.5%), Asia (6.9%), and America (3.1%). About 66.3% of the subjects were high school educated, whereas 31.3% were bachelor's degree holders and 2.5% were graduate degree holders. A majority of the participants were employed (75%). Overall, 70 (21.9%) participants reported having a chronic disease and 266 (83.1%) were taking medication for acute disorders (**Table 1**).

Knowledge and Current Practice Toward Counterfeit Medications

Study participants' knowledge and current practice toward counterfeit medications are summarized in **Table 2**. Out of all

TABLE 2 | Frequency table for knowledge and practice items.

Knowledge and practice items	Response	Frequency	Percentages
Are you aware of any Hazards that might be associated with the use of the Counterfeit medications	Yes	166	51.9%
	No	154	48.1%
Do you agree with the statement that Counterfeit medications are harmless	Disagree	268	83.8%
	Neutral	16	5%
	Agree	36	11.3%
Counterfeit medicines are a national health problem in your country	Disagree	68	21.3%
	Neutral	132	41.3%
	Agree	120	37.5%
Do you make sure that the medication is certified by the regulated authority	Yes	188	58.8%
	No	132	41.3%
How frequently have you encountered Counterfeit medications?	Never/Rarely	286	89.4%
	Sometimes	26	8.1%
	Always/Often	8	2.5%
Have you ever reported the Counterfeit medications to concerned authority	Yes	8	2.5%
	No	312	97.5%

TABLE 3 | Frequency table for counterfeit identification items ($n = 320$).

Counterfeit identification item	Never *n* (%)	Rarely *n* (%)	Sometimes *n* (%)	Often *n* (%)	Always *n* (%)	Mean ± (SD)
Generic name	18 (5.6%)	20 (6.3%)	42 (13.1%)	88 (27.5%)	152 (47.5%)	4.05 (±1.17)
Trade name	26 (8.1%)	32 (10%)	64 (20%)	62 (19.4%)	136 (42.5%)	3.78 (±1.31)
Net weight/Size/dose	28 (8.8%)	38 (11.9%)	48 (15%)	60 (18.8%)	146 (45.6%)	3.81 (±1.36)
Indication	6 (1.9%)	16 (5%)	46 (14.4%)	76 (23.8%)	176 (55%)	4.25 (±1)
Usage/how to use	4 (1.3%)	18 (5.6%)	26 (8.1%)	76 (23.8%)	196 (61.3%)	4.38 (±0.94)
Cautions/warnings	10 (3.1%)	30 (9.4%)	50 (15.6%)	112 (35%)	118 (36.9%)	3.93 (±1.1)
Storage conditions	16 (5%)	48 (15%)	76 (23.8%)	88 (27.5%)	92 (28.7%)	3.6 (±1.2)
Country of origin	22 (6.9%)	54 (16.9%)	70 (21.9%)	92 (28.7%)	82 (25.6%)	3.49 (±1.2)
Manufacturing details	92 (28.7%)	72 (22.5%)	80 (25%)	44 (13.8%)	32 (10%)	2.55 (±1.31)
Barcode	184 (57.5%)	80 (25%)	26 (8.1%)	16 (5%)	14 (4.4%)	1.73 (±1.1)
Batch number	208 (65%)	66 (20.6%)	28 (8.8%)	8 (2.5%)	10 (3.1%)	1.58 (±0.97)
Production/Expiry date	6 (1.9%)	4 (1.3%)	20 (6.3%)	74 (23.1%)	216 (67.5%)	4.53 (±0.82)

n, frequency; %, percentage.

participants, 51.9% were aware of the hazards of counterfeit medications and 83.8% disagreed with the statement that counterfeit medications are harmless. In this study, 120 (37.5%) of the respondents believed that counterfeit medicines constitute a national health problem in their countries and 188 (58.8%) indicated that it is important to ensure that medicines were certified and registered by a regulatory authority. As for participants' personal experiences with counterfeit medications, 286 (89.4%) never or rarely encountered them, 26 (8.1%) sometimes encountered them, and 8 (2.5%) often or always encountered them. Only eight participants (2.5%) had ever reported counterfeit medications to the relevant authority.

Identification of Counterfeit Medications

In this study, 98 participants (30.6%, 95% CI 25.6–35.7%) correctly identified the counterfeit medications. **Table 3** shows participant's responses to the counterfeit medications' identification items. The most often identified piece of label information was production date or expiration date (4.53 ± 0.82), followed by instructions of use (4.38 ± 0.94), and the generic drug name (4.1 ± 1.17). The least often identified pieces of label information were batch number (1.58 ± 0.97), barcode (1.73 ± 1.1), and manufacturing details (2.55 ± 1.31) (**Table 3**).

Table 4 presents the counterfeit medications identification rate according to demographic factors. Participants who were male ($p = 0.048$), older ($p = 0.006$), single ($p = 0.012$), and highly educated had a significantly higher counterfeit medication identification rate. Moreover, there was a significant association between geographic regions and counterfeit medication identification rate ($p = 0.021$). Participants from the Middle East had a significantly lower counterfeit medication identification rate compared to those from other regions.

Table 5 shows the association between the counterfeit medication identification rate and participants' knowledge and practice toward counterfeit medications. Participants

TABLE 4 | Counterfeit identification according to demographic factors.

	Proportional of awareness about counterfeit identification		
Variable	**Groups**	**Frequency (%)**	***P*-value**
Sex	Male	62 (35.2%)	0.048
	Female	36 (25%)	
Age	18–24	14 (38.9%)	0.006
	25–34	28 (40%)	
	35–44	14 (21.2%)	
	45–54	22 (21.6%)	
	≥55	20 (43.5%)	
Marital status	Single	30 (42.9%)	0.012
	Married	68 (27.2%)	
Regions	Europe	8 (33.3%)	0.021
	Asia	12 (54.5%)	
	Africa	22 (28.9%)	
	America	6 (60%)	
	Middle East	50 (26.6%)	
Education	High school	62 (29.2%)	0.022
	Bachelor's degree	30 (30%)	
	Postgraduate	6 (75%)	
Employment status	Employed	74 (30.8%)	0.889
	Unemployed	24 (30.0%)	
Chronic disease	Yes	20 (28.6%)	0.673
	No	78 (31.2%)	
Take Medication in case of acute disorders	Yes	80 (30.1%)	0.636
	No	18 (33.3%)	

p-values reported above are for comparisons between variable levels "categories–levels" using the chi-square and fisher exact tests.

who reported checking the certification medications ($p = 0.002$), those who frequently encountered counterfeit medications ($p = 0.003$), and those who reported the counterfeit medications to the relevant authorities ($p < 0.0001$) had a significantly higher counterfeit medication identification rate.

Factors Associated With Counterfeit Mediation Identification Rate

We performed a univariate and multivariate logistic regression analysis to identify factors that were highly correlated with counterfeit medication identification rate. The univariate analysis showed that the following factors significantly increased the counterfeit medication identification rate: male sex (OR 3.61, 95% CI 2.52–5.16), older age (OR 1.93, 95% CI 1.02–3.66), single marital status (OR 2.01, 95% CI 1.16–3.48), Asian geography (OR 3.31, 95% CI 1.35–8.14), American geography (OR 4.14, 95% CI 1.12–7.28), graduate education (OR 7.26, 95% CI 1.43–11.95), a habit of checking the certification of medications (OR 2.20, 95% CI 1.32–3.67), frequent encountering of counterfeit medications (OR 7.73, 95% CI 1.53–12.1), and reporting counterfeit medications to the relevant authorities (OR 6.32, 95% CI 1.43–14.23).

In multivariate analysis, counterfeit medication identification rate was significantly associated with older age ($p = 0.016$), being single ($p = 0.001$), Asian geography ($p = 0.001$), American geography ($p = 0.019$), a habit of checking the certification of medications ($p = 0.015$), and reporting counterfeit medications to the relevant authorities ($p < 0.0001$) (**Table 6**).

DISCUSSION

This study explored public knowledge and practice toward counterfeit drugs using a cross-sectional study design. Over half of the participants (51.9%) were aware of the hazards of counterfeit medications, and the vast majority (83.8%) disagreed with the statement that counterfeit medications are harmless. In contrast, a previous study of Italian healthcare professionals reported much lower knowledge of the characteristics of falsified medicines: Between 25 and 50% of the respondents were unaware that counterfeit medications could contain additives, a lower dose of the active ingredient, and/or incorrect ingredients, and only a quarter of the respondents knew that counterfeit drugs could be lethal, this difference between our study and the Italian study could possibly be due to the fact that Legal online sale of medicines in Italy has started being regulated only recently. In addition, awareness of our respondents is clearly higher (28).

Few studies in the literature have addressed public awareness and knowledge of counterfeit medicine. The few that have focused mostly on exploring and combating counterfeit drugs in the developing world. 93.4% of respondents in a Lebanese study showed they were aware of the term counterfeit medicines. Another Lebanese qualitative study demonstrated a gap in participants' awareness regarding counterfeit medicines, and the majority of participants could not define counterfeit medicines. In Qatar, a similar study revealed that pharmacists had higher awareness than public regarding counterfeit medicines and its societal consequences.

In general, our results are in line with other studies from different countries regrading public knowledge and practice toward counterfeit medications (25–30).

Whereas in our study 30.6% (95% CI 25.6–35.7%) of the participants could correctly identify counterfeit medications, a similar study conducted in England ($n = 320$) reported that 62.8% of the participants were aware of the presence of falsified products purchased online and 11.9% had encountered counterfeit items, of whom only 0.9% reported the counterfeit items to the authorities (31, 32).

We found that more highly educated participants had a higher counterfeit medication identification rate. Furthermore, participants from countries in the Middle East had a significantly lower counterfeit medication identification rate compared to participants from other regions. A previous study on public awareness and identification of counterfeit drugs in Tanzania reported that 55.6% of participant were able to distinguish between a genuine vs. counterfeit drugs while 44.4% failed to identify (24, 33).

Counterfeit medicine identification rate in our study was significantly associated with older age ($p = 0.016$), single marital

TABLE 5 | Counterfeit identification according to knowledge and practice factors.

Knowledge and practice items	Proportional of awareness about counterfeit identification		
	Response	**Frequency (%)**	***P*-value**
Are you aware of any hazards that might be associated with the use of the Counterfeit medications	Yes	52 (31.3%)	0.778
	No	46 (29.9%)	
Do you agree with the statement that Counterfeit medications are harmless	Disagree	80 (29.9%)	0.479
	Neutral	4 (25%)	
	Agree	14 (38.9%)	
Counterfeit medicines is a national health problem in your country	Disagree	26 (38.2%)	0.253
	Neutral	40 (30.3%)	
	Agree	32 (26.7%)	
Do you make sure that the medication is certified by the regulated authority	Yes	70 (37.2%)	0.002
	No	28 (21.2%)	
How frequently have you encountered Counterfeit medications	Never/Rarely	80 (28.0%)	0.003
	Sometimes	12 (46.2%)	
	Always/Often	6 (75%)	
Have you ever reported the Counterfeit medications to concerned authority	Yes	8 (100%)	<0.0001
	No	90 (28.8%)	

p-values reported above are for comparisons between variable levels "categories–levels" using the chi-square and fisher exact tests.

TABLE 6 | Univariate and multivariate analysis of factors associated with counterfeit identification.

Factors	Counterfeit identification							
	Univariate				**Multivariate**			
	OR	**95% CI**		***P*-value**	**OR**	**95% CI**		***P*-value**
Female	Ref.				—	—	—	—
Male	1.63	1.002	2.66	0.049	—	—	—	—
<55 years	Ref.				Ref.			
≥55 years	1.93	1.02	3.66	0.043	2.46	1.184	5.104	0.016
Married	Ref.				Ref.			
Single	2.01	1.16	3.48	0.013	3.200	1.651	6.201	0.001
Middle East	Ref.							
Europe	1.38	0.556	3.42	0.487	1.658	0.620	4.435	0.314
Asia	3.31	1.35	8.14	0.009	5.150	1.930	10.75	0.001
Africa	1.124	0.622	2.03	0.698	1.559	0.784	3.099	0.205
America	4.14	1.12	7.28	0.03	5.710	1.338	8.372	0.019
High school	Ref.				—	—	—	—
Bachelor's degree	1.04	0.62	1.74	0.891	—	—	—	—
Postgraduate	7.26	1.43	11.95	0.017	—	—	—	—
Do you make sure that the medication is certified by the regulated authority								
No	Ref.							
Yes	2.20	1.32	3.67	0.002	1.99	1.144	3.48	0.015
Encountered Counterfeit medications								
Never/Rarely	Ref.				—	—	—	—
Sometimes	2.21	0.98	4.978	0.056	—	—	—	—
Always/Often	7.73	1.53	12.074	0.013	—	—	—	—
Reported the Counterfeit medications to concerned authority								
No	Ref.				Ref.			
Yes	6.32	1.43	14.23	0.000	4.56	1.78	12.98	0.000

P-values <0.05 were considered statistically significant, "—" not included in the multivariate logistic regression model. OR, odds ratio; CI, confidence interval.

status ($p = 0.001$), Asian geography ($p = 0.001$), and American geography ($p = 0.019$). In contrast, in the Tanzanian study, age, sex, education level, and marital status were not associated with ability to identify counterfeit drugs (24).

Overall, this study highlights the need for awareness and educational campaigns about the safety and efficacy of medicines, and the importance of avoiding counterfeit drugs. Healthcare providers must be actively involved in educating patients and the public on the adverse consequences of counterfeit drugs and measures to identify them. Pharmacists, doctors, and nurses—in addition to pharmaceutical companies and medication distributors—should be constantly vigilant about drug falsification so that they are prepared to deal with suspicious drug products (22).

CONCLUSION

Drug counterfeiting is a threat to every nation's public health and economy. Only 30.6% of the participants able to identify properly the counterfeit medications. There is a dire need to raise awareness among general population through different awareness and educational campaigns to help identifying counterfeit drug products. The involvement of healthcare professionals is crucial in this regard.

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 Al Ain University (COP/2019/33). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FE-D and KF designed the study. FE-D, AJ, and SA-H responsible for data collection. FE-D and AJ analyzed and interpreted the data. All authors drafted, reviewed, and approved the manuscript.

ACKNOWLEDGMENTS

We would like to thank our colleagues for their participation in this study and their support of our work in this way; they helped us obtain results of better quality.

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frontiers in Pharmacology

ORIGINAL RESEARCH
published: 16 November 2021
doi: 10.3389/fphar.2021.732912

Cost-Effectiveness Analysis of Camrelizumab Versus Chemotherapy as Second-Line Treatment of Advanced or Metastatic Esophageal Squamous Cell Carcinoma

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Background: This study aimed to analyze the cost effectiveness of camrelizumab in the second-line treatment of advanced or metastatic esophageal squamous cell carcinoma in China.

Methods: On the basis of the ESCORT clinical trial, a partitioned survival model was constructed to simulate the patient's lifetime quality-adjusted life years (QALYs), lifetime costs, and incremental cost-effectiveness ratio (ICER). One-way sensitivity and probability sensitivity analyses were performed to test the stability of the model.

Results: Treatment of esophageal squamous cell carcinoma with camrelizumab added 0.36 QALYs and resulted in an incremental cost of $1,439.64 compared with chemotherapy, which had an ICER of $3,999 per QALY gained. The ICER was far lower than the threshold of willingness to pay for one time the GDP per capita in China. Sensitivity analysis revealed that the ICERs were most sensitive to the cost of drugs, but the parameters did not have a major effect on the results of the model.

Conclusion: Camrelizumab is likely to be a cost-effective option compared with chemotherapy for patients with advanced or metastatic esophageal squamous cell carcinoma. This informs patient selection and clinical path development.

Keywords: cost-effectiveness, esophageal cancer, esophageal squamous cell carcinoma, chemotherapy, camrelizumab

OPEN ACCESS

Edited by:
Mohamed Izham Mohamed Ibrahim, Qatar University, Qatar

Reviewed by:
Keith Tolley, Independent Researcher, Derbyshire, United Kingdom
Xin Ye, Shandong University, China

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *29 June 2021*
Accepted: *15 October 2021*
Published: *16 November 2021*

Citation:
Cai H, Xu B, Li N, Zheng B, Zheng Z and Liu M (2021) Cost-Effectiveness Analysis of Camrelizumab Versus Chemotherapy as Second-Line Treatment of Advanced or Metastatic Esophageal Squamous Cell Carcinoma. Front. Pharmacol. 12:732912. doi: 10.3389/fphar.2021.732912

INTRODUCTION

The world has approximately 572,000 new cases of esophageal cancer and 508,000 deaths every year. The number of new cases of and deaths from esophageal cancer in China ranks sixth and fourth places among all malignant tumors, respectively (Sung et al., 2021). Esophageal cancer could be divided into esophageal squamous cell carcinoma, esophageal adenocarcinoma, and other subtypes. Esophageal squamous cell carcinoma accounts for more than 90% of esophageal cancer (Arnold et al., 2015). The incidence of esophageal squamous cell carcinoma is increasing in some Asian countries. Half of the global esophageal squamous cell carcinoma cases occur in China (Zhang et al., 2012; Sung et al., 2021). Most patients are already at an advanced stage when they are diagnosed with

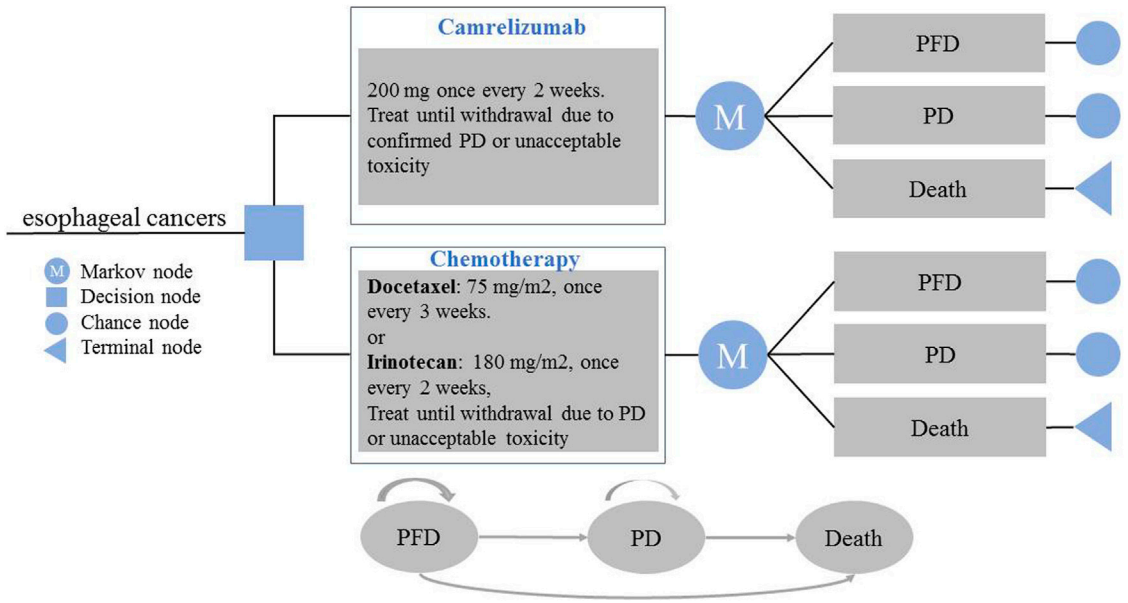

FIGURE 1 | Model Structure of a Decision Tree Combining the Partitioned Survival Model. PFD, progression-free disease; PD, progressive disease.

local invasion or distant metastasis. The prognosis of advanced or metastatic esophageal squamous cell carcinoma is poor, and the overall 5-year survival rate is less than 20% (Torre et al., 2016). Therefore, advanced or metastatic esophageal squamous cell carcinoma has gradually become a more difficult problem in the treatment of tumor diseases.

Platinum drugs combined with fluorouracil or Paclitaxel are the standard first-line treatment option for the treatment of esophageal squamous cell carcinoma, but after the progress of first-line treatment, the choice of second-line treatment is limited (Shah, 2015; Kojima et al., 2020). The median survival time after failure of first-line chemotherapy is only 5–10 months (Sun et al., 2021). Thus, finding more cost-effective second-line treatment drugs is very important. Immune checkpoint inhibitors (ICIs) are more effective and has lower incidence of adverse reactions than chemotherapy. They have become the choice of second-line treatment for patients (Kojima et al., 2020). Camrelizumab, a high-affinity, fully humanized, selective IgG4-κ monoclonal antibody against PD-1, has shown activity across a wide range of solid tumors (Fan et al., 2021; Peng et al., 2021; Yang et al., 2021; Zhou et al., 2021). The Chinese guidelines recommend camrelizumab as a second-line treatment for distant metastatic esophageal cancer (CSCO, 2020). The ESCORT study has shown that second-line camrelizumab significantly improved the overall survival (OS) of patients with advanced or metastatic esophageal squamous cell carcinoma compared with chemotherapy, with a manageable safety profile (Huang et al., 2020).

Camrelizumab officially entered China's National Medical Insurance in March 2021, with a price reduction of 85.2% (Nation Healthcare Security Administration, 2020). After the price reduction, whether camrelizumab may become an cost-effective second-line treatment has become an issue of great interest to medical insurance, doctors, and patients. Therefore, in this study, a cost-effectiveness analysis of camrelizumab was conducted in the second-line treatment of advanced or metastatic esophageal squamous cell carcinoma.

MATERIALS AND METHODS

Model Structure

The target population of the study was patients with advanced or metastatic esophageal squamous cell carcinoma who previously failed to receive first-line chemotherapy. The patients were assigned to receive either camrelizumab or chemotherapy (docetaxel or irinotecan). A partitioned survival model was established to reflect the disease progression. The model included three states: progression-free disease (PFD), progressive disease (PD), and death. The three states are mutually exclusive. All patients were assumed to enter the model in the PFD state, and that they could maintain their designated health state or develop into another health state in each cycle (**Figure 1**). The relative 5-year survival rate is 8% or less for patients diagnosed with metastatic disease; thus, the time horizon of the model was set to 10 years (ASCO, 2020; Cancer Information Service, 2020). The model period was set to 1 month to facilitate model operation and parameter calculation. The main results of the model output were total cost, incremental cost-effectiveness ratio (ICER), and quality-adjusted life years (QALYs). ICER refers to the additional cost required for each additional QALY. Cost and utility were discounted at a rate of 5% (Liu, 2020). All costs were converted to USD, with an average RMB exchange rate of $1 to 6.8974 Yuan for the full year of 2020 (National Bureau of statistics of China, 2020). In addition, 1–3 times the national per capita GDP in 2020 ($10,503.52) was used as the willingness-to-pay (WTP) threshold (World

TABLE 1 | Basic parameters input to the model and the ranges of the sensitivity analyses.

Variable	Baseline value	Lower limit	Upper limit	Source
Log-logistic PFS survival model				
Camrelizumab	γ = 2.0011; λ = 0.1471	—	—	Huang et al. (2020)
Chemotherapy	γ = 3.1368; λ = 0.08394	—	—	Huang et al. (2020)
Weibull PFS survival model				
Camrelizumab	γ = 1.1296; λ = 0.1965			Huang et al. (2020)
Chemotherapy	γ = 1.9527; λ = 0.1282			Huang et al. (2020)
Log-logistic OS survival model				
Camrelizumab	γ = 1.2879; λ = 0.04461	—	—	Huang et al. (2020)
Chemotherapy	γ = 2.1592; λ = 0.01946	—	—	Huang et al. (2020)
Weibull OS survival model				
Camrelizumab	γ = 1.3018; λ = –0.04380			Huang et al. (2020)
Chemotherapy	γ = 1.4487; λ = 0.04345			Huang et al. (2020)
Health utilities				
Progression-free disease	0.741	0.593	0.889	Zhang et al. (2020b)
Progressive disease	0.581	0.465	0.697	Zhang et al. (2020b)
Anemia	–0.074	–0.037	–0.110	Tan et al. (2018)
Decreased neutrophil count	–0.090	–0.059	–0.120	Tan et al. (2018)
Vomiting	–0.048	–0.016	–0.080	Tan et al. (2018)
Drug cost per mg, US $				
Camrelizumab	2.16	1.08	2.16	Nation Healthcare Security Administration. (2020)
Docetaxel	1.77	0.26	14.95	YoaZH. (2020)
Irinotecan	1.64	0.88	4.65	YoaZH. (2020)
Drug administration costs, US $				
Follow-up cost per cycle	7.47	6.52	8.47	Zhang et al. (2020b)
Best supportive care cost per cycle	16.98	4.68	46.77	Zhang et al. (2020b)
SAE management cost, US $				
Anemia	73.68	55.27	92.11	Zhang et al. (2020b)
Decreased neutrophil count	67.56	200.66	55.27	Zhang et al. (2020b)
Vomiting	98.33	63.64	140.46	Guy et al. (2019)
Body surface area, m^2	1.72	1.50	1.90	Zeng et al. (2013)
Discount rate	0.05	0	0.08	Liu. (2020)

PFS, progression-free survival; OS, overall survival; SAE, severe adverse event.

Health Organization, 2011; Liu, 2020; National Bureau of statistics of China, 2020). The TreeAge Pro 2020 software package was used to build the model and conduct statistical analysis.

Clinical Data

The clinical efficacy and safety data of the second-line treatment for advanced or metastatic esophageal squamous cell carcinoma were mainly from the ESCORT clinical trial (Huang et al., 2020). The ESCORT study is a randomized, open, multi-center phase III clinical study. It is the world;s first and largest clinical study of camrelizumab in Chinese patients with advanced/metastatic esophageal squamous cell carcinoma who previously failed first-line chemotherapy. A total of 228 patients received camrelizumab monotherapy, and 220 patients received chemotherapy (docetaxel or irinotecan). The eligible patients had histological or cytological diagnosis of esophageal squamous cell carcinoma; advanced, recurrent, or distant metastatic disease; and showed progression on previous first-line chemotherapy. The main exclusion criteria included CNS metastases and a history of anti-PD-1 or anti-PD-L1 therapy (Huang et al., 2020). GetData Graph Digitizer 2.26 (http://www.getdata-graph-digitizer.com) was used to obtain points on the survival rates of the Kaplan–Meier curves. Following Hoyle et al. (Hoyle and Henley, 2011), R software was used to reconstruct the individual data, which were then fitted by exponential, gamma, gompertz, Weibull, loglogistic and lognormal distribution. The best fitting distribution was selected by visual inspection, the lowest value of the Akaike information criterion (AIC), and Bayesian information criterion (Zhang et al., 2020a) (**Supplementary Table S1**). The log-logistic distribution function was used to simulate the PFS and OS curves of the two schemes. We performed internal and external model validations (Goldstein et al., 2015). The internal validation showed that the PFS and OS curves closely approximated those presented in the clinical trials (**Supplementary Figures S1, S2**). In the external validation, we compared the survival curves used in this study with those for the same treatment in other published studies. PFS and OS curves were compared with those from ORIENT-2 study (Xu et al., 2020), as shows in **Supplementary Figures S3, S4**. The survival function of log-logistic distribution at time t was $S(t) = 1/(1+\lambda t^{\gamma})$ to calculate the scale parameter λ and the shape parameter γ (Ishak et al., 2013; Diaby et al., 2014). The Weibull distribution as the next best fitting function was also used to project lifetime survival curves in our model. The key clinical inputs are given in **Table 1**.

Cost and Utility

The study only considered direct medical costs, including drug acquisition, follow-up, best supportive treatment, and severe

adverse event (SAE) management costs. In accordance with the ESCORT clinical research and guidelines (CSCO, 2020; Huang et al., 2020), 200 mg carrelizumab was administered intravenously on the first day of every 2 weeks, 75 mg/m^2 docetaxel was provided on the first day of every 3 weeks, and 180 mg/m^2 of irinotecan was administered intravenously on the first day every 2 weeks. Treatment was continued until disease progression or unacceptable toxicity. The cost effectiveness of the two scenarios was discussed to avoid the effect of the course of drugs on the results. In the first scenario, camrelizumab was assumed to be used for six (IQR 4–13) courses, docetaxel for three (2–3) courses, and irinotecan for four (2–5) courses in accordance with the results of ESCORT (Huang et al., 2020). A shorter time horizon (3, 5 and 7 years) was also considered in this scenario. In the second scenario, both groups continued treatment until the disease progressed. The proportion of patients receiving specific chemotherapy regimens was not defined in the clinical trials. The model assumed that the patients had equal opportunities to receive docetaxel and irinotecan. The average body surface area of the patients in the model was 1.72 m^2 (1.5–1.9 m^2) (Zeng et al., 2013). After the failure of second-line treatment, the best third-line treatment was not clear, and the specific scheme was not shown in the ESCORT study. Therefore, the best support treatment was regarded as the treatment after progression.

The cost of camrelizumab was derived from the negotiated price of China's national medical insurance (Nation Healthcare Security Administration, 2020). The cost of docetaxel and irinotecan was the median of the bidding price of drugs in different provinces (YaoZH, 2020). Only the SAE of grade ≥3 was considered (Guy et al., 2019; Zhang et al., 2020b). The incidence rate of anemia in the camrelizumab group was 3%, while the incidence rates of anemia, decreased neutrophil count, and vomiting in the chemotherapy group were 5.0, 15.0, and 5%, respectively (Huang et al., 2020). Other costs are shown in **Table 1**.

The utility value represents the health-related quality of life for each health state. The ESCORT trail did not involve health utility. Thus, the utility in the model was obtained from other public literature (Tan et al., 2018; Zhang et al., 2020b; National Institute for Health and Care Excellence, 2021), utility values for the PFD and PD health states were taken from EQ-5D data from a global, randomised, placebo-controlled, double-blind, phase 3 study, which recruited adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma. The utility of PFD in the two groups was assumed to be consistent, but SAE (grade ≥3) could affect the utility. After disease progression, the utility of all patients in PD state was 0.581 (Zhang et al., 2020b; National Institute for Health and Care Excellence, 2021). All utility values are shown in **Table 1**.

Sensitivity Analysis

One-way sensitivity analysis was performed to determine the influence of different parameters on ICER when changing within a certain range. The current price of camrelizumab fluctuated by 50% downward as the value range. The variation range of other parameters was the 95% confidence interval or the base value of the parameter ±25%. The discount rate was 0–8% (Liu, 2020). The results were presented in the form of tornado diagram. The horizontal axis of the cyclone graph represented the influence range of each parameter on ICER, and the vertical axis represented the parameter name. The degree of influence of the factors that have an influence on the evaluation result decreased from top to bottom.

In the probability sensitivity analysis, the parameters were set as random variables with specific distribution, and 10,000 Monte Carlo simulation was used to run the model to evaluate the overall robustness of the research results. The utility and the transition probability parameter were assumed to conform to the β distribution, and the cost parameter was assumed to conform to the γ distribution (Briggs et al., 2012). The results were represented by scatter plots and cost-acceptance curves.

RESULTS

Basic-Case Analysis

Compared with the chemotherapy group, camrelizumab group showed an incremental cost of $1,439.64. The incremental effectiveness was 0.36 QALY and the ICER was $3,999.00/QALY in the first scenario. When both groups continued treatment until the disease progressed, the incremental cost of the camrelizumab group was $2,319.44 and the ICER was $6,442.89/QALY. In both scenarios, the ICER was far less than the WTP threshold of one time the GDP ($10503.52/QALY), that is, the camrelizumab group had an absolute cost-effective advantage. The results of basic-case analysis are shown in **Table 2**. The results of scenario analysis on a shorter time horizon are shown in **Supplementary Table S2**.

Sensitivity Analysis

The results of one-way sensitivity analysis are shown in **Figure 2**. The main factors with a great effect on ICER were the cost of docetaxel, irinotecan, best supportive treatment, and camrelizumab. The ICER value of the model did not exceed the threshold of one time per capita GDP with the change in all uncertainty parameters, basically consistent with the conclusion of basic-case analysis.

The results of probabilistic sensitivity analysis are shown in **Supplementary Figure S3**. All the scatter points in the scatter plot were below the threshold, **Supplementary Figure S3** indicating that camrelizumab was more cost-effective than chemotherapy in all cases. The cost-effectiveness acceptance curve is showed in **Figure 3**. When the WTP threshold was $3,151.06, the probability of cost-effectiveness advantage of camrelizumab was 14.4%. When the WTP threshold was $6,302.11, the probability of cost-effectiveness advantage was 92.5%. With the increase in the threshold, the possibility of camrelizumab to cost-effective increased; when the WTP threshold was $10,503.52, the probability of cost-effectiveness advantage was 100%.

DISCUSSION

Tumor immunotherapy, especially PD-1/PD-L1 ICIs, has shown rapid progress in the field of tumor treatment in recent years, and

TABLE 2 | Summary of base-case analyses.

Factor	Camrelizumab	Chemotherapy	Incremental camrelizumab vs. chemotherapy
QALYs			
Total	0.83	0.47	0.36
	0.59[a]	0.25[a]	0.34[a]
PFD	0.27	0.15	0.12
PD	0.56	0.32	0.24
LY	1.33	0.80	0.53
	0.92[a]	0.42[a]	0.50[a]
Costs (US, $)[b]			
Total	4,643.77	3,204.13	1,439.64
	3,872.10[a]	2,452.95[a]	1,419.15[a]
PFD	2,781.21	2,143.88	637.33
PD	1,862.56	1,060.25	802.31
Drug	2,520.67	1,638.97	881.7
Follow-up	792.50	508.23	284.27
Best supportive treatment	1,293.62	736.39	557.23
SAE	36.98	320.54	−283.56
Costs (US, $)[c]			
Total	5,971.02	3,651.58	2,319.44
	5,210.87[a]	2,852.34[a]	2,358.53[a]
PFD	4,108.46	2,591.32	1,517.14
PD	1862.56	1,060.25	802.31
Drug	3,833.05	2,039.42	1,793.63
Follow-up	788.11	476.90	311.21
Best supportive treatment	1,293.63	736.40	557.23
SAE	56.23	398.86	−342.63
ICER, $/QALY			3,999.00[b]
			4,173.97[b,a]
			6,442.89[c]
			6,936.85[c,a]

QALYs, quality-adjusted life-years; PFD, progression-free disease; PD, progressive disease; LY, life years; SAE, severe adverse event; ICER, incremental cost-effectiveness ratio.
[a]Results of the Weibull survival model; Unlabeled: Results of the loglogistic survival model.
[b]First scenario: camrelizumab for six courses, docetaxel for three courses, and irinotecan for four courses.
[c]Second scenario: treatment until the disease progressed.

it has become another important tumor treatment method after surgery, radiotherapy, and chemotherapy. Considering the expected growth of immunotherapy for cancer treatment in the next few years, expenditures on patients with cancer could undoubtedly increase. The high cost of ICI treatment also brings a heavy financial burden to patients and their families. Some patients are forced to abandon ICI treatment because they could not afford it. Anticancer drugs should be more reasonable, inexpensive, and beneficial to people to finally realize their therapeutic significance. Camrelizumab entered China's National Medical Insurance catalog for the first time, and it was the only ICI to enter this catalog. The original price of camrelizumab was $2,870.52 per 200 mg, and after price reduction, it was $424.51 per 200 mg (Nation Healthcare Security Administration, 2020). The price reduction is very large. It reduces the economic burden of patient medication, thus considerably increasing the availability of ICIs. Compared with traditional chemotherapy, camrelizumab could effectively prolong the OS and improve the objective remission rate. Therefore, evaluating its cost efficiency is necessary. In the present study, the cost efficiency of camrelizumab in the treatment of ESCC was evaluated for the first time through the establishment of an economic model method and the synthesis of the latest evidence.

The optimal treatment cycle of ICIs is currently unclear. Patients who discontinue ICIs due to toxicity or other reasons may continue to show clinical benefit (Emens et al., 2017). In the established model, the influence of the duration of drug treatment on the results was considered. The results showed that compared with the ICER value of chemotherapeutic regimens, that of camrelizumab was lower than the WTP threshold of one time the GDP per capita, and camrelizumab demonstrated an absolute cost-effectiveness advantage in all scenarios. The price of drugs was the most important influencing factor, but the various parameters in the model did not have a major effect on the results of the model.

In accordance with the recommendations of the 2020 edition of the Chinese Pharmacoeconomics Guide (Liu, 2020), the present study adopted per capita GDP as the threshold of WTP. On the basis of China's national conditions, whether a higher threshold of WTP should be adopted as the evaluation standard for cancer drugs remains to be further explored. The cost-acceptance curve indicated that the possibility of cost efficiency of camrelizumab could be further improved with the

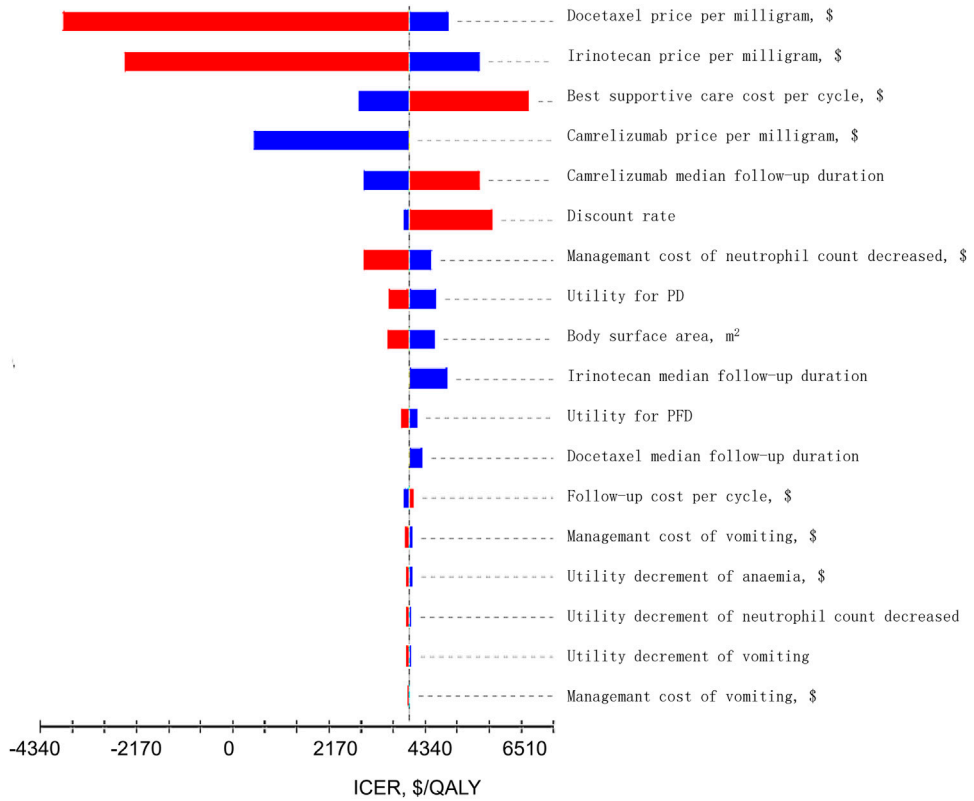

FIGURE 2 | Tornado Diagrams of Univariable Sensitivity Analyses. The dotted line intersecting the red and blue bars represents the ICER of $3,999.00 per QALY from the base case results. The red bars represents the influence of the parameter on the result after the base value rises. The blue bars represents the influence of the parameter on the result after the base value drops.

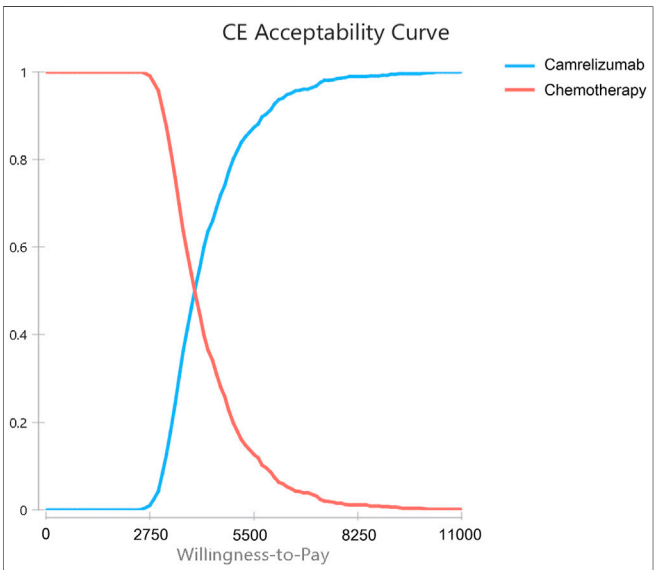

FIGURE 3 | Cost-effectiveness Acceptability Curves. Results of probabilistic sensitivity analyses for camrelizumab versus chemotherapy after 10,000 Monte Carlo simulations, which indicates the probability of cost-effectiveness at different willingness-to-pay thresholds based on the uncertainty of the parameters.

increase in threshold, and the conclusion of the model did not change.

At present, the economic research on ICIs for the treatment of esophageal cancer is very limited. In a recent study, a Markov model was established to compare the cost effectiveness of nivolumab and chemotherapy from the perspective of Chinese society. Compared with chemotherapy, nivolumab increased by 0.107 QALYs and US$14,627.90, and the ICER was US$136,709.35/QALY. With a threshold of US$29,306.43/QALY, nivolumab may not have the cost-effective advantage (Zhang et al., 2020b). Compared with previous studies, the present study evaluated the cost efficiency of camrelizumab in the treatment of esophageal squamous cell carcinoma by using the partitioned survival model and combining with the best clinical evidence. The main reason for the difference between the results of nivolumab and that of the present study is that the ICIs of the two studies are different. Nivolumab is not included in the National Medical Insurance catalog, and the price difference between nivolumab and camrelizumab is very large. Differences in clinical efficacy and safety also exist between the two drugs, and the angle of study differs. These differences may be the reasons for the inconsistency between the two studies.

This study still has certain limitations. First, the model survival data originated from a published phase 3 clinical trial, and any bias

in the trial could affect the results of this study. ESCORT is the only multicenter phase III clinical trial investigating camrelizumab in the treatment of esophageal squamous cell carcinoma. Given the strict inclusion and exclusion criteria, such as being younger and having fewer complications, patients entering clinical trials may be different from real-world patients. However, the ESCORT study is the best clinical evidence that could be found thus far, and it is a large-scale clinical study with good design. We did not have access to individual patient data from the ESCORT trials. Digitalization of the reported survival curves was used to replicate the survival data. This approach provides a reasonable, although not perfect, approximation to the actual survival data observed in the trials. The study explored alternative approaches to modelling survival such as scenario analyses using the loglogistic and Weibull distributions. The Weibull distribution gave similar results to the base-case analysis. Although there is a wide range of other functions available, these models performed reasonably well when compared with the observed survival. Therefore, the survival curve based on ESCORT research and simulation still has good accuracy and credibility. Second, no other head-to-head clinical trials were available. This study failed to compare the cost efficiency of camrelizumab with other treatment options. Third, different treatment options may be used after the disease progresses. The guidelines do not specify the third-line treatment plan for advanced or metastatic esophageal squamous cell carcinoma, and the third-line treatment plan is more complicated in clinical practice. The treatment plan after disease progression in the study was assumed to be the best supportive treatment to simplify the model, which may be different from the true state of the disease treatment. Fourth, only the SAE of grade 3 and above was considered when calculating cost and utility. The adverse events of grades 1 and 2 are usually mild, and they have a minimal effect on cost and utility. One-way sensitivity analysis showed that the results were not sensitive to the relevant parameters of SAE. Given that the results of this assessment reflected the general clinical practice of advanced esophageal squamous cell carcinoma, they may be valuable references for doctors and decision makers.

CONCLUSION

Compared with chemotherapy, the second-line treatment of advanced or metastatic esophageal squamous cell carcinoma with camrelizumab not only could improve the quality of life of patients and prolong their survival time but also reduce the incidence of adverse reactions. It also has a cost-effective advantage in Chinese population.

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

HC: Data curation, Investigation, Writing- Original draft preparation. NL: Conceptualization, Methodology, Writing-Reviewing and Editing. BZ and ZZ: Software. ML: Supervision, Visualization.

FUNDING

This study was supported by Fujian Provincial Department of Science and Technology (Grant No. 2018Y9037) of the People's Republic of China and the National Natural Science Foundation of China (Grant No. 71804025).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.732912/full#supplementary-material

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frontiers in Pharmacology

ORIGINAL RESEARCH
published: 03 December 2021
doi: 10.3389/fphar.2021.734654

Contextualising the Perceptions of Pharmacists Practicing Clinical Pharmacy in South Africa—Do We Practice what We Preach?

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The National Department of Health published their Quality Standards for Healthcare Establishments in South Africa and introduced the National Health Insurance, with the pilot phase that commenced in 2012. The system requires an adequate supply of pharmaceutical personnel and the direct involvement of clinical pharmacists throughout the medication-use process to ensure continuity of care, minimised risk with increasing improvement of patient outcomes. The study aimed to provide insight into the pressing issues of clinical pharmacy practice in South Africa, and sets out to contextualise the current profile of the pharmacist performing clinical functions. The study used a quantitative, explorative, cross-sectional design. The population included pharmacists from private and public tertiary hospitals. A questionnaire was administered, using Typeform™. Ethics approval was obtained from Sefako Makgatho Health Sciences University, National Department of Health and Private Healthcare groups. Categorical data were summarised using frequency counts and percentages; continuous data were summarised by mean values and standard deviations. The sample size included 70 pharmacists practicing clinical pharmacy (private sector $n = 59$; public sector $n = 11$). Most participants hold a BPharm degree (busy with MPharm qualification) (64%; $n = 70$). No statistical significance was found between participants in private and public practice. Most pharmacist agreed (32% (private); $n = 59$) and strongly agreed (45% (public); $n = 11$) to have sufficient training to perform pharmaceutical care. The majority respondents felt that interventions made by the pharmacist improved the rational use of medicine (47% (private); 55% (public). Pharmacist interventions influence prescribing patterns (42% (private); 64% (public); and reduce polypharmacy (41% (private); 55% (public). The clinical functions mostly performed were evaluation of prescriptions (private 90%; public 82%), while the top logistical function is daily ordering of medication (40.7%; private), and checking of ward stock (36%; public). Although not all pharmacists appointed in South Africa has completed the MPharm degree in clinical pharmacy, the pharmacists at ward level perform numerous clinical functions, even if only for a small part of their workday. This paper sets the way to standardise practices of clinical pharmacy in South Africa, with a reflection on the differences in practice in different institutions.

Keywords: pharmacy practice, clinical functions, pharmacy education, pharmaceutical care, clinical pharmacy

OPEN ACCESS

Edited by:
Kingston Rajiah, International Medical University, Malaysia

Reviewed by:
Junhao Jiang, Chongqing Medical University, China
Shazia Qasim Jamshed, Sultan Zainal Abidin University, Malaysia

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *01 July 2021*
Accepted: *17 November 2021*
Published: *03 December 2021*

Citation:
Bronkhorst E, Schellack N and Gous AGS (2021) Contextualising the Perceptions of Pharmacists Practicing Clinical Pharmacy in South Africa—Do We Practice what We Preach? Front. Pharmacol. 12:734654. doi: 10.3389/fphar.2021.734654

INTRODUCTION

In South Africa, there is a marked inequality to medicine access. The WHO states that in South African Health Care, the private sector accounts for 81% of healthcare spending of the gross GPP for health (8.5%), while only serving around 15% of the population. Private healthcare currently accounts for disproportionate availability of facilities as well as extreme misdistribution of pharmaceutical personnel between the private and public sector (Labonté et al., 2015; Meyer et al., 2017).

Furthermore, like many other countries in Africa, South Africa faces a shortage of skilled health workers, including physicians, nurses, dentists and pharmacists. The shortage of key human resources, together with the worsening burden of infectious disease in Sub Saharan Africa (including HIV, TB and malaria), is some of the challenges faced by the current healthcare system (Boschmans et al., 2015).

In 2011, the National Department of Health (NDoH) published their Quality Standards for Healthcare Establishments in South Africa, which describes the global development of quality improvement for healthcare facilities. The NDoH, also introduced the National Health Insurance (NHI) with the pilot phase that commenced in 2012 (National Department of He, 2015). The system will be dependent upon an adequate supply of pharmaceutical personnel, including pharmacists, pharmacist-assistants and pharmacy support personnel (3) The NHI will require the direct involvement of clinical pharmacists throughout the medication-use process, to ensure continuity of care, minimised risk and even reduced mortalities with an increasing improvement of patient outcomes (Labonté et al., 2015; Meyer et al., 2017). Pharmacists are required to play a role in patient safety, clinical governance and care by reducing adverse events caused by medication or medication errors. In this regard, an improvement of medication reconciliation services can improve medication safety (Labonté et al., 2015; Meyer et al., 2017). According to the Quality Standards for Healthcare Establishments, pharmacists must also ensure that medicines are readily available to patients (National Department of He, 2011).

Although the functions described in the Quality Standards for Healthcare Establishments (NDoH) are expected from pharmacists, South Africa has an estimated under-provision of pharmacists of around 60%, with only around 35% working in the institutional section (Labonté et al., 2015; Meyer et al., 2017). This leads to a burden on institutional pharmacists to provide pharmacy-based functions like dispensing and procurement. It may also lead to suboptimal clinical care, leaving the pharmacist with minimal or no time to perform ward-based functions like medication review and patient counselling, leading to suboptimal clinical care (South African Pharmacy Council, 2012).

In developed areas if the world, like Europe and the United States, clinical pharmacy are well established, and also include specialist services including clinical pharmacy in the emergency department and geriatric services (Morgan et al., 2018; Van der Linden et al., 2020). Although elsewhere in Africa, countries like Kenya and Nigeria offer training to clinical pharmacists, isolated clinical pharmacy workshops were only offered in South Africa in the early 1980's (Summers, 1991). However, training for clinical pharmacists developed rapidly thereafter, making South Africa the continent leaders in clinical pharmacy. Globally, there are many differences in the way that pharmacists practice clinical pharmacy (Miller et al., 2011). For the purposes of this paper, clinical pharmacy can be defined as "a health science specialty that embodies the application, by pharmacists, of the scientific principles of pharmacology, toxicology pharmacokinetics and therapeutics to the care of patients," (ACCP). Few hospitals in SA provide patient-specific services that frees up a clinical pharmacist from distributive and dispensing responsibilities (Pickette et al., 2010; Bronkhorst et al., 2018). In South Africa, the work climate in which clinical pharmacy is practiced is changing. Private hospital settings in South Africa have created posts for pharmacists, performing clinical oriented work, requiring a post-graduate degree in clinical pharmacy and preferably antimicrobial stewardship training. Pharmacists with postgraduate qualification in clinical pharmacy are limited, and private institutions make use of ward pharmacists to perform pharmaceutical care (Sasocp, 2013). Although South Africa is continually developing and evaluating programmes to assess use of medicines in the country and monitor the care of patients (Pickette et al., 2010; Bronkhorst et al., 2018), clinical pharmacy services across institutions cannot be generalised and requires further investigation.

The South African Pharmacy Council (SAPC) accepted the postgraduate curriculum that leads to specialist registration for clinical pharmacists, and postgraduate degree programmes with the aim to train clinical pharmacists are offered by universities (Pickette et al., 2010; Bronkhorst et al., 2018). However, it cannot be implemented until the registration of the specialisation is in place and accepted by the NDoH. Unfortunately, no standardised required level of education for practice purposes for clinical pharmacists are in place, which leads to different levels of pharmaceutical care offered in different institutions.

The difference between hospital pharmacy and clinical pharmacy as set out by the SAPC, lies in the involvement of the clinical pharmacist as a pharmaceutical partner in the multi professional health care team, as well as the role the clinical pharmacist must play in development and implementation of evidence based policies and procedures. The clinical pharmacist must also perform research and add to the academic community by publishing the research (South African Pharmacy Council (SAPC), 2010; South African Pharmacy Council, 2014).

To provide insight into the pressing issues of clinical pharmacy practice in South Africa, the paper sets out to contextualise the current profile of the pharmacists performing clinical functions as well as the different clinical functions performed in the public and private sector of the health care system.

Key concepts.

Educational background: In this study, educational background is seen as the highest qualification of the participant relating to pharmacy.

Clinical Pharmacy: can be defined as "a health science specialty that embodies the application, by pharmacists, of the scientific principles of pharmacology, toxicology pharmacokinetics and therapeutics to the care of patients" (ACCP)

Clinical Pharmacist: registered pharmacist trained in clinical aspects of patient care.

Ward Pharmacist: A registered pharmacist who becomes an integral and indispensable part of the professional health team of the hospital/institution.

Pharmaceutical Care: originally defined by Hepler and Strand as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life".

MATERIALS AND METHODS

Study Design and Duration

The study was an explorative, cross-sectional study, collecting quantitative data. The data collection period was 3 months.

Study Population and Sample

The study population included all pharmacists who are performing clinical pharmacy or rendering pharmaceutical care duties with a patient-centred approach. As clinical pharmacy in SA is developing, few qualified clinical pharmacists are available in practise, rendering services in the in-patient setting. The study population was identified using purposive sampling from a previous study, which identified pharmacists rendering clinical services at ward level (14) and included 86 pharmacists from private as well as public tertiary hospitals from an estimated 110 practicing clinical pharmacists currently in SA (Bronkhorst et al., 2018). Private healthcare groups and NDoH provided e-mail addresses for potential participants, after obtaining ethical clearance.

Data Collection Instrument

The scope of practice of a clinical pharmacist, and specific pharmaceutical care functions (Kaboli et al., 2006; South African Pharmacy Council, 2014) was used to develop a questionnaire on the different clinical functions a clinical pharmacist performs. A pilot test was performed with five eligible participants in the field, and data was not included in the results. The electronic platform Typeform™ was utilised to administer questionnaires and collect data. The questionnaire determined the level of qualification of the pharmacist performing pharmaceutical care, as well as the different functions performed at ward-level. The link was shared with participants *via* e-mail, and fortnightly follow-ups were made for a period of 2 months.

Data Collection and Analysis

This questionnaire provided information on the level of education of pharmacists rendering clinical pharmacy services, either as a clinical pharmacist or as ward pharmacist. Different functions ward-based pharmacists perform as part of their duties were identified. Data was collated on an Excel™ spreadsheet, and analysed quantitatively, to determine the number of pharmacists rendering pharmaceutical care, and the amount of time spent on these services.

Categorical data (e.g., demographic characteristics, qualifications, etc.) were summarised by frequency counts and percentage calculations with 95% confidence intervals. Continuous data (e.g., the years in practice and the time spend on ward activities) were summarised by mean values and standard deviations. Differences in continuous (percentages) data between public and private sector participants were compared by the Fisher Exact test. Pearson and Spearman correlation coefficients and 95% confidence intervals were calculated to determine differences between the private and public sectors. P-values less than 0.05 were considered significant. Bonferonni corrections were applied to p-values of public sector data, as the sample size were smaller than that for private sector. All statistical analyses were performed on SAS (SAS Institute Inc., Carey, NC, United States), Release 9.4.

RESULTS

Participant Enrolment and Response Rate

The sample size included 86 identified pharmacists from 130 hospitals, 72 ($n = 79$) in the private sector and 14 ($n = 79$) in the public sector. In the private sector, seven pharmacists resigned from the time of identification, thus the questionnaire was distributed to 65 pharmacists. Pharmacists were grouped according to geographic location and questionnaires were distributed electronically per province. A very good response rate for both the public and private sector was obtained; 59 ($n = 65$; 88.61%) and 11 ($n = 14$; 78.57%) respectively, resulting in an overall response rate of 88.61%. **Figure 1** depicts the enrolment process and the study population as grouped geographically.

Demographic Profile of Pharmacists Practicing Clinical Pharmacy.

Female participants represented 87.14% ($n = 70$) of the study population, while most participants (50%; $n = 70$) were in the age group 31–40 years of age and hold a BPharm degree (64.28%; $n = 70$). No statistical significance was found between demographic data of participants in the private sector and those in the public sector. More than half of pharmacists (54.29%; $n = 70$) reported that they spend only 1–2 hours per day in the ward doing clinical pharmacy activities. The demographic data of the participants are depicted in **Table 1**.

Perceptions of Pharmacists Regarding Pharmaceutical Care and Educational Background

Most pharmacist in the private sector (32.2%; $n = 59$) agreed and in the public sector strongly agreed (45.45%; $n = 11$) that they have the necessary training to perform pharmaceutical care. The majority of respondents felt that interventions made by the pharmacist improved the rational use of medicine (47.46% in the private sector; $n = 59$ and 54.55% in the public sector; $n = 11$). They are of the opinion that their interventions can influence prescribing patterns in their institution (42.37% in the private sector; $n = 59$ and 63.63% in the public sector; $n = 11$) and that interventions may reduce polypharmacy (40.67% in the private sector; $n = 59$ and 54.55% in the public sector; $n = 11$). No statistical significance was detected between the opinions of pharmacists in the private and public sector ($p = 0.2380–0.7615$). **Table 2** depicts the perceptions of pharmacists in the private and public sectors as well as the statistical significance between the opinions of the two groups.

As shown in **Table 3**, no statistical significance ($p = 0.662$) could be found between the actual qualification held by participants and their opinion on whether they have the necessary qualification to perform clinical pharmacy functions. Participants who obtained a Master's degree felt divided with five ($n = 21$) strongly agreeing that they have the necessary qualifications, and five disagreed.

Current Practice of Clinical Pharmacy

Pharmacists indicated the type of functions they perform in the ward setting. The functions were separated into clinical functions, which included adverse drug reaction monitoring, evaluating prescriptions, checking medication safety, discussing medication related problems with prescribers, education to nursing staff, doctors and patients, medication reconciliation, ward rounds and therapeutic drug monitoring. The logistical functions included checking expiry dates of ward stock, cytotoxic admixing, daily ordering of medication and ordering of ward stock and scheduled drugs. The clinical function that is performed most is the checking and evaluation of prescriptions (private sector 89.9% and the public sector 81.8%) while the top logistical function for the private sector is daily ordering of medication (40.7%), while in the public sector it is the checking of ward stock and expiry dates (36.4%). The top six clinical functions, with a 95% confidence interval is depicted in **Figure 2**, and the top five logistical functions, with a 95% confidence interval is depicted in **Figure 3**. The differences between the private and public sector are indicated.

DISCUSSION

In a previous study it was found that paper surveys achieved significantly higher (43.4 vs 43.4%33.7%) response rates compared to online surveys (Guo et al., 2016). Reasons stated for this phenomenon include factors like complicated login procedures, trouble with web navigation and unclear instructions. The response rate in this study was very high, compared to those stated in literature, possibly because the population was a secondary sample from a previous study (South African Pharmacy Council (SAPC), 2010; South African Pharmacy Council, 2014), purposively and a link to the questionnaire was provided via e-mail, which made the process easier. Furthermore, although motivation to participate in research are low (Adefuye et al., 2020), the high response rate is possible because of participants' previous experience with research, as they possess a post-graduate degree.

The majority of the participants were female, and in the age group 20–30 years, which is representative of the pharmacy community in South Africa. The SAPC reported that around 62% of the pharmacy workforce comprises of women and the greater part of pharmacists in South Africa are younger, with most pharmacists falling in the age group below 35 years (Pharmacy Council, 2018).

Both in the public and private sectors, with staff-shortages more pronounced in public than in private institutional sectors (South African Pharmacy Council (SAPC), 2010; South African Pharmacy Council, 2014), the majority of pharmacists felt that provided more time, their involvement in ward-based pharmaceutical care can improve the rational use of medication, influence prescribing practice and reduce polypharmacy in their different settings. Furthermore, they felt that standardised positions with specialist certification, as found in the US, might enhance practice. Many studies around the world have been published to support this belief (De Jager et al., 2014; Francis and Abraham, 2014; Kim et al., 2015; Gorman and Slavik, 2016). Contrary to this a study performed in Australia, found clinical interventions provided by basic level pharmacists to be poorly coordinated, although effective (Buss et al., 2018).

From the findings of this study, the top clinical functions pharmacists spend time on include adverse drug reaction monitoring, evaluating prescriptions, checking medication safety, medication reconciliation, ward rounds and therapeutic drug monitoring. The role of clinical pharmacists in medication errors, adverse drug events, therapeutic drug monitoring and antimicrobial stewardship (Ali et al., 2013; Williams et al., 2013; Sebaaly et al., 2015; Truter et al., 2017; Van Kemseke et al., 2017; Schellack et al., 2018) have been described extensively, both internationally and nationally. In a study from Finland, it was noted that medication reconciliation increased with 63% with the increase of clinical pharmacy services in hospitals over a 5 year period, improving medication safety with 87% (Schepel et al., 2019). Furthermore, the role of the pharmacist in specialty settings like critical care, neonatology, cardiology and infectious diseases has been described (De Jager et al., 2014; Francis and Abraham, 2014; Kim et al., 2015; Gorman and Slavik, 2016). In developed countries it has also be expanded to describe the clinical pharmacists role in the emergency department, geriatrics, ambulatory care and recently, management of

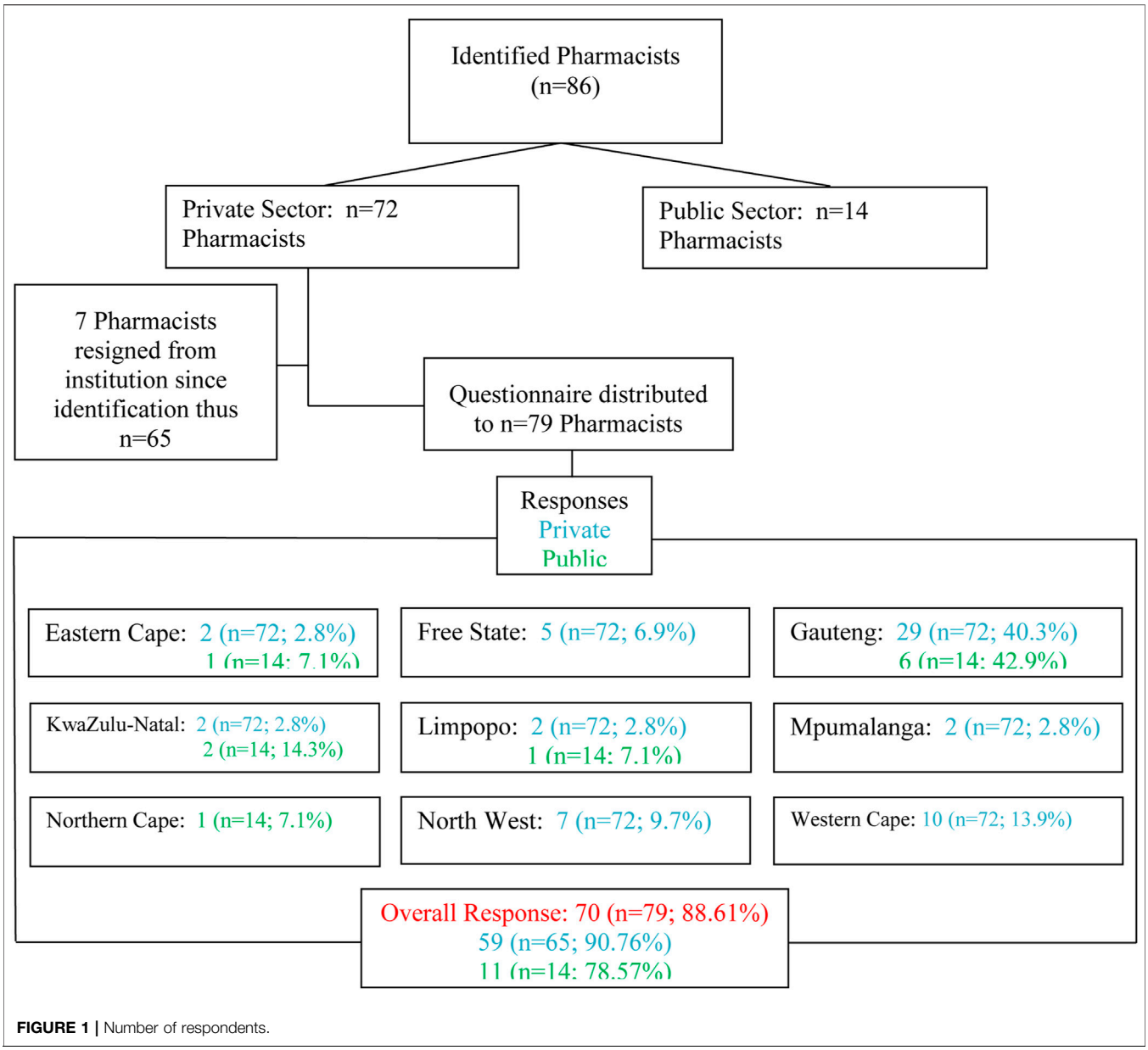

FIGURE 1 | Number of respondents.

COVID-19 (Morgan et al., 2018; Paudyal et al., 2020; Van der Linden et al., 2020). In SA, these functions are described by the SAPC in their GPP (South African Pharmacy Council (SAPC), 2010) document, although not specifically at specialist level, managing specific patient groups. As the registration process for clinical pharmacists by the SAPC and NDoH are not finalised (Gous and Schellack, 2014), there exist a lack of specific policy regarding the functions to fulfil as a clinical pharmacist in SA.

In this study, the opinions of pharmacists did not differ regarding pharmaceutical practice, regardless of their highest qualification. The Master's degree in Clinical Pharmacy offered by the Sefako Makgatho Health Sciences University (SMU), consist of a didactic modular component (2 years) and a research component (De Jager et al., 2014; Francis and Abraham, 2014; Kim et al., 2015; Gorman and Slavik, 2016). Many of the pharmacists participating in the study completed the modular component of their degree, but are still busy with the research component, hence did not obtain the degree yet. In a study performed in China, is was concluded that specific efforts must be made to improve pharmacist competence in order to improve pharmaceutical care (Xi et al., 2019). Differences between older and younger pharmacists, or longer experience with clinical work were also insignificant. This were different in a study done in Russia, that indicated that younger pharmacists (20–30 years old) do significantly fewer activities like prescription validation and evaluation of patient satisfaction than their older counterparts

TABLE 1 | Demographic Profile of the participants.

		Public	Private	Total	p-value[a]
Sex	Female	9 (12.86%)	52 (74.29%)	61 (87.14%)	0.6249
	Male	2 (2.86%)	7 (10.0%)	9 (12.86%)	
Age	20–30 years	3 (4.29%)	12 (17.14%)	15 (21.43%)	0.1909
	31–40 years	6 (8.57%)	29 (41.43%)	35 (50%)	
	41–50 years	2 (2.86%)	4 (5.71%)	6 (8.57%)	
	Older	0 (0%)	14 (20%)	14 (20%)	
Qualification	Dip Pharm	0 (0%)	1 (1.43%)	1 (1.43%)	0.0143
	BPharm	3 (4.29%)	42 (60.0%)	45 (64.28%)	
	MPharm/MSc(Med)	7 (10.0%)	14 (20.0%)	21 (30%)	
	PharmD/PhD	1 (1.43%)	1 (1.43%)	2 (2.86%)	
Societies	PSSA	6 (8.57%)	31 (44.29%)	37 (52.86%)	0.5347
	SAAHIP	3 (4.29%)	14 (20.0%)	17 (24.28%)	
	SASOCP	5 (7.14%)	33 (47.14%)	38 (54.29%)	
	Other	0 (0%)	12 (17.14%)	12 (17.14%)	
Years' Experience	0–5 years	3 (4.29%)	11 (15.71%)	14 (20.00%)	0.0798
	6–10 years	2 (2.86%)	23 (32.86%)	25 (35.71%)	
	11–20 years	5 (7.14%)	9 (12.86%)	14 (20%)	
	More than 20 years	1 (1.43%)	16 (22.86%)	17 (24.29%)	
Years Clinical Experience	0–1 year	3 (4.29%)	16 (22.86%)	19 (27.14%)	0.7194
	2–3 years	6 (8.57%)	28 (40.0%)	34 (48.57%)	
	4–5 years	2 (2.86%)	7 (10.0%)	9 (12.86%)	
	More than 5 years	0 (0%)	8 (11.43%)	8 (11.43%)	
Hours spend in ward	1–2 h	9 (12.86%)	29 (41.43%)	38 (54.29%)	0.0891
	3–4 h	0 (0%)	18 (25.71%)	18 (25.71%)	
	4–6 h	0 (0%)	4 (5.71%)	4 (5.71%)	
	7–8 h	2 (2.86%)	9 (12.86%)	10 (14.29%)	

[a]*Statistical significance were derived from using Fisher's Exact test.*

TABLE 2 | Perceptions of pharmacists.

	Strongly agree		Agree		Neutral		Disagree		Strongly disagree		p-value[a]
	Private	Public	Private	Public	Private	Public	Private	Public	Private	Public	
Do you have the necessary training to do your work?	13	5	19	2	11	1	13	1	5	0	0.4206
	22.03%	45.45%	32.20%	18.18%	18.64%	9.09%	22.03%	9.09%	8.47%	0%	
Interventions made by the pharmacist improved the rational use of medicine	28	6	16	2	5	0	5	1	5	2	0.7651
	47.46%	54.55%	27.12%	18.18%	8.47%	0%	8.47%	9.09%	8.47%	18.18%	
Interventions made by the pharmacists can influence prescribing patterns	25	7	18	1	8	1	4	0	4	2	0.3026
	42.37%	63.63	30.51%	9.09%	13.56%	9.09%	6.78%	0%	6.78%	18.18%	
Interventions made by the pharmacist can reduce the practice of polypharmacy	24	6	21	3	6	0	6	0	2	2	0.2380
	40.67%	54.55%	35.59%	27.27%	10.16%	0%	10.16%	0%	3.39%	18.18%	

[a]*Statistical significance were derived from using the Fisher's Exact test.*

(Cordina et al., 2008). The study concluded that pharmacists in South Africa are performing a variety of functions at ward level, which include clinical functions as well as logistical functions.

This study can not be generalised to the general pharmacist population in South Africa. However, it is a good representation of clinical pharmacy services in South Africa, as it included the input from between 78 and 88% of pharmacists practicing clinical pharmacy in both public and private healthcare facilities.

STRENGTHS AND LIMITATIONS

To the knowledge of the researcher, this is the first study in South Africa, which sought to engage pharmacists in pharmaceutical practice-based research on a large scale. A limitation was that the participants did not have the option to state if they were in the process of obtaining a Master's degree, leading to indistinct clarification of qualification between the role of the dispensing pharmacists and pharmacists performing clinical functions.

TABLE 3 | Opinion on Qualification compared to Qualification.

Opinion: Do you have the necessary qualification to perform clinical pharmacy functions?	BPharm[b]	MPharm/MSc(Med)	PharmD/PhD	Total	p-value[a]
Strongly Agree	11	5	1	17	$p = 0.662$
Agree	13	6		19	
Neutral	9	3		12	
Disagree	9	5		14	
Strongly Disagree	2	2	1	5	

[a]*Statistical significance were derived from using Fisher's Exact test with Bonferoni corrections.*
[b]*BPharm including enrolled for continued studies.*

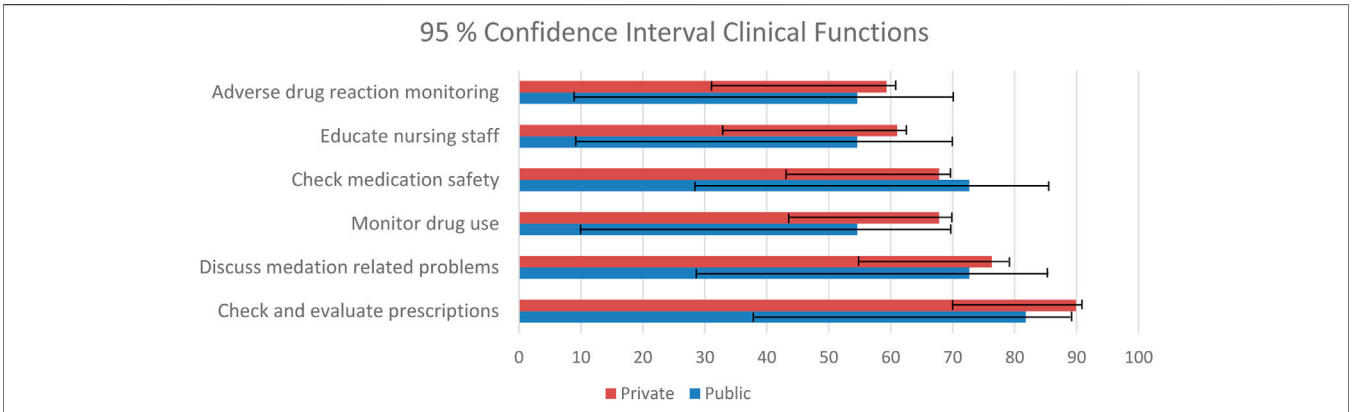

FIGURE 2 | Clinical functions.

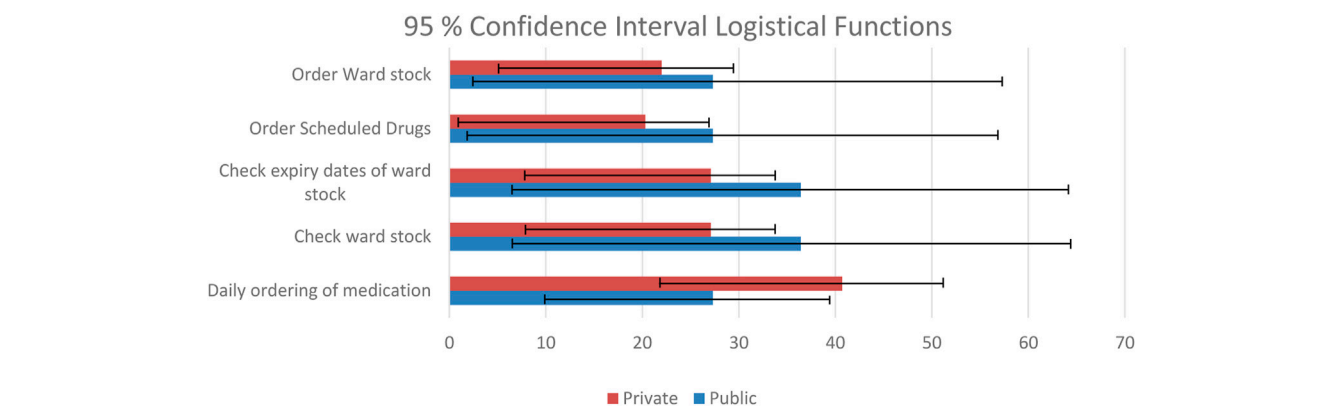

FIGURE 3 | Logistical functions.

RECOMMENDATION

A certification system for qualified clinical pharmacists needs to be put in place, with an expectation of dedicated posts for clinical pharmacists. The influence of such a system, with dedicated posts for clinical pharmacists, may be evaluated retrospectively after implementation, to evaluate to influence of adequate time in the workday on the quality of clinical services provided to patients. The benefit of implementing a certification system will be to standardise the practice of clinical pharmacy services across

different facilities, ensuring uniform delivery of clinical pharmacy practice. A future study on the perceptions of physicians, nurses and dispensing pharmacists will highlight the role of the clinical pharmacist in the multidisciplinary team.

CONCLUSION

Many studies worldwide have shown the positive impact a clinical pharmacist can bring about in the healthcare setting. Even though clinical pharmacy in South Africa are rapidly developing, few pharmacists in positions are holding a MPharm degree in clinical pharmacy. Because of this fact, institutions are appointing pharmacists in the process of obtaining the degree. However, the pharmacists performing clinical functions at ward level perform numerous clinical functions, even if they spend only a small part of their workday in the wards. Around 90% of pharmacists doing clinical work evaluate prescriptions for medication errors in the ward setting. Pharmacists in South Africa are of the opinion that by doing clinical work, they reduce medication errors and improve prescribing patterns in their standard practices of clinical pharmacy. To compensate for the shortages of human resourses in pharmacy, pharmacists in clinical roles also fulfill some logistical functions like daily ordering of patient medication and ward-stock.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

The authors would like to acknowledge all clinical pharmacists that participated in the research for this work.

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ORIGINAL RESEARCH
published: 17 May 2022
doi: 10.3389/fphar.2022.710617

Effectiveness of Community Pharmacy Diabetes and Hypertension Care Program: An Unexplored Opportunity for Community Pharmacists in Pakistan

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *16 May 2021*
Accepted: *21 March 2022*
Published: *17 May 2022*

Citation:
Malik M, Hussain A, Aslam U, Hashmi A, Vaismoradi M, Hayat K and Jamshed S (2022) Effectiveness of Community Pharmacy Diabetes and Hypertension Care Program: An Unexplored Opportunity for Community Pharmacists in Pakistan. Front. Pharmacol. 13:710617. doi: 10.3389/fphar.2022.710617

Background: The effective management of patients diagnosed with both Diabetes as well as Hypertension is linked with administration of efficacious pharmacological therapy as well as improvement in adherence through counseling and other strategies. Being a part of primary healthcare team, community pharmacists can effectively provide patient care for chronic disease management. The objective of the study was to evaluate the impact of pharmacist counseling on blood pressure and blood glucose control among patients having both hypertension and diabetes attending community pharmacies in Pakistan.

Method: A randomized, controlled, single-blind, pre-post-intervention study design was used. The respondents included patients diagnosed with diabetes mellitus (Type I or II) and hypertension visiting community pharmacies to purchase their regular medicine. A simple random sampling technique using the lottery method was used to select community pharmacies in groups A (intervention, $n = 4$) and group B (control, $n = 4$). The total number of patients was 40 in each group, while estimating a dropout rate of 25%. The patients in the intervention group received special counseling. Blood pressure and blood glucose were checked after every 15 days for 6 months. Prevalidated tools such as the hypertension knowledge level scale, the diabetes knowledge questionnaire 24, and a brief medication questionnaire was used. Data were coded and analyzed using SPSS 21. Wilcoxon test ($p < 0.05$) was used to compare pre-post intervention knowledge regarding the disease, while the Mann-Whitney test ($p < 0.05$) was used to find differences in medication adherence among control and intervention groups.

Results: A significant improvement in mean knowledge scores of patients with diabetes (16.02 ±2.93 vs. 19.97 ±2.66) and hypertension (15.60 ±3.33 vs. 18.35 ±2.31) in the intervention group receiving counseling for 6 months than control group ($p < 0.05$) was noted. Furthermore, the fasting blood glucose levels (8.25 ±1.45) and systolic BP (130.10 ±6.89) were significantly controlled after 6 months in the intervention group.

Conclusion: The current study results concluded that community pharmacists' counselling has a positive impact on blood glucose and blood pressure management among patients suffering with both diabetes and hypertension.

Keywords: diabetes, hypertension, blood pressure, community pharmacist, Pakistan

INTRODUCTION

Throughout the world, the burden of disease due to chronic metabolic disorders is rising at an alarming rate (Schultz et al., 2021). Diabetes mellitus and hypertension are the most common chronic and noncommunicable diseases that affect the majority of the population residing in developed and developing countries (Smith et al., 2021). The prolonged hyperglycemia as well as increased blood pressure is related with long-term impairment, dysfunction, and failure of different organs, including eyes, kidneys, nerves, heart, and blood vessels (Kwakye et al., 2021). Pakistan has been ranked third in the burden of diabetes with a prevalence of 33 million adults in 2021 (IDF, 2021). Furthermore, according to an estimate, every one in four adults is diagnosed with hypertension in Pakistan (Benedict et al., 2018). Various factors contribute to the ineffective management of diabetes and hypertension, including low health literacy, inadequate knowledge, and poor self-care behaviors. Poor blood glucose and blood pressure control have been reported in individuals with low health literacy and poor numeracy skills (Withidpanyawong et al., 2019). The chances of non-compliance to prescriber recommendations are increased due to dissatisfaction, poor relationship with patient, long waiting times, and high cost of follow-up visits. The use of multiple medications and increased frequency of drugs also leads to non-compliance in management of these chronic diseases. Furthermore, the absence of a cost-effective and friendly healthcare system is one of the main contributors to patient nonadherence to medication (Prudencio et al., 2018). Limited time and resources, inappropriate prescribing, improper assessment of patient needs, no proper goal setting and reduced motivation for patients are just a few of the barriers faced by physicians (Stanton-Robinson et al., 2018). Ineffective communication skills of health care professionals and lack of appropriate counseling and shared decision-making skills also contribute to failure of effective management of these chronic disorders (Milosavljevic et al., 2018).

The increasing incidence of diabetes mellitus and hypertension has emphasized the development and implementation of effective management programs for both diseases at the primary health care level. One such intervention suggests the participation of community pharmacists in the management of chronic diseases which has resulted in positive results in various healthcare settings (Godman et al., 2020). Community pharmacists can play an important role in the treatment of diabetes and hypertension by helping patients achieve their therapeutic and lifestyle goals (Machen et al., 2019). A study conducted in Japan reported that interventions focused on lifestyle modifications by community pharmacists improved glycemic control in patients with Type II diabetes mellitus. After 6 months of intervention, the patients had improved HbA1c levels, as well as the number of drugs used to control blood glucose was also reduced (Okada et al., 2016). As experts in drug therapy, drug selection, and patient education, community pharmacists can be excellent additions to the multidisciplinary primary health care team, contributing to better patient care. A study conducted in Canada showed that the addition of a pharmacist to the primary care team for the treatment of hypertension and type II diabetics can lead to improved blood pressure and glucose control through medication assessments, history and physical examinations and patient counseling services (Simpson et al., 2015). Despite new medications and specific care for patients with diabetes mellitus and hypertension, control of glycemic parameters, blood pressure, and lipid profile remains largely inadequate in Pakistan. Factors that include the absence of pharmacists at community pharmacies and the lack of appropriate counseling led to the irrational use of drugs (Hayat et al., 2019; Hayat et al., 2020). Therefore, the present study was designed to evaluate the impact of patient counseling by community pharmacists on blood pressure and glucose control among patients with diabetes and hypertension in twin cities of Pakistan.

METHOD

Study Design

A randomized, controlled, single-blind, pre-post-intervention study design was used to evaluate the impact of community pharmacist counseling on blood pressure and glucose control of patients attending community pharmacies in Pakistan who suffer from both hypertension and diabetes. Community pharmacies were randomly selected, which reduced the likelihood of selection and confounding bias in determining outcomes. Participants and community pharmacists were kept blinded on the allocation of participants to the control and intervention groups to reduce information bias. Study approval (ERC/HU 029) was obtained from the Ethics Committee of Hamdard University. Informed written consent was taken by all the community pharmacists from the patients willing to participate in the study.

Study Site and Respondents

The study sites were community pharmacies located in twin cities (Islamabad and Rawalpindi) of Pakistan. The respondents included patients diagnosed with both diabetes mellitus (Type I or II) and hypertension visiting community pharmacies for purchasing their regular medicine.

Inclusion Criteria and Exclusion Criteria

Patients diagnosed with diabetes mellitus (Type I or II) and hypertension with an HbA1c value ≥ 7% and BP greater than 140/90 mmHg at the time of diagnosis were included in the study. Patients diagnosed with any concurrent endocrine disorder (such as thyroid disorders, obesity, and gestational diabetes), cardiac heart failure, end-stage renal disease, hepatitis, or cancer were excluded from the study. Patients already receiving counseling for diabetes and hypertension were also not included.

Sample Size and Sampling Technique

Eight community pharmacies located in twin cities were selected in the pre-intervention phase. A simple random sampling technique using the lottery method was used to select community pharmacies in groups A (intervention, $n = 4$) and group B (control, $n = 4$). A list of registered community pharmacists was obtained from the District Health Office of Islamabad and Rawalpindi (DHO), which helped to select community pharmacists randomly. Pharmacists working in these community pharmacies included in group A (intervention group) were trained, while no training was given to pharmacists working in community pharmacies included in group B (control group). Out of eight selected community pharmacies, the pharmacists working at these pharmacies who were willing to participate were included in the study. Out of eight pharmacists, six were males. In terms of qualification, six had Pharm. D degree while two had done M. Phil. in Pharmacy Practice. Moreover, the pharmacists had working experience as three had the experience of more than 5 years, four had the experience of 1 year, while one had the experience of 2 years. According to WHO, at least thirty encounters must be included in each group to assess the impact of the intervention. The total number of patients was 40 in each group, while estimating a dropout rate of 25%. The convenience sampling technique was used to select patients who visited community pharmacies. Ten patients were selected from each community pharmacy after taking their consent to participate in the study.

Design and Implementation of the Development of the Intervention Material

The objectives, content and intervention format were designed after a series of discussions with different stakeholders. The training material content was developed from the International Diabetes Federation Diabetes Education Module (Unwin et al., 2010) and Pharmacy- Based Hypertension Management Model: Protocol and Guidelines (World Health Organization, 2005). The name of the training module was recommended as 'Clinical Skills for the Management of Diabetes Mellitus and Hypertension'.

General Description of Training

The community pharmacists were trained by the principal and co-investigators at community pharmacies.

1) Training Aids used

The pharmacists were also provided with brochures and one-pagers related to diabetes and hypertension management and counseling, glucose and blood pressure log sheets, glucometer, BP measuring devices, and questionnaires to assess disease knowledge and medication adherence. Pharmacists were also provided patient kits containing disease brochures, diet charts, BP, and glucose monitoring cards.

2) Post Training Data Collection

Patients in the intervention group received special counseling sessions by the community pharmacist, whereas those in the control group received the usual pharmacy services, i.e., dispensing medications and providing information regarding medication administration. Patients enrolled in the control and intervention group were required to visit the community pharmacy every 15 days for 6 months during the study. At enrollment, patients in the intervention group received counseling on the disease, its complications, medication, lifestyle modifications, and self-monitoring of the disease. Each patient also received consultations based on individual needs. Patient kits were provided along with counseling. The duration of counseling was a minimum of 20 min. Blood pressure and blood glucose were monitored for each patient in both control and intervention groups at each visit by community pharmacists using digital glucometers and mercury sphygmomanometers. Fasting blood glucose was measured on each visit. The patient was instructed to follow the 8-h fasting protocol prior to testing. HbA1c values were not mentioned as they were not directly performed at the community pharmacy setting; however, the pharmacist reviewed the HBa1c values carried out by an independent lab.

Data Collection Tools

Pre-validated tools were used for the study. Written permission had been obtained from the respective organization. A pre-validated tool, Diabetes Knowledge Questionnaire 24 (Bukhsh et al., 2017), was used to assess diabetes knowledge. The Urdu version was utilized for this study. The questionnaire comprised 24 questions related to the etiology of diabetes, symptoms, lifestyle modifications, and complications. The scoring of the DKQ-24 included the sum of all correct items of each respondent. One point was given to each correct answer and no point for the incorrect option. The score range of the tool is 0–24, and the higher score indicates better patient knowledge regarding diabetes. The second prevalidated tool used for the assessment of hypertension knowledge was the Hypertension Knowledge Level Scale (Erkoc et al., 2012). The questionnaire comprised twenty-two questions related to the definition, drug compliance, lifestyle, diet, and complications. The HK-LS scoring included the sum of all correct items of each respondent. One point was given to each correct answer and no point for the incorrect option. The score range of the tool is 0–22. Higher scores indicate better patient knowledge about hypertension. Medication adherence to diabetes and hypertension medicine was assessed using the Brief Medication Questionnaire (Demoz et al., 2020). The tool BMQ is comprised of eleven questions divided into three screens according to the barriers faced by the patient: Regimen screen that asks patients about the administration of medication in the past week, a Belief

screen that deals with questions related to effects of the drug and side effects and a recall screen comprised of questions related to remembrance of potential difficulties during the administration of medicines. The Brief Medication Questionnaire Adherence Risk Scale score ranges from 0 to 4, with "0" indicating no self-reported non-adherence or barriers to adherence and "4" indicating the presence of self-reported non-adherence and three types of barriers (belief or motivational barrier, recall barrier, and access barrier). A score of 1 is given in each question if the patient reports adherence to the current regimen. A score of 0 is given if the patient reports non-adherence to medications (Shehab et al., 2016). A score ≥1 indicates a positive screen for a particular barrier. Blood pressure and glucose log sheets were designed to monitor BP and glucose after every 15 days. The mean readings were calculated after 3 months and 6 months.

Reliability of Tools

Pilot testing was conducted on 10% of the sample to check the reliability of all three tools. The Cronbach's alpha value was found to be 0.813 for Hypertension Knowledge Level Scale, 0.80 for Diabetes Knowledge Questionnaire 24, and 0.761 for the Brief Medication Questionnaire, respectively.

Data Collection Procedure and Data Analysis

Data were collected by community pharmacists trained by the principal and co-investigators. The questionnaires were administered by the pharmacists to the respondents at baseline and after 6 months. Selected community pharmacists monitored blood pressure and glucose after every 15 days for 6 months. After data collection, data were coded and entered in SPSS version-21. To check the distribution of the data, a skewness test was performed. Descriptive statistics comprising of frequency and percentages were calculated. Wilcoxon test ($p < 0.05$) was used to compare pre-post intervention knowledge regarding diabetes and hypertension. Mann-Whitney test ($p < 0.05$) was used to find differences among medication adherence among control and intervention groups and pre-and post-intervention.

RESULTS

Demographic Characteristics

Of the 40 respondents to the control group, 57.5% ($n = 23$) were males, while 42.5% ($n = 17$) were females. Of the total respondents, 20% ($n = 8$) had diabetes for the past 1–3 years, whereas 10% ($n = 4$) had a history of diabetes for more than 6 years. The majority of the respondents had a history of hypertension for more than 6 years (32.5%, $n = 13$). However, among the respondents to the intervention group, 52.5% ($n = 21$) were men, while 47.5% ($n = 19$) were women. Out of the total respondents, 25% ($n = 10$) had diabetes for the past 1–3 years, whereas 7.5% ($n = 3$) had a history of diabetes for more than 6 years. The majority of the respondents had a history of hypertension for 1–3 years (37.5%, $n = 15$). A detailed description is given (**Table 1**).

Impact of Community Pharmacist Counseling on Knowledge of Patients With Diabetes and Hypertension in Intervention Group

The results of the present study showed that the mean knowledge scores regarding diabetes mellitus and hypertension among the control group at baseline were (13.95 ± 3.11) and (14.67, ± 2.48) respectively, which did not show any improvement after 6 months, i.e., (12.72 ± 3.47) and (14.32 ± 2.42). Mean knowledge scores regarding diabetes mellitus among intervention group at baseline was (16.02 ± 2.93) which was improved after 6 months to (19.97 ± 2.66). Although the mean knowledge scores regarding hypertension among the intervention group at baseline was 15.60 ± 3.33 which improved after 6 months to 18.35 ± 2.31. A detailed description is given (**Table 2**).

Comparison of Pre-Post Intervention Knowledge of Patients With Diabetes Mellitus and Hypertension

Significant difference was observed ($p \leq 0.05$) in pre-post intervention knowledge regarding diabetes and hypertension management. Knowledge of patients was improved regarding different aspects of diabetes and hypertension management after counseling by community pharmacists. A detailed description is given (**Table 3**).

Impact of Community Pharmacist Counseling on Blood Glucose and Blood Pressure Management at Baseline, 3 and 6 Months among Control and Intervention Group

The results of the study showed that the mean fasting blood glucose levels at baseline among control (11.60 ±1.50) and intervention (11.92 ±2.15) groups was quite similar. However, the fasting blood glucose level improved at 3 months (9.32 ±1.99) and after 6 months (8.25 ±1.48) in intervention group. At baseline, the mean systolic blood pressure between the control group (142.15 ±9.36) and the intervention group (145.85 ±10.88) did not show any significant differences. On the other hand, systolic BP decreased between the intervention group at 3 months (130.18 ±10.85) and 6 months (130.10 ±6.89). A detailed description is given (**Table 4**).

Impact of Community Pharmacist Counseling on Blood Glucose and Blood Pressure Management at Baseline, 3 and 6°Months according to Different Demographic Variables Intervention Group

The results of the present study highlighted that a reduction was observed in fasting blood glucose level, systolic and diastolic blood pressure among all demographic variables. Respondents aged 31–40 years showed a comparatively greater decrease in blood glucose from baseline (11.90 ±2.38) after 3 months (9.38, ±2.22) and 6 months (9.01, ±1.52). Moreover, respondents aged

TABLE 1 | Respondents demographic characteristics.

Demographic characteristics	Control group n (%)	Intervention group n (%)
Age		
20–30 years	5 (12.5)	3 (7.5)
31–40 years	12 (30)	11 (27.5)
41–50 years	13 (32.5)	15 (37.5)
51–60 years	6 (15)	8 (20)
>60 years	4 (10)	3 (7.5)
Gender		
Male	23 (57.5)	21 (52.5)
Female	17 (42.5)	19 (47.5)
Level of Education		
Matric	3 (7.5)	5 (12.5)
Intermediate	5 (12.5)	3 (7.5)
Graduate	23 (57.5)	23 (57.5)
Postgraduate	4 (10)	6 (15)
Illiterate	5 (12.5)	3 (7.5)
Duration of Diabetes Mellitus		
<1 year	3 (7.5)	4 (10)
1–3 years	8 (20)	10 (25)
4–6 years	25 (62.5)	23 (57.5)
>6 years	4 (10)	3 (7.5)
Duration of Hypertension		
<1 year	4 (10)	3 (7.5)
1–3 years	8 (20)	15 (37.5)
4–6 years	15 (37.5)	12 (30)
>6 years	13 (32.5)	10 (25)

TABLE 2 | Impact of community pharmacist counseling on knowledge of patients with diabetes and hypertension in intervention group.

Indicators	Diabetes mellitus				Hypertension			
	Baseline control	After 6 Months control	Baseline intervention	After 6 Months intervention	Baseline control	After 6 Months control	Baseline intervention	After 6 Months intervention
Mean[a] (±SD)	13.95 (±3.11)	12.72 (±3.47)	16.02 (±2.93)	19.97 (±2.66)	14.67 (±2.48)	14.32 (±2.42)	15.60 (±3.33)	18.35 (±2.31)
Median	13.00	13.00	16.50	20.00	15.00	15.00	16.00	19.00

[a]*Higher mean scores show better knowledge.*

TABLE 3 | Comparison of pre-post intervention knowledge of patients with diabetes mellitus and hypertension.

Knowledge		N	Mean rank	Sum of ranks	Diabetes knowledge		Hypertension knowledge	
					z-value	p-value	z-value	p-value
Diabetes Knowledge	Negative Ranks	2	6.00	15.00	-5.109	**0.003**	-6.125	**0.002**
	Positive Ranks	36	19.50	525.00				
	Ties	2						
	Total	40						
Hypertension Knowledge	Negative Ranks	4	7.00	14.00				
	Positive Ranks	33	22.15	750.00				
	Ties	3						
	Total	40						

Bold values show Significant differences.

31–40 years also showed comparatively greater decrease in systolic blood pressure from baseline (142.50, ±17.67) after 3 months (129, ±12.72) and 6 months (122, ±14.14). Male respondents had comparatively improved blood glucose level (8.87, ±1.47) and systolic blood pressure (127.22, ±7.11) after 6 months. A detailed description is given (**Table 5**).

Comparison of Medication Adherence Among Pre and Post Intervention Group of Diabetic and Hypertensive Patients

Significant difference ($p \leq 0.05$) was observed in regimen screen, belief screen and recall screen of diabetes medication adherence among pre and post intervention groups. Moreover, significant

TABLE 4 | Impact of community pharmacist counseling on blood glucose and blood pressure management at baseline, 3 and 6 months among control and intervention group.

Indicators	Control group			Intervention group		
	Baseline	Three Months	Six Months	Baseline	Three Months	Six Months
Fasting Blood Glucose (mmol/L) Mean ± SD	11.60 (±1.50)	11.88 (±1.62)	11.54 (±1.56)	11.92 (±2.15)	9.32 (±1.99)	8.25 (±1.48)
Systolic BP (mmHg) Mean ± SD	142.15 (±9.36)	140.75 (±7.93)	145.48 (±6.69)	145.85 (±10.88)	130.18 (±10.85)	130.10 (±6.89)
Diastolic BP (mmHg) Mean ± SD	95.00 (±8.85)	96.50 (±8.36)	97.00 (±6.90)	95.08 (±10.96)	91.68 (±6.25)	88.83 (±5.38)

difference ($p \leq 0.05$) was observed in regimen screen and recall screen of hypertension medication adherence among pre and post intervention groups. No difference ($p \geq 0.05$) was observed in access screen of diabetes medication adherence and access and belief screen of hypertension medication adherence among pre and post intervention group. A detailed description is given (**Table 6**).

DISCUSSION

The provision of pharmaceutical care plays an important role in achieving the specified goals for patients with hypertension as well as diabetes mellitus. Pharmaceutical care and medication management services provided by community pharmacists can improve blood pressure as well as blood glucose level and improve quality of life. The results of the present study showed that the knowledge regarding diabetes mellitus and hypertension improved over 6 months in the intervention group that received counseling from a community pharmacist. The post-intervention group had better knowledge regarding disease, medication use, and complications of diabetes and hypertension. Similar findings were reported in a study conducted in France where the knowledge regarding diabetes and hypertension improved after counseling by community pharmacists (Delage et al., 2021). Pharmaceutical care programs initiated by community pharmacists can improve blood pressure and glycemic goals (Venkatesan et al., 2012). A significant reduction was observed in fasting blood glucose in the intervention group compared to the control group after 3 and 6 months. The intervention group showed a significant decrease in systolic blood pressure as compared to the control group after 3 and 6 months. Furthermore, a significant reduction was observed in diastolic blood pressure among the intervention group. This might be because community pharmacists are qualified personnel in a better position to clarify/answer different misconceptions or queries of patients. Similar findings were reported by studies conducted in numerous countries, where pharmacist counseling led to improved blood glucose levels, blood pressure, and lipid control (McAlister et al., 2014; Butt et al., 2016; Lakey et al., 2020; Reeves et al., 2021). Males in the current study reported better post-intervention diabetes and hypertension control than females. Similar findings were reported in several countries including Egypt, where a significant improvement in diabetes and hypertension management was reported after community pharmacist counseling (Khalaf et al., 2019). Better qualification was identified as an important factor in the present study, which helped improve disease management after receiving counseling from a community pharmacist. This might be due to the fact that better qualification helps in better understanding of different facts and terminologies related to disease knowledge as it helps the patient to clarify concepts by asking more questions after receiving the counseling. Similar results were reported in a study conducted in India where patients having better qualifications reported improved diabetes and hypertension management after receiving counseling by community pharmacists (Venkatesan et al., 2012).

Community pharmacists have a major role in optimizing medication therapy and improving patient adherence (Fikri-Benbrahim et al., 2013). The results of the current study showed that medication adherence improved among patients with diabetes and hypertension. The majority of the patients started to take their medicines on time after 6 months in the intervention group. Similar results were reported by a study conducted in China where medication adherence was improved after receiving counseling by community pharmacists (Li et al., 2021). Moreover, the patients enrolled in the present study believed that the drug worked for them. The majority of them agreed that they remembered the doses of their medications for hypertension and diabetes and did not worry about the side effects of the drugs. Similar findings were reported in a study conducted in China where patient adherence was improved after community pharmacist intervention (Li et al., 2021).

The results of this study helped to affirm the role of community pharmacist as an integral member of primary care services to maximize the quality of provided care and to develop a framework for medication therapy management for chronic diseases such as diabetes and hypertension that matches the specific needs of the population. The development and implementation of the current community pharmacist-led diabetes and hypertension program provide robust evidence for the stakeholders to further develop various community pharmacist-led innovative services in Pakistan.

LIMITATIONS

A few of the limitations faced during the conduction of this study included time and financial constraints. The respondents were followed up for only 6 months, so the long-term benefits of this community pharmacy model could not be observed at length. The study findings may not be generalized to other parts of the country as it was conducted within twin cities of Pakistan.

TABLE 5 | Comparison of the impact of community pharmacist counseling on the management of blood glucose level and blood pressure at baseline, 3 and 6 months according to different demographic variables between intervention group.

Demographic variables	Outcome measures	Intervention group		
		Fasting Blood Glucose (mmol/L) Mean (±SD)	Systolic BP (mmHg) Mean (±SD)	Diastolic BP (mmHg) Mean (±SD)
Age				
20–30 years	Baseline	11.07 (±2.46)	149.43 (±12.13)	99.00 (±5.65)
	3 Months	10.43 (±2.37)	137 (±9.55)	87.50 (±3.53)
	6 Months	10.00 (±1.99)	129 (±7.31)	87.50 (±3.53)
31–40 years	Baseline	11.90 (±2.38)	142.50 (±17.67)	99.14 (±8.27)
	3 Months	9.38 (±2.22)	129 (±12.72)	90 (±5.77)
	6 Months	9.01 (±1.52)	122 (±14.14)	83.57 (±4.75)
41–50 years	Baseline	11.52 (±1.65)	142.27 (±10.57)	98.64 (±9.66)
	3 Months	11.91 (±1.55)	131.91 (±10.44)	87.27 (±6.46)
	6 Months	11.54 (±1.06)	129.36 (±5.95)	86.73 (±4.10)
51–60 years	Baseline	11.05 (±2.47)	146.15 (±10.99)	98.70 (±8.64)
	3 Months	10.25 (±1.76)	131.15 (±11.36)	85.10 (±6.17)
	6 Months	10.10 (±1.55)	130.36 (±5.95)	85.10 (±6.17)
>60 years	Baseline	12.07 (±2.46)	152.15 (±10.99)	100.70 (±8.64)
	3 Months	11.43 (±2.37)	149.15 (±9.99)	99.70 (±7.69)
	6 Months	11.02 (±1.99)	149.15 (±9.99)	99.70 (±7.69)
Gender				
Male	Baseline	11.84 (±1.99)	146.07 (±11.15)	94.23 (±7.86)
	3 Months	9.23 (±1.86)	131.89 (±10.03)	86.92 (±6.304)
	6 Months	8.87 (±1.47)	127.22 (±7.11)	83.08 (±5.96)
Female	Baseline	11.09 (±2.23)	148.46 (±10.87)	96.04 (±8.77)
	3 Months	9.52 (±2.10)	133.08 (±12.33)	92.56 (±7.22)
	6 Months	9.12 (±1.45)	130.46 (±6.57)	92.56 (±7.22)
Level of Education				
Matric	Baseline	11.51 (±2.02)	147.60 (±10.15)	99.50 (±9.84)
	3 Months	8.99 (±1.89)	141.50 (±12.25)	96.20 (±4.82)
	6 Months	8.60 (±1.10)	141.50 (±12.25)	96.20 (±4.82)
Intermediate	Baseline	11.27 (±2.26)	145.00 (±13.69)	99.67 (±7.50)
	3 Months	9.53 (±2.14)	149.78 (±13.24)	99.67 (±7.50)
	6 Months	8.87 (±1.44)	146.11 (±6.00)	94.20 (±4.82)
Graduate	Baseline	11.85 (±2.36)	135.92 (±10.16)	89.54 (±8.52)
	3 Months	9.28 (±2.21)	132.15 (±8.18)	85.38 (±5.93)
	6 Months	9.06 (±1.78)	132.15 (±8.18)	85.38 (±5.93)
Postgraduate	Baseline	11.00 (±1.00)	140.50 (±11.25)	98.20 (±4.82)
	3 Months	8.00 (±1.20)	136.92 (±10.16)	90.54 (±8.52)
	6 Months	7.00 (±1.00)	127.45 (±6.88)	82.54 (±5.18)
Illiterate	Baseline	11.16 (±1.60)	140.86 (±11.76)	92.71 (±7.41)
	3 Months	10.59 (±1.56)	139.14 (±10.52)	92.71 (±7.41)
	6 Months	10.59 (±1.56)	139.14 (±10.52)	90.14 (±6.98)
Duration of Diabetes Mellitus				
1–3 years	Baseline	11.82 (±2.17)	147.67 (±10.52)	98.67 (±6.05)
	3 Months	9.17 (±1.98)	130.83 (±12.41)	81.67 (±4.08)
	6 Months	8.55 (±0.914)	129.17 (±7.36)	80.00 (±8.36)
4–6 years	Baseline	11.15 (±1.69)	144.00 (±11.91)	98.38 (±9.02)
	3 Months	8.50 (±1.52)	129.13 (±11.85)	85.00 (±4.62)
	6 Months	8.30 (±1.18)	125.00 (±8.01)	81.88 (±2.58)
>6 years	Baseline	11.24 (±2.15)	149.00 (±10.65)	94.11 (±7.43)
	3 Months	9.66 (±2.04)	134.68 (±9.18)	88.79 (±6.24)
	6 Months	9.22 (±1.62)	127.89 (±6.30)	83.95 (±5.15)
Duration of Hypertension				
1–3 years	Baseline	11.12 (±2.48)	143.20 (±10.06)	95.00 (±5.70)
	3 Months	10.32 (±2.41)	127.00 (±10.95)	85.00 (±5.00)
	6 Months	9.56 (±1.62)	126.00 (±4.18)	80.00 (±8.36)
4–6 years	Baseline	11.41 (±2.48)	147.29 (±10.95)	96.29 (±7.34)
	3 Months	8.80 (±2.30)	132.57 (±9.72)	85.71 (±6.07)
	6 Months	8.49 (±1.74)	124.29 (±8.38)	81.88 (±2.58)
>6 years	Baseline	11.69 (±1.84)	147.79 (±11.09)	98.00 (±9.48)
	3 Months	9.15 (±1.73)	132.88 (±11.00)	86.75 (±6.42)
	6 Months	8.81 (±1.28)	128.33 (±6.54)	83.95 (±5.15)

TABLE 6 | Comparison of pre and post intervention medication adherence among diabetic and hypertensive patients.

Adherence indicators	*n*	Mean ranks	Sum of ranks	Test statistics	p-value
Diabetes Medication Adherence					
Regimen Screen	Baseline: 40	Baseline: 48.03	Baseline: 1921.00	499.000	**0.001**
	Six months: 40	Six months: 32.98	Six months: 1319.00		
Belief Screen	Baseline: 40	Baseline: 21.45	Baseline: 858.00	38.000	**0.001**
	Six months: 40	Six months: 59.55	Six months: 2382.00		
Recall Screen	Baseline: 40	Baseline: 20.50	Baseline: 820.00	0.000	**0.001**
	Six months: 40	Six months: 60.50	Six months: 2420.00		
Access Screen	Baseline: 40	Baseline: 40.50	Baseline: 1620.00	800.000	0.568
	Six months: 40	Six months: 40.50	Six months: 1620.00		
Hypertension Medication Adherence					
Regimen Screen	Baseline: 40	Baseline: 48.79	Baseline: 1951.00	468.500	**0.001**
	Six months: 40	Six months: 32.98	Six months: 1288.50		
Belief Screen	Baseline: 40	Baseline: 43.36	Baseline: 1734.50	685.500	0.152
	Six months: 40	Six months: 37.64	Six months: 1505.50		
Recall Screen	Baseline: 40	Baseline: 45.05	Baseline: 1802.00	618.000	**0.051**
	Six months: 40	Six months: 35.95	Six months: 1438.00		
Access Screen	Baseline: 40	Baseline: 41.63	Baseline: 1665.00	800.000	0.568
	Six months: 40	Six months: 39.38	Six months: 1575.00		

Mann-Whitney Test (p ≥ 0.05).
Bold values show Significant differences.

CONCLUSION

The current study proved the effectiveness of the pilot model of community pharmacy Diabetes and Hypertension Care Program implemented in twin cities of Pakistan. The study concluded that community pharmacist counseling had a positive impact on diabetes and hypertension management as it has helped patients in achieving their desired blood pressure and blood glucose goals, including improvement in their medication adherence. Better health literacy and socioeconomic status can also help perceive counseling positively, leading to better diabetes and hypertension management. The effectiveness of the pilot model suggests that pharmacist-led diabetes and hypertension management programs must be initiated at community pharmacies across the country where pharmacists can provide education regarding disease, its management and self-care activities.

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 Ethical Committee of Hamdard University (ERC/HU 029). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: MM and AHu. Data collection: UA, AHu, and MM. Formal analysis: MM. Methodology: KH, MV, SJ, and MM. Resources: MM and AHu. Software: MM. Supervision: KH and SJ. Original draft: MM, UA, and AHu. Critical review and editing: KH, SJ and AHu. All authors have approved the final manuscript.

ACKNOWLEDGMENTS

The authors would like to thank all participants of the study.

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