EVIDENCE FOR ASSESSING DRUG SAFETY AND DRUG USE IN OLDER PEOPLE

EDITED BY: Vera Maria Vieira Paniz, Fabiane Raquel Motter, Luciane Cruz Lopes, Marcio Galvão Oliveira, Ria Benko and Brian Godman

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EVIDENCE FOR ASSESSING DRUG SAFETY AND DRUG USE IN OLDER PEOPLE

Topic Editors:
Vera Maria Vieira Paniz, University of the Rio dos Sinos Valley, Brazil
Fabiane Raquel Motter, University of Sorocaba, Brazil
Luciane Cruz Lopes, University of Sorocaba, Brazil
Marcio Galvão Oliveira, Universidade Federal da Bahia, Brazil
Ria Benko, University of Szeged, Hungary
Brian Godman, University of Strathclyde, United Kingdom

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EDITORIAL
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Editorial: Evidence for Assessing Drug Safety and Drug Use in Older People

Luciane Cruz Lopes[1], Ria Benko[2,3,4], Marcio Galvão Oliveira[5], Vera Maria Vieira Paniz[6], Brian Godman[7,8,9] and Fabiane Raquel Motter[1]*

[1]Graduate Course in Pharmaceutical Sciences, University of Sorocaba (Uniso), São Paulo, Brazil, [2]Institution of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary, [3]Central Pharmacy, Albert Szent Györgyi Medical Center, University of Szeged, Szeged, Hungary, [4]Department of Emergency Medicine, Albert Szent Györgyi Medical Center, University of Szeged, Szeged, Hungary, [5]Multidisciplinary Health Institute, Federal University of Bahia, Vitória da Conquista, Brazil, [6]Postgraduate Program in Collective Health, University of Vale do Rio dos Sinos (UNISINOS), São Leopoldo, Brazil, [7]Strathclyde Institute of Pharmacy and Biomedical Sciences, Faculty of Science, University of Strathclyde, Glasgow, United Kingdom, [8]Centre of Medical and Bio Allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates, [9]Division of Public Health Pharmacy and Management, School of Pharmacy, Sefako Makgatho Health Sciences University, Pretoria, South Africa

Keywords: drug safety, adverse drug reactions, medication without harm, older patients, deprescribing, potentially inappropriate medications

Editorial on the Research Topic

Evidence for Assessing Drug Safety and Drug Use in Older People

Prescribing for older patients presents several challenges. Older people often suffer from two or more chronic diseases (multimorbidity) and therefore use a greater number of medications compared to other age groups. As a result, they are more susceptible polypharmacy, and associated drug-related problems, including potentially inappropriate medication (PIM), drug ineffectiveness, drug interactions, and adverse drug events (Nobili et al., 2011; Aggarwal et al., 2020). Consequently, optimizing drug therapy is a crucial part of caring for an elderly individual. This is increasingly important given the rising number of older adults across countries in the coming years, with one in six of the world's population over 60 by 2050 and the associated resource implications (World Health Organization, 2021).

Many studies (Oliveira et al., 2012; Shah and Hajjar, 2012; Khatter et al., 2021; Xu et al., 2021) point out that polypharmacy is a risk factor for PIM, particularly for older patients. The more medications a patient are taking, the more likely they are to have an adverse drug event (ADE), potentially experience a drug-drug interaction, take a PIM, or be non-compliant to one or more of the medications prescribed (Shah and Hajjar, 2012).

This Research Topic included 23 articles and nine of them (Ambrož et al.; Candeias et al.; Chen et al.; Kardas et al.; Kurczewska-Michalak et al.; Machado-Duque et al.; Perpétuo et al.; Schneider et al.; Bobrova et al.) studied PIM and polypharmacy in older adults. Four of them (Kardas et al.; Khatter et al., 2021; Machado-Duque et al.; Schneider et al.) estimate the prevalence of PIM or polypharmacy in older adults.

In recent years, several strategies and tools have been developed to identify the inappropriate prescribing of medications. Typically, adaptations and selections have to be made depending on the setting and the medications available in a country (Motter et al., 2018; Motter et al., 2019). STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert to Right Treatment) are criteria typically used as a tool for clinicians to review PIMs in older adults and have been endorsed as best practice by some organizations. The study of Bobrova et al. developed an integrated PIM clinical decision support tool for identification of drug-related problems among geriatric patients in geriatric multi-morbid polypharmacy patients, using the EU-PIM and EURO-

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****Correspondence:***
Luciane Cruz Lopes
Luslopesbr@gmail.com

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FORTA lists, with a focus on high-risk medications. The articles from Candeias et al. and Perpétuo et al. analyzed the concordance and prevalence of PIM different tools.

In particular, polypharmacy is known to cause a higher risk of ADEs as well as drug-drug interactions, which often leads to poor compliance with prescribed medicines. All these negatively impact on the health of patients as well as increase the risk of geriatric syndromes, e.g., cognitive impairment or falls. An important disparity is the difference of sex and gender in the proportion of types of medication used among older patients Lu et al., which needs to be factored into future prescribing.

Avoidable ADEs are the consequences of inappropriate drug prescribing including inappropriate polypharmacy. This, in turn, leads to increased costs and health care expenditures (Maher et al., 2014). The studies of Alnijadi et al. and Katsuno et al. analyzed the direct cost of managing adverse drug events and that of avoidable ADEs as well as cost-related medication non-compliance with medicines on healthcare utilization and patient-reported outcomes. Consequently, we are seeing health authorities across countries instigate activities to improve prescribing in the older adults and reduce ADEs and their associated costs, with these activities likely to grow with an increasing older population (MacBride-Stewart et al., 2021).

Numerous factors contribute to the appropriateness and comprehensive quality of drug prescribing. The process of prescribing a medication is multifaceted and includes: verifying that a drug is indicated and avoiding overuse of medicines for prevention, selecting the best drug, determining a dose and duration appropriate for the patient's physiologic status, monitoring for effectiveness and toxicity, educating the patient about expected side effects, and indications for seeking a consultation.

Zazzara et al. verified the medication use and costs among older adults aged 90 years and conclude that the persistent use of preventive medications highlights the potential lack of awareness regarding medication rationalization among clinicians and provided guidance for optimizing prescriptions. Chen et al. identified factors that have an impact on the management of potentially inappropriate prescribing and concluded that gerontology practitioners should be prudent in applying clinical guidelines to provide personalized, comprehensive assessment of decision making of prescriptions, especially in socioeconomically deprived areas. Qu et al. explored the relationship between drug literacy and frailty and conclude that the first was an important consideration in the development, implementation, and evaluation of frailty.

Approaches to decrease inappropriate prescribing in older adults include educational interventions, peer comparison feedback, computerized order entry and decision support, multidisciplinary team care led by physicians, clinical pharmacists, and combinations of these approaches (Rochon, 2022). The scoping review of (Kurczewska-Michalak et al.) published in this Research Topic mapped available interventions and more complex strategies to prevent and manage polypharmacy in the older adults and discussed their potential implementation. The authors concluded that the development of strategies for the detection and prevention of drug-related problems is important to guide and support clinical decision-making and strengthen research into drug safety. This is an essential condition for achieving wide-ranging improvements in the management of older patients. Whilst different approaches have been identified to avoid drug-related problems in older patients, there is still insufficient information about their clinical importance or their public health impact. The authors also suggested that guidance on polypharmacy management in older adults is still limited. Initiatives to understand and conceptualize healthcare professional's barriers and enablers can be used to increase knowledge translation and strengthen capacity for appropriate interventions in routine clinical practice (Motter et al., 2021).

This Research Topic also included studies comparing the efficacy and safety of anticoagulants or antiplatelets in cardiovascular disease (Wawruch et al.; Zhao et al.; Li et al.). This is important as there were concerns with excessive bleeding in the elderly when dabigatran, the first non-vitamin K antagonist oral anticoagulants (NOAC) was first launched (Malmström et al., 2013). Physician knowledge has now grown, with more recent studies comparing key issues such as effectiveness and safety among the NOACs (Mueller et al., 2019; Komen et al., 2021).

Studies that analyzed the safety and efficacy of medications in other common problems in older patients were also included in this Research Topic. Two studies (Huang et al.; Yang et al.) estimated the efficacy of propofol in adult or older patients with different conditions. Two systematics reviews (Huang et al.; Zhang et al.) studied the efficacy and safety of drug use in secondary care. Gao et al. conducted a network meta-analysis to summarize all available evidence about relative effectiveness of different pharmacotherapy of macular edema secondary to retinal vein occlusion. Yu et al. conducted a cross-sectional study, analyzing the trends in the topical prescription's treatment of old patients with dry eye disease.

Optimizing the use of medications is increasingly recognized as an important pillar in the health care of older people. Collectively, this Research Topic highlights pertinent concerns related to the safe use of medications in this age group and promotes awareness of optimizing older adults' medication regimens. The results demonstrate that improving the quality of medication use and medication safety are still important challenges for healthcare professionals who care for older patients. Other initiatives are required for this field to reach its full potential of optimizing drug use in older patient to improve their health care outcomes within available resources.

AUTHOR CONTRIBUTIONS

LL and FM contributed to the design and to the analysis of results. RB, MO, VP, and BG made additional analysis. All authors contributed to the manuscript and approved the submitted version.

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Non-Persistence With Antiplatelet Medications Among Older Patients With Peripheral Arterial Disease

Martin Wawruch[1], Jan Murin[2], Tomas Tesar[3]*, Martina Paduchova[4], Miriam Petrova[1], Denisa Celovska[2], Beata Havelkova[5], Michal Trnka[6] and Emma Aarnio[7,8]*

[1]Institute of Pharmacology and Clinical Pharmacology, Faculty of Medicine, Comenius University, Bratislava, Slovakia, [2]1st Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia, [3]Department of Organization and Management of Pharmacy, Faculty of Pharmacy, Comenius University, Bratislava, Slovakia, [4]Department of Angiology, Health Centre, Trnava, Slovakia, [5]General Health Insurance Company, Bratislava, Slovakia, [6]Institute of Medical Physics, Biophysics, Informatics and Telemedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia, [7]Institute of Biomedicine, University of Turku, Turku, Finland, [8]School of Pharmacy, University of Eastern Finland, Kuopio, Finland

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Edited by:
Ria Benko,
University of Szeged, Hungary

Reviewed by:
Joris Komen,
Utrecht University, Netherlands
Karel Urbánek,
Palacký University Olomouc, Czechia

***Correspondence:**
Martin Wawruch
martin.wawruch@gmail.com
Tomas Tesar
tesar@fpharm.uniba.sk

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Introduction: Antiplatelet therapy needs to be administered life-long in patients with peripheral arterial disease (PAD). Our study was aimed at 1) the analysis of non-persistence with antiplatelet medication in older PAD patients and 2) identification of patient- and medication-related characteristics associated with non-persistence.

Methods: The study data was retrieved from the database of the General Health Insurance Company. The study cohort of 9,178 patients aged ≥ 65 years and treated with antiplatelet medications was selected from 21,433 patients in whom PAD was newly diagnosed between 01/2012 and 12/2012. Patients with a 6 months treatment gap without antiplatelet medication prescription were classified as non-persistent. Characteristics associated with non-persistence were identified using the Cox regression.

Results: At the end of the 5 years follow-up, 3,032 (33.0%) patients were non-persistent. Age, history of ischemic stroke or myocardial infarction, clopidogrel or combination of aspirin with clopidogrel used at the index date, higher co-payment, general practitioner as index prescriber and higher overall number of medications were associated with persistence, whereas female sex, atrial fibrillation, anxiety disorders, bronchial asthma/chronic obstructive pulmonary disease, being a new antiplatelet medication user (therapy initiated in association with PAD diagnosis), and use of anticoagulants or antiarrhythmic agents were associated with non-persistence.

Conclusion: In patients with an increased probability of non-persistence, an increased attention should be paid to improvement of persistence.

Keywords: peripheral arterial disease, antiplatelet medications, non-persistence, discontinuation, atrial fibrillation, anxiety disorders

INTRODUCTION

Our manuscript is focused on older patients with peripheral arterial disease (PAD) of lower limbs, a chronic atherosclerotic disease affecting the peripheral vasculature of lower limbs. It is associated with limb-related symptoms and complications such as intermittent claudication, ischemic rest pain, and critical limb ischemia. PAD may result in gangrene of the affected limb requiring amputation. Since atherosclerosis represents a generalized process affecting the whole cardiovascular (CV) system, PAD is associated with an increased risk of CV events (ischemic stroke, myocardial infarction (MI) and CV death) (Agrawal and Eberhardt, 2015; Bonaca and Creager, 2015; Morley et al., 2018). PAD is a relatively frequent disease, its prevalence increasing with advancing age. According to the systematic review by Fowkes et al. (2013), 202 million people were affected with PAD globally in 2010, 69.7% of them in low- or middle-income countries. In high-income countries, the prevalence of PAD at age 45–49 years was 5.3% among women and 5.4% among men and, at age 85–89 years, it was 18.4% among women and 18.8% among men.

Besides the management of modifiable risk factors (smoking cessation, pharmacologic treatment of high blood pressure, increased blood glucose levels, and dyslipoproteinemia), PAD treatment includes administration of antiplatelet agents, inhibitors of angiotensin-converting enzyme/angiotensin receptor blockers and statins. Platelet hyperaggregability in PAD patients as well as an important role of platelets in the atherosclerotic process justify the use of antiplatelet agents in the treatment of PAD (Aboyans et al., 2018; Bevan and White Solaru, 2020).

Adherence to antiplatelet medication represents the basic requirement for successful treatment of PAD patients. Although medications used in treatment of CV diseases have improved significantly, adherence to these medications remains unsatisfactory (Xu et al., 2020). The issue of medication adherence is particularly relevant in case of asymptomatic conditions (e.g., treatment of CV risk factors) (Burnier, 2019). Adherence includes three interrelated phases: initiation, implementation and persistence. Initiation represents the start of using the prescribed medication. Implementation reflects the extent to which a patient´s actual dosing corresponds to the prescribed dosing (from initiation until the last dose). Persistence refers to the length of time between initiation and discontinuation (Vrijens et al., 2012; De Geest et al., 2018). Since antiplatelet therapy needs to be administered life-long in PAD patients, we focused our study on the issue of non-persistence with this medication.

In the literature there is a lack of information about adherence to medications used in secondary prevention in older PAD patients. The study by Qvist et al. (2019) evaluated adherence to antiplatelet and statin therapy; however, besides PAD patients, it included also subjects with abdominal aortic aneurysm, and the age of participants was limited to the range of 65–74 years. Persistence was defined as an absence of treatment gap > 100 days between two prescription renewals. No predictors of persistence were found in the study. To fill in this gap in the literature and describe patterns of persistence with antiplatelet therapy in older PAD patients, our study was aimed at 1) the analysis of non-persistence and 2) identification of patient- and medication-related characteristics associated with non-persistence. To the best of our knowledge, our study is the first one to evaluate these issues to such an extent.

METHODS

Database and Study Population

The study data was retrieved from the database of the General Health Insurance Company. It is the largest health insurance provider in Slovakia covering approximately 63% of the population. In this database, 21,433 patients in whom PAD was newly diagnosed between January 1 and December 31, 2012 were identified. Among the patients in this database, antiplatelet medication use was recorded in 15,382 patients. Out of these patients, those aged ≥ 65 years (n = 9,892) were selected. Patients with only one antiplatelet medication prescription during the 5 years follow-up period (n = 604) and those who changed their health insurance company (n = 110) were excluded. After the exclusion of these patients, there remained a sample of 9,178 patients used as the study cohort for further evaluations (**Figure 1**). This database of 21,433 patients represented a source of data in our previous study focused on non-persistence with statin treatment in older patients with PAD (Wawruch et al., 2019). In Slovakia, aspirin is available as an over-the-counter drug, but in case of diseases in whose treatment aspirin is fully indicated (e.g., PAD), it is prescribed by a physician. Consequently, its use in PAD patients can be traced via registers.

Analysis of Non-Persistence

The index date of our retrospective cohort study was the date of the first dispensation of antiplatelet medication at a pharmacy after the diagnosis of PAD. From the index date, patients were followed for 5 years or up to the date of their death if it occurred during the follow-up period. Patients who died were censored to avoid their misclassification as non-persistent subjects.

Non-persistence was identified according to the treatment gap period which was defined as a 6 months period without any antiplatelet medication prescription observed after the estimated date of the last day covered by the last package of the prescribed medication. All tablets in previous packages were considered when calculating the length of the period covered by medication (i.e., tablets carried over in case of early prescriptions). The start of non-persistence was set at the first day after the end of the period covered by the prescribed medication, i.e., the first day of treatment gap. Antiplatelet medications were considered as a medication group, i.e., persistence with particular antiplatelet agents, besides the initial treatment, was not examined. Except for ticlopidine, dosing of one tablet per day was considered to calculate the number of tablets of antiplatelet medications needed for a certain time period. In case of ticlopidine, twice daily administration was considered. Patients with a treatment gap

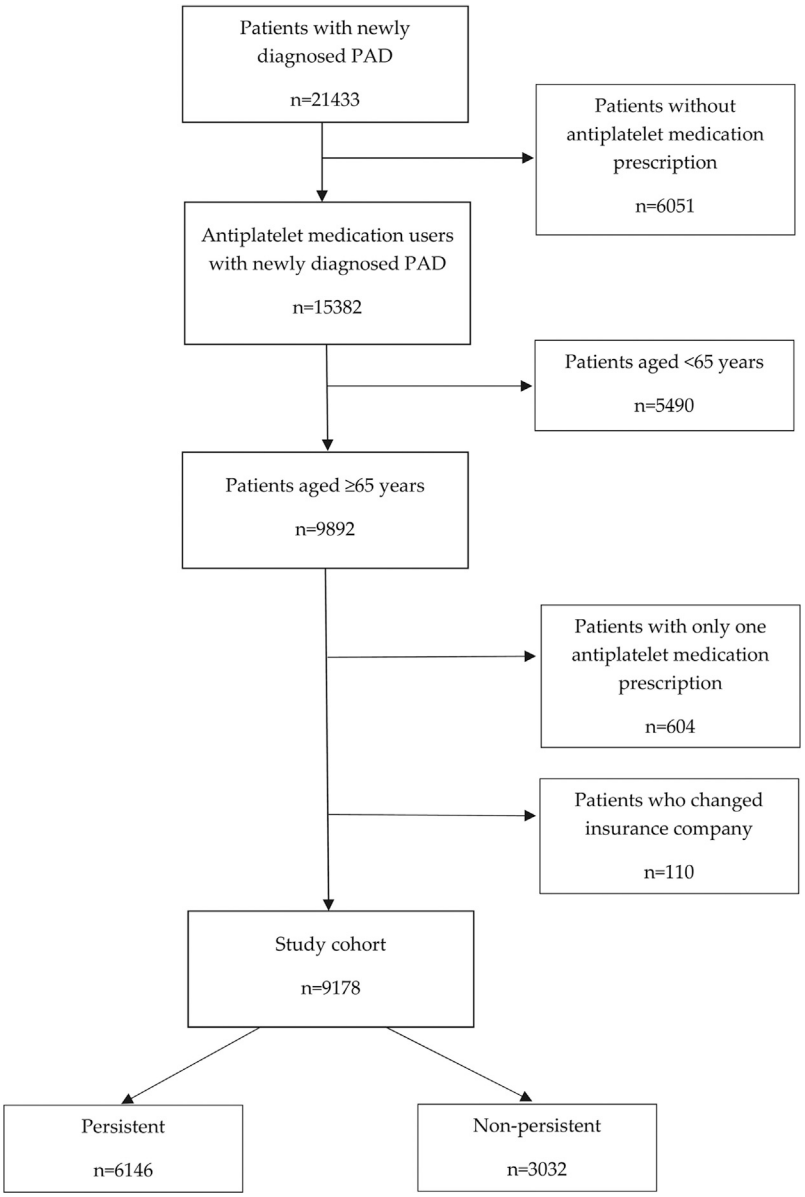

FIGURE 1 | Flow chart of the study cohort (*n* = 9,178).

period were classified as non-persistent and those without such period were considered as persistent.

Analysis of Factors Associated With Non-Persistence

Data on patient- and medication-related characteristics, evaluated as factors potentially associated with non-persistence, were collected at the time of inclusion in the study cohort. The following characteristics were analyzed:

a) Socio-demographic characteristics: age, gender, university education, and employment.
b) History of CV events: ischemic stroke, transient ischemic attack (TIA), and MI during 5 years before the index date.
c) Number of comorbid conditions and particular comorbidities. Data on comorbid conditions were collected in accordance with the 10th revision of the International Classification of Diseases (ICD-10, 1992) (**Supplementary Table S1**).
d) Antiplatelet medication-associated characteristics: initially (i.e., on the index date) administered antiplatelet agent(s), whether the patient was a new (antiplatelet treatment initiated in association with PAD diagnosis) or prevalent (administered already before PAD diagnosis) user of antiplatelet medication, patient's co-payment per

one month, and whether the antiplatelet medication was prescribed initially after the PAD diagnosis by a general practitioner or a specialist. To identify new users, a period of at least 2 years without antiplatelet medication prescription before PAD diagnosis was required.

e) The overall number of medications, the number of CV co-medications and particular CV medications identified according to ATC codes (Guidelines for ATC Classification and DDD Assignment, 2018) (**Supplementary Table S2**)

Statistical Analysis

Continuous variables were expressed as means ± standard deviations, and categorical variables as frequencies and percentages.

Categorical variables were compared between persistent and non-persistent patients using the χ^2-test. The Mann-Whitney U test was applied to compare continuous variables between the two patient groups. This non-parametric test was used because of non-Gaussian distribution of evaluated variables. The distribution of continuous variables was analyzed by the Kolmogorov-Smirnov test.

The Life table analysis was used to identify numbers and proportions of patients who became non-persistent during each particular year of the 5 years follow-up period. To analyze the development of non-persistence during the follow-up period in relation to the initially used antiplatelet medication, and to clearly illustrate the differences in non-persistence among patients with particular antiplatelet agents, the Kaplan-Meier model was applied. To identify the significance of these differences, the log-rank test was used. To identify patient- and medication-related characteristics associated with non-persistence, the Cox proportional hazards model was applied. Hazard ratios and corresponding 95% confidence intervals were determined for each characteristic. The Cox regression included all variables evaluated as factors potentially associated with non-persistence. We checked the proportional hazards assumption using Schoenfeld residuals, and this assumption was met (Newman, 2001).

All tests were carried out at the significance level of $\alpha = 0.05$. The statistical software IBM SPSS for Windows, version 27, was used (IBM SPSS Inc., Armonk, NY, United States).

Sensitivity Analyses

To evaluate the potential confounding caused by the inclusion of both new and prevalent antiplatelet medication users, we performed a stratified Cox regression analysis of factors associated with non-persistence separately in the two mentioned groups. To analyze the possible influence of the length of the treatment gap period used to identify non-persistence on the results of our study, a sensitivity analysis using shorter (1–5 months) and longer (12 months) treatment gaps was performed. Since the 5 years follow-up is a relatively long period of time, we identified factors associated with non-persistence in a sensitivity analysis with a shorter 3 years follow-up period.

RESULTS

The baseline characteristics of the study cohort (n = 9,178) are summarized in **Table 1**. During the first, second, third, fourth, and fifth year of the follow-up, 14.7, 7.3, 5.4, 3.8, and 1.8% of patients, respectively, became non-persistent with antiplatelet medications. At the end of the 5 years follow-up, 3,032 (33.0%) patients were identified as non-persistent with antiplatelet medications.

The Kaplan-Meier analysis revealed a significant difference ($p < 0.001$ according to the log-rank test) in persistence among the groups of patients created according to the particular antiplatelet agents used initially at the time of PAD diagnosis (aspirin, clopidogrel, ticlopidine and combination of aspirin with clopidogrel). The sharpest decline of the survival curve can be seen with aspirin, and the curve of patients with combination of aspirin and clopidogrel indicates the lowest likelihood of treatment discontinuation **(Figure 2)**.

Table 2 shows the results of the Cox proportional hazards model which analyzed potential association between patient- and medication-related characteristics and non-persistence. Age, history of ischemic stroke or MI, clopidogrel or combination of aspirin and clopidogrel as the initial antiplatelet medication, higher patient's co-payment, general practitioner as index prescriber and higher overall number of medications appeared as protective factors decreasing the patient's likelihood of non-persistence. On the other hand, female sex, atrial fibrillation, anxiety disorders, bronchial asthma/chronic obstructive pulmonary disease (COPD), being a new antiplatelet medication user, use of anticoagulants or antiarrhythmic agents represented factors associated with increased probability of non-persistence.

Sensitivity Analyses

The distribution of patient- and medication-associated characteristics in the groups of new and prevalent antiplatelet medication users is shown in **Supplementary Table S3**. Factors associated with non-persistence evaluated separately in the groups of new and prevalent antiplatelet medication users are listed in **Supplementary Table S4**. In the analysis performed in the group of prevalent users, almost the same factors associated with non-persistence as those in the main analysis, which included both new and prevalent users, were found. The only exceptions were: history of MI and anxiety disorders represented factors influencing persistence in the main cohort but not in the group of prevalent users, while mineralocorticoid receptor antagonists were associated with persistence only in the group of prevalent users but not in the main cohort. On the other hand, in the group of new users only age and the use of combination of aspirin and clopidogrel at the time of inclusion in the study were associated with persistence.

The inverse relationship between the length of the treatment gap period (1–6, 12 months) and the proportion of non-persistent patients was confirmed **(Table 3)**. The 6 month period defining non-persistence may be considered as optimal choice since the use of shorter (1–5 months) or longer (12 months) treatment gap periods may lead to over- or

TABLE 1 | Baseline characteristics of the study cohort.

Factor	All (*n* = 9,178)	Persistent (*n* = 6,146)	Non-persistent (*n* = 3,032)	*p*
Socio-demographic characteristics				
Age	75.2 ± 6.8	76.0 ± 7.1	73.7 ± 6.0	<**0.001***
Female sex	5,285 (57.6)	3,413 (55.5)	1,872 (61.7)	<**0.001**
University education	637 (6.9)	393 (6.4)	244 (8.0)	**0.003**
Employed patients	448 (4.9)	258 (4.2)	190 (6.3)	<**0.001**
History of cardiovascular events[a]				
History of ischemic stroke	1,756 (19.1)	1,314 (21.4)	442 (14.6)	<**0.001**
History of TIA	715 (7.8)	488 (7.9)	227 (7.5)	0.446
History of MI	577 (6.3)	445 (7.2)	132 (4.4)	<**0.001**
Comorbid conditions				
Number of comorbid conditions	2.8 ± 1.6	2.9 ± 1.6	2.6 ± 1.6	<**0.001***
Arterial hypertension	7,551 (82.3)	5,218 (84.9)	2,333 (76.9)	<**0.001**
Chronic heart failure	739 (8.1)	563 (9.2)	176 (5.8)	<**0.001**
Atrial fibrillation	1,124 (12.2)	736 (12.0)	388 (12.8)	0.259
Diabetes mellitus	3,866 (42.1)	2,739 (44.6)	1,127 (37.2)	<**0.001**
Hypercholesterolemia	3,577 (39.0)	2,361 (38.4)	1,216 (40.1)	0.118
Dementia	815 (8.9)	644 (10.5)	171 (5.6)	<**0.001**
Depression	1,082 (11.8)	745 (12.1)	337 (11.1)	0.159
Anxiety disorders	2,816 (30.7)	1,876 (30.5)	940 (31.0)	0.640
Parkinson's Disease	444 (4.8)	326 (5.3)	118 (3.9)	**0.003**
Epilepsy	246 (2.7)	179 (2.9)	67 (2.2)	**0.049**
Bronchial asthma/COPD	2,106 (22.9)	1,397 (22.7)	709 (23.4)	0.484
Antiplatelet agent related characteristics				
Initial antiplatelet agent				
Aspirin	6,391 (69.6)	4,103 (66.8)	2,288 (75.5)	<**0.001**
Clopidogrel	1,562 (17.0)	1,121 (18.2)	441 (14.5)	
Ticlopidine	639 (7.0)	462 (7.5)	177 (5.8)	
Aspirin + clopidogrel	586 (6.4)	460 (7.5)	126 (4.2)	
New antiplatelet agent user[b]	1,314 (14.3)	737 (12.0)	577 (19.0)	<**0.001**
Patient´s co-payment (EUR)[c]	1.4 ± 1.2	1.5 ± 1.3	1.3 ± 1.1	<**0.001***
General practitioner as index prescriber	6,678 (72.8)	4,626 (75.3)	2,052 (67.7)	<**0.001**
Cardiovascular co-medication				
Number of medications	8.1 ± 2.6	8.3 ± 2.5	7.8 ± 2.8	<**0.001***
Number of CV medications	5.0 ± 2.3	5.1 ± 2.3	4.8 ± 2.3	<**0.001***
Anticoagulants	1,917 (20.9)	1,300 (21.2)	617 (20.3)	0.374
Cardiac glycosides	744 (8.1)	578 (9.4)	166 (5.5)	<**0.001**
Antiarrhythmic agents	654 (7.1)	416 (6.8)	238 (7.8)	0.058
Beta-blockers	1,789 (19.5)	1,241 (20.2)	548 (18.1)	**0.016**
Thiazide diuretics	1,991 (21.7)	1,313 (21.4)	678 (22.4)	0.275
Loop diuretics	2,177 (23.7)	1,655 (26.9)	522 (17.2)	<**0.001**
Mineralocorticoid receptor antagonists	722 (7.9)	575 (9.4)	147 (4.8)	<**0.001**
Calcium channel blockers	2,856 (31.1)	1,918 (31.2)	938 (30.9)	0.792
RAAS inhibitors	7,659 (83.4)	5,188 (84.4)	2,471 (81.5)	<**0.001**
Statin	6,319 (68.8)	4,168 (67.8)	2,151 (70.9)	**0.002**
Lipid lowering agents other than statins[d]	902 (9.8)	596 (9.7)	306 (10.1)	0.550

In case of categorical variables, values represent the frequency and the percentages are provided in parentheses (% of n*). In case of continuous variables, means ± standard deviations are provided. TIA–transient ischemic attack; MI–myocardial infarction; COPD–chronic obstructive pulmonary disease; CV–cardiovascular; RAAS–renin-angiotensin-aldosterone system;* p*–statistical significance between persistent and non-persistent patients according to the* χ^2*-test; *Statistical significance according to the Mann-Whitney U test; In case of statistical significance (*p < *0.05), the values are expressed in bold.*

[a]*The time period covered by "history"–5 years before the index date of this study.*

[b]*New antiplatelet agent user–patient in whom antiplatelet treatment was initiated in association with the diagnosis of peripheral arterial disease.*

[c]*Co-payment–calculated as the cost of antiplatelet treatment paid by the patient per month.*

[d]*Lipid lowering agents other than statins–ezetimibe and fibrates.*

underestimation of non-persistence. In the sensitivity analysis which used the Cox model with a shorter 3 years follow-up period, the same characteristics, except for hypercholesterolemia, as those in the main model with a 5 years follow-up were associated with non-persistence. Hypercholesterolemia was associated with non-persistence only in the Cox model with a 3 years follow up period but not in one with a 5 years follow-up **(Supplementary Table S5)**.

DISCUSSION

Our study focused on the analysis of non-persistence with antiplatelet treatment in older PAD patients revealed some important findings. The proportion of PAD patients who became non-persistent with antiplatelet medication during the 5 years follow-up period (33.0%) can be considered as high. In the Cox regression model, factors associated with increased or

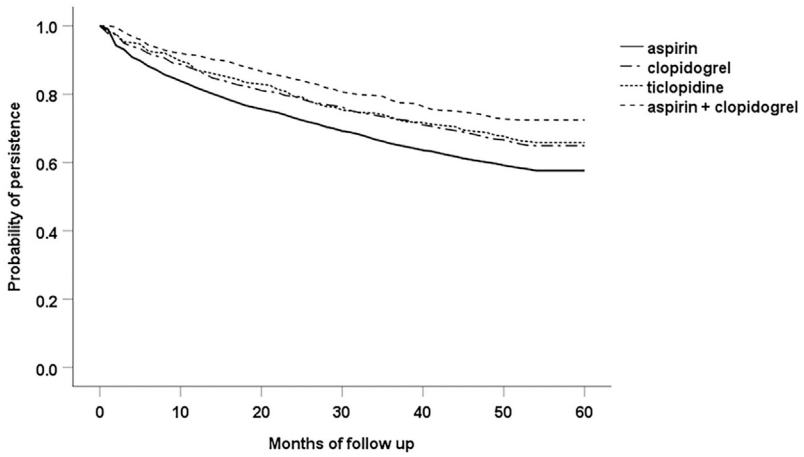

FIGURE 2 | Persistence among the groups of patients with particular antiplatelet agents used at the index date of the study.

decreased probability of non-persistence were identified. To the best of our knowledge, there are almost no similar studies evaluating the issue of non-persistence with antiplatelet medications used in secondary prevention of PAD in older patients. As we have mentioned previously in the Introduction, the only study similar to ours was the study by Qvist et al. (2019) which focused on adherence to antiplatelet and statin treatment in patients with PAD and abdominal aortic aneurysm. However, in contrast to our study, characteristics associated with non-persistence with antiplatelet medications were not found in that study. For the reasons mentioned above, we compared our results mostly with the studies analyzing persistence with antiplatelet treatment in patients after MI or stroke/TIA. The recommendations for the use of antiplatelet agents in recent guidelines of the European Society of Cardiology on the diagnosis and treatment of PAD by Aboyans et al. (2018) do not basically differ from those in the previous guideline by Tendera et al. (2011) which represented the actual guideline for the treatment of PAD at the time of inclusion of patients in our study.

Among socio-demographic characteristics evaluated in our study, higher age was associated with persistence, while female sex was associated with non-persistence. Better persistence in older PAD patients may indicate a careful medication-taking behavior in this age group of patients who are used to take concurrently several medications. Similarly to our study, in the systematic review by Jang and Zuniga (2020), older age was associated with persistence, while female sex was associated with non-persistence. That systematic review was focused on observational studies evaluating adult ischemic stroke or TIA patients, and reported poor persistence with antiplatelet agents, anticoagulants, and statins. Female sex was associated with poorer persistence also in the retrospective observational database study by Liu et al. (2019) which analyzed initiation of and persistence with antiplatelet medications among patients with acute coronary syndromes. Patients with no gaps of ≥ 30 days in antiplatelet treatment were considered persistent. The findings of our study do not make it possible to explain why female gender was associated with non-persistence. One possible factor contributing to the increased risk of non-persistence in women may be the fact that, in general, women experience adverse drug reactions (ADRs) more frequently than men (Miller, 2001; Franconi et al., 2007). ADRs may consequently lead to treatment discontinuation.

Certain comorbid conditions, namely atrial fibrillation, anxiety disorders and asthma/COPD as well as some CV co-medications like anticoagulants and antiarrhythmic agents were associated with non-persistence in our study cohort. Increased risk of bleeding associated with concurrent use of antiplatelet agents and anticoagulants may serve as one possible explanation of an increased likelihood of antiplatelet treatment discontinuation in older PAD patients with atrial fibrillation (Hindricks et al., 2021). According to a nationwide population-based cohort study by Green et al. (2016), atrial fibrillation was associated with a higher risk of treatment breaks in DAPT among patients undergoing percutaneous coronary intervention after an acute MI. Anxiety is associated with a fear of developing ADRs which may be responsible for treatment discontinuation (Sundbom and Bingefors, 2013). Anxiety has previously been reported to be a patient factor affecting adherence to medications in older adults in the systematic review by Yap et al. (2016). Patients who interrupted DAPT had a higher rate of some comorbidities including COPD in the study by Ferreira-González et al. (2012). Their study was focused on the analysis of risk of major cardiac events associated with discontinuation of DAPT in patients after drug-eluting stent implantation.

In our study cohort, PAD patients who initiated antiplatelet treatment with clopidogrel or DAPT (combination of aspirin and clopidogrel) had better persistence in comparison with those treated with aspirin alone. The positive association of DAPT with persistence may be related to its use after stenting in patients undergoing percutaneous coronary intervention after acute MI (Ibanez et al., 2018). History of MI and ischemic stroke

TABLE 2 | Multivariate analysis of the association between patient- and medication-related characteristics and the likelihood of non-persistence (*n* = 9,178).

Factor	Hr (95% CI)
Socio-demographic characteristics	
Age	**0.98 (0.97–0.98)**
Female sex	**1.26 (1.16–1.37)**
University education	1.10 (0.96–1.26)
Employed patients	1.13 (0.97–1.32)
History of cardiovascular events[a]	
History of ischemic stroke	**0.87 (0.78–0.97)**
History of TIA	1.08 (0.93–1.24)
History of MI	**0.82 (0.68–0.98)**
Comorbid conditions	
Number of comorbid conditions	0.92 (0.83–1.02)
Arterial hypertension	0.96 (0.83–1.11)
Chronic heart failure	1.03 (0.84–1.25)
Atrial fibrillation	**1.56 (1.33–1.84)**
Diabetes mellitus	0.89 (0.78–1.01)
Hypercholesterolemia	1.13 (0.99–1.29)
Dementia	0.84 (0.69–1.01)
Depression	1.07 (0.91–1.25)
Anxiety disorders	**1.17 (1.03–1.34)**
Parkinson's Disease	1.02 (0.82–1.27)
Epilepsy	1.04 (0.79–1.36)
Bronchial asthma/COPD	**1.20 (1.04–1.37)**
Antiplatelet agent related characteristics	
Initial antiplatelet agent	
Aspirin	1.00
Clopidogrel	**0.83 (0.73–0.94)**
Ticlopidine	0.88 (0.73–1.07)
Aspirin + clopidogrel	**0.60 (0.49–0.74)**
New antiplatelet agent user[b]	**1.44 (1.28–1.62)**
Patient's co-payment (EUR)[c]	**0.94 (0.89–0.98)**
General practitioner as index prescriber	**0.81 (0.74–0.88)**
Cardiovascular co-medication	
Number of medications	**0.95 (0.93–0.97)**
Number of CV medications	0.99 (0.95–1.03)
Anticoagulants	**1.15 (1.04–1.28)**
Cardiac glycosides	1.03 (0.86–1.22)
Antiarrhythmic agents	**1.33 (1.13–1.55)**
Beta-blockers	0.95 (0.86–1.06)
Thiazide diuretics	1.09 (0.99–1.20)
Loop diuretics	0.94 (0.83–1.05)
Mineralocorticoid receptor antagonists	0.84 (0.69–1.01)
Calcium channel blockers	1.07 (0.97–1.17)
RAAS inhibitors	1.02 (0.91–1.15)
Statin	1.01 (0.93–1.11)
Lipid lowering agents other than statins[d]	1.04 (0.92–1.18)

Values represent hazard ratios (95% confidence intervals). In case of statistical significance (p < 0.05), the values are expressed in bold. TIA–transient ischemic attack; MI–myocardial infarction; COPD–chronic obstructive pulmonary disease; CV–cardiovascular; RAAS–renin-angiotensin-aldosterone system.

[a]The time period covered by "history"–5 years before the index date of this study.

[b]New antiplatelet agent user–patient in whom antiplatelet treatment was initiated in association with the diagnosis of peripheral arterial disease.

[c]Co-payment–calculated as the cost of antiplatelet treatment paid by the patient per month.

[d]Lipid lowering agents other than statins–ezetimibe and fibrates.

represented factors associated with persistence in our study. This result may indicate better awareness of the importance of antiplatelet treatment in PAD patients with other conditions where antiplatelet medication is fully indicated in secondary prevention (Arnan et al., 2014; Kernan et al., 2014; Ibanez et al., 2018).

In our study, being a new user of antiplatelet medication appeared as a factor associated with non-persistence. Analogously, in the study by Qvist et al. (2019), among antiplatelet medication non-users at baseline, 57% persisted, whereas among users at baseline, 79% persisted with their antiplatelet therapy during the 5 years follow-up. After the first acute coronary syndrome-related hospitalization, patients who had prior use of antiplatelet agents were more likely to persist with this medication also in the study by Liu et al. (2019).

Higher co-payment was associated with persistence in our study cohort. The design of our study does not make it possible to explain this result. In contrast to our results, according to the claims database study by Burke et al. (2010), higher medication co-payment had a negative impact on persistence with antiplatelet therapy among ischemic stroke survivors. In their study, non-persistence was defined as an absence of medication refilling within 30 days from the run-out date of the prior prescription.

Increasing overall number of medications appeared as a protective factor associated with persistence in our study. Polypharmacy was associated with persistence also in our previous study focused on the analysis of non-persistence with antiplatelet medications in older patients after a TIA (Wawruch et al., 2017). In our study, index prescriber being a general practitioner rather than a specialist was associated with persistence. Similar association was found in our previous study focused on non-persistence with statins in older PAD patients (Wawruch et al., 2019).

Our study has some limitations which should be taken into consideration when interpreting its results. The database of the General Health Insurance Company, which served as a source of data for our study, was primarily constituted for insurance and reimbursement purposes and not for research. For this reason, it is impossible to identify the reasons for discontinuation and distinguish who decided to discontinue the treatment (i.e., the patient or the physician). Moreover, the database does not make it possible to identify whether patients actually took their medications as prescribed. We did not have access to data beyond the end of the study period. For this reason, it was impossible to identify the 6 months treatment gap during the period of less than 6 months before the end of the follow up. Inclusion of prevalent users in our study cohort (i.e., patients taking a therapy for a certain period of time before the index date of the study) can cause two types of biases: 1) prevalent users "survived" the early period of pharmacotherapy; this may cause selection bias, and 2) covariates of prevalent users at the time of inclusion in the study may be significantly affected by the drug itself (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, 2020). Since PAD represents one of manifestations of atherosclerosis, which is a systemic process affecting the whole vasculature, PAD patients often use antiplatelet agents at the time of PAD diagnosis, e.g., because of coronary artery disease or after stroke/TIA. In our study, new users represented only 14.3% of the cohort of 9,178 patients. Exclusion of remaining 85.7% of patients would lead to a substantial confounding. This was the reason why we decided to prefer also to include prevalent users. On the other hand, the large

TABLE 3 | Sensitivity analysis of the effect of different lengths of treatment gap period defining non-persistence.

	Treatment gap to define non-persistence (months)						
	1	2	3	4	5	6	12
				Non-persistent patients			
1st year	3,897 (42.5)	2,861 (31.2)	2,187 (23.8)	1,804 (19.7)	1,524 (16.6)	1,350 (14.7)	832 (9.1)
2nd year	844 (9.2)	782 (8.5)	780 (8.5)	770 (8.4)	729 (7.9)	670 (7.3)	552 (6.0)
3rd year	333 (3.6)	445 (4.9)	476 (5.2)	498 (5.4)	493 (5.4)	498 (5.4)	441 (4.8)
4th year	190 (2.1)	296 (3.2)	340 (3.7)	333 (3.6)	346 (3.8)	353 (3.8)	344 (3.7)
5th year	140 (1.5)	221 (2.4)	223 (2.4)	202 (2.2)	194 (2.1)	161 (1.8)	18 (0.2)
Total	5,404 (58.9)	4,605 (50.2)	4,006 (43.6)	3,607 (39.3)	3,286 (35.8)	3,032 (33.0)	2,187 (23.8)

Values represent the frequency, and the percentages are provided in parentheses (% of n = *9,178).*

sample size which covers all administrative regions of the Slovak Republic and detailed and precise data on drug dispensations and patients' comorbid conditions represent the strengths of our study.

Despite the limitations mentioned above, our study revealed that younger patients, females, subjects in whom aspirin as monotherapy was administered at the index date, patients without history of MI or ischemic stroke, those with atrial fibrillation, anxiety disorders, bronchial asthma/COPD, subjects with lower overall number of medications and with lower co-payment, new antiplatelet medication users in whom this therapy was initiated in association with PAD diagnosis, and patients treated with anticoagulants or antiarrhythmic agents represent the groups of PAD patients in whom an increased likelihood of antiplatelet treatment discontinuation may be expected.

CONCLUSION

Our study revealed a relatively high proportion of older PAD patients who discontinued antiplatelet treatment (33.0%) at some point during the 5 years follow-up. This finding indicates that non-persistence with antiplatelet medications in older PAD patients represents an important public health issue. Factors characterizing patients with an increased probability of non-persistence make it possible to identify patient groups that require increased attention aimed at the improvement of persistence with antiplatelet medication.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data that support the findings of this study are available from the General Health Insurance Company but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the General Health Insurance Company. Requests to access the datasets should be directed to MW, martin.wawruch@gmail.com.

ETHICS STATEMENT

Under legislative provisions of Slovakia, this register-based study did not require approval of an Ethical Committee. The patient data were available to us only anonymously under the license of the General Health Insurance Company. The rules of personal data confidentiality were fully respected.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. MW, JM, and TT organized the database and performed the statistical analysis. MW wrote the first draft of the manuscript. All authors wrote sections of the manuscript. MW, JM, TT, and MPe managed the project. All authors contributed to manuscript revision, read, and approved the submitted version.

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.687549/full#supplementary-material

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Potentially Inappropriate Prescriptions of Antipsychotics for Patients With Dementia

Manuel Enrique Machado-Duque[1,2], *Luis Fernando Valladales-Restrepo*[1,2], *Juan Alberto Ospina-Cano*[3], *María José Londoño-Serna*[3] and *Jorge Enrique Machado-Alba*[*1]

[1]Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira-Audifarma S.A, Pereira, Colombia, [2]Grupo de Investigación Biomedicina, Facultad de Medicina, Fundación Universitaria Autónoma de Las Américas, Pereira, Colombia, [3]Semillero de Investigación en Farmacoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira, Pereira, Colombia

Dementias are neurodegenerative and progressive diseases of the central nervous system. The objective of this study was to determine the frequency of potentially inappropriate prescriptions of antipsychotics in a group of patients diagnosed with dementia in Colombia. This was a cross-sectional study based on a population database for drug dispensing that identified prescriptions of antidementia drugs, antipsychotics, and other drugs for patients with a diagnosis of dementia. Descriptive statistics and bivariate and multivariate analyses were performed. A total of 11,372 patients with dementia were identified; 66.6% were women, and the mean age was 80.5 ± 9.6 years. Alzheimer's disease was the most frequent diagnosis (76.6%). A total of 69.0% of patients received antidementia drugs. A total of 37.1% of patients received some antipsychotic, especially atypical antipsychotics (31.0%). Increased age, being treated with memantine, simultaneously presenting with anxiety, depression, and psychotic disorders, and concomitantly receiving anticonvulsants, bronchodilators and benzodiazepines were associated with a greater probability of being prescribed antipsychotics. More than one-third of patients with dementia received antipsychotic prescriptions, which are considered potentially inappropriate because they can worsen cognitive decline and favor the occurrence of adverse events.

Keywords: (MeSH): dementia, alzheimer disease, dementia vascular, antipsychotic agents, pharmacoepidemiology

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****Correspondence:***
Jorge Enrique Machado-Alba
machado@utp.edu.co

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INTRODUCTION

Dementia is a neurodegenerative and progressive disease of the central nervous system characterized by chronic, global and generally irreversible deterioration of cognitive ability (Prince et al., 2013). Dementia may be due to a variety of underlying pathophysiological processes; the most common is Alzheimer's disease (50–75%), followed by vascular dementia (20%), dementia with Lewy bodies (5%), and frontotemporal dementia (5%) (Cunningham et al., 2015).

Global rates of dementia are increasing rapidly, in line with population aging. The prevalence of dementia is 2–3% in the 70–75 age group, increasing to 25% in those over 85 (Rizzi et al., 2014). At advanced ages, women are more likely to develop dementia due to Alzheimer's disease, while the prevalence of vascular dementia is higher in men (Rizzi et al., 2014).

The pathophysiological processes underlying dementia are not yet fully understood; however, it is known that all involve pathological protein accumulation (Kocahan and Doğan, 2017). These pathological accumulations are associated with synaptic failure, neuronal loss and atrophy that can have different anatomical distribution patterns (Frisoni et al., 2015).

Neuropsychiatric symptoms, including agitation, aggressiveness, paranoid delusions, and hallucinations, are widely prevalent among dementias, especially in the moderate and severe disease stages, which require either pharmacological or nonpharmacological intervention (Cerejeira et al., 2012). Very often, nonpharmacological management is sufficient to control symptoms, but sometimes, the severity of the disorder, the involvement in the patient, or the risk to oneself or others makes using drugs, including antipsychotics, necessary to control symptoms (Calsolaro et al., 2021). However, the Beers criteria and the STOPP/START criteria consider antipsychotics as potentially inappropriate prescriptions in this group of patients because they are associated with a greater number of adverse outcomes, such as cerebrovascular events and greater functional decline and mortality, and thus recommend avoiding their use unless there are no alternatives for the management of behavioral disorders or delirium ("American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults," 2019; O'Mahony et al., 2015).

It has been shown that patients treated with antipsychotics can frequently present with anticholinergic side effects, such as orthostatic hypotension, confusion, drowsiness, cognitive impairment, and an increased risk of severe extrapyramidal effects that can be fatal (Schneider et al., 2006a; Schneider et al., 2006b; Calsolaro et al., 2021; Vina Latin Small Letter et al., 2021). In addition, the DART-AD trial found an increased risk of mortality in patients older than 65 years with dementia treated with any class of antipsychotics, both in the short term (12 weeks) and long term (over 48 months) (Hereu and Vallano, 2011).

The inadequate use of antipsychotics and the lack of precautions in their prescription for Colombian patients with different types of dementia are unknown. Therefore, the objective of this study was to determine the frequency of potentially inappropriate prescriptions of antipsychotics in a group of patients diagnosed with dementia in Colombia between October and December of 2019, as well as to identify the medications used, comorbidities and possible variables associated with the use of these antipsychotics in this older adult population.

MATERIALS AND METHODS

Study Design and Patients

A cross-sectional study was conducted on the prescription patterns of antipsychotic drugs for patients diagnosed with dementia in out-patient setting. The data were obtained from a population database for drug dispensing that contains information on approximately 8.5 million people affiliated with the Health System of Colombia through six health insurance companies, corresponding to approximately 30.0% of the active affiliated population covered by the contributory or paid regime and 6.0% of the population covered by the state-subsidized regime, which serves 17.3% of the Colombian population.

Patients aged 50 years or older of either sex and seen as outpatients were selected in the main cities of Colombia, with a diagnosis of dementia who received a drug prescription in any month in the period from October 1 to December 31, 2019, were included (Medication for the treatment of any comorbidity or dementia in which an International Classification of Diseases (ICD-10) diagnostic code for dementia is used or registered). Identification was performed based on ICD-10 codes, considering the following diagnoses: Alzheimer's disease (F000-F002, F009, G300, G301, G308 and G309), vascular dementia (F010-F013, F018 and F019), dementia in Parkinson's disease (F023), dementia in Huntington's disease (F022), dementia in Pick's disease or frontotemporal dementia (F020), dementia in HIV (F024), dementia in Creutzfeldt-Jakob disease (F021) and unspecified dementias (F03X and F028).

The information of each dispensing and variables associated with the prescription is obtained from the pharmacies and the clinical registry, they are kept in a database with all the information and subsequently consulted through business intelligence, validated by validated by two members of the research group, identifying strange and missing values, until having a dataset with the included patients and being able to analyze it, and subsequently analyzed. Their drug dispensing records during the observation period were analyzed to identify the use of antipsychotics and all comedications. Those with incomplete information and those with two or more different dementia diagnoses were excluded.

Variables

Based on the information on the consumption of drugs of the affiliated population, systematically obtained by the dispensing company (Audifarma SA), a database was designed that allowed collecting the following groups of variables: 1). Sociodemographic: sex, age, city, and geographic region of residence; 2). Clinical: type of dementia diagnosed and comorbidities. 3). Comorbidities: identified from the diagnoses reported using ICD-10 codes for the selected patients. They were categorized by number of comorbidities. The main cardiovascular, endocrine, rheumatologic, urological, renal, psychiatric, neurological, digestive, respiratory, and cancer diseases were identified; 4). Drugs for dementia treatment: acetylcholinesterase inhibitors (rivastigmine, donepezil, galantamine) and NMDA receptor antagonists (memantine); 5). Prescribed antipsychotics: Typical: chlorpromazine, fluphenazine, haloperidol, levomepromazine, pipotiazine, propericiazine, thioridazine, and trifluoperazine; and Atypical: amisulpride, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sulpiride, and ziprasidone; and 6). Comedications were grouped into the following categories: 1) antidiabetics (oral and subcutaneous), 2) antihypertensives and diuretics, 3) lipid-lowering drugs; 4) antiulcers, 5) antidepressants, 6) benzodiazepines, 7) thyroid

hormone, 8) anticonvulsants, 9) antiarrhythmics, 10) antihistamines, 11) bronchodilators and inhaled corticosteroids, 12) opioid analgesics, 13) nonopioid analgesics, 14) platelet antiaggregants, and 15) anticoagulants.

Ethical Statement

The protocol was approved by the Bioethics Committee of Universidad Tecnológica de Pereira in the "research without risk" category (Code: 02–130420). The ethical principles established by the Declaration of Helsinki were respected. No personal data were collected from the patients.

Data Analysis

The data were analyzed with the statistical package SPSS Statistics, version 26.0 for Windows (IBM, United States). A descriptive analysis was performed; qualitative variables are presented as frequencies and proportions, and quantitative variables are presented as measures of central tendency and dispersion. Quantitative variables were compared using Student's t-test or ANOVA, and categorical variables were compared using the χ^2 test. Binary logistic regression models were fitted using "prescribed antipsychotics" as the dependent variable; the covariates were the variables that were significantly associated with the dependent variable in the bivariate analyses and variables with biological plausibility to explain the outcome (prescription of an antipsychotic). A statistical significance level of $p < 0.05$ was adopted.

RESULTS

A total of 11,372 patients with a diagnosis of dementia were identified, distributed in 154 different cities or municipalities. The mean age was 80.5 ± 9.6 years (range: 50.0–105.1 years), and 66.6% ($n = 7,573$) were women. A total of 78.8% ($n = 8,958$) of the patients resided in capital cities, and the majority were in the Pacific Region (n = 3,009; 26.5%), followed by the Bogotá-Cundinamarca Region (n = 2,982; 26.2%), Caribbean Region (n = 2,758; 24.3%), Central Region (n = 2081; 18.3%), Eastern Region (n = 519; 4.6%) and Amazonia-Orinoquía Region (n = 23; 0.2%).

Most patients had a diagnosis of Alzheimer's disease (n = 8,711; 76.6%), followed by unspecified dementia (n = 1767; 15.5%), vascular dementia (n = 657; 5.8%), dementia in Parkinson's disease (n = 201; 1.8%), frontotemporal dementia (n = 21; 0.2%), dementia in Huntington's disease (n = 9; 0.1%) and dementia in HIV ($n = 6$; 0.1%). A total of 69.0% ($n = 7,841$) were receiving pharmacological treatment for dementia, mainly rivastigmine (n = 4,843; 42.6%), followed by memantine (n = 3,756; 33.0%), donepezil (n = 164; 1.4%) and galantamine (n = 164; 1.4%).

Of the total number of patients identified, 4,222 (37.1%) had been prescribed at least one antipsychotic, distributed among 10 different antipsychotic drugs, with the use of atypical antipsychotics (n = 3,526, 31.0%) predominating over the use of typical antipsychotics (n = 1,023, 9.0%), with some patients receiving more than one of these drugs. Of the patients who were prescribed antipsychotics, 86.6% (n = 3,656) received a single drug, and 13.4% (n = 566) received two or more. The most commonly used antipsychotic was quetiapine, followed by levomepromazine and risperidone. The most commonly used pharmaceutical forms were tablets ($n = 3,482$; 30.6%), followed by oral solution (n = 1,026; 9.0%) and injectable solution (n = 82; 0.7%) (**Table 1**).

TABLE 1 | Antipsychotics prescriptions for a group of patients with dementia in Colombia, 2019.

Antipsychotic	Frequency n = 11,372	%
Atypical	3,526	31.0
Quetiapine (tablet)	2,686	23.6
Risperidone	525	4.6
Tablet	399	3.5
Oral solution	120	1.1
Injectable	12	0.1
Clozapine (tablet)	312	2.7
Olanzapina (tablet)	185	1.6
Aripiprazol (tablet)	17	0.1
Paliperidone	10	0.1
Injectable	9	0.1
Tablet	1	0.0
Amisulpiride (tablet)	1	0.0
Typical	1,023	9.0
Levomepromazine	600	5.3
Oral solution	541	4.8
Tablet	63	0.6
Haloperidol	489	4.3
Oral solution	438	3.9
Injectable	57	0.5
Tablet	27	0.2
Pipothiazine (injectable)	6	0.1

Comorbidities and Comedications

A total of 77.8% (n = 8,853) of all patients had some chronic disease. Of these, 42.9% (n = 3,805) had one disease, 31.8% (n = 2,812) had two diseases and 25.3% ($n = 2,236$) had three or more diseases. The 10 comorbidities that were most common in all patients were arterial hypertension (n = 4,922; 43.3%), diabetes mellitus (n = 1,547; 13.6%), urinary incontinence (n = 1,530; 13.5%), bipolar affective disorder (n = 993; 8.7%), anxiety disorders (n = 751; 6.6%), hypothyroidism (n = 769; 6.8%), depressive disorders (n = 751; 6, 6%), chronic kidney disease ($n = 643$; 5.7%), chronic obstructive pulmonary disease ($n = 465$; 4.1%) and benign prostatic hyperplasia (n = 434; 3.8%). Upon grouping, cardiovascular diseases were the most frequent (n = 5,169; 45.5%), followed by other psychiatric disorders ($n = 2,644$; 23.3%) and endocrine (n = 2,470; 21.7%), urological (n = 2029; 17.8%), neurological ($n = 1,059$; 9.3%), rheumatic ($n = 776$, 6.8%), gastrointestinal (n = 602; 5.3%) and respiratory (n = 501; 4.4%) diseases.

The most prescribed comedications were antihypertensives and diuretics ($n = 6,902$, 60.7%), followed by antidepressants (n = 5,198; 45.7%), nonopioid analgesics ($n = 3,696$; 32.5%), antiulcers (n = 3,384; 29.8%), platelet antiaggregants (n = 3,125; 27.5%), lipid-lowering drugs (n = 2,915; 25.6%), thyroid hormone (n = 2,558; 22.5%), oral and subcutaneous antidiabetic drugs and

TABLE 2 | Comparison of sociodemographic, clinical and pharmacological variables with types of dementia in a group of patients in Colombia, 2019.

Variables	Alzheimer's disease		Unspecified dementias		Vascular dementia		Dementia in Parkinson's disease		Other dementias	
	n = 8,711	%	*n* = 1767	%	*n* = 657	%	*n* = 201	%	*n* = 36	%
Woman	5,945	68.2	1,151	65.1	375	57.1	87	43.3	15	41.7
Age (mean; SD)	80.7 ± 9.5		80.5 ± 10.1		80.9 ± 9.7		77.7 ± 9.5		68.4 ± 9.6	
Geographic regions	–	–	–	–	–	–	–	–	–	–
Pacific region	2045	23.2	599	33.9	299	45.5	75	37.3	11	30.6
Bogotá-cundinamarca region	2,304	26.4	523	29.6	110	16.7	34	16.9	11	30.6
The caribbean region	2,332	26.8	297	16.8	83	12.6	36	17.9	10	27.8
Central region	1,591	18.3	298	16.9	145	22.1	46	22.9	1	2.8
Eastern region	444	5.1	46	2.6	17	2.6	9	4.5	3	8.3
Amazon region-orinoquía	15	0.2	4	0.2	3	0.5	1	0.5	0	0.0
With chronic comorbidities	6,748	77.5	1,349	76.3	559	85.1	170	84.6	27	75.0
1 pathology	2,914	33.5	595	33.7	232	35.3	52	24.9	12	33.3
2 pathologies	2,132	24.5	426	24.1	175	23.1	70	34.8	9	25.0
≥3 pathologies	1702	19.5	328	18.6	152	23.1	48	23.9	6	16.7
Cardiovascular pathologies	3,998	45.9	776	43.9	314	47.8	71	35.3	10	27.8
Psychiatric pathologies	2013	23.1	407	23.0	155	23.6	56	27.9	13	36.1
Endocrine pathologies	1924	22.1	365	20.7	147	22.4	30	14.9	4	11.1
Urological pathologies	1,533	17.6	285	16.1	159	24.2	47	23.4	5	13.9
Neurological pathologies	696	8.0	170	9.6	95	14.5	91	45.3	7	19.4
Use of antidementiants	6,571	75.4	897	50.8	314	47.8	50	24.9	9	25.0
Rivastigmine	3,917	45.0	686	38.8	192	29.2	42	20.9	6	16.7
Memantine	3,372	38.7	238	13.5	134	20.4	8	4.0	4	11.1
Donepezil	146	1.7	13	0.7	5	0.8	0	0.0	0	0.0
Galantamine	134	1.5	21	1.2	8	1.2	1	0.5	0	0.0
Use of antipsychotics	3,139	36.0	712	40.3	279	42.5	70	34.8	22	61.1
Atypical	2,680	30.8	537	30.4	226	34.4	66	32.8	17	47.2
Quetiapine	2031	23.3	416	23.5	178	27.1	49	24.4	12	33.3
Risperidone	447	5.1	52	2.9	18.0	2.7	6	3.0	2	5.6
Clozapine	217	2.5	61	3.5	21	3.2	10	5.0	3	8.3
Typical	705	8.1	232	13.1	74	11.3	5	2.5	7	19.4
Levomepromazine	427	4.9	127	7.2	37	5.6	5	2.5	4	11.1
Haloperidol	314	3.6	129	7.3	42	6.4	1	0.5	3	8.3
Pipothiazine	4	0.0	2	0.1	0	0.0	0	0.0	0	0.0
Comedications	–	–	–	–	–	–	–	–	–	–
Antihypertensives and diuretics	5,267	60.5	1,078	61.0	439	66.8	103	51.2	15	41.7
Antidepressants	3,922	45.0	851	48.2	321	48.9	88	43.8	16	44.4
Non-opioid pain relievers	2,786	32.0	593	33.6	228	34.7	77	38.3	12	33.3
Antiulcer	2,517	28.9	572	32.4	214	32.6	67	33.3	14	38.9
Platelet antiaggregants	2,353	27.0	472	26.7	250	38.1	44	21.9	6	16.7

**Other dementias: Includes dementia in Huntington's disease, frontotemporal dementia, and dementia in human immunodeficiency virus infection.*

insulins (*n* = 2004; 17.6%), anticonvulsants (*n* = 1,491; 13.1%) and bronchodilators and inhaled corticosteroids (*n* = 1,416; 12.5%).

Bivariate Comparisons by Type of Dementia

Alzheimer's disease, unspecified dementia and vascular dementia predominated in women and occurred at a higher mean age. Patients with vascular dementia and Parkinson's disease presented with comorbidities with greater frequency. Rivastigmine and memantine were the most commonly used antidementia drugs for all types of dementia, especially Alzheimer's disease. The prescription of antipsychotics was more common for patients with vascular dementia, with the use of atypical antipsychotics prevailing for all types of dementia; the lowest frequencies of use of typical antipsychotics were found for patients with dementia in Parkinson's disease. The use of antihypertensives and diuretics predominated for all patients, while platelet antiaggregants were prescribed more for patients with vascular dementia (**Table 2**).

Multivariate Analysis

Binary logistic regression analysis was performed to determine the factors associated with the use of antipsychotics for patients diagnosed with dementia. Female sex, diagnosis of Alzheimer-type dementia, and being treated with rivastigmine decreased the probability of being prescribed an antipsychotic. Increased age, being treated with memantine, presenting concomitantly with anxiety, depression, and psychotic disorders, and receiving

TABLE 3 | Multivariate analysis of the variables associated with the prescription of antipsychotics for a group of patients with dementia in Colombia, 2019.

Variable	*p*	ORa	95% CI	
			Lower	Upper
Female gender	<0.01	0.814	0.745	0.889
Age less than 65 years	Ref	Ref		
Age between 65 and 74 years	<0.01	1.398	1.153	1.694
Age between 75 and 84 years	<0.01	1.656	1.388	1.975
Age greater than or equal to 85 years	<0.01	1.916	1.604	2.29
Be treated in Bogotá D.C/Cundinamarca	0.004	0.856	0.771	0.95
Diagnosis of Alzheimer's dementia	0.009	0.86	0.769	0.963
Being treated for dementia with rivastigmine	<0.01	0.835	0.764	0.913
Being treated for dementia with memantine	0.017	1.121	1.021	1.232
Anxiety (comorbidity)	<0.01	13.107	10.783	15.93
Depression (comorbidity)	<0.01	2.184	1.853	2.574
Osteoporosis (comorbidity)	0.014	0.661	0.475	0.919
Psychotic disorders (comorbidity)	<0.01	10.273	6.961	15.162
Concomitant use of antiepileptic drugs	<0.01	1.9	1.686	2.142
Concomitant use of benzodiazepines	<0.01	1.946	1.644	2.302
Concomitant use of bronchodilators	0.001	1.237	1.092	1.403
Concomitant use of lipid-lowering drugs (statins)	<0.01	0.839	0.761	0.924

Binary logistic regression: adjusted for sex, age, place of treatment, type of dementia, treatment of dementia, comorbidities, and comedications. ORa, Adjusted Odds Ratio; CI95%, Confidence interval.

anticonvulsants, bronchodilators and benzodiazepines simultaneously were associated with a greater probability of being prescribed antipsychotics (**Table 3**).

DISCUSSION

The present study was able to determine the prescription and the potentially inappropriate use of antipsychotics for patients diagnosed with dementia in six health insurance entities in Colombia. The results of this study are of great interest because a high frequency of use of antipsychotics was found in this specific group of patients, who may be at risk of adverse events. With these results, a baseline for the problem is established, which may be useful for making better informed decisions and improving the use of these drugs.

The mean age of the analyzed patients was close to 80 years, consistent with what has been described in different studies conducted worldwide, i.e., a typical age of presentation of dementias above 65 years (Prince et al., 2013; Arvanitakis et al., 2019). Regarding the sex of the patients, approximately two-thirds of the study population were women, which is also consistent with what has been described in the world population (Goodman et al., 2017; Valladales-Restrepo et al., 2019). The most prevalent type of dementia was Alzheimer's disease, a finding that agrees with reports on the prevalence of dementia worldwide and imparts confidence and validity to the results of this study (Cunningham et al., 2015). Additionally, the most commonly used antidementia drug in the evaluated patients was rivastigmine, agreeing with the data reported in different studies (Jia et al., 2016; Calvo-Torres et al., 2019). In addition, a diagnosis of Alzheimer-type dementia acted as a protective factor for the prescription of antipsychotics, unlike that seen for other types of dementia, a finding that may be explained by the difference in the frequency of psychotic symptoms, agitation and insomnia among the different causes of dementia (Collins et al., 2020).

It was found that more than one-third of patients diagnosed with dementia were prescribed at least one antipsychotic, putting these patients at particular risk of adverse reactions and worsening of symptoms, a result that is similar to those reported in studies conducted in Norway by Langballe et al. (2013) and in Germany by Schulze et al. (2012) (Schulze et al., 2013; Langballe et al., 2014), who found a frequencies of use of 30.4 and 39.8%, respectively. Additionally, it is noteworthy that there was a predominance of prescriptions for atypical antipsychotics over typical antipsychotics, a relationship that contrasts with results from studies by Schulze et al. and Langballe et al., in which 24.4 and 19.5% of patients with dementia received typical antipsychotics, respectively (Schulze et al., 2013; Langballe et al., 2014).

The most commonly used antipsychotic was quetiapine; in contrast, in the United States, the use of olanzapine predominates, and in Norway, the use of risperidone predominates (Kamble et al., 2009; Langballe et al., 2014; Maust et al., 2015). This trend in Colombia may be due to the off-label use of quetiapine as a sedative-hypnotic (Dolder and McKinsey, 2010).

Cardiovascular disease was the most prevalent comorbidity in almost half of patients with Alzheimer's disease. It has been described that the presence of systolic hypertension can be a modifiable risk factor for the onset of cognitive decline and vascular dementia and that its control with antihypertensive treatment reduces the development of Alzheimer's disease, as well as of other dementias, in the future (Gorelick et al., 2011). In addition, it is noteworthy that coronary and atherosclerotic carotid disease are risk factors for the onset of cognitive decline and vascular dementia (Rosano et al., 2005; Zhong et al., 2012).

The association of having a diagnosis of osteoporosis with a lower probability of being prescribed an antipsychotic in this group of patients with dementia contrasts with the results of a study by Crews et al. (2012), which found a significant relationship between the use of antipsychotics and a decrease in bone mineral density (Crews and Howes, 2012) as well as a slightly higher risk of having a hip fracture (Jalbert et al., 2010), which should serve as an alert to avoid their use in these patients. In turn, the use of lipid-lowering drugs was also associated with a lower risk of receiving antipsychotics, which supports the findings by Shen et al., who showed that statins can help in the treatment of schizophrenia, based on reduced scores on the positive symptoms, negative symptoms and general subscales of the Positive and Negative Syndrome Scale (PANNS) (Shen et al., 2018). However, the mechanism by which statins reduce psychotic symptoms in these patients is still unclear, but it has been proposed that they can also protect patients with dementia from the onset of this type of manifestation (Shen et al., 2018).

There are reports of a possible association between pulmonary diseases and an increased risk of developing dementia (Liao et al., 2015; Peng et al., 2015). The use of short-acting bronchodilators, such as salbutamol and terbutaline, can cause symptoms such as anxiety, insomnia, motor restlessness and agitation, which may provide an explanation for the greater probability of patients who also have dementia being prescribed antipsychotics (Román, 2011).

The difference found for patients who received rivastigmine, who showed a lower probability of being prescribed an antipsychotic, may be because rivastigmine is used for patients with mild to moderate dementia (Cruz Jentoft and Hernández, 2014), whereas the use of memantine, whose indication of use is for more severe forms of the disease, may imply that patients are more symptomatic and therefore require antipsychotics (Fink et al., 2020).

In this study, it was found that having a concomitant diagnosis of dementia and anxiety markedly increases the likelihood of being prescribed an antipsychotic despite the risks associated with them, making the surveillance, symptom control and appropriate use of psychotropic drugs more important. In addition to the high frequency of comorbidities, studies conducted in people with dementia living in the community found that many behavioral symptoms are closely related to anxiety (Ferretti et al., 2001; Neville and Teri, 2011).

An expected finding was the relationship between psychotic disorders and being prescribed an antipsychotic, although all these drugs are considered potentially inappropriate prescriptions in patients with dementia, with the exception of cases in which there are no alternatives due to severe behavioral and psychotic symptoms (Magierski et al., 2020). The association between dementia and depression with a greater probability of being prescribed an antipsychotic has also been reported (Neil et al., 2003; Nemeroff, 2005; Byers and Yaffe, 2011). In this analysis, more than 45% of patients with dementia received some antidepressant, a finding that should incite clinicians to consider the need to add, or not, new drugs to this group of patients and the risks involved.

In this study, it was found that the concomitant use of anticonvulsants increased, by almost two-fold, the probability of being prescribed an antipsychotic, a result that may be due to the need to share the same objective to modulate symptoms such as anxiety, depression, apathy, and psychosis and control the behavioral symptoms of patients with dementia who do not respond to typical therapy; however, it cannot be ruled out that anticonvulsants are indicated for the control of seizures (Magierski et al., 2020).

In addition to anticonvulsants, the concomitant use of benzodiazepines seems to double the probability of being prescribed an antipsychotic; however, in this study, due to its cross-sectional observational nature, it cannot be established which was used first. Benzodiazepines are useful in the control of symptoms such as aggressiveness, sleep disturbances and anxiety, which may be associated with the fact that these patients have more behavioral disturbances (Donoghue and Lader, 2010; Dell'osso and Lader, 2013), but it cannot be ruled out that these drugs were used for indications such as panic attacks or anxiety disorders. However, the chronic use of benzodiazepines can worsen behavioral problems due to their amnesic and disinhibitory effects (Rayner et al., 2006).

This analysis has limitations characteristic of observational studies performed using a drug dispensing database. There was a lack of a review of medical records to verify the severity and time since onset of dementia and hence the need for certain drugs. The effectiveness of the therapy and the safety problems that were actually generated with the prescription of antipsychotics were also not evaluated. However, the results can be extrapolated to populations with similar insurance status and drug access characteristics.

Based on the above findings, it can be concluded that more than one-third of this group of Colombian patients diagnosed with dementia were being prescribed some antipsychotic that could potentially worsen their clinical picture and cause adverse events. The progressive increase in age, concomitant suffering from anxiety, depression or some psychotic disorder, and combined use with anticonvulsants and bronchodilators were associated with a greater probability of being prescribed an antipsychotic. Our findings can be used by clinicians and all those responsible for the care of patients with dementia to offer therapies with lower risks to these specific groups. Further studies are needed to explore the safety of these drugs in the context of real life.

DATA AVAILABILITY STATEMENT

The database with all the information necessary to carry out the analyzes is deposited in protocols.io, https://doi.org/10.17504/protocols.io.bt7qnrmw.

ETHICS STATEMENT

The protocol was approved by the Bioethics Committee of Universidad Tecnológica de Pereira in the "research without risk" category. The ethical principles established by the Declaration of

Helsinki were respected. No personal data were collected from the patients. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM: conceptualization, methodology, formal analysis, investigation, data curation. LV: conceptualization, methodology, data curation, writing original draft. JO: investigation, data curation. ML: investigation, data curation. JM: methodology, validation, formal analysis, resources, writing, review and editing, supervision.

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High Prevalence of Multimorbidity and Polypharmacy in Elderly Patients With Chronic Pain Receiving Home Care are Associated With Multiple Medication-Related Problems

Juliana Schneider[1], *Engi Abd Elhady Algharably*[1], *Andrea Budnick*[2], *Arlett Wenzel*[2], *Dagmar Dräger*[2] *and Reinhold Kreutz*[1]*

[1]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Clinical Pharmacology and Toxicology, Berlin, Germany, [2]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Medical Sociology and Rehabilitation Sciences, Berlin, Germany

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Marcio Galvão Oliveira,
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Winicker Norimed GmbH, Germany

***Correspondence:**
Reinhold Kreutz
reinhold.kreutz@charite.de

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Aim: To measure the extent of polypharmacy, multimorbidity and potential medication-related problems in elderly patients with chronic pain receiving home care.

Methods: Data of 355 patients aged ≥65 years affected by chronic pain in home care who were enrolled in the *ACHE* study in Berlin, Germany, were analyzed. History of chronic diseases, diagnoses, medications including self-medication were collected for all patients. Multimorbidity was defined as the presence of ≥2 chronic conditions and levels were classified by the Charlson-Comorbidity-Index. Polypharmacy was defined as the concomitant intake of ≥5 medications. Potentially clinically relevant drug interactions were identified and evaluated; underuse of potentially useful medications as well as overprescription were also assessed.

Results: More than half of the patients (55.4%) had moderate to severe comorbidity levels. The median number of prescribed drugs was 9 (range 0–25) and polypharmacy was detected in 89.5% of the patients. Almost half of them (49.3%) were affected by excessive polypharmacy (≥10 prescribed drugs). Polypharmacy and excessive polypharmacy occurred at all levels of comorbidity. We detected 184 potentially relevant drug interactions in 120/353 (34.0%) patients and rated 57 (31.0%) of them as severe. Underprescription of oral anticoagulants was detected in 32.3% of patients with atrial fibrillation whereas potential overprescription of loop diuretics was observed in 15.5% of patients.

Conclusion: Multimorbidity and polypharmacy are highly prevalent in elderly outpatients with chronic pain receiving home care. Medication-related problems that could impair safety of drug treatment in this population are resulting from potentially relevant drug interactions, overprescribing as well as underuse.

Keywords: chronic pain, comorbidity, drug-drug interactions, elderly, medication-related problems, multimorbidity, outpatient, polypharmacy

INTRODUCTION

Over the last few decades, the population of older adult has grown worldwide especially in the developed countries (Mathers et al., 2015). Between 2000 and 2016, the global life expectancy increased by 5.5 years with a mean age of 72 years (World Health Organization, 2019). The number of individuals having two or more chronic conditions, referred to as multimorbidity has also increased with population aging according to a WHO World Health Survey reporting data from 28 countries between 2001 and 2004 (Afshar et al., 2015). The average number of chronic diseases per patient aged over 60 years was estimated to be 5.3 in men and 5.7 in women in Germany (Kostev and Jacob, 2018). Multimorbidity is associated with poorer health outcomes (Xu et al., 2017), higher mortality rates (McPhail, 2016) and impacts profoundly on healthcare utilization and costs (McPhail, 2016).

Polypharmacy is a common clinical consequence of multimorbidity in older adults encompassing not only prescribed but also over-the-counter medications including among others herbal supplements (Pitkälä et al., 2016). Commonly defined as the concomitant use of ≥5 medications daily (Masnoon et al., 2017), polypharmacy is a formidable problem posing a multitude of negative health outcomes (Maher et al., 2014). It increases the risk of adverse drug reactions, adverse drug events (e.g., falls, fractures, and acute kidney injury), inappropriate medication, medication errors, drug-drug interactions (DDI) and increased risk of mortality (Maher et al., 2014; Chang et al., 2020). Moreover, polypharmacy reduces adherence to appropriate pharmacotherapy and may contribute to physical disability and lower cognitive functions (Wastesson et al., 2018). Optimizing prescribing for elderly is of paramount importance as it can improve health outcomes in multimorbid vulnerable patients e.g., patients with chronic pain. Those patients are particularly susceptible to high multimorbidity burdens as well as risk of polypharmacy (Hubbard et al., 2015; Nakad et al., 2020). Moreover, a strong association was found between a high burden of comorbidity and pain severity in elderly (Leong et al., 2007; Blyth et al., 2008). We therefore aimed to analyze the extent of multimorbidity and polypharmacy in elderly chronic pain patients receiving home care and assessed potential medication-related problems in this target group.

MATERIAL AND METHODS

Design and Setting

The current analysis is a planned pre-specified subanalysis of the *ACHE* study ("Development of a Model for PAin Management in Older Adults ReCeiving Home CarE") in Germany. Briefly, *ACHE* was an observational cross-sectional analysis of a population-based cohort of older adults which focused on pain management in home care and has been described previously in detail (Schneider et al., 2020). Ethical approval was obtained by the local ethical committee of the Charité, Universitätsmedizin Berlin (EA1/368/14). Written informed consent was obtained from all participants or their legal guardians in case of cognitive impairment.

Study Population

Home-dwelling elderly with chronic pain recruited between 09/2017 and 10/2018 in the framework of *ACHE*, aged ≥65 years receiving home care in the city of Berlin, Germany, were eligible for the study (n = 355). As cognitively impaired older adults are also at increased risk of multimorbidity and the negative consequences of polypharmacy, patients with cognitive impairment were also eligible for inclusion in *ACHE*. Hence, patients were enrolled independently from their cognitive status as determined by the Mini Mental Status Examination (MMSE) (Tombaugh and McIntyre, 1992).

Data Collection

Five trained investigators interviewed the participants, collected demographic data, the level of care as well as the education level (highest school education and highest professional education) and documented the concurrent medications used regularly or as needed based on drug packages and medication plans available at participants' homes. According to the Pharmaceutical Care Network Europe (PCNE) classification (Griese-Mammen et al., 2018), we performed an intermediate medication review (PCNE type 2A) based on medication history and patient information. Medications were documented by means of the Instrument for Database-assisted Online recording for Medication (IDOM) (Mühlberger et al., 2003) that based on the data provided by the AOK Research Institute (WIdO). In total, 91 (2.5%) drugs were excluded from medication analysis according to our pre-specified criteria (**Figure 1**).

For the assessment of comorbidities, history of chronic diseases was obtained by thoroughly reviewing the participants' medical records, physician reports, nursing records as well as self-reported diagnoses. Polypharmacy was defined as the concomitant intake of ≥5 medications whereas excessive polypharmacy as ≥10 medications, taken regularly or on-demand (Wastesson et al., 2018). Our analysis encompassed all medications including nutraceuticals prescribed by physician(s) or used in self-medication and focused on pharmacologically active ingredients. Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system. We checked for relevant DDI, over- and underprescriptions in the concurrently prescribed medications within the general context of medication errors defined as events happening during drug treatment and could cause harm to the patient [Pharmacovigilance Risk Assessment Committee (PRAC), 2015]. Regarding the prescription frequency of drug classes and their relevance to our target group, clinically relevant DDI were checked for anticoagulants, diuretics, and statins, namely simvastatin, using our available institutional drug information system AiDKlinik® and their severity was rated on a case-by-case basis by three clinical pharmacologists/pharmacists (JS, EA, RK) according to our pre-defined criteria. In our evaluation of DDI, we also took into account the vulnerable nature of elderly patients and their susceptibility to more risk and more harmful consequences of DDI than that expected in younger patients.

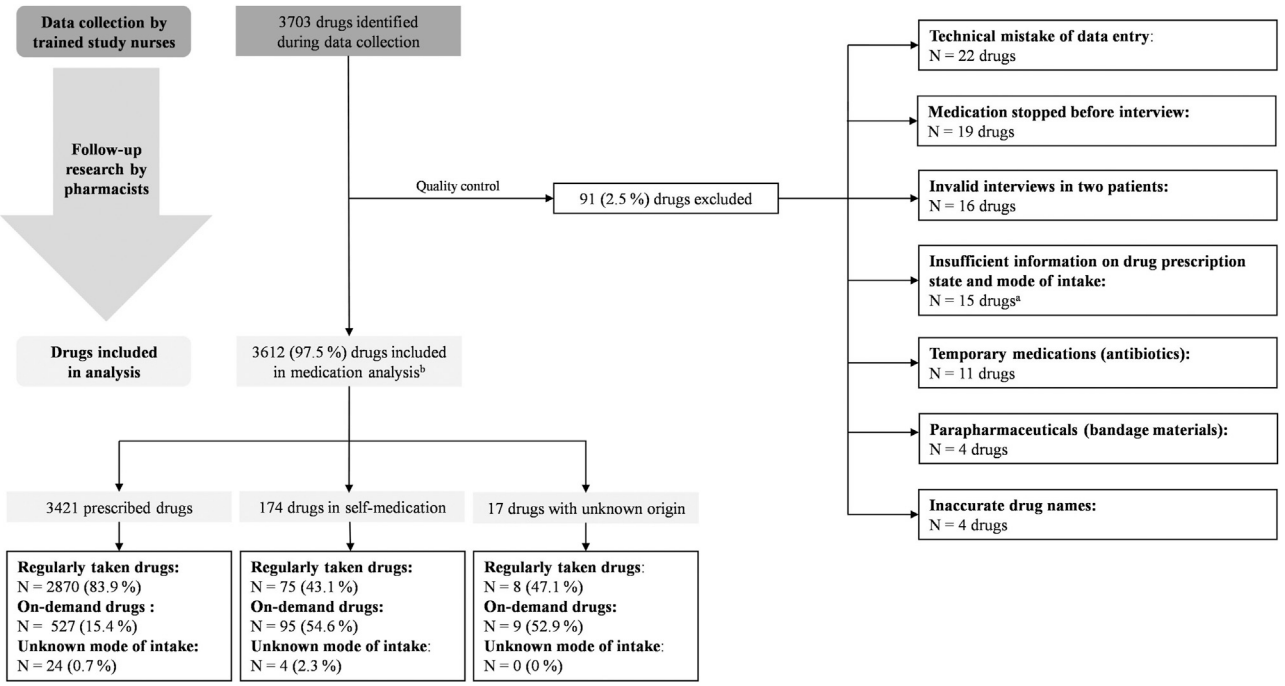

FIGURE 1 | Flow-diagram showing medication screening and selection process. [a]All drugs were non-prescription drugs. [b]Different patients may use the same drug.

Instruments and Measures

The individuals' burden of current diseases in chronic pain patients was assessed by the original Charlson-Comorbidity-Index (CCI) (Charlson et al., 1994) which is a widely used multimorbidity score in older adults (Diederichs et al., 2011). It represents a weighted index of comorbidity based on 19 chronic diseases according to International Classification of Diseases (ICD) diagnosis codes that are weighted differently according to the relative mortality risk (Charlson et al., 1987). We adapted the CCI for use in our population to include also self-reported diagnoses terms when physician reports or nursing records were unavailable. Furthermore, we checked for other chronic diseases such as hypertension, coronary artery disease and atrial fibrillation (AF) besides those listed in the CCI. Multimorbidity was defined as the presence of ≥2 chronic conditions (Kostev and Jacob, 2018). Levels of comorbidity were classified according to the original CCI score as: 0 (no comorbidity), 1–2 (low comorbidity), 3–4 (moderate comorbidity) and ≥5 (severe comorbidity) (Charlson et al., 1987).

We used the CHA_2DS_2-VASc [Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled) – Vascular disease, Age 65–74, and Sex category (female)] score for patients with AF to evaluate their risk of thromboembolism (Hindricks et al., 2021).

Data Analysis

Descriptive statistics were used to describe patients' demographics, multimorbidity and medications. Variables were checked for normal distribution by Shapiro-Wilk test and non-parametric tests were used according to the type of variable (continuous or categorical). We used Mann-Whitney U test to check the association of the CCI score (continuous) with sex (categorical), prevalence of polypharmacy (categorical) and excessive polypharmacy (categorical). Chi-squared test was used to examine the association between sex and both polypharmacy and excessive polypharmacy as well as the association of comorbidity levels (categorical) with level of care (categorical) and education level [highest school education (categorical) and highest professional education (categorical)]. Spearman's correlation was used to test the correlation between the CCI score and the number of prescribed medications (continuous), age (continuous) and MMSE score (continuous). Kruskal-Wallis H test was used for associations between number of prescribed medications (continuous) and levels of comorbidity (categorical with >2 groups). The post-hoc Dunn-Bonferroni test was applied for pairwise comparison between the groups. In addition, we used the Jonckheere-Terpstra test to check for an overall trend between the groups and calculated the corresponding Kendall's tau-b (τ) correlation coefficient. Data were analyzed using IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY). Two-tailed statistical significance was assessed at level 0.05.

RESULTS

Study Population

A total of 355 patients met the formal inclusion criteria of the *ACHE* study and data were analyzed as two cohorts: the medication-analysis cohort and the multimorbidity cohort

TABLE 1 | Patients' characteristics.

Characteristics	Population for medication analysis			Population for multimorbidity analysis		
	Total *N* = 353 (99.4%)	Women *N* = 253 (71.7%)	Men *N* = 100 (28.3%)	Total *N* = 334 (94.1%)	Women *N* = 239 (71.6%)	Men *N* = 95 (28.4%)
Age (years)	82.2 ± 7.5	83.0 ± 7.1	80.2 ± 8.3	82.2 ± 7.6	82.8 ± 7.1	80.4 ± 8.5
Care level (%)[a]						
1	11.3	9.9	15.0	11.7	10.5	14.7
2	44.8	45.4	43.0	46.1	46.9	44.2
3	21.0	20.2	23.0	21.2	20.1	24.2
4	12.7	13.8	10.0	11.4	12.5	8.4
5	7.4	7.1	8.0	6.9	6.7	7.4
nd	2.8	3.6	1.0	2.7	3.3	1.1
MMSE (%)[b,c]						
0–17 points	22.7	23.8	20.0	19.1	20.5	15.8
18–23 points	15.7	15.5	16.0	16.2	15.5	17.9
24–30 points	61.6	60.7	64.0	64.7	64.0	66.3
Number of all drugs[d] [median, (range)]	10 [0–25]	10 [0–22]	10 [2–25]	10 [0–25]	10 [0–22]	10.5 [2–25]
Number of prescribed drugs[d] [median, (range)]	9 [0–25]	9 [0–22]	10 [2–25]	10 [0–25]	10 [0–22]	10 [2–25]
Polypharmacy (%)[d] (≥ 5 prescribed drugs)	89.5	89.7	89.0	89.2	89.5	88.3
Excessive polypharmacy (%)[d] (≥ 10 prescribed drugs)	49.3	48.2	52.0	51.4	50.2	54.3

nd, not determined; MMSE, Mini Mental State Examination.

[a]According to § 15 SGB XI, the level of care is based on the degree of self-dependence and ranges from 1 (lowest degree) to 5 (most severe impairment with special requirements for nursing care).

[b]The MMSE-score was calculated for 352/353 of the medication population.

[c]According to the MMSE classification (Tombaugh and McIntyre, 1992): 0–17 points (severe cognitive impairment), 18–23 points (mild cognitive impairment), 24–30 points (no cognitive impairment).

[d]Medication data for 333/334 of the multimorbidity population were available.

(**Table 1**). For the medication-analysis cohort, data for 353 (99.4%) patients (mean age 82.2 ± 7.5 years, 71.7% females) were available including 22.7% of patients with severe cognitive impairment (MMSE ≤17 points). For the multimorbidity cohort, data of 334 (94.1%) patients (82.2 ± 7.6 years, 71.6% females) were available and 19.1% of them had severe cognitive impairment.

The most common diseases found in the multimorbidity cohort were hypertension (78.4%), congestive heart failure (CHF) (41.3%), diabetes with/without organ damage (32.1%), dementia (27.2%), coronary heart diseases (26.9%) and chronic pulmonary diseases (25.1%) (**Table 2**). Overall, CCI ranged from 0 to 13 with a median score of 3 (IQR: 2–4) in both men and women with more than half of the patients (55.4%) having moderate to severe comorbidity levels (**Figure 2**). Sex, age, cognitive state, level of care, education level did not significantly affect comorbidity scores. The prevalence of multimorbidity (≥2 chronic diseases) according to the original CCI was 73.7%, and 91.6% when additional disorders detected in the population were counted (**Table 2**).

Medication State

Among the medication-analysis cohort, 3,703 medication products were screened during data collection yielding 3,612 (97.5%) medication products for analysis after screening for data quality as per our preset criteria (**Figure 1**). Of those, 3,421 (94.7%) medication products were prescribed by physicians and 174 (4.8%) were used in self-medication, while for 17 (0.5%) medication products, the prescription mode could not be verified. According to the ATC code, analgesics, diuretics, antithrombotics, renin-angiotensin system (RAS) blockers were most frequently prescribed [**Supplementary Table S1** of the Electronic Supplementary Material (ESM)]. The median number of prescribed drugs was 9 (range 0–25), and 10 (range 0–25) when self-medication was accounted for (**Table 1**). A highly significant positive correlation was found between the CCI and the number of prescribed drugs ($r_s = 0.345$, $p < 0.001$). The prevalence of polypharmacy (≥5 prescribed drugs) was 89.5% ($n = 316$) and almost half of the patients ($n = 174$; 49.3%) were affected by excessive polypharmacy (≥10 prescribed drugs) (**Figure 3**). There were no sex-specific differences for the prevalence of either polypharmacy or excessive polypharmacy (Chi-squared test, $p = 0.842$, and $p = 0.522$, respectively). Patients affected by prescribed polypharmacy had significantly higher CCI scores (median: 3, range 0–13) than patients without polypharmacy (median: 2, range 0–5, Mann Whitney test, $U = 3077.5$, $p < 0.001$). Similarly, excessive polypharmacy was also associated with higher CCI scores (median: 4, range 0–13, Mann-Whitney test, $U = 9271.5$, $p < 0.001$). Moreover, significant associations were found between the number of prescribed medications and different levels of comorbidity (Kruskal-Wallis test, $H = 36.3$, $p < 0.001$). The adjusted p-values of the post-hoc analysis are shown in **Figure 4**. In addition, we found an overall

TABLE 2 | Prevalence of comorbidities among elderly receiving home care (*N* = 334).

Comorbid condition	Assigned weights for comorbidities in the CCI	Patients with comorbidity, N (%)[a]
Comorbidities covered by the CCI		
Congestive heart failure	1	138 (41.3)
Dementia	1	91 (27.2)
Chronic pulmonary disease	1	84 (25.1)
Peripheral vascular disease	1	78 (23.4)
Diabetes[b] with organ damage	2	77 (23.1)
Cerebrovascular disease	1	74 (22.2)
Connective tissue disease	1	50 (15.0)
Myocardial infarction	1	43 (12.9)
Ulcer disease	1	43 (12.9)
Any tumor	2	44 (13.2)
Moderate or severe renal disease	2	39 (11.7)
Diabetes[b] without organ damage	1	30 (9.0)
Mild liver disease	1	27 (8.1)
Hemiplegia	2	16 (4.8)
Metastatic solid tumor	6	6 (1.8)
Moderate or severe liver disease	3	3 (0.9)
Leukemia	2	2 (0.6)
Lymphoma	2	1 (0.3)
AIDS	6	0 (0)
Additional comorbidities detected in *ACHE*		
Hypertension	–	262 (78.4)
Coronary heart disease	–	90 (26.9)
Atrial fibrillation	–	65 (19.5)
Hemiparesis	–	62 (18.6)
Other arrhythmias	–	49 (14.7)
Prostate disorders	–	35 (10.5)

CCI, Charlson Comorbidity Index.
[a]*Patients may have more than one comorbidity.*
[b]*Diabetes includes all patients treated with insulin or oral hypoglycemics, but not diet alone.*

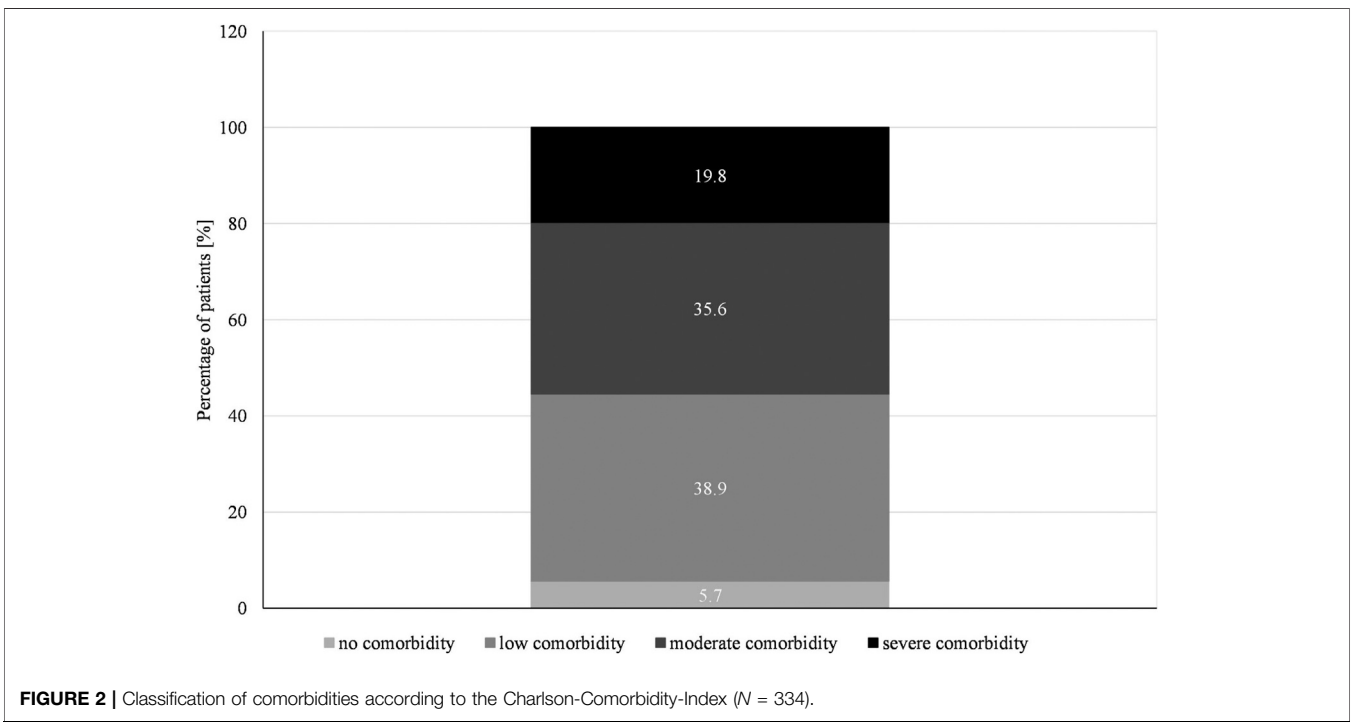

FIGURE 2 | Classification of comorbidities according to the Charlson-Comorbidity-Index (*N* = 334).

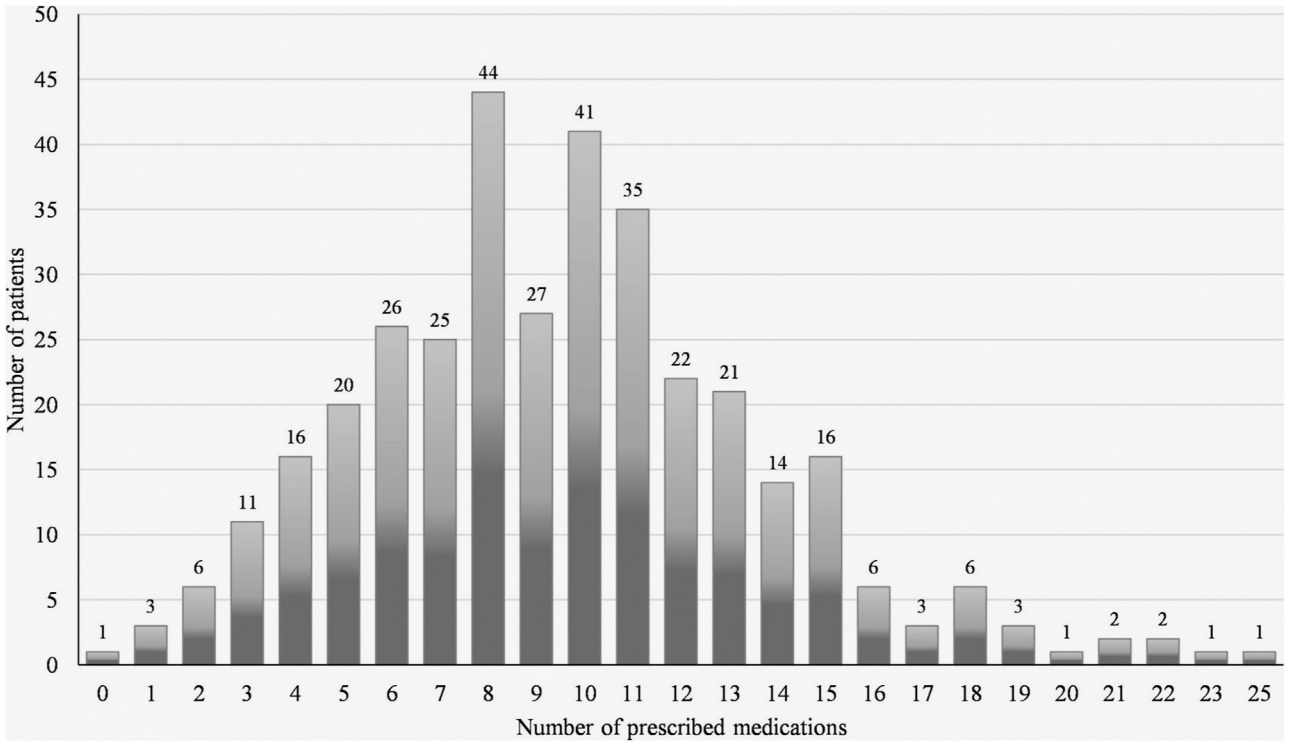

FIGURE 3 | Number of prescribed medications among elderly receiving home care (*N* = 353).

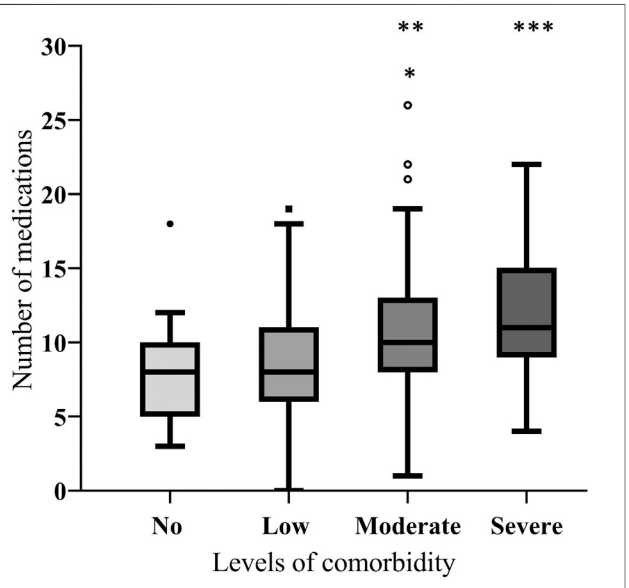

FIGURE 4 | Boxplot diagram: Number of prescribed drugs grouped by different comorbidity levels.*$p < 0.05$ vs. no comorbidity; **$p < 0.01$ vs. low comorbidity; ***$p < 0.001$ vs. low comorbidity; ***$p < 0.001$ vs. no comorbidity.

positive trend between these groups ($\tau = 0.262$, $p < 0.001$). Polypharmacy and excessive polypharmacy were detected in all levels of comorbidity.

Medication Errors Detected in Selected Drugs/Drug Classes (Anticoagulants, Diuretics, and Simvastatin)

In total, 184 clinically relevant potential DDI from which 57 (31.0%) evaluated as severe were detected in more than a third (34.0%) of patients in the medication-analysis cohort (**Supplementary Table S2** of the ESM). DDI lacking clear clinical meaning or consequences were not presented. Over- and underprescription of drugs were detected.

Anticoagulants

Drug-Drug Interactions

A total of 80 patients received anticoagulants in the medication analysis cohort for which 27 potential and 12 severe interactions were detected in 28 (35.0%) patients (**Supplementary Table S2** of the ESM).

Underprescription (Subgroup Analysis for AF)

In our multimorbidity cohort, 65/334 (19.5%) patients (mean age 82.8 ± 7.4 years) had AF (**Table 2**). All of them achieved a CHA_2DS_2-VAS score ≥2 (median: 5; range 3–8) but only 44 (67.7%) patients were anticoagulated with direct oral anticoagulants (DOAC) or vitamin-K-antagonist (VKA), while 21 (32.3%) received no oral anticoagulants; of these, 19 patients were ≥75 years old. The three most prescribed anticoagulants were apixaban (36.4%), phenprocoumon (29.5%) and rivaroxaban (20.5%).

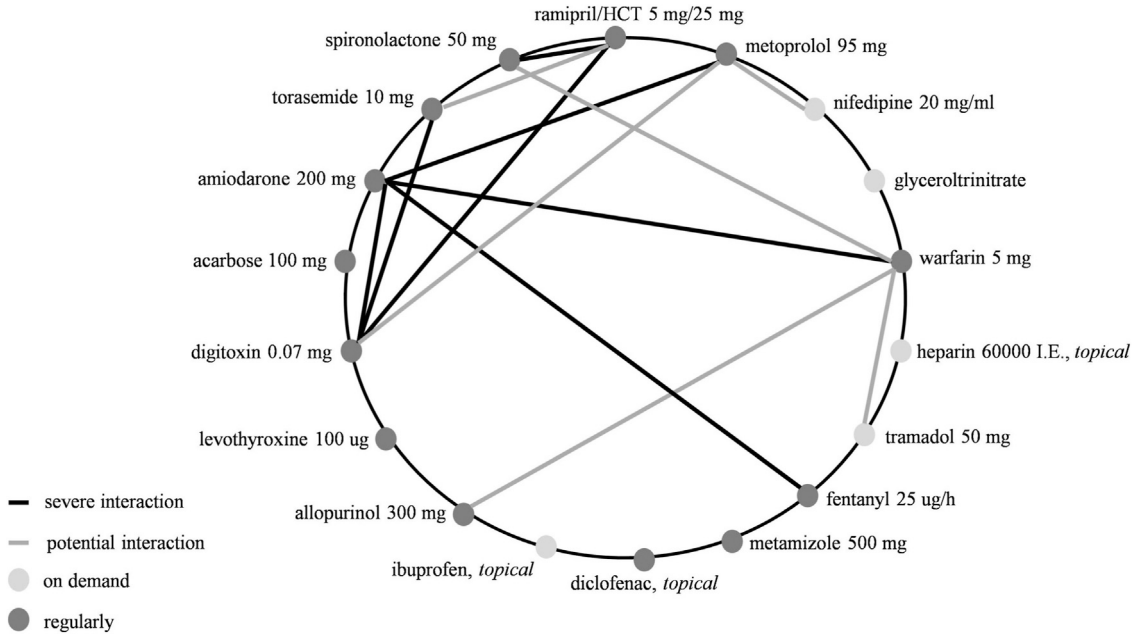

FIGURE 5 | Drug-drug interactions of prescribed medication in one patient.

Diuretics

Drug-Drug Interactions

Among the diuretics, all diuretic agents including potassium-sparing diuretics were included in DDI evaluation amounting to 281 diuretic prescriptions in 224 patients. We found 131 potential DDI, 36 (27.5%) of them were evaluated as severe (**Supplementary Table S2** of the ESM).

Overprescription (Subgroup Analysis for Loop Diuretics)

A total of 195/334 (59.9%) patients were treated with diuretics. By far, the most commonly prescribed diuretic was torasemide, prescribed in 160 (82.1%) patients. Loop diuretics were combined with thiazide/thiazide-like diuretics in 11/195 (5.6%) patients. In one patient, torasemide and furosemide were even co-prescribed. Among 174 (89.2%) patients receiving loop diuretics, 27 (15.5%) patients had no documented indication for CHF, advanced chronic kidney disease or edema.

Simvastatin

Overall, 85/353 (24.1%) patients took simvastatin once daily in an average dose of 29.9 ± 14.5 mg. We found 17 potential DDI between simvastatin and other drugs (e.g., amlodipine, dronedarone, colchicine, ranolazine). Of these, 11 interactions were rated as severe (**Supplementary Table S2** of the ESM).

Demonstration of Patient Case Study Affected by Excessive Polypharmacy and DDI

One patient (83 years, female) for whom we checked the whole DDI profile appears of interest (**Figure 5**). The patient had following comorbidities: hypertension, CHF, AF, diabetes with organ damage, connective tissue disease, edema, and hemiparesis. She was prescribed 18 different drugs by the physician. The patient had suffered a stroke in the past, had a CHA_2DS_2-VASc score of 8 and a CCI score of 5. We identified 13 potential clinically relevant interactions. Of these, seven could be severe (**Supplementary Table S2** and **Figure 5**).

DISCUSSION

The present study revealed that multimorbidity and polypharmacy along with the consequences of polypharmacy (e.g., higher risk of medication errors, DDI, inappropriate medication use) were highly prevalent in our cohort of older adults with chronic pain receiving home care that also included patients with severe cognitive impairment. To the best of our knowledge, this is the first cross-sectional prospective study in Germany to examine the burden of multimorbidity and polypharmacy in this setting involving chronic pain patients. Chronic pain has been reported to be associated with high burden of comorbid diseases and high risk of polypharmacy (Fishbain, 2005; Paladini et al., 2015; Jokanovic et al., 2016). In one study, chronic pain was independently associated with higher daily drug consumption (Ersoy and Engin, 2018).

We found a median CCI score of 3 (IQR: 2–4) in both men and women and an overall range of 0–13. More than half of the patients (55.4%) had moderate (35.6%) to severe (19.8%) comorbidity levels (**Figure 2**). However, these values could be still underestimated considering patients for whom morbidity scores could not be determined due to lack of self-report or medical records. In addition, all patients, by virtue of our study design, had chronic pain. CCI scores ≥3 have been correlated with an increased risk of hospital readmission (Halfon et al., 2002),

while scores ≥5 correlated significantly with mortality and high risk of medication errors (Charlson et al., 1987; Rabenberg et al., 2019). The KORA-Age study (mean age 73.4 ± 6.1 years) reported a median number of conditions of 2 (IQR: 1–3) and a multimorbidity (≥2 chronic conditions) prevalence of 58.6% (95% CI: 57.0-60.2) (Kirchberger et al., 2012). Our higher multimorbidity rate (91.6%) could be ascribed to the home care setting and the older age of our patients. For the assessment of comorbidities, Kirchberger et al. (Kirchberger et al., 2012) also used a CCI generated self-reported diagnoses and included hypertension, eye diseases, mental and neurological diseases, that were deemed highly relevant for exploring multimorbidity in the elderly (Kirchberger et al., 2012). Bravo and colleagues also extended the Charlson list of 19 comorbidities to include 10 other disorders being significant to mortality or functional decline in long-term care setting such as valvular heart diseases (Bravo et al., 2002). Despite the limitation of the CCI to detect other relevant disorders, the CCI is still widely used to investigate comorbidity in geriatric patients in healthcare research (Jorgensen et al., 2012; Abizanda et al., 2014; Rochon et al., 2014; Gellert et al., 2019).

The median number of prescribed drugs was 9 (range 0–25) and 10 (range 0–25) when self-medication was included. In nursing homes in Germany, an average of 5.9 ± 3 (range 0–16) drugs prescribed concomitantly per resident was reported (Kolzsch et al., 2012), while in general practice, a mean of 4.2 ± 2.7 in men and women aged ≥60 years, about 37% of whom were affected by polypharmacy (≥5 prescribed drugs) (Kostev and Jacob, 2018). We found a higher prevalence of polypharmacy (89.5%) with almost half of the patients (49.3%) having excessive polypharmacy (≥10 prescribed drugs) in our study, which may relate to the high multimorbidity prevalence in our study as a driver for polypharmacy. The mean number of prescribed medications was significantly associated with higher CCI-based morbidity levels supporting the reciprocal link between multimorbidity and polypharmacy. The latter acts as a driver for medication-related morbidity and increases the chance of DDI to which elderly patients are more vulnerable. In our target group, potential DDI were detected in a third of patients.

DDI involving simvastatin, a well-known substrate of cytochrome P450 (CYP) 3A4 (Tiwari et al., 2006) predisposing to myotoxicity were detected. The risk of myotoxicity is elevated with older age as muscle mass decreases (Kellick et al., 2014), with renal impairment, and high dose therapy (Tiwari et al., 2006).

As a case study, we demonstrated the overall DDI profile of a multimorbid female patient affected by excessive polypharmacy and experiencing a complex drug regimen. For this patient, we detected several DDI involving anticoagulants and diuretics. This case also illustrates an increased number of prescribed drugs proportional to a high CCI, with a comorbidity score of 5. Notably, guideline-based treatments for several diseases facilitate polypharmacy as illustrated in this patient treated for CHF, hypertension and AF and was therefore included in the AF subgroup analysis.

Patients with AF and a CHA_2DS_2-VASc score ≥2 should be anticoagulated with DOAC or VKA due to risk of stroke (Hindricks et al., 2021). In our study, 19.5% of patients had AF with a median CHA_2DS_2-VASc score of 5 (range 3–8). However, about a third (32.3%) of them did not receive anticoagulant therapy with either DOAC or VKA suggesting a state of underprescription of potentially useful medications. Though current AF management guidelines recommend oral anticoagulant treatment at age ≥75 years regardless of additional risk factors for stroke (Hindricks et al., 2021), underuse of oral anticoagulant treatment in the elderly with AF has been previously reported (Zarraga and Kron, 2013; Steinberg et al., 2015; Kreutz et al., 2018).

Diuretics, commonly prescribed in the elderly, often cause hypovolemia and hyponatremia which increase the risk of falling that was associated with higher morbidity and mortality in older adults (Maher et al., 2014). Elderly hypertensive patients were more likely to develop hyponatremia after age 75 years (Diaconu et al., 2014). Loop diuretics were prescribed in 15.5% of patients without a documented appropriate indication. This includes edematous disorders due to CHF, hepatic cirrhosis or nephrotic syndrome, and advanced renal insufficiency (Sarafidis et al., 2010). Additionally, 5.6% of patients on diuretics received concomitantly loop diuretics and thiazide/thiazide-like diuretics. Overprescription of loop diuretics without appropriate indication has been reported in 27.5% of nursing home residents (Kölzsch et al., 2010). The concomitant use of spironolactone and ramipril as illustrated in our patient case increases the risk of hyperkalemia; a potentially severe DDI to which the elderly are more sensitive due to potassium homeostasis abnormalities, disorders e.g., diabetes mellitus or use of drugs e.g., RAS blockers and potassium-sparing diuretics (Hunter and Bailey, 2019).

Suboptimal prescribing in elderly includes, besides unnecessary prescribing or overprescribing, underuse or underprescribing of indicated medications (Devik et al., 2018). The latter is defined as failure to prescribe a potentially useful drug and has become a frequent problem leading to adverse clinical consequences e.g., stroke in high risk patients undertreated for atrial fibrillation (Kuijpers et al., 2008). Polypharmacy can also be a driver for medication underuse reported to occur in over 40% of patients with polypharmacy (Kuijpers et al., 2008).

This study is the first to examine the burden of multimorbidity and polypharmacy in older adults with chronic pain receiving home care. The strengths of our study lie in the rigorous evaluation of the drug profile including self-medication and drugs prescribed regularly or on-demand as well as including patients with severe cognitive impairment. In contrast to previous studies that excluded patients with cognitive impairment (Markotic et al., 2013; Nawai et al., 2017), patients with cognitive impairment were eligible for inclusion in *ACHE*. However, the following limitations are acknowledged:

First, this is a cross-sectional cohort study. As such, patients were interviewed once; follow-up data of patients were not available. In addition, contacts with the treating physician were not implemented in the study design. Hence, it was not possible to assess the persistence of polypharmacy or notify the physician in case of suspected DDI or trace the outcome of the potential DDI whether a corrective action was taken by the physician or a follow-up for clinical condition was undertaken. Second, our sample size

was small, and the study reflects local data to the city of Berlin regarding patients with chronic pain in the home care setting which may limit the generalizability of our findings concerning prevalence rates of multimorbidity and polypharmacy and its consequences. Nevertheless, we preferred to analyze qualitatively the prescribed medications rather than to systematically report the prevalence of medication errors, DDI and inappropriate medication use to get an insight into the consequences of polypharmacy in multimorbid chronic pain patients. This highlights also how significant DDI could be regardless of their actual prevalence and helps instigate awareness on the harmful effects of DDI in this group.

CONCLUSION

Multimorbidity and polypharmacy are highly prevalent in elderly outpatients with chronic pain receiving home care. Regular monitoring and evaluation of medications in this population appears thus important together with strategies aiming to optimize therapy by addressing differential aspects of medication-related problems including drug interactions, overprescribing as well as underuse.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data are archived in the Institute of Clinical Pharmacology and Toxicology, Charité – Universitätsmedizin Berlin, and can be accessed by all interested researchers on site. Requests to access the datasets should be directed to RK, reinhold.kreutz@charite.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethical committee of the Charité-Universitätsmedizin Berlin (EA1/368/14). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design and concept: DD, RK, AB, AW, JS, and EA. Analysis: JS, EA, and RK. All authors participated in the interpretation of the results, drafting, and reviewing the manuscript, and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.686990/full#supplementary-material

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Relationship Between Medication Literacy and Frailty in Elderly Inpatients With Coronary Heart Disease: A Cross-Sectional Study in China

*Jiling Qu, Ting Zhou, Mengxin Xue, Huiping Sun, Yijing Shen and Yongbing Liu**

School of Nursing, Yangzhou University, Yangzhou, China

Background: Mastering medication literacy may be related to medication safety, and the identification of frailty is very important for the prognosis of coronary heart disease (CHD). Few studies have examined the relationship between medication literacy and frailty in patients with CHD. The aim of this study was to investigate the state of medication literacy and frailty in patients with CHD and to explore the relationship between medication literacy and frailty.

Methods: A cross-sectional investigation evaluated 295 inpatients with CHD recruited from hospitals in Yangzhou, China. Demographic and clinical data on participants were collected using a general information questionnaire. The Chinese medication literacy scale was used to evaluate medication literacy. The Fried Frailty Phenotype scale was used to evaluate frailty. Univariate analysis employed chi-square test and Kruskal-Wallis H test to examine the potential factors affecting frailty. Taking frailty status as the outcome variable, the ordered logistic regression model was used to analyze the relationship between the degree of medication literacy and frailty. Spearman's correlation analysis was used to analyze the correlation between medication literacy and frailty.

Results: A total of 280 elderly CHD inpatients were included in the analysis. There were 116 (41.4%) individuals with inadequate medication literacy and 89 (31.8%) frail individuals. Ordered logistic regression analysis showed that the age ($p < 0.001$, $OR = 1.089$), Charson Comorbidity Index ($p = 0.029$, $OR = 1.300$), number of medications taken ($p = 0.012$, $OR = 1.137$), and medication literacy ($p < 0.05$, $OR > 1$) were independent predictors of debilitating risk factors. The population with inadequate medication literacy had a 2.759 times greater risk of frailty than adequate medication literacy ($p < 0.001$, $OR = 2.759$); The population with marginal medication literacy had a 2.239 times greater risk of frailty than adequate medication literacy ($p = 0.010$, $OR = 2.239$). Spearman's correlation analysis showed that the medication literacy grade was associated with the frailty grade in elderly CHD patients ($R = -0.260$, $p < 0.001$).

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****Correspondence:***
Yongbing Liu
bingbing19950806@163.com

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Conclusion: The study showed a significant correlation between medical literacy and frailty in patients with CHD. The results suggested that medication literacy was an important consideration in the development, implementation, and evaluation of frailty.

Keywords: medication literacy, frailty, elderly, inpatients, coronary heart disease, relationship

INTRODUCTION

Frailty is defined as a series of syndromes caused by a decreased physiological reserve, such as decreased body function and chronic diseases (Schoufour et al., 2017). It seriously affects the health status and increases the risk of falls, fractures, infections, suicide, disability, and death among older people (Cunha et al., 2019; Houghton et al., 2020; Kurobe et al., 2021). The prevalence of frailty ranges from 10 to 60% in older adults in cardiovascular care (Afilalo et al., 2014). Frailty is an independent prognostic marker of the composite of mortality, reinfarction, and mortality in patients aged ≥75 years admitted due to myocardial infarction (Alonso Salinas et al., 2018). Studies have shown that higher aging trajectories in frailty scores were associated with elevated risks for cardiovascular, other-cause, and all-cause death among older Japanese individuals receiving health checkups (Taniguchi et al., 2020). Frailty is reversible, but requires intervention. A recent review and meta-analysis have shown that only 3% of frail older people spontaneously reverted to a robust state at a later date (Rodriguez-Mañas and Fried, 2015; Kojima et al., 2019). In order to reduce the incidence of death and complications in patients with coronary heart disease (CHD), it is essential to screen for frailty in a timely fashion, find the influencing factors of frailty in patients with CHD, and carry out an effective intervention according to these factors (Kang et al., 2015).

Patients with CHD usually require oral medications to achieve and maintain effective symptom control and prevent disease progression (Zhong et al., 2016). Good medication literacy is the premise of ensuring drug use safety (Li et al., 2020). The term "medication literacy" first appeared in a government document of the Committee of the Regulatory Agency for Medicines Safety and Healthcare Products in the United Kingdom in 2005. It referred to health literacy as "a series of skills required to obtain, understand and use drug information" (Shen et al., 2018). Pharmacy practices and laws vary widely around the world. In order to help healthcare workers around the world realize the importance of medical literacy in drug use, Pouliot et al. (Pouliot et al., 2018) consulted international experts using the Delphi method and proposed an expert consensus on the concept of medication literacy, which refers to the ability of individuals to obtain, understand, communicate, calculate, and process specific drug information and make informed drug treatment and health decisions in order to achieve safe and effective drug use. Research has shown that low health literacy is associated with frailty (Hou, 2019), and medication literacy is the embodiment of health literacy in the field of medicine (Raynor, 2009). Frailty is associated with an increased susceptibility to adverse drug events and drug-related injuries (Liau et al., 2021). However, there is no direct evidence of a link between medication literacy and frailty.

Therefore, the purpose of our study was to investigate the relationship between medication literacy and frailty in elderly patients with CHD in order to describe a new and targeted intervention problem for healthcare personnel, improve the quality of patient life, and reduce the risk of complications.

MATERIALS AND METHODS

Design, Setting, and Participants

The study was approved by the Ethics Review Committee of the School of Nursing, Yangzhou University (Ethical Batch Number: YZUHL20200012). A cross-sectional survey was conducted in a cardiology ward of a tertiary hospital in Yangzhou, Jiangsu Province, China between August 2020 and January 2021. The convenient sampling method was used to extract the research subject data.

Subjects were eligible if they met the following inclusion criteria: 1) age ≥60 years and good communication skills; 2) met the diagnostic criteria of coronary atherosclerotic heart disease of the American Heart Association; and 3) provided informed consent and voluntarily participated in the study. Patients were excluded if they had any of the following conditions: 1) acute or terminal stage of a disease, severe cardiopulmonary and renal insufficiency; 2) patients with grade IV cardiac function; and 3) engaged in healthcare-related work currently or before retirement.

Our study is a cross-sectional study, according to the cross-sectional sample size calculation formula, which is: $N = Z^2_{\alpha/2}P\ (1\text{-}P)/d^2$. According to existing studies (Hou et al., 2019), the frailty incidence (P) of elderly hospitalized patients with CHD evaluated by the fried frailty phenotype scale was 20.8%. In our study, we set $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$, allowable error (d) = 5%; After calculation, the required sample size was 253 cases. Considering that invalid questionnaires constitute 10% of the total cases, the required sample size was 278 cases. A total of 295 questionnaires were sent out in the present study, and 15 invalid questionnaires were eliminated. Thus, a total of 280 valid questionnaires were finally recovered, with an effective recovery rate of 94.9%.

Survey Procedures

Inpatients anonymously filled out questionnaires after signing the informed consent form. The survey was conducted *via* one-to-one and face-to-face interviews. The interviewees were all postgraduate students from School of Nursing, Yangzhou University who had received similar training. The same assistive tools were used to measure frailty and medication literacy. If the respondents were illiterate or unable to fill in the forms by themselves, the investigators read the questionnaire to them and assisted them in completing it. After the

questionnaire was completed, the researcher checked and retrieved it immediately. If there were omissions or obvious mistakes, the researcher assisted the patient in correcting them.

Data Collection

General Condition Questionnaire

The investigators designed a self-administered general condition questionnaire, which included questions about age, sex, body mass index (BMI), education level, marital status, economic status, smoking status, drinking status, Charson Comorbidity Index (CCI), and number of medications taken. The patients who were unsure of their height and weight were measured on site. The medication number inquiry was as follows: How many drugs did you take for more than 3 months before hospitalization?

Chinese Version of the Medication Literacy Scale

The Chinese Version of the Medication Literacy Scale was used to evaluate medication literacy. This scale was originally developed by Sauceda et al. (2012) from the University of Texas at El Paso in the United States. Zheng et al. (2016) sinicized the English version of the scale. The retest reliability of the Chinese scale was 0.885 and the sub-half reliability was 0.840. The correlation coefficient between each item and the total score of the scale was 0.427–0.587. The scale was composed of four simulated drug use scenarios containing 14 items and was scored on a two-point scale (1 point for correct answers and 0 points for wrong answers). The score for each item was added to the total score of the questionnaire. The higher the score, the higher the patient's level of medication literacy. Patients with scores >10 were considered to have "adequate medication literacy". Those with scores of 4–10 were considered to have "marginal medication literacy", whereas patients with scores <4 were considered to have "inadequate medication literacy". This scale is mainly used to measure the ability of patients to read, understand, calculate, and deal with drug-related problems in the medical information environment in order to evaluate the level of their medication literacy.

Fried Frailty Phenotype Scale

The frailty assessment was based on the Fried Frailty Phenotype Scale proposed by Fried et al. (Fried et al., 2001) at the School of Medicine at Johns Hopkins University in 2001. There are five items on the scale, including weight loss, slowness, weakness, low physical activity, and exhaustion.

1) Weight loss: It is an unintentional loss of ≥4.5 kg or a loss of ≥5% body weight in the past 1 year.
2) Slowness: The time required to walk 4.6 m at a normal speed was used as an indicator of slowness. Slow walking speed was defined as ≥6 s when a male is >173 cm in height and a female is >159 cm in height or 7 s when a male is ≤173 cm in height and a female is ≤159 cm in height.
3) Weakness: Hydraulic dynamometer was used to measure grip strength as an indicator of weakness. Older adults in a sitting position used the dominant hand to grip an object three times and the researcher recorded the maximum value. Criteria proposed by Fried et al. (2001) was used to define the weakness.
4) Low physical activity: The International Physical Activity Questionnaire was used to assess physical activity (Liou et al., 2008); Males who expended <383 kcal/w and females who expended <270 kcal/w were considered to have low physical activity.
5) Exhaustion: Poor endurance and energy were assessed using the depression scale, specifically, to check whether the answer to either of these questions is yes: "Last week, I felt like everything I did needed an effort"; "I can't walk forward". If positive response was given to either of these questions, the participant was thought to be exhausted.

Each item scored one point if it was present. Otherwise, no points were scored. Patients with scores ≥3 were considered as "frail", those with scores of one to two were considered as "pre-frail", and patients with a score of 0 were considered as "not frail". This scale is easy to evaluate objectively and it is widely used. In the present study, Cronbach's α coefficient of the questionnaire was 0.671.

Statistical Analysis

Data were analyzed using SPSS (version 26.0, Chicago, IL, United States) software. A p-value of < 0.05 was considered statistically significant.

Descriptive statistical methods were used to describe the inpatient's baseline characteristics, level of medication literacy, and frailty. Univariate analysis used the chi-square test and Kruskal-Wallis H test to examine the influencing factors of frailty. The frailty status was used as the outcome variable to conduct the ordered multi-classification logistic regression analysis for multivariate analysis. Spearman's correlation analysis was used to analyze the correlation between medication literacy and frailty.

RESULTS

General Characteristics of Participants

A total of 280 elderly CHD inpatients were included in the analysis. The characteristics of the inpatients with CHD are shown in **Table 1**. The study included 137 (48.9%) males and 143 (51.1%) females. The median patient age was 73.0 (68.0–79.0) years. The median number of drugs used in the patients was 3.0 (1.0–5.0).

Chinese Version of the Medication Literacy Scale

The medication literacy of elderly patients with CHD is shown in **Table 2**. The median medication literacy score was 2.0 (0.0–3.0). There were 116 (41.4%) people with inadequate medication literacy, 70 (25.0%) with marginal medication literacy, and 94 (33.6%) with adequate medication literacy. The highest accuracy of item 9 was 165 (58.9%), and the lowest accuracy of item 11 was 76 (27.1%).

TABLE 1 | | Characteristics of inpatients with CHD (*N* = 280).

Variable name	—	No. of participants (*N* = 280)	Percentage (%)
Sex	Male	137	48.9
—	Female	143	51.1
Education (year)	≤9	207	73.9
—	≥10	73	26.1
Marital status	Free	201	71.8
—	Unaccompanied	79	28.2
Monthly income	<2000	113	40.4
—	2000–5,000	112	40.0
—	>5,000	55	19.6
Smoke	No	170	60.7
—	Yes	110	39.3
Drink	No	174	62.1
—	Yes	106	37.9

TABLE 2 | | Medication literacy for inpatients with CHD (*N* = 280).

Items	No. of participants who answered correctly (*n* = 280)	Percentage (%)
Case scenario 1	—	—
1 According to the label, how many times a day should your mother inject the medicine?	157	56.1
2 Please show me how much medicine you should put into the syringe in the morning and mark the amount on the syringe	124	44.3
3 According to the instructions, please tell us or point out where the three parts of the body where your mother can inject the medicine are?	106	37.9
4 According to the instructions, please tell me what is the right angle at which you should inject the medicine?	95	33.9
5 Looking at the prescription, if your mother's medicine runs out, where should you get a new prescription?	130	46.4
Case scenario 2	—	—
6 Looking at the instructions on this box, what is the dose of the medicine you should give to your niece?	137	48.9
7 If you know the medicine dosage that your niece needs to take, please mark on the cup up to what line you should pour the medicine	118	42.1
8 According to the directions, what is the maximum dosage your niece should take?	110	39.3
Case scenario 3	—	—
9 Looking at this prescription, what is the name of the medicine that you need to buy at the pharmacy?	165	58.9
10 According to the prescription, how many pills should you take?	112	40
11 Looking at this bottle, the medicine in the bottle has a similar purpose compared to the medicine on the prescription. If you need to take 30 pills to treat the infection, how many boxes should you buy to have the correct amount of antibiotic required by the original prescription?	76	27.1
Case scenario 4	—	—
12 Looking at the box, when does the medicine go out of date?	143	51.1
13 According to the directions, what is or what are the active ingredients in each pill?	145	51.8
14 Please look carefully at the box. For what reason should you stop taking the medicine?	133	47.5

Fried Frailty Phenotype Scale

The frailty of elderly patients with CHD is shown in **Table 3**. The median frailty score was 6.0 (0.0–12.7). There were 80 (28.6%) patients who were not frail, 111 (39.6%) who were considered pre-frail, and 89 (31.8%) frail individuals. The highest satisfaction for item 3 was 167 (59.6%), and the lowest satisfaction for item 1 was 43 (15.4%).

Associated Factors of Frailty in Elderly Patients With CHD

Results for univariate analysis of frailty determinants for inpatients with CHD are shown in **Table 4**. A total of four factors were significantly associated with frailty. Compared to the population with adequate medication literacy, those with marginal medication literacy and inadequate medication literacy were more likely to be in a frail state ($p < 0.001$). Older patients ($p < 0.001$), those with a higher CCI ($p < 0.001$), and individuals who used more drugs ($p < 0.001$) were more likely to be in a frail state.

The frailty grade (frailty, pre-frailty, and non-frailty) was taken as the dependent variable. The age, CCI, number of medications taken, and medication literacy were used as the independent variables. Ordered logistic regression analysis was then conducted. **Table 5** represents the results of logistic regression analysis for frailty determinants for inpatients with

TABLE 3 | | Fried for inpatients with CHD (*N* = 280).

Items	No. of participants (*n* = 280)	Percentage (%)
1 Weight loss	43	15.4
2 Slowness	96	34.3
3 Weakness	167	49.6
4 Low physical activity	79	28.2
5 Exhaustion	99	35.4

CHD. The results showed that the age ($p < 0.001$, $OR = 1.089$), CCI ($p = 0.029$, $OR = 1.300$), number of medications taken ($p = 0.012$, $OR = 1.137$), and medication literacy ($p < 0.05$, $OR > 1$) were independent predictors of debilitating risk factors. The population with inadequate medication literacy had a 2.759 times greater risk of frailty than adequate medication literacy ($p < 0.001$, $OR = 2.759$); The population with marginal medication literacy had a 2.239 times greater risk of frailty than adequate medication literacy ($p = 0.010$, $OR = 2.239$).

Correlation Between Frailty and Medication Literacy in Elderly Patients With CHD

Spearman's correlation analysis of the medication literacy grade and frailty grade in elderly CHD patients showed that the medication literacy grade was associated with frailty grade in elderly CHD patients ($R = -0.260$, $p < 0.001$), which was statistically significant.

DISCUSSION

This population-based cross-sectional study described the medication literacy and frailty in a group of Chinese inpatients with CHD and explored the correlation between medication literacy and frailty.

Based on the analysis results, 107 people (44.03%) had inadequate medication literacy, 59 people (24.28%) had marginal medication literacy, and 77 people (31.69%) had adequate medication literacy. The incidence of inadequate medication literacy in this study was higher than the 20.0% in the Zheng et al. study (Zheng et al., 2019). The reasons for this

TABLE 4 | | Results of univariate analysis of frailty determinants for inpatients with CHD (*N* = 280).

Variable name	—	Number of cases (Percentage %)			$\chi 2$ /*H*	*P*
	—	Not frail (*n* = 80)	Prefrail (*n* = 111)	Frail (*n* = 89)		
Age	—	68.5 (64.0–72.0)[a]	73.0 (69.0–79.3)[a]	78.0 (73.0–84.0)[a]	68.021[b]	<0.001
Sex	Male	44 (32.1)	57 (41.6)	36 (26.3)	4.002[c]	0.135
	Female	36 (25.2)	54 (37.8)	53 (37.1)	—	—
BMI	—	24.1 (22.2–30.0)[a]	24.2 (22.2–25.7)[a]	23.8 (21.1–27.2)[a]	0.393[b]	0.822
Education (year)	≤9	52 (25.1)	87 (42.0)	68 (32.9)	4.732[c]	0.094
	≥10	28 (38.4)	24 (32.9)	21 (28.8)	—	—
Marital status	Yes	64 (31.8)	76 (37.8)	61 (30.3)	3.731[c]	0.158
	No	16 (20.3)	35 (44.3)	28 (35.4)	—	—
Monthly income	<2000	29 (25.7)	47 (41.6)	37 (32.7)	1.236[c]	0.874
	2000–5,000	35 (31.3)	44 (39.3)	33 (29.5)	—	—
	>5,000	16 (29.1)	20 (36.4)	19 (34.5)	—	—
Smoke	No	45 (26.5)	67 (39.4)	58 (34.1)	1.415[c]	0.493
	Yes	35 (31.8)	44 (40)	31 (28.2)	—	—
Drink	No	42 (24.1)	70 (40.2)	62 (35.6)	5.341[c]	0.069
	Yes	38 (35.8)	41 (38.7)	27 (25.5)	—	—
CCI	—	1.5 (0–3)[a]	3 (2–5)[a]	4 (2–6)[a]	32.336[b]	<0.001
Number of medications	—	3 (2–3)[a]	4 (3–5)[a]	4 (4–5)[a]	53.562[b]	<0.001
Medication literacy	Inadequate	21 (18.1)	49 (42.2)	46 (39.7)	22.289[c]	<0.001
	Marginal	18 (25.7)	25 (35.7)	27 (38.6)	—	—
	Adequate	41 (43.6)	37 (39.4)	16 (17)	—	—

[a]*Notes: median (IQR)*
[b]*Kruskal-Wallis H test*
[c]*chi-square test.*

TABLE 5 | | Results of logistic regression analysis of frailty determinants for inpatients with CHD (*N* = 280).

Effect		*β*	SE	Wald	*P*	*OR*	95%CI
Age	—	0.085	0.021	16.170	<0.001	1.089	0.044 ~ 0.126
CCI	—	0.262	0.120	4.777	0.029	1.300	0.027 ~ 0.498
Number of medications	—	0.128	0.051	6.366	0.012	1.137	0.028 ~ 0.227
Medication literacy	Inadequate	1.015	0.283	12.886	<0.001	2.759	0.461 ~ 1.569
	Marginal	0.806	0.316	6.495	0.011	2.239	0.186 ~ 1.425
	Adequate	—	—	—	—	—	—

may be related to age. The subjects of the present study were the elderly (≥60 years old), while those in the Zheng et al. study were adults ≥18 years old. This suggested that the levels of medication literacy among the elderly was more worrying. Memory and comprehension gradually decrease with age due to deterioration of the physical functions. In addition, the elderly hold relatively traditional views and their ability to accept new things is weak. Therefore, the knowledge and skills related to drug use are insufficient, and the level of medication literacy is low. It has been suggested that medical staff should pay attention to drug education of the elderly in clinical practice (Hao, 2018). The use of more intuitive charts or concise wording can also encourage family members to participate in medication management in order to improve the elderly patients' medication literacy.

Using correlation analysis, the present study found that the level of medication literacy was negatively correlated with the state of frailty ($R = -0.260$, $p = 0.001$). It is consistent with the research results by Liu et al. (2020). That is, the higher the level of medication literacy, the lower the degree of frailty. Ordered logistic regression analysis found that medication literacy was an independent predictor of frailty. This is consistent with Uemura et al. research results (Uemura et al., 2021). This may be because it is difficult for patients with inadequate medication literacy to understand information related to medication, and they cannot effectively cooperate with treatment directions, which is more likely to lead to health status decline and then the occurrence of frailty. Therefore, attention should be paid to medication literacy to reduce the risk of debilitating status deterioration in patients with CHD with limited drug knowledge. Secondary CHD prophylaxis usually includes antiplatelet agents (aspirin adenosine diphosphate receptor antagonists clopidogrel or ticagrelor), angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, statins, beta-blockers, and nitrates (Szummer et al., 2017). If patients suffer from other diseases, the number of treatment drugs increases. Thus, CHD patients often face the problem of multiple drug use (Duan and Jing, 2019). Adequate medication literacy makes it easier for patients to obtain correct drug information, maintain good medication habits, and effectively cooperate with treatment, which is more conducive to maintaining good health status, thus reducing the probability of frailty. Medication literacy programs can be used to achieve this goal (Shen et al., 2019). Health lectures, group discussions, personalized consultation, demonstration of teaching skills, practical exercises, automatic reminders, medication boxes, and medication cards can be utilized to comprehensively improve patients' literacy in all aspects of medication knowledge, attitude, skills, and behaviors.

Besides medication literacy, age, CCI, and number of medicines have been reported to be significant determinants using logistic regression. These results are consistent with the findings from previous studies (Vetrano et al., 2019; Xu et al., 2021; Palmer et al., 2019). Therefore, an integrated multifaceted approach is needed to improve frailty in patients with chronic disease.

The present study had the following advantages: The findings showed that medication literacy is related to frailty, whereas most of the previous studies have concentrated on the relationship between health literacy and frailty. The results of the present study will improve the understanding of the impact of medication literacy on health status. There were some limitations in this report. First, this study had a cross-sectional design, which could only explain the correlation between medication literacy and frailty in patients with CHD, but could not prove a causal relationship. In subsequent studies, follow-up will be added to dynamically observe the effect of medication literacy on frailty. Second, this study was conducted in a tertiary hospital in China, and the results may not be representative. More multicenter cohort studies with a larger sample size should be conducted.

CONCLUSION

The study showed that there was an association between medication literacy and frailty in patients with CHD. Medication literacy was an important consideration in the development, implementation, and evaluation of frailty. The study also provided preliminary information for the development of effective healthcare interventions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Review Committee of the School of Nursing, Yangzhou University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL conceived the study. JQ, TZ, MX, HS, and YS collected, verified, and analyzed the data. JQ drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content.

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Prescription of Potentially Inappropriate Medication in Older Inpatients of an Internal Medicine Ward: Concordance and Overlap Among the EU(7)-PIM List and Beers and STOPP Criteria

*Carla Perpétuo[1,2], Ana I. Plácido[1,3], Daniela Rodrigues[1,3], Jorge Aperta[1,2], Maria Piñeiro-Lamas[4,5], Adolfo Figueiras[4,5,6], Maria Teresa Herdeiro[7] and Fátima Roque[1,3,8]**

[1]Health Sciences School, Polytechnic Institute of Guarda, Guarda, Portugal, [2]Local Health Unit of Guarda, Guarda, Portugal, [3]Research Unit for Inland Development, Polytechnic Institute of Guarda (UDI/IPG), Guarda, Portugal, [4]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública- CIBERESP), Santiago de Compostela, Spain, [5]Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain, [6]Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain, [7]Department of Medical Sciences, Institute of Biomedicine (iBiMED-UA), University of Aveiro, Aveiro, Portugal, [8]Health Science Research Center (CICS/UBI), University of Beira Interior, Covilhã, Portugal

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***Correspondence:**
Fátima Roque
froque@ipg.pt

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Background: Age-related comorbidities prone older adults to polypharmacy and to an increased risk of potentially inappropriate medication (PIM) use. This work aims to analyze the concordance and overlap among the EU(7)-PIM list, 2019 Beers criteria, and Screening Tool of Older Person's Prescriptions (STOPP) version 2 criteria and also to analyze the prevalence of PIM.

Methods: A retrospective cohort study was conducted on older inpatients of an internal medicine ward. Demographic, clinical, and pharmacological data were collected, during March 2020. After PIM identification by the EU(7)-PIM list, Beers criteria, and STOPP v2 criteria, the concordance and overlap between criteria were analyzed. A descriptive analysis was performed, and all the results with a *p*-value lower than 0.05 were considered statistically significant.

Results: A total of 616 older patients were included in the study whose median age was 85 (Q1–Q3) (78–89) years. Most of the older patients were male (51.6%), and the median (Q1–Q3) number of days of hospitalization was 17 (13–22) days. According to the EU(7)-PIM list, Beers criteria, and STOPP criteria, 79.7, 92.0, and 76.5% of older adults, respectively, used at least one PIM. A poor concordance (<63.4%) among criteria was observed. An association between PIM and the number of prescribed medicines was found in all applied criteria. Moreover, an association between the number of PIMs and diagnoses of endocrine, nutritional, and metabolic diseases, mental, behavioral, and neurodevelopmental disorders, and circulatory system diseases and days of hospitalization was observed according to Beers criteria, and that with diseases of the

circulatory system and musculoskeletal system and connective tissue was observed according to STOPP criteria.

Conclusion: Despite the poor concordance between the EU(7)-PIM list, 2019 Beers, and STOPP v2 criteria, this work highlights the need for more studies in inpatients to develop strategies to facilitate the identification of PIM to decrease the high prevalence of PIM in hospitalized patients. The poor concordance among criteria also highlights the need to develop new tools adapting the existing criteria to medical ward inpatients.

Keywords: potentially inappropriate medication, internal medicine ward, older adults, EU(7)-PIM list, AGS 2019 Beers criteria, STOPP v2 criteria

INTRODUCTION

Age-related pharmacokinetic and pharmacodynamics changes cause a decrease in the ability to adapt to external environment alterations, increased susceptibility to the disease, a lesser capacity to recovery that causes a modified response to medications, greater susceptibility to the occurrence of adverse drug reactions (ADRs) (Alvis and Hughes, 2015; Gutierrez Valencia et al., 2016; Giardina et al., 2018), and an upsurge need for health resources (Stegemann et al., 2010).

Polypharmacy, the use of five or more medicines (Lee et al., 2020), is quite common in patients with multiple comorbidities and is considered a factor for functional decline in older adults, which increases the chance of medication-related problems (Garcia-Caballero et al., 2018; Lee et al., 2020). Overall, polypharmacy is associated with increased consumption of potentially inappropriate medication (PIM) (Oktora et al., 2020).

In this context, medicines are considered appropriate for older adults, when there is a clear, evidence-based indication that these medicines are generally well tolerated and have a favorable benefit/risk ratio in older adults (Laroche et al., 2019).

PIMs are medicines in which the potential risk of occurrence of ADR may be greater than the clinical benefit (Renom-Guiteras et al., 2015) that can be driven from their use, particularly when there is scientific evidence of alternatives that may be safer, so it becomes essential to optimize the prescription of medicines in aged population (Renom-Guiteras et al., 2015; Grina and Briedis, 2017). Several tools using explicit or implicit criteria have been developed to allow the identification of PIM and prevent PIM-associated negative outcomes (Chang and Chan, 2010; Kaufmann et al., 2014; Lucchetti and Lucchetti, 2017; Motter et al., 2018). Because older inpatients are at particular risk of PIM (Sinvani et al., 2013; Nothelle et al., 2017), it is fundamental to understand what drives the use of PIM in hospitals to design interventions to restraint PIM use in this setting. According to our knowledge, the overlap and concordance among criteria remain poorly reported in all settings. Therefore, we sought to analyze the concordance and overlap between the EU(7)-PIM list, 2019 Beers criteria, and Screening Tool of Older Person's Prescriptions (STOPP) version 2 (v2) criteria in the identification of PIM in older adult inpatients in a general internal medicine ward. Also, the prevalence of PIM, using the EU(7)-PIM list, Beers criteria, and STOPP criteria, will be analyzed.

MATERIALS AND METHODS

Source of Data and Study Population

A retrospective cohort study was performed to examine the overlap and concordance between the EU(7)-PIM list, 2019 American Geriatric Society (AGS) Beers criteria, and STOPP v2 criteria on the detection of PIM among older inpatients of an internal medicine ward of a first-level hospital belonging to the NUTS II (Nomenclatura das Unidades Territoriais para Fins Estatísticos/Nomenclature of Territorial Units for Statistics) area of Portugal defined by the Regional Administration of Health Center (Administração Regional de Saúde do Centro/ ARS-C). The hospital where the study takes place covers a total of 51243 older adults (PORDATA, 2020) and has a total of 68 beds in the general internal medicine ward.

Eligible to participate in the study were all older patients (aged ≥65) admitted in the internal medicine ward during 2019 and hospitalized for at least 4 days, during 2019. Data were encoded and retrospectively collected, during March 2020, from the hospital's electronic medical record and included patient age, patient gender (male/female), patient diagnoses, hospitalization days, drugs prescribed, and also medical and laboratory tests. This study obtained the ethical approval of the hospital ethical committee and authorization from the hospital board (ref. 01167) on February 7, 2020. All data were retrospectively encoded without any possibility of identification and were treated according to the European Union (EU) General Data Protection Regulation (GDPR).

Data Collection

All drugs prescribed to older patients during the study period were analyzed and PIM identified by the three tools used by two independent researchers (CP and DR), and any disagreement regarding PIM classification was resolved by a third researcher (FR) (**Supplementary Tables 1–10**).

PIM detection tools used were as follows:

a) The EU(7)-PIM list was developed through the consensus of experts from seven European countries: Estonia, Finland, France, Germany, Holland, Spain, and Sweden (Renom-Guiteras et al., 2015). The purpose of this list is to enable the identification and comparison of PIM prescription profiles for the elderly across the European community. This list comprises 275 active substances, 7 classes of drugs,

belonging to 55 therapeutic classes, and 34 pharmacotherapeutic groups. In this work, the list adapted to Portuguese reality was used (Rslbodrigues et al., 2020).

b) 2019 AGS Beers criteria (American Geriatrics Society Beers Criteria® Update Expert, 2019) developed in the United States are one of the most used tools and use explicit criteria. This tool has already undergone several revisions, the last being 2019, and includes six tables: table 2 listing "potentially inappropriate medications in older patients apart from the clinical condition," table 3 "medication use in older adults due to drug–disease or drug–syndrome interactions that may exacerbate the disease or syndrome," table 4 "potentially inappropriate medications in older patients considering the clinical condition," table 5 listing "potentially inappropriate medications—drugs to be used with caution in older adults," table 6 listing "potentially clinically important drug–drug interactions that should be avoided in older adults," and table 7 listing "medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults" (American Geriatrics Society Beers Criteria Update Expert, 2019).

c) STOPP v2 criteria (O'mahony et al., 2015). The STOPP/START criteria were created in 2008 and also emerged as an European response to drug-related problems (DRPs), to identify whether the medical prescription is suitable for older adults (O'mahony et al., 2015). The list was revised in 2015 and is organized by physiological systems. The STOPP/START tool includes 114 criteria: 80 STOPP criteria and 34 START criteria (O'mahony et al., 2015).

Drugs were classified according to the Anatomical and Therapeutic Chemical Classification (WHO, 2021), and patients' diagnoses were classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10 Second Edition).

Statistical Analysis

Numerical and ordinal data were presented in frequency and percentage and using mean, median, percentile 25 and percentile 75, and standard error. A comparative analysis was performed between the results obtained for the three PIM identification tools, and the agreement between them was determined through the Lin coefficient. The prevalence of PIM was defined as the number of patients taking at least one PIM and was calculated using 95% CI. A medicine was considered a PIM if it is identified for at least one tool.

The pro package from the statistical software R was used to estimate the sample size. The sample size was computed using an estimated prevalence of 50% with a margin error of 4%. To ensure the precision of the data, the program reported that the sample should have at least 601 patients. This study included all the 616 patients that have been admitted to the internal medicine ward of the hospital, during 2019.

The free statistical software R (v4.0.0) was used to perform statistical analysis. A generalized linear model was developed for the dependent variables. Bivariate analysis was performed to select independent variables with a p-value < 0.2. The selected variables were studied in multivariate analysis, and those that had greater statistical significance were successively eliminated, on the condition that the coefficients of the main exposure variables did not change by more than 10% and that Schwarz's Bayesian Information Criterion (BIC) improved. Considering hospitalization days as a dependent variable, a risk analysis was performed using Cox regression.

To correlate PIM identified with the multiple diagnoses of the patients, the total number of diagnoses per patient was added to the generalized linear model as the Independent variable and the number of PIMs identified as the dependent variable. The model was adjusted according to the sex and age of the patients.

RESULTS

Study Population Characteristics

During the study period, 662 older patients were admitted to the internal medicine ward. Of these, 46 were excluded from the study because hospitalization was less than 4 days. **Table 1** shows the characteristics of the 616 older patients included in the study. The median (Q1–Q3) age was 85.00 (78–89) years, and 48.16% of the participants were female. The median (Q1–Q3) number of hospitalization days was 12.00 (8–20), and the median (Q1–Q3) number of medicines taken per patient during the hospitalization period was 17.00 (13–22). Of the total number of older people included in the study, 547 (88.7%) were discharged from the hospital, 13 (2.1%) were transferred from another ward or another hospital, and 67 patients (9.1%) died.

A total of 3,873 diagnoses were registered for all the included patients. 21.4% of the diagnoses belong to the group of diseases related to the circulatory system, 16.4% to endocrine, nutritional, and metabolic diseases, and 10.7% to respiratory system diseases (**Table 1**).

Prevalence of PIM According to the EU(7)-PIM List and Beers and STOPP Criteria

Of 11159 prescribed medicines (mean per patient 18.12 ± 7.33), 285 were different active substances and were analyzed using the EU(7)-PIM list and Beers and STOPP criteria to evaluate the prevalence of PIM (**Table 2** and **Table 3**).

According to the EU(7)-PIM list adapted to Portuguese reality, 63 of the analyzed medicines were considered PIM, with a total of 1,146 PIMs detected in our sample. The median (Q1–Q3) number of PIMs per patient was 2 (1–3). It was also observed that 79.70% of the participants take at least one PIM (**Table 2**). The maximum number of PIMs per patient detected was 10, consumed by one patient (0.20%). The majority of the patients (51.30%) take one or two PIMs. Overall, the most consumed PIMs according to the EU(7)-PIM list were metoclopramide, haloperidol, and bisacodyl consumed by 31.2, 23.2, and 17.9% of our sample, respectively, representing a total of 38.9% of the PIMs identified by the EU(7)-PIM list (**Table 3**; **Supplementary Table 1**).

TABLE 1 | Study population characteristics.

Study population Characteristics N (%)	**Participants N = 616**
Age (years)	—
Median (Q1–Q3)	85.00 (78.0–89.0)
65–74	98 (15.90%)
75–84	206 (33.40%)
≥85	312 (50.70%)
Sex	—
Female	298 (48.40%)
Male	318 (51.60%)
Hospitalization days	—
Median (Q1–Q3)	12 (8–20)
Range (minimum and maximum)	4–90
No. of prescribed drugs	—
Median (Q1–Q3)	17 (13–22)
Range (minimum and maximum)	4–50
ICD-10 diagnostics	N = 3,873
A00-B99, certain infectious and parasitic diseases	96 (2.50%)
C00-D49, neoplasms	79 (2.00%)
D50-D89, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	220 (5.70%)
E00-E89, endocrine, nutritional, and metabolic diseases	636 (16.40%)
F0-F99, mental, behavioral, and neurodevelopmental disorders	140 (3.60%)
G00-G99, diseases of the nervous system	82 (2.10%)
H00-H59, diseases of the eye and adnexa	11 (0.30%)
H60-H95, diseases of the ear and mastoid process	14 (0.40%)
I00-I99, diseases of the circulatory system	829 (21.40%)
J00-J99, diseases of the respiratory system	415 (10.70%)
K00-K95, diseases of the digestive system	125 (3.20%)
L00-L99, diseases of the skin and subcutaneous tissue	50 (1.30%)
M00-M99, diseases of the musculoskeletal system and connective tissue	80 (2.10%)
N00-N99, diseases of the genitourinary system	396 (10.20%)
Q00-Q99, congenital malformations, deformations, and chromosomal abnormalities	1 (0.00%)
R00-R99, symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	278 (7.20%)
S00-T88, injury, poisoning, and certain other consequences of external causes	53 (1.40%)
V00-Y99, external causes of morbidity	32 (0.8%)
Z00-Z99, factors influencing health status and contact with health services	336 (8.70%)

Q1- percentile 25, Q3-percentile 75

TABLE 2 | Number of PIMs identified in our sample according to the EU(7)-PIM list and Beers and STOPP criteria.

Frequency of PIMs	**Tool**		
	EU(7)-PIM list	**Beers criteria**	**STOPP criteria**
	N (PCT; 95% CI)	**N (PCT; 95% CI)**	**N (PCT; 95% CI)**
0	125 (20.30; 0.17–0.24)	37 (6.0; 0.04–0.08)	145 (23.50; 0,20–0.27)
1	153 (24.80; 0.22–9.29)	106 (17.20; 0.14–0.20)	165 (26.80; 0.23–0.31)
2	163 (26.50; 0.23–0.30)	152 (24.70; 0.21–0.28)	130 (21.10; 0.18–0.25)
3	76 (12.4; 0.10–0.15)	126 (20.50; 0.17–0.24)	88 (14.30; 0.12–0.17)
4	52 (8.40; 0.06–0.11)	76 (12.30; 0.10–0.15)	37 (6.90; 0.04–0.08)
≥5	46 (7.50; 0.06–0.10)	119 (19.30; 0.16–0.23)	51 (8.30; 0.06–0.11)

According to Beers criteria, considering 77 analyzed medicines, we have identified a total of 1,829 PIMs. It was also observed that 94.00% of the patients take at least one PIM, 17.20% of the participants take one PIM, and 0.20% take thirteen PIMs. Most of the patients (62.40%) take more than one and less than four PIMs (**Table 2**). The median (Q1–Q3) number of PIMs per patient observed was 3 (2–4). Furosemide, metoclopramide, and haloperidol were the most consumed PIMs, used by 71.0, 31.20, and 24.00% of the inpatients, respectively, representing a total of 42.50% of the PIMs detected by this tool (**Table 3**; **Supplementary Table 2**).

According to table 2 of the Beers criteria ("potentially inappropriate medications in older patients apart from the clinical condition"), the participants consumed a total of 979 PIMs (**Supplementary Table 3**), with metoclopramide and haloperidol being the most consumed, taken by 192 and 148

TABLE 3 | The five most consumed PIMs according to the EU(7)-PIM list and Beers and STOPP criteria.

Position	EU(7)-PIM list	*n*	% PIM	Beers 2019	*n*	% PIM	STOPP v2	*n*	% PIM
1	Metoclopramide	192	a) 16.75% b) 31.20%	Furosemide	437	a) 23.90% b) 71%	Haloperidol	148	a) 12.80% b) 24%
2	Haloperidol	143	a) 12.10% b) 23.20%	Metoclopramide	192	a)10.50% b) 31.20%	Quetiapine	88	a) 7.60% b) 14.30%
3	Bisacodyl	110	a) 10.4% b) 20%	Haloperidol	148	a) 8.10% b) 24.00%	Spironolactone	79	a) 6.80% b) 12.80%
4	Alprazolam	58	a) 4.90% b) 9.40%	Spironolactone	107	a) 5.90% b) 17.40%	Lorazepam	69	a) 6.00% b) 11.2%
5	Digoxin	57	a) 4.80% b) 9.20%	Quetiapine	88	a) 4.80% b) 14.30%	Oxazepam	65	a) 5.60% b) 10.50%

a) percentage of PIMs per tool; b) percentage of PIMs per patient (N = 616).

participants, respectively. The application of **Table 3** ("potentially inappropriate medications in older patients considering the clinical condition") of the Beers criteria detected a total of 221 PIMs (**Supplementary Table 4**). The application of table 4 of Beers criteria ("potentially inappropriate medications—drugs to be used with caution in older adults") allows the detection of 1,226 drugs that should be used with caution in older adults (**Supplementary Table 5**). The application of table 5 of Beers criteria (potentially clinically important drug–drug interactions that should be avoided in older adults) identified 263 potential drug–drug interactions that should be avoided in older patients (**Supplementary Table 6**). The application of table 6 of Beers criteria (medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults) revealed the presence of six PIMs (**Supplementary Table 7**). The frequency of anticholinergic drugs was 133 (table 7 of Beers criteria) (**Supplementary Table 8**).

It was possible to apply 40 specific STOPP criteria to the prescribed medication, obtaining a total of 1156 PIMs. According to this tool, 76.50% of our sample consume at least one PIM, 26.80% of the sample consume one PIM, 8.30% of the sample consume five or more PIMs, and 0.50% consume ten PIMs (**Table 3**). The median (Q1–Q3) number of PIMs per participant was 2 (1–3). The section of the STOPP criteria where the highest number of PIMs was obtained was section K, which refers to drugs that predictably increase the risk of falls in elderly people by 42.3%. The amount of PIMs obtained when applying each of the criteria is greater than the amount of PIMs found in table 6 (1,156 PIMs) since several drugs can be PIMs due to multiple criteria (**Supplementary Table 9**).

Concordance and Overlap Among the EU(7)-PIM List, Beers Criteria, and STOPP Criteria

After the analysis of PIM by each tool, we observed that, according to the EU(7)-PIM list and Beers criteria, metoclopramide should be used with caution in older adults (EU(7)-PIM list) and is considered a PIM in older adults, and apart from the clinical condition (Beers criteria), this drug was considered a PIM in all patients that use it. According to STOPP criteria, metoclopramide can exacerbate Parkinsonian symptoms, in patients with Parkinson disease, so this drug is a PIM in 13 patients.

Haloperidol was the most prevalent PIM identified by the STOPP criteria, the second most prevalent according to the EU(7)-PIM list, and the third most observed according to Beers criteria. In the 148 patients that take haloperidol, 143 use a single dose superior to 2 mg or take more than 5 mg/d, and for these reasons, it was considered a PIM according to the EU(7)-PIM list. According to STOPP criteria, this drug predictably increases the risk of falls in older people (may cause gait dyspraxia, Parkinsonism), and according to the Beers criteria, haloperidol should be avoided in older adults, and this is the main reason for considering haloperidol a PIM in all patients that use it.

Bisacodyl was one of the most prevalent PIMs identified by the EU(7)-PIM list; due to the duration of treatment (>3 days), according to Beers and STOPP criteria, this drug is not a PIM. All applied criteria considered alprazolam a PIM, and the common reason according to the tools used is because this drug should be avoidable in older adults independently of their clinical condition. According to Beers criteria, furosemide should be avoided in older adults and is considered a PIM in all patients that use it. According to STOPP criteria, furosemide is a loop diuretic for dependent ankle edema without clinical, biochemical, or radiological evidence of heart and liver failure, nephrotic syndrome, or renal failure (leg elevation and/or compression hosiery usually being more appropriate) and may exacerbate incontinence.

Therefore, spironolactone being considered a PIM by all applied criteria, the reasons and the number of patients with this PIM are divergent. According to the EU(7)-PIM list of the 107 patients that use spironolactone, only 23 use a dose more than 25 mg/day (the reason for PIM); according to Beers criteria, this drug should be avoided in older adults, so it is considered a PIM in all patients (107) that use it. STOPP criteria considered that 79 patients use spironolactone as a PIM because in these patients' serum, potassium was not regularly monitored. Beers and STOPP criteria considered quetiapine as a PIM in all patients that use it because this drug should be avoided in older adults (Beers criteria) and predictably increases the risk of falls in older people (STOPP criteria); according to the EU(7)-PIM list, this drug is not a PIM. Lorazepam is a PIM by all applied criteria,

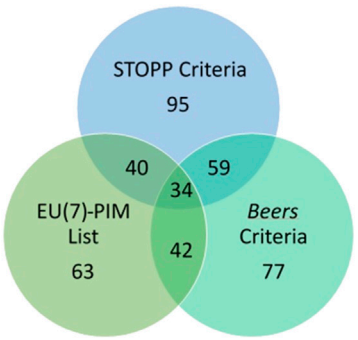

FIGURE 1 | PIM identified by the EU(7)-PIM list, AGS 2019 Beers criteria, and STOPP version 2 criteria.

according to the EU(7)-PIM list in 31 of the 69 patients that use it due to the high dose (>1 mg/d). According to Beers criteria, this drug should be avoided in older adults and is considered a PIM in all patients (69) that use it. According to the STOPP criteria, lorazepam is a PIM in all patients because it may cause reduced sensorium and, in patients with acute or chronic respiratory failure, there is a risk of exacerbation of respiratory failure.

Considering the three PIM classification tools applied, the EU(7)-PIM list has 42 PIMs in common with the 2019 Beers criteria and 40 PIMs in common with version 2 of the STOPP criteria, whereas the 2019 Beers criteria have 59 PIMs in common with version 2 of the STOPP criteria. The three tools have in common 34 drugs (**Figure 1**).

PIM-Associated Therapeutic Groups According to the Applied Criteria

To better understand the concordance between the different tools, PIMs identified by each tool were grouped according to the anatomical group (**Table 4**), and it was observed that, of the 1,901 prescribed medicines belonging to the alimentary tract and metabolism, 19.52% were considered PIM according to the EU(7)-PIM list, 11.00% were PIM according to Beers criteria, and only 1.84% were classified as PIM by the STOPP criteria. The analysis of the 2,283 medicines belonging to the cardiovascular system group by the EU(7)-PIM list, Beers criteria, and STOPP criteria revealed that 9.33, 29.04, and 12.57%, respectively, are PIM.

According to the STOPP criteria, 11.36% of the 220 prescribed medicines of the group systemic hormonal preparations, except sex hormones and insulins, were PIM; according to the Beers criteria, only 0.9% of these groups of medicines are PIM; and according to the EU(7)-PIM list, none of them are PIM. Regarding the medicines from the musculoskeletal system group, 24.50% were PIM according to the EU(7)-PIM list, 25.83% were PIM according to the Beers criteria, and only 11.26% were PIM according to the STOPP criteria. We also observed that, of the 1,913 medicines belonging to the nervous system group, 24.26% were PIM according to the EU(7)-PIM list, 41.92% were PIM according to the Beers criteria, and 39.36% were PIM according to the STOPP criteria. According to the EU(7)-PIM list, the most prescribed PIM pharmacotherapeutic groups are the musculoskeletal system (24.50%), nervous system (24.26%), and alimentary tract and metabolism (19.56%). The most frequent PIM, according to Beers criteria, belongs to the nervous system group. According to the STOPP criteria, the most frequent PIM belongs to the pharmacotherapeutic groups—nervous system (39.36%), cardiovascular system (12.57%), and systemic hormonal preparations, except sex hormones and insulins (11.36%).

To analyze the agreement between the three criteria, we used Lin's concordance correlation coefficient and observed a poor concordance between criteria (**Table 5**).

PIM-Associated Factors

An association between the PIM detected through the application of the Beers criteria and patients with diagnoses of endocrine, nutritional, and metabolic diseases (ICD-10; E00-E89), mental, behavioral, and neurodevelopmental disorders (ICD-10; F01-F99), and circulatory system diseases (ICD-10;

TABLE 4 | Prevalence of PIM identified in our sample according to the pharmacological group.

Pharmacological groups (1° level anatomical group)	Prescribed medicine (N)	Tool		
		EU(7)-PIM list	Beers criteria	STOPP criteria
		N (PCT; 95% CI)	N (PCT; 95% CI)	N (PCT; 95% CI)
A-alimentary tract and metabolism	1901	371 (19.52%; 0.18–0.21)	209 (11.00%; 0.01–0.12)	35 (1.84%; 0.01–0.03)
B-blood and blood-forming organs	2,606	49 (1.88%; 0.014–0.02)	76 (2.92%; 0.02–0.04)	24 (0.92%; 0.01–0.01
C-cardiovascular system	2,283	213 (9.33%; 0.08–0.11)	663 (29.04%; 0.27–0.31)	287 (12.57%; 0.11–0.14)
D-dermatologicals	28	0	0	0
G-genitourinary system and sex hormones	144	2 (1.39%; 0.00–0.05)	0	2 (1.39%; 0.00–0.05)
H-systemic hormonal preparations, except sex hormones and insulins	220	0	2 (0.9%; 0.00–0.03)	25 (11.36; 0.07–0.16)
J-anti-infective for systemic use	1,043	2 (0.19%; 0.00–0.01)	30 (2.88; 0.02–0.04)	0
L-antineoplastic and immunomodulating agents	17	0	0	0
M-musculo-skeletal system	151	37 (24.50%; 0.18–0.32)	39 (25.83; 0.19–0.34)	17 (11.26%; 0.07–0.17)
N-nervous system	1913	464 (24.26%; 0.22–0.26)	802 (41.92%; 0.40–0.44)	753 (39.36%; 0.37–0.42)
P-antiparasitic products, insecticides, and repellents	2	0	0	0
R-respiratory system	800	8 (1%; 0.00–0.02)	8 (1%; 0.00–0.02)	13 (1.63%; 0.01–0.02)
S-sensory organs	27	0	0	0
V-various	24	0	0	0

TABLE 5 | LIN concordance correlation coefficient.

PIM tool	CCC (95% CI)
EU(7)-PIM list vs. STOPP	0.581 (0.521–0.635)
EU(7)-PIM list vs. *Beers*	0.596 (0.549–0.640)
STOPP vs. *Beers*	0.633 (0.583–0.678)

I00-I99) was observed (**Table 6**). PIMs detected by STOPP criteria are associated with patients diagnosed with diseases of the circulatory system (ICD-10; I00-I99) and with diseases of the musculoskeletal system and connective tissue (ICD-10; M00-M99). It was observed that the variable days of hospitalization only obtained statistical significance in relation to the PIM obtained with the application of the Beers criteria. The impact of the number of diagnoses on the effect of PIM is found to be small (OR~1) and statistically significant (**Table 6**).

DISCUSSION

According to our knowledge, this is the first study assessing the concordance and overlap of three distinct PIM-detecting tools EU(7)-PIM list, 2019 AGS Beers criteria, and STOPP v2 criteria in hospitalized patients. The low overlap and concordance between tools highlight the need to develop a PIM-detecting tool for patients exposed to a high number of PIMs ($\approx 80\%$, in all tools used) and reinforce the fact that general internal medicine patients are at risk of PIM (Hudhra et al., 2016; Blanc et al., 2018a; Blanc et al., 2018b). Although being developed for different drug markets and different populations, these criteria are the most used. For this reason, analyzing the concordance among tools is essential to understand the applicability of each tool in a specific population, country, and setting. Because multiple comorbidities are frequent among internal medicine inpatients, a tool focusing on geriatric internal medicine patients should be implemented to alert the physician to an eventual PIM prescription.

Despite the scarcity of studies comparing the use of PIM tools in all settings and the lack of studies in internal medicine inpatients, a study carried out in Chinese hospitalized patients reported a moderate concordance between 2015 Beers criteria and STOPP v2 criteria (Ma et al., 2019). Moreover, a Brazilian study performed in home-dwelling population of 60 or more years of age concluded that there was a high concordance among 2015 Beers criteria, STOPP v2 criteria, and the EU(7)-PIM list (Novaes et al., 2017). However, in a recent systematic review, a substantial difference was found between the individual medications identified by the Beers and STOPP/START criteria, highlighting the need for research in this area (Thomas and Thomas, 2019). The poor concordance among criteria observed in our sample of Portuguese internal medicine inpatients can be due to the applicability requirements of each list; theoretically, criteria with fewer applicability requirements might detect fewer PIMs than those using criteria that require more specific information, differential medication availability between countries (Chang and Chan, 2010; Thomas and Thomas, 2019). According to the EU(7)-PIM list, to consider the medicine as a PIM, it is only necessary to know the mediation profile of the patients including the duration of treatment and dosage of some medicine (Renom-Guiteras et al., 2015). The Beers criteria judge each medicine as a PIM based not only on the medication profile of a patient but also on the pathologies of the patients as well as the laboratory results (By the American Geriatrics Society Beers Criteria Update Expert, 2019). To apply the STOPP criteria, it is imperative to know the entire medication history, clinical information of the patient, and laboratory (O'mahony et al., 2015; By the American Geriatrics Society Beers Criteria Update Expert, 2019; Carvalho et al., 2019). The greater sensibility of previous versions of STOPP criteria was demonstrated by others (Gallagher and O'mahony, 2008; Hamilton et al., 2011; Wickop et al., 2016), but according to

TABLE 6 | Factors associated with PIM prevalence.

PIM tool	Variable	Adjusted RR (95% CI)	*p*-Value
EU(7)-PIM list	Total medicines per patient	1.06 (1.06–1.07)	<0.001
	Total diagnoses per patient	0.98 (0.975–1.00)	0.0065
2019 AGS Beers criteria	Total medicines per patient	1.05 (1.05–1.06)	<0.001
	Total diagnoses per patient	0.99 (0.98–1.00)	0.0053
	E00-E89, endocrine, nutritional, and metabolic diseases	0.96 (0.92–1.00)	0.0382
	F01-F99, mental, behavioral, and neurodevelopmental disorders	1.12 (1.01–1.23)	0.0283
	I00-I99, diseases of the circulatory system	1.08 (1.05–1.12)	<0.001
STOPP v2 criteria	Total medicines per patient	1.06 (1.05–1.07)	<0.001
	Total diagnoses per patient	0.98 (0.97–1.00)	0.017
	I00-I99, diseases of the circulatory system	1.05 (1–1.09)	0.0477
	M00-M99, diseases of the musculoskeletal system and connective tissue	0.82 (0.67–1.00)	0.0491
EU(7)-PIM list	Total medicines per patient	1.064 (1.0575–1.070)	<0.001
	Total diagnoses per patient	0.983 (0.9715–0.995)	0.0065
2019 AGS Beers criteria	Total medicines per patient	1.054 (1.0495–1.059)	<0.001
	Total diagnoses per patient	0.986 (0.9765–0.996)	0.0053
STOPP v2 criteria	Total medicines per patient	1.063 (1.0555–1.07)	<0.001
	Total diagnoses per patient	0.984 (0.9715–0.997)	0.017

Blanco-Reina et al. (2019), STOPP v2 has a poor concordance with the previous version (Blanco-Reina et al., 2019).

The number of PIMs identified varies among criteria, and in the inpatient setting, the prevalence of PIM changes from 1% to as high as 50% and is highly dependent on the tool used to define PIM (Franceschi et al., 2008; Rothberg et al., 2008; Page et al., 2010). A study carried out in Portuguese nursing homes and day-care centers detected a PIM prevalence of 64.4% when applying the EU(7)-PIM list, 56% when applying the 2015 Beers criteria, and 85.5% when applying the STOPP v2 criteria (Monteiro et al., 2020). Another study carried out in Chinese inpatients reported a prevalence of PIM of 58.1 and 44.0% using 2015 Beers criteria and 2014 STOPP (Ma et al., 2019). A Brazilian study performed in a home-dwelling population of sixty or more years of age observed a prevalence of PIM of 50, 46.2, and 59.5% using, respectively, 2015 Beers criteria, 2015 STOPP criteria, and the EU(7)-PIM list (Novaes et al., 2017). In our study, the percentage of patients with at least one PIM also varied among criteria: according to the EU(7)-PIM list and STOPP criteria, near 80% of the patients had at least one PIM, and according to Beers criteria, more than 90% of the patients consume one PIM. Another study in patients discharged from a hospital using the EU(7)-PIM list and the STOPP criteria observed a prevalence of PIM similar to that observed in our study (Mucalo et al., 2017).

The overlap of three criteria revealed that the drugs that act on the nervous system are the most common, making a total of 20, and haloperidol is the most frequent PIM. Haloperidol is an antipsychotic drug that can help relieve disorders such as delusions or hallucinations in schizophrenic situations, but it can also be used in older patients with agitation or aggression, which thus may explain the high consumption of this medication in the study population (Potter et al., 2006). Several studies report that delirium is associated with substantial rates of morbidity and mortality in inpatients, which becomes a growing problem due to increased life expectancy. Haloperidol is currently the drug of choice for the treatment of delirium (Schrijver et al., 2014; Ostinelli et al., 2017; Herling et al., 2018a; Herling et al., 2018b).

The knowledge of the pharmacotherapeutic profile of each patient allowed the application of the EU(7)-PIM list and the identification of 63-PIM–related medicines, performing a total of 1,146 PIMs. These observations allowed concluding that the inpatients included in this study consume a high number of PIMs in comparison with other studies using this tool in European older inpatients (Mucalo et al., 2017; Bobrova et al., 2019; Wamil et al., 2019).

According to Beers criteria, our patients presented 1,829 PIMs related to the prescription of 77 different medicines. According to our knowledge, this is the first study that uses the AGS 2019 Beers criteria with inpatients. However, in comparison with studies using 2015 Beers criteria, our sample presented a very high prevalence of PIM (Juliano et al., 2018; Thomas et al., 2020; Zhang et al., 2020).

A Portuguese study reported that the STOPP/START criteria are useful tools to perform medication review in nursing home patients and changes of drug therapy because besides detecting PIM, they also allowed the detection of DRPs related to the non-drug treatment despite existing indication (Silva et al., 2014). The application of STOPP criteria allowed concluding that, according to these criteria, the number of PIMs prescribed to older inpatients follows that observed in studies from Canada (Thomas et al., 2020) and Spain (Martin et al., 2017) but is very high when compared with the number of PIMs observed in Malaysia (Loganathan et al., 2019) and Swiss (Urfer et al., 2016).

In our sample of older inpatients, it was observed that the number of PIMs per patient increases with the increased number of prescribed medicines and the time of hospitalization. According to Wickop et al. (2016), the number of medicines has a significant effect on the amount of PIMs detected. (Wickop et al., 2016).

The mean age of the included participants reflects the high life expectancy observed in Portugal (INE, 2017; PORDATA, 2020). The high number of prescribed medicines is probably due to the multiple comorbidities presented by the inpatients. According to the literature, the inpatient setting may predispose older adults to new prescriptions and probably unnecessary drugs (Page et al., 2010). In an acute care setting, it is difficult to convince physicians to change or discontinue chronic medication, particularly if the medication is not related to the reason for hospitalization (Page et al., 2010). Moreover, we observed a trend of increased polypharmacy with the length of stay in the hospital. Despite the scarcity of studies characterizing the medication profile of internal medicine inpatients, a study pointed out that the mean of prescribed drugs increases from 5.6 (at hospital admission) to 7.6 (at discharge) (Vonbach et al., 2008). Other studies demonstrate that the number of regular medicines in hospitalized older patients is high, and according to Connor et al. (2020), the median number can range from 11 (IGR 8 to 15) (at hospital admission) to 9 (at discharge). According to Hubbard et al. (2015), the mean number of regular medicines per day ranges from 7.1 to 7.6 at admission and discharge, respectively.

This study demonstrated that the number of medicines is associated with the use of PIM detected by the EU(7)-PIM list and Beers and STOPP criteria; indeed, polypharmacy is associated with the use of PIM in older adults (Steinman et al., 2006).

Although the consensus-based lists of medications, such as the EU(7)-PIM list, Beers criteria, and STOPP criteria, were valuable tools to detect PIM in older adults, the data of this study only represent the patients that have been admitted during 2019 to the internal medicine ward; for these reasons (specific setting and the limited number of samples), they cannot be generalized to the whole hospital population (Tanaka et al., 2015). Moreover, potential ADRs associated with PIM prescriptions were not evaluated because the hospital's electronic medical record used did not include information regarding ADRs.

However, the information collected in this study reinforces the need to optimize criteria adapted to the internal medicine and implement strategies that support the physician's decision when prescribing a possible PIM but always leaving the possibility of judgment and medical decision. Adaptation of these tools to a consensus tool for specific condition was already done for the management of pain and inflammation in older adults (Motter et al., 2019).

The high number of PIMs observed during this study highlights the need for interventional studies to improve medication appropriateness among hospitalized older patients (Thomas and Thomas, 2019), particularly in internal medicine wards where there is a frequent need to change medication to achieve stabilization of patients. The increased risk of polypharmacy-related ADR (Schmiedl et al., 2018) in older patients demonstrates the need for clinical practice guidelines in polymedicated older patients and the development of educational interventions to promote and improve the use of PIM tools by healthcare professionals.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in the article/**Supplementary Material**, and further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comissão de Ética para a Saúde da ULS da Guarda, EPE. Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial and direct contribution to the work and approved it for publication. FR and MH coordinated the project. CP and JA involved in acquisition of data. AF, AIP, CP, DR, FR, MP-L, and MH analyzed and interpreted data. AIP and CP drafted the article. AF, AIP, DR, FR, JA, MP-L, and MH critically revised the article.

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SUPPLEMENTARY MATERIAL

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Trends in Topical Prescriptional Therapy for Old Patients With Dry Eye Disease in Six Major Areas of China: 2013–2019

Zhenwei Yu[1], *Xiaoyan Wu*[2], *Jianping Zhu*[1], *Jiayi Jin*[2,3], *Yuhua Zhao*[4]* *and Lingyan Yu*[5]*

[1]Department of Pharmacy, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2]Department of Pediatrics, Shaoxing Shangyu People's Hospital of Shaoxing, Shaoxing, China, [3]Biomedical Research Center, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [4]Department of Pharmacy, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou, China, [5]Department of Pharmacy, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

The prevalence of dry eye disease (DED) in old patients are high, corresponding to a substantial economic burden. In this cross-sectional study, we analyzed the trends in the topical prescriptional treatment of old patients with DED in six major areas of China. Information on topical drug prescriptions for DED patients aged above 60 years was extracted from the Hospital Prescription Analysis Cooperative Program of China database. Trends in yearly prescriptions and cost were analyzed. The data were further stratified by patient age and sex, drug class, and specific drug. A total of 130,734 prescriptions from 52 hospitals located in six major areas of China were analyzed. The number of prescripptions per year for patients with DED increased from 13,308 in 2013 to 22,074 in 2019, with a corresponding increase in cost of all topical drugs from 1,490,014 Chinese Yuan (CNY) to 2,618,206 CNY. Drugs for the treatment of DED accounted for the largest proportion of the total cost in each year. Ocular lubricants were the main pharmacotherapy agent. Sodium hyaluronate use increased over time, and the drug was used by 65.9% of patients by the end of the study. Pranoprofen was the second most frequently used drug. The most frequently used drugs for co-incident disease were antimicrobials. Treatment patterns for DED haven't changed, and the most frequently used drug combination was sodium hyaluronate and pranoprofen. In summary, prescription for old patients with DED and the cost of treatment are increasing. Ocular lubricants are the main treatment option, while sodium hyaluronate is the most frequently used drug. The observed trends can lead to more efficient allocation of health care resources in China.

Keywords: dry eye, eye drop, ocular lubricant, artificial tear, sodium hyaluronate, prescription

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Ria Benko,
University of Szeged, Hungary

Reviewed by:
Konstantin Tihomirov Tachkov,
Medical University Sofia, Bulgaria
Yihe Chen,
Harvard Medical School,
United States

***Correspondence:**
Yuhua Zhao
zhaoyuhua1987@126.com
Lingyan Yu
lingyanyu@zju.edu.cn

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INTRODUCTION

Dry eye disease (DED) is a common multifactorial ocular surface disorder characterized by eye discomfort, disabling pain, and fluctuating vision, which can affect vision-related quality of life and reduce working time (Clayton, 2018). The precise etiology of DED is unclear, but it may be caused or exacerbated by multiple factors including medications, contact lenses, ocular surgery, computer use, and low-humidity environments (Clayton, 2018). The prevalence of DED varies by country, but all

show an increasing trend (Courtin et al., 2016; Dana et al., 2019b; Siffel et al., 2020; Stapleton et al., 2017). It is reported that the prevalence of DED by symptoms and signs were 13.55% in Chinese people, corresponding to a total of 170.09 million affected individuals (Song et al., 2018). Advanced age is positively associated with an increased prevalence among people (Farrand et al., 2017; Song et al., 2018). For people aged over 60 years, the prevalence raised to 34.4% (Liu et al., 2014). Thus, DED affects the life quality of old patients substantially (McDonald et al., 2016). More public health attention and action are needed to improve the management of DED.

DED can be treated but not cured; the goal of treatment is to increase the patient's quality of life by reducing symptoms (Marshall and Roach, 2016). Management strategies should consider the cause and severity of the disease and address the various disease components (Clayton, 2018). There are many classes of drug on the market for DED treatment including ocular lubricants, anti-inflammatory drops, essential fatty acids, and so on. Topical formulations offer several advantages such as simple, convenience and painless use (Agarwal et al., 2021). However, many treatments are poorly supported by evidence-based practices (Jones et al., 2017), and the efficacy of some (e.g., cyclosporine) is debated (Seitzman and Lietman, 2018). Pharmacotherapeutic approaches also vary by country because of differences in the understanding of DED etiology (Waduthantri et al., 2012; Watanabe, 2018). Ocular lubricant formulations such as sodium hyaluronate drops are favored by those who attribute DED to insufficient tear production (Watanabe, 2018). To date, there have been few reports on the usage of topical treatments for old patients with DED; however, greater awareness of the trends can improve health care resource utilization (McDonald et al., 2016). To address this issue, we carried out a cross-sectional study in six major areas to assess the trends in topical prescriptional pharmacotherapy for old patients with DED in China from 2013 to 2019.

METHODS

Study Design

This prescription-based cross-sectional study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Reference number, 20191011–18). The requirement for informed consent was waived as part of the approval because of the retrospective nature of the study.

Data Source and Study Population

Prescription data were extracted from the database of the Hospital Prescription Analysis Cooperative Program, which has been widely used in Chinese pharmaco-epidemiology studies (Yu et al., 2019; Yu et al., 2020a; Yu et al., 2020b; Yu et al., 2020c; Yu et al., 2020d; Yu et al., 2020e). Participating hospitals provided data on prescriptions to the program for each sampling day. There were forty randomized sampling days per year, with 10 days in each quarter. Prescription data included the date, patients' code, sex, age, and diagnosis, as well as the generic name and price of the prescribed drug.

Prescription data from fifty-two hospitals in Beijing, Hangzhou, Chengdu, Guangzhou, Shanghai, and Tianjin were selected. These hospitals participated continuously in the program from 2013 to 2019 and were located in the north, west, south, and east of China, thus covering a wide geographic area and yielding data representative of the whole country. Prescriptions meeting the following criteria were included: 1) prescriptions for patients with a diagnosis of DED, with no restrictions regarding diagnostic criteria and disease severity; 2) prescriptions for patients aged 60 years old and above; 3) prescriptions written by an ophthalmologist between 2013 and 2019; and 4) prescriptions for at least one topical drug. Prescriptions with incomplete information were excluded from the analysis.

Assessment of Drug Use

Only topical ocular medications were assessed in this study. Prescriptions were divided into drugs for the treatment of DED and those for co-incident diseases. The following types of drug were used for DED treatment: 1) ocular lubricants; 2) nonsteroidal anti-inflammatory drugs (NSAIDs); 3) corticosteroid; 4) vitamin A preparation; and 5) immunosuppressant (Jones et al., 2017). Drugs for the treatment of co-incident disease included the following: 1) anti-microbial agents; 2) growth factor preparations; 3) anti-allergy drugs; 4) glaucoma drugs; 5) cataract drugs; 6) complementary drugs; and 7) other.

Drug usage was assessed by prescription numbers, irrespective of whether it was new or a refill, and cost. Cost was calculated by adding the price of all analyzed drugs in Chinese Yuan (CNY). Trends in yearly prescriptions and cost were analyzed and further stratified by sex, age, drug class, and specific drug. The treatment pattern was classified as monotherapy or combined therapy with drugs for DED treatment.

Statistical Analysis

Data were processed using Access software (Microsoft, Redmond, WA, United States). The rank-sum test was used to evaluate the statistical significance of overall trends in prescriptions and cost; the chi-squared test was used to compare prescriptions in males vs. females in each year; and the Cochran-Armitage trend test was used to assess trends in prescribed drugs and drug classes. Trends in percentages were assessed by log-linear analysis. All statistical analyses were performed using R v.3.3.0 software (http://www.R-project. org). A p value < 0.05 was considered statistically significant.

RESULTS

Inclusion of Prescriptions and Overall Trends in Prescriptions and Cost

A total of 130,734 prescriptions from 52 hospitals were included in the analysis. All included hospitals were state owned. Of these,

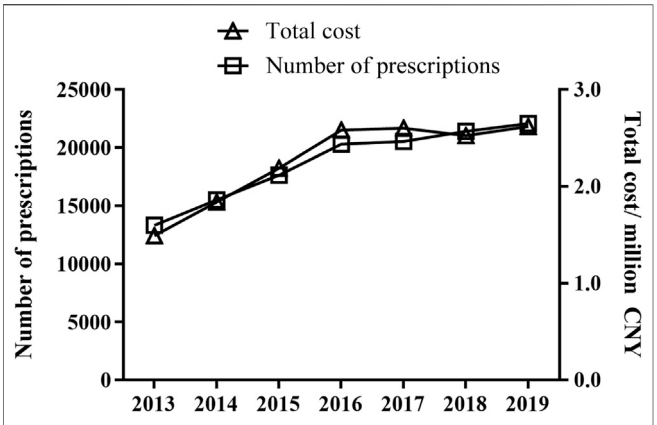

FIGURE 1 | Trends in prescription numbers and cost of topical drugs for DED treatment. Cost was calculated in Chinese Yuan.

48 were tertiary hospitals and eight were secondary hospitals. Yearly prescription for old patients with DED increased markedly from 13,308 in 2013 to 22,074 in 2019 ($p < 0.05$) (**Figure 1**). The corresponding cost also increased from CNY 1,490,014 to CNY 2,618,206 ($p < 0.05$).

The demographic information of old DED patients for the included prescriptions is shown in **Table 1**. Nearly half of the patients were between sixty and 70 years of age. Moreover, the proportion of patients at this age increased over time ($p < 0.05$). The prescriptions of female were more than the prescriptions of male in each year (Chi-square test, all $p < 0.05$).

Trends in Drugs for DED Treatment

Drugs for DED treatment accounted for more than 70 percent of the total prescription cost of topical drugs prescribed to old patients with DED (**Figure 2A**). Yearly prescription and cost of each drug are shown in **Tables 2** and **3**. The main drugs were ocular lubricant formulations containing sodium hyaluronate, polyvinyl alcohol (PVA), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC), and polyethylene glycol (PEG). Sodium hyaluronate was the most frequently prescribed ocular lubricant formulation and was used by more than half of the patients. Prescriptions for sodium hyaluronate and the corresponding cost both showed increasing trends over time (both $p < 0.05$). PVA drops were the second most frequently prescribed ocular lubricant formulation at the end of study. Meanwhile, the other three lubricants (HPMC and CMC and PEG) were used by progressively lesser percentages of patients (all $p < 0.05$).

NSAIDs are the second largest class of drugs for DED treatment. Pranoprofen was the second most frequently used drug throughout the study, and its use increased both in terms of percentage of prescriptions ($p < 0.05$). Corticosteroid and vitamin A preparation were used by only a small fraction of patients. Flurometholone was the most frequently used corticosteroid, and its use increased progressively in prescriptions and cost (both $p < 0.05$). However, it was used by <5% of patients at the end of the study. There was no significant trend in terms of the percentage of patients using vitamin A palmitate eye gel, the only vitamin A preparation ($p > 0.05$). Cyclosporine and tacrolimus were seldom used.

Trends in the Use of Drugs for the Treatment of Co-incident Diseases

Yearly prescriptions and cost of drugs for treating co-incident diseases are shown in **Table 4** and **Figure 2A**. The most frequently used drugs for co-incident diseases were antimicrobial agents and growth factor preparations. The former showed an increasing trend in visits ($p < 0.05$), while the latter did not ($p > 0.05$). Notably, the use of anti-allergy and glaucoma drugs increased over time (both $p < 0.05$).

Trends in Treatment Patterns

Trends in treatment patterns are shown in **Figure 2B**. Monotherapy and dual therapy were used in about 80% of prescriptions. However, the fractions of each treatment pattern showed no significant trends during the study period (all $p > 0.05$) and treatment patterns had changed. The most frequently used drug combination in each year of the study was sodium hyaluronate and pranoprofen.

DISCUSSION

This is the first study evaluating the patterns and trends of DED topical presscriptional treatment in old patients. As data were derived from many hospitals located in six major areas of China,

TABLE 1 | Demographic information of old DED patients for the included prescriptions.

	Number of patients (%)							P_1	P_2
	2013	2014	2015	2016	2017	2018	2019		
Age (years)									
61–70	6,381 (47.9)	7,612 (49.1)	8,776 (49.8)	10,333 (50.9)	10,458 (51.0)	11,125 (52.0)	11,671 (52.9)	0.003	<0.001
71–80	5,054 (38.0)	5,477 (35.3)	6,025 (34.2)	6,415 (31.6)	6,405 (31.2)	6,385 (29.8)	6,513 (29.5)	0.036	<0.001
80 up	1873 (14.1)	2,422 (15.6)	2,835 (16.1)	3,542 (17.5)	3,658 (17.8)	3,884 (18.2)	3,890 (17.6)	0.003	0.006
Sex									
Male	4,744 (35.6)	5,414 (34.9)	6,117 (34.7)	7,077 (34.9)	7,052 (34.4)	7,252 (33.9)	7,451 (33.8)	0.007	0.084
Female	8,564 (64.4)	10,097 (65.1)	11,519 (65.3)	13,213 (65.1)	13,469 (65.6)	14,142 (66.1)	14,623 (66.2)	0.003	0.084
Total	13,308	15,511	17,636	20,290	20,521	21,394	22,074	0.003	-

P_1, p-value for trend in number of prescriptions, assessed by Mann–Kendall trend test; P_2, p-value for trend in proportion of prescriptions, assessed by log-linear analysis.

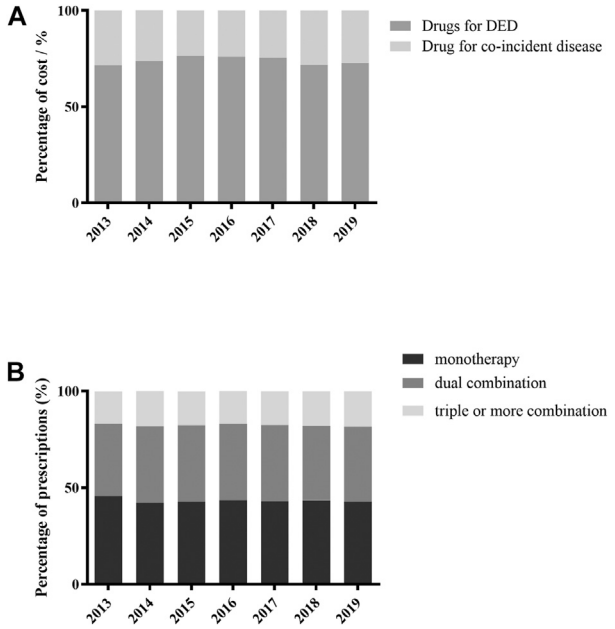

FIGURE 2 | Trends in drug classes for DED treatment. **(A)** Trends in the costs of drugs for the treatment of DED and co-incident disease. **(B)** Trends in patterns of DED topical treatment.

the results are representative of the aged Chinese population. We found that the prescription numbers and cost of DED treatment increased from 2013 to 2019. Ocular lubricants were the major drug used for treatment, and sodium hyaluronate eye drops were the most frequently prescribed drug.

The growing number of yearly prescriptions may reflect an increasing prevalence of DED in the Chinese population. It is reported there is no significant difference in prevalence rate of urban China and rural China (Liu et al., 2014). Although the included hospitals mainly locate in major cities, sampling bias may be neglected. Age was shown to be a risk factor for DED (Song et al., 2018; Dana et al., 2019b), and our study was focused on patients over the age of 60 years. Patients aged between 61 and 70 years were the major part and kept on increasing. This may be associated with the increased use of electronic devices (Courtin et al., 2016). Other possible reasons for the increase in yearly prescriptions include greater awareness of DED among doctors, improvements in diagnostic technologies, and higher demand for care. There were more prescriptions for female patients than for male patients, and this finding is consistent with the reported sex disparity in DED prevalence (Dana et al., 2019b; Siffel et al., 2020).

Ocular lubricants are designed to support the quality and quantity of tear film and are the first-line treatment for DED in many countries (Dogru et al., 2013; Jones et al., 2017). It was also the main drug used to treat DED in China, in contrast to the United States where the more costly cyclosporine is most frequently used (Clayton, 2018; Seitzman and Lietman, 2018). Moreover, many ocular lubricants are over-the-counter drugs and patients can get these drugs from community pharmacy, and the use rate of ocular lubricant may be higher than the result of our study. Nearly all ocular lubricant formulations can relieve DED symptoms and may improve visual acuity and protect against ocular damage (Moshirfar et al., 2014). However, randomized trials of their efficacy have been limited by a small sample size and poor study design (Pucker et al., 2012). Most ocular lubricant formulations have similar efficacy (Pucker et al., 2012), although CMC-, HPMC-, and hyaluronate-based formulations have been shown to be the most effective in improving patient comfort levels (White et al., 2014). These three formulations accounted for the majority of prescriptions

TABLE 2 | Prescription for topical drugs for the treatment of dry eye disease.

Drug class	Drug	2013	2014	2015	2016	2017	2018	2019	P_1	P_2
Lubricant	Sodium hyaluronate	7,013 (52.7)	7,831 (50.5)	9,322 (52.9)	11,297 (55.7)	11,786 (57.4)	13,759 (64.3)	14,544 (65.9)	0.003	0.002
	PVA	1,174 (8.8)	1770 (11.4)	2,340 (13.3)	2,837 (14.0)	2,705 (13.2)	2,667 (12.5)	2,667 (12.1)	0.172	0.190
	HPMC	1,628 (12.2)	1894 (12.2)	1868 (10.6)	1877 (9.3)	1,647 (8.0)	849 (4.0)	775 (3.5)	0.133	0.002
	CMC	1,045 (7.9)	2082 (13.4)	2,165 (12.3)	1,657 (8.2)	1,486 (7.2)	999 (4.7)	732 (3.3)	0.133	0.027
	PEG	972 (7.3)	1,033 (6.7)	1,169 (6.6)	1,226 (6.0)	1,165 (5.7)	962 (4.5)	913 (4.1)	0.548	0.001
	Carbomer	469 (3.5)	606 (3.9)	682 (3.9)	495 (2.4)	623 (3.0)	489 (2.3)	439 (2.0)	0.548	0.012
	Other	249 (1.9)	224 (1.4)	258 (1.5)	221 (1.1)	212 (1.0)	81 (0.4)	110 (0.5)	-	-
NSAID	Pranoprofen	1,313 (9.9)	1778 (11.5)	2,441 (13.8)	3,222 (15.9)	3,336 (16.3)	2,627 (12.3)	3,171 (14.4)	0.072	0.148
	Diclofenac	489 (3.7)	604 (3.9)	642 (3.6)	790 (3.9)	1,017 (5.0)	1,623 (7.6)	2023 (9.2)	0.003	0.007
Corticosteroid	Flurometholone	264 (2.0)	348 (2.2)	438 (2.5)	544 (2.7)	641 (3.1)	807 (3.8)	870 (3.9)	0.003	<0.001
	Prednisolone	39 (0.3)	66 (0.4)	60 (0.3)	96 (0.5)	130 (0.6)	148 (0.7)	148 (0.7)	0.010	0.003
	Other	19 (0.1)	4 (0.0)	2 (0.0)	0 (0.0)	13 (0.1)	44 (0.2)	39 (0.2)	-	-
Vitamin-A preparation	Vitamin-A palmitate	219 (1.6)	321 (2.1)	333 (1.9)	330 (1.6)	327 (1.6)	358 (1.7)	459 (2.1)	0.036	0.879
Immunosuppressant	Cyclosporine	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
	Tacrolimus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	-	-

Data are expressed as prescription number (percent of total prescriptions). Artificial tears are expressed by major ingredients. PVA: polyvinyl alcohol. HPMC: hydroxy propyl methyl cellulose. CMC: carboxyl methyl cellulose. PEG: polyethylene glycol. P_1, p-value for trend in number of prescriptions, assessed by Mann–Kendall trend test; P_2, p-value for trend in proportion of prescriptions, assessed by log-linear analysis.

TABLE 3 | Cost of topical drugs for the treatment of dry eye disease.

Drug class	Drug	2013	2014	2015	2016	2017	2018	2019	P_1	P_2
Lubricant	Sodium hyaluronate	529,991 (35.6)	550,109 (29.9)	676,814 (30.9)	890,512 (34.5)	959,859 (36.9)	1,029,898 (40.8)	1,075,786 (41.1)	0.003	0.043
	PVA	144,385 (9.7)	239,248 (13.0)	338,354 (15.5)	409,161 (15.9)	335,415 (12.9)	309,423 (12.3)	316,742 (12.1)	0.548	0.716
	HPMC	94,935 (6.4)	116,954 (6.4)	121,819 (5.6)	115,754 (4.5)	110,219 (4.2)	47,464 (1.9)	40,848 (1.6)	0.133	0.003
	CMC	72,236 (4.8)	169,387 (9.2)	194,181 (8.9)	141,559 (5.5)	131,788 (5.1)	84,128 (3.3)	61,511 (2.3)	0.230	0.053
	PEG	70,620 (4.7)	77,082 (4.2)	84,856 (3.9)	85,507 (3.3)	80,774 (3.1)	58,418 (2.3)	56,326 (2.2)	0.548	<0.001
	Carbomer	25,451 (1.7)	32,403 (1.8)	36,812 (1.7)	23,540 (0.9)	29,155 (1.1)	20,366 (0.8)	18,017 (0.7)	0.133	0.003
	Other	8,512 (0.6)	8,581 (0.5)	10,827 (0.5)	9,917 (0.4)	8,923 (0.3)	1,454 (0.1)	1,662 (0.1)	-	-
NSAID	Pranoprofen	89,325 (6.0)	120,933 (6.6)	164,023 (7.5)	217,887 (8.4)	221,848 (8.5)	143,050 (5.7)	165,911 (6.3)	0.133	0.997
	Diclofenac	13,472 (0.9)	18,142 (1.0)	18,677 (0.9)	34,029 (1.3)	46,014 (1.8)	79,506 (3.1)	102,670 (3.9)	0.003	0.002
Corticosteroid	Flurometholone	5,539 (0.4)	7,718 (0.4)	10,120 (0.5)	12,100 (0.5)	14,729 (0.6)	16,335 (0.6)	17,647 (0.7)	0.003	<0.001
	Prednisolone	1,350 (0.1)	2,324 (0.1)	2,196 (0.1)	3,293 (0.1)	4,166 (0.2)	4,768 (0.2)	5,050 (0.2)	0.007	0.003
	Other	1862 (0.1)	372 (0.0)	120 (0.0)	0 (0.0)	1,020 (0.0)	3,272 (0.1)	17,874 (0.7)	-	-
Vitamin-A preparation	Vitamin-A palmitate	9,494 (0.6)	15,119 (0.8)	14,098 (0.6)	17,586 (0.7)	19,749 (0.8)	17,287 (0.7)	21,970 (0.8)	0.036	0.341
Immunosuppressant	Cyclosporine	300 (0.0)	150 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
	Tacrolimus	0 (0.0)	0 (0.0)	0 (0.0)	779 (0.0)	0 (0.0)	0 (0.0)	3,117 (0.1)	-	-

Data are expressed as cost in Chinese Yuan (percent of total cost). Artificial tears are expressed by major ingredients. PVA: polyvinyl alcohol. HPMC: hydroxy propyl methyl cellulose. CMC: carboxyl methyl cellulose. PEG: polyethylene glycol. P_1, p-value for trend in number of prescriptions, assessed by Mann–Kendall trend test; P_2, p-value for trend in proportion of prescriptions, assessed by log-linear analysis.

in our analysis, with the hyaluronate-based formulation being the most frequently prescribed (**Table 2**). Ocular lubricants have good safety profiles and ophthalmologists may take this into consideration when prescribing for old patients. However, the reasons for its widespread use as well as its pharmaco-economic profile require further investigation. There is no evidence for the superior efficacy of PVA-based formulations (Nelson and Farris, 1988; McDonald et al., 2002); however, their prescription increased over the study period and ranked second in terms of cost among all DED drugs. Perhaps this growth could be attributed to more aggressive marketing efforts.

A variety of topical NSAID formulations have been used to treat DED. NSAIDs were the second largest class of drugs for DED treatment in this study, and their use increased progressively in both prescription numbers and cost. The most frequently studied NSAIDS in literatures are pranoprofen, diclofenac acid, ketorolac, and indomethacin (Rolando et al., 2002; Aragona et al., 2005; Chen et al., 2014). Only two of these—pranoprofen and diclofenac—were among the drugs prescribed in our study. Results from clinical trials have shown that some NSAIDs—especially diclofenac—can reduce corneal sensitivity in DED patients; moreover, diclofenac suppressed hyperosmolarity-induced apoptosis of corneal cells (Sawazaki et al., 2014). However, more studies are needed to determine which NSAID is the most effective (Aragona et al., 2005). The increased use of topical NSAIDs warrants attention as sporadic cases of corneal melting have been reported in DED patients (Isawi and Dhaliwal, 2007). Moreover, there is little known about the effects of long-term topical NSAID use, as the treatment duration was no more than 1 month in most studies (Jones et al., 2017). Additionally, the reason for the frequent use of pranoprofen should be investigated as it is not normally recommended in treatment guidelines.

Topical glucocorticoid eye drops can effectively relieve signs and symptoms of DED (Thulasi et al., 2017), but there are adverse effects, such as glaucoma and cataract, associated with long-term corticosteroid use. Thus, topical corticosteroid should be used cautiously, and pulse treatment is a common option. Unsurprisingly, topical corticosteroid accounted for a small fraction of prescriptions in our study. Among corticosteroids, fluorometholone, and loteprednol have a lower risk of increasing intraocular pressure and inducing cataract formation (Mataftsi et al., 2011; Sheppard et al., 2016; Jones et al., 2017). Nearly 80% of the corticosteroid prescriptions in China were for fluorometholone; thus, the current evidence supports the clinical application of corticosteroids.

Topical cyclosporine was the first drug approved for DED treatment and is widely prescribed by ophthalmologists in North America (Clayton, 2018). It was previously reported that cyclosporine accounted for 99% of the total expenditure for DED drugs (Seitzman and Lietman, 2018); however, we found that it is rarely used in China. Asian countries have a different view of DED etiology from that of the United States, recognizing tear instability rather than inflammation as the main cause for DED (Watanabe, 2018). Uncertain efficacy, side effects, and high cost also limit the use of these drugs (de Paiva et al., 2019; White et al., 2019; White et al., 2020).

TABLE 4 | Prescription for specific drug classes used to treat co-incident disease.

Drug class	ATC code	2013	2014	2015	2016	2017	2018	2019	*p*
Anti-microbial agent	S01 A/C	3,877	4,737	4,720	5,394	5,561	6,304	6,357	0.007
Wound healing agent	-	2,141	2,387	2,104	2,330	2028	2,557	2,611	0.368
Antiallergy	S01G	527	520	571	700	772	847	873	0.007
Glaucoma drug	S01E	662	771	921	1,215	1,393	1,615	1,561	0.007
Cataract drug	-	878	883	1,008	1,133	1,168	807	650	>0.999
Complementary medicine	-	126	228	242	356	369	441	410	0.007
Other	-	94	77	99	58	121	170	314	-

p-*value for trend in number of prescriptions were assessed by Mann–Kendall trend test. Main drugs of wound healing agents are basic fibroblast growth factor preparations and epidermal growth factor preparations. Main drug of cataract drugs is Pirenoxine Sodium.*

In addition to drugs for DED treatment, patients may be using other drugs for co-incident disease. Our analysis showed that while drugs for DED represented the largest proportion of the total cost, anti-microbial agents, growth factor preparations, and anti-allergy agents were frequently prescribed. This result is in accordance with epidemiologic findings that microbial infection, surgery/corneal ulcer, and allergic disease are common comorbidities of DED (Shimazaki et al., 2020). The high number of visits for glaucoma drugs among DED patients may indicate the growing prevalence of this comorbidity, which should be noted by clinicians (Dana et al., 2019a).

Monotherapy was implemented in less than half of the patients observed in our study, which suggests that the standard therapeutic approach did not yield satisfactory outcomes in most cases. The level of patient-reported satisfaction with over-the-counter formulations including hyaluronate is about 64% (Gomes and Santo, 2019). However, the efficacy of hyaluronate plus pranoprofen—the most frequently used drug combination for DED treatment—is not supported by clinical evidence, despite the proven efficacy of each drug as monotherapy (McDonald et al., 2002; Chen et al., 2014). This raises a concern for the overuse of these drugs. Combinations of three or more drugs are restricted by the need for frequent administration.

This study had some limitations. Firstly, the outcomes of DED treatment with eye drops were not documented in the database used in our study. And they require more detailed investigation. Secondly, the cohort was not stratified by DED phenotype or severity. Thirdly, we were unable to determine whether the topical formulations contained preservatives based on the available information. Finally, we did not include oral drugs and non-prescription drugs for DED treatment in our analysis.

CONCLUSION

We analyzed trends in DED topical prescriptional treatment over a seven -year period in old Chinese patients. The prescription numbers and corresponding cost associated with DED both showed increasing trends over the study period, highlighting the need for better clinical management of old patients with DED. Ocular lubricants were the most frequently used drug for DED treatment, and this tendency may reflect the view among Chinese physicians that tear instability is main cause of DED.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Sir Run Shaw Hospital, Zhejiang University School of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: YZ, LY; Data curation: ZY, LY. Formal analysis: LY, XW, JZ, JJ, ZY; Funding acquisition: ZY; Investigation: ZY, XW; Methodology: ZY, LY, JZ, JJ; Resources: ZY; Validation: LY, XW, JZ, JJ; Visualization: LY, JP, JJ; Writing-original draft: ZY; Writing-review and editing: YZ, LY.

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Comparison Between Decitabine and Azacitidine for Patients With Acute Myeloid Leukemia and Higher-Risk Myelodysplastic Syndrome: A Systematic Review and Network Meta-Analysis

Jiale Ma[1,2] *and Zheng Ge*[1*†]

[1]Department of Hematology, Zhongda Hospital, School of Medicine, Southeast University, Institute of Hematology Southeast University, Nanjing, China, [2]Department of Hematology, Xuzhou Central Hospital, Xuzhou, China

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Luciane Cruz Lopes,
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Yale University, United States

***Correspondence:**
Zheng Ge
zhengge@seu.edu.cn

†ORCID:
Zheng Ge
orcid.org/0000-0002-5925-2996

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Background: The hypomethylating agents (HMAs) azacitidine (AZA) and decitabine (DAC) have been widely used in patients with acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (HR-MDS). However, few direct clinical trials have been carried out to compare the efficacy and adverse events (AEs) between these two agents. The clinical choice between them is controversial. A systematic review and network meta-analysis (NMA) was performed to compare the efficacy, safety, and survival of DAC and AZA in AML and HR-MDS patients.

Methods: We systematically searched MEDLINE, Embase, Web of Science, and Cochrane Library through March 15, 2021. Randomized controlled trials (RCTs) on AML or HR-MDS patients comparing the efficacy and safety between DAC and AZA or comparing one of HMAs to conventional care regimens (CCR) were selected.

Results: Eight RCTs (n = 2,184) were identified in the NMA. Four trials compared AZA to CCR, and four compared DAC to CCR. Direct comparisons indicated that, compared to CCR, both AZA and DAC were associated with higher overall response (OR) rate (AZA vs. CCR: relative risk (RR) = 1.48, 95% CI 1.05–2.1; DAC vs. CCR: RR = 2.14, 95% CI 1.21–3.79) and longer overall survival (OS) (AZA vs. CCR: HR = 0.64, 95% CI 0.50–0.82; DAC vs. CCR: HR = 0.84, 95% CI 0.72–0.98), and AZA showed higher rate of complete remission with incomplete blood count recovery (CRi) (HR = 2.52, 95% CI 1.27–5). For the indirect method, DAC showed a higher complete remission (CR) rate than AZA in patients with both AML (RR = 2.28, 95% CI 1.12–4.65) and MDS (RR = 7.57, 95% CI 1.26–45.54). Additionally, DAC significantly increased the risk of 3/4 grade anemia (RR = 1.61, 95% CI: 1.03–2.51), febrile neutropenia (RR = 4.03, 95% CI: 1.41–11.52), and leukopenia (RR = 3.43, 95% CI 1.64–7.16) compared with AZA. No statistical significance was found for the other studied outcomes.

Conclusion: Compared to CCR, both AZA and DAC can promote outcomes in patients with AML and HR-MDS. DAC showed higher efficacy especially CR rate than AZA (low-

certainty evidence), while AZA experienced lower frequent grade 3/4 cytopenia than patients receiving DAC treatment.

Keywords: decitabine, azacitidine, acute myeloid leukemia, higher-risk myelodysplastic syndrome, network meta-analysis

INTRODUCTION

Acute myeloid leukemia (AML) and higher-risk myelodysplastic syndromes (HR-MDS) are heterogeneous hematologic malignancies with clinical manifestations of anemia, hemorrhage, and infection (Arber, 2019). HR-MDS are defined as patients with intermediate-2 or high-risk score by the International Prognostic Scoring System (IPSS) or with intermediate, high, or very high-risk score by the Revised International Prognostic Scoring System (IPSS-R) (Pfeilstocker et al., 2016). HR-MDS are aggressive disorders with rapid progression to AML, with a poor prognosis despite intensive chemotherapy (IC). The annual incidence rates of AML are higher than 4.2 per 100,000 per year (Shallis et al.,2019). The 2- and 5-year overall survival (OS) rates of elderly AML patients are approximately 10 and 2%, respectively (Menzin et al., 2002; Daly and Paquette, 2019). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be the only curative treatment for HR-MDS and AML (Stone, 2009). Limited by HLA-matching donor, physical status, ages, costs, treatment-related mortality (TRM), and graft-versus-host disease (GVHD), many patients are ineligible for allo-HSCT. Therefore, it is urgent to develop an effective therapeutic approach for these patients who are ineligible for transplantation.

Azacitidine (AZA) and decitabine (DAC) are lower-intensity chemotherapy agents and have been approved to treat MDS by the Food and Drug Administration (FDA). On September 1, 2020, FDA approved oral AZA for the maintenance treatment of patients with AML. Hypomethylating agents (HMAs) have become the standard therapy for patients with HR-MDS or AML who are not candidates for allo-HSCT and intensive chemotherapies (Sanz, 2019). These two agents are slightly different in structure: AZA is a ribonucleoside, while DAC is a deoxyribonucleoside (Lyko and Brown, 2005). Both AZA and DAC act by depletion of DNA methyltransferases. However, these two agents have different mechanisms of action: 80–90% of AZA is integrated into RNA, leading to abnormal ribosome assembly and inhibiting tumor-related protein synthesis; 10%–20% can also be converted into 5-aza-2'-deoxycytidine by the action of ribonucleotide reductase to bind to DNA, thereby inhibiting DNA methyltransferase and leading to the reexpression of tumor suppressor genes. While DAC is incorporated only into DNA, high-dose DAC inhibits DNA cross-linking and synthesis through cytotoxicity, and low-dose DAC exerts DNA demethylation by inhibiting DNA methyltransferase, reactivating silent tumor suppressor genes (Stresemann and Lyko, 2008; Hollenbach et al., 2010). Preclinical studies have shown that DAC is more effective than AZA in antileukemia activity *in vivo* (Cany et al., 2018); however, clinical data indicate that AZA is more effective than DAC. Observational studies of these two agents have shown similar efficacy and toxicity profiles in the treatment of refractory anemia with excessive blasts (MDS-RAEB) (Salim et al., 2016). Compared with CCR, both AZA and DAC have shown delayed progression to AML (Fenaux et al., 2009; Kantarjian et al., 2006; Lubbert et al., 2011; Silverman et al., 2002). However, only AZA has shown a significant advantage in OS compared with CCR (median OS, 24.5 vs. 15 months, respectively) in patients with HR-MDS and AML with 20–30% marrow blasts (Fenaux et al., 2009), establishing it as the first-line treatment of choice for those patients who are unfit for transplant (Santini et al., 2010).

Up to now, direct comparison of AZA and DAC has been performed in rare randomized trials, leading to the dilemma choice of these two agents for patients and physicians. Several meta-analyses have been conducted to compare the efficacy and safety of AZA and DAC in MDS or AML patients. None of them made a comparison in HR-MDS and AML. Therefore, the objective of this study was to compare the efficacy, safety, and survival of AZA and DAC in patients with HR-MDS and AML.

METHODS

We prospectively registered the current review in the PROSPERO database (registration number: CRD42021245905). The Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy (PRISMA-DTA) studies guideline was followed in preparing this systematic review.

Search Strategy

We systematically searched all studies published in MEDLINE (*via* PubMed), Web of Science, Cochrane Library, and Embase through March 15, 2021, without time or language restrictions. Keywords included "hypomethylating agents", "azacitidine", "decitabine", "myelodysplastic syndrome", and "acute myeloid leukopenia". The detailed search strategies were listed in **Supplementary Table S1**.

Study Selection, Inclusion, and Exclusion Criteria

All randomized controlled trials (RCTs) comparing HMAs to CCR (including best supportive care (BSC), low-dose Ara-C (LDA), and IC) or AZA to DAC in patients with HR-MDS and AML were included in this study, regardless of publication status and language. Reviews, case reports, meta-analyses, and preclinical and observational studies were excluded. Two reviewers (Jiale Ma and Zheng Ge) screened all references identified through our search and inclusion criteria. Disagreements were settled by discussion of the two reviewers and involved a third independent reviewer if necessary.

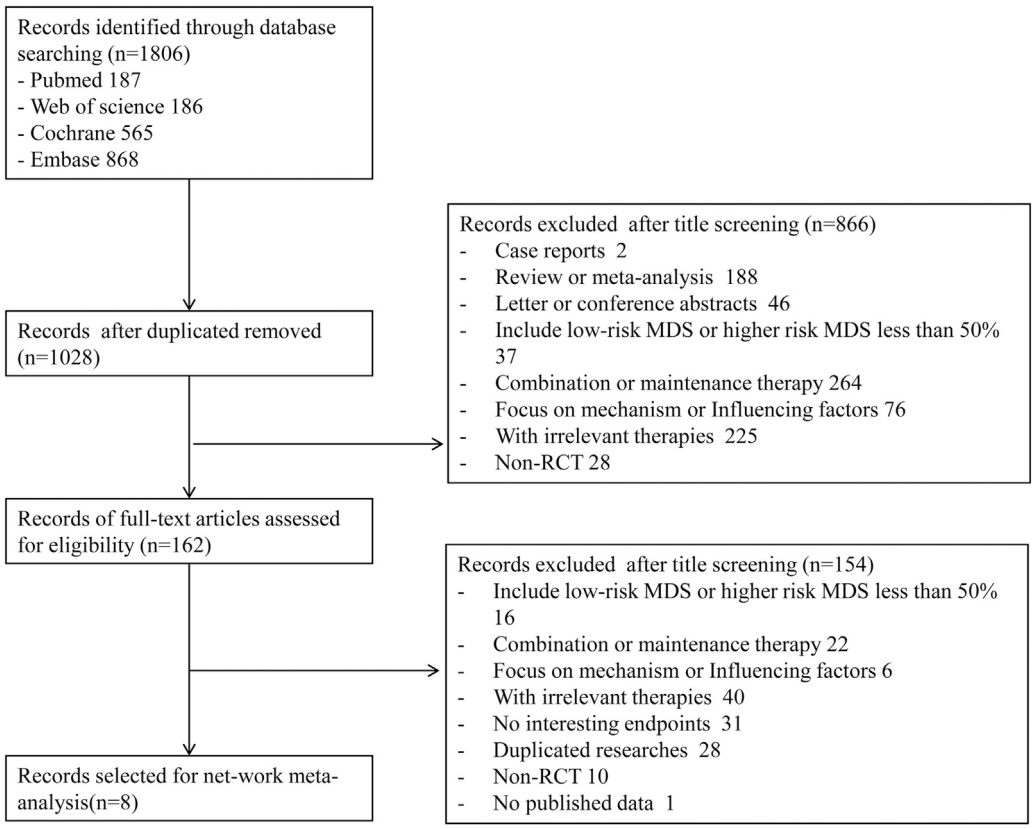

FIGURE 1 | Flowchart presenting the steps of the literature search and selection.

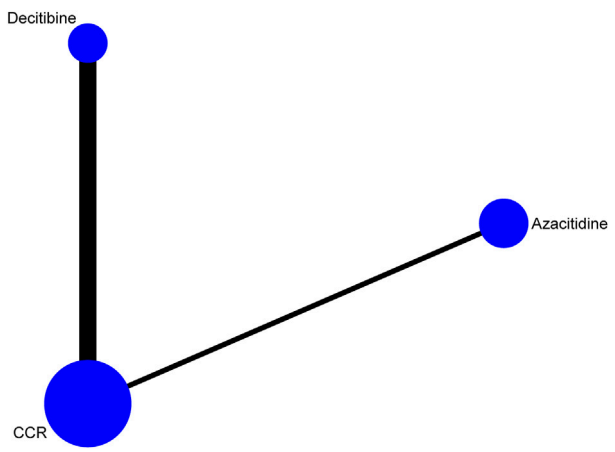

FIGURE 2 | Network of interventional treatments comparing types of acute myeloid leukemia and higher-risk myelodysplastic syndrome (CR). The sizes of the nodes represent the total sample size for each treatment. Line thickness and the numbers beside the lines correspond to the number of trials. CCR, conventional care regimens.

Phases II and III and RCTs were selected in this systematic review and network meta-analysis (NMA). Adult patients diagnosed with AML and/or MDS were selected. The treatment options included single agent AZA or DAC, or comparison of these two drugs against each other, or comparison of them to CCR without previous allo-HSCT or other chemotherapies. Of note, in MDS studies, the included population of higher-risk MDS should be more than 60% of all MDS patients. In other words, the included population should be mainly HR-MDS. Additionally, at least one of the relevant outcomes should be reported in the trial including objective remission (OR), complete remission (CR), complete remission with incomplete blood count recovery (CRi), complete remission with incomplete platelet recovery (CRp), partial response (PR), hematological improvement (HI), marrow complete remission (mCR) rates, or AEs or at least one form of survival data.

Exclusion criteria included patients with therapy-related disease; prior treatment with AZA, DAC, chemotherapy, immunotherapy, or planned allo-HSCT.

Date Extraction and Clinical Endpoint

Extracted data included 1) study characteristics (author, publication year, and study type); 2) patient characteristics (age, gender, WHO/FAB classification, disease stage using IPSS criteria, karyotype risk, and ECOG score); 3) the hypomethylating treatment regimen; 4) the outcome measures [CR, CRi, CRp, PR, HI, mCR, overall response (OR) rates, drug-

TABLE 1 | Characteristics of publications (**Supplementary Material**).

Study, year	Type	Intervention (dose, schedule)	Patients enrolled	Female	Age, median	WHO classification	FAB classification	IPSS	Karyotape risk	ECOG	Median cycles	Efficacy	Grade3/4) adverse events	Median OS (months)
Fenaux et al. (2009)	Phase III	Aza (75 mg/m2/d*7d per 28-day cycle for at least 6 cycles)	179	47	69 (42–83)	RAEB-1 14, RAEB-2 98, CMML-1 1, CMML-2 10, AML 55, Indterminate 1	RAEB 104, RAEB-T 61, CMML 6, AML 1	IPSS-1 5, IPSS-2 76, High 82	Favorable 83, Intermediate 37, Unfavorable 50, unknown 9	0: 78,1: 86, ≥2: 13, unknown: 2	9 (4–15)	OR 138, CR 30, PR 21, HI 87	Neutropenia 159, thrombocytopenia 149, anaemia 100,death 82	24.5
		CCR(BSC 105, LDA49, intensivechemotherapy 25)	179	60	70 (38–88)	RAEB-1 17, RAEB-2 95, CMML-1 0, CMML-2 5, AML 58, Indterminate 4	RAEB 103, RAEB-T 62, CMML 5, AML 1	IPSS-1 13, IPSS-2 70, High 85	Favorable 84, Intermediate 39, Unfavorable 50, unknown 6	0: 80,1: 86, ≥2: 10, unknown: 3	NA	OR 72, CR 14, PR 7, HI 51	Neutropenia 126, thrombocytopenia 132, anaemia 112, death 113	15
Dombret et al. (2015)	Phase III	Aza(75 mg/m2/d*7d per 28-day cycle for at least 6 cycles)	241	102	75(64–91)	AML	AML	–	–		6(1–28)	OR 75, Cri 20, CR 47, PR 3	Febrile neutropenia 66, pneumonia 45, leukopenia 16, hypokalemia 12, neutropenia 62, thrombocytopenia 56, anaemia 37, death 193	10.4
		CCR (BSC, LDAC(20 mg bid *10d per 28-day treatment cycle for at least 4 cycles),IC (Ara-c100-200 mg/m2/ d *7d, daunorubicin 45-60 mg/m2/d*3d or idarubicin 9-12 mg/ m2/d*3d)	247	98	75(65–89)	AML	AML	–	–	–	2 (1-3) IC cycles, and 4 (1-25) LDAC cycles, and the median exposure to BSC only was 65 (6-535) days	OR 65, Cri 8,CR 54 , PR 3	Febrile neutropenia 70, pneumonia 33, leukopenia 19, hypokalemia 18, neutropenia 54, thrombocytopenia 53, anaemia 43, death 201	6.5
Kantarjian et al. (2012)	Phase III	Dec (20 mg/m(2)/d*5d per 28-day cycle)	242	105	73(64–89)	AML	AML	–	Favorable NA, Intermediate 152, Unfavorable 87, unknown NA	1: 184, ≥2: 58	NA	OR 49, Cri 24, CR 38, CRp 5, PR 6	Febrile neutropenia 76, pneumonia 51, leukopenia 47, hypokalemia 27, neutropenia 76, thrombocytopenia 95, anaemia 80,dyspnea 16, death 197	7.7
		CCR (BSC or cytarabine 20 mg/m(2)/ d as a subcutaneous injection for 10 consecutive days every 4 weeks)	243	92	73(64–91)	AML	AML	–	Favorable NA, Intermediate 154, Unfavorable 87, unknown NA	1: 183, ≥2: 60	NA	OR 28, Cri 7, CR 18, CRp 1, PR 9	Febrile neutropenia 51, pneumonia 43, leukopenia 20, hypokalemia 24, neutropenia 42, thrombocytopenia 77,anaemia 60,dyspnea 14, death 199	5
Lübbert et al. (2011)	Phase II	Dec (15 mg/m2 q8h *3 d,every 6-week cycles)	119	43	69(60–90)	MDS	RAEB 61,RAEB-T 40,CMML 10, AML 1	IPSS-1 8, IPSS-2 64, High 46, unknown 1	Favorable 38, Intermediate 8, Unfavorable 57, unknown 15	0: 29,1: 76, ≥2: 14,	4	OR 41,CR 16,PR 7, HI 18	Febrile neutropenia 29, pneumonia 66, neutropenia 54, thrombocytopenia 20,anaemia NA,death 99	10.1
		BSC	114	41	70(60–86)	MDS	RAEB 64,RAEB-T 35,CMML 4, AML 1	IPSS-1 8, IPSS-2 63, High 42, unknown 1	Favorable 29, Intermediate 17, Unfavorable 51, unknown 17	0: 25,1: 72, ≥2: 17	NA	OR 28, Cri 7, CR 18, CRp 1, PR 9	Febrile neutropenia 8, pneumonia 57, neutropenia 40, thrombocytopenia 18,anaemia NA, death 96	8.5
Seymour et al. (2017)	RCT	Aza (75 mg/m2/d*7d per 28-day cycle)	129	48	76 (64–90)	AML	AML	–	Favorable NA, Intermediate 63, Unfavorable 66,	1: 94, ≥2: 35	5(1–27)	OR 33, Cri 7, CR 25, PR 1	Febrile neutropenia 29, pneumonia 24, leukopenia 8, hypokalemia	8.9

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of publications (Supplementary Material).

Study, year	Type	Intervention (dose, schedule)	Patients enrolled	Female	Age, median	WHO classification	FAB classification	IPSS	Karyotape risk	ECOG	Median cycles	Efficacy	Grade3/4) adverse events	Median OS (months)
													9,neutropenia 28, thrombocytopenia 33,anaemia 19,dyspnea 6, sepsis 7, death NA	
		CCR	133	55	75 (65–87)	AML	AML	–	Favorable NA, Intermediate 61, Unfavorable 72,	1: 104, ≥2: 29	2	OR 25, Cri 3, CR 20, PR 2	Febrile neutropenia 43, pneumonia 18,, leukopenia 10, hypokalemia 10, neutropenia 25, thrombocytopenia 27,anaemia 21,dyspnea 4, sepsis 9, death NA	4.9
Fenaux et al. (2010)	Phase III	Aza (75 mg/m2/d*7d per 28-day cycle for at least 6 cycles)	55	18	70(52–80	AML	AML	–	Favorable 19, Intermediate 38, Unfavorable 14, unknown 3	0: 16,1: 35, ≥2: 4, unknown 0	NA	CR 10	Neutropenia 50, thrombocytopenia 48,anaemia 30,death NA	24.5
		CCR	58	17	70(50–83)	AML	AML	–	Favorable 33, Intermediate 43, Unfavorable 13, unknown 2	0: 22,1: 34, ≥2: 0, unknown 2	NA	CR 9	Neutropenia 44, thrombocytopenia 44, anaemia 36, death NA	16
Kantarjian et al. (2006)	Phase III	Dec(15mg/m2 q8h*3d,every 6 weeks)	89	30	70(65–76)	NA	RA 12, RARS 7, RAEB 47, RAEB-T 17, CMML 6	IPSS-1 28, IPSS-2 38, High 23	NA	0: 21,1: 61, ≥2: 4, unknown 0	3(0–9)	OR 27, CR 8, PR 7, HI 12	Febrile neutropenia 23, pneumonia 15, leukopenia 22, neutropenia 87, thrombocytopenia 85, anaemia 12, death 12	14
		BSC	81	24	70(62–74)	NA	RA 12, RARS 4, RAEB 43, RAEB-T 14, CMML 8	IPSS-1 24, IPSS-2 36, High 21	NA	0: 28,1: 48, ≥2: 4, unknown 1	NA	OR 6,HI 6	Febrile neutropenia 4, pneumonia 9, leukopenia 7,neutropenia 50, thrombocytopenia 43, anaemia 15, death 18	14.9
Becker et al. (2015)	Phase III	Dec (15 mg/m2 q8h *3 d,every 6-week cycles)	40	11	69.5(61–90)	MDS	RAEB-t	IPSS-1 2, IPSS-2 12, High 26	Favorable 16, Intermediate 4, Unfavorable 14, unknown 6	0: 8,1: 29, ≥2: 3	NA	OR 12, CR 4, PR 2, HI 6	NA	8
		BSC	35	11	69(61–80)	MDS	RAEB-t	IPSS-1 0, IPSS-2 13, High 22		0: 10,1: 19, ≥2: 6	NA	OR 0, CR 0, PR 0, HI 0	NA	6

AZA, azacitidine; DAC, decitabine; CCR, conventional care regimens (including best supportive care, low-dose cytarabine, and intensive chemotherapy); BSC, best supportive care; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts transformation; NA, not available; OR, objective remission; CR, complete remission, CRi, complete remission with incomplete blood count recovery; CRp, complete remission with incomplete platelet recovery; PR, partial response; HI, hematological improvement; mCR, marrow complete remission.

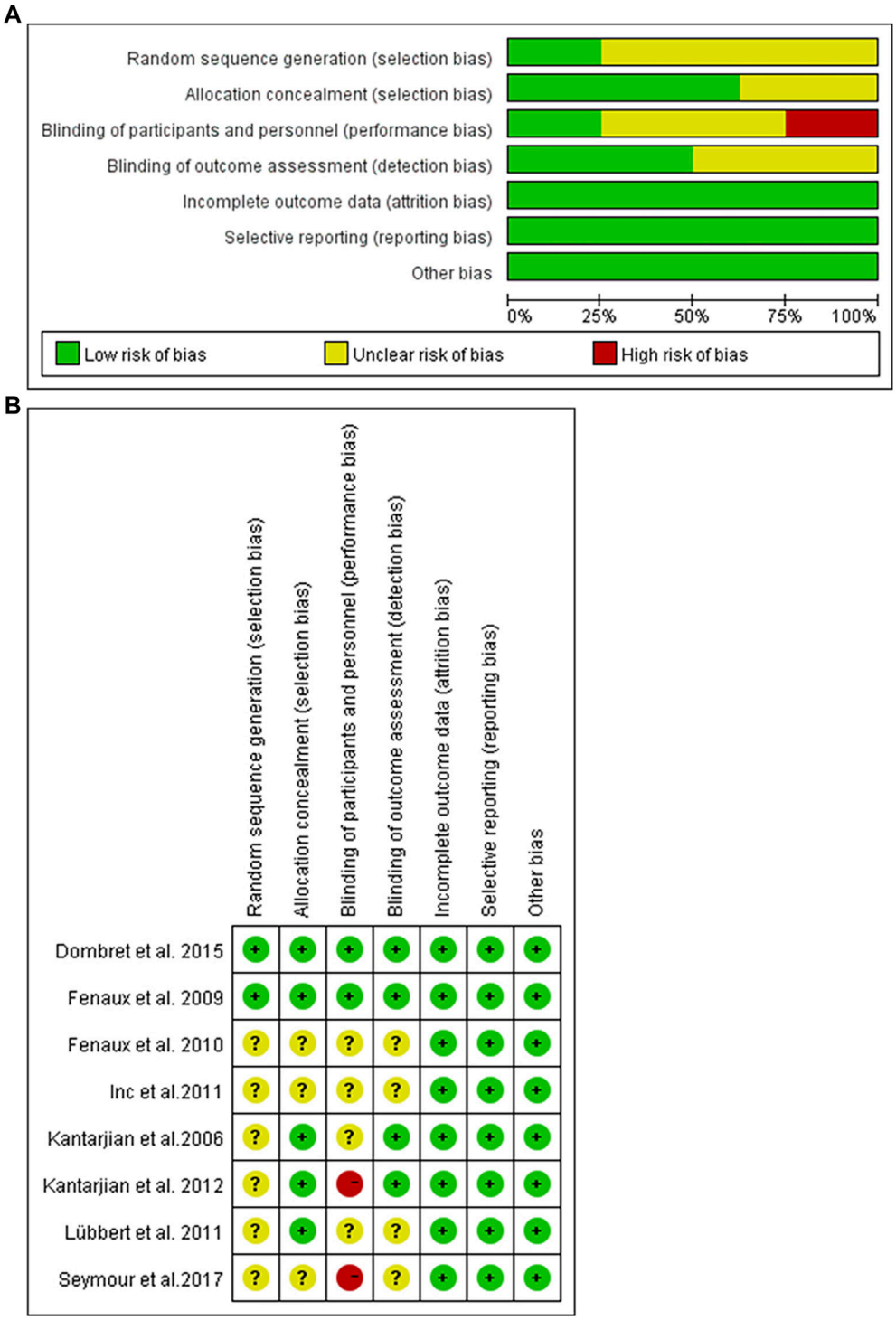

FIGURE 3 | Risk of bias graph. **(A)** Authors' judgments about each risk of bias item presented as percentages across all included studies. **(B)** Risk of bias summary. Authors' judgments about each risk of bias item for each included study.

related AEs rate, and OS]. The primary outcomes were efficacy (response rate measured by a total number of included patients) and AEs. The second outcomes were OS of all patients. In the absence of information or supplemental data from the authors, the response rate was calculated according to a validated imputation method (Furukawa et al., 2005).

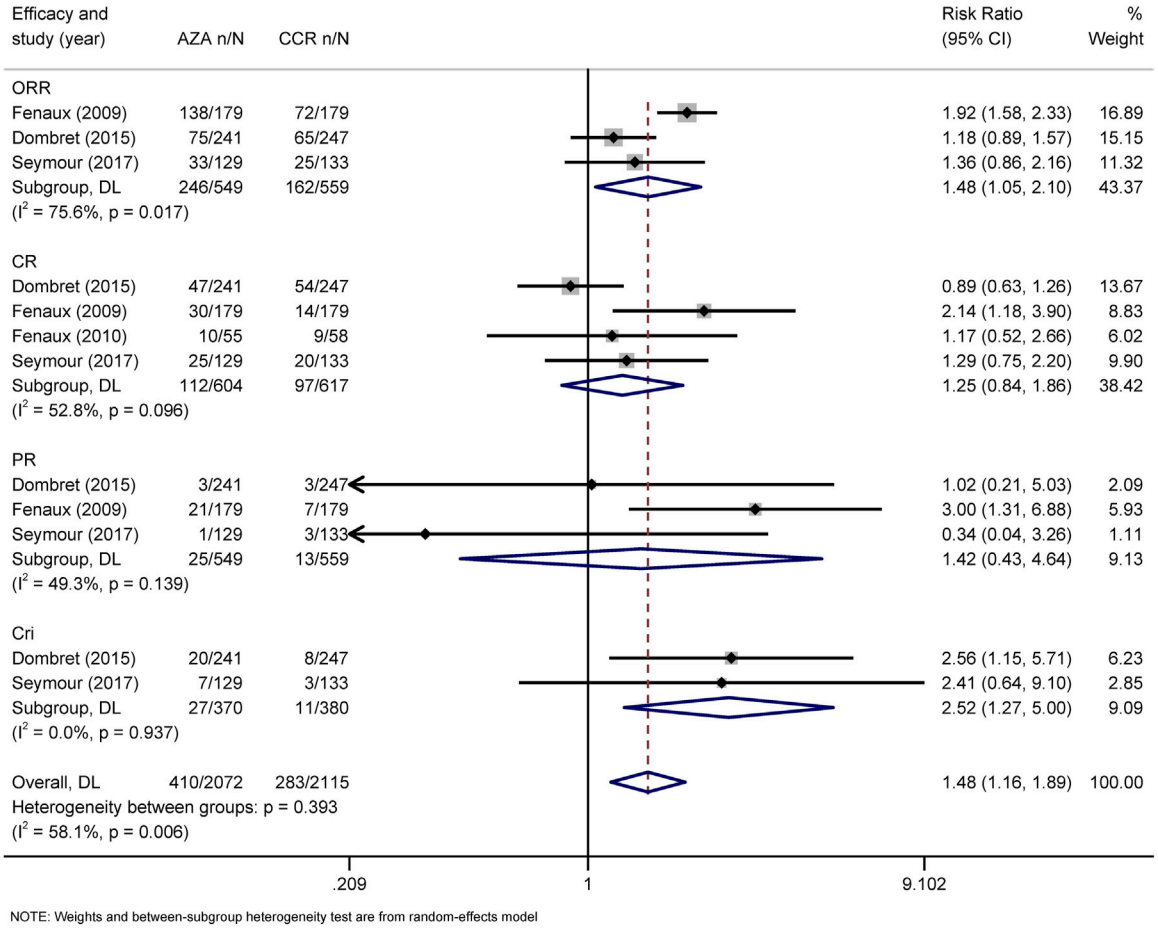

FIGURE 4 | Forest plot of efficacy of azacitidine vs. conventional care regimens (direct evidence-RR). Forest plot represents the direct comparison of efficacy between AZA and CCR. RR, relative risks; 95%CIs, 95% confidence intervals; CCR, conventional care regimens; n, total number of events; N, total number of patients.

Quality Assessment

Cochrane Handbook for Systematic Reviews of Interventions was used to assess the bias of each included RCT. The criteria for evaluation included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias was assessed as low, unclear, or high.

Statistical Analysis

All the NMAs were performed by using the meta-analysis program of STATA 14.0 software (Stata Corporation, Texas) and Review Manager 5.4 software (Cochrane Collaboration, Oxford, United Kingdom). Direct pairwise meta-analyses were first performed to estimate the available relative effects of the competing interventions using the random effects model. The binomial distribution was used to calculate and express relative risks (RRs) and 95% confidence intervals (95% CIs). Heterogeneity parameters (I^2) for each pairwise comparison were quantified to express a percentage of variability, and that is due to true differences between studies rather than sampling error (Higgins and Thompson, 2002). All analyses were performed by using the Mantel–Haenszel (M–H) method.

We performed an NMA to analyze all comparisons among interventions for each outcome. This is because NMA takes advantage of two statistical approaches. First, the use of indirect comparisons can help us to estimate the effect of intervention A versus intervention B, indirectly if both A and B have been compared against an intervention C. Second, the combination of direct and indirect comparisons allows reviewers to obtain more precise estimates (Nino-Serna et al., 2020). In the presence of both direct and indirect evidence, the NMA provided a combined effect estimate. A random effects model of NMA was conducted for each outcome using the multivariate meta-analysis approach. For each outcome and a connected network of studies, we performed a frequentist framework NMA if the assumptions of between-study homogeneity, transitivity, and consistency of evidence across treatment comparisons were judged to be justifiable (Baker and Kramer, 2002; Cipriani et al., 2013). Inconsistency network models were used to test the global consistency of direct and indirect estimates for pairwise comparisons, and node-splitting

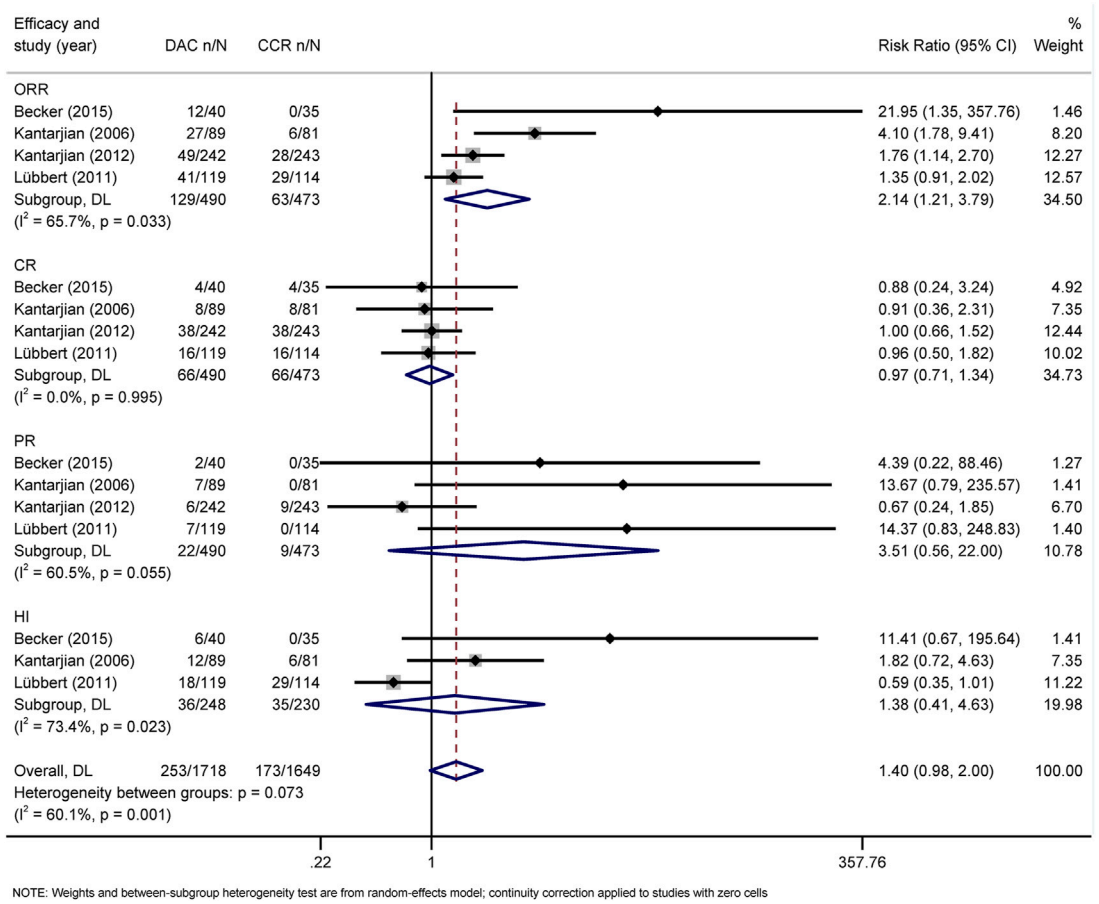

FIGURE 5 | Forest plot of efficacy of decitabine vs. conventional care regimens (direct evidence-RR).

method models were used to test the local inconsistency. Design-by-treatment interaction models (Higgins et al., 2012) were used to statistically evaluate the consistency. We assume that the treatment comparisons have common heterogeneity because the included treatments have the same properties and sharing common heterogeneity parameters is clinically reasonable. The graph and summary of risk of bias were created to assess the bias within studies. Surface under the cumulative ranking (SUCRA) (Salanti et al., 2011) probabilities were used to rank the treatment for the outcome. For patients with HR-MDS or AML, larger SUCRA values indicate higher rank of the treatment. In addition, a clustered ranking plot was constructed using SUCRA values for efficacy and safety outcomes to obtain information on meaningful groups of treatments that maximize benefits for efficacy and safety outcomes.

RESULTS

Literature Search Results

A total of 1,806 records were obtained with the search strategy. After removing 778 duplicates, 1,028 records were screened by title and abstract. A total of 866 records were excluded due to ineligibility. 162 records of full-text articles were assessed for eligibility. 154 records were excluded after screening full-text articles. Of note, the results of Becker et al. (2015)'s study in 2015 were a subgroup analysis of the randomized phase III study 06,011 of the EORTC Leukemia Cooperative Group and German MDS Study Group (GMDSSG) (Lubbert et al., 2011). Despite being a same study, these two articles focused on different aspects. Lubbert et al.'s study involved all risk-stratified MDS patients, while Becker et al.'s study included only RAEB-t patients, which was more representative in the high-risk group. If we only include Becker et al.'s study, the other middle- and high-risk patients of the entire experimental group will be ignored. After weighing it, repeatedly, we included both studies in the statistical analysis, although it may bring selected offsets. Finally, eight trials were eligible for extraction for this NMA (**Figure 1**). As indicated in the network plot (**Figure 2**), AZA vs. CCR and DAC vs. CCR are the most prevalent comparisons.

Publication Characteristics

The characteristics of publication were listed in **Table 1**. Eight RCTs involved 2,184 patients with a median age of 71.1 years (IQR 68.4–73.8). Four RCTs involved a number of 1,221 patients compared to AZA (75 mg/m2/day for 7 days every 28-day cycle for at least six cycles) and the CCR, including BSC, LDA, and I. Four RCTs involving 963 patients compared DAC (15–20 mg/

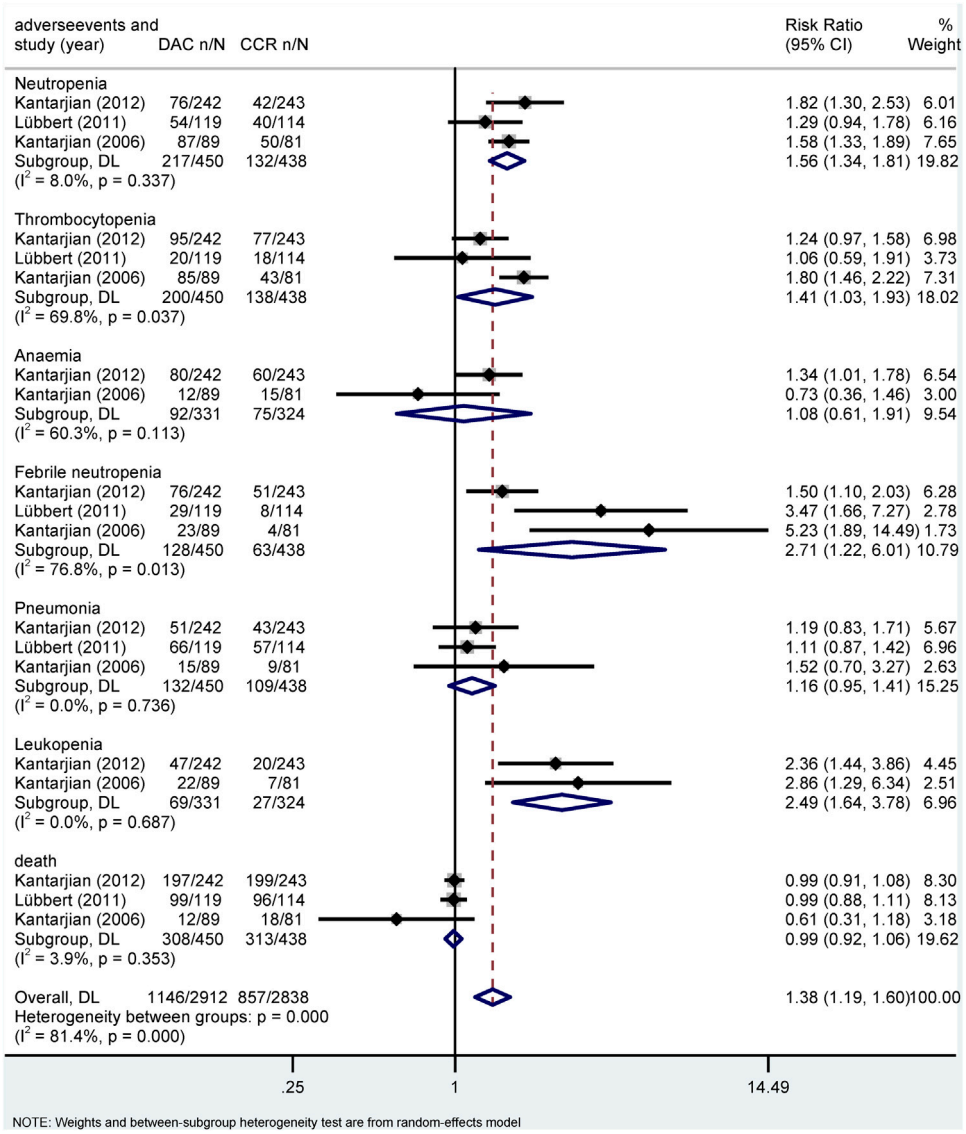

FIGURE 6 | Forest plot of efficacy represents the direct and indirect comparison.

m2/day for 3–5 days every 4 28-day cycles) to CCR. Among the eight RCTs, four were about the application of HMA in MDS, and four were in AML. According to IPSS scores, more than 70% of patients had intermediate-2 or high-risk MDS (Becker et al., 2015; Fenaux et al., 2009; Kantarjian et al., 2006; Lubbert et al., 2011; Inc E et al., 2014). The Eastern Cooperative Oncology Group (ECOG) performance status scores of patients from seven trials are between 0 and 2. For response data, all trials with MDS applied International Working Group (IWG) 2,000 response criteria (Cheson et al., 2000), and all trials with AML applied IWG 2004 response criteria (Creutzig and Kaspers, 2004). AEs were assessed with the National Cancer Institute's Common Toxicity Criteria, version 2.0/3.0. Grade 3–4 AEs are the main research (http://ctep.cancergov/reporting/ctc_archive.html).

Risk of Bias

The risk of bias among studies ranges from low and unclear to high. Random sequence generation was adequate in two trials, whereas allocation concealment was achieved in six trials and blinding of outcome assessor in two trials. In addition, selective reporting and incomplete outcome data were low risk in all trials. The graph and summary of the risk of bias are shown in **Figure 3**.

Assessment of Inconsistency

Inconsistency tests between direct and indirect estimates in AZA versus DAC were nonsignificant ($p > 0.05$), indicating that indirect estimates were not different to direct evidence. The estimation of NMA inconsistency between AZA and DAC was listed in **Supplementary Table S2**. The overall level of each treatment met the consistency assumption ($p > 0.05$).

TABLE 2 | Summary of the SUCRA of efficacy and high-grade side effects.

Outcome and data	AZA	DAC	CCR	*p*-value of the design-by-treatment test
Overall response rate	63.7	84.3	2.1	0.625
Complete remission	44.1	97.6	8.3	0.074
Partial remission	47.4	82.1	20.6	0.54
Complete remission with incomplete blood count recovery	6.39	85.9	0.2	0.553
Hematology improvement	64.7	55.4	29.8	0.876
Neutropenia	49.9	0.1	100	0.005
Thrombocytopenia	47.8	13	89.2	0.434
Anemia	96	4.9	49.1	0.037
Febrile neutropenia	97.1	0.3	62.7	0.009
Pneumonia	16.5	37.6	91.9	0.589
Leukopenia	86.6	0	63.4	0.002
Hypokalemia	82.8	24.7	42.5	0.324
Death	83	45.2	21.8	0.489

SUCRA, surface under the cumulative ranking curve.

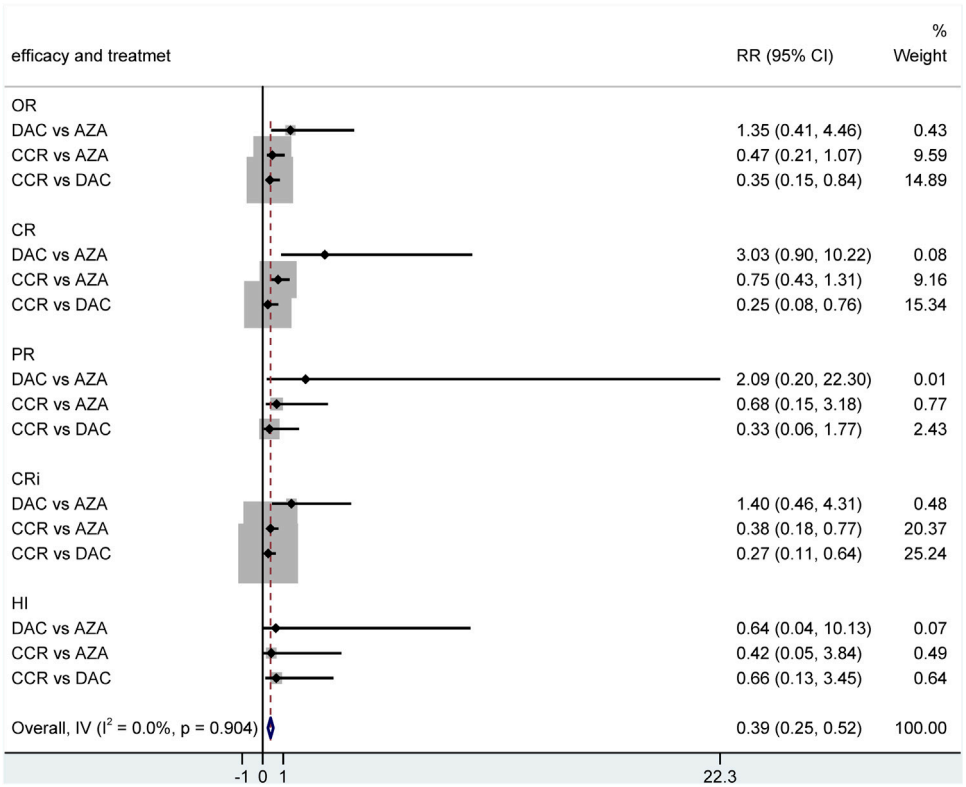

FIGURE 7 | Forest plot of grade 3/4 adverse events of azacitidine vs. conventional care regimens (direct evidence-RR).

Results of NMA

Comparison of Efficacy Between Decitabine and Azacitidine

The primary efficacy endpoints were OR, CR, PR, CRi, and HI rates. IWG 2000 response criteria were used in all patients with MDS, while IWG2003 response criteria were applied in patients with AML. Direct comparison of HMAs with CCR showed that AZA significantly increased the rates of OR (RR = 1.48, 95% CI 1.05–2.1) and CRi (HR = 2.52, 95% CI 1.27–5) (**Figure 4**), while DAC only increased the rate of OR (RR = 2.14, 95% CI 1.21–3.79) (**Figure 5**). Concerned about the high heterogeneity (I^2 > 50%), a subgroup analysis by disease type was estimated. In AML, AZA showed a higher CRi rate than CCR (RR = 2.52, 95% CI 1.27–5.00) (**Supplementary Figure S1**). In MDS, DAC significantly increased the PR rate than CCR (RR = 9.78, 95% CI 1.83–52.09) (**Supplementary Figure**

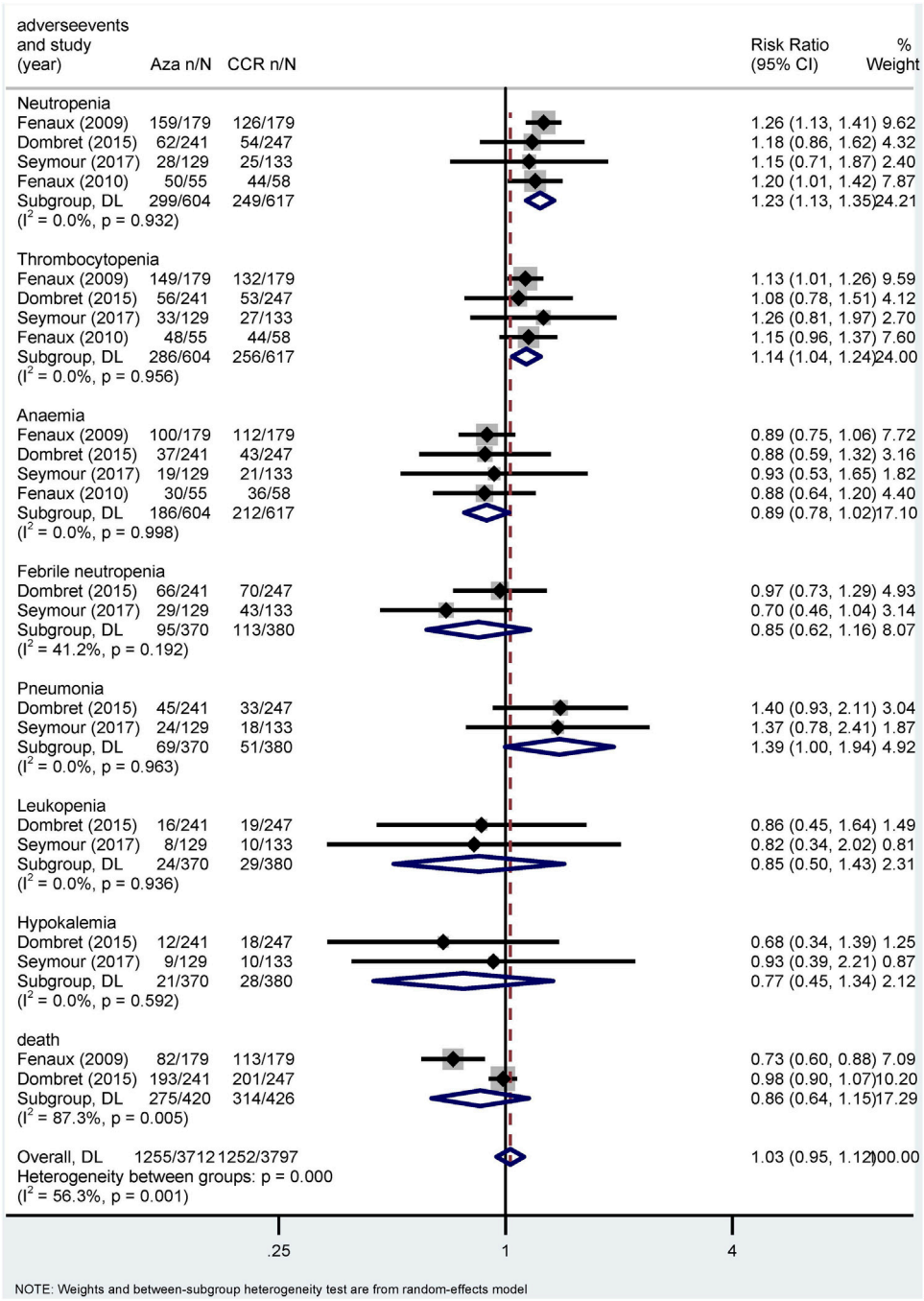

FIGURE 8 | Forest plot of grade 3/4 adverse events of decitabine vs. conventional care regimens (direct evidence-RR).

S4). There were no statistically significant differences in other outcomes.

For NMA, there were no statistically significant differences in terms of OR, CR, PR, CRi, and HI between DAC and AZA (**Figure 6**; **Table 2**). However, when performing subgroup analysis by disease type, DAC showed a higher CR rate than AZA both in AML (RR = 2.28, 95% CI 1.12–4.65) (**Supplementary Figure S3**) and in MDS (RR = 7.57, 95% CI 1.26–45.54) (**Supplementary Figure S6**).

Comparison of Grade 3/4 Adverse Events (HTEs) Between Decitabine and Azacitidine

Hematological toxicity was the most common adverse event in HMA treatment, which included leukopenia, neutropenia,

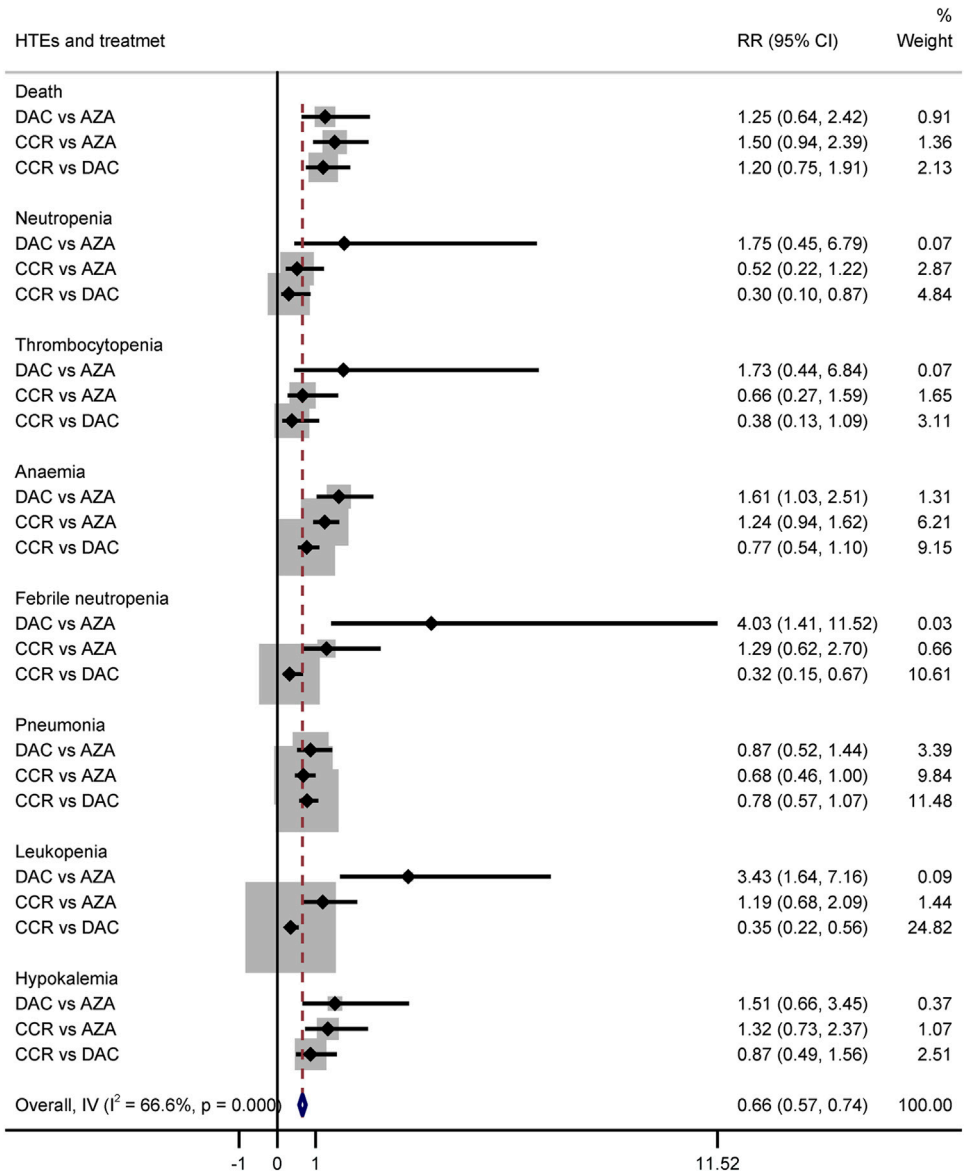

FIGURE 9 | Forest plot of grade 3/4 adverse events represents the direct and indirect comparison.

thrombocytopenia, anemia, and febrile neutropenia. Additionally, nonhematological adverse reactions such as pneumonia and hypokalemia also occurred in patients with HR-MDS or AML. In this study, a total of 2,135 patients from eight studies who received HMAs were included for analysis (Dombret et al., 2015; Fenaux et al., 2009; Fenaux et al., 2010; Kantarjian et al., 2006; Kantarjian et al., 2012; Lubbert et al., 2011; Seymour et al., 2017; Inc E et al., 2014). Subgroup of direct comparisons showed that, compared to CCR, AZA significantly increased the risk of grade 3/4 neutropenia (RR = 1.23, 95% CI: 1.13–1.35) and thrombocytopenia (RR = 1.14, 95% CI: 1.04–1.24) (**Figure 7**), and DAC increased the risk of grade 3/4 neutropenia (RR = 1.56, 95% CI: 1.34–1.81), thrombocytopenia (RR = 1.41, 95% CI: 1.03–1.93), febrile neutropenia (RR = 2.71, 95% CI: 1.22–6.01), and leukopenia (RR = 2.49, 95% CI: 1.64–3.78) (**Figure 8**). In AML, AZA significantly increased the risk of grade 3/4 neutropenia (RR = 1.19, 95% CI: 1.03–1.37) (**Supplementary Figure S2**). In MDS, DAC increased the risk of grade 3/4 neutropenia (RR = 1.50, 95% CI: 1.25–1.79), febrile neutropenia (RR = 4.00, 95% CI: 2.2–7.28), and leukopenia (RR = 2.86, 95% CI: 1.29–6.34) (**Supplementary Figure S5**). There was no statistically significant difference found in other studied outcomes.

The results of the indirect comparison of AZA and DAC showed that DAC significantly increased the risk of high-grade anemia (RR = 1.61, 95% CI: 1.03–2.51), febrile neutropenia (RR = 4.03, 95% CI: 1.41–11.52), and leukopenia (RR = 3.43, 95% CI: 1.64–7.16) compared with AZA (**Figure 9**). The results were the

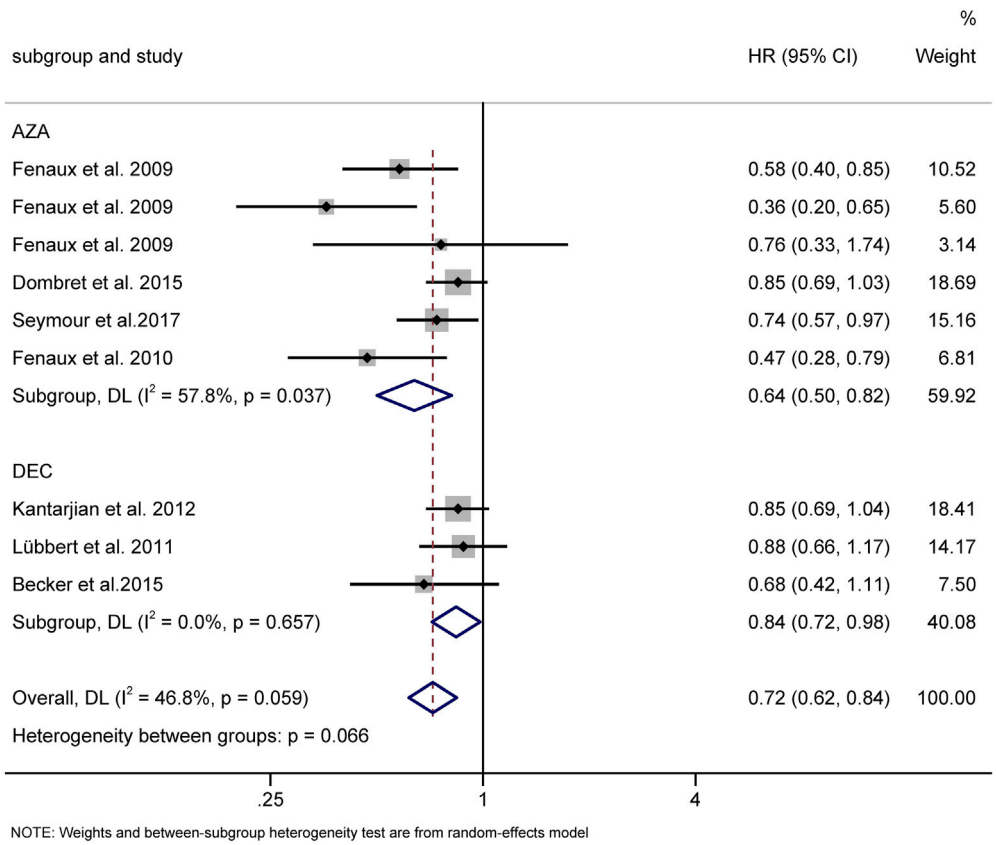

FIGURE 10 | Overall survival of AZA and DAC compared to CCR. AZA, azacitidine; Dec, decitabine; CCR, conventional care regimens.

same in patients with AML (**Supplementary Figure S3**). There was no statistical significance in the association of other HTEs in groups treated with DAC compared with AZA.

Comparison of Survival Between Decitabine and Azacitidine

Seven RCTs were available for the analysis of median OS for HMAs vs. CCR (Becker et al., 2015; Dombret et al., 2015; Fenaux et al., 2009; Fenaux et al., 2010; Kantarjian et al., 2012; Lubbert et al., 2011; Seymour et al., 2017). Compared with CCR, both AZA (HR = 0.64, 95% CI 0.50–0.82) and DAC (HR = 0.84, 95% CI 0.72–0.98) prolonged OS (**Figure 10**)

DISCUSSION

As common HMAs, AZA and DAC are widely used in clinical setting. Both of them have similar clinical effects. However, the clinical choice between them is controversial. In this systematic review and NMA, we aimed to evaluate the comparative efficacy and AEs of AZA and DAC in patients with HR-MDS and AML. In the direct comparisons of HMAs and CCR, we have demonstrated that both AZA and DAC are likely to have better outcomes compared to conventional care regimens (CCR) (including BSC, LDA, and IC) in terms of efficacy and OS. NMA comparisons between AZA and DAC showed that there were no statistically significant differences in efficacy, while the efficacy sorting showed that DAC demonstrated a higher CR rate than AZA in patients with both AML and MDS. Overall, it seems that there is no superiority of one agent over the other in terms of response rates. However, with regard to the safety profile, patients receiving DAC experienced more frequent grade 3/4 cytopenia especially anemia, febrile neutropenia, and leukopenia than patients receiving AZA treatment.

A previous systematic review and NMA published in 2018 compared both HMAs agents to CCR in patients with MDS and has identified four trials. The results showed that HMAs overall improved survival and time to transformation or death (Almasri et al., 2018). Zhang et al. (2021) recently reported a meta-analysis of HMAs for elderly patients with AML. The results showed that HMAs improved the OS and CR rate compared with CCR and also increased the incidence of neutropenia, thrombocytopenia, and pneumonia. Another recent systematic review and NMA identified 1,086 elderly patients with AML from three RCTs to indirectly compare the efficacy and safety of DAC and AZA. The direct comparisons results showed that AZA significantly reduced mortality, while DAC was not compared to CCR. The indirect head-to-head comparisons showed that AZA significantly reduced the mortality rate and anemia. Patients treated with AZA were more likely to achieve CR compared to

DAC (Wen et al., 2020). Liu et al. (2021) recently published an NMA which identified six RCTs with 1,072 MDS patients and three RCTs with 1,256 AML patients treated with HMAs. The results showed that, in MDS, AZA showed better AML-free survival, whereas DAC demonstrated higher CR and ORR, and AZA obtained better OS with lower toxicity. In AML, DAC had the possibility of achieving superior CR, ORR, and OS, while the toxicity was relatively higher. Taking these results together, all of the direct comparisons between HMAs and CCR are consistent with our findings. However, for the indirect comparisons of AZA and DAC, both of Almasri et al. (2018) and Wen et al. (2020)'s NMAs showed that AZA was more likely to improve CR compared to DAC, despite being with low-certainty evidence. This was different from our analysis. Our study showed that DAC had the possibility of achieving superior OR, CR, PR, and CRi than AZA, but there were no statistically significant differences in all response rates between the DAC and AZA groups. This finding is consistent with Zhang et al. (2021) and Liu et al.'s studies and a retrospective study of AZA versus DAC in patients with refractory anemia with excess blast (Salim et al., 2016). These differences can be interpreted as follows: a) heterogeneity and publication bias could not be obtained because of the small number of trials investigating each agent; b) our study mainly focused on higher-risk MDS and AML patients, while the previous study included all risk-stratified MDS patients, and the influence of different risk-stratified subgroups cannot be ruled out.

As for the comparisons of high grades AEs for AZA and DAC, previous retrospective studies indicated that patients who received AZA experienced less frequent episodes of grade 3/4 cytopenia and infectious episodes than DAC (Lee et al., 2013a; Lee et al., 2013b). Lee et al. reported more grade 3/4 cytopenia (87 vs. 67%, respectively) and infectious episodes in the DAC group (15.7 cytopenia episodes per 100 cycles vs. 11.8 infectious episodes per 100 cycles) (Lee et al., 2013b). Likewise, Je-Hwan Lee et al. found that high-grade neutropenia occurred more frequently in the DAC group than the AZA group (79.6 vs. 72.2%) (Lee et al., 2013a). Similarly, in our study, DAC demonstrated a higher risk of grade 3/4 anemia, leukopenia, and febrile neutropenia compared with AZA. In our study, we find that, compared with CCR, HMAs demonstrated higher grade 3/4 cytopenia and infectious episodes. This finding is consistent with Gao et al. (2018)'s study.

However, no randomized trial has been ever conducted directly to compare AZA and DAC in AML patients, and a rare randomized trial has been carried out for higher-risk MDS patients. The overwhelming majority of RCTs included in this study were indirect comparisons, and low certainty of the evidence was found when comparing AZA and DAC. Therefore, more head-to-head clinical trials are still required. Additionally, given the limited number of included trials, heterogeneity, network consistency, and publication bias could not be adequately assessed. In studies of MDS patients, we mainly included studies with HR-MDS of more than 60%. Data of some lower-risk patients were also included. This may lead to bias in the results. Optimally, a risk stratification model could be developed to analyze the effects of HMAs in different risk groups. Subgroup analysis could not be assessed due to the paucity of data. This analysis was not robust to sensitivity analyses based on meta-analysis model choice.

CONCLUSION

Compared to CCR, AZA and DAC can promote outcomes in patients with AML and HR-MDS. In patients with MDS, DAC demonstrated a higher CR rate than AZA. There were no statistically significant differences between DAC and AZA in other outcomes and in patients with AML. However, AZA experienced lower frequent grade 3/4 leukopenia than patients receiving DAC treatment. For patients with AML or HR-MDS who are unfit for IC or HSCT, both AZA and DAC are available to use. Concerned about the lower hematological toxicity, AZA may be a better choice for elderly patients. However, the available indirect evidence comparing the two agents warrants very low certainty and cannot reliably confirm the superiority of either agent. More head-to-head prospective randomized clinical trials are needed. In the meantime, the choice of either agent should be driven by patients' preferences, drug availability, and costs.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

JM and ZG reviewed the references. JM performed data analysis and wrote the manuscript. ZG supervised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.701690/full#supplementary-material

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Gender Disparities in Anti-dementia Medication Use among Older Adults: Health Equity Considerations and Management of Alzheimer's Disease and Related Dementias

Z. Kevin Lu[1]*, *Xiaomo Xiong*[1], *Xinyuan Wang*[2] and *Jun Wu*[3]

[1]Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina, Columbia, SC, United States, [2]Key Laboratory of Cardiovascular and Cerebrovascular Medicine, School of Pharmacy, Nanjing Medical University, Nanjing, China, [3]Department of Pharmaceutical and Administrative Sciences, Presbyterian College School of Pharmacy, Clinton, SC, United States

Objective: The prevalence of Alzheimer's disease and related dementias (ADRD) in women is higher than men. However, the knowledge of gender disparity in ADRD treatment is limited. Therefore, this study aimed to determine the gender disparities in the receipt of anti-dementia medications among Medicare beneficiaries with ADRD in the U.S.

Methods: We used data from the Medicare Current Beneficiary Survey 2016. Anti-dementia medications included cholinesterase inhibitors (ChEIs; including rivastigmine, donepezil, and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (including memantine). Descriptive analysis and multivariate logistic regression models were implemented to determine the possible gender disparities in the receipt of anti-dementia medications. Subgroup analyses were conducted to identify gender disparities among beneficiaries with Alzheimer's disease (AD) and those with only AD-related dementias.

Results: Descriptive analyses showed there were statistically significant differences in age, marital status, and Charlson comorbidities index (CCI) between Medicare beneficiaries who received and who did not receive anti-dementia medications. After controlling for covariates, we found that female Medicare beneficiaries with ADRD were 1.7 times more likely to receive anti-dementia medications compared to their male counterparts (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.19–2.45). Specifically, among Medicare beneficiaries with AD, females were 1.2 times more likely to receive anti-dementia medications (Odds Radio: 1.20; 95% confidence interval: 0.58–2.47), and among the Medicare beneficiaries with only AD-related dementias, females were 1.9 times more likely to receive anti-dementia medications (OR: 1.90; 95% CI: 1.23–2.95).

Conclusion: Healthcare providers should be aware of gender disparities in receiving anti-dementia medications among patients with ADRD, and the need to plan programs of care to support both women and men. Future approaches to finding barriers of prescribing,

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Ria Benko,
University of Szeged, Hungary

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Mayo Clinic, United States
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***Correspondence:**
Z. Kevin Lu
lu32@email.sc.edu

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receiving and, adhering to anti-dementia medications by gender should include differences in longevity, biology, cognition, social roles, and environment.

Keywords: alzheimer's disease and related diseases, ADRD, anti-dementia medications, gender disparities, medicare

BACKGROUND

Alzheimer's disease and related dementias (ADRD) are typical neurodegenerative diseases, including Alzheimer's disease (AD) and common AD-related dementias, such as Lewy body dementia, vascular dementia, and mild cognitive impairment (Galasko et al., 1994; Deb et al., 2017). ADRD are characterized by a decline in memory leading to loss of daily activities and the fifth leading cause of death among the adults aged 65 years or older in the U.S. (Galasko et al., 1994; Deb et al., 2017; Matthews et al., 2019). According to *2019 Alzheimer's disease facts and figures*, the total number of Alzheimer's patients was more than five million in 2019 and is expected to increase to 13.8 million by 2050 in the United States (US) (Alzheimer's Association, 2019). The total annual costs of patients with ADRD are projected to increase to more than 1.1 trillion in 2050 in the US, with a fourfold increase in government spending under Medicare and Medicaid in the U.S (Alzheimer's Association, 2019). Since there is still no treatment for curing ADRD currently, slowing the progression of ADRD is crucial to reducing the burden of patients (Hampel et al., 2018; McMichael et al., 2020).

Anti-dementia medications are a class of drugs used to slow the progression of ADRD (Anand et al., 2017; McMichael et al., 2020). To date, the anti-dementia medications approved by the US Food and Drug Administration (FDA) can be divided into two categories, including cholinesterase inhibitors (ChEIs; including rivastigmine, donepezil, and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonists (including memantine) (Anand et al., 2017). Several reviews show that many randomized controlled trials (RCTs) have confirmed the effectiveness of these drugs in improving cognitive, behavioral problems, and neuropsychiatric symptoms (Birks, 2006; Winblad et al., 2007; van de Glind et al., 2013). A study also shows that persistent treatment with anti-dementia medications can slow the clinical progression of ADRD (Rountree et al., 2009). The clinical guidelines for anti-dementia medications recommend that cholinesterase inhibitors are effective for mild to moderate ADRD, while memantine is helpful for moderate to severe ADRD (O'Brien et al., 2017).

Gender disparities have always been an unresolved issue in patients with ADRD. Evidence has documented differences between men and women in terms of brain structure and function over the lifespan (Azad et al., 2007; Cosgrove et al., 2007; Mielke et al., 2014), and proposed some part of the mechanism for explaining the gender imbalance in ADRD, including biological explanation (genetics, hormones) and social explanation (education, occupation, cognitive activity) (Azad et al., 2007; Cosgrove et al., 2007; Mielke et al., 2014). Also, studies show that the prevalence of women with ADRD is significantly higher than that of men (Winblad et al., 2016; Alzheimer's Disease International, 2015). Medicare is a federal health insurance program for people who are 65 or older, certain younger people with disabilities, and people with End-Stage Renal disease (Centers for Medicare and Medicaid Services, 2021a). Given that females constitute the majority of Medicare beneficiaries (National Committee to Preserve Social Security and Medicare, 2021), and that anti-dementia drugs are perennially in the top 15 therapeutic classes of drugs covered under Part D (Koller et al., 2016), it's critical to understand the gender disparities in the receipt of anti-dementia medications among Medicare beneficiaries with ADRD. However, to date, little evidence has investigated the gender disparities among the beneficiaries with ADRD.

This study used a nationally representative database to determine the gender disparities in the receipt of anti-dementia medications among Medicare beneficiaries with ADRD. Given that evidence has shown that females are more likely to use preventive care services compared to males (Vaidya et al., 2012; Owens, 2018), we hypothesized that compared to male Medicare beneficiaries with ADRD, those female beneficiaries are more likely to receive anti-dementia medications.

METHODS

Study Design and Data Source

We conducted a retrospective cross-sectional study to determine gender disparities in the receipt of anti-dementia medications among Medicare beneficiaries. Data were derived from the Medicare Current Beneficiary Survey (MCBS) in 2016. MCBS is a nationally comprehensive and authoritative survey of Medicare beneficiaries, which is sponsored by the Centers for Medicare and Medicare Services (CMS) (Adler, 1994; Centers for Medicare and Medicaid Services, 2021b). The core purpose of MCBS is to help CMS manage the Medicare program and understand the health and welfare of beneficiaries (Adler, 1994; Centers for Medicare and Medicaid Services, 2021b). The MCBS sample is selected from Medicare Administrative Enrollment (MAE) data using a rotating panel design that tracks each beneficiary up to 4 years with 12 interviews (Adler, 1994; Centers for Medicare and Medicaid Services, 2021b). When participants are no longer able to conduct in-person interviews due to unconsciousness, they can name proxy respondents to answer survey questions on their behalf. MCBS releases three data set annually, which collect a wealth of information about Medicare beneficiaries' demographic characteristics, insurance, health status, and the usage and cost of all medical services (Adler, 1994; Centers for Medicare and Medicaid Services, 2021b). Then the information is merged with

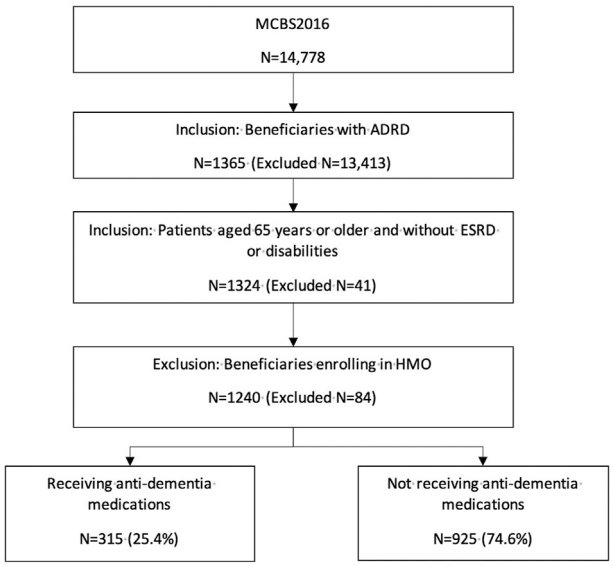

FIGURE 1 | Flowchart of study population selection.

Medicare part A and B claims and finally formed a continuous, multi-purpose survey (Adler, 1994; Centers for Medicare and Medicaid Services, 2021b).

Study Population

Prevalent patients with ADRD aged 65 years or older were identified if any of their claims between January 1, 2016, through December 31, 2016 included the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for AD and AD-related dementias. Specifically, the ICD-10 CM codes for AD was G30. AD-related dementias included Lewy-body associated dementia (G31.83), mild cognitive impairment (G31.84), frontotemporal dementia (G31.0), vascular dementia (F01), and non-specific dementias (G31.1, F00, F02, F03, F05.1). These codes were derived from the chronic conditions data warehouse algorithms (Gorina and Kramarow, 2011).

We excluded participants who were eligible for the Medicare program due to end-stage renal disease (ESRD) or disability, and those who joined the Health Maintenance Organization (HMO) during the study period.

Measures

Anti-dementia medications were identified based on the U.S. FDA's prescription database (U.S. Food and Drug Administration, 2021). The FDA's prescription database covers all drugs that have been approved by the FDA to be marketed in the US cholinesterase inhibitors included rivastigmine, donepezil, galantamine, and memantine is the only available NMDA receptor antagonist (Rountree et al., 2009; U.S. Food and Drug Administration, 2021). MCBS participants who received anti-dementia medications were identified if they had at least one prescription of cholinesterase inhibitors and the NMDA receptor antagonists in the study period.

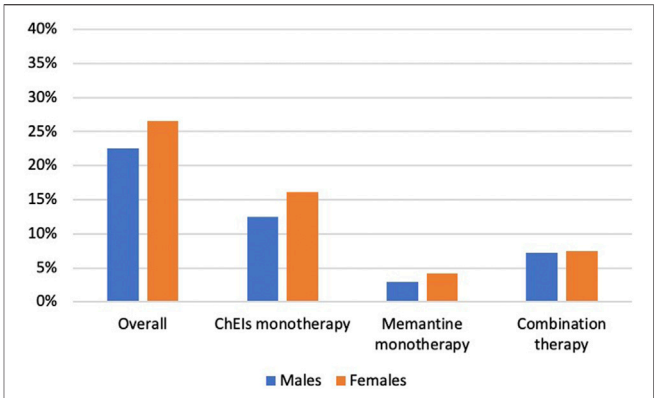

FIGURE 2 | Proportion of the receipt of different types of anti-dementia medications by gender. ADRD: Alzheimer's diseases and related dementias; AD: Alzheimer's disease; ChEIs: cholinesterase inhibitors.

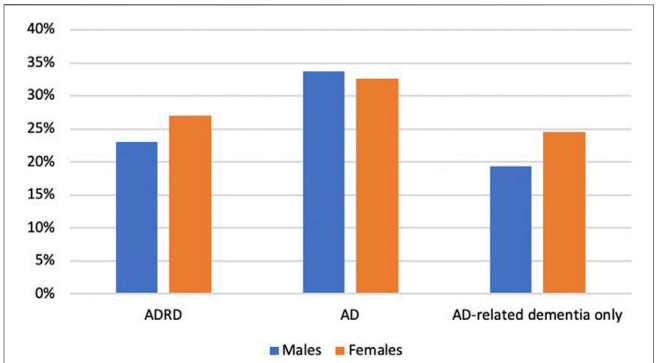

FIGURE 3 | Proportion of the receipt of different types of anti-dementia medications by types of ADRD: Alzheimer's diseases and related dementias; AD: Alzheimer's disease; ChEIs: cholinesterase inhibitors.

Covariates were based on previous research on similar topics using MCBS (Bhattacharjee et al., 2012; Brown-Guion et al., 2013; Lee and Khan, 2016). We extracted demographic, socioeconomics, and health-related factors used as covariates. Demographic factors included age (≥65 and <75, ≥75 and <85, and ≥85), race (Hispanic Caucasian, Non-Hispanic African American, Hispanic, and others), marital status (married and non-married), living county (non-Rural, micropolitan, and metropolitan), census region (Northeast, North central/Midwest, South, and West), and educational attainment (<High school graduate, high school graduate, > high school graduate). Socioeconomic factors included income (<$25,000, ≥ $25,000 and < $50,000, ≥ $50,000 and < $75,000, and ≥ $75,000). Health-related factors included Charlson comorbidity index (CCI; 0, 1, 2, ≥3). Specifically, both demographic and socioeconomic factors were identified based on the MCBS's survey data, while the CCI was calculated based on Medicare claims (Formiga et al., 2009).

Statistical Analysis

Descriptive analysis was used to compare the difference in the characteristics between users and non-users of anti-dementia medications among Medicare beneficiaries with ADRD. Chi-

square tests were used to compare the difference in the categorical variables. Multivariate logistic regression models were used to estimate the association between gender and the receipt of anti-dementia medications after controlling for covariates. We also conducted two subgroup analyses, one for beneficiaries with AD and the other for those with only AD-related dementias. SAS software (version 9.4; Statistical Analysis Systems, NC, USA) was used to perform the statistical analyses, and the level of statistical significance was set at $p < 0.05$.

RESULTS

1,240 Medicare beneficiaries with ADRD were identified out of 14,778 beneficiaries in MCBS 2016 based on the inclusion and exclusion criteria (**Figure 1**). Among the beneficiaries with ADRD, 315 (25.4%) received anti-dementia medications, and 925 (74.6%) did not receive. A total of 85 (22.6%) males received anti-dementia medications, compared with 230 (26.6%) in females. Specifically, the proportion of the receipt of ChEIs monotherapy was 12.5% among males and 16.1% among females, the proportion of the receipt of memantine monotherapy was 2.9% among males and 4.2% among females. The proportion of combination therapy was 7.2% among males and 7.4% among females (**Figure 2**). In addition, 29 out of 86 (33.7%) male patients with AD received anti-dementia medications, while it was 72 out of 221 (32.6%) among females. Meanwhile, 56 out of 290 (19.3%) male patients with AD-related dementias received the medications, and it was 158 out of 643 (24.6%) among female patients (**Figure 3**). According to **Table 1**, Compared to those who did not receive anti-dementia medications, Medicare beneficiaries with ADRD who received the medication were more likely to be aged between 75 and 85 years ($p = 0.006$), not married ($p = 0.032$), and have fewer comorbidities ($p = 0.007$).

After controlling for covariates, female Medicare beneficiaries with ADRD were 1.7 times more likely to receive anti-dementia medications compared to males (odds ratio [OR]: 1.71; 95%

TABLE 1 | Base-line demographics and comparison.

Factors	Non-users N = 925, no	%	Users N = 315, no	%	*p*-value
Gender					0.136
Male	291	31.5	85	27.0	
Female	634	68.5	230	73.0	
Age					0.006
≥65 and <75	91	9.8	31	9.8	
≥75 and <85	273	29.5	123	39.0	
≥85	561	60.6	161	51.1	
Marital status					0.032
Married	658	71.9	205	65.5	
Non married	257	28.1	108	34.5	
Race					0.535
Non-Hispanic Caucasian	777	86.6	267	87.8	
Non-Hispanic African American	90	10.0	24	7.9	
Hispanic	30	3.3	13	4.3	
Others	35	3.9	31	10.2	
Living county					0.146
Rural	65	7.0	17	5.4	
Micropolitan	138	14.9	61	19.4	
Metropolitan	722	78.1	237	75.2	
Census Region					0.094
Northeast	178	19.3	63	20.0	
North Central/Midwest	210	22.8	83	26.3	
South	380	41.2	134	42.5	
West	155	16.8	35	11.1	
Education					0.379
< High school graduate	176	24.9	77	29.2	
High school graduate	363	51.4	131	49.6	
> High school graduate	167	23.7	56	21.2	
Family income					0.374
< $25,000	584	67.0	186	62.4	
≥ $25,000 and < $50,000	153	17.6	65	21.8	
≥ $50,000 and < $75,000	92	10.6	34	11.4	
≥ $75,000	42	4.8	13	4.4	
CCI					0.007
0	135	14.6	50	15.9	
1	251	27.1	115	36.5	
2	197	21.3	57	18.1	
≥3	342	37.0	93	29.5	

CCI: Charlson comorbidity index.

TABLE 2 | Results of logistic regression among beneficiaries with ADRD (N = 1,240).

Variables	OR	Lower limit	Upper limit
Gender			
Male	Ref		
Female	1.71	1.19	2.45
Age			
≥65 and <75	Ref		
≥75 and <85	1.29	0.76	2.21
≥85	0.77	0.45	1.30
Marital status			
Married	Ref		
Non married	1.27	0.88	1.82
Race			
Non-Hispanic Caucasian	Ref		
Non-Hispanic African American	0.77	0.44	1.36
Hispanic	1.35	0.61	2.99
Others	2.13	0.91	5.03
Living county			
Rural	Ref		
Micropolitan	1.64	0.82	3.27
Metropolitan	1.36	0.72	2.55
Census region			
Northeast	Ref		
North Central/Midwest	1.20	0.76	1.90
South	0.99	0.64	1.51
West	0.69	0.39	1.22
Education			
< High school graduate	Ref		
High school graduate	0.79	0.54	1.15
> High school graduate	0.62	0.38	1.02
Family income			
< $25,000	Ref		
≥ $25,000 and < $50,000	1.41	0.95	2.11
≥ $50,000 and < $75,000	1.23	0.75	2.02
≥ $75,000	1.04	0.47	2.30
CCI			
0	Ref		
1	1.37	0.87	2.15
2	0.70	0.41	1.17
≥3	0.65	0.41	1.04

The ref group represents the row in the variable column.
ADRD: Alzheimer's disease and related dementias; CCI: Charlson comorbidity index; OR: Odds ratio; Ref: Reference.

confidence interval [CI]: 1.19–2.45; **Table 2**). 307 and 933 Medicare beneficiaries with AD and AD-related dementias only were identified for subgroup analysis, respectively. According to **Table 3**, Among Medicare beneficiaries with AD, compared to males, females were 1.2 times more likely to receive anti-dementia medications, however, it's not statistically significant (OR: 1.20; 95% CI: 0.58–2.47). Based on **Table 4**, among the group of Medicare beneficiaries with only AD-related dementias, compared to males, females were 1.9 times more likely to receive anti-dementia medications (OR: 1.90; 95% CI: 1.23–2.95). The goodness of fit of each regression model can be found in **Supplementary Material**.

DISCUSSION

This study analyzed nationally representative data on 1,240 Medicare beneficiaries with ADRD aged 65 years or older to investigate gender disparities in the receipt of anti-dementia medications. Our study found gender disparities in the receipt of anti-dementia medications among Medicare beneficiaries with ADRD. Specifically, female Medicare beneficiaries with ADRD are 1.7 times more likely to receive anti-dementia medications compared to their male counterparts.

The overall proportion of the receipt of anti-dementia medications was 26.1%, which was consistent with a previous study using Medicare claims that found 26% of patients with ADRD receiving at least one anti-dementia medication (Zuckerman et al., 2008). However, compared to some studies conducted in countries other than the US, the prevalence of using anti-dementia medications in our study is relatively low. A cross-sectional study in Finland found that 69% of patients in home care and residential care with dementia used anti-dementia medications (Kuronen et al., 2015). In a registry-based study in Sweden, more than 80% of AD patients used anti-dementia drugs, and in another study using registry in Spain, more than

TABLE 3 | Results of logistic regression among beneficiaries with AD (N = 307).

Variables	OR	Lower limit	Upper limit
Gender			
Male	Ref		
Female	1.20	0.58	2.47
Age			
≥65 and <75	Ref		
≥75 and <85	1.18	0.37	3.77
≥85	0.48	0.15	1.55
Marital status			
Married	Ref		
Non married	0.82	0.39	1.72
Race			
Caucasian	Ref		
African American	0.88	0.33	2.35
Hispanic	0.98	0.39	2.45
Asian	0.77	0.25	2.42
Living county			
Rural	Ref		
Micropolitan	5.55	1.11	27.62
Metropolitan	2.74	0.62	12.19
Census region			
Northeast	Ref		
North Central/Midwest	0.88	0.33	2.35
South	0.98	0.39	2.45
West	0.77	0.25	2.42
Education			
< High school graduate	Ref		
High school graduate	0.72	0.32	1.59
> High school graduate	0.69	0.25	1.95
Family income			
< $25,000	Ref		
≥ $25,000 and < $50,000	1.98	0.81	4.83
≥ $50,000 and < $75,000	1.44	0.54	3.86
≥ $75,000	1.01	0.20	5.14
CCI			
0	Ref		
1	2.38	0.95	5.96
2	0.79	0.28	2.26
≥3	0.62	0.23	1.65

The ref group represents the row in the variable column.
AD: Alzheimer's disease; CCI: Charlson comorbidity index; OR: Odds ratio; Ref: Reference.

TABLE 4 | Results of logistic regression among beneficiaries with AD-related dementias (N = 993).

Variables	OR	Lower limit	Upper limit
Gender			
Male	Ref		
Female	1.90	1.23	2.95
Age			
≥65 and <75	Ref		
≥75 and <85	1.20	0.64	2.24
≥85	0.85	0.46	1.57
Marital status			
Married	Ref		
Non married	1.42	0.92	2.20
Race			
Caucasian	Ref		
African American	0.72	0.37	1.40
Hispanic	0.76	0.26	2.22
Asian	1.94	0.72	5.20
Living county			
Rural	Ref		
Micropolitan	1.34	0.61	2.96
Metropolitan	1.21	0.59	2.46
Census region			
Northeast	Ref		
North Central/Midwest	1.30	0.77	2.22
South	0.95	0.58	1.56
West	0.57	0.28	1.15
Education			
< High school graduate	Ref		
High school graduate	0.75	0.48	1.17
> High school graduate	0.56	0.31	1.02
Family income			
< $25,000	Ref		
≥ $25,000 and < $50,000	1.33	0.83	2.12
≥ $50,000 and < $75,000	1.16	0.63	2.12
≥ $75,000	1.16	0.46	2.97
CCI			
0	Ref		
1	1.14	0.66	1.96
2	0.60	0.32	1.13
≥3	0.65	0.37	1.12

The ref group represents the row in the variable column.
AD: Alzheimer's disease; CCI: Charlson comorbidity index; OR: Odds ratio; Ref: Reference.

50% of dementia patients were found receiving anti-dementia medications (Johnell et al., 2008; Avila-Castells et al., 2013). The reasons for such low prescribing rates in the United States are unclear and might require future research to investigate.

Our results do not explain why female Medicare beneficiaries with ADRD are more likely to receive anti-dementia medications. We posit that this could reflect the notion that the prevalence of ADRD is higher in women and that women are at a greater risk compared to men (Mielke et al., 2014). About two-thirds of patients diagnosed with AD dementia are women, and healthcare providers focus too much on female patients with ADRD despite evidence showing that there is no sex or gender difference in risk factors or mechanisms (Mazure and Swendsen, 2016). In addition, over the past few decades, the improvement in education and careers in women may have led to female patients being more willing to receive primary care and medications (Matthews et al., 2013; Langa et al., 2017). An article has demonstrated that women tend to use more services and spend more health care costs than men, and men often have insufficient awareness of medical treatment (Owens, 2018). It is also important to note that men and women may respond differently to anti-dementia medications, some systematic reviews have confirmed the importance of controlling the symptoms of patients with ADRD (Fox et al., 2012; Matsunaga et al., 2014). Evidence from observational studies has shown that in the treatment of donepezil and rivastigmine, the response of female patients is significantly better than that of male patients (Scacchi et al., 2014). The perception of a higher benefit from anti-dementia medications in female patients compared with male patients with ADRD may determine the gender disparities in receiving anti-dementia medications.

Although we found significant gender disparities in the receipt of anti-dementia medications among patients with ADRD and those with only AD-related dementia, there were no significant disparities among patients with AD. Among patients with AD, the proportion of males and females receiving anti-dementia medications was 33.7 and 32.6%, respectively. Meanwhile, the proportion of patients with AD receiving anti-dementia medication was higher than that of patients with only AD-related dementia. Patients with AD were more likely to be recommended for medications by their physicians than those with only AD-related dementias only. In this case, the gender difference might be reduced. In addition, there were no gender disparities in the receipt of anti-dementia medication before controlling for covariates. However, although we found no significant association between receipt of anti-dementia medication and any covariate, gender disparities emerged after controlling for covariates using multivariate logistic regression, implying that some covariates may have an impact on the receipt of antidementia medications. Future research should focus on identifying influential predictors of receipt of anti-dementia medications among patients with ADRD.

Gender disparities combine environmental, social, and cultural differences between women and men (Institute of Medicine (US) et al., 2001), which indicates that the gender disparities in ADRD are not only on biological factors, but also on education, nursing, and psychological health (Nebel et al., 2018). More and more evidence has indicated that sex and gender will affect the etiology, performance, and treatment results of many diseases. Compared with other medical fields such as cardiovascular disease, research on gender differences in ADRD is still in its infancy. Salim S. Virani et al. have found that a better understanding of gender differences can improve the care and treatment of patients with cardiovascular disease (Virani et al., 2015). We speculate that the same positive results may occur for patients with ADRD.

To our knowledge, this study is the first research to determine the gender disparities of Medicare beneficiaries in receiving anti-dementia medications. The anti-dementia medications included in our study are in line with the recommendation of the latest available treatment guideline for AD in the US (Winslow et al., 2011). Our study can provide important information for ADRD patients, healthcare providers, and policymakers in future clinical practice. First, special attention by healthcare providers or family caregivers

should be given to male patients with ADRD and increase the use of anti-dementia drugs, as they are more likely to ignore their health status and spend less money on healthcare compared with their female counterparts (Langa et al., 2017). In future clinical practice, strategies such as increasing home care providers, education by emphasizing the importance of being adherent to anti-dementia drugs for male patients can be considered. Secondly, our findings from this study warrant the need to plan programs of care to support both women and men living with ADRD, their families, and their communities. Also, identifying where there are differences provides the potential for better treatment and care for both women and men. Finally, observational studies on the response of men and women to anti-dementia drugs are still controversial, Gallucci M (Gallucci et al., 2016) and Wattmo C's (Wattmo et al., 2011) studies have pointed out that the response to cholinesterase inhibitors treatment and longitudinal cognitive outcomes were better in males, while Haywood WM et al. indicated there is no significant sex difference (Haywood and Mukaetova-Ladinska, 2006). On the other hand, there is no data on sex-related pharmacokinetic anti-dementia medications. Overall, whether and how gender affects the effectiveness and safety of anti-dementia medications needs further studies and we should increase efforts to collect data on gender disparities, such as in post-marketing surveillance studies (Clerici et al., 2012).

However, this study also has several limitations. First, in order to achieve a sample size that is sufficient to detect the effect size, we did not include some health-related covariates with too many missing values, such as body mass index (BMI), difficulty in activities of daily living (ADL), and instrumental activities of daily living (IADL). Second, this study was unable to measure the disease severity of cognitive impairment due to a lack of related information, which may influence anti-dementia drug use. Third, the results of this study only reflected the prescribing patterns of anti-dementia medication in older patients covered by Medicare in the US. The conclusion might not be generalized to other US populations covered by other public or private insurance plans and populations in other countries. Finally, due to the cross-sectional design, we could not draw a causal conclusion on the receipt of anti-dementia medication between male and female Medicare beneficiaries with ADRD.

CONCLUSION

In conclusion, our study found that gender disparities exist in the receipt of anti-dementia medications among Medicare beneficiaries with ADRD. Gender is rooted in biology, but it is primarily shaped by environment and experience. Healthcare providers should understand the gender disparities in receipt of anti-dementia drugs and provide interventions to improve prescribing patterns and patient adherence, not only on biological gender, but also on education, nursing, and psychological health factors.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: MCBS is Available for purchase from CMS after execution of an approved data use agreement. Requests to access these datasets should be directed to https://www.cms.gov/research-statistics-data-and-systems/research/mcbs.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Concept and design: KL, XX Acquisition, analysis, and/or interpretation of data: KL, XX and JW Drafting of the manuscript: KL, XX and XW. Critical revision of the manuscript for important intellectual content: KL Statistical analysis: XX.

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SUPPLEMENTARY MATERIAL

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Older Age, Polypharmacy, and Low Systolic Blood Pressure Are Associated With More Hypotension-Related Adverse Events in Patients With Type 2 Diabetes Treated With Antihypertensives

Martina Ambrož[1], Sieta T. de Vries[1], Klaas Hoogenberg[2] and Petra Denig[1]*

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]Department of Internal Medicine, Martini Hospital, Groningen, Netherlands

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Fabiane Raquel Motter, University of Sorocaba, Brazil

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***Correspondence:**
Martina Ambrož
m.ambroz@umcg.nl

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Background and Aims: Low systolic blood pressure (SBP) levels while being treated with antihypertensives may cause hypotension-related adverse events (hrAEs), especially in the elderly, women, and frail patients. We aimed to assess the association between the occurrence of hrAEs and low SBP levels, age, sex, and polypharmacy among patients with type 2 diabetes (T2D) treated with antihypertensives.

Methods: In this cohort study, we used the Groningen Initiative to ANalyse Type 2 diabetes Treatment (GIANTT) database which includes patients managed for T2D in primary care from the north of the Netherlands. Patients treated with ≥1 antihypertensive drug and ≥1 SBP measurement between 2012 and 2014 were included. The outcome was the presence of an hrAE, i.e. postural hypotension, dizziness, weakness/tiredness, and syncope in 90 days before or after the lowest recorded SBP level. Age (≥70 vs. <70 years), sex (women vs. men), polypharmacy (5–9 drugs or ≥10 drugs vs. <5 drugs), and SBP level (<130 or ≥130 mmHg) were included as determinants. Logistic regression analyses were conducted for age, sex and polypharmacy, including the SBP level and their interaction, adjusted for confounders. Odds ratios (OR) with 95% confidence intervals (CI) are presented.

Results: We included 21,119 patients, 49% of which were ≥70 years old, 52% were women, 57% had polypharmacy, 61% had an SBP level <130 mmHg and 5.4% experienced an hrAE. Patients with an SBP level <130 mmHg had a significantly higher occurrence of hrAEs than patients with a higher SBP level (6.2 vs. 4.0%; ORs 1.41, 95%CI 1.14–1.75, 1.43, 95%CI 1.17–1.76 and 1.33, 95%CI 1.06–1.67 by age, sex, and polypharmacy, respectively). Older patients (OR 1.29, 95%CI 1.02–1.64) and patients with polypharmacy (OR 5–9 drugs 1.27, 95%CI 1.00–1.62; OR ≥10 drugs 2.37, 95% CI 1.67–3.37) were more likely to experience an hrAE. The association with sex and the interactions between the determinants and SBP level were not significant.

Conclusion: Low SBP levels in patients with T2D treated with antihypertensives is associated with an increase in hrAEs. Older patients and those with polypharmacy are particularly at risk of hrAEs. Age, sex, and polypharmacy did not modify the risk of hrAEs associated with a low SBP level.

Keywords: type 2 diabetes, systolic blood pressure, adverse events, elderly, sex differences, polypharmacy, overtreatment

INTRODUCTION

Blood pressure targets for patients with type 2 diabetes (T2D) are commonly lower in comparison to the general population because of their increased risk of cardiovascular (CV) morbidity and mortality (Cryer et al., 2016; American Diabetes Association, 2020; Cosentino et al., 2020). Several guidelines and clinical trials suggest to lower SBP below 130 or even 120 mmHg in all patients with T2D, implying that the benefits outweigh possible risks of treatment (Beckett et al., 2011; Warwick et al., 2015; Xie et al., 2016; Bangalore et al., 2017; Williams et al., 2018; American Diabetes Association, 2020). However, there are concerns that treatment to low SBP levels increases the occurrence of adverse events (AEs) (Benetos et al., 2016; Sinclair et al., 2019; Group et al., 2021). A meta-analysis from 2016 which included almost 180,000 participants, several of which had T2D, observed that a reduction of SBP below 130 mmHg prevents one major CV event but is associated with six treatment discontinuations due to intercurrent conditions or serious AEs (Thomopoulos et al., 2016). Further, lower SBP levels have been associated with higher mortality in T2D patients older than 75 years vs. 60–75 years treated with antihypertensive drugs (van Hateren et al., 2010), which suggests that the optimal SBP target may differ across subpopulations. Also, the occurrence of treatment-related AEs seems to differ between patient groups since studies have shown a higher risk of drug-related AEs among women (Fan et al., 2008; Zopf et al., 2008; Yu et al., 2016; de Vries et al., 2019), older, and frail patients (Zopf et al., 2008; Davies and O'Mahony, 2015; Holm et al., 2017; Sink et al., 2018).

Several studies from clinical practice show that up to 20% of patients with T2D have SBP levels <130 mmHg while receiving multiple antihypertensive drugs or medication treatment intensification (Kerr et al., 2012; de Vries et al., 2014; Sonmez et al., 2020). This percentage is even higher in the elderly or frail, where more than half of the patients have SBP levels <130 mmHg (Sussman et al., 2015; McCracken et al., 2017). These low SBP levels can lead to hypotension-related AEs, including syncope, tiredness, and postural hypotension (Group et al., 2015; Bangalore et al., 2017), and could indicate overtreatment with antihypertensives. Although one might expect that specific patient groups are more vulnerable for these AEs when they are treated to low blood pressure levels, no significant age-by-treatment interaction effect was seen in adults included in the SPRINT trial (Sink et al., 2018). However, participants with diabetes, history of stroke, heart failure, dementia or standing SBP less than 110 mmHg were excluded from this trial. Since T2D can affect the CV and renal system, patients with T2D may have a different risk of AEs from antihypertensive treatment than those without T2D (Wu et al., 2009). Whether the occurrence of hypotension-related AEs in T2D patients treated to low SBP levels is affected by age or other patient characteristics is unknown.

Our aim was to assess the association between the occurrence of hypotension-related AEs and low SBP levels, age, sex, and polypharmacy among patients with T2D treated with antihypertensives in general practice. Our first hypothesis was that patients with low SBP levels but also older patients, women, and those with polypharmacy more often experience a hypotension-related AE. Furthermore, we aimed to assess whether age, sex, and polypharmacy influence the association between low SBP levels and hypotension-related AEs. We hypothesized that the risk of hypotension-related AEs when having low SBP levels is intensified in older patients, females, and those with polypharmacy. Insight in possible differences in such risks among patient groups is important to guide more personalized treatment of hypertension in patients with T2D.

MATERIALS AND METHODS

Study Design and Population

In this cross-sectional cohort study, we used the Groningen Initiative to ANalyse Type-2 diabetes Treatment (GIANTT; www.giantt.nl) database. This database contains anonymous electronic medical records data of patients managed for T2D in primary care from the northern part of the Netherlands.

We included patients with at least one SBP measurement between the years 2012 and 2014. The day of the lowest SBP measurement in this time period was defined as index date. In case the lowest SBP level was recorded multiple times, the date of the first measurement was used. Patients had to have a practitioner confirmed diagnosis of T2D before the index date, had to be 18 years or older at the index date, and had to have at least 90 days of medical history before and 90 days of follow-up after index date to be included in our study. Patients without a prescription of an antihypertensive drug (anatomic therapeutic chemical (ATC) classification codes C02, C03, C07, C08, C09) in 90 days before the index date were excluded. Data were available from 189 general practices in the study period, after excluding data from three practices that had not documented any hypotension-related diagnostic codes in the study period.

We obtained an exemption letter for full ethical approval from the University Medical Center Groningen Medical Ethics Review Board (reference number M20.252895), since we used anonymous medical record data for this study.

Outcome Variable

Our primary outcome was the presence of a hypotension-related AE in the 90 days before or after index date. This time window was chosen because an AE may be documented after the

measurement of a low SBP, or the blood pressure may have been measured after the occurrence of an AE. The AEs were chosen based on the literature (Group et al., 2015; Bangalore et al., 2017), and defined with International Classification of Primary Care (ICPC) diagnostic codes used in Dutch primary care. The following diagnostic codes were included as hypotension-related AEs: K88 (postural hypotension), N17 (dizziness, vertigo), A04 (weakness, tiredness, lethargy), and A06 (syncope).

Determinants

Age (≥70 vs. <70 years), sex (women vs. men), polypharmacy (polypharmacy (5–10 drugs) or hyper polypharmacy (≥10 drugs) vs. no polypharmacy) and SBP level (<130 mmHg vs. ≥130 mmHg) were included as determinants that may influence the occurrence of hypotension-related AEs. Age, sex and SBP level measured in the practice as documented at index date were used. Polypharmacy was based on the number of medications at the 3rd pharmacological subgroup level of the ATC classification that a patient was prescribed in a period of 90 days up to the index date in addition to the one antihypertensive drug all patients had been prescribed by design.

Confounders

The following patient characteristics available from the medical record data in GIANTT that may be associated with the selected AEs and with the SBP level and/or can differ between patients with different age, sex and polypharmacy, were included as potential confounders: glycated hemoglobin A1c (HbA1c) level (continuous variable), duration of diabetes (<10 years or ≥10 years), smoking status (smoker or non-smoker), diastolic blood pressure level (continuous variable), body mass index (BMI; continuous variable), presence of decreased estimated glomerular filtration rate (eGFR; ≤60 mL/min/1.73 m^2; calculated using the serum creatinine from GIANTT and Chronic Kidney disease Epidemiology Collaboration formula or extracted from the database if creatinine levels were missing), presence of albuminuria (albumin creatinine ratio ≥30 mg/g or albumin in 24 h urine ≥300 mg), presence of dyslipidemia (defined as low density lipoproteins (LDL) ≥2.5 mmol/L), prescribed lipid lowering medication (none, 1 drug, ≥2 drugs) and glucose lowering medication (none, 1 oral drug, ≥2 oral drugs and/or insulin). Laboratory values were extracted as the last value in 180 days up to the index date or, in case that was not available, the first value in 90 days after index date. Diabetes duration was calculated on index date. Smoking status was assessed in the 180 days up to index date. BMI was calculated based on patients' weight closest to the index date in the 5 years before or 1 year thereafter and the most recent height recorded any time before or after index date. If height and/or weight were not available, the BMI as entered in GIANTT was used. Presence of prescriptions was calculated in the 90 days up to index date.

Missing Data

There were no missing values for the determinants and the primary outcome. Confounders with less than 30% of missing values were imputed using multiple imputation by chained equation (MICE) (White et al., 2011). Patients with a missing value for albuminuria (59%) were classified as not having albuminuria, since such testing is less likely in patients without expected kidney damage. None of the other confounders had more than 30% missing values.

Analyses

Demographics were analyzed descriptively for patients with and without hypotension-related AEs. For each of the determinants, a logistic regression analysis was conducted including the SBP level and the interaction between SBP level and age, sex, and polypharmacy. These analyses were adjusted for the potential confounders to assess the odds ratios (ORs) for the occurrence of hypotension-related AEs. In the analysis of polypharmacy, there was no adjustment for glucose and lipid lowering therapy since these variables are part of the calculation of polypharmacy. In the analyses where age, sex, or polypharmacy were not used as a determinant, they were included as continuous (age and polypharmacy) or dichotomous (sex) confounding variables.

Several sensitivity analyses were conducted. First, we conducted a sensitivity analysis using a higher cut-off level for age of 80 years and using both higher and lower cut-off levels for SBP of 140 and 120 mmHg, respectively. Next, we expanded the definition of the outcome to include other less specific ICPC diagnostic codes that may be related to hypotension: A80 (trauma, injury), L75 (femur fracture), L76 (other fracture), L81 (musculoskeletal injury), S16 (bruise, concussion) and S17 (abrasion, scratch).

All analyses were conducted in Stata version 14 (Stata Corp., College Station, TX). *p*-values <0.05 were considered statistically significant and ORs with 95% confidence intervals (CIs) are presented.

RESULTS

We included 21,119 patients with T2D treated with antihypertensives who met our inclusion criteria (**Supplementary Figure S1**), of which 1,135 (5.4%) experienced a hypotension-related AE (**Table 1**). Forty nine percent of the included patients were older than 70 years, 52% were women, 57% had polypharmacy or hyper polypharmacy and 61% had the lowest SBP level below 130 mmHg. Patients who experienced a hypotension-related AE were more often women, older, had a longer diabetes duration and had more often eGFR ≤60 ml/min/1.73 m^2 (**Table 1**). Almost half of the patients with a recorded AE had postural hypotension. Complete data were available for 52% of the patients.

Associations With the Occurrence of Hypotension-Related AEs

Older patients more often experienced a hypotension-related AE than younger patients (6.6 vs. 4.2%; **Figure 1A**). In the logistic regression analysis, this main effect of age was statistically significant (OR 1.29, 95% CI 1.02–1.64; **Figure 2A**).

Women more often experienced a hypotension-related AE than men (5.8 vs. 4.9%; **Figure 1B**), but this difference was not statistically significant (OR 1.06, 95% CI 0.84–1.32; **Figure 2B**).

TABLE 1 | Patient characteristics.

	No adverse event (N = 19,984)	Adverse event (N = 1,135)
Female; N (%)	10,275 (51)	632 (56)
Lowest SBP in mmHg; mean ± SD	125 ± 14	121 ± 16
Lowest SBP <130 mmHg, N (%)	12,079 (60)	802 (71)
Age; mean ± SD	69 ± 11	71 ± 12
Age ≥70 years; N (%)	9,753 (49)	685 (60)
Polypharmacy; N (%)		
no	8,818 (44)	351 (31)
polypharmacy	9,277 (46)	574 (51)
hyper polypharmacy	1,889 (9)	210 (19)
Number of antihypertensives; N (%)		
1	6,708 (34)	347 (31)
2	6,700 (34)	341 (30)
3 or more	6,576 (33)	447 (39)
HbA1c in %; mean ± SD	6.9 ± 1.0	7.0 ± 1.0
missing	976 (5)	62 (5)
Diabetes duration ≥10 years; N (%)	5,459 (27)	358 (32)
BMI in kg/m^2; mean ± SD	30.4 ± 5.6	30.4 ± 5.5
missing	793 (4)	69 (6)
DBP in mmHg; mean ± SD	73 ± 10	71 ± 11
missing	216 (1)	10 (1)
eGFR ≤60 ml/min/1.73m^2; N (%)	4,121 (21)	347 (31)
missing	4,045 (20)	143 (13)
Smoking; N (%)	2,797 (14)	150 (13)
missing	4,770 (24)	233 (21)
LDL cholesterol ≥2.5 mmol/L; N (%)	7,259 (36)	421 (37)
missing	5,718 (29)	298 (26)
Albuminuria; N (%)	396 (2)	21 (2)
missing	11,913 (60)	630 (56)
Hypotension related adverse event; N (%)		
Postural hypotension (K88)		534 (47)
Weakness, tiredness (A04)		336 (30)
Dizziness, vertigo (N17)		229 (20)
Syncope (A06)		117 (10)

SBP, systolic blood pressure; HbA1c, glycated hemoglobin A1c; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

Patients prescribed more comedication more often experienced a hypotension-related AE (no polypharmacy 3.8%, polypharmacy 5.8% and hyper polypharmacy 10.0%; **Figure 1C**). In the logistic regression analyses, the effects of polypharmacy and hyper polypharmacy were statistically significant (OR polypharmacy vs. no polypharmacy 1.27, 95% CI 1.00–1.62 and OR hyper polypharmacy vs. no polypharmacy 2.37, 95% CI 1.67–3.37; **Figure 2C**).

Patients with SBP levels <130 mmHg more often experienced a hypotension-related AE than those with SBP ≥130 mmHg (6.2 vs. 4.0%; **Figure 1**). Statistically significant higher occurrence of AEs with lower SBP levels was shown in all conducted analyses (**Figure 2**): age (OR 1.41, 95% CI 1.14–1.75), sex (OR 1.43, 95% CI 1.17–1.76) and polypharmacy (OR 1.33, 95% CI 1.06–1.67).

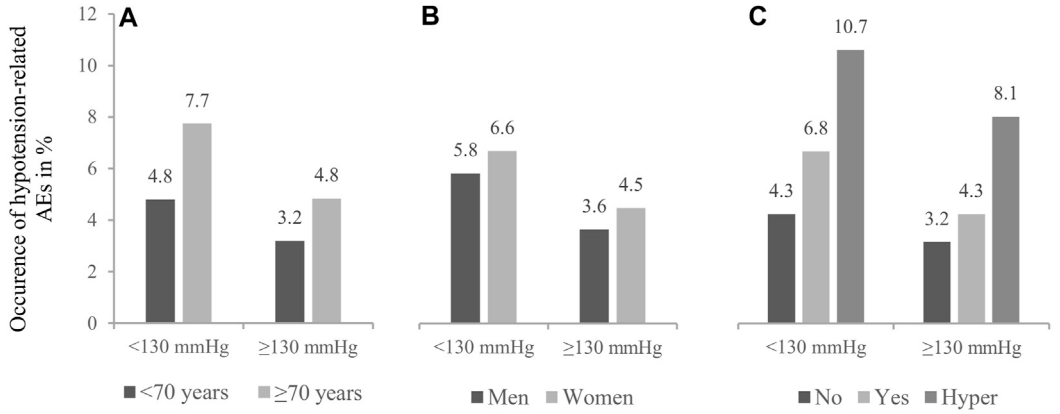
Modifying Effect of Age, Sex, and Polypharmacy on the Occurrence of AEs in Patient Treated to Low SBP Level

The interactions between the determinants and SBP level <130 mmHg were not statistically significant (OR for interaction with age 1.01, 95% CI 0.77–1.33 in **Figure 2A**; OR for interaction with sex 0.98, 95% CI 0.75–1.27 in **Figure 2B**; OR for interaction with polypharmacy 1.17, 95% CI 0.87–1.56 and OR for interaction with hyper polypharmacy 0.95, 95% CI 0.63–1.42 in **Figure 2C**). This indicates that older patients, women, and patients with polypharmacy or hyper polypharmacy are not at additional risk of hypotension-related AEs when having SBP levels <130 mmHg than younger patients, men, and patients with no polypharmacy when having low SBP levels.

Sensitivity Analyses

The sensitivity analysis with a higher cut-off level for age showed that patients aged ≥80 years experienced more hypotension-related AEs than younger patients (7.8 vs. 4.8%), but this main effect was no longer statistically significant (OR 1.08, 95% CI 0.82–1.41; **Supplementary Figures S2, S3**).

The analysis using an SBP cut-off of 120 mmHg showed similar results as the main analysis (**Supplementary Figures S4, S5**). When using an SBP cut-off of 140 mmHg (**Supplementary Figure S6**) the effects of SBP level and age became non-significant (**Supplementary Figure S7**). Furthermore, patients with polypharmacy but not with hyper polypharmacy were at an additional risk of



SBP at index date (mmHg)*	Age (years)		Sex		Polypharmacy			Total AEs (%)
	<70	≥70	Men	Women	No	Yes	Hyper	
<130	322/6678	480/6203	357/6177	445/6704	225/5232	415/6141	162/1508	6.2
≥130	128/4003	205/4235	146/4035	187/4203	126/3937	159/3710	48/591	4.0
Total AEs (%)	4.2	6.6	4.9	5.8	3.8	5.8	10.0	5.4

FIGURE 1 | Occurrence of hypotension-related adverse events (AEs) per systolic blood pressure (SBP) level by **(A)** age, **(B)** sex and **(C)** polypharmacy. The table below presents the numbers of AEs per total number of patients in that group. *Index date is defined as the lowest SBP level between 2012 and 2014.

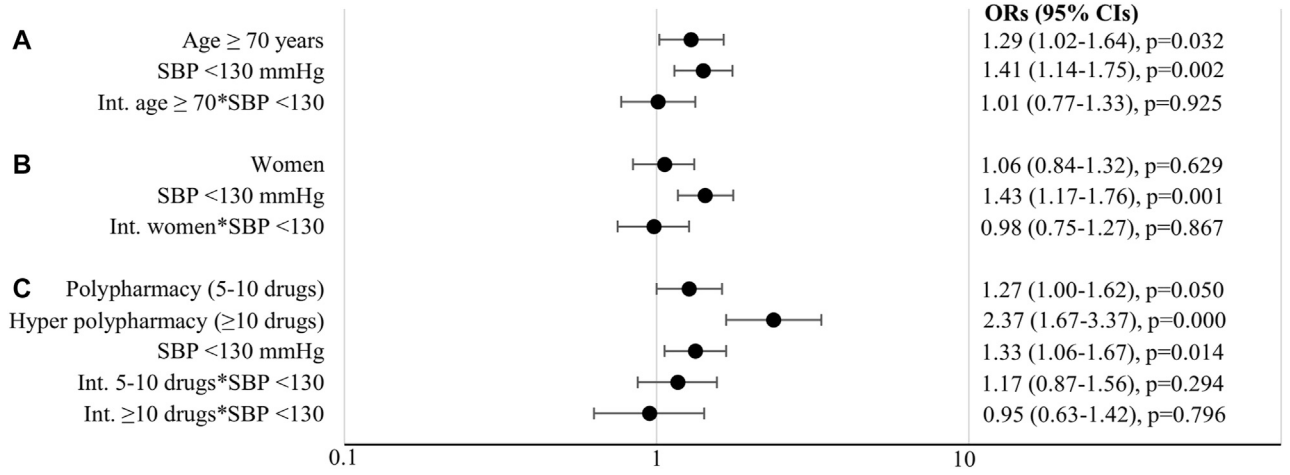


FIGURE 2 | Odds ratios (OR) with 95% confidence intervals (CIs) and *p*-values for **(A)** age, **(B)** sex, **(C)** polypharmacy, with systolic blood pressure (SBP) and their interactions. Age and sex analyses were adjusted for glycated hemoglobin A1c, diabetes duration, body mass index, smoking, diastolic blood pressure, estimated glomerular filtration rate, glucose lowering therapy, dyslipidemia, lipid lowering therapy, albuminuria, number of comedication and sex or age; polypharmacy analysis was adjusted for the same variables except for glucose and lipid lowering therapy. Int., interaction.

hypotension-related AEs at SPB levels <140 mmHg when compared to patients without polypharmacy (polypharmacy OR 1.52, 95% CI 1.02–2.28; hyper polypharmacy OR 1.16, 95% CI 0.66–2.04; **Supplementary Figure S7**). None of the other interactions were statistically significant.

Each of the additional AEs in the extended list occurred in 2–10% of patients who experienced an AE (**Supplementary Table S1**). The analyses including these additional AEs showed similar results as the main analyses (**Supplementary Figures S8, S9**).

DISCUSSION

This study among T2D patients treated with antihypertensives showed that older age, polypharmacy, and low SBP levels were all independently related to experiencing more hypotension-related AEs. The higher occurrence of hypotension-related AEs among patients with low SBP levels was not significantly aggravated by older age, female sex, or polypharmacy.

Several studies in non-diabetic populations have shown a higher occurrence of AEs in older patients (Zopf et al., 2008; Davies and O'Mahony, 2015; Holm et al., 2017) and in one study also no significant interaction between age and SBP level on AEs was observed (Sink et al., 2018). Our results showing a higher occurrence of AEs at older age without an interaction with SBP level are therefore in line with these previous studies. Nevertheless, a meta-analysis of clinical trials, several of which included T2D patients, showed an increased risk of hypotension in patients younger than 65 years, which they assumed was a consequence of more intensive antihypertensive treatment in younger patients (Thomopoulos et al., 2018). Although they observed slightly higher increment of discontinuations in the older patients, the ratio between risks and benefits was similar in older and younger patients. We found no significant differences in the occurrence of hypotension-related AEs between older and younger patients when using the SBP level 140 mmHg as a cut-off value. Our findings confirm the clinical trial data in a real-world setting of patients with T2D and suggests that lowering SBP levels below 140 mmHg seems safe in patients of all ages. Nevertheless, patients with T2D treated with antihypertensives reaching SBP levels below 130 mmHg should be closely monitored for the occurrence of hypotension-related AEs and possible overtreatment, regardless of age.

In our study, women had a slightly higher occurrence of hypotension-related AEs than men, but this difference was not significant after adjusting for possible confounders. This is not in line with other studies showing increased occurrence of AEs in women (Fan et al., 2008; Zopf et al., 2008; Holm et al., 2017; Sim et al., 2018; de Vries et al., 2019). Most of these studies, however, used different methods in reporting of AEs and often no adjustments were made for confounding of SBP level or age.

We saw a generally higher occurrence of hypotension-related AEs in patients prescribed more medication, which was independent of the SBP level. This is in line with several studies showing a higher occurrence of AEs in patients prescribed more medication or those with a greater comorbidity burden (Zopf et al., 2008; Sim et al., 2018; Sink et al., 2018; Hanlon et al., 2020). In one study, also no significant interaction between frailty and SBP levels on AEs was found (Sink et al., 2018). In itself, the occurrence of hypotension-related AEs in those prescribed more medication was high. Amongst those with hyper polypharmacy, almost 11% of patients with SBP level <130 mmHg and more than 8% of patients with SBP level ≥130 mmHg experienced a hypotension-related AE. Whether this is due to the actual large number of medication or underlying diseases in unknown, but it can cause a great burden on the healthcare system, the patients' health state and their quality of life. Sufficient attention for negative effects of hypertension treatment in patients with hyper polypharmacy is warranted.

Overall, patients reaching low SBP levels had a higher occurrence of hypotension-related AEs then those with higher SPB levels. This is in line with previous studies and meta-analyses (ACCORD Study Group et al., 2010; Group et al., 2015; Bangalore et al., 2017; Frey et al., 2019). Of note is our finding that this was independent of the patients' age, sex, and number of medications. This implies that attention for hypotension-related AEs is generally required in patients treated to low SBP levels. The occurrence of AEs is a common reason for poor medication adherence (Leporini et al., 2014). To increase the likelihood of adherence to the antihypertensive treatment, possible benefits and risks of treatment should be weighted, and a personalized SBP target should be discussed with the patient (American Diabetes Association, 2020) and occasionally reevaluated during treatment. Unless the patient is adequately informed about the benefits and possible AEs of intensive treatment and agrees with it, less intensive treatment with higher SBP targets should be considered.

The strength of our study is using real-world data from almost all T2D patients treated in a large number of general practices in the north of the Netherlands. It should be noted that this region consists mostly of Caucasian people. The results may not be generalizable to other populations. Further, we conducted several sensitivity analyses using different age and SBP level cut-offs and AE definitions to validate our findings and further explore the relationship between SBP and the occurrence of hypotension-related AEs. Several limitations mostly related to the use of a database with routinely recorded primary care data must be acknowledged. First, it is possible that the general practitioners were not aware of or did not record all AEs that were experienced by patients, or that there were errors in the coding. A comparison with a recent clinical trial (Sink et al., 2018) of patients without diabetes showed somewhat similar rates of hypotension (2.5% in our study compared to 1.6% in the clinical trial). For some AEs we observed lower occurrences, for example, syncope (0.6 vs. 1.8%, respectively). In general, we do not expect that the recording of AEs would differ across patients but some patients might report more AEs to their prescribers than others (Loikas et al., 2015). Also, although we selected AEs which are related to hypotension, we cannot guarantee that these AEs were caused by a low SBP level. We conducted a post hoc analysis using only those AEs which occurred at the same time or after the low SBP level was recorded to reduce the chance of the two events not being connected. This analysis revealed similar results (**Supplementary Figures S10, S11**). Nevertheless, there can be other causes for the AEs, also for the common postural hypotension in our study. Further, the number of SBP measurements varied between patients, with 2% of patients having only one measurement in the study period. It is not clear to what extent this might bias our findings. Next, some of the included confounders had almost a third of missing values. We used multiple imputation for these variables to reduce possible bias. Furthermore, we included polypharmacy as an indicator of comorbidity. Other measures, such as frailty, were unfortunately not recorded in our data. Last, we did not include the type of drug or drug dose or treatment duration in the analysis. Although this might explain part of the differences in the occurrence of AEs between different subpopulations, this is not expected to affect the associations between the SBP levels and hypotension-related AEs.

To conclude, the observed higher occurrence of hypotension-related AEs in older patients, patients with polypharmacy and those with low SBP levels indicates that there should be sufficient attention

for hypotension-related AEs in those patients. Contrary to our expectation, age, sex, and polypharmacy did not increase the risk of hypotension-related AEs associated with a low SBP level in patients with type 2 diabetes. Possible negative effects of medication treatment to low SBP targets in clinical practice should be regularly evaluated in all patients with T2D. Personalized treatment targets may be warranted to reduce hypotension-related AEs, but also other underlying problems and treatment options should be explored with these patients.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available on reasonable request and according to procedures as stipulated on www.giantt.nl. Requests to access these datasets could be directed to p.denig@umcg.nl.

AUTHOR CONTRIBUTIONS

MA. contributed to the development and formulation of the research question, conducted the analysis, contributed to the interpretation of data, wrote the manuscript, and edited the manuscript. STdV. contributed to the development and formulation of the research question, conducted the analysis, contributed to the interpretation of data, and reviewed and edited the manuscript. KH. contributed to the development and formulation of the research question, the interpretation of data, and reviewed and edited the manuscript. PD. contributed to the development and formulation of the research question, development of the analysis, the interpretation of data, and reviewed and edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.728911/full#supplementary-material

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Dexmedetomidine Versus Propofol for Patients With Sepsis Requiring Mechanical Ventilation: A Systematic Review and Meta-Analysis

Po Huang, Xiangchun Zheng, Zhi Liu and Xiaolei Fang**

Beijing Dongfang Hospital, Beijing University of Traditional Chinese Medicine, Beijing, China

Purpose: This meta-analysis was performed to access the influence of dexmedetomidine versus propofol for adult patients with sepsis undergoing mechanical ventilation.

Materials and Methods: NCBI PUBMED, Cochrane Library, Embase, China National Knowledge Internet (CNKI), and China Biological Medicine (CBM) were searched. Revman 5.3 and Stata software (version 12.0, Stata Corp LP, College Station, TX, United States) were used for meta-analysis.

Results: Fifteen studies were included, and the data from the included studies were incorporated into the meta-analysis. Also, the result shows that compared with propofol, dexmedetomidine does not reduce 28-day mortality [risk ratios (RR) =0.97, 95% confidence interval (CI) =0.83–1.13, p = 0.70]. However, our analysis found that dexmedetomidine could reduce intensive care unit (ICU) stays {standard mean difference (SMD): −0.15; 95% CI: [−0.30–(−0.01)], p = 0.03}, duration of mechanical ventilation {SMD: −0.22; 95% CI: [−0.44–(−0.01)], p = 0.043}, sequential organ failure assessment (SOFA) {SMD: −0.41; 95% CI: [−0.73–(−0.09)], p = 0.013}, levels of interleukin-6 (IL-6) at 24 h (SMD: −2.53; 95% CI: −5.30-0.24, p = 0.074), and levels of CK-MB at 72 h {SMD: −0.45; 95% CI: [−0.83–(−0.08)], p = 0.017}.

Conclusions: This meta-analysis (MA) suggests that in terms of 28-day mortality, sepsis patients with the treatment of dexmedetomidine did not differ from those who received propofol. In addition, more high-quality trials are needed to confirm these findings.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/#recordDetails, identifier CRD42021249780.

Keywords: sepsis, mechanical ventilation, dexmedetomidine, propofol, meta-analysis

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Fabiane Raquel Motter, University of Sorocaba, Brazil

Reviewed by:
Yahya Shehabi, Monash University, Australia
Luis Laranjeira, Eli Lilly, Portugal

****Correspondence:***
Zhi Liu
liuzhi_725@126.com
Xiaolei Fang
fangxiaolei_586@126.com

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INTRODUCTION

According to the recent reports, approximately 21% of septic patients required mechanical ventilation in the United States (Rashmi et al., 2018). As we all know, patients with prolonged mechanical ventilation suffer from higher mortality and hospital costs (Goligher Ewan et al., 2018; Louise, 2020). Besides, appropriate sedation measures are necessary for patients with sepsis undergoing mechanical ventilation because these measures are taken to avoid a series of adverse

reactions caused by mechanical ventilation, including anxiety and delirium (Ohta et al., 2020). It had been reported that the early deep sedation was associated with the increased ventilation duration and the mortality (Yahya et al., 2012). Given this, the guidelines recommend dexmedetomidine or propofol to be applied to adult patients receiving mechanical ventilation for targeting mild sedation (Shankar et al., 2016).

As a potent α2 agonist with antianxiety, sedative, analgesic, and sympathetic properties, dexmedetomidine (DEX) is widely used in ICU for mild sedation (Flieller Lauren et al., 2019). Propofol, chemically known as 2,6-diisopropylphenol, is a type of rapid and short-acting intravenous anesthetic commonly used clinically for induction of anesthesia, maintenance of anesthesia, and sedation in critical patients in ICU. It has the advantages of fast onset of anesthesia induction, rapid recovery and perfect functional recovery, and low incidence of postoperative nausea and vomiting (Doi et al., 2020). However, both the drugs have side effects, and there are differences in wake and inflammation between them (Li et al., 2021). Besides, it still remains unknown whether these two drugs affect the research outcomes on mechanical ventilation for adult patients with sepsis.

Recently, some randomized controlled trials have been conducted with respect to the comparison of DEX and propofol in the treatment of sepsis. However, there is still much controversy in the effects of DEX and propofol on mortality, ICU stays, and incidence of adverse events. Against this background, it is necessary to systematically evaluate the efficacy and safety of DEX and propofol in the treatment of sepsis with mechanical ventilation so as to provide evidence-based evidence.

METHODS

The preferred reporting items for systematic review and a meta-analysis (PRISMA) statement (Nikola et al., 2013) have provided the details of meta-analysis, and all the reviews should be conducted according to the content of PRISMA. Therefore, our meta-analysis was performed based on the recommendations and checklist from PRISMA.

Search Strategy

We searched the relevant studies from Pubmed, Cochrane Library, Embase, CNKI, and CBM from their inception to May 2021.

Eligibility Criteria of Original Studies

Diagnostic criteria of sepsis: infection combined with SOFA ≥2.

Inclusion criteria: the original studies we selected should meet PICOS as follows: 1) participants: mechanically ventilated adult patients with sepsis, regardless of the country, region, gender, or nationality; 2) interventions: dexmedetomidine with continuous intravenous pumping; 3) control: propofol with continuous intravenous pumping; 4) outcomes: primary outcome mainly refers to the 28-day mortality; secondary outcomes cover ICU stays, duration of mechanical ventilation, incidence of adverse events, sequential organ failure assessment (SOFA), levels of interleukin-6 (IL-6) at 24 h, and levels of CK-MB at 72 h; 5) study design: the study was designed as the randomized controlled trial (RCT).

Exclusion criteria: the exclusion criteria were a supplement to the inclusion criteria, and those studies which meet the following conditions will be excluded: 1) the duplicate publications, 2) the participants were children, 3) the diagnostic criteria of sepsis were ambiguous, and 4) the data cannot be used or their source is unknown.

Study Selection

Two reviewers independently screen the studies according to the preset criteria for inclusion and exclusion, in which the title and the abstract are the main references. Meanwhile, the full text will be checked if necessary. Once the two independent reviewers diverge in the definition of the included study, the third independent reviewer will intervene in time and actively resolve within the group. If the diverge still cannot be solved, the agreement will be reached by consensus.

Data Extraction and Quality Assessment

Based on pre-planned results, the related information from the identified studies is extracted by two reviewers independently. For example, this information, including first author, year of publication, sample size, interventions, controls, and results, should be recorded in detail and edited into a table form. Once the two independent reviewers diverge in the definition of the included study, the third independent reviewer intervenes in time and actively resolves within the group. If it still cannot be solved, the agreement will be reached by consensus.

In addition, the quality of the included studies is assessed by two reviewers independently. Also, the Jadad Scale is used to evaluate the quality of randomized controlled trials. According to the principle, 1–4 indicates a low-quality study and 5–7 indicates a high-quality study, and the maximum of Jadad score is 7.

Data Synthesis

Revman 5.3 and Stata 12.0 software (Stata Corp LP, College Station, TX, United States) are used to analyze the following information: 28-day mortality, ICU stays, duration of mechanical ventilation, incidence of adverse events, SOFA, levels of IL-6 at 24 h, and levels of CK-MB at 72 h. Based on the recommendations of Cochrane Handbook of Systematic Reviews, risk ratios (RRs) and 95% confidence intervals (CIs) are employed to evaluate the dichotomous results. For continuous results, the standard mean difference (SMD) and its 95% CI are selected. Heterogeneity between studies is evaluated by the I^2 test. The fixed-effect model is applied if there is no or low heterogeneity ($I^2 \leq 25\%$). Otherwise, the randomized effect model will be employed if there exists heterogeneity ($I^2 > 25\%$). Also, publication bias is also evaluated (the number of studies ≥10 in one outcome).

Subgroup Analysis

Subgroup analysis was conducted in the outcome of 28-day mortality based on the evidence covering studies published in English versus non-English, high Jadad score (≥5) versus low

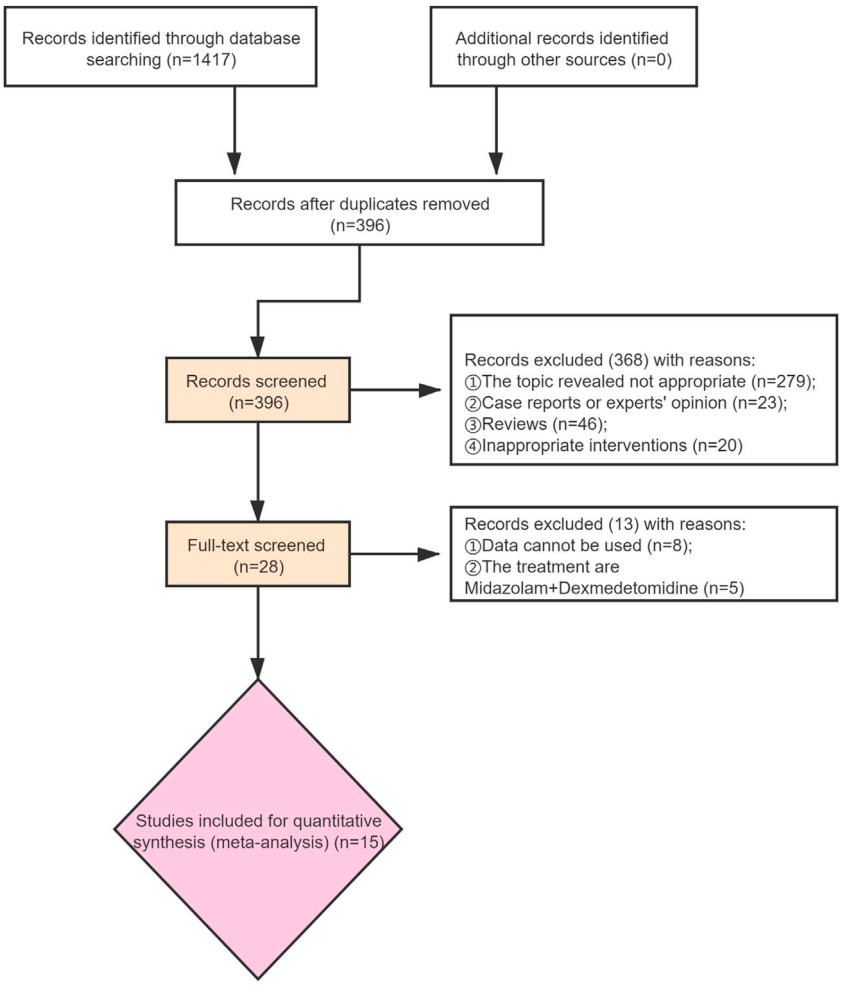

FIGURE 1 | Flow chart of included studies selection.

Jadad score, and high dose of dexmedetomidine (≥0.5 μg/kg/h) versus low dose of dexmedetomidine.

PROSPERO Registration

Before the meta-analysis was formally conducted, we registered the topics, the inclusion and exclusion criteria, the outcomes, and the statistical analysis methods on PROSPERO so as to show the whole process of the meta-analysis in a more open and transparent way. The details of PROSPERO registration could refer to https://www.crd.york.ac.uk/prospero/#recordDetails.

RESULTS

Included Studies

A total of 1,417 records were identified, and 396 records were obtained after removing duplicate publications. After that, 368 studies were removed by screening the titles and abstracts. This means that 28 studies have been further screened through reading the full text. It was found among them that the data of nine studies cannot be accessible, and the intervention measures of five studies do not meet the inclusion criteria. In total, 1,871 participants in 15 studies were included (**Figure 1**). The details of included studies are shown in **Table 1**.

Quality Assessment of the Included Studies

The quality of the included studies was evaluated by the Jadad Scale, which covers the generation of random sequences, allocation concealment, the blinding method, and reasons for withdrawal or dropout. The result showed that most of the included studies obtained low scores, among which there were only four studies with high scores (Kawazoe et al., 2017; Ding et al., 2019; Liu et al., 2020; Zhan et al., 2020). The details are demonstrated in **Supplementary Table S1**.

Primary Outcome

The primary outcome reflected in the included studies is the 28-day mortality. A total of 13 studies (Meng, et al., 2014; Guo, et al., 2016; Lei and Li, 2016; Kawazoe, et al., 2017; Zhou, 2017; Cai,

TABLE 1 | The characteristics of the included studies.

Study	No. of participants	Intervention		Outcomes
		Experimental group	Control group	
Meng et al. (2014)	N = 40 (T = 20; C = 20)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Duration of mechanical ventilation, levels of IL-6 at 24 h
Guo et al. (2016)	N = 30 (T = 14; C = 16)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Duration of mechanical ventilation
Lei et al, 2016)	N = 58 (T = 29; C = 29)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, levels of CK-MB at 72 h
Zhou (2017)	N = 80 (T = 40; C = 40)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, levels of CK-MB at 72 h
Kawazoe et al. (2017)	N = 201 (T = 100; C = 101)	Dexmedetomidine	Propofol	28-day mortality, Duration of mechanical ventilation, Incidence of adverse events
Ding et al. (2019)	N = 282 (T = 131; C = 152)	Dexmedetomidine	Propofol	ICU stays, Incidence of adverse events, levels of CK-MB at 72 h
Liu JQ et al. (2019)	N = 200 (T = 100; C = 100)	Dexmedetomidine	Propofol	28-day mortality, Duration of mechanical ventilation
Wang QS et al. (2019)	N = 101 (T = 42; C = 59)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Incidence of adverse events, levels of IL-6 at 24 h
Wang YF et al. (2019)	N = 63 (T = 31; C = 32)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Incidence of adverse events
Liu SC et al. (2019)	N = 63 (T = 31; C = 32)	Dexmedetomidine	Propofol	Incidence of adverse events, SOFA, levels of IL-6 at 24 h
Xu (2019)	N = 50 (T = 25; C = 25)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Duration of mechanical ventilation, levels of IL-6 at 24 h
Cai et al. (2019)	N = 60 (T = 30; C = 30)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Duration of mechanical ventilation, Incidence of adverse events, SOFA
Liu Z et al. (2020)	N = 102 (T = 51; C = 51)	Dexmedetomidine	Propofol	28-day mortality, ICU stays, Duration of mechanical ventilation, SOFA
Wei GW et al. (2020)	N = 119 (T = 60; C = 59)	Dexmedetomidine	Propofol	28-day mortality, Incidence of adverse events

et al., 2019; Wang et al., 2019; Wang et al., 2019; Xu, 2019; Guowen and Bingyi, 2020; Liu et al., 2020; Zhan et al., 2020; Hughes Christopher et al., 2021) reported 28-day mortality according to the cases of 1,521 participants. Then, random effect models were utilized. Subgroup analysis was conducted according to studies published in English and non-English, high scores of Jadad and low scores of Jadad, high doses of DEX (≥0.5 μg/kg/h) and low doses of DEX. The result showed that there was no difference between the DEX group and propofol group in all the three subgroups (**Figures 2–4**).

Secondary Outcomes

ICU Stays

A total of 10 studies (Meng et al., 2014; Guo, et al., 2016; Lei and Li, 2016; Zhou, 2017; Cai, et al., 2019; Ding, et al., 2019; Wang et al., 2019; Wang et al., 2019; Xu, 2019; Zhan et al., 2020) employed ICU stays as the evaluation index. The results indicated that the DEX group could reduce ICU stays in comparison with the propofol group {SMD: −0.15; 95% CI: [−0.30–(−0.01), p = 0.03]} (**Figure 5**).

Duration of Mechanical Ventilation

There were six studies (Meng, et al., 2014; Guo, et al., 2016; Wang et al., 2019; Xu, 2019; Cai, et al., 2019; Zhan et al., 2020) which reported the duration of mechanical ventilation. We selected the fixed effect model since there was no heterogeneity in both the subgroups (I^2 = 9.1%). Also, the meta-analysis showed that compared with propofol, DEX could reduce the duration of mechanical ventilation {SMD: −0.22; 95% CI: [−0.44-(−0.01), p = 0.043]} (**Supplementary Figure S1**).

Incidence of Adverse Events

Seven studies (Kawazoe et al., 2017; Cai et al., 2019; Ding et al., 2019; Liu et al., 2019; Wang et al., 2019; Wang et al., 2019; Guowen and Bingyi, 2020) recorded the incidence of adverse events, which was evidenced by 889 participants. The results demonstrated that there was no difference in incidence of adverse events between the group of DEX and propofol [RR = 0.64, 95% CI = (0.37,1.11), p = 0.11] (**Supplementary Figure S2**).

SOFA

Three studies (Cai, et al., 2019; Liu et al., 2019; Zhan et al., 2020) with 225 participants reported SOFA. The results demonstrated that SOFA decreased in the group of DEX in comparison with the group of propofol {SMD: −0.41; 95% CI: [−0.73–(−0.09), p = 0.013]} (**Supplementary Figure S3**).

Levels of IL-6 at 24 h and Levels of CK-MB at 72 h

Random effect models were utilized (I^2 > 75%) in the above two outcomes. The results showed that there was no influence on levels of IL-6 at 24 h in the group of DEX in comparison with that in the group of propofol (SMD: −2.53; 95% CI: [−5.30–0.24], p = 0.074) (**Supplementary Figure S4**). The levels of CK-MB at 72 h decreased in the group of DEX in comparison with that in the group of propofol {SMD: −0.45; 95% CI: [−0.83– (−0.08), p = 0.017]} (**Supplementary Figure S5**).

DISCUSSION

Findings

The analysis aims to access the efficacy and safety of DEX in patients with sepsis with the treatment of mechanical ventilation. The results showed that for patients with sepsis, the application of DEX had no advantage (28-day survival) compared with that of propofol. However, our analysis found that the use of DEX could decrease ICU stays, duration of mechanical ventilation, incidence of adverse events, SOFA, and levels of CK-MB at 72 h except the

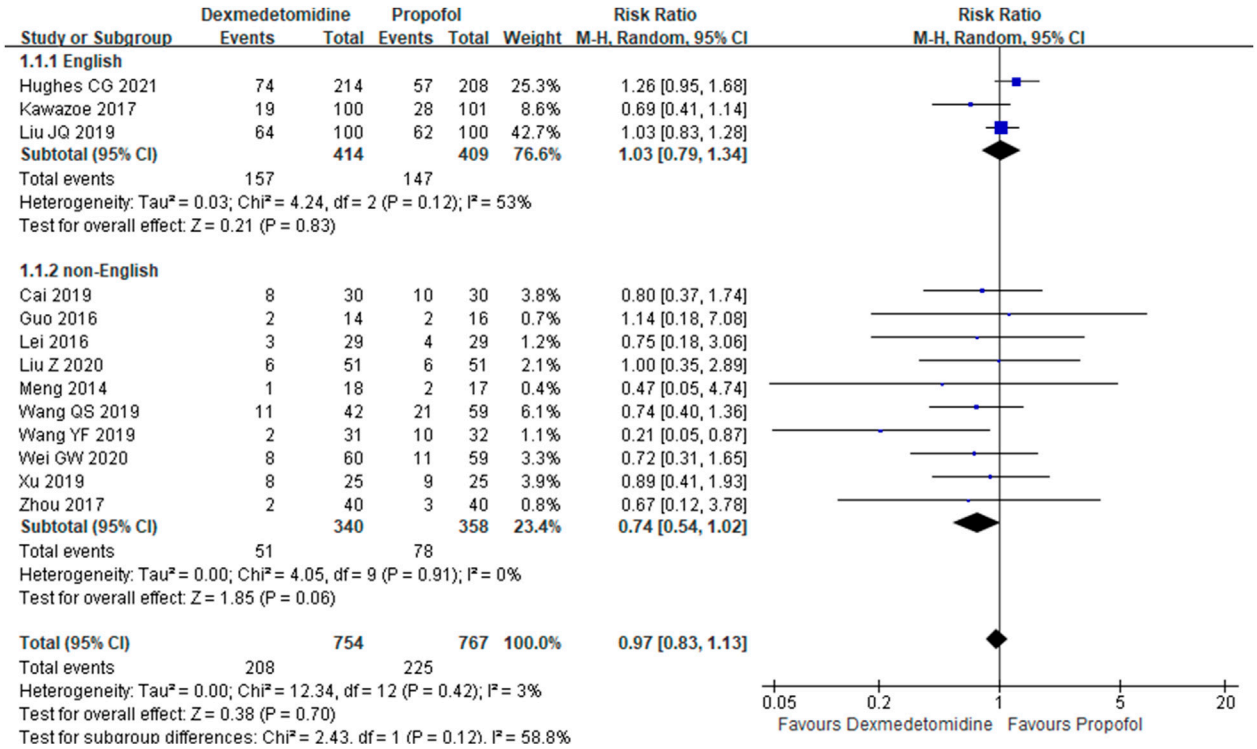

FIGURE 2 | Forest plot of 28-day mortality.

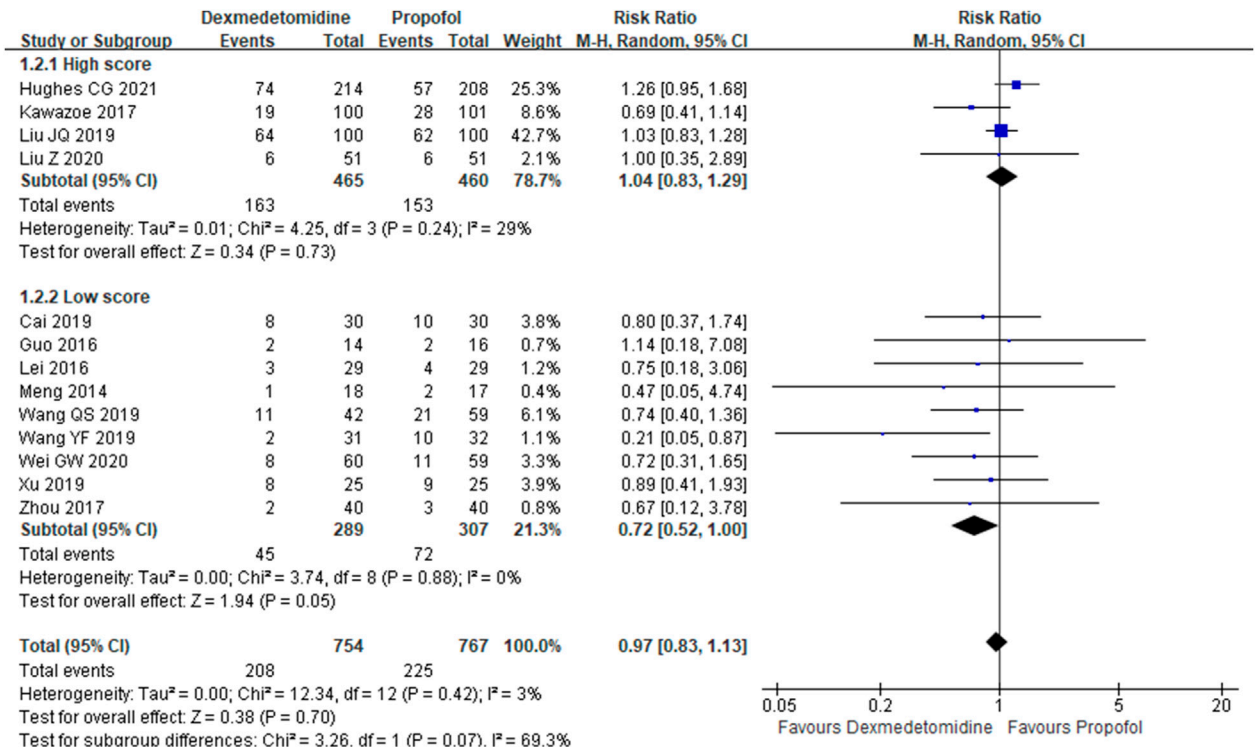

FIGURE 3 | Forest plot of ICU stays.

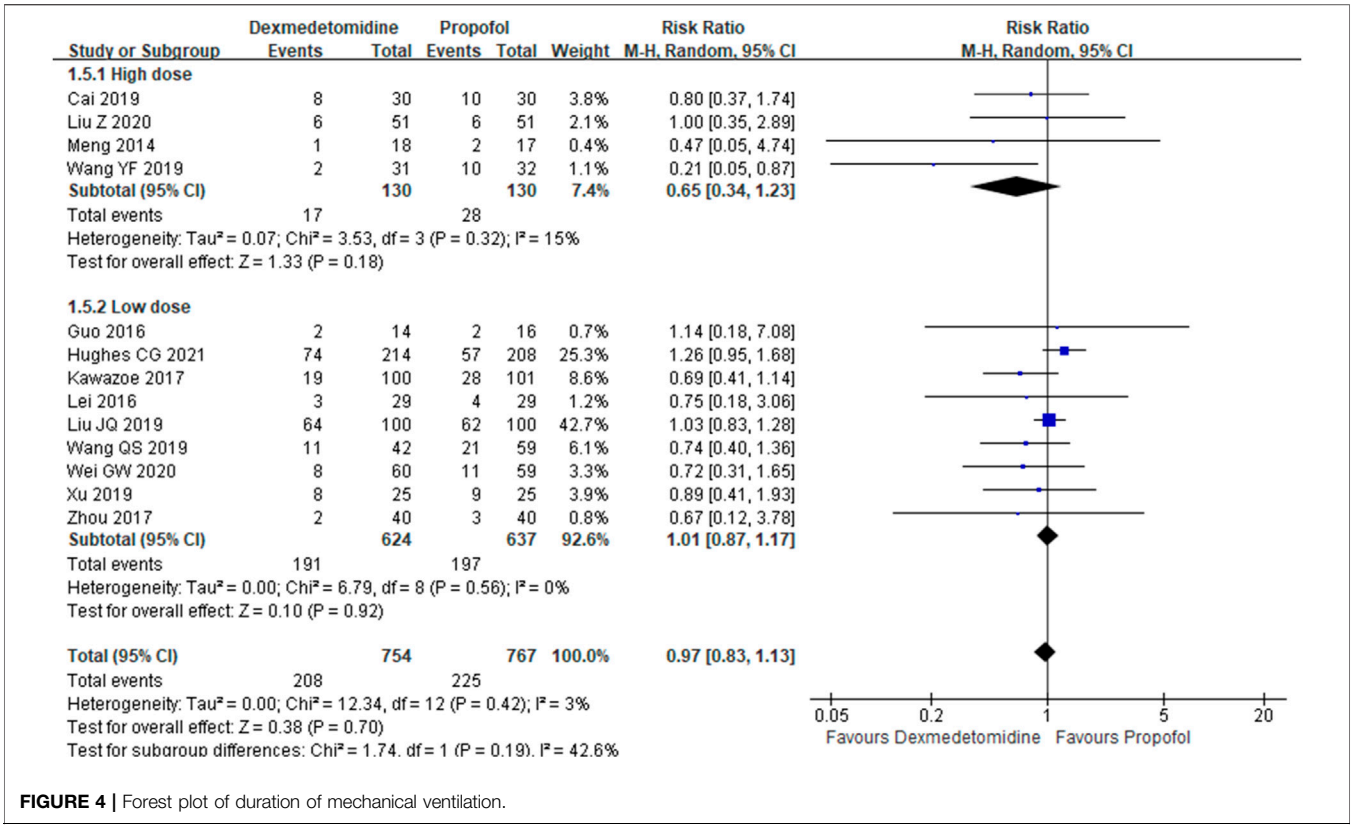

FIGURE 4 | Forest plot of duration of mechanical ventilation.

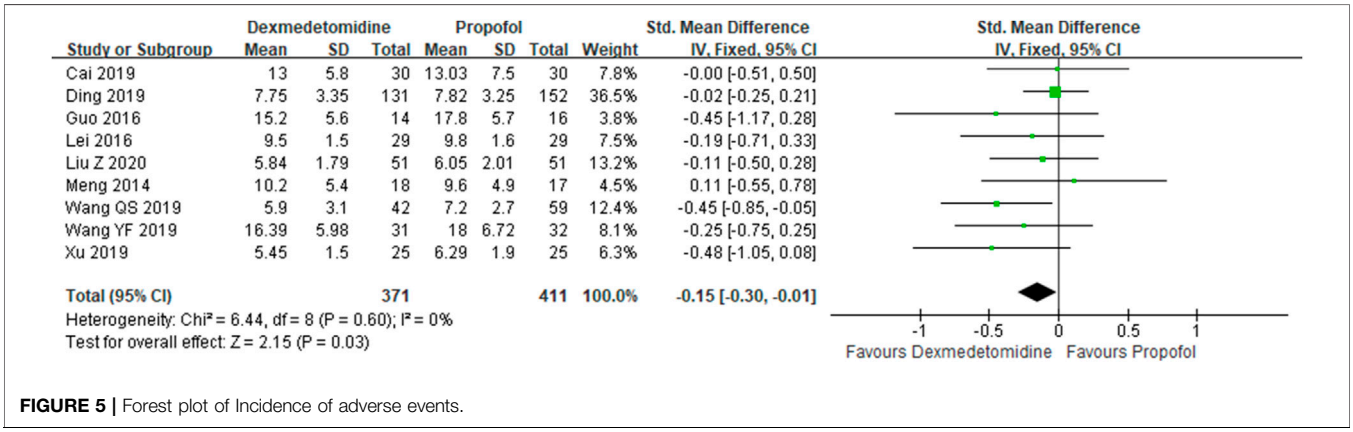

FIGURE 5 | Forest plot of Incidence of adverse events.

level of IL-6 at 24 h (**Table 2**). Thus, based on our analysis, this kind of an important outcome is supposed to be investigated further.

Analysis

Compared with propofol, DEX has been reported to improve patient's ability to communicate pain (Senem et al., 2020). As is known to all, in 2010, a significant randomized controlled trial named MENDS was conducted by Pandharipande PP, et al., which showed that DEX could reduce 28-day mortality in patients with sepsis, compared with those receiving lorazepam (Pandharipande Pratik et al., 2010). This result has brought great interest to researchers. Since then, a large number of studies have been carried out on the treatment of patients suffering from sepsis with dexmedetomidine. In 2017, Kawazoe et al. (2017) conducted a randomized controlled study (DESIRE) to evaluate the efficacy and safety of esmolol in septic shock. The results showed that dexmedetomidine did not obtain statistical significance in mortality. This is a negative result which may affect the use of dexmedetomidine in sepsis. However, we found that although there was no statistical significance, the study may have identified a clinically important advantage of dexmedetomidinean 8% reduction in 28-day mortality. Most randomized controlled trials select 28-day mortality as the primary outcome. In fact,

TABLE 2 | Summary of meta-analysis.

Outcomes	Subgroup	No. of studies	No. of participants	Effect size (95% CI)	*p*
28-day mortality	non-English	10	698	RR, 0.74 (0.54, 1.02)	0.06
	English	3	823	RR, 1.03 (0.79, 1.34)	0.83
	Overall	13	1,521	RR, 0.97 (0.83, 1.13)	0.70
	Low score	9	596	RR, 0.72 (0.52, 1.00)	0.05
	High score	4	925	RR, 1.04 (0.83, 1.29)	0.73
	Overall	13	1,521	RR, 0.97 (0.83, 1.13)	0.70
	High dose	4	260	RR, 0.65 (0.34, 1.23)	0.18
	Low dose	9	1,261	RR, 1.01 (0.87, 1.17)	0.92
	Overall	12	1,521	RR, 0.97 (0.83, 1.13)	0.70
ICU stays	NA	10	966	SMD, -0.16 (-0.29, -0.02)	0.03
Duration of mechanical ventilation	NA	6	345	SMD, −0.22 (−0.44, −0.01)	0.043
Incidence of adverse events	NA	7	889	RR, 0.64 (0.37, 1.11)	0.11
SOFA	NA	3	225	SMD, −0.41 (-0.73, -0.09)	0.013
Levels of IL-6 at 24 h	NA	3	191	SMD, −2.53 (−5.30, 0.24)	0.074
Levels of CK-MB at 72 h	NA	3	420	SMD, −0.45 (−0.83, −0.08)	0.017

Note: SOFA, sequential organ failure assessment; RR, relative risks; WMD, weighted mean difference.

long-term outcomes are very important in the research of sepsis. Until 2021, the latest research conducted by Hughes CG et al. (Hughes Christopher et al., 2021) selected 28-day mortality and 90-day mortality as the survival outcomes. The results said that for mechanically ventilated adult patients with sepsis, DEX did not decrease 90-day mortality in comparison with propofol (38 vs. 39%).

With respect to 28-day mortality, why are results of some studies negative and our results of meta-analysis positive? First, the sample size in most of the included studies is small, which limited the statistical power. For example, the DESIRE study showed a tendency to decrease 28-day mortality, and it is possible that the increase of the sample size would yield positive results. Second, the severity of patients with sepsis included in each study was different, and the therapeutic effect of DEX was also different. For example, the results from DESIRE studies demonstrated that DEX could reduce 28-day mortality (HR 0.39; 95%CI: 0.16–0.91; $p = 0.03$) for sepsis patients with APACHE II ≥23. Therefore, with the deepening of relevant researchers, subgroup analysis of sepsis severity can be carried out in the future to further determine the appropriate population of DEX.

Why is dexmedetomidine beneficial for sepsis? According to the pharmacological mechanism of DEX, it is characterized by sedative and analgesic effects on the nerve activity as well as the inhibitory effect on the sympathetic nerve by activating the α2 receptor (Mohammed et al., 2020). Recently, more and more attention has been paid to the research on organ damage related to sepsis. The heart is one of the organs most frequently damaged by sepsis. The pathogenesis of sepsis cardiac dysfunction is varied, and mitochondrial damage is one of the important mechanisms (Yang and Zhang, 2021). Thus, the mechanism of DEX may manifest that the adrenergic pathway is activated by the α2 receptor, accelerating the metabolism and production of glucose in the body, replenishing and reconstructing damaged mitochondria in time, so as to relieve patient's pain and anxiety as a way to protect their myocardial function.

We know that DEX could reduce the high heart rate, and based on the results, we found that DEX could reduce CK-MB levels. This finding indirectly suggests that DEX indeed has a protective effect on cardiac functions with the mechanism of inhibiting excessive sympathetic response, reducing myocardial oxygen consumption, alleviating myocardial mitochondrial damage, and improving the energy metabolism. Of course, more investigation on its mechanism remains to be launched.

Surprisingly, research studies on the effects of dexmedetomidine other than sedation have also been fruitful. Existing research results have shown that the non-sedative effects of dexmedetomidine mainly include anti-inflammatory and organ protection in an efficient way (Mohammed et al., 2020). The mechanism of action may be related to the activation of the cholinergic anti-inflammatory pathway as well as the cell layer, which needs further confirmation. In addition, our analysis did not demonstrate that DEX reduces IL-6 levels in comparison with propofol. Therefore, DEX may not offer advantages over propofol in terms of anti-inflammatory functions.

Strengths and Limitations

Although two similar reviews have been published (Gao et al., 2019; Chen et al., 2020), there are some differences between our review and the two exiting reviews. First, most of the studies were not included in the exiting two reviews, which became an obstacle to the credibility of the results. Second, our review covers the largest number of studies.

There are several limitations in our meta-analysis. First, only four studies (Kawazoe et al., 2017; Ding et al., 2019; Liu et al., 2020; Hughes Christopher et al., 2021) were published in English. This would limit the extrapolation of results. Second, the sample size is so small in some of the included studies that the statistical power is limited. Third, since the sepsis patients received the comprehensive intervention, the influence of other united medications cannot be excluded.

CONCLUSIONS

This meta-analysis suggests that the 28-day mortality in sepsis patients with the treatment of dexmedetomidine did not differ from those who received propofol. Besides, more high-quality trials are needed to confirm these findings.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

PH and XF created the research idea and designed the study. PH, XZ, and ZL acquired the data. PH, ZL, and XF analyzed and interpreted the data. PH and ZL performed the statistical analysis. Each author contributed significant and intellectual content to the article drafting and assumed responsibility for the overall work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.717023/full#supplementary-material

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Comparison of Safety and Efficacy Between Clopidogrel and Ticagrelor in Elderly Patients With Acute Coronary Syndrome: A Systematic Review and Meta-Analysis

Xiangkai Zhao[1,2,3,4,5†], *Jian Zhang*[1,2,3,4,5†], *Jialin Guo*[1,2,3,4,5], *Jinxin Wang*[1,2,3,4,5], *Yuhui Pan*[1,2,3,4,5], *Xue Zhao*[1,2,3,4,5], *Wentao Sang*[1,2,3,4,5], *Kehui Yang*[1,2,3,4,5], *Fengyang Xu*[1,2,3,4,5], *Feng Xu*[1,2,3,4,5]* and *Yuguo Chen*[1,2,3,4,5]*

[1]Department of Emergency Medicine, Qilu Hospital, Shandong University, Jinan, China, [2]Chest Pain Center, Qilu Hospital, Shandong University, Jinan, China, [3]Shandong Provincial Clinical Research Center for Emergency and Critical Care Medicine, Institute of Emergency and Critical Care Medicine of Shandong University, Qilu Hospital, Shandong University, Jinan, China, [4]Key Laboratory of Emergency and Critical Care Medicine of Shandong Province, Key Laboratory of Cardiopulmonary-Cerebral Resuscitation Research of Shandong Province, Shandong Provincial Engineering Laboratory for Emergency and Critical Care Medicine, Qilu Hospital, Shandong University, Jinan, China, [5]The Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education, Chinese Ministry of Health and Chinese Academy of Medical Sciences, The State and Shandong Province Joint Key Laboratory of Translational Cardiovascular Medicine, Qilu Hospital, Shandong University, Jinan, China

Background: Dual antiplatelet therapy combining aspirin with a P2Y12 adenosine diphosphate receptor inhibitor is a therapeutic mainstay for acute coronary syndrome (ACS). However, the optimal choice of P2Y12 adenosine diphosphate receptor inhibitor in elderly (aged ≥65 years) patients remains controversial. We conducted a meta-analysis to compare the efficacy and safety of ticagrelor and clopidogrel in elderly patients with ACS.
Methods: We comprehensively searched in Web of Science, EMBASE, PubMed, and Cochrane databases through 29th March, 2021 for eligible randomized controlled trials (RCTs) comparing the efficacy and safety of ticagrelor or clopidogrel plus aspirin in elderly patients with ACS. Four studies were included in the final analysis. A fixed effects model or random effects model was applied to analyze risk ratios (RRs) and hazard ratios (HRs) across studies, and I^2 to assess heterogeneity.

Results: A total number of 4429 elderly patients with ACS were included in this analysis, of whom 2170 (49.0%) patients received aspirin plus ticagrelor and 2259 (51.0%) received aspirin plus clopidogrel. The ticagrelor group showed a significant advantage over the clopidogrel group concerning all-cause mortality (HR 0.78, 95% CI 0.63–0.96, I^2 = 0%; RR 0.79, 95% CI 0.66–0.95, I^2 = 0%) and cardiovascular death (HR 0.71, 95% CI 0.56–0.91, I^2 = 0%; RR 0.76, 95% CI 0.62–0.94, I^2 = 5%) but owned a higher risk of PLATO major or minor bleeding (HR 1.46, 95% CI 1.13–1.89, I^2 = 0%; RR 1.40, 95% CI 1.11–1.76, I^2 = 0%). Both the groups showed no significant difference regarding major adverse cardiovascular events (MACEs) (HR 1.06, 95% CI 0.68–1.65, I^2 = 77%; RR 1.04, 95% CI 0.69–1.58, I^2 = 77%).

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Luciane Cruz Lopes, University of Sorocaba, Brazil

Reviewed by:
Fathi M. Sherif, University of Tripoli, Libya
Kyeong Ho Yun, School of Medicine, Wonkwang University, South Korea

***Correspondence:**
Feng Xu
xufengsdu@126.com
Yuguo Chen
chen919085@sdu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Conclusion: For elderly ACS patients, aspirin plus ticagrelor reduces cardiovascular death and all-cause mortality but increases the risk of bleeding. Herein, aspirin plus ticagrelor may extend lifetime for elderly ACS patients compared with aspirin plus clopidogrel. The optimal DAPT for elderly ACS patients may be a valuable direction for future research studies.

Keywords: elderly patients, ticagrelor, clopidogrel, acute coronary syndrome, meta-analysis

INTRODUCTION

Dual antiplatelet therapy (DAPT) combining aspirin with a P2Y12 inhibitor is recommended in patients with ACS (Roffi et al., 2016; Ibanez et al., 2018; Collet et al., 2021). The common P2Y12 inhibitors contain ticagrelor, clopidogrel, prasugrel, and cangrelor (Valgimigli et al., 2018). Elderly ACS patients are commonly accompanied with a higher risk of recurrent ischemic events as well as bleeding complications, raising a critical challenge of selecting the optimal antiplatelet medicine (Capodanno and Angiolillo, 2010). The current guidelines did not give a clear answer to this question (Valgimigli et al., 2018). The problem of antiplatelet strategies in elderly ACS patients had received more clinical attention in recent years, and high-quality clinical studies have been published successively.

Contemporary data from observational studies and randomized controlled trials (RCTs) showed conflicting reports regarding the preference of ticagrelor or clopidogrel in elderly ACS patients. The results of the POPular AGE trial revealed that among elderly patients with non-ST elevation acute coronary syndrome (NSTE-ACS), clopidogrel reduced bleeding events without increasing the combined endpoints of all-cause mortality, myocardial infarction, stroke, and bleeding (Gimbel et al., 2020). However, the summary from a study about the efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese ACS patients showed that ticagrelor reduced the risk of MACEs without increasing the risk of bleeding (Wang and Wang, 2016). Besides, several subgroup data of RCTs drew debatable conclusions, and the analysis from the SWEDEHEART registry showed that aspirin plus ticagrelor was associated with a higher mortality, provoking some uncertainties on its use among the elderly (Wallentin et al., 2009; Husted et al., 2012; Capranzano and Angiolillo, 2020; Szummer et al., 2020). Current research studies could not give a perfect answer to this problem. Herein, we planned to conduct a meta-analysis to compare the efficacy and safety of ticagrelor and clopidogrel in elderly patients with ACS.

MATERIALS AND METHODS

Data Sources and Study Search Strategy

We comprehensively searched in Web of Science, EMBASE, PubMed, and Cochrane databases through 29th March, 2021 for eligible randomized controlled trials (RCTs) using the following keywords: "acute coronary syndrome," "unstable angina," "acute myocardial infarction," "STEMI," "NSTEMI," "dual therapy," "clopidogrel," and "ticagrelor."

Inclusion and Exclusion Criteria

Publications were included if they met the following conditions: 1) the design was a randomized clinical trial, 2) studies contained patients with acute coronary syndrome who were aged ≥65 years, 3) studies compared ticagrelor with clopidogrel, and 4) studies reported all-cause mortality, cardiovascular death, myocardial infarction, stroke, or any bleeding events.

We excluded studies that 1) did not report subgroup results about patients aged ≥65 years and 2) were not designed for humans.

Data Extraction and Endpoints

Two reviewers (Xiangkai Zhao and Jian Zhang) independently extracted data based on the clinical characteristics of the patients, antiplatelet drugs, inclusion criteria, exclusion criteria, and outcomes after a 1-year follow-up.

The primary endpoints were defined as critical death events (all-cause mortality and cardiovascular death). The secondary endpoints were MACEs (a composite of cardiovascular death, myocardial infarction, or stroke) and bleeding events (PLATO major bleeding, PLATO minor bleeding, fatal bleeding, and PLATO major bleeding or PLATO minor bleeding).

Methodological Quality

The study selection, data collection, analysis, and reporting of the results were performed on the basis of the Cochrane Handbook for Systematic Reviews of Interventions published by the Cochrane Collaboration. We conducted statistical analysis using the RevMan 5 [Review Manager (RevMan) computer program, version 5.4.1, the Cochrane Collaboration, 2020]. Heterogeneity was assessed by the Q-statistic ($p \leq 0.05$ was considered statistically significant) and I^2 statistical test. Publication bias was visually estimated by using funnel plots. The fixed effects model ($I^2 \leq 50\%$) or random effects model ($I^2 > 50\%$) was used to analyze risk ratios (RRs) or hazard ratios (HRs) across studies. Sensitivity analysis was carried out by using the method of checking the influence of an individual trial on the pooled endpoints by excluding each trial solely. Any discrepancies between the reviewers were solved by discussion. Risk of bias composites randomization generation, allocation concealment, blinding assessment, completeness of follow-up, absence of selective reporting, and other potential biases. The risk of bias of each study was assessed by the Cochrane Collaboration tool. The Grading of Recommendation, Assessment,

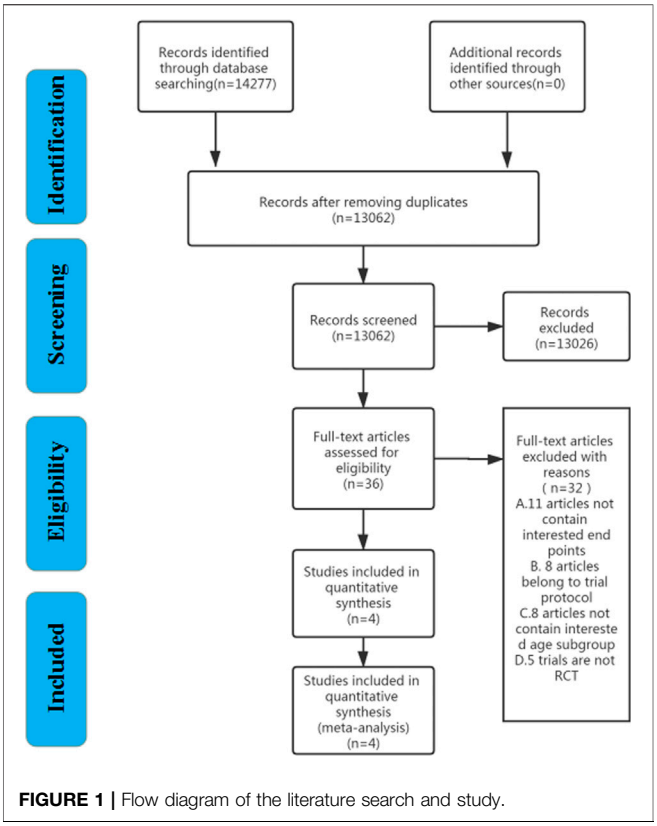

FIGURE 1 | Flow diagram of the literature search and study.

Development, and Evaluation (GRADE) tool was used for the assessment of the reliability of each outcome. The certainty of the evidence was appraised as high, moderate, low, or very low.

COMPLIANCE WITH ETHICS GUIDELINES

We conducted this study based on previously published studies, and no patients or public were involved in this study.

RESULTS

Study Selection

In total, 13,062 articles were identified through the Web of Science, EMBASE, PubMed, and Cochrane databases (**Supplementary Table S1**). 13,026 articles were excluded by screening the title and abstract. At last, a total of 36 articles in full text were read, and only four clinical trials (Wallentin et al., 2009; Wang and Wang, 2016; Park et al., 2019; Gimbel et al., 2020) fulfilled the eligibility criteria. The literature search and screening processes are presented in **Figure 1**.

Major Characteristics of the Included Studies

The characteristics of the included studies are shown in **Table 1**. Four studies were included in the final analysis, and all four were prospective randomized controlled trials and reported their results for the 1-year follow-up period. A total number of 4,429 elderly patients with ACS were included in this analysis, 2,170 (49.0%) patients received aspirin plus ticagrelor, and 2,259 (51.0%) received aspirin plus clopidogrel. All participants were 65 years or older. ACS patients were treated with ticagrelor or clopidogrel on the basis of aspirin.

Risk of Bias and Study Quality

The assessment of the risk of bias of each study is shown in **Supplementary Figure S1**, and all four trials had shown a low risk of bias. GRADE assessment shows that the outcomes of MACEs, all-cause mortality, cardiovascular death, MI, and stroke are of high quality, and PLATO major bleeding, PLATO minor bleeding, fatal bleeding, PLATO major or minor bleeding, and stent thrombosis are of low quality (**Supplementary Table S2**). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to improve the reporting quality of our study (**Supplementary Table S3**).

Primary Outcomes

After a 1-year follow-up, elderly ACS patients who received ticagrelor performed a lower event rate in all-cause mortality (HR 0.78, 95% CI 0.63–0.96, I^2 = 0%; RR 0.79, 95% CI 0.66–0.95, I^2 = 0%) (**Figure 2**) and cardiovascular death (HR 0.71, 95% CI 0.56–0.91, I^2 = 0%; RR 0.76, 95% CI 0.62–0.94, I^2 = 5%) (**Figure 3**).

Secondary Outcomes

After 1 year of receiving DAPT therapy, ticagrelor showed clinical equipoise in terms of MACEs (HR 1.06, 95% CI 0.68–1.65, I^2 = 77%; RR 1.04, 95% CI 0.69–1.58, I^2 = 77%) (**Figure 4**), MI (HR 0.92, 95% CI 0.74–1.15, I^2 = 44%; RR 0.94, 95% CI 0.77–1.14, I^2 = 45%) (**Supplementary Figure S2**), stroke (HR 1.55,95% CI 0.98–2.46, I^2 = 0%; RR 2.05, 95% CI 1.31–3.22, I^2 = 0%) (**Supplementary Figure S3**), and stent thrombosis (RR 0.44, 95% CI 0.06–3.42, I^2 = 57%) (**Supplementary Figure S4**). As for bleeding risk, the patients who received ticagrelor showed a higher risk of PLATO major or minor bleeding (HR 1.46, 95% CI 1.13–1.89, I^2 = 0%; RR 1.40, 95% CI 1.11–1.76, I^2 = 0%) (**Figure 5**). When focused on lethal bleeding (RR 2.71, 95% CI 0.8–9.13, I^2 = 44%) (**Figure 6**), both PLATO major bleeding (HR 1.39, 95% CI 0.94–2.04, I^2 = 0%; RR 1.38, 95% CI 0.95–2.00, I^2 = 0%) (**Supplementary Figure S5**) and PLATO minor bleeding (HR 1.37, 95% CI 1.00–1.90, I^2 = 0%; RR 1.33, 95% CI 0.99–1.80, I^2 = 0%) (**Supplementary Figure S6**) groups showed a similar risk.

DISCUSSION

The primary finding of our study is that after a 1-year follow-up, aspirin plus ticagrelor reduced all-cause mortality and cardiovascular death but owned a higher risk of PLATO major or minor bleeding than aspirin plus clopidogrel. Our findings provided a new clinical thought for a better choice of P2Y12 adenosine diphosphate receptor inhibitor for elderly ACS patients.

TABLE 1 | Characteristics of the included trials.

	Duk-Woo 2020		Gimbel et al. (2020)		Huidong Wang and Wang (2016)		Wallentin et al. (2009)	
	Ti	Cl	Ti	Cl	Ti	Cl	Ti	Cl
Study type	RCT		RCT		RCT		RCT	
Age (years)	≥65		≥70		≥65		≥75	
Number of patients	172	177	502	500	100	100	1396	1482
Men	ND		65%	63%	69%	66%	56.5%	
Hypertension	ND		73%	73%	79%	82%	75.2%	
Diabetes	ND		30%	29%	42%	39%	28.1%	
Dyslipidemia	ND		65%	65%	84%	79%	46.1%	
Prior MI	ND		27%	24%	17%	15%	26.5%	
Prior PCI	ND		24%	20%	3%	5%	14.6%	
Prior CABG	ND		17%	17%	0	0	8.9%	
CHF	ND		ND	ND	13%	19%	10.5%	
TIA	ND		8%	7%	16%	14%	4.8%	
Smoker	ND		13%	14%	37%	41%	10%	
Diagnosis								
STEMI	ND		0	0	37%	32%	25.9%	
NSTEMI	ND		86%	86%	44%	47%	52.6%	
Unstable angina	ND		11%	11%	19%	21%	19.1%	
Coronary angiography during study	ND		90%	88%	86%	83%	44%	
PCI during study	ND		48%	46%	75%	71%	23.2%	
CABG during study	ND		17%	16%	0	0	8.1%	
Drug dose								
LD	180 mg.bid	600 mg.qd	180 mg.bid	300 or 600 mg.qd	180 mg.bid	300 mg.qd	180 mg.bid	300–600 mg.qd
MD	90 mg.bid	75 mg.qd	90 mg.bid	75 mg.qd	90 mg.bid	75 mg.qd	90 mg.bid	75 mg.qd
Follow-up (month)	12		12		12		12	
Clinical events	MACEs and PLATO major or minor bleeding		MACEs and PLATO major and minor bleeding,12,3,4,5,6,7,8		MACEs, 1,2,3,4,5,6, and 7		MACEs,1,2,3,4, and 8	

Ti, ticagrelor; Cl, clopidogrel; LD, loading dose; MD, maintenance dose; MACEs, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, chronic cardiac failure; TIA, transient ischemic attack; STEMI, ST segment elevation myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; ND, no data; qd, once a day; bid, twice a day. 1 = all-cause mortality, 2 = cardiovascular death, 3 = MI, 4 = stroke, 5 = PLATO major bleeding, 6 = plato minor bleeding, 7 = life-threatening bleeding, 8 = stent thrombosis.

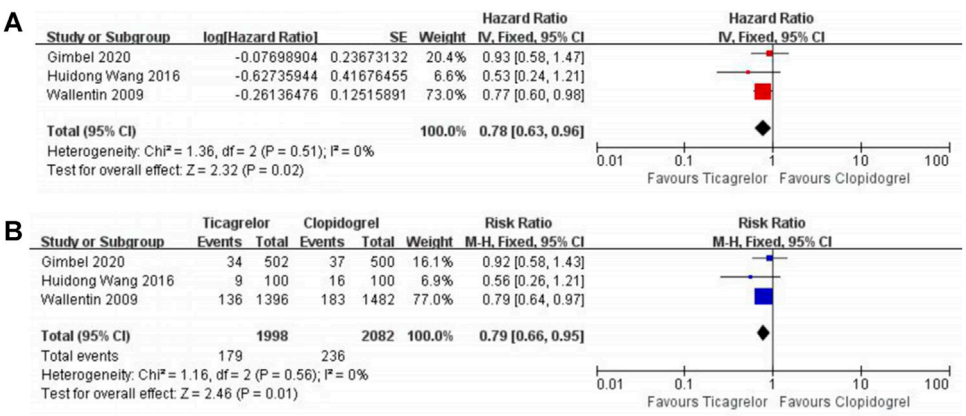

FIGURE 2 | Meta-analysis with HR **(A),** RR **(B)**, and 95% CI for all-cause mortality. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI. The size of the box is proportional to the weight of the study in the meta-analysis. HR, hazard ratio; RR, risk ratio; CI, confidence interval.

Dual antiplatelet therapy combining aspirin with a P2Y12 adenosine diphosphate receptor inhibitor is a standard regimen for ACS. For the included RCTs, all studies were conducted on the basis of aspirin, so the end events were used for comparing the safety and efficacy between clopidogrel and ticagrelor.

The current guidelines recommended aspirin plus ticagrelor in patients with acute coronary syndrome (Valgimigli et al., 2018), but there was no explicit suggestion for elderly ACS patients. According to the report of the Philippine Heart Association ACS registry, the incidence of ACS was higher in the elderly (Reano

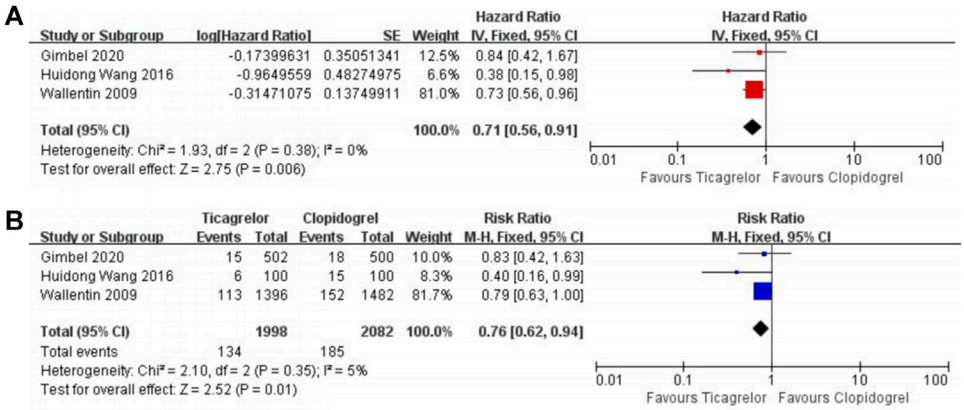

FIGURE 3 | Meta-analysis with HR **(A),** RR **(B)**, and 95% CI for cardiovascular death. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI. The size of the box is proportional to the weight of the study in the meta-analysis. HR, hazard ratio; RR, risk ratio; CI, confidence interval.

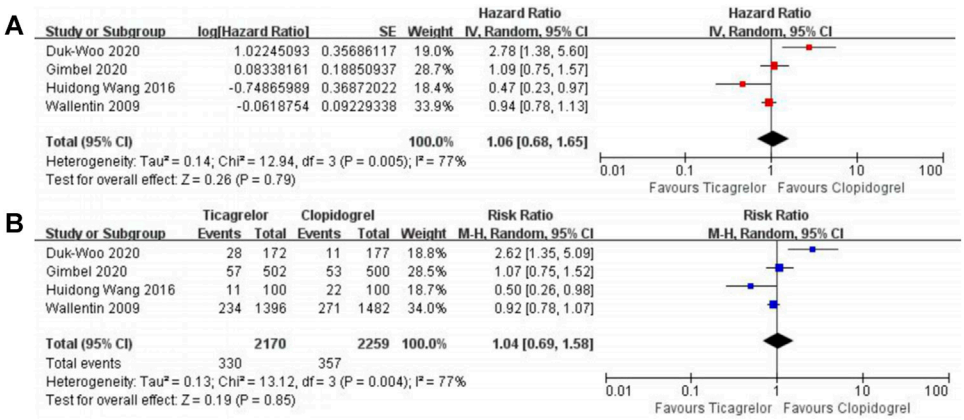

FIGURE 4 | Meta-analysis with HR **(A),** RR **(B)**, and 95% CI for the composite of cardiovascular death, myocardial infarction, and stroke. The boxes are the relative risk estimates from each study; the horizontal bars are 95% CI. The size of the box is proportional to the weight of the study in the meta-analysis. HR, hazard ratio; RR, risk ratio; CI, confidence interval.

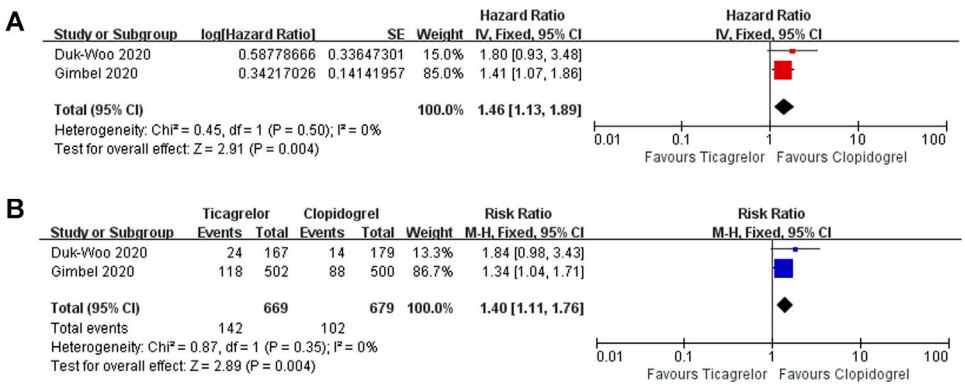

FIGURE 5 | Meta-analysis with HR **(A),** RR **(B)**, and 95% CI for the PLATO major bleeding or minor bleeding. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI. The size of the box is proportional to the weight of the study in the meta-analysis. HR, hazard ratio; RR, risk ratio; CI, confidence interval.

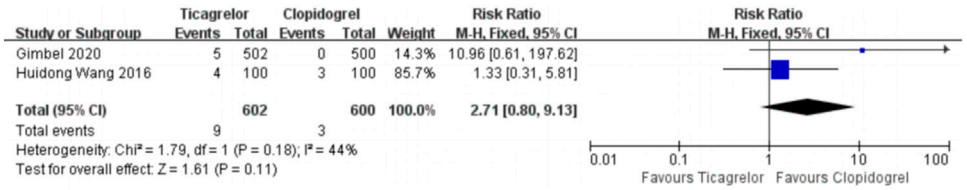

FIGURE 6 | Meta-analysis with RR and 95% CI for fatal bleeding. Boxes are the relative risk estimates from each study; the horizontal bars are 95% CI. The size of the box is proportional to the weight of the study in the meta-analysis. HR, hazard ratio; RR, risk ratio; CI, confidence interval.

et al., 2020). At the same time, older age groups were often excluded from clinical studies. Thus, the optimal choice of P2Y12 adenosine diphosphate receptor inhibitor for elderly patients was necessary to be confirmed as soon as possible. Data from different studies did not reach a consensus for this academic problem. In the famed PLATO study, the ticagrelor group showed significant advantages in reducing the risk of cardiovascular death (HR 0.73, CI 0.56–0.96, $p = 0.47$) and all-cause mortality (HR 0.77, CI 0.60–0.98, $p = 0.76$) *versus* clopidogrel in the subgroup which contained patients aged ≥75 years old, without increasing the overall bleeding risk (HR 1.02, CI 0.82–1.27, $p = 0.89$) (Wallentin et al., 2009). However, an RCT aiming to explore efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese ACS patients drew a different conclusion. Ticagrelor owned an extra advantage in reducing the risk of a composite of cardiovascular death, MI, and stroke (HR 0.473, CI 0.230–0.976, $p = 0.043$) (Wang and Wang, 2016). Surprisingly, the results of the POPular AGE trial revealed that ticagrelor increased the risk of bleeding with no superior co-primary net clinical benefit outcome (Gimbel et al., 2020), which posed a challenge to the traditional opinion about the ticagrelor advantage theory and stimulated our interests in exploring this issue. Our research studies supported the ticagrelor advantage theory that ticagrelor could reduce the risk of all-cause mortality and cardiovascular death. In other words, ticagrelor may extend survival time for elderly ACS patients compared with clopidogrel.

For the outcomes of MACEs, ticagrelor and clopidogrel showed comparable clinical benefits. The probable sources of heterogeneity for the outcomes of MACEs may come from different age cutoffs (Wallentin et al., 2009). The study by Wallentin et al. (2009) had cutoffs of 65 years (HR) and 75 years (RR), and the remaining study data had cutoffs of 65 (Wang and Wang, 2016), 70 (Gimbel et al., 2020), and 75 (Park et al., 2019) years. According to our results, when focusing on all-cause mortality and cardiovascular death solely, ticagrelor showed a significant advantage compared to clopidogrel in elderly ACS patients. Our results suggested that ticagrelor may have a higher application value in the advanced age-group.

Shreds of evidence suggested that ticagrelor had a higher risk of bleeding (Gimbel et al., 2020; Johnston et al., 2020; Silvain et al., 2020). Our research studies further confirmed this issue. Ages of the patients and drug properties were crucial reasons for higher bleeding risk. Age was a validated predictor of adverse prognosis, and the risk of bleeding increased with age (Eagle et al., 2004). Elderly patients with ACS often have multiple comorbidities, as well as a gradual decline in organismal function with advancing age. Age-related changes in thrombotic status, decreased vascular repair capacity, and clinical factors may lead to a greater difference in the safety of antiplatelet agents in the elderly than in young patients (Lopes and Alexander, 2009). As for the medication itself, ticagrelor works faster and more effectively. Ticagrelor has a binding site different from adenosine diphosphate, making its inhibition reversible. Besides, it can activate *CYP2C19* without the liver, so ticagrelor has a stronger antiplatelet effect than clopidogrel (Birkeland et al., 2010; Guan et al., 2018). Stronger antiplatelet effect is commonly associated with a higher risk of bleeding, so an appropriate antiplatelet strategy is important for ACS patients, especially for elderly patients.

A higher risk of bleeding is not an absolute contraindication to the application of ticagrelor. According to our results, ticagrelor is a preferable choice compared with clopidogrel in reducing the occurrence of death in most elderly ACS patients. The occurrence of fatal or irreversible bleeding events is one of the main factors affecting the long-term survival of patients. Our results revealed that ticagrelor or clopidogrel shared a similar risk of fatal bleeding. Additional management measures were necessary for patients with ACS who were under a higher bleeding risk. For this issue, a recent clinical investigation indicated that ticagrelor monotherapy might be a suitable alternative option (Mehran et al., 2019). In addition, shortening DAPT duration (Palmerini et al., 2017) and enhancing the education of high-risk patients and their families are valuable in preventing bleeding events. Fatal or irreversible ischemia was also a clinically significant event for elderly ACS patients, the ATLAS ACS 2-TIMI 51 revealed an interesting phenomenon, and rivaroxaban therapy at an oral dose of 2.5 mg twice daily in patients treated with aspirin and clopidogrel was associated with a net reduction in fatal or irreversible events (Gibson et al., 2018). Therefore, with reasonable precautions, the risk of bleeding with ticagrelor could be minimized as much as possible.

Our meta-analysis has several advantages over previous research studies. First, we were the first to systematically conduct a meta-analysis of clopidogrel *versus* ticagrelor in elderly patients with ACS. Second, we used both RR and HR to comprehensively demonstrate the findings. Third, for high bleeding risk, we conducted a systematic analysis and gave reasonable monitoring and preventive suggestions. Finally, this meta-analysis gave a new direction for the prospective studies.

There are several limitations to our meta-analysis. First, our meta-analysis only contains four RCTs which may not reflect the real world, and two datasets of the included articles come from the subgroup analysis. We could not get individual patient data, so a detailed age-stratified analysis or the analysis of other

bleeding definitions could not be performed. Second, in the study of the POPular AGE trial, 5% of patients in the ticagrelor group received prasugrel, which may result in the final results being subjected to some errors. Third, two studies are open-labeled randomized trials, introducing the potential for latent performance bias. In addition, we found the heterogeneity of Duk-Woo 2020 was significant when the heterogeneity tests were performed by sequential deletion. The probable reason might be that most patients received percutaneous coronary intervention in Duk-Woo 2020.

CONCLUSION

Our results reveal that aspirin plus ticagrelor reduces cardiovascular death and all-cause mortality but increases the risk of PLATO major bleeding or PLATO minor bleeding when compared with aspirin plus clopidogrel in elderly ACS patients. Herein, aspirin plus ticagrelor may extend lifetime for elderly ACS patients compared with aspirin plus clopidogrel. The low sample size of current studies cannot support a definite conclusion for this vital issue. Further studies focusing on DAPT of elderly ACS patients with larger population are still needed.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

XZ and JZ: writing—original draft. JG: methodology, software, and visualization. JW, YP, XZ, WS, KY, and FYX: data curation. FX and YC: writing—reviewing and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.743259/full#supplementary-material

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Potentially Inappropriate Medications and Potential Prescribing Omissions in Elderly Patients Receiving Post-Acute and Long-Term Care: Application of Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment Criteria

Catarina Candeias[1,2], *Jorge Gama*[3], *Márcio Rodrigues*[1,4,5], *Amílcar Falcão*[6,7] and *Gilberto Alves*[1,4,8]*

[1]CICS-UBI–Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal, [2]UMP–Union of Portuguese Mercies, Lisboa, Portugal, [3]CMA-UBI–Centre of Mathematics and Applications, University of Beira Interior, Covilhã, Portugal, [4]ESALD-IPCB–Dr. Lopes Dias School of Health, Polytechnic Institute of Castelo Branco, Castelo Branco, Portugal, [5]UDI-IPG–Research Unit for Inland Development, Polytechnic Institute of Guarda, Guarda, Portugal, [6]CIBIT–Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, Coimbra, Portugal, [7]Laboratory of Pharmacology, Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal, [8]UFBI–Pharmacovigilance Unit of Beira Interior, University of Beira Interior, Covilhã, Portugal

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Edited by:
Marcio Galvao Oliveira,
Universidade Federal da Bahia, Brazil

Reviewed by:
Roger E. Thomas,
University of Calgary, Canada
Wuraola Akande-Sholabi,
University of Ibadan, Nigeria

***Correspondence:**
Gilberto Alves
gilberto@fcsaude.ubi.pt

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Background: Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria have been used to detect potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs). These criteria were applied to geriatric Portuguese patients receiving post-acute and long-term care to assess the prevalence and predictors of PIMs and PPOs.

Methods: An observational, retrospective, cross-sectional and multicenter study was performed in 161 patients (aged ≥65 years) from eight Units for Integrated Continuous Care.

Results: In these studied patients (mean age: 81.6, 64% female, median number of medications: 9) PIMs were detected in 85.1% and PPOs in 81.4% of patients. While PIMs mainly involved the central nervous system and psychotropic drugs (66.5%), PPOs were mostly related to musculoskeletal system (55.3%) and cardiovascular (39.8%) system. A subsequent analysis with logistic regression found the female gender, the hospital provenience, and the number of medications as predictors of PIMs. Predictors of PPOs were the Charlson Comorbidity Index and history of recent fractures.

Conclusion: PIMs and PPOs were highly prevalent in the studied patients receiving post-acute and long-term care in Units for Integrated Continuous Care. Therefore, STOPP/START criteria might be an effective tool for improving prescribing quality and clinical outcomes in these frail elderly patients.

Keywords: STOPP criteria, START criteria, inappropriate prescribing, prescribing omissions, elderly, Portuguese patients

INTRODUCTION

Potentially inappropriate prescribing refers either to 1) potentially inappropriate medications (PIMs), the use of drugs where no clear clinical indication exists (*overprescribing*) or the use of an indicated drug where the risk outweighs the benefit or when a safer or more effective alternative is available (*misprescribing*) or 2) potential prescribing omissions (PPOs), not prescribing a beneficial medicine for which there is a clear clinical indication (*underprescribing*) (O'Mahony and Gallagher, 2008; O'Connor et al., 2012; Moriarty et al., 2015). In older people, this subject has been increasingly explored because of the relationship between potentially inappropriate prescribing and negative clinical outcomes, namely the occurrence of adverse drug reactions (ADRs) (Lindley et al., 1992; Hedna et al., 2015), risk of hospitalization, hospital readmission, lower quality of life, and even mortality (Akazawa et al., 2010; Dedhiya et al., 2010; Brown et al., 2014; Cahir et al., 2014; Thomas et al., 2020). This may be related to polypharmacy, which has been identified as a determinant factor for potentially inappropriate prescribing (Akazawa et al., 2010; Cahir et al., 2010; Bradley et al., 2012). Another concern is the cost, since the total expenditure on potentially inappropriate prescribing has been reported to be 9% of the global expenditure on pharmaceuticals in people aged 70 or over (Cahir et al., 2010). Moreover, in PIM users it was found an increase of 33% in healthcare medical costs comparatively with nonusers (Akazawa et al., 2010). Besides, it is also important to consider the potential impact of aging in drug elimination, because aging involves progressive impairments in the functional reserve of multiple organs such as liver and kidneys (Thomas, 2020). Considering that the number of people aged 65 years or over is projected to double, from 703 million to 1.5 billion, between 2019 and 2050, reaching a proportion of 16% worldwide (United Nations, D.o.E.a.S.A., Population Division, 2019) the high prevalence of PIMs in the elderly (Akazawa et al., 2010; Brown et al., 2014; Onder et al., 2014) is a current problem that will likely to be even worse in the future in this age group. Therefore, potentially inappropriate prescribing is a major concern that claims for measures that allow the detecting and reducing of its occurrence.

In order to improve prescribing, screening tools based on explicit criteria have been extensively used, being the earliest the Beers list (Beers et al., 1991), which was mainly applicable in the United States of America and has been updated in 2019 (American Geriatrics Society Beers Criteria® Update Expert Panel, 2019). Although this list was undoubtedly important to the advances in the study of PIMs, the criteria used could not be easily applied in European countries. Therefore, in the last decade, a European-based tool was also developed to detect PIMs and PPOs, respectively: 1) the Screening Tool of Older People's Prescriptions (STOPP); and 2) Screening Tool to Alert to Right Treatment (START) (Gallagher et al., 2008; O'Mahony et al., 2015). The STOPP and START criteria consist of a list of PIMs and a list of PPOs, respectively, which complement each other. STOPP criteria can play an important role in reducing PIMs rates (Hill-Taylor et al., 2016), while START criteria aim to reduce underprescribing (Cherubini et al., 2012) by identifying PPOs. Meanwhile, Corsonello et al. (2012) reported that the STOPP/START criteria, compared to the Beers criteria, show a greater ability to predict ADRs and prevent potentially inappropriate prescribing. In addition, the STOPP/START criteria seemed to afford a good inter-rater reliability when the evaluations carried out by pharmacists from different sectors were compared (Ryan et al., 2009a). However, for that, it is important to have full access to the clinical information; otherwise, PIMs and PPOs detection can be overestimated and underestimated, respectively (Ryan et al., 2013b).

The STOPP/START criteria have been applied to different target populations of different settings [such as hospital, nursing homes, community-dwelling, primary care, and post-acute care (PAC) and long-term care (LTC)]. For instance, a meta-analysis of 28 studies in elderly patients showed that the prevalence of PIMs and PPOs was high, with the highest values observed in hospitalized patients and nursing homes, compared to community dwelling-individuals for national outpatient databases small community studies (Thomas, 2016). In another meta-analysis, including both PAC and LTC patients, it was demonstrated that the STOPP/START criteria may be effective in improving prescribing quality, clinical, humanistic and economic outcomes (Hill-Taylor et al., 2016). However, while Hill-Taylor et al. (2016) reported less falls, delirium episodes, hospital length-of-stay, care visits, and medication costs, they found no association with improvements in quality of life or mortality. More recent evidence, Thomas et al. (2020) suggests that both PIMs and PPOs were significantly associated with hospital readmission and mortality within 6 months.

In Portugal, there are few examples of investigations using the START/STOPP criteria (Silva et al., 2015; da Costa et al., 2016). However, no one to the best of our knowledge has included the Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCIs) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI). Therefore, the present study was carried out to: 1) determine the prevalence of PIMs and PPOs (overall and per individual STOPP and START criteria, respectively); and 2) potential predictors of PIMs and PPOs among demographic and clinical features of elderly patients who received PAC/LTC in UCCIs of the RNCCI.

PATIENTS AND METHODS

Study Design, Setting, and Participants

An observational, retrospective, cross-sectional, multicenter study was performed in 161 patients aged ≥65 years from UCCIs in the central region of Portugal, between June 2015 and April 2016. The UCCIs belong to the category of patient units and provide continuous support to frail people, for rehabilitation in PAC and for people with mental, social, and physical limitations who need LTC. According to each patient needs and goals established, the length of stay usually varied between

30 and 180 consecutive days. All patients are monitored by a multidisciplinary team of various professionals, such as doctors, nurses, pharmacists, physiotherapists, social workers, psychologists, speech therapists, occupational therapists, and nutritionists. To reduce bias associated with the type of hospitalization and healthcare team, the data were collected from eight UCCIs.

The retrospective nature of the study did not affect healthcare provision to patients, and informed consent was not required. Patients' data were anonymized through the attribution of an alphanumeric code and access restricted to the first author. The subsequent analysis was performed exclusively using the encoded data.

Data Sources

Data were mainly collected from RNCCI's platform, which is an online tool implemented in the RNCCI in Portugal. In this platform, all relevant patient information is recorded, namely, discharge summaries, periodic evaluations performed by different professionals (such as physicians, nurses, physiotherapists, psychologists, social workers, and nutritionists), diagnoses, prescribed drugs, medical exams, nutrition status, dependence in activities of daily life, products spent (e.g., ostomy, wound or incontinence products), identification of need for social support and results of medical scales application (e.g., risk of falls, pressure ulcer risk assessment, calculation of the risk of developing type 2 diabetes mellitus in the next 10 years and pain evaluation). In addition, patient clinical history was complemented with other existent documents (e.g., patient diary) whenever possible and necessary.

Data Collection and Analysis

A detailed analysis was used for each patient by a pharmacist, including demographic and clinical data, namely, all current diagnoses (not only those coded through ICD-9-CM), relevant clinical information reported from the first medical evaluation (before to the actual internment) until discharge and an update on the latest therapeutic list. All pharmaceutical dosage forms including oral, parenteral, topical, ophthalmological, and inhaled medications, taken on a regular basis (excluding SOS medications) were considered. If a fixed-dose combination of drugs was used in the same medication, it was only counted as one. Polypharmacy (intake of ≥5 drugs per day), comorbid diseases, Charlson Comorbidity Index (Charlson et al., 1987) (CCI ≥ 4 and CCI ≥ 6), dependency in activities of daily life (ADL), risk of falls (medium to high), malnutrition/anorexia, obesity, pressure ulcers and history of recent fractures were also considered as geriatric syndromes. Continuous variables were expressed as mean ± standard deviation, median and inter-quartile range (P25; P75), and categorical variables as the number of observations (absolute frequency) and percentages (relative frequency). To identify the determinants of PIMs and PPOs, variables with a significant association with PIMs or PPOs at the univariate level were tested using a multivariate analysis. Logistic regression analysis, with logit link function, was performed using the forward selection method based on the Wald test to find independent predictors associated with PIMs or PPOs. Also, odds ratios (ORs) were adjusted for possible confounding variables, and results were reported only for variables with a $p < 0.1$. The Hosmer-Lemeshow test was performed to assess the goodness of fit, whereas the area under the receiver operating characteristic curve allowed the evaluation of discriminatory power of the model and its sensitivity/specificity. Differences were considered statistically significant when $p < 0.05$ and the confidence interval (CI) was set at 95%. IBM SPSS Statistics version 23 was used to analyse all the data.

RESULTS

Characteristics of the Study Population

Table 1 details patients' demographic characteristics and medical history. From 161 patients 103 were female (64.0%). The average age of patients was 81.6 years and the medical history demonstrated higher provenience from the hospital (50.9%). The median length-of-stay in UCCIs was 93 days and 61 patients returned home (37.9%; **Table 1**). Of the remaining 100, the highest number either died during the internment (28 patients) or has been transferred to another RNCCI response (28 patients; **Table 1**). **Table 2** demonstrates that inpatients frequently took a median of 9 (P25: 6; P75: 11) drugs per day, totaling a median of 10 (P25: 7; P75: 13) daily oral doses, a CCI median of 6 (P25: 5; P75: 7) and 21 patients were fed by enteral nutrition (13.0%). Regarding geriatric syndromes, 147 patients had polypharmacy, 143 had high levels of dependency and 131 presented risk of falls (91.3, 88.8, and 81.4%, respectively; **Table 2**). Most common comorbidities were hypertension (68.3%), cerebrovascular disease (34.8%), depression (34.2%), diabetes mellitus (33.5%) and constipation (33.5%; **Table 3**).

Potentially Inappropriate Medications

According to STOPP criteria, patients had a median of 3 [1; 4] PIMs (range 0–10), with 85.1% of them presenting at least one and about a fifth had five or more PIMs in their list of prescriptions (**Table 4**). Sections with higher frequency of PIMs were found in "Central Nervous System and psychotropic drugs" (66.5%) and "drugs that predictably increase the risk of falls in older people" (65.8%). Among "Central Nervous System and psychotropic drugs" section, the most common PIMs in patients were benzodiazepines for ≥4 weeks (D5; 51.6%; **Table 5**), tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (D1; 15.5%; **Table 5**), and anticholinergics/antimuscarinics in patients with delirium or dementia (D7; 13.7%; **Table 5**). Among "drugs that predictably increase the risk of falls in older people" were benzodiazepines (K1; 54.0% **Table 5**) and neuroleptics (K2; 24.8%; **Table 5**).

In the multivariate analysis (**Table 6**), PIMs were found to be significantly associated with gender (F/M) (OR = 4.04, 95%CI: 1.27; 12.84), hospital provenience (OR = 3.43, 95%CI: 1.10; 10.69), number of medications (OR = 1.32, 95%CI: 1.09; 1.60), cerebrovascular disease (OR = 0.29, 95%CI: 0.10; 0.89) and Parkinson's disease (OR = 0.06, 95%CI: 0.00; 0.84).

TABLE 1 | Demographic characteristics and medical history of study population (*N*=161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

		STOPP criteria				START criteria			
	Total	**PIMs**	**No PIMs**	**Not adjusted OR (95%CI)**	***p*[a]**	**PPOs**	**No PPOs**	**Not adjusted OR (95%CI)**	***p*[a]**
Demographic characteristics									
Age (years)				1.01 (0.95; 1.07)	0.827			1.04 (0.99; 1.10)	0.123
Mean ± SD	81.6 ± 7.4	81.7 ± 7.0	81.3 ± 9.8			82.0 ± 7.4	79.7 ± 7.6		
Median (P25; P75)	82 (76.5; 86.5)	82 (77; 86)	80.5 (74; 88.5)			82 (78; 87)	78.5 (75; 85)		
Gender, *n* (%)									
Male	58 (36.0)	43 (31.4)	15 (62.5)	1		48 (36.6)	10 (33.3)	1	
Female	103 (64.0)	94 (68.6)	9 (37.5)	3.64 (1.48; 8.98)	0.005	83 (63.4)	20 (66.7)	0.87 (0.37; 2.00)	0.734
Medical history									
Provenience/Origin, *n* (%)									
Hospital	82 (50.9)	74 (54.0)	8 (33.3)	2.74 (1.09; 6.87)	0.031	65 (49.6)	17 (56.7)	0.79 (0.35; 1.80)	0.575
Residence	70 (43.5)	54 (39.4)	16 (66.7)	1		58 (44.3)	12 (40.0)	1	
Nursing home	5 (3.1)	5 (3.6)	0 (0.0)	—		4 (3.1)	1 (3.3)	0.83 (0.09; 8.07)	0.871
Primary care	2 (1.2)	2 (1.5)	0 (0.0)	—		2 (1.5)	0 (0.0)	—	
Other	2 (1.2)	2 (1.5)	0 (0.0)	—		2 (1.5)	0 (0.0)	—	
Provenience/Origin, *n* (%)									
Hospital	82 (50.9)	74 (54.0)	8 (33.3)	2.35 (0.94; 5.85)	0.067	65 (49.6)	17 (56.7)	0.75 (0.34; 1.68)	0.487
Residence or other	79 (49.1)	63 (46.0)	16 (66.7)	1		66 (50.4)	13 (43.3)	1	
Length of stay				1.00 (1.00; 1.01)	0.182			1.00 (1.00; 1.00)	0.652
Mean ± SD	146.1 ± 190.7	154.8 ± 204.0	96.0 ± 62.3			149.3 ± 183.9	131.8 ± 221.1		
Median (P25; P75)	93 (65; 163.5)	98 (65; 167.5)	90 (68.5; 95)			97 (79; 168)	90 (42.5; 112)		
Discharge to, *n* (%)									
Residence	61 (37.9)	47 (34.3)	14 (58.3)	0.26 (0.05; 1.23)	0.088	44 (33.6)	17 (56.7)	0.52 (0.06; 4.76)	0.561
Death	28 (17.4)	26 (19.0)	2 (8.3)	1.00 (0.13; 7.64)		27 (20.6)	1 (3.3)	5.40 (0.29; 101.28)	0.260
Another RNCCI response	28 (17.4)	26 (19.0)	2 (8.3)	1	1.000	22 (16.8)	6 (20.0)	0.73 (0.07; 7.53)	0.794
Social option/response	20 (12.4)	16 (11.7)	4 (16.7)	0.31 (0.05; 1.88)	0.201	17 (13.0)	3 (10.0)	1.13 (0.10; 13.44)	0.921
Nursing home	17 (10.6)	15 (10.9)	2 (8.3)	0.58 (0.07; 4.53)	0.601	16 (12.2)	1 (3.3)	3.20 (0.17; 61.02)	0.439
Other or not referred	6 (3.7)	6 (4.4)	0 (0.0)	—		5 (3.8)	1 (3.3)	1	
Emergency department	1 (0.6)	1 (0.7)	0 (0.0)	—		0 (0.0)	1 (3.3)	—	

CI, confidence interval; OR, odd ratio; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; SD, standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions.

[a]*Wald test.*

TABLE 2 | Clinical features of study population (*N* = 161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

		STOPP criteria				START criteria			
	Total	**PIMs**	**No PIMs**	**Not adjusted OR (95%CI)**	***p*[a]**	**PPOs**	**No PPOs**	**Not adjusted OR (95%CI)**	***p*[a]**
Clinical features									
Enteral Nutrition, *n* (%)									
Yes	21 (13.0)	19 (13.9)	2 (8.3)	1.77 (0.39; 8.15)	0.463	19 (14.5)	2 (6.7)	2.38 (0.52; 10.80)	0.263
No	140 (87.0)	118 (86.1)	22 (91.7)	1		112 (85.5)	28 (93.3)	1	
Medication per patient				1.30 (1.11; 1.53)	0.002			1.12 (0.98; 1.27)	0.086
Mean ± SD	8.84 ± 3.32	9.20 ± 3.19	6.79 ± 3.40			9.06 ± 3.38	7.90 ± 2.93		
Median (P25; P75)	9 (6; 11)	9 (7; 11)	7 (4.5; 8)			9 (6; 11)	8 (5; 10)		
Number of doses				1.51 (1.02; 1.30)	0.024			1.04 (0.94; 1.15)	0.407
Mean ± SD	10.20 ± 4.14	10.51 ± 4.03	8.42 ± 4.41			10.33 ± 4.22	9.63 ± 3.79		
Median (P25; P75)	10 (7; 13)	10 (8; 13)	8 (6; 11)			10 (7; 13)	10 (6; 12)		
Comorbid diseases				0.99 (0.68; 1.46)	0.976			2.10 (1.35; 3.29)	0.001
Mean ± SD	1.70 ± 1.14	1.70 ± 1.16	1.71 ± 1.04			1.85 ± 1.15	1.07 ± 0.83		
Median (P25; P75)	2 (1; 2)	2 (1; 2)	2 (1; 2)			2 (1; 3)	1 (0; 2)		
CCI				1.13 (0.87; 1.47)	0.376			1.56 (1.17; 2.06)	0.002
Mean ± SD	5.83 ± 1.71	5.88 ± 1.71	5.54 ± 1.69			6.03 ± 1.66	4.93 ± 1.64		
Median (P25; P75)	6 (5; 7)	6 (5; 7)	5 (4; 6.5)			6 (5; 7)	5 (4; 6)		
Geriatric syndromes, *n* (%)									
Polypharmacy (≥5 drugs/day)									
Yes	147 (91.3)	129 (94.2)	18 (75.0)	5.38 (1.67; 17.28)	0.005	121 (92.4)	26 (86.7)	1.86 (0.54; 6.40)	0.324
No	14 (8.7)	8 (5.8)	6 (25.0)	1		10 (7.6)	4 (13.3)	1	
Comorbid diseases ≥ 2									
Yes	86 (53.4)	73 (53.3)	13 (54.2)	0.97 (0.40; 2.30)	0.936	77 (58.8)	9 (30.0)	3.33 (1.42; 7.82)	0.006
No	75 (46.6)	64 (46.7)	11 (45.8)	1		54 (41.2)	21 (70.0)	1	
CCI ≥ 4									
Yes	149 (92.5)	127 (92.7)	22 (91.7)	1.16 (0.24; 5.63)	0.859	124 (94.7)	25 (83.3)	3.54 (1.04; 12.07)	0.043
No	12 (7.5)	10 (7.3)	2 (8.3)	1		7 (5.3)	5 (16.7)	1	
CCI ≥ 6									
Yes	85 (52.8)	74 (54.0)	11 (45.8)	1.39 (0.58; 3.32)	0.460	76 (58.0)	9 (30.0)	3.22 (1.37; 7.58)	0.007
No	76 (47.2)	63 (46.0)	13 (54.2)	1		55 (42.0)	21 (70.0)	1	
Dependency in ADL									
Yes	143 (88.8)	120 (87.6)	23 (95.8)	0.31 (0.04; 2.42)	0.262	120 (91.6)	23 (76.7)	3.32 (1.17; 9.46)	0.025
No	18 (11.2)	17 (12.4)	1 (4.2)	1		11 (8.4)	7 (23.3)	1	
Fall Risk (medium or high)									
Yes	131 (81.4)	113 (82.59	18 (75.0)	1.57 (0.56; 4.37)	0.388	109 (83.2)	122(73.3)	1.80 (0.71; 4.57)	0.215
No	30 (18.6)	24 (17.5)	6 (25.0)	1		22 (16.8)	8 (26.7)	1	
Malnutrition/anorexia									
Yes	7 (4.3)	5 (3.6)	2 (8.3)	0.42 (0.08; 2.28)	0.313	5 (3.8)	2 (6.7)	0.56 (0.10; 3.01)	0.495
No	154 (95.7)	132 (96.4)	22 (91.7)	1		126 (96.2)	28 (93.3)	1	
Obesity									
Yes	22 (13.7)	19 (13.9)	3 (12.5)	1.13 (0.31; 4.15)	0.857	17 (13.0)	5 (16.7)	0.75 (0.25; 2.21)	0.597
No	139 (86.3)	118 (86.1)	21 (87.5)	1		114 (87.0)	25 (83.3)	1	
Pressure ulcers at discharge									
Yes	27 (16.8)	25 (18.2)	2 (8.3)	2.46 (0.54; 11.13)	0.244	24 (18.3)	3 (10.0)	2.02 (0.57; 7.21)	0.279
No	134 (83.2)	112 (81.8)	22 (91.7)	1		107 (81.7)	27 (90.0)	1	
History of recent fractures									
Yes	46 (28.6)	39 (28.5)	7 (29.2)	0.97 (0.37; 2.51)	0.944	44 (33.6)	2 (6.7)	7.07 (1.61; 31.09)	0.010
No	115 (71.4)	98 (71.5)	17 (70.8)	1		87 (66.4)	28 (93.3)	1	

ADL, dependency in activities of daily life; CCI, Charlson Comorbidity Index; CI, confidence interval; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; OR, odd ratio; SD, standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions.
[a]*Wald test.*

Potential Prescribing Omissions

According to START criteria, patients had a median of 2 [1; 3] PPOs (range 0–6), with 81.4% of them having at least one PPO and more than half of patients had one or two PPOs (**Table 4**). Most associated systems with PPOs were "Musculoskeletal System" (55.3%) and "Cardiovascular System" (39.8%). In the "Musculoskeletal System", the highest frequency of PPOs was associated with "vitamin D supplementation in elderly people

TABLE 3 | Most common/significant comorbidities of study population (*N* = 161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

Most common/ significant comorbidities, *n* (%)	Total	STOPP criteria				START criteria			
		PIMs	No PIMs	Not adjusted OR (95%CI)	*p*[a]	PPOs	No PPOs	Not adjusted OR (95%CI)	*p*[a]
Hypertension									
Yes	110 (68.3)	96 (70.1)	14 (58.3)	1.67 (0.69; 4.07)	0.257	92 (70.2)	18 (60.0)	1.57 (0.69; 3.57)	0.280
No	51 (31.7)	41 (29.9)	10 (41.7)	1		39 (29.8)	12 (40.0)	1	
Cerebrovascular disease									
Yes	56 (34.8)	42 (30.7)	14 (58.3)	0.32 (0.13; 0.77)	0.011	47 (35.9)	9 (30.0)	1.31 (0.55; 3.08)	0.543
No	105 (65.2)	95 (69.3)	10 (41.7)	1		84 (64.1)	21 (70.0)	1	
Depression									
Yes	55 (34.2)	52 (38.0)	3 (12.5)	4.28 (1.22; 15.07)	0.023	45 (34.4)	10 (33.3)	1.05 (0.45; 2.43)	0.916
No	106 (65.8)	85 (62.0)	21 (87.5)	1		86 (65.6)	20 (66.7)	1	
Diabetes mellitus									
Yes	54 (33.5)	45 (32.8)	9 (37.5)	0.82 (0.33; 2.01)	0.656	46 (35.1)	8 (26.7)	1.49 (0.61; 3.61)	0.379
No	107 (66.5)	92 (67.2)	15 (62.5)	1		85 (64.9)	22 (73.3)	1	
Constipation									
Yes	54 (33.5)	51 (37.2)	3 (12.5)	4.15 (1.18; 14.61)	0.027	47 (35.9)	7 (23.3)	1.84 (0.73; 4.61)	0.194
No	107 (66.5)	86 (62.8)	21 (87.5)	1		84 (64.1)	23 (76.7)	1	
Dementia									
Yes	47 (29.2)	43 (31.4)	4 (16.7)	2.29 (0.74; 7.10)	0.152	43 (32.8)	4 (13.3)	3.18 (1.04; 9.68)	0.042
No	114 (70.8)	94 (68.6)	20 (83.3)	1		88 (67.2)	26 (86.7)	1	
Urinary incontinence									
Yes	45 (28.0)	42 (30.7)	3 (12.5)	3.10 (0.88; 10.94)	0.080	41 (31.3)	4 (13.3)	2.96 (0.97; 9.04)	0.056
No	116 (72.0)	95 (69.3)	21 (87.5)	1		90 (68.7)	26 (86.7)	1	
Rheumatic Disease									
Yes	38 (23.6)	31 (22.6)	7 (29.2)	0.71 (0.27; 1.87)	0.488	29 (22.1)	9 (30.0)	0.66 (0.27; 1.60)	0.362
No	123 (76.4)	106 (77.4)	17 (70.8)	1		102 (77.9)	21 (70.0)	1	
Congestive heart failure									
Yes	36 (22.4)	32 (23.4)	4 (16.7)	1.52 (0.49; 4.78)	0.471	34 (26.0)	2 (6.7)	4.91 (1.11; 21.70)	0.036
No	125 (77.6)	105 (76.6)	20 (83.3)	1		97 (74.0)	28 (93.3)	1	
Arrhythmia									
Yes	29 (18.0)	26 (19.0)	3 (12.5)	1.64 (0.46; 5.91)	0.450	29 (22.1)	0 (0.0)	—	—
No	132 (82.0)	111 (81.0)	21 (87.5)	1		102 (77.9)	30 (100.0)		
Benign prostatic hypertrophy									
Yes	28 (48.3)	21 (48.8)	7 (46.7)	1.09 (0.34; 3.54)	0.885	27 (56.3)	1 (10.0)	11.57 (1.36; 98.67)	0.025
No	30 (51.7)	22 (51.2)	8 (53.3)	1		21 (43.8)	9 (90.0)	1	
Renal disease									
Yes	23 (14.3)	21 (15.3)	2 (8.3)	1.99 (0.44; 9.11)	0.375	20 (15.3)	3 (10.0)	1.62 (0.45; 5.86)	0.461
No	138 (85.7)	116 (84.7)	22 (91.7)	1		111 (84.7)	27 (90.0)	1	
Chronic pulmonary obstructive disease									
Yes	20 (12.4)	15 (10.9)	5 (20.8)	0.47 (0.15; 1.43)	0.184	19 (14.5)	1 (3.3)	4.92 (0.63; 38.29)	0.128
No	141 (87.6)	122 (89.1)	19 (79.2)	1		112 (85.5)	29 (96.7)	1	
Non-metastatic solid tumor									
Yes	20 (12.4)	19 (13.9)	1 (4.2)	3.70 (0.47; 29.05)	0.213	16 (12.2)	4 (13.3)	0.90 (0.28; 2.93)	0.867
No	141 (87.6)	118 (86.1)	23 (95.8)	1		115 (87.8)	26 (86.7)	1	
Hemiplegia									
Yes	15 (9.3)	12 (8.8)	3 (12.5)	0.67 (0.18; 2.58)	0.563	13 (9.9)	2 (6.7)	1.54 (0.33; 7.23)	0.582
No	146 (90.7)	125 (91.2)	21 (87.5)	1		118 (90.1)	28 (93.3)	1	
Parkinson's disease									
Yes	6 (3.7)	3 (2.2)	3 (12.5)	0.16 (0.03; 0.83)	0.029	3 (2.3)	3 (10.0)	0.21 (0.04; 1.10)	0.065
No	155 (96.3)	134 (97.8)	21 (87.5)	1		128 (97.7)	27 (90.0)	1	
Metastatic solid tumor									
Yes	5 (3.1)	5 (3.6)	0 (0.0)	—	—	4 (3.1)	1 (3.3)	0.91 (0.10; 8.48)	0.936
No	156 (96.9)	132 (96.4)	24 (100.0)			127 (96.9)	29 (96.7)	1	
Angina									
Yes	4 (2.5)	3 (2.2)	1 (4.2)	0.52 (0.05; 5.17)	0.573	3 (2.3)	1 (3.3)	0.68 (0.07; 6.77)	0.742
No	157 (97.5)	134 (97.8)	23 (95.8)	1		128 (97.7)	29 (96.7)	1	
Osteoporosis									
Yes	3 (1.9)	3 (2.2)	0 (0.0)	—	—	2 (1.5)	1 (3.3)	0.45 (0.04; 5.13)	0.520
No	158 (98.1)	134 (97.8)	24 (100.0)			129 (98.5)	29 (96.7)	1	158 (98.1)
Glaucoma									
Yes	3 (1.9)	3 (2.2)	0 (0.0)	—	—	2 (1.5)	1 (3.3)	0.45 (0.04; 5.13)	0.520
No	158 (98.1)	134 (97.8)	24 (100.0)			129 (98.5)	29 (96.7)	1	

CI, confidence interval; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; OR, odd ratio; SD, standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions.

[a]*Wald test.*

TABLE 4 | Number of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs), according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria, respectively (*N* = 161).

Number of PIMs/PPOs	STOPP criteria (*n*, %)	START criteria (*n*, %)
0	24 (14.9)	30 (18.6)
1	23 (14.3)	36 (22.4)
2	32 (19.9)	47 (29.2)
3	33 (20.5)	28 (17.4)
4	16 (9.9)	13 (8.1)
5	16 (20.5)	6 (3.7)
6	10 (6.2)	1 (0.6)
≥7	7 (4.3)	0 (0.0)
Total	137 (85.1)	131 (81.4)
Mean ± SD	2.8 ± 2.1	1.9 ± 1.4
Median (P25; P75)	3 [1; 4]	2 [1; 3]

SD, standard deviation.

who are housebound or experiencing falls or with osteopenia" (E5; 46%; **Table 5**) followed by "vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than −2.5 in multiple sites" (E3; 27.3%; **Table 5**). Among "Cardiovascular System" the highest frequency of PPOs was associated with "angiotensin-converting enzyme inhibitor with systolic heart failure and/or documented coronary artery disease" (A6; 17.4%; **Table 5**), and "antiplatelet therapy (aspirin, clopidogrel, prasugrel or ticagrelor, with a documented history of coronary, cerebral or peripheral vascular disease)" (A3; 13.7%; **Table 5**).

In the multivariate analysis (**Table 7**), PPOs were found to be independently associated with the number of CCI (OR = 2.14, 95%CI: 1.46; 3.14), history of recent fractures (OR = 13.90, 95% CI: 2.83; 68.36), Parkinson's disease (OR = 0.08, 95%CI: 0.01; 0.61) and metastatic solid tumor (OR = 0.03, 95%CI: 0.00; 0.59).

DISCUSSION

Main Findings

The prevalence among inpatients was similar for PIMs (85.1%) and PPOs (81.4%), considering the application of the STOPP and START criteria, respectively. The most involved drugs in PIMs were from the central nervous system group, while PPOs were associated with drugs from the musculoskeletal and cardiovascular system groups. The most common overuses were associated with benzodiazepines as a predictable increase in the risk of falls and when used for longer than 4 weeks. Omissions were more frequently related to the lack of vitamin D supplements, calcium-vitamin D supplements, angiotensin-converting enzyme inhibitors, and antiplatelet agents. Female gender, hospital provenience, and a higher number of prescription drugs were found to be associated with a higher risk for PIMs. In contrast, patients with cerebrovascular disease and Parkinson's disease had the lowest risk of PIMs. On the other hand, patients with a higher value of CCI and with recent fractures had a higher risk for PPOs, while Parkinson's disease and metastatic solid tumors were shown to be protective diagnoses for PPOs.

Considering the main findings obtained in our study, it should be highlighted that the number of PIMs per patient (2.8) is lower, but the number of PPOs per patient is higher (1.9), than the reported in a recent study focused on patients admitted to acute care hospitals (3.55 and 0.72, respectively) (Thomas and Nguyen, 2020). On the other hand, the prevalence of PIMs detected in our study (85.1%) is higher than that reported in the literature, in which it ranges from patients 35–77% in patients ≥65 years old (Gallagher and O'Mahony, 2008; Lang et al., 2010; Gallagher P. et al., 2011; Dalleur et al., 2012; Liu et al., 2012; Wahab et al., 2012; Frankenthal et al., 2013; Tosato et al., 2014; San-Jose et al., 2015; Thomas and Thomas, 2019). A higher prevalence of PPOs was also found in our study (81.4%), since the reported values in literature ranged from 34 to 65% (Barry et al., 2007; Lang et al., 2010; Gallagher P. et al., 2011; Dalleur et al., 2012; Liu et al., 2012; Frankenthal et al., 2013; San-Jose et al., 2015). However, PIM rates vary according to each setting: 15–46% in community-dwelling (Galvin et al., 2014; Hedna et al., 2015; Thomas and Thomas, 2019), 21–38% in primary care (Ryan et al., 2009b; Cahir et al., 2010; Bradley et al., 2012; Bradley et al., 2014; Castillo-Paramo et al., 2014; Vezmar Kovacevic et al., 2014), and 48–79% in nursing homes (Garcia-Gollarte et al., 2012; Ubeda et al., 2012; Ryan et al., 2013a); and the same pattern was reported for PPO rates: 30% in community-dwelling (Galvin et al., 2014), 23–51% in primary care (Ryan et al., 2009b; Castillo-Paramo et al., 2014; Vezmar Kovacevic et al., 2014), and 42–74% in nursing homes (Garcia-Gollarte et al., 2012; Ubeda et al., 2012; Ryan et al., 2013a)). Regarding national data, the application of the STOPP/START criteria is scarce. However, Borges et al. (2012) have already identified PPOs in 68% of 91 elderly patients admitted to a stroke unit, Moraes et al. (2013) reported a prevalence of PIMs and PPOs of 74 and 29%, respectively, in 100 patients admitted to a hospital and da Costa et al. (2016) reported PIMs and PPOs of 75 and 43%, respectively, in 161 elderly patients in nursing homes.

Although the prevalence of PIMs and PPOs is generally higher than that reported in the literature, some underlying aspects of existing studies could make this comparison difficult. For instance, Gallagher P. et al. (2011) found a total PIMs prevalence of 51.3% and a global PPOs prevalence of 59.4% considering six European hospitals, but individually different results were observed, for instance a PIMs prevalence of 77.3% in Geneva and a PPOs prevalence of 72.7% in Perugia. In addition, some studies only applied a subset of the STOPP/START criteria (Wahab et al., 2012; Bradley et al., 2014; Galvin et al., 2014), which can result in lower prevalence (Bradley et al., 2014) and misleading direct comparisons. Thus, pulling out the three most frequent PIMs (D5, K1 and K2) and PPOs (A6, E3 and E5) the results would be substantially lower (69 and 60%, respectively). Moreover, of the 81 STOPP criteria, the three most prevalent (D5, K1 and K2) accounted for almost half (47%) of the total of PIMs detected (445). The same happened for the START criteria, with the three most prevalent (A6, E3 and E5) of the 34 criteria accounting for 47% of the total PPOs detected (302). Finally, there are also factors considered by several studies as predictors for PIMs and PPOs that assumed

TABLE 5 | Frequency of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria respectively (*N* = 161).

			***n* (%)**
STOPP criteria	A	Indication of medication	27 (16.8)
	A1	Any drug prescribed without an evidence-based clinical indication.	15 (9.3)
	A3	Any duplicate drug class prescription.	15 (9.3)
	B	Cardiovascular System	28 (17.4)
	B9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence.	10 (6.2)
	B12	Aldosterone antagonists with concurrent potassium-conserving drugs without monitoring of serum potassium.	7 (4.3)
	C	Antiplatelet/Anticoagulant Drugs	9 (5.6)
	C7	Ticlopidine in any circumstances.	5 (3.1)
	D	Central Nervous System and Psychotropic Drugs	107 (66.5)
	D1	Tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention.	25 (15.5)
	D2	Initiation of tricyclic antidepressants as first-line antidepressant treatment.	11 (6.8)
	D5	Benzodiazepines for ≥ 4 weeks.	83 (51.6)
	D7	Anticholinergics/antimuscarinics in patients with delirium or dementia.	22 (13.7)
	D9	Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia unless symptoms are severe and other treatments have failed.	8 (5.0)
	D11	Acetylcholinesterase inhibitors with a known history of persistent bradycardia heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate.	6 (3.7)
	D14	First-generation antihistamines.	8 (5.0)
	E	Renal System	0 (0.0)[a]
	F	Gastrointestinal System	22 (17.7)
	F2	Proton-pump inhibitors for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks.	10 (6.2)
	F3	Drugs likely to cause constipation in patients with chronic constipation where non-constipating alternatives are appropriate.	12 (7.5)
	G	Respiratory System	14 (8.7)
	G5	Benzodiazepines with acute or chronic respiratory failure.	13 (8.1)
	H	Musculoskeletal System	1 (0.2)
	I	Urogenital System	1 (0.2)
	J	Endocrine System	0 (0.0)[a]
	K	Drugs that predictably increase the risk of falls in older people	106 (65.8)
	K1	Benzodiazepines	87 (54.0)
	K2	Neuroleptic drugs	40 (24.8)
	K4	Hypnotic Z-drugs	9 (5.6)
	L	Analgesic Drugs	18 (11.2)
	L2	Use of regular (as distinct from *pro re nata*) opioids without concomitant laxative.	12
	L3	Long-acting opioids without short-acting opioids for break-through pain.	8 (5.0)
	N	Antimuscarinic/Anticholinergic Drug Burden	8 (5.0)
START criteria	A	Cardiovascular System	64 (39.8)
	A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.	5 (3.1)
	A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.	22 (13.7)
	A5	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years.	15 (9.3)
	A6	Angiotensin Converting Enzyme inhibitor with systolic heart failure and/or documented coronary artery disease.	28 (17.4)
	A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.	18 (11.2)
	B	Respiratory System	12 (7.5)
	B1	Regular inhaled 2 agonist or antimuscarinic bronchodilator (e.g., ipratropium, tiotropium) for mild to moderate asthma or chronic obstructive pulmonary disease.	10 (6.1)
	C	Central Nervous System and Eyes	19 (11.8)
	C2	Non-tricyclic antidepressant drug in the presence of persistent major depressive symptoms.	12 (7.5)
	D	Gastrointestinal System	0 (0.0)[a]
	E	Musculoskeletal System	89 (55.3)
	E3	Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores.	44 (27.3)
	E5	Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia.	74 (46.0)
	F	Endocrine System	6 (3.7)
	F1	Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker (if intolerant of Angiotensin Converting Enzyme inhibitor) in diabetes with evidence of renal disease, i.e., dipstick proteinuria or microalbuminuria (>30 mg/24 hours) with or without serum biochemical renal impairment.	6 (3.7)
	G	Urogenital System	22 (13.7)
	G1	Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.	12 (7.5)
	G2	5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.	18 (11.2)

(Continued on following page)

TABLE 5 | (*Continued*) Frequency of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria respectively (*N* = 161).

		***n* (%)**
H	Analgesics	12 (7.5)
H2	Laxatives in patients receiving opioids regularly.	12 (7.5)
I	Vaccines	0 (0.0)[a]

[a]*Not applicable.*

TABLE 6 | Predictors of potentially inappropriate medications (PIMs), according to Screening Tool of Older People's Prescriptions (STOPP) criteria, in the study population (*N* = 161).

	Total	**PIM**	**No PIM**	**Adjusted OR (95% CI)**	***p*[a]**
Gender, *n* (%)					
Male	58 (36.0)	43 (31.4)	15 (62.5)	1	
Female	103 (64.0)	94 (68.6)	9 (37.5)	4.04 (1.27; 12.84)	0.018
Provenience/Origin, *n* (%)					
Hospital	91 (56.5)	83 (60.6)	8 (33.3)	3.43 (1.10; 10.69)	0.034
Residence or other	70 (43.5)	54 (39.4)	16 (66.7)	1	
Medication per patient				1.32 (1.09; 1.60)	0.005
Mean ± SD	8.84 ± 3.32	9.20 ± 3.19	6.79 ± 3.40		
Median (P25; P75)	9 (6; 11)	9 (7; 11)	7 (4.5; 8)		
History of recent fractures					
Yes	46 (28.6)	39 (28.5)	7 (29.2)	0.31 (0.09; 1.06)	0.062
No	115 (71.4)	98 (71.5)	17 (70.8)	1	
Cerebrovascular disease					
Yes	56 (34.8)	42 (30.7)	14 (58.3)	0.29 (0.10; 0.89)	0.030
No	105 (65.2)	95 (69.3)	10 (41.7)	1	
Depression					
Yes	55 (34.2)	52 (38.0)	3 (12.5)	4.02 (0.88; 18.42)	0.073
No	106 (65.8)	85 (62.0)	21 (87.5)	1	
Dementia					
Yes	47 (29.2)	43 (31.4)	4 (16.7)	4.62 (0.98; 21.85)	0.054
No	114 (70.8)	94 (68.6)	20 (83.3)	1	
Parkinson's disease					
Yes	6 (3.7)	3 (2.2)	3 (12.5)	0.06 (0.00; 0.84)	0.037
No	155 (96.3)	134 (97.8)	21 (87.5)	1	

CI, confidence interval; OR, odd ratio; SD, standard deviation.

[a]*Wald test; OR's adjust with all the variables of* ***Tables 1–3*** *without null frequencies, but we only show the results for the variables that* p < *0.1; Omnibus test:* p < *0.001; Hosmer and Lemeshow test:* p = *0.291; area under the receiver operating characteristic curve = 0.866 [95% CI: (0.801; 0.931),* p < *0.001]; Sensitivity = 79.6% and Specificity = 87.5% are simultaneously maximized for the cutoff probability 0.8109.*

high prevalence in the study population and may contribute to the PIM and PPO rates, such as the number of daily medications [median of 9 (6; 11)], which are higher than those in other studies (Gallagher and O'Mahony, 2008; Ryan et al., 2009b; Lang et al., 2010; Liu et al., 2012; Ubeda et al., 2012; Moraes et al., 2013; Ryan et al., 2013a; Castillo-Paramo et al., 2014); the Charlson Comorbidity Index (CCI) [median of 6 (5; 7)] is also higher than in published data (Gallagher P. et al., 2011; Frankenthal et al., 2013; Castillo-Paramo et al., 2014).

Concerning to most common PIMs, the results are consistent with literature that has reported benzodiazepines (Cahir et al., 2010; Bradley et al., 2012; Dalleur et al., 2012; Garcia-Gollarte et al., 2012; Liu et al., 2012; Ubeda et al., 2012; Wahab et al., 2012; Vezmar Kovacevic et al., 2014; San-Jose et al., 2015), neuroleptics (Garcia-Gollarte et al., 2012; Liu et al., 2012; Bradley et al., 2014), tricyclic antidepressants, anticholinergic/antimuscarinic drugs (Garcia-Gollarte et al., 2012), loop diuretics and proton-pump inhibitors (Cahir et al., 2010; Bradley et al., 2012; Garcia-Gollarte et al., 2012; Wahab et al., 2012; Bradley et al., 2014) as the drug classes mainly involved. The analysis of drugs commonly associated with PPOs is also similar to several other studies that have reported vitamin D (Pyszka et al., 2010), vitamin D and calcium (Barry et al., 2007; Lang et al., 2010; Dalleur et al., 2012; Garcia-Gollarte et al., 2012; Ubeda et al., 2012; San-Jose et al., 2015), angiotensin-converting enzyme inhibitors (Pyszka et al., 2010; Liu et al., 2012), antiplatelet therapy (Barry et al., 2007; Liu et al., 2012), beta-blockers, 5-alpha reductase, statins (Barry et al., 2007; Pyszka et al., 2010; Dalleur et al., 2012; Garcia-Gollarte et al., 2012; Liu et al., 2012), laxatives, alpha-1 receptor blockers and non-tricyclic antidepressants (Lang et al., 2010) as more frequent PPOs.

Relatively to the predictors of PIMs, in our study and also in the literature, female gender has been frequently associated with PIMs (Nyborg et al., 2012; Martins et al., 2015; Barry et al., 2016). Polypharmacy is also commonly identified as a PIM predictor, either as an intake of ≥4 drugs (Bradley et al., 2014; Vezmar Kovacevic et al., 2014), ≥5 drugs (Bradley et al., 2012; Galvin et al.,

TABLE 7 | Predictors of potential prescribing omissions (PPOs), according to Screening Tool to Alert to Right Treatment (START) criteria, in the study population (*N* = 161).

	Total	PPOs	No PPOs	Adjusted OR (95% CI)	*p*[a]
Gender, *n* (%)					
Male	58 (36.0)	48 (36.6)	10 (33.3)	1	
Female	103 (64.0)	83 (63.4)	20 (66.7)	0.38 (0.14; 1.05)	0.063
CCI				2.14 (1.46; 3.14)	<0.001
Mean ± SD	5.83 ± 1.71	6.03 ± 1.66	4.93 ± 1.64		
Median (P25; P75)	6 (5; 7)	6 (5; 7)	5 (4; 6)		
History of recent fractures					
Yes	45 (28.0)	41 (31.3)	4 (13.3)	13.90 (2.83; 68.36)	0.001
No	116 (72.0)	90 (68.7)	26 (86.7)	1	
Non-metastatic solid tumor					
Yes	20 (12.4)	16 (12.2)	4 (13.3)	0.29 (0.07; 1.26)	0.099
No	141 (87.6)	115 (87.8)	26 (86.7)	1	
Parkinson's disease					
Yes	6 (3.7)	3 (2.3)	3 (10.0)	0.08 (0.01; 0.61)	0.015
No	155 (96.3)	128 (97.7)	27 (90.0)	1	
Metastatic solid tumor					
Yes	5 (3.1)	4 (3.1)	1 (3.3)	0.03 (0.00; 0.59)	0.021
No	156 (96.9)	127 (96.9)	29 (96.7)	1	

CCI, Charlson Comorbidity Index; CI, confidence interval, OR, odd ratio; SD, standard deviation.

[a]*Wald test; OR's adjust with all the variables of* ***Tables 1–3*** *without null frequencies, but we only show the results for the variables that* p < *0.1; Omnibus test:* p < *0.001; Hosmer and Lemeshow test:* p = *0.744; area under the receiver operating characteristic curve = 0.826 [95% CI: (0.747; 0.905),* p < *0.001]; Sensitivity = 77.9% and Specificity = 76.7% are simultaneously maximized for the cutoff probability 0.7631.*

2014), ≥10 drugs (Gallagher P. et al., 2011; San-Jose et al., 2015) or an increased number of medications (Lang et al., 2010; Wahab et al., 2012; Ryan et al., 2013a; Frankenthal et al., 2013; Castillo-Paramo et al., 2014). The hospital provenience of the patients was not directly tested, but living in an institutional setting was recognized as a predictor of PIMs (Lang et al., 2010), as well as a longer stay at the nursing home (Chen et al., 2012). Among comorbidities, depression is mentioned in the literature (Azermai et al., 2011) but only had a significant association with OR non-adjusted; cerebrovascular disease seemed to be a protective factor, which may be related to a higher supervision or more frequent revision of the therapeutic list of these patients (Zhang et al., 2009); and Parkinson's disease was also considered to be a protective factor, but no valid reason was found.

Regarding PPOs, they were associated with high values of CCI, in accordance with the literature because the most frequently mentioned factors are comorbidity (CCI) (Frankenthal et al., 2013; Castillo-Paramo et al., 2014), the CCI values higher or equal to 2 (Gallagher P. et al., 2011; Lang et al., 2012), and also multimorbidity (Lang et al., 2010; San-Jose et al., 2015). Fractures have also been cited as predictors (Dalleur et al., 2012) but diagnoses of Parkinson's disease and metastatic solid tumors are the main findings as protective determinants of PPOs.

Although no other predictors were found, it has been further reported in the literature a history of falls and previous hospitalizations for PIMs (Lang et al., 2010; Frankenthal et al., 2013), and being aged ≥75 years (Vezmar Kovacevic et al., 2014) or ≥85 years (Gallagher P. et al., 2011) for PPOs.

Strengths and Limitations

The utilization of a common online electronic health platform is an advantage, which permits access to diverse data from all healthcare units included in the sample, such as discharge summaries and several evaluations of the patient from different professionals that allow identification of major clinical data (such as diagnosis, medical history, list of drugs, periodic evaluations, dependency status) and scales for pain evaluation and risk of falls, which help to analyze criteria such as analgesic drugs and the need for calcium-vitamin D supplements. However, the inclusion of eight different healthcare units implies the analysis of eight different multidisciplinary teams that detail information in different ways and fields and, therefore, certain data were sometimes incomplete or even nonexistent; in some cases, it was possible to fill it through internal medical records, other online tools or by information from other settings where the patient was evaluated. Thus, improved access to patients' information could reduce the time to collect the necessary data to apply medication review criteria and contribute to a larger sample that could allow obtaining better confidence intervals and would be more representative of the Portuguese population and elderly patients receiving PAC/LTC.

Studies have already shown that STOPP/START criteria have good inter-rater reliability between multiple physicians practicing in different centers of Europe (Ryan et al., 2009a; Gallagher et al., 2009); however, it can be difficult to obtain an unequivocal and unquestionable application of certain criteria. Limited length-of-stay, lack of specific medical information or even the interpretation of some criteria led to several limitations, comments, and suggestions regarding the application of STOPP/START criteria discussed along with the study. For instance, it is difficult to understand whether the behavioral and psychological characteristics of dementia are severe enough to justify the use of neuroleptic antipsychotics or to have 100% certainty that a sleep disorder is due to psychosis or dementia. Furthermore, it may not be easy to find alternative drugs for chronic pain treatment in cases of opioid-induced constipation or to ensure that there is no relevance of having a proton-pump inhibitor prescribed in a polymedicated patient with a history of peptic ulcer.

Implications for Research and/or Practice

Overall, STOPP/START criteria are easy, practical, and fast to apply. Considering the results obtained herein, STOPP/START criteria proved to be a suitable tool for use in PAC/LTC settings, as it has also been internationally demonstrated in other clinical settings. Ryan et al. (2013b) concluded that there is an overestimation of PIMs and an underestimation of PPOs if both criteria are used in the absence of sufficient clinical information. Therefore, the availability of detailed clinical data chronologically organized is essential, as well as drug lists that have complete information (dose, dosage, dosage forms, and administration route and frequency). Besides, the codification of diagnosis and medications by international classifications used worldwide (ATC and ICD-9-CM) would guarantee the universality of the results and would improve comparisons regardless of nationality.

Future Perspectives

In Portugal, it is imperative to perform studies at larger scales and across all levels of healthcare response, not only to evaluate the national prevalence of PIMs and PPOs but, more importantly, to understand if the trend of existing studies remains high compared to international literature. For these could be important to incentive the pharmacists to introduce the information related to the medication in the online platform that is used by all UCCIs at a national level. In addition, alerts could be programmed to identify PIMs and PPOs, similarly to what happens with the software SENATOR®.

More intensive pharmaceutical interventions can substantially reduce the frequency of PIMs and PPOs, which were already exposed in interventional studies focusing on different healthcare settings (Gallagher PF. et al., 2011; Lang et al., 2012; Dalleur et al., 2014; Frankenthal et al., 2014; Garcia-Gollarte et al., 2014). Lang et al. (Lang et al., 2012) obtained a decrease from 77 to 19% for PIMs and 65–11% for PPOs. Moreover, Garcia-Gollarte et al. (2014) achieved a PIM reduction from 67 to 44% in the intervention group.

It is also crucial to evaluate the compatibility of the application of STOPP and START criteria with the available data from electronic settings [as recently it was made in the US for nursing homes (Khodyakov et al., 2016)], and to improve databases, by modifying or adding relevant information indispensable to apply these criteria. Furthermore, it would be also essential to create a Portuguese version of STOPP/START criteria, as already done in other countries (Delgado Silveira et al., 2015; Lang et al., 2015), and to adapt it to the national market, which would involve modifications in some criteria (such as the removal of prochlorperazine in the STOPP criteria about its use with parkinsonism or the replacement of "hypnotic Z-drugs" by "zolpidem," which is the only Z-drug available in Portugal).

Despite the extensive literature on inappropriate prescribing generated over the last decade, much remains to be done regarding its implementation in clinical practice. Thus, further studies to assess the relationship between mis/over/underuse of drugs and adverse events (as hospitalizations, falls, deaths) should be performed with depth, as soon as possible, including an analysis of inherent costs.

CONCLUSION

PIMs and PPOs are highly prevalent in geriatric patients and, therefore, more proactive interventions are needed to improve this scenario. The drugs most frequently identified as PIMs were those belonging to the central nervous system group, while PPOs were associated with drugs acting in the musculoskeletal and cardiovascular systems. The most common overuses were associated with benzodiazepines, which are predictors of an increased risk of falls, particularly when used for longer than 4 weeks. Omissions were more frequently related to the lack of vitamin D supplements, calcium-vitamin D supplements, angiotensin-converting enzyme inhibitors, and antiplatelet agents. Female gender, hospital provenience, and the higher number of medications prescribed were related to a higher rate of PIMs, in contrast to cerebrovascular disease and Parkinson's disease. PPOs were associated with CCI and a history of recent fractures, while Parkinson's disease and a metastatic solid tumor appeared to be protective. The fact that three specific criteria represent almost half of the total PIMs and PPOs show that targeted interventions can substantially improve the appropriateness of medication. Further national investigation is required, as well as international studies, focusing on the relationship between PIMs/PPOs and clinically relevant adverse events in order to better explore its consequences on patients' health and to realize its economic impact.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the protocol of this study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of Beira Interior (CE-FCS-2015-030). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CC: Conceptualization, Methodology, Validation, Resources, Formal analysis, Writing—original draft, Supervision, Visualization, Project administration. JG: Software, Formal analysis. MR: Writing–review and editing. AF: Conceptualization, Supervision, Project administration, Writing—review and editing. GA: Conceptualization, Methodology, Supervision, Visualization, Project administration, Writing–review and editing.

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frontiers in Pharmacology

SYSTEMATIC REVIEW
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The Efficacy and Safety of Revefenacin for the Treatment of Chronic Obstructive Pulmonary Disease: A Systematic Review

*Jiaxing Zhang[1†], Yihong Xie[2†], Joey Sum-wing Kwong[3], Long Ge[4], Rui He[5], Wenyi Zheng[5], Jing Han[6], Rui Zhang[1], Huaye Zhao[1], Yuru He[2] and Xiaosi Li[2]**

[1]Department of Pharmacy, Guizhou Provincial People's Hospital, Guiyang, China, [2]Department of Pharmacy, Hospital of Chengdu Office of People's Government of Tibetan Autonomous Region, Chengdu, China, [3]Global Health Nursing, Graduate School of Nursing Science, St. Luke's International University, Tokyo, Japan, [4]Evidence Based Social Science Research Centre, School of Public Health, Lanzhou University, Lanzhou, China, [5]Department of Laboratory Medicine, Experimental Cancer Medicine, Karolinska Institute, Stockholm, Sweden, [6]Department of Respiratory, Guizhou Provincial People's Hospital, Guiyang, China

Background Revefenacin (REV) is a novel once-daily long-acting muscarinic antagonist (LAMA) in the treatment of moderate to very severe chronic obstructive pulmonary disease (COPD). This systematic review incorporating a dose-response meta-analysis aimed to assess the efficacy and safety of REV.

Methods PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, VIP database, and Wanfang database were searched from their inception to April 2020. We included randomized controlled trials (RCTs) which evaluated the efficacy and safety of REV in COPD patients. Two reviewers independently performed study screening, data extraction, and risk of bias assessment. Outcomes consisted of the mean change in trough Forced Expiratory Volume in 1 second (FEV_1) from baseline, adverse events (AEs), and serious adverse events (SAEs). A dose-response meta-analysis using the robust error meta-regression method was conducted. We used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.

Results Nine RCTs (3,121 participants) were included in this systematic review. The meta-analyses indicated that 175 μg/day REV could significantly improve the trough FEV_1 (MD=143.67, 95%CI: 129.67 to 157.68; I^2=96%; 809 participants; studies=4; low quality) without increasing the risk of AEs (OR=0.98, 95%CI: 0.81 to 1.18; I^2=34%; 2,286 participants; studies=7; low quality) or SAEs (OR=0.89, 95%CI: 0.55 to 1.46; I^2=0%; 2,318 participants; studies=7; very low quality) compared to placebo. Furthermore, the effect of REV in increasing trough FEV_1 was dose-dependent with an effective threshold of 88 μg/day (R^2 = 0.7017). Nevertheless, only very low-quality to low-quality evidence showed that REV at a dose of 175 μg/day was inferior to tiotropium regarding the long-term efficacy, and its safety profile was not superior to tiotropium or ipratropium.

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***Correspondence:**
Xiaosi Li
lixiaosiyyy@126.com

†These authors have contributed equally to the work and share first authorship

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Conclusion Current evidence shows that REV is a promising option for the treatment of moderate to very severe COPD. Due to most evidence graded as low quality, further studies are required to compare the efficacy, long-term safety and cost-effectiveness between REV and other LAMAs in different populations.

Clinical Trial Registration: [PROSPERO], identifier [CRD42020182793]

Keywords: chronic obstructive pulmonary disease, long-acting muscarinic antagonist, systematic review, dose-response meta-analysis, revefenacin

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities (GOLD., 2021). Significant exposure to noxious particles or gases and host factors including abnormal lung development usually contribute to the pathogenesis (GOLD., 2021). Based on Burden of Obstructive Lung Disease (BOLD) and other large scale epidemiological studies, a meta-analysis estimated that the number of COPD cases was 384 million in 2010, with a global prevalence of 11.7% (95% confidence interval (CI): 8.4–15.0%) (Adeloye et al., 2015). Around 3.2 million people died from COPD each year, making it the third leading cause of death worldwide (World Health Organization, 2007; Burney et al., 2015; Global Burden of Disease Study Collaborators, 2015; Halpin et al., 2019). In the latest Global Burden of Disease (GBD) analysis, COPD entered the top 10 causes of years of life lost (YLL), increasing from the 11th position in 2007 to seventh in 2017 (GBD 2017 Causes of Death Collaborators, 2018). Another GBD study also predicted that deaths from COPD would rise to 4.4 million per year in 2040 and by then, COPD would be the fourth most important cause of YLL (Foreman et al., 2018). With the increasing exposure to risk factors (e.g., smoking) and aging of the world's population, the prevalence of COPD is expected to rise over the next 40 years and by 2060 there may be more than 5.4 million deaths from COPD and its related conditions annually (Lopez et al., 2006; GBD 2017 Causes of Death Collaborators, 2018; World Health Organization, 2020), which will induce a substantial and elevated economic burden (Lozano et al., 2012; Vos et al., 2012). In the European Union, COPD accounted for 56% (38.6 billion Euros) of the cost on respiratory disease which took up about 6% of the total annual healthcare budget (European Respiratory Society on behalf of the Forum of International Respiratory Societies (FIRS), 2017). In the United States, the estimated direct and indirect costs of COPD were $32 billion and $20.4 billion, respectively (Guarascio et al., 2013).

In absence of conclusive evidence supporting any existing medications which can modify the long-term decline in lung function for COPD (Anthonisen et al., 1994; Burge et al., 2000; Pauwels et al., 1999; Tashkin et al., 2008; Vestbo et al., 1999), the purpose of pharmacological therapy for COPD is to ameliorate symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status. As the first-line therapy to address COPD symptoms and prevent exacerbations (GOLD., 2021), long-acting muscarinic antagonists (LAMAs) can improve the effectiveness of pulmonary rehabilitation (Casaburi et al., 2005; Kesten et al., 2008) and reduce exacerbation and related hospitalization (Karner et al., 2014; Melani A.S., 2015) by durably blocking the bronchoconstrictor effects of acetylcholine on M_3 muscarinic receptors expressed in airway smooth muscle (Melani A.S., 2015). Revefenacin (REV), a novel once-daily LAMA for nebulization, was approved for the treatment of COPD by the United States Food and Drug Administration (FDA) in November 2018 (Highlights Of Prescribing Information, 2021). Several randomized trials (Donohue et al., 2019a; Donohue et al., 2019b; Donohue et al., 2019c; Ferguson et al., 2019; Krishna et al., 2017; Mahler et al., 2019; Quinn et al., 2018; Sethi et al., 2020; Siler et al., 2020; Theravance Biopharma, 2021a; Theravance Biopharma, 2021b) investigating the use of REV concluded that it was effective and safe in the treatment of COPD. Nevertheless, evidence has not been systematically assessed. To better understand and interpret available evidence, we conducted a systematic review incorporating a dose-response meta-analysis to evaluate the efficacy and safety of REV in patients with COPD.

MATERIALS AND METHODS

We reported our study following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Supplementary Table S1**). The study was prospectively registered on International Prospective Register of Systematic Review (PROSPERO, CRD42020182793).

Search Strategy

PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) were searched using the search strategies detailed in **Supplementary Table S2**, from their inception to April 2020. ClinicalTrials.gov was also searched using the term of "Revefenacin". The China National Knowledge Infrastructure (CNKI), VIP database, and Wanfang database were also searched with Chinese terms. We reviewed the references from relevant review articles and included studies to find additional studies.

Eligibility Criteria

We included studies meeting the following criteria: 1) Randomized controlled trials (RCTs) published in English or Chinese; 2) participants with confirmed moderate to very severe COPD (Stage 2, three or four according to the GOLD Guidelines);

3) the intervention was REV irrespective of dosage and schedule; 4) the comparisons included placebo, tiotropium (TIO), and ipratropium (IPR); 5) studies reporting at least one of the following outcomes: the mean change from baseline in trough forced expiratory volume in 1 s (FEV_1) as the efficacy outcome; adverse events which were subdivided into total adverse events (AEs) and serious adverse events (SAEs) by ICH GCP standards as the safety endpoints. We excluded duplicated studies or conference abstract without available raw data.

Study Selection and Data Extraction

Two authors independently screened the titles and abstracts of all studies searched using predetermined inclusion criteria. The full texts of any potentially relevant articles were retrieved for detailed review. We resolved any disagreements by discussion. We used a pre-designed data collection form to extract data from each eligible study. The following data were extracted: 1) authors; 2) year of publication; 3) country or region where the study conducted; 4) study design and use of control; 5) number of participants in each group; 6) population characteristics (e.g., gender, age, body mass index (BMI), race, etc.); 7) outcomes and their definitions, categorical or numerical data for assessment of included outcomes; 8) Sources of funding.

Risk of Bias Assessment

Two authors independently assessed the risk of bias of each included RCT using the checklist developed by Cochrane Collaboration (Higgins et al., 2011; Higgins et al., 2020), including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias. We categorized the judgement to be low, high or unclear risk of bias and created a "risk of bias summary" using the Review Manager Software (RevMan 5.3). As for crossover studies, a revised tool to assess the risk of bias in crossover trials (RoB 2) was used to assess the risk of bias (Higgins et al., 2021). Any disagreements about the risk of bias were resolved by discussion.

Statistical Synthesis

If more than one study reported the same outcome, a pairwise meta-analysis was conducted. To compare the differences between REV and control groups, odds ratios (ORs) were used for the incidence of AEs or SAEs and mean differences (MDs) were calculated for FEV_1, with corresponding 95% confidence intervals (CIs). We choose to use OR since a recent study have pointed out that it is better than risk ratio (RR) in clinical trials, where RR are not a portable estimator (Doi et al., 2020). As to the change from baseline in trough FEV_1, per-protocol analyses were performed according to the data of patients who completed the trial. As to the AEs and SAEs, we conducted analyses based on the safety population which included all subjects who were randomized into the study and received at least one dose of study drug. For studies with zero-events in either of the arms, the continuity correction (add 0.5) was employed to estimate the OR and variance; for studies with zero-events in both arms, we impute OR = 1 for them while use continuity correction to estimate the variance (Xu et al., 2021). In addition, considering the unstable nature of rare events, as suggested by the guideline, we employed a sensitivity analysis by using Mantel-Haenszel risk difference (RD) estimator for the meta-analyses (Xu et al., 2021). We pooled ORs with the Mantel-Haenszel method, and MDs with the inverse variance method using RevMan 5.3, respectively. Statistical heterogeneity among studies was examined by the Chi-square test and quantified by the I^2 statistic (Higgins et al., 2011). A fixed-effects model was applied to synthesize data when heterogeneity was not significant (I^2<30%), while a random-effects model was used when heterogeneity was significant (I^2>30%) and could not be explained by subgroup analyses or in terms of clinical or methodological features of the trials. We explored sources of heterogeneity based on the subgroup analyses including type of control groups and different dose of REV. The sensitivity analyses were performed by omitting the crossover studies.

The robust error meta-regression method (Xu et al., 2018) was used to summarize relationship between the dosage and response (efficacy and safety) of REV. This was achieved by treating the dosage as dependent variable (dose) while the efficacy and safety as the independent variables of study level. Under this meta-regression method, each study was regarded as a cluster within a whole population, as a solution to pool the dose-response relationship and to address the potential correlations among within-study effects. The potential dose-response relationship was fitted through a restricted cubic spline function with three random knots automatically generated. The Wald test by assuming the coefficients of non-linear terms to zero was employed to investigate whether a non-linear relationship exists (Xu et al., 2019).

The Quality of Evidence Assessment

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to rate the quality of evidence, which rated evidence from systematic review and meta-analysis as high, moderate, low, or very low quality, by considering risk of bias, indirectness, inconsistency, imprecision, and publication bias (Guyatt et al., 2011).

RESULTS

Search Results

A total of 163 publications were obtained from literature search and the selection process is shown in **Figure 1**. Eleven articles (Donohue et al., 2019a; Donohue et al., 2019b; Donohue et al., 2019c; Ferguson et al., 2019; Krishna et al., 2017; Mahler et al., 2019; Quinn et al., 2018; Sethi et al., 2020; Siler et al., 2020; Theravance Biopharma, 2021a; Theravance Biopharma, 2021b) reporting nine RCTs with 3,121 participants were included in this systematic review. As shown in **Table 1**, two RCTs were multicenter studies, and the other seven were single-center studies. Both parallel (n = 6) and crossover study design (n = 3) were used. The dosage of REV in intervention group ranged from 22 to 700 μg/day, and it was compared with placebo (7 RCTs, 701 participants), IPR (1 RCT, 32 participants), and TIO (2 RCTs, 460 participants). The follow-up time ranged from 1 day to

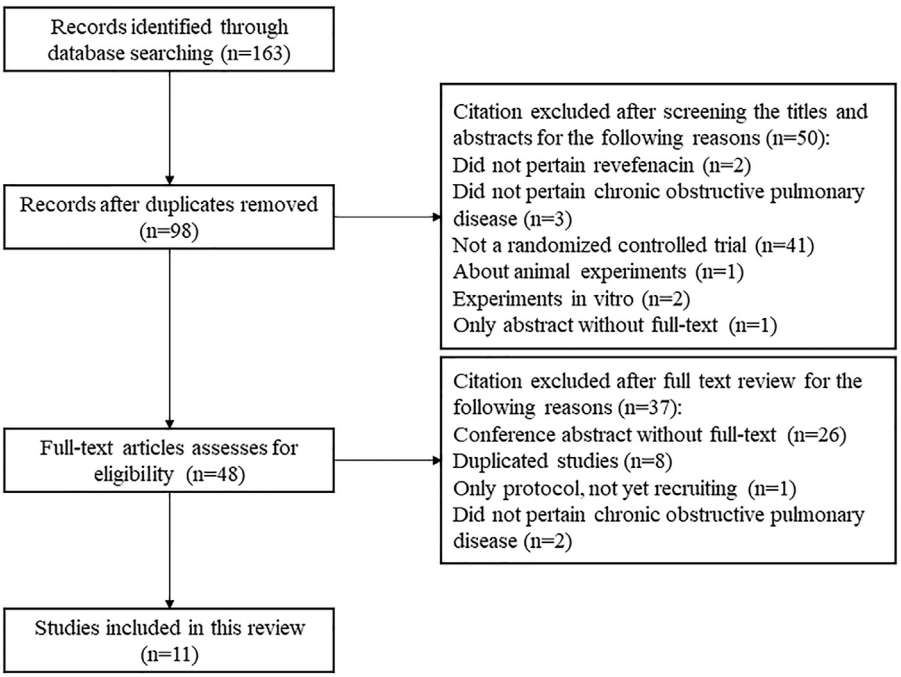

FIGURE 1 | Flow diagram of study selection process for this systematic review.

52 weeks after the first treatment. Two RCTs identified from ClinicalTrials.gov are yet to be published in full and thus the baseline characteristics of their enrolled participants were unclear. For the other seven RCTs, the mean age and mean BMI of participants were 61.4–65.1 years and 27.9–29.6 kg/m^2, respectively, and the proportion of ICS/LABA users varied from 0 to 53.88%.

Quality of Included Studies

As shown in **Figure 2**, one study (NCT03095456) had low risk of selection bias for clearly describing the methods (centralized randomization) of randomization and allocation concealment, while the others were unclear because the information about selection participants was not reported. Triple (participant, care provider, and investigator) and quadruple (participant, care provider, investigator, and outcome assessor) blinding methods were applied in three RCTs (NCT02040792, NCT02459080, NCT02512510) and three RCTs (NCT02040792, NCT03095456, NCT03573817), respectively, therefore all the included studies had low risk of performance bias and detection bias. Four studies (NCT02040792, NCT03095456, NCT03573817, NCT02109172) had low risk of attribution bias, as there was no loss of follow-up or missing data was appropriately addressed (e.g., applying ITT analysis which could underestimate the efficacy of the intervention). Nevertheless, other three studies (NCT02518139, NCT02459080, NCT02512510) had high risk of attribution bias due to high loss of follow-up (>15%). Although all the studies mentioned registration information and had an available protocol, data from some outcomes of interest (i.e., AEs, SAEs, FEV_1) in six studies (NCT02040792, NCT02518139, NCT02459080, NCT02512510, NCT03095456, NCT03573817) were inconsistent with the information on ClinicalTrial.gov. Therefore, the reporting bias risk of these studies was high. Since Theravance Biopharma, Inc. supported all the studies and their employees participated in the executing and writing process of six studies (NCT02040792, NCT02518139, NCT02459080, NCT02512510, NCT03095456, NCT03573817), the risk of bias caused by conflict of interest was high. Due to the limited number of the included studies for the same outcome, publication bias investigation was not performed. As to the three crossover studies (NCT01704404, NCT02109172, and NCT03064113), the overall risk of bias was assessed as "some concerns" (**Table 2**).

Results From the Meta-analysis

The Change From Baseline in Trough FEV_1

Six trials involving 2,093 participants reported the change from baseline in trough FEV_1. Among them, four trials (NCT02040792, NCT02459080, NCT02512510, and NCT01704404) compared REV with placebo at different doses, one trial (NCT02518139) compared REV with TIO at different follow-up time (4-weeks, 13-weeks, 26-weeks, 39-weeks, and 52-weeks), whereas the rest one (NCT03095456) made plain comparison between REV and TIO. In subgroup analyses, we found that both dose and therapeutic course of REV contribute to the heterogeneity, so the results were presented according to the control group, the dose and the therapeutic course (**Table 3**). In contrast to placebo, all different doses of REV could significantly improve the trough FEV_1. Yet this effect would be weakened with the longer course of treatments. Despite that trials NCT02459080 and NCT02512510 reported the change from baseline in trough

TABLE 1 | Characteristics of included studies.

Registered ID of Trials	Study setting	Study design	Intervention vs. Control Group (n)	Age (years)	Gender: Male (%)	BMI (kg/m^2)	Race: white (%)	Current smokers (%)	Current ICS/ LABA users (%)	Baseline FEV_1 (ml)	Follow-up time after first treatment (weeks)	Outcomes
NCT02040792	United States	Parallel	Placebo, Qd (70) REV, 44 μg, Qd (68) REV, 88 μg, Qd (71) REV, 175 μg, Qd (71) REV, 350 μg, Qd (74)	61.9 ± 8.63	178 (50.28)	27.9 ± 5.93	324 (91.52)	190 (53.67)	130 (36.72	1,283 ± 457	4	A; B; C
NCT02518139	United States	Parallel	REV, 88 μg, Qd (364) REV, 175 μg, Qd (335) TIO, 18 μg, Qd (356)	64.4 ± 8.97	616 (58.39)	28.8 ± 6.6 29.1 ± 6.8 28.8 ± 6.3	977 (92.61)	489 (46.35)	560 (53.08)	1,350 ± 520 1,340 ± 490 1,310 ± 490	52	A; B; C
NCT02459080	United States	Parallel	placebo, Qd (209) REV, 88 μg, Qd (212) REV, 175 μg, Qd (198)	64.1 ± 8.87	317 (51.21)	29.4 ± 6.6 29.1 ± 6.2 29.6 ± 7.2	564 (91.11)	301 (48.63)	260 (42.00)	1,400 ± 500 1,300 ± 400 1,400 ± 500	12	A; B; C
NCT02512510	United States	Parallel	placebo, Qd (208) REV, 88 μg, Qd (205) REV, 175 μg, Qd (197)	63.4 ± 8.95	302 (49.51)	29.3 ± 6.9 29.2 ± 7.7 28.9 ± 7.0	545 (89.34)	286 (46.88)	249 (40.82)	1,300 ± 500 1,300 ± 500 1,300 ± 500	12	A; B; C
NCT03095456	United States	Parallel	REV, 175 μg, Qd (102) TIO, 18 μg, Qd (104)	65.1 ± 8.13	124 (60.19)	NA	185 (89.80)	96 (46.60)	111 (53.88)	900 ± 500	4	A; B; C
NCT03573817	United States	Parallel	REV, 175 μg, Qd + FOR, 20 μg, Bid (63) Placebo, Qd + FOR, 20 μg, Bid (59)	63.7 ± 8.56	69 (56.56)	29.17 ± 6.475	116 (95.08)	69 (56.56)	28 (22.95)	1,340 ± 480 1,340 ± 500	6	B; C

(Continued on following page)

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

Registered ID of Trials	Study setting	Study design	Intervention vs. Control Group (n)	Age (years)	Gender: Male (%)	BMI (kg/m^2)	Race: white (%)	Current smokers (%)	Current ICS/ LABA users (%)	Baseline FEV_1 (ml)	Follow-up time after first treatment (weeks)	Outcomes
NCT01704404	United KingdomNorthern Ireland New Zealand	Crossover	REV, 22 μg, Qd (40) REV, 44 μg, Qd (39) REV, 88 μg, Qd (39) REV, 175 μg, Qd (39) REV, 350 μg, Qd (39) REV, 700 μg, Qd (40) Placebo, Qd (59)	63.9 (45–75)	33 (55.93	28.8 ± 5.92	59 (100)	NA	0 (0)	1,600 ± 500	1	A; B; C
NCT02109172	United States	Crossover	REV, 44 μg, Bid (64) REV, 175 μg, Qd (64) Placebo, Qd (64)	40–65: n = 39 y≥ 65: n = 25	37 (57.81)	NA	NA	NA	NA	NA	1	B; C
NCT03064113 Or U1111-1,120–8,290	South Africa New Zealand	Crossover	Placebo, Qd (32) REV, 350 μg, Qd (32) REV, 700 μg, Qd (32) IPR, 500 μg, Qd (32)	18–65: n = 22 y≥ 65: n = 10	22 (68.75%)	27.72 ± 8.0	28 (87.5)	NA	NA	1900 ± 500	1 day	B; C

n: sample size; BMI: body mass index; FEV_1: Forced Expiratory Volume in 1 s; REV: revefenacin; TIO: tiotropium; FOR: formoterol; IPR: ipratropium; NA: not applicable; A: change from baseline in trough FEV_1; B: total adverse events (AEs); C: serious adverse events (SAEs).

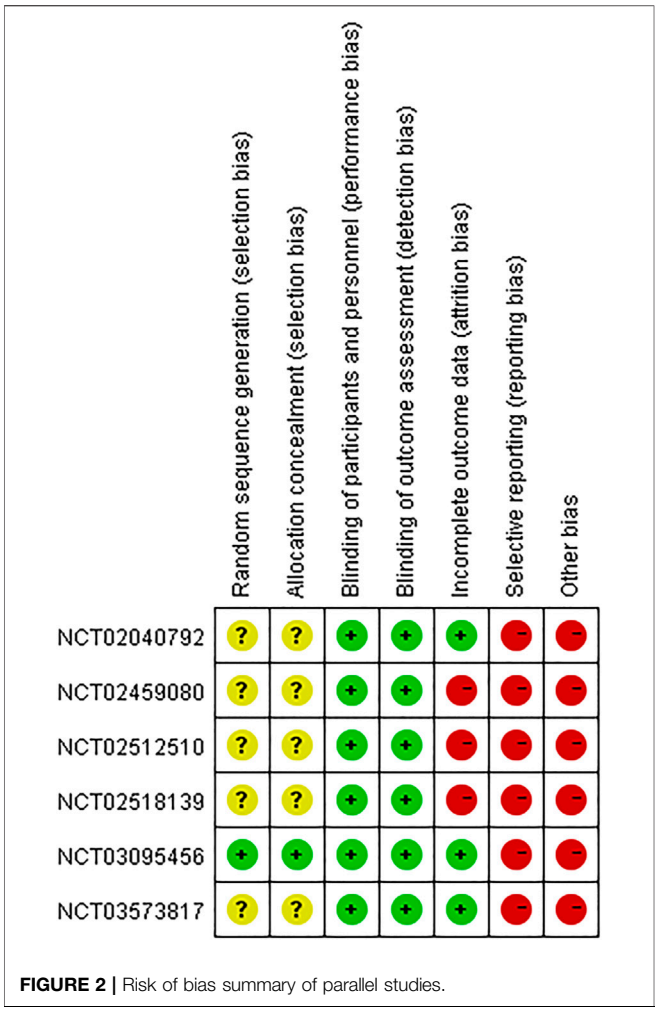

FIGURE 2 | Risk of bias summary of parallel studies.

FEV_1 for 88 μg/day REV vs. placebo at 12-weeks, the heterogeneity between the two trials was significantly high (I^2 = 100%). Therefore, we described their respective results rather than the pooling results. In the dose-response meta-analysis, there was a potential non-linear association (R^2 = 0.7017) of the REV dose with the change from baseline in trough FEV_1 (**Figure 3**). The predicted dose-specific mean changes from baseline in trough FEV_1 were 27.43 (95%CI: 13.55–68.41) ml at a dose of 22 μg/day, 54.41 (95%CI: 22.50–86.31) ml at a dose of 44 μg/day, 97.96 (95%CI: 77.72–118.21) ml at a dose of 88 μg/day, 119.47 (95%CI: 104.21–134.74) ml at a dose of 175 μg/day, 121.86 (95%CI: 112.79–130.92) ml at a dose of 350 μg/day, and 126.63 (95%CI: 112.13–141.12) ml at a dose of 700 μg/day. Interestingly, 88 μg/day seemed to be a threshold dose above which the change from baseline in trough FEV1 began to slow down (**Figure 3**). Patients who received 175 μg/day REV experienced improvement of trough FEV_1 on average of 143.67 ml higher than those who received placebo (MD = 143.67, 95%CI: 129.67 to 157.68; I^2 = 96%; 809 participants; studies = 4; low quality; **Table 4**). Patients treated with 175 μg/day REV gained increment of trough FEV_1 on average of 13.51 ml higher than TIO at 4 weeks (MD = 13.51, 95%CI: 8.32 to 18.69; I^2 = 66%; 791 participants; studies = 2; very low quality; **Table 4**), but this effect was reversed at 52 weeks (MD = -39.2, 95%CI: 41.82 to 36.58; 433 participants; study = 1; low quality; **Table 4**). The sensitivity analyses showed that the results including crossover studies were consistent with those omitting crossover studies (**Supplementary Table S3**).

The Incidence of Any Adverse Events

The AEs were reported in all trials including 3,121 participants. As presented in **Table 5**, most AEs were mild, transient, and reversible. A limited association (R^2 = 0.1787) of the REV dose with the total AEs incidence was present (**Supplementary Figure S1**). The predicted dose-specific RRs of the REV dose were 1.03 (95%CI: 1.00–1.07) at a dose of 22 μg/day, 1.02 (95%CI: 0.99–1.06) ml at a dose of 44 μg/day, 1.00 (95%CI: 0.97–1.04) ml at a dose of 88 μg/day, 0.96 (95%CI: 0.92–1.01) ml at a dose of 175 μg/day, 0.89 (95%CI: 0.81–0.97) ml at a dose of 350 μg/day, and 0.76 (95%CI: 0.64–0.90) ml at a dose of 700 μg/day. On average, the decrease in total AEs was 0.05% (RR = 0.9995, 95% CI: 0.9992–0.9998; p = 0.009) between 0 and the maximum dose. Furthermore, tests of interaction showed no evidence of different therapeutic course subgroup effect for total AEs in comparison of REV vs. PLA (**Supplementary Figure S2**). Notably, the incidence of total AEs in REV group was significantly lower than that in TIO group at 4 weeks (OR = 0.22, 95%CI: 0.11–0.45, $p < 0.0001$), while the difference became not significant at 52 weeks (OR = 0.82, 95%CI: 0.61–1.10, p = 0.19). Patients who received REV were the equivalent likely to undergo total AEs as

TABLE 2 | Risk of bias summary of cross-over studies.

Registered ID of Trials	Risk of bias arising from the randomization process	Risk of bias arising from period and carryover effects	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias
NCT01704404	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
NCT02109172	Some concerns	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
NCT03064113	Some concerns	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns

TABLE 3 | The results of the pairwise meta-analysis of change from baseline in trough FEV_1.

Group	Follow-up time	*N*	*n*	Heterogeneity	Model	*MDs(ml)*	95%*CIs*	*P*
REV 22 vs PLA	1 week	1	37 vs. 56	*NA*	*NA*	53.40	(45.79, 61.01)	<0.00001
REV 44 vs PLA	1 week	1	32 vs. 56	*NA*	*NA*	55.00	(46.70, 63.30)	<0.00001
	4 weeks	1	60 vs. 55	*NA*	*NA*	51.80	(42.59, 61.01)	<0.00001
REV 88 vs PLA	1 week	1	35 vs 56	*NA*	*NA*	75.30	(67.45, 83.15)	<0.00001
	4 weeks	1	63 vs. 55	*NA*	*NA*	187.40	(178.35, 196.45)	<0.00001
	12 weeks	1	161 vs. 146	*NA*	*NA*	79.22	(75.72, 82.72)	<0.00001
	12 weeks	1	152 vs. 150	*NA*	*NA*	160.50	(156.27, 164.73)	<0.00001
REV 175 vs PLA	1 week	1	33 vs. 56	*NA*	*NA*	114.10	(105.96, 122.24)	<0.00001
	4 weeks	1	59 vs. 55	*NA*	*NA*	166.60	(157.33, 175.87)	<0.00001
	12 weeks	2	310 vs. 296	I^2 = 0%, p = 0.58	Fixed	146.91	(144.20, 149.63)	<0.00001
REV 350 vs PLA	1 week	1	38 vs. 56	*NA*	*NA*	94.40	(86.90, 101.90)	<0.00001
	4 weeks	1	63 vs. 55	*NA*	*NA*	170.60	(161.59, 179.61)	<0.00001
REV 700 vs PLA	1 week	1	35 vs. 56	*NA*	*NA*	81.60	(73.75, 89.45)	<0.00001
REV 88 vs TIO	4 weeks	1	317 vs. 330	*NA*	*NA*	-29.00	(–30.82, –27.18)	<0.00001
	13 weeks	1	287 vs. 307	*NA*	*NA*	-16.00	(–17.96, –14.04)	<0.00001
	26 weeks	1	239 vs. 283	*NA*	*NA*	-14.80	(–16.99, –12.61)	<0.00001
	39 weeks	1	223 vs. 265	*NA*	*NA*	-10.20	(–12.51, –7.89)	<0.00001
	52 weeks	1	212 vs. 248	*NA*	*NA*	-42.70	(–45.12, –40.28)	<0.00001
REV 175 vs TIO	4 weeks	2	371 vs. 420	I^2 = 66%, p = 0.08	Random	13.51	(8.32, 18.69)	<0.00001
	13 weeks	1	243 vs. 307	*NA*	*NA*	2.70	(0.55, 4.85)	<0.00001
	26 weeks	1	210 vs. 283	*NA*	*NA*	15.40	(13.03, 17.77)	<0.00001
	39 weeks	1	189 vs. 265	*NA*	*NA*	-8.30	(–10.85, –5.75)	<0.00001
	52 weeks	1	185 vs. 248	*NA*	*NA*	-39.20	(–41.82, –36.58)	<0.00001

FEV_1: Forced Expiratory Volume in 1 s; N: the number of included trials; n: the number of participants; MDs: mean differences; 95%CIs: 95% confidence intervals; REV 22: revefenacin 22 μg/day; REV 44: revefenacin 44 μg/day; REV 88: revefenacin 88 μg/day; REV 175: revefenacin 175 μg/day; REV 350: revefenacin 350 μg/day; REV 700: revefenacin 700 μg/day; PLA: placebo; TIO: tiotropium; Fixed: fixed-effects model; Random: random-effects model; NA: not applicable.

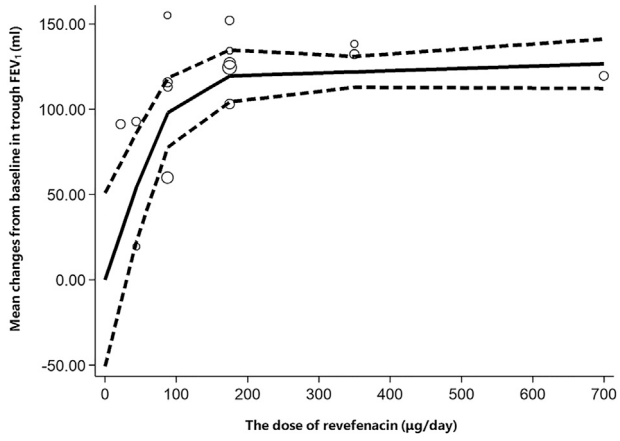

FIGURE 3 | Increase in dose (μg/day) of revefenacin and change from baseline in trough FEV1 (ml). The solid line is the nonlinear prediction of the mean change from baseline in trough FEV_1 and the dotted lines indicate the 95% confidence interval. The threshold is 88 μg/day. FEV_1: Forced Expiratory Volume in 1 s.

placebo patients (OR = 0.98, 95%CI: 0.81 to 1.18; I^2 = 34%; 2,286 participants; studies = 7; low quality; **Figure 4**, **Table 3**), TIO patients (OR = 0.44, 95%CI: 0.12 to 1.60; I^2 = 91%; 1,262 participants; studies = 2; very low quality; **Supplementary Figure S3**, **Table 4**), or IPR patients (OR = 0.66, 95%CI: 0.23 to 1.94; 96 participants; study = 1; very low quality; **Figure 4**, **Table 4**). The sensitivity analyses showed that the results including crossover studies were consistent with those omitting crossover studies (**Supplementary Figure S4**).

The Incidence of SAEs

All the nine trials reported 200 SAEs, and the most common SAEs was COPD worsening or exacerbation (1.39%, **Table 6**). A weak association (R^2 = 0.1325) of the REV dose with the SAEs incidence existed (**Supplementary Figure S5**). The predicted dose-specific RRs of the REV dose were 0.99 (95%CI: 0.95–1.04) at a dose of 22 μg/day, 0.97 (95%CI: 0.93–1.02) ml at a dose of 44 μg/day, 0.94 (95%CI: 0.88–0.99) ml at a dose of 88 μg/day, 0.86 (95%CI: 0.78–0.96) ml at a dose of 175 μg/day, 0.74 (95%CI: 0.60–0.90) ml at a dose of 350 μg/day, and 0.54 (95%CI: 0.36–0.81) ml at a dose of 700 μg/day. The average decrement in risk of SAEs between 0 and the maximum dose was 0.1% (RR = 0.9990, 95%CI: 0.9984–0.9998; p = 0.020). Yet we found no evidence of different therapeutic course effect for this outcome in comparison of REV vs. PLA (**Supplementary Figure S6**). Patients treated with REV were the similar likely to experience SAEs as placebo patients (OR = 0.89, 95%CI: 0.55 to 1.46; I^2 = 0%; 2,318 participants; studies = 7; very low quality; **Figure 5**, **Table 4**), TIO patients (OR = 0.86, 95%CI: 0.61 to 1.21; I^2 = 0%; 1,262 participants; studies = 2; low quality; **Figure 5**, **Table 4**), or IPR patients (OR = 1.00, 95%CI: 0.13 to 7.43; 96 participants; study = 1; low quality; **Figure 5**, **Table 4**). These results were consistent with the sensitivity analyses by using Mantel-Haenszel RD (**Supplementary Figure S7**). The sensitivity analyses showed that the results including crossover studies were consistent with those omitting crossover studies (**Supplementary Figure S8**).

TABLE 4 | GRADE summary of findings for intervention versus controls in patients with chronic obstructive pulmonary disease (COPD).

Patient or population	Settings	Intervention	Comparison	Outcomes (timeframe)	Relative effect (95%CI)	No. of participants	Absolute effect estimate (95%CI)	Quality of evidence	Comments
Individuals with COPD	Outpatient	Revefenacin 175 μg/day	Placebo	Change from baseline in trough FEV_1 (ml) (From 10 week to 12 weeks)	NA	809 patients in 4 RCTs	143.67 higher (129.67 higher to 157.68 higher)	Low[a, b, c]	Revefenacin 175 μg/day might improve lung function compared to placebo.
Individuals with COPD	Outpatient	Revefenacin 175 μg/day	Tiotropium 18 μg/day	Change from baseline in trough FEV_1 (ml) (At 4 weeks)	NA	791 patients in 2 RCTs	13.51 higher (8.32 higher to 18.69 higher)	Very low[a, d]	Revefenacin 175 μg/day might improve lung function compared to tiotropium in the short term.
Individuals with COPD	Outpatient	Revefenacin 175 μg/day	Tiotropium 18 μg/day	Change from baseline in trough FEV_1 (ml) (At 52 weeks)	NA	433 patients in one RCT	39.2 lower (41.82 lower to 36.58 lower)	Low[a,d]	Revefenacin 175 μg/day might not improve lung function compared to tiotropium in the long term.
Individuals with COPD	Outpatient	Revefenacin 22–700 μg/day	Placebo	Any adverse events (From 1 day to 12 weeks)	Odds ratio: 0.98 (0.81–1.18)	2,286 patients in 7 RCTs	5 fewer (51 fewer to 41 more)	Low[a]	Revefenacin might not increase the risk of any adverse events compared to placebo.
Individuals with COPD	Outpatient	Revefenacin 88–175 μg/day	Tiotropium 18 μg/day	Any adverse events (From 4 to 52 weeks)	Odds ratio: 0.44 (0.12–1.60)	1,262 patients in 2 RCTs	197 fewer (477 fewer to 92 more)	Very low[a,e,f]	Revefenacin might not increase the risk of any adverse events compared to tiotropium.
Individuals with COPD	Outpatient	Revefenacin 350–700 μg/day	Ipratropium 500 μg/day	Any adverse events (At 1 day)	Odds ratio: 0.66 (0.23–1.94)	96 patients in one RCT	63 fewer (158 fewer to 133 more)	Very Low[a,f,g]	Revefenacin might not increase the risk of any adverse events compared to ipratropium.
Individuals with COPD	Outpatient	Revefenacin 22–700 μg/day	Placebo	Serious adverse events (From 1 day to 12 weeks)	Odds ratio: 0.89 (0.55–1.46)	2,318 patients in 7 RCTs	4 fewer (14 fewer to 14 more)	Very low[a,f]	Revefenacin might not increase the risk of serious adverse events compared to placebo.
Individuals with COPD	Outpatient	Revefenacin 88–175 μg/day	Tiotropium 18 μg/day	Serious adverse events (From 4 to 52 weeks)	Odds ratio: 0.86 (0.61–1.21)	1,262 patients in 2 RCTs	16 fewer (46 fewer to 23 more)	Low[a]	Revefenacin might not increase the risk of serious adverse events compared to tiotropium.
Individuals with COPD	Outpatient	Revefenacin 350–700 μg/day	Ipratropium 500 μg/day	Serious adverse events (At 1 day)	Odds ratio: 1.00 (0.13–7.43)	96 patients in one RCT	0	Low[g,h]	Revefenacin might not increase the risk of serious adverse events compared to ipratropium.

CI: confidence interval; FEV_1: Forced Expiratory Volume in 1 s; RCT: randomized controlled trial; PLA: placebo; [a]: very serious risk of bias (unclear selection bias, high risk of attribution, reporting, and other bias); [b]: very considerable inconsistence (I^2 = 96%, high heterogeneity caused by different timeframe and disparate results across studies); [c]: upgraded because all plausible confounding would reduce demonstrated effect and the dose-response gradient was strong; [d]: considerable heterogeneity (I^2 = 66%); [e]: very considerable inconsistence (I^2 = 91%, high heterogeneity caused by different timeframe and non-overlapping 95% CIs); [f]: wide 95% CI with a lower limit <0.75 and an upper limit >1.25; [g]: serious risk of bias (unclear selection and other bias); [h]: small sample size.

DISCUSSION

This systematic review summarized the evidence of efficacy and safety of REV in patients with moderate to very severe COPD and used a novel meta-analysis method to account for the dose-response relationship of the trough FEV_1, AEs, and SAEs with REV dose. Low-quality evidence suggests that, compared to placebo, 175 μg/day REV might improve the lung function (increment of trough FEV_1 on average of 143.67 ml higher than placebo) without elevating the risk of AEs or SAEs. However, only very low-quality to low-quality evidence demonstrates that the safety profile of REV at a dose of

TABLE 5 | The incidence of non-serious adverse events for revefenacin.

Non-serious adverse events	Events	Total	Incidence (%)
Infections and infestations	—	—	—
Nasopharyngitis	83	2,450	3.39
Upper respiratory tract infection	75	2,450	3.06
Bronchitis	34	2,450	1.39
Urinary tract infection	31	2,450	1.27
Sinusitis	31	2,450	1.27
Tooth infection	1	2,450	0.04
Viral infection	1	2,450	0.04
Acute sinusitis	1	2,450	0.04
Ear Infection	1	2,450	0.04
Furuncle	1	2,450	0.04
Investigations	—	—	—
Electrocardiogram T wave peaked	3	2,450	0.12
Metabolism and nutrition disorders	—	—	—
Gout	2	2,450	0.08
Nervous system disorders	—	—	—
Headache	103	2,450	4.20
Dizziness	1	2,450	0.04
Tremor	1	2,450	0.04
Respiratory, thoracic and mediastinal disorders	—	—	—
Chronic obstructive pulmonary disease exacerbation	273	2,450	11.14
Cough	95	2,450	3.88
Dyspnea	90	2,450	3.67
Pneumonia	21	2,450	0.86
Dysphonia	1	2,450	0.04
Chest Discomfort	2	2,450	0.08
Rhinorrhea	3	2,450	0.12
Oropharyngeal pain	6	2,450	0.24
Rhonchi	1	2,450	0.04
Sputum increased	1	2,450	0.04
Gastrointestinal disorders	—	—	—
Diarrhea	27	2,450	1.10
Gastroesophageal reflux disease	16	2,450	0.65
Nausea	16	2,450	0.65
Dry mouth	3	2,450	0.12
Oral discomfort	1	2,450	0.04
Inguinal hernia	1	2,450	0.04
Vomiting	1	2,450	0.04
General disorders	—	2,450	—
Fatigue	4	2,450	0.16
Oedema	2	2,450	0.08
Injury, poisoning and procedural complications	—	—	—
Contusion	6	2,450	0.24
Muscle contusion	1	2,450	0.04
Eye swelling	1	2,450	0.04
Eye contusion	1	2,450	0.04
Procedural pain	1	2,450	0.04
Musculoskeletal and connective tissue disorders	—	—	—
Back pain	37	2,450	1.51
Arthralgia	15	2,450	0.61
Pain in extremity	1	2,450	0.04
Muscle spasms	1	2,450	0.04
Musculoskeletal pain	1	2,450	0.04
Neck pain	1	2,450	0.04
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	—	—	—
Basal cell carcinoma	1	2,450	0.04
Skin and subcutaneous tissue disorders	—	2,450	—
Rash	6	2,450	0.24
Dermatitis contact	2	2,450	0.08
Skin lesion	1	2,450	0.04
Vascular disorders		2,450	
Hypertension	27	2,450	1.10
Hematoma	2	2,450	0.08
Blood pressure increased	1	2,450	0.04

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TABLE 5 | (*Continued*) The incidence of non-serious adverse events for revefenacin.

Non-serious adverse events	Events	Total	Incidence (%)
Hypotension	1	2,450	0.04
Coronary artery insufficiency	1	2,450	0.04
Psychiatric disorders	—	—	—
Insomnia	1	2,450	0.04

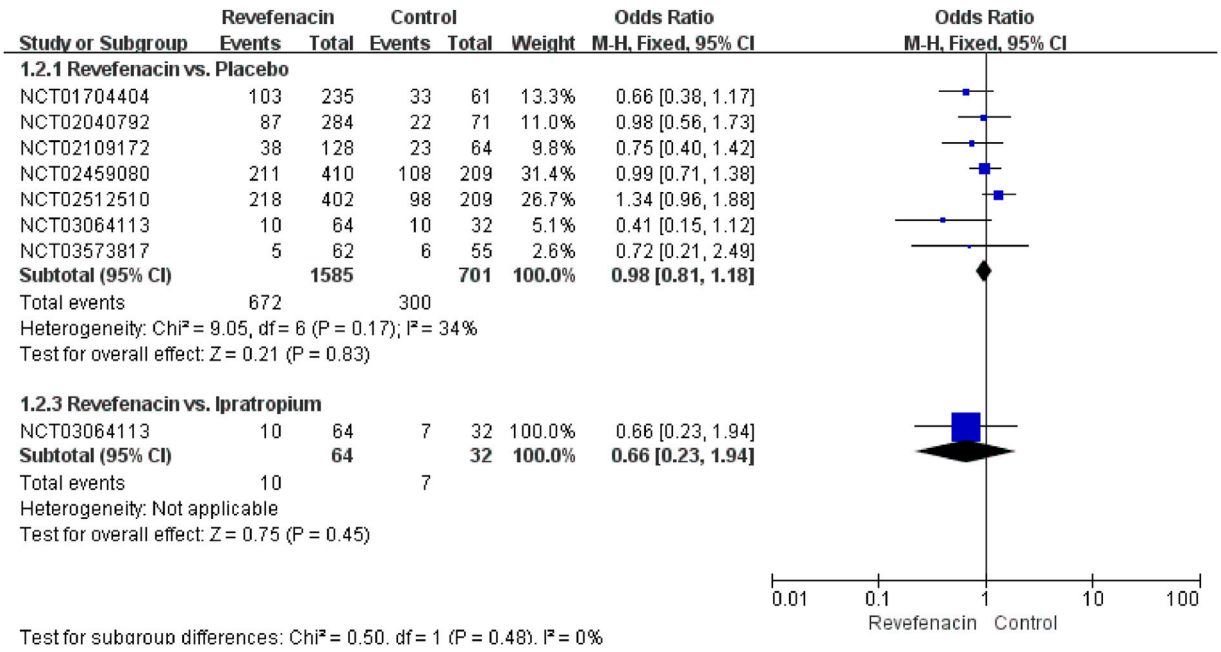

FIGURE 4 | Total adverse events for revefenacin in patients with chronic obstructive pulmonary disease.

175 μg/day is similar to TIO and IPR but its long-term efficacy is inferior to TIO (decrease of trough FEV_1 on average of 39.2 ml lower than TIO). The effect of REV in increasing trough FEV_1 was correlated to the dose with a threshold value of 88 μg/day. Notably, the efficacy of REV would be weakened with the extension of therapeutical course.

Despite the serious risk of bias and inconsistence, the confidence rating of evidence regarding the efficacy of REV vs. placebo might be enhanced by the dose-response gradient which was consistent with the results *in vitro* (Pulido-Rios et al., 2013). The novel robust error meta-regression method had some merits of reducing the probability of type I error caused by repeated analyses, so it was utilized to investigate the dose-response relationship. This relationship was non-linear and included three phases based on REV dose: 0–88 μg/day, 88–175 μg/day, and 175–700 μg/day. The change from baseline in trough FEV_1 dramatically escalated with the increasing dose of REV from 0 to 88 μg/day. Thereafter, the growth rate started to slow down and achieved a plateau phase when the dose exceeded 175 μg/day due to a ceiling effect. Our finding is coincided with current suggestion where 88 and 175 ug/day REV are considered as appropriate doses for investigating longer-term safety and efficacy of REV (Krishna et al., 2017). To explore the heterogeneity of trough FEV_1 regarding 88 μg/day of REV vs. placebo at 12-weeks, we compared the baseline of participants in trial NCT02512510 with that in trial NCT02459080. Unfortunately, there was no significant difference in baseline characteristics. Hence, one possible reason for explaining the heterogeneity is that a dose of 88 μg/day was the threshold of the dose-response curve and some patients in the study might not receive the full benefits of the treatment, suggesting that a higher dose would be more optimal for all participants. Different from efficacy, there was no significant dose-response relationship between dose and the incidence of AEs or SAEs and the safety profile of REV was comparable to placebo. In addition, a previous study also reported that concurrent long-acting β-agonists (LABA) would slightly raise the incidence of AEs for patients receiving REV at a dose of 88 μg/day rather than those receiving REV at a dose of 175 μg/day (Donohue et al., 2019c). Thereby 175 μg/day has been approved as a standard dose by the United States FDA (Highlights Of Prescribing Information, 2021).

The effect of REV at a dose of 175 μg/day in improving the trough FEV_1 was superior to TIO within 26 weeks but then got

TABLE 6 | The incidence of serious adverse events for revefenacin.

Serious adverse events	Events	Total	Incidence (%)
Cardiac disorders	—	—	—
Myocardial infarction	6	2,450	0.24
Acute myocardial infarction	6	2,450	0.24
Angina unstable	3	2,450	0.12
Coronary artery occlusion	2	2,450	0.08
Cardiac failure congestive	2	2,450	0.08
Coronary Artery Insufficiency	1	2,450	0.04
Atrial fibrillation	1	2,450	0.04
Silent myocardial infarction	1	2,450	0.04
Acute coronary syndrome	1	2,450	0.04
Cardiac arrest	1	2,450	0.04
Angina pectoris	1	2,450	0.04
Bradycardia	1	2,450	0.04
Coronary artery disease	1	2,450	0.04
Tachycardia	1	2,450	0.04
Gastrointestinal disorders	—	—	—
Small intestinal obstruction	3	2,450	0.12
Upper gastrointestinal hemorrhage	3	2,450	0.12
Colitis	2	2,450	0.08
Diverticulum intestinal hemorrhagic	2	2,450	0.08
Pancreatitis acute	2	2,450	0.08
Intestinal obstruction	1	2,450	0.04
Gastric volvulus	1	2,450	0.04
Abdominal pain	1	2,450	0.04
Gastrointestinal hemorrhage	1	2,450	0.04
Nausea	1	2,450	0.04
Pancreatic mass	1	2,450	0.04
Rectal hemorrhage	1	2,450	0.04
Vascular disorders			
Hypertension	1	2,450	0.04
Hypotension	1	2,450	0.04
Accelerated hypertension	1	2,450	0.04
Aortic aneurysm	1	2,450	0.04
Circulatory collapse	1	2,450	0.04
Peripheral arterial occlusive disease	1	2,450	0.04
Endocrine disorders			
Goitre	1	2,450	0.04
General disorders	—	—	—
Non-cardiac chest pain	5	2,450	0.20
Chest pain	5	2,450	0.20
Impaired healing	1	2,450	0.04
Cardiac death	1	2,450	0.04
Systemic inflammatory response syndrome	1	2,450	0.04
Hepatobiliary disorders			
Jaundice	1	2,450	0.04
Infections and infestations	—	—	—
Pneumonia	12	2,450	0.49
Cellulitis	4	2,450	0.16
Bronchitis	3	2,450	0.12
Appendicitis	2	2,450	0.08
Bronchitis bacterial	1	2,450	0.04
Pneumonia para-influenzae viral	1	2,450	0.04
Diverticulitis	1	2,450	0.04
Pneumonia bacterial	1	2,450	0.04
Abscess neck	1	2,450	0.04
Infected skin ulcer	1	2,450	0.04
Ludwig angina	1	2,450	0.04
Osteomyelitis	1	2,450	0.04
Post procedural infection	1	2,450	0.04
Sepsis	1	2,450	0.04
Injury, poisoning and procedural complications	—	—	—
Femur fracture	1	2,450	0.04
Hip fracture	1	2,450	0.04
Lower limb fracture	1	2,450	0.04

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TABLE 6 | (*Continued*) The incidence of serious adverse events for revefenacin.

Serious adverse events	Events	Total	Incidence (%)
Multiple fractures	1	2,450	0.04
Road traffic accident	1	2,450	0.04
Upper limb fracture	1	2,450	0.04
Musculoskeletal and connective tissue disorders	—	—	—
Osteoarthritis	4	2,450	0.16
Cervical spinal stenosis	2	2,450	0.08
Musculoskeletal chest pain	2	2,450	0.08
Rheumatoid arthritis	1	2,450	0.04
Muscular weakness	1	2,450	0.04
Spinal column stenosis	1	2,450	0.04
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	—	—	—
Lung neoplasm malignant	2	2,450	0.08
Small cell lung cancer	2	2,450	0.08
Colon cancer	2	2,450	0.08
Lung adenocarcinoma	2	2,450	0.08
Uterine leiomyoma	1	2,450	0.04
Brain cancer metastatic	1	2,450	0.04
Colon cancer stage 0	1	2,450	0.04
Hepatic cancer	1	2,450	0.04
Lung carcinoma cell type unspecified stage IV	1	2,450	0.04
Ovarian cancer	1	2,450	0.04
Prostate cancer	1	2,450	0.04
Pancreatic carcinoma	1	2,450	0.04
Squamous cell carcinoma	1	2,450	0.04
Breast cancer	1	2,450	0.04
Nervous system disorders	—	—	—
Transient ischemic attack	1	2,450	0.04
Migraine	1	2,450	0.04
Carotid artery stenosis	1	2,450	0.04
Depressed level of consciousness	1	2,450	0.04
Syncope	1	2,450	0.04
Renal and urinary disorders	—	—	—
Renal artery stenosis	1	2,450	0.04
Reproductive system and breast disorders	—	—	—
Benign prostatic hyperplasia	1	2,450	0.04
Respiratory, thoracic and mediastinal disorders	—	—	—
Chronic obstructive pulmonary disease	34	2,450	1.39
Acute respiratory failure	8	2,450	0.33
Dyspnea	2	2,450	0.08
Pulmonary embolism	2	2,450	0.08
Respiratory failure	2	2,450	0.08
Bronchiectasis	1	2,450	0.04
Pleural effusion	1	2,450	0.04
Pulmonary granuloma	1	2,450	0.04
Pulmonary mass	1	2,450	0.04
Pneumothorax	1	2,450	0.04
Hypoxia	1	2,450	0.04
Skin and subcutaneous tissue disorders	—	—	—
Hyperhidrosis	1	2,450	0.04
Subcutaneous emphysema	1	2,450	0.04
Psychiatric disorders	—	—	—
Panic attack	1	2,450	0.04
Bipolar disorder	1	2,450	0.04
Metabolism and nutrition disorders	—	—	—
Lactic acidosis	1	2,450	0.04

inferior after 39 weeks. On one hand, the disproportionate number of poor performers who discontinued TIO during the final 3 months of treatment (Donohue et al., 2019b) could partially account for this phenomenon. On the other hand, the distinct mechanism of drug action should also be considered, as REV exhibits pharmacological effects through selective inhibition of M_3 receptor at the smooth muscle leading to bronchodilation, while TIO blocks both M_3 and M_1 receptors to take more prolonged effects (Li and Yang, 2019). Given that REV with novel biphenyl carbamate tertiary amine structure is different from TIO with quaternary ammonium feature (Donohue et al., 2019d; Montuschi and Ciabattoni, 2015),

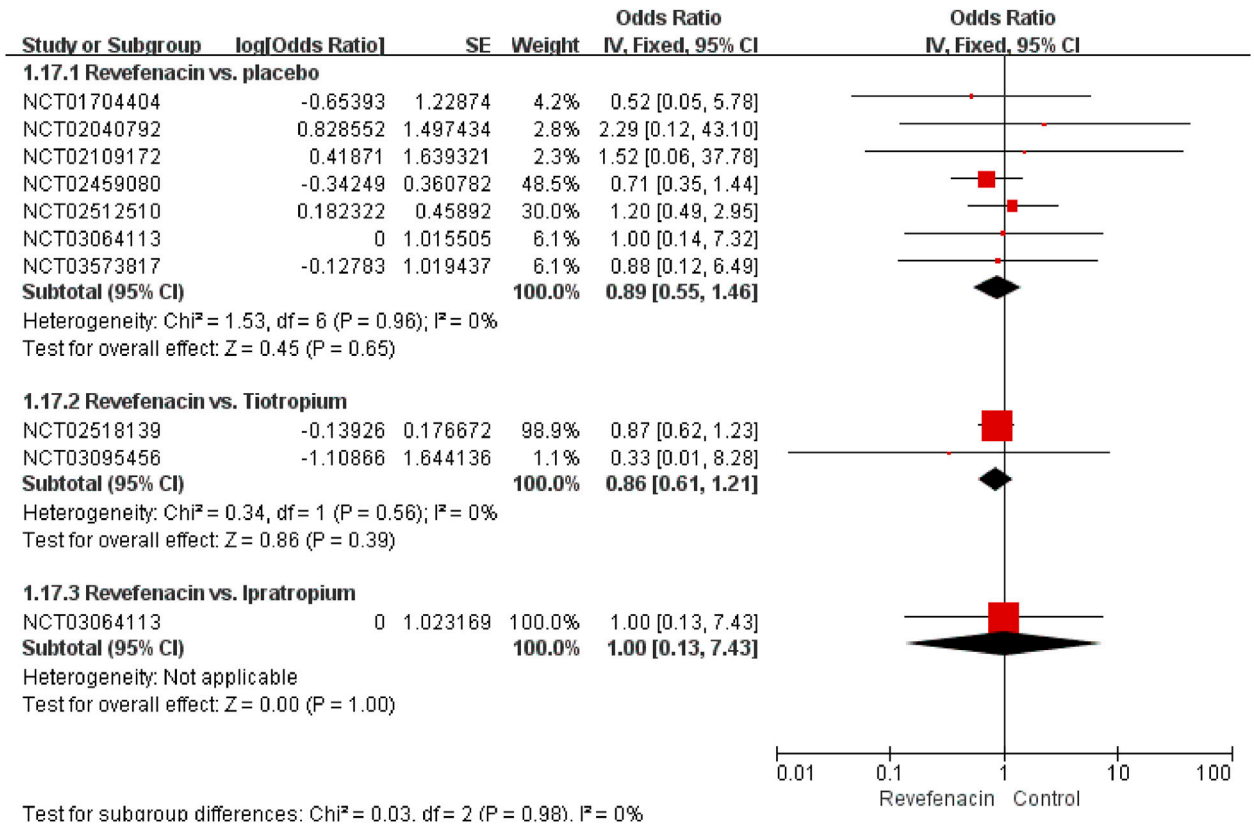

FIGURE 5 | Serious adverse events for revefenacin in patients with chronic obstructive pulmonary disease.

REV was supposed to have higher metabolic lability and more rapid systemic clearance than TIO (Babu and Morjaria, 2017; GlaxoSmithKline. Incruse, 2021) in terms of minimizing systemically mediated AEs. Nonetheless, this systematic review did not show any significant advantage of REV in reducing the risk of AEs or SAEs compared to TIO or IPR, which might be ascribed to underpowered sample size. Although present evidence showed that REV was not preferable to TIO both in efficacy and safety, certain COPD patients with chronic muscle weakness, or cognitive or visual impairment or diminished manual dexterity may still particularly benefit from the use of this once-daily nebulized delivery LAMA (Bonini and Usmani, 2015; Tashkin D. P., 2016). As the evidence about the efficacy and safety of REV vs. TIO was mainly from two trials (NCT02518139 and NCT03095456) with high risk of attribution, reporting, and other bias, its confidence rating was graded as very low to low quality.

This systematic review also found the therapeutical course would influence the efficacy in improving trough FEV_1, which could be explained by the progression of COPD with longer follow-up time. Considering the limited data from trials, we did not evaluate the association of reduced efficacy with treatment course. Furthermore, the proportion of ICS/LABA users varied a lot among all the included trials, which probably brought heterogeneity to the results of meta-analyses. Nevertheless, a subgroup analysis (Sethi et al., 2020) found that REV produced similar improvements from baseline in trough FEV_1 in the non-LABA and LABA groups despite more AEs reported in the LABA.

There are several limitations in this study. As we only included RCTs, the results may not have good generalizability for strict inclusion criteria and small sample size. Particularly, the representativeness of participants was compromised because all the trials were conducted in the United States, the United Kingdom, Northern Ireland, New Zealand, and South Africa where most of the participants were white. In addition, these trials were not sensitive to assess treatment-related rare AEs (incidence ≤0.01%) due to relatively lower power of test and shorter follow-up term. Furthermore, the quality of evidence was subpar for the high risk of attribution and reporting bias in primary studies. Moreover, the language restriction for English and Chinese could also reduce the generalizability of our results. Therefore, prospective, multicenter, RCTs with larger samples, different populations, and better methodological design are urgently needed in this field. Although the course of treatment would influence the efficacy of REV, we performed the dose-response meta-analysis without adjusting this confounder due to limited data from the trials, suggesting that the non-linearity relationship between dosage and improvements in the through FEV_1 of REV should be interpreted with caution. Finally, even

though study design and concomitant medication such as formoterol in NCT03573817 would also be the possible source of heterogeneity, we did not assess the effect of these factors on the results due to small quantity of trials with the same outcomes.

To conclude, based on the findings of our systematic review and dose-response meta-analysis of RCTs, REV appears to be a promising option for the treatment of moderate to very severe COPD. Considering the low confidence rating of evidence, further studies are warranted to compare the efficacy, long-term safety and cost-effectiveness between REV and other LAMAs (TIO) in different populations. Although most studies used the FEV_1 to evaluate the efficacy of REV in treatment of COPD, but FEV_1 should just be set as a surrogate outcome. Therefore, the clinical benefit of REV in patients with COPD should be further evaluated. And researchers should increase focus on those important endpoints (e.g., death, exacerbations requiring antibiotics or oral steroids, hospitalizations due to exacerbation of COPD, exacerbations requiring a short course of an oral steroid or antibiotic, etc.) and patient-reported outcomes in the further research due to few trials reporting such related endpoints.

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

JZ, YX and XL did the literature search, collected the data, and drafted the manuscript. JS-K, RH, WZ, LG, YH, RZ, HZ, and JH revised the final manuscript. All authors conceived and designed the study, analyzed and interpreted the data, did the quality assessment, and revised and approved the manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.667027/full#supplementary-material

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Evaluation of the Direct Costs of Managing Adverse Drug Events in all Ages and of Avoidable Adverse Drug Events in Older Adults in Japan

Hayato Katsuno[1,2], *Tomoya Tachi*[1,2]*, *Takuya Matsuyama*[1], *Mayuko Sugioka*[1], *Satoshi Aoyama*[2], *Tomohiro Osawa*[2], *Yoshihiro Noguchi*[1], *Masahiro Yasuda*[2], *Chitoshi Goto*[2], *Takashi Mizui*[2] *and Hitomi Teramachi*[1,3]*

[1]*Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, Gifu, Japan,* [2]*Department of Pharmacy, Gifu Municipal Hospital, Gifu, Japan,* [3]*Laboratory of Community Health Pharmacy, Gifu Pharmaceutical University, Gifu, Japan*

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***Correspondence:**
Tomoya Tachi
tachi@gifu-pu.ac.jp
Hitomi Teramachi
teramachih@gifu-pu.ac.jp

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In Japan, medical costs are increasing annually, and the increase in national medical costs, particularly in the direct cost of managing adverse drug events, is high. An in-depth understanding of these costs is important for their reduction. This study aimed to calculate the direct cost of managing adverse drug events in all ages, including older adults, and that of avoidable adverse drug events in older adults. We conducted a retrospective survey on patients aged 1 year or older who visited Gifu Municipal Hospital in Japan. We investigated and calculated the direct cost of managing adverse drug events and that of avoidable adverse drug events based on the Beers Criteria Japanese version (BCJ) and "Guidelines for medical treatment and its safety in the elderly 2015" (GMTSE-2015) in inpatients and outpatients. Among 6,504 patients, 11.1% visited the hospital or were hospitalized due to adverse drug events. The direct costs per patient with adverse drug events were 21,281 and 22,590 yen (166 and 176 euros as on September 13, 2021) for outpatients, and 853,175 and 874,582 yen (6,648 and 6,815 euros) for inpatients of all ages and older adults, respectively. The direct costs of avoidable adverse drug events per patient using drugs listed in the BCJ and GMTSE-2015 for older adults were 3,212 and 3,341 yen (25 and 26 euros) for outpatients, and 55,548 and 80,246 yen (433 and 625 euros) for inpatients, respectively. In sum, considering both inpatients and outpatients in the whole country, the direct costs of managing adverse drug events were 804.53 billion and 597.19 billion yen (6,269 million and 4,653 million euros) per year for all ages and older ages, respectively. The direct cost of avoidable adverse drug events in older adults was 83.43–258.44 billion yen (650–2,013 million euros) per year. We found that, in Japan, high medical costs are often caused by managing adverse drug events, and that the costs of avoidable adverse drug events in older adults based on the BCJ and GMTSE-2015 account for a substantial proportion of the medical cost. Therefore, by using the BCJ and GMTSE-2015, avoiding adverse drug events and reducing medical costs may be possible.

Keywords: adverse drug event, direct cost, inpatient, older adult, outpatient

INTRODUCTION

Globally, medical costs are increasing annually (The Organisation for Economic Co-operation and Development, 2021). In the United States and Japan, the national medical costs in 2015 were 3,051,508 million dollars and 42,364.4 billion yen, representing an increase of 5.9 and 3.8% from the previous year, respectively (Ministry of Health, Labour and Welfare in Japan, 2015; The Organisation for Economic Co-operation and Development, 2021). In Japan, medical costs for adults aged 65 and over, which were 25,127.6 billion yen, increased by 5.1% from the previous year, and those for older adults exceeded 50% of the total medical costs (Ministry of Health, Labour and Welfare in Japan, 2015). Thus, measures to reduce these ever-increasing medical costs should be taken.

A substantial proportion of hospital consultations is attributable to adverse drug events. During 1990–2020, the proportion of outpatient visits and hospitalizations due to adverse drug events has varied from 5.5 to 35.0% (Hanlon et al., 1997; Honigman et al., 2001; Gandhi et al., 2003) and 1.3 to 30.4% (Dartnell et al., 1996; Chan et al., 2001; Senst et al., 2001; Onder et al., 2002; Wawruch et al., 2009; Ruiter et al., 2012; Parameswaran Nair et al., 2017), respectively. In Japan, 1.7% of hospitalizations are attributable to inappropriate drug use (Koinuma et al., 2006). The prevalence of adverse drug events resulting in hospital consultations is a relevant factor of the high costs of managing adverse drug events in hospitals. Therefore, every country calculates the direct costs of managing adverse drug events, including treatment and examination, which were evaluated to be quite high (Bates et al., 1997; Carrasco-Garrido et al., 2010; Leendertse et al., 2011; Rottenkolber et al., 2011; Stark et al., 2011). However, there are no data for Japan; therefore, it is important to evaluate the cost in Japan. It is important to clarify the costs of managing adverse drug events and to evaluate the contribution of the costs to overall medical costs.

Studies have been conducted to determine which drugs should be avoided and discontinued by older adults (Opondo et al., 2012; Wickop and Langebrake, 2014; Lucchetti and Lucchetti, 2017; Nothelle et al., 2017), and results have shown that 2.9–38.5% of older adults' prescriptions are potentially inappropriate (Opondo et al., 2012). To determine which drugs should be avoided and discontinued by the elderly, the Beers Criteria Japanese version (BCJ) was published by the National Institute of Public Health in 2008 (National Institute of Public Health, 2010), and the "Guidelines for medical treatment and its safety in the elderly 2015" (hereinafter referred to as GMTSE-2015) was published by the Japan Geriatrics Society in 2015 (The Japan Geriatrics Society, 2015; Kojima et al., 2016). In the previous study, we investigated the prevalence of older patients targeted by the BCJ and GMTSE-2015, and we clarified the prevalence and background/factor of adverse drug events occurred (Tachi et al., 2019). The avoidance of adverse drug events by appropriate prescriptions results in a reduction of cost of managing adverse drug events. The calculation of costs of preventable adverse drug events is important to understand its effect on overall medical costs. This calculated cost has been reported (Rothschild et al., 2002; Leendertse et al., 2011; Slight et al., 2018). The costs that can be reduced by using the criteria for drugs that should be avoided and considered for discontinuation by older adults, such as those listed in the BCJ and GMTSE-2015, should also be identified in Japan.

We conducted a retrospective survey with patients who visited a hospital in Japan to calculate the direct cost of managing adverse drug events. Further, we calculated the degree of this reduction using the BCJ and GMTSE-2015 as references.

MATERIALS AND METHODS

Participants

The target patients were outpatients and inpatients aged at least 1 year who visited Gifu Municipal Hospital (Gifu, Japan), excluding outpatients and inpatients with reservations, between July 1 and December 31, 2015, and took one or more drugs, excluding investigational drugs, during the visit. Patients hospitalized immediately after their hospital visit as outpatients were included as inpatients.

With 609 beds, Gifu Municipal Hospital is a typical general hospital in Japan, providing primary and secondary care to the city of Gifu and its suburbs.

Investigations and Evaluations

The survey was conducted retrospectively using electronic medical records. The survey items were sex, age, drugs used at the time of hospital visit or hospitalization, disease, presence or absence of adverse drug events, and length of hospitalization in case of inpatients. For people aged 65 years and above, we investigated whether they used the drugs listed in the BCJ and GMTSE-2015.

Drugs were classified according to the YJ code (unique code for each item listed on the NHI drug price standard) used in Japanese insurance claims. Meanwhile, diseases were classified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 2016).

Adverse drug events were extracted in accordance with the Global Trigger Tool (Institute for Healthcare Improvement, 2003), and events' severity was evaluated using the Common Terminology Criteria for Adverse Events Version 5.0 (Japan Clinical Oncology Group, 2017). The causality was categorized into "possible," "probable/likely," and "certain," using the Causality Assessment System published by Uppsala Monitoring Centre (UMC) (World Health Organization – Uppsala Monitoring Centre, 2012). Two pharmacists with at least 10 years of clinical experience and, where necessary, a physician determined these adverse drug events and classified their severity and causality.

Calculation of Direct Costs of Managing Adverse Drug Events

In this study, we evaluated direct costs from the perspective of medical cost payers under the public medical insurance system.

TABLE 1 | Calculation of costs.

Equation 1	$Cout, nat = Cout, targ \times [\frac{(Nout, nat - Nout, nat, 0y) \times 365 \times Nout, targ}{Nout, hosp}]$
Equation 2	$Cin, nat = Cin, targ \times [\frac{(Nin, nat - Nin, nat, 0y) \times 365 \times Nin, targ}{31.9 \times Nin, hosp}]$
Equation 3	$Cout, nat, BCJ = Cout, targ, BCJ \times (\frac{Nout, nat, older \times 365 \times Nout, targ, BCJ}{Nout, hosp, older})$
Equation 4	$Cout, nat, GMTSE = Cout, targ, GMTSE \times (\frac{Nout, nat, older \times 365 \times Nout, targ, GMTSE}{Nout, hosp, older})$
Equation 5	$Cin, nat, BCJ = Cin, targ, BCJ \times (\frac{Nin, nat, older \times 365 \times Nin, targ, BCJ}{41.7 \times Nin, hosp, older})$
Equation 6	$Cin, nat, GMTSE = Cin, targ, GMTSE \times (\frac{Nin, nat, older \times 365 \times Nin, targ, GMTSE}{41.7 \times Nin, hosp, older})$

[Equation 1]: $C_{out,\ nat}$, *the direct costs of managing adverse drug events in outpatients in the whole country;* $C_{out,\ targ}$, *the direct costs of managing adverse drug events per patient who visited the hospital regardless of the visit reasons;* $N_{out,\ nat}$, *the total number of outpatients on the overview of the 2014 patient survey;* $N_{out,\ nat,\ 0y}$, *the total number of 0-year-old outpatients on the overview of the 2014 patient survey;* $N_{out,\ targ}$, *the number of outpatients with more than one drug used during their hospital visit without reservation between July 1 and December 31, 2015;* $N_{out,\ hosp}$, *the number of outpatients aged 1 year or older who visited the hospital between July 1 and December 31, 2015.*

[Equation 2]: $C_{in,\ nat}$, *the direct costs of managing adverse drug events in inpatients in the whole country;* $C_{in,\ targ}$, *the direct costs of managing adverse drug events per patient admitted to the hospital regardless of the reasons;* $N_{in,\ nat}$, *the total number of inpatients on the overview of the 2014 patient survey;* $N_{in,\ nat,\ 0y}$, *the total number of 0-year-old inpatients on the overview of the 2014 patient survey;* $N_{in,\ targ}$, *the number of inpatients with more than one drug used at their hospitalization without reservation between July 1 and December 31, 2015;* $N_{in,\ hosp}$, *the number of inpatients aged 1 year or older who were admitted to the hospital between July 1 and December 31, 2015.*

[Equations 3 and 4]: $C_{out,\ nat,\ BCJ}$ *and* $C_{out,\ nat,\ GMTSE}$; *the direct costs of avoidable adverse drug events based on the BCJ and GMTSE in older outpatients in the whole country, respectively;* $C_{out,\ targ,\ BCJ}$ *and* $C_{out,\ targ,\ GMTSE}$, *the direct costs of avoidable adverse drug events per older outpatient using the drugs listed in the BCJ and GMTSE regardless of the visit reason, respectively;* $N_{out,\ nat,\ older}$, *the number of over-65-year-old outpatients in a day on the overview of the 2014 patient survey;* $N_{out,\ targ,\ BCJ}$ *and* $N_{out,\ targ,\ GMTSE}$, *the number of older outpatients using more than one drugs listed in the BCJ and GMTSE during their hospital visit without reservation between July 1 and December 31, 2015, respectively;* $N_{out,\ hosp,\ older}$, *the number of older outpatients who visited the hospital between July 1 and December 31, 2015.*

[Equations 5 and 6]: $C_{in,\ nat,\ BCJ}$ *and* $C_{in,\ nat,\ GMTSE}$, *the direct costs of avoidable adverse drug events based on the BCJ and GMTSE-2015 in older inpatients in the whole country, respectively;* $C_{in,\ targ,\ BCJ}$ *and* $C_{in,\ targ,\ GMTSE}$, *the direct costs of avoidable adverse drug events per older inpatient using the drugs listed in the BCJ and GMTSE-2015 regardless of the hospitalization reason, respectively;* $N_{in,\ nat,\ older}$, *the number of over-65-year-old inpatients on the overview of the 2014 patient survey;* $N_{in,\ targ,\ BCJ}$ *and* $N_{in,\ targ,\ GMTSE}$, *the number of older inpatients using more than one drug listed in the BCJ and GMTSE-2015 at their hospitalization without reservation between July 1 and December 31, 2015, respectively;* $N_{in,\ hosp,\ older}$, *the number of older patients who were admitted to the hospital between July 1 and December 31, 2015.*

The direct costs of managing adverse drug events were evaluated in outpatients who visited the hospital due to such events and inpatients who were admitted to the hospital due to the same. Direct costs due to avoidable adverse drug events in older adults were evaluated in older patients who visited (outpatients) or were admitted to (inpatients) the hospital due to adverse drug events caused by the drugs listed in the BCJ and GMTSE-2015. For those who visited or were admitted to the hospital for reasons other than adverse drug events, the direct costs were recorded as 0 yen.

We calculated the direct costs by stratifying outpatients and inpatients because information on the numbers of outpatients and inpatients is available in Japan's domestic statistical data (Ministry of Health, Labour and Welfare in Japan, 2014). The direct costs were extrapolated to the national level (whole country) by linear regression, based on an overview of the 2014 patient survey (Ministry of Health, Labour and Welfare in Japan, 2014). Please see the detailed calculations in **Supplementary Material**.

Direct Costs of Managing Adverse Drug Events in Outpatients

For all ages, older adults (>65-year-olds), and <65-year-olds, we calculated the direct costs of managing adverse drug events per patient who visited the hospital due to these events (the sum of the direct cost for outpatients with adverse drug events divided by the number of outpatients with adverse drug events) ($C_{out,\ ade}$). In addition, we calculated the direct costs of managing adverse drug events per patient who visited the hospital regardless of the visit reason (the sum of the direct cost for outpatients with adverse drug events divided by the number of all outpatients targeted in this study) ($C_{out,\ targ}$). We then obtained the direct costs of managing adverse drug events in outpatients in the whole country ($C_{out,\ nat}$) using Equation 1; (**Table 1**).

Direct Costs of Managing Adverse Drug Events in Inpatients

For all ages, older adults, and <65-year-olds, we calculated the direct costs of managing adverse drug events per patient admitted to the hospital due to these events (the sum of the direct cost for inpatients with adverse drug events divided by the number of outpatients with adverse drug events) ($C_{in,\ ade}$). In addition, we calculated the direct costs of managing adverse drug events per patient admitted to the hospital regardless of the reason (the sum of the direct cost for inpatients with adverse drug events divided by number of all inpatients targeted in this study) ($C_{in,\ targ}$). When then obtained the direct costs of managing adverse drug events in inpatients in the whole country ($C_{in,\ nat}$) using Equation 2; (**Table 1**).

Direct Cost of Avoidable Adverse Drug Events in Older Outpatients

For the older outpatients who used the drugs listed in the BCJ and GMTSE-2015, we calculated the direct costs of avoidable adverse drug events per older outpatient using the drugs listed in the BCJ and GMTSE-2015 regardless of the visit reason (the sum of the direct cost in older outpatients with adverse drug events due to the drugs listed in the BCJ and GMTSE-2015 divided by the number of all the older outpatients who used the drugs listed in the BCJ and GMTSE-2015 targeted in this study) ($C_{out,\ targ,\ BCJ}$ and $C_{out,\ targ,\ GMTSE}$, respectively). We then obtained the direct

TABLE 2 | Patient characteristics.

	All			Older adults			<65-year-olds		
	All (n = 6,504)	Adverse drug events at the time of hospital visits and hospitalization		All (n = 3,011)	Adverse drug events at the time of hospital visits and hospitalization		All (n = 3,493)	Adverse drug events at the time of hospital visits and hospitalization	
		Present (n = 720)	Absent (n = 5,784)		Present (n = 463)	Absent (n = 2,548)		Present (n = 257)	Absent (n = 3,236)
Sex [n (%)]									
Male	3,210 (49.4)	348 (48.3)	2,862 (49.5)	1,509 (50.1)	242 (52.3)	1,267 (49.7)	1,701 (48.7)	106 (41.2)	1,595 (49.3)
Female	3,294 (50.6)	372 (51.7)	2,922 (50.5)	1,502 (49.9)	221 (47.7)	1,281 (50.3)	1,792 (51.3)	151 (58.8)	1,641 (50.7)
Age (average ± standard deviation)	51.2 ± 29.9	64.4 ± 22.8	49.6 ± 30.3	78.0 ± 7.5	78.3 ± 7.6	77.9 ± 7.5	28.1 ± 21.6	39.4 ± 19.6	27.2 ± 21.5
Number of drugs used (average ± standard deviation)	5.3 ± 4.2	8.0 ± 4.7	5.0 ± 4.1	6.8 ± 4.2	8.5 ± 4.3	6.5 ± 4.1	4.0 ± 3.8	7.0 ± 5.1	3.7 ± 3.5
Inpatients [n (%)]	2,501 (38.5)	359 (49.9)	2,142 (37.0)	1,536 (51.0)	272 (58.7)	1,264 (49.6)	965 (27.6)	87 (33.9)	878 (27.1)
Length of hospitalization [days, median (range)]	11 (1–1,048)	13 (1–130)	11 (1–1,048)	15 (1–1,048)	14 (1–130)	15 (1–1,048)	7 (1–535)	9 (2–119)	6 (1–535)
Disease [n (%)]									
Certain infectious and parasitic diseases	1,517 (23.3)	185 (25.7)	1,332 (23.0)	673 (22.4)	100 (21.6)	573 (22.5)	844 (24.2)	85 (33.1)	759 (23.5)
Neoplasms	1,058 (16.3)	211 (29.3)	847 (14.6)	797 (26.5)	156 (33.7)	641 (25.2)	261 (7.5)	55 (21.4)	206 (6.4)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1,147 (17.6)	198 (27.5)	949 (16.4)	680 (22.6)	136 (29.4)	544 (21.4)	467 (13.4)	62 (24.1)	405 (12.5)
Endocrine, nutritional and metabolic diseases	2,739 (42.1)	415(57.6)	2,324 (40.2)	1,742 (57.9)	294 (63.5)	1,448 (56.8)	997 (28.5)	121 (47.1)	876 (27.1)
Mental and behavioral disorders	1,244 (19.1)	176 (24.4)	1,068 (18.5)	572 (19.0)	91 (19.7)	481 (18.9)	672 (19.2)	85 (33.1)	587 (18.1)
Diseases of the nervous system	1,661 (25.5)	233 (32.4)	1,428 (24.7)	915 (30.4)	137 (29.6)	778 (30.5)	746 (21.4)	96 (37.4)	650 (20.1)
Diseases of the eye and adnexa	1,228 (18.9)	190 (26.4)	1,038 (17.9)	802 (26.6)	136 (29.4)	666 (26.1)	426 (12.2)	54 (21.0)	372 (11.5)
Diseases of the ear and mastoid process	540 (8.3)	63 (8.8)	477 (8.2)	280 (9.3)	34 (7.3)	246 (9.7)	260 (7.4)	29 (11.3)	231 (7.1)
Diseases of the circulatory system	3,074 (47.3)	478 (66.4)	2,596 (44.9)	2,302 (76.5)	370 (79.9)	1,932 (75.8)	772 (22.1)	108 (42.0)	664 (20.5)
Diseases of the respiratory system	3,393 (52.2)	326 (45.3)	3,067 (53.0)	1,367 (45.4)	189 (40.8)	1,178 (46.2)	2,026 (58.0)	137 (53.3)	1,889 (58.4)
Diseases of the digestive system	3,486 (53.6)	487 (67.6)	2,999 (51.8)	2,027 (67.3)	328 (70.8)	1,699 (66.7)	1,459 (41.8)	159 (61.9)	1,300 (40.2)
Diseases of the skin and subcutaneous tissue	1,555 (23.9)	185 (25.7)	1,370 (23.7)	767 (25.5)	104 (22.5)	663 (26.0)	788 (22.6)	81 (31.5)	707 (21.8)
Diseases of the musculoskeletal system and connective tissue	1,742 (26.8)	244 (33.9)	1,498 (25.9)	1,076 (35.7)	168 (36.3)	908 (35.6)	666 (19.1)	76 (29.6)	590 (18.2)
Diseases of the genitourinary system	1,916 (29.5)	279 (38.8)	1,637 (28.3)	1,223 (40.6)	192 (41.5)	1,031 (40.5)	693 (19.8)	87 (33.9)	606 (18.7)
Pregnancy, childbirth and the puerperium	99 (1.5)	3 (0.4)	96 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	99 (2.8)	3 (1.2)	96 (3.0)
Certain conditions originating in the perinatal period	29 (0.4)	1 (0.1)	28 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	29 (0.8)	1 (0.4)	28 (0.9)
Congenital malformations, deformations and chromosomal abnormalities	11 (0.2)	1 (0.1)	10 (0.2)	2 (0.1)	0 (0.0)	2 (0.1)	9 (0.3)	1 (0.4)	8 (0.2)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere Classified	1,766 (27.2)	211 (29.3)	1,555 (26.9)	827 (27.5)	120 (25.9)	707 (27.2)	939 (26.9)	91 (35.4)	848 (26.2)
Injury, poisoning and certain other consequences of external causes	749 (11.5)	95 (13.2)	654 (11.3)	373 (12.4)	70 (15.1)	303 (11.9)	376 (10.8)	25 (9.7)	351 (10.8)

costs of avoidable adverse drug events based on the BCJ and GMTSE-2015 in older outpatients in the whole country [$C_{out,\ nat,\ BCJ}$ and $C_{out,\ nat,\ GMTSE}$) using Equations 3 and 4] (**Table 1**).

Direct Cost of Avoidable Adverse Drug Events in Older Inpatients

For the older inpatients who used the drugs listed in the BCJ and GMTSE-2015, we calculated the direct costs of avoidable adverse drug events per older inpatient using the drugs listed in the BCJ and GMTSE-2015 regardless of the hospitalization reason (the sum of the direct cost of adverse drug events in older inpatients due to the drugs listed in the BCJ and GMTSE-2015 divided by the number of all the older inpatients targeted in this study who used the drugs listed in the BCJ and GMTSE-2015) ($C_{in,\ targ,\ BCJ}$ and $C_{in,\ targ,\ GMTSE}$, respectively). We then obtained the direct costs of avoidable adverse drug events based on the BCJ and GMTSE-2015 in older inpatients in the whole country ($C_{in,\ nat,\ BCJ}$ and $C_{in,\ nat,\ GMTSE}$) using Equations 5 and 6; (**Table 1**).

Ethical Considerations

This study was approved by the ethics committee of Gifu Municipal Hospital (approval number: 349) and Gifu Pharmaceutical University (approval number: 28–8).

RESULTS

Analysis for All Ages, Older Adults, and <65-Year-Olds

Patient Characteristics

Table 2 shows the patient characteristics for all ages, older adults, and <65-year-olds. Among all ages, 49.4% were male, the age was 51.2 ± 29.9 years (mean ± standard deviation), and

TABLE 3 | Drug categories.

	All (n = 34,357)	Adverse drug events at the time of hospital visits and hospitalization		Suspected drugs (n = 1,227)	Prevalence of adverse drug events (%)
		Present (n = 5,720)	Absent (n = 28,637)		
Drugs used at the time of visit [n (%)]					
Agents affecting central nervous system	6,957 (20.2)	1,088 (19.0)	5,869 (20.5)	314	4.5
Agents affecting peripheral nervous system	261 (0.8)	40 (0.7)	221 (0.8)	8	0.7
Agents affecting sensory organs	163 (0.5)	14 (0.2)	149 (0.5)	0	0.0
Cardiovascular agents	6,514 (19.0)	1,188 (20.8)	5,326 (18.6)	203	3.1
Respiratory organ agents	2,229 (6.5)	192 (3.4)	2,037 (7.1)	9	0.4
Digestive organ agents	6,517 (19.0)	1,086 (19.0)	5,431 (19.0)	29	0.4
Hormones	896 (2.6)	199 (3.5)	697 (2.4)	53	5.9
Urogenital and anal organ agents	659 (1.9)	102 (1.8)	557 (1.9)	9	1.4
Other agents affecting individual organs	8 (0.0)	3 (0.1)	5 (0.0)	0	0.0
Vitamins	1,203 (3.5)	222 (3.9)	981 (3.4)	2	0.2
Nutrients, tonics	430 (1.3)	69 (1.2)	361 (1.3)	1	0.2
Blood and body fluid agents	1,739 (5.1)	378 (6.6)	1,361 (4.8)	190	15.5
Dialysis agents	1 (0.0)	0 (0.0)	1 (0.0)	0	0.0
Other agents affecting metabolism	2,304 (6.7)	385 (6.7)	1,919 (6.7)	87	3.8
Cellular function activating agents	3 (0.0)	1 (0.0)	2 (0.0)	0	0.0
Antineoplastic drugs	443 (1.3)	229 (4.0)	214 (0.7)	191	43.1
Allergic agents	1,322 (3.8)	115 (2.0)	1,207 (4.2)	8	0.6
Crude drugs	13 (0.0)	1 0.0	12 (0.0)	1	7.7
Traditional Chinese medicines	697 (2.0)	101 (1.8)	596 (2.1)	15	2.2
Other crude drugs and Chinese medicine formulations	9 (0.0)	1 (0.0)	8 (0.0)	0	0.0
Antibiotics	1,009 (2.9)	101 (1.8)	908 (3.2)	50	5.0
Chemotherapeutics	634 (1.8)	147 (2.6)	487 (1.7)	28	4.4
Biological preparations	14 (0.0)	9 (0.2)	5 (0.0)	8	57.1
Antiparasitic drugs	8 (0.0)	1 (0.0)	7 (0.0)	0	0.0
Dispensing medicines	18 (0.1)	2 (0.0)	16 (0.1)	0	0.0
Other agents not mainly for therapeutic purpose	8 (0.0)	3 (0.1)	5 (0.0)	1	12.5
Alkaloidal narcotics	37 (0.1)	16 (0.3)	21 (0.1)	8	21.6
Non-alkaloidal narcotics	26 (0.1)	7 (0.1)	19 (0.1)	0	0.0
Over-the-counter drugs	232 (0.7)	18 (0.3)	214 (0.7)	10	4.3

the number of drugs used was 5.3 ± 4.2. The most common disease was "diseases of the digestive system" (53.6%). Among older adults, 50.1% were male, the age was 78.0 ± 7.5 years, and the number of drugs used was 6.8 ± 4.2. The most common disease was "diseases of the circulatory system" (76.5%).

Adverse Drug Events

Among the patients surveyed, 11.1% (720/6,504) visited the hospital and were hospitalized due to adverse drug events. The total number of adverse drug events that led to visits was 1,065, which included multiple adverse drug events at the time of hospital visits and hospitalization.

Table 3 shows the drug categories. The prevalence of adverse drug events was the highest for biological preparations (57.1%), followed by antineoplastic drugs (43.1%) and alkaloidal narcotics (21.6%). The prevalence of adverse drug events was 4.3% for over-the-counter drugs.

Table 4 shows the likely causality, classification, and severity of adverse drug events. Most events were "possible" (75.1%), classified as "gastrointestinal disorders" (25.4%), and "grade 2" (38.5%), respectively.

Direct Costs for Management of Adverse Drug Events

Table 5 shows the direct costs of managing adverse drug events in outpatients. The direct costs per patient who visited the hospital due to adverse drug events ($C_{out,\ ade}$) were 21,281 and 22,590 yen (166 and 176 euros as on September 13, 2021) for all ages and older adults, respectively.

For all ages, the direct cost per patient who visited the hospital regardless of the visit reasons ($C_{out,\ targ}$) was 1,919 yen (15 euros), and the direct cost in the whole country ($C_{out,\ nat}$) was 115.73 billion yen (902 million euros) per year. For older adults, the direct cost per patient who visited the hospital regardless of the visit reasons ($C_{out,\ targ}$) was 2,925 yen (23 euros), and the direct cost in the whole country ($C_{out,\ nat}$) was 59.69 billion yen (465 million euros) per year.

Table 5 shows the direct costs of managing adverse drug events in inpatients. The direct costs per patient admitted to the hospital due to adverse drug events ($C_{in,\ ade}$) were 853,175 and 874,582 yen (6,648 and 6,815 euros) for all ages and older adults, respectively.

For all ages, the direct cost per patient admitted to the hospital regardless of hospitalization reasons ($C_{in,\ targ}$) was 122,467 yen (954 euros) and that of the whole country ($C_{in,\ nat}$) was 688.80

TABLE 4 | Adverse drug events.

	All (n = 1,065)	Outpatients			Inpatients		
		All (n = 493)	Older adults (n = 247)	<65-year-olds (n = 246)	All (n = 572)	Older adults (n = 425)	<65-year-olds (n = 147)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
A. Likelihood of causality							
Possible	800 (75.1)	432 (87.6)	216 (87.4)	216 (87.8)	368 (64.3)	271 (63.8)	97 (66.0)
Probable/likely	231 (21.7)	47 (9.5)	22 (8.9)	25 (10.2)	184 (32.2)	145 (34.1)	39 (26.5)
Certain	34 (3.2)	14 (2.8)	9 (3.6)	5 (2.0)	20 (3.5)	9 (2.1)	11 (7.5)
B. Classification							
Blood and lymphatic system disorders	31 (2.9)	4 (0.8)	2 (0.8)	2 (0.8)	27 (4.7)	21 (4.9)	6 (4.1)
Cardiac disorders	25 (2.3)	11 (2.2)	5 (2.0)	6 (2.4)	14 (2.4)	13 (3.1)	1 (0.7)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	10 (0.9)	10 (2.0)	6 (2.4)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.1)	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	270 (25.4)	146 (29.6)	62 (25.1)	84 (34.1)	124 (21.7)	94 (22.1)	30 (20.4)
General disorders and administration site conditions	83 (7.8)	48 (9.7)	19 (7.7)	29 (11.8)	35 (6.1)	17 (4.0)	18 (12.2)
Hepatobiliary disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Immune system disorders	26 (2.4)	20 (4.1)	10 (4.0)	10 (4.1)	6 (1.0)	3 (0.7)	3 (2.0)
Infections and infestations	35 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	35 (6.1)	18 (4.2)	17 (11.6)
Injury, poisoning and procedural complications	72 (6.8)	34 (6.9)	27 (10.9)	7 (2.8)	38 (6.6)	36 8.5)	2 (1.4)
Investigations	145 (13.6)	28 (5.7)	13 (5.3)	15 (6.1)	117 (20.5)	80 (18.8)	37 (25.2)
Metabolism and nutrition disorders	103 (9.7)	37 (7.5)	25 (10.1)	12 (4.9)	66 (11.5)	54 (12.7)	12 (8.2)
Musculoskeletal and connective tissue disorders	3 (0.3)	2 (0.4)	0 (0.0)	2 (0.8)	1 (0.2)	1 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	130 (12.2)	92 (18.7)	41 (16.6)	51 (20.7)	38 (6.6)	32 (7.5)	6 (4.1)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	14 (1.3)	5 (1.0)	2 (0.8)	3 (1.2)	9 (1.6)	5(1.2)	4 (2.7)
Renal and urinary disorders	26 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	26 (4.5)	24 (5.6)	2 (1.4)
Reproductive system and breast disorders	6 (0.6)	5 (1.0)	4 (1.6)	1 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	27 (2.5)	10 (2.0)	8 (3.2)	2 (0.8)	17 (3.0)	16 (3.8)	1 (0.7)
Skin and subcutaneous tissue disorders	35 (3.3)	24 (4.9)	9 (3.6)	15(6.1)	11 (1.9)	3 (0.7)	8 (5.4)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	22 (2.1)	16 (3.2)	13 (5.3)	3 (1.2)	6 (1.0)	6 (1.4)	0 (0.0)
C. Severity							
Grade 1	241 (22.6)	170 (34.5)	71 (28.7)	99 (40.2)	71 (12.4)	49 (11.5)	22 (15.0)
Grade 2	410 (38.5)	272 (55.2)	147 (59.5)	125 (50.8)	138 (24.1)	99 (23.3)	39 (26.5)
Grade 3	301 (28.3)	40 (8.1)	23 (9.3)	17 (6.9)	261 (45.6)	190 (44.7)	71 (48.3)
Grade 4	110 (10.3)	11 (2.2)	6 (2.4)	5 (2.0)	99 (17.3)	84 (19.8)	15 (10.2)
Grade 5	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.7)	0 (0.0)

billion yen (5,367 million euros) per year. For older adults, the direct cost per patient who was admitted to the hospital regardless of the hospitalization reasons ($C_{in,\ targ}$) was 154,874 yen (1,207 euros), and at the country level, it was ($C_{in,\ nat}$) was 537.50 billion yen (4,188 million euros) per year.

In sum, combining inpatients and outpatients, the direct costs of managing adverse drug events were 804.53 billion yen (6,269 million euros) per year for all ages and 597.19 billion yen (4,654 million euros) per year for older ages for the whole country.

Analysis of Patients Who Used the Drugs Listed in the BCJ and GMTSE-2015

Patient Characteristics

Table 6 shows the background of older adults who used the drugs listed in the BCJ and GMTSE-2015. The most common diseases among outpatients according to the BCJ were related to the circulatory system (90.2%), and those according to GMTSE-2015 were related to the digestive system (88.0%). The prevalence of adverse drug events in outpatients was 3.3% (17/519) and 5.6% (59/1,045) according to the BCJ and GMTSE-2015,

respectively. The most common diseases among inpatients, according to both the BCJ and the GMTSE-2015, were related to the circulatory system (77.8 and 76.5%, respectively). The prevalence of adverse drug events in inpatients was 4.8% (23/481) and 9.2% (107/1,159) according to the BCJ and GMTSE-2015, respectively.

Calculation of Cost of Avoidable Adverse Drug Events in Older Adults

Table 7 shows the direct cost of avoidable adverse drug events in older adults based on the BCJ and the GMTSE-2015. For the patients using drugs listed in the BCJ and GMTSE-2015, the direct costs of avoidable adverse drug events per patient ($C_{out,\ targ,\ BCJ}$ and $C_{out,\ targ,\ GMTSE}$) were 3,212 and 3,341 yen (25 and 26 euros) for outpatients and the direct costs ($C_{in,\ targ,\ BCJ}$ and $C_{in,\ targ,\ GMTSE}$) were 55,548 and 80,246 yen (433 and 625 euros) for inpatients, respectively. Meanwhile, the direct costs for the whole country per year ($C_{out,\ nat,\ BCJ}$ and $C_{out,\ nat,\ GMTSE}$) were 23.06 billion and 48.30 billion yen (180 million and 376 million euros) for outpatients and the direct costs ($C_{in,\ nat,\ BCJ}$ and $C_{in,\ nat,\ GMTSE}$) were 60.37 billion and 210.14 billion yen (470 and 1,637 million euros) for inpatients, respectively.

On combining inpatients and outpatients, the direct cost of avoidable adverse drug events in older adults was 83.43–258.44 billion yen (650–2,014 million euros) per year for the whole country.

DISCUSSION

We conducted a retrospective survey to evaluate the direct cost of managing adverse drug events and the potential reduction of direct costs using the BCJ and GMTSE-2015.

Adverse drug events were the reason for 9.0% of all outpatient visits in Japan. This is consistent with the findings of various other studies reporting that adverse drug events are the reason for 5.5–53% of outpatient visits (Hanlon et al., 1997; Honigman et al., 2001; Gandhi et al., 2003). Furthermore, they accounted for 14.4% of all hospitalizations in this study, which is higher than the finding of another Japanese study that reported only 1.7% of hospitalizations owing to adverse drug events (Koinuma et al., 2006). This is probably because the report by Koinuma was limited to adverse drug events due to inappropriate prescription. Further, the number of visits due to adverse drug events caused by antineoplastic drugs increased with outpatient cancer chemotherapy. However, the current findings are in line with various reports worldwide; that is, the rate of hospitalization due to adverse drug events ranges from 1.3 to 30.4% (Dartnell et al., 1996; Chan et al., 2001; Onder et al., 2002; Wawruch et al., 2009; Ruiter et al., 2012; Parameswaran Nair et al., 2017).

During a medical economic assessment, direct costs of medical resources are estimated using the so-called micro-costing method (Gold et al., 1996; Drummond et al., 2005). The micro-costing method calculates the sum of the direct costs of each clinic/technical fee including medical supplies and drugs. Japan's public medical insurance system is mainly based on the conception of the micro-costing method. In Japan's public medical insurance system, outpatient costs are paid through fees-for-service whereas inpatient costs are paid for by the coexistence of package pricing and fee-for-service. In this study, we evaluated the direct costs from the perspective of medical cost payers under the public medical insurance system. From this perspective, the direct cost of managing adverse drug events corresponds to the total costs payable by patients and/or health insurance association pertaining to the hospital visit and hospitalization caused by adverse drug events. The direct cost of managing adverse drug events considered to be 0 yen when the reason for the hospital visit and hospitalization is not due to adverse drug events.

The direct cost per patient who visited the hospital due to adverse drug events was 21,281 yen, which is somewhat similar to that of Germany (381 euros, that is, 48,893 yen) (Stark et al., 2011). In contrast, the direct cost per patient admitted to the hospital due to adverse drug events was 853,175 yen. Meanwhile, in the Netherlands, Spain, and Germany, the direct cost per patient admitted to the hospital due to adverse drug events was

TABLE 5 | Direct costs for management of adverse drug events (all ages, older adults and < 65 year-olds).

	All (n = 361)	Older adults (n = 191)	<65 year-olds (n = 170)
A. Outpatients			
The direct costs per patient who visited the hospital due to adverse drug events [$C_{out,\ ade}$] (yen)	21,281 (≅166 euros)	22,590 (≅176 euros)	19,809 (≅154 euros)
The direct cost per patient who visited the hospital regardless of the visit reasons [$C_{out,\ targ}$] (yen)	1,919 (≅15 euros)	2,925 (≅23 euros)	1,332 (≅10 euros)
The direct costs in the whole country [$C_{out,\ nat}$] (yen/year)	115.73 billion (≅902 million euros)	59.69 billion (≅465 million euros)	55.47 billion (≅432 million euros)
	All (n = 359)	**Older adults (n = 272)**	**<65 year-olds (n = 87)**
B. Inpatients			
The direct costs per patient who admitted to the hospital due to adverse drug events [$C_{in,\ ade}$] (yen)	853,175 (≅6,648 euros)	874,582 (≅6,815 euros)	786,247 (≅9,127 euros)
The direct costs per patient who was admitted to the hospital regardless of the reasons [$C_{in,\ targ}$] (yen)	122,467 (≅954 euros)	154,874 (≅1,207 euros)	70,884 (≅552 euros)
The direct costs in the whole country [$C_{in,\ nat}$] (yen/year)	688.80 billion (≅5,367 million euros)	537.50 billion (≅4,188 million euros)	140.40 billion (≅1,094million euros)

TABLE 6 | Background of patients with the drugs listed in the Beers Criteria Japanese version and "Guidelines for medical treatment and its safety in the elderly 2015".

	BCJ			GMTSE-2015		
	All (n = 519)	Adverse drug events at the time of hospital visits		All (n = 1,045)	Adverse drug events at the time of hospital visits	
		Present (n = 17)	Absent (n = 502)		Present (n = 59)	Absent (n = 986)
A. Outpatients						
Sex [n (%)]						
Male	224 (43.2)	8 (47.1)	216 (43.0)	476 (45.6)	28 (47.5)	448 (45.4)
Female	295 (56.8)	9 (52.9)	286 (57.0)	569 (54.4)	31 (52.5)	538 (54.6)
Age (average ± standard deviation)	77.7 ± 6.8	79.0 ± 6.6	77.7 ± 6.8	78.2 ± 7.2	79.3 ± 7.7	78.2 ± 7.1
Number of drugs used (average±standard deviation)	8.2 ± 4.1	7.8 ± 2.8	8.3 ± 4.1	7.8 ± 4.2	8.2 ± 4.2	7.8 ± 4.2
Disease [n (%)]						
Certain infectious and parasitic diseases	166 (32.0)	2 (11.8)	164 (32.7)	337 (32.2)	14 (23.7)	323 (32.8)
Neoplasms	125 (24.1)	3 (17.6)	122 (24.3)	308 (29.5)	10 (16.9)	298 (30.2)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	173 (33.3)	2 (11.8)	171 (34.1)	361 (34.5)	15 (25.4)	346 (35.1)
Endocrine, nutritional and metabolic diseases	393 (75.7)	13 (76.5)	380 (75.7)	799 (76.5)	46 (78.0)	753 (76.4)
Mental and behavioral disorders	256 (49.3)	9 (52.9)	247 (49.2)	421 (40.3)	26 (44.1)	395 (40.1)
Diseases of the nervous system	319 (61.5)	8 (47.1)	311 (62.0)	578 (55.3)	30 (50.8)	548 (55.6)
Diseases of the eye and adnexa	266 (51.3)	9 (52.9)	257 (51.2)	491 (47.0)	24 (40.7)	467 (47.4)
Diseases of the ear and mastoid process	94 (18.1)	3 (17.6)	91 (18.1)	186 (17.8)	9 (15.3)	177 (18.0)
Diseases of the circulatory system	468 (90.2)	13 (76.5)	455 (90.6)	908 (86.9)	49 (83.1)	859 (87.1)
Diseases of the respiratory system	320 (61.7)	9 (52.9)	311 (62.0)	654 (62.6)	36 (61.0)	618 (62.7)
Diseases of the digestive system	459 (88.4)	15 (88.2)	444 (88.4)	920 (88.0)	51 (86.4)	869 (88.1)
Diseases of the skin and subcutaneous tissue	252 (48.6)	6 (35.3)	246 (49.0)	504 (48.2)	29 (49.2)	475 (48.2)
Diseases of the musculoskeletal system and connective tissue	314 (60.5)	7 (41.2)	307 (61.2)	602 (57.6)	29 (49.2)	573 (58.1)
Diseases of the genitourinary system	317 (61.1)	12 (70.6)	305 (60.8)	600 (57.4)	30 (50.8)	570 (57.8)
Pregnancy, childbirth and the puerperium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Certain conditions originating in the perinatal period	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital malformations, deformations and chromosomal abnormalities	2 (0.4)	0 (0.0)	2 (0.4)	2 (0.2)	0 (0.0)	2 (0.2)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	297 (57.2)	9 (52.9)	288 (57.4)	590 (56.5)	33 (55.9)	557 (56.5)
Injury, poisoning and certain other consequences of external causes	73 (14.1)	3 (17.6)	70 (13.9)	150 (14.4)	13 (22.0)	13 (13.9)

	BCJ			GMTSE-2015		
	All (n = 481)	Adverse drug events at the time of hospital visits		All (n = 1,159)	Adverse drug events at the time of hospital visits	
		Present (n = 23)	Absent (n = 458)		Present (n = 107)	Absent (n = 1,052)
B. Inpatients						
Sex [n (%)]						
Male	238 (49.5)	12 (52.2)	226 (49.3)	624 (53.8)	58 (54.2)	566 (53.8)
Female	243 (50.5)	11 (47.8)	232 (50.7)	535 (46.2)	49 (45.8)	486 (46.2)
Age (average ± standard deviation)	78.4 ± 7.6	81.4 ± 8.5	78.2 ± 7.5	78.7 ± 7.8	80.3 ± 7.6	78.5 ± 7.8
Number of drugs used (average ± standard deviation)	9.3 ± 4.3	9.3 ± 3.7	9.3 ± 4.3	8.3 ± 4.0	9.7 ± 4.2	8.1 ± 3.9
Length of hospitalization [days, median (range)]	15 (1–187)	15 (4–65)	15 (1–187)	15 (1–242)	14 (1–65)	16(1–242)
Disease [n (%)]						
Certain infectious and parasitic diseases	64 (13.3)	1 (4.3)	63 (13.8)	160 (13.8)	4 (3.7)	156 (14.8)
Neoplasms	106 (22.0)	2 (8.7)	104 (22.7)	270 (23.3)	19 (17.8)	251 23.9)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	60 (12.5)	5 (21.7)	55 (12.0)	159 (13.7)	21 (19.6)	138 (13.1)
Endocrine, nutritional and metabolic diseases	211 (43.9)	11 (47.8)	200 (43.7)	564 (48.7)	66 (61.7)	498 (47.3)
Mental and behavioural disorders	51 (10.6)	3 (13.0)	48 (10.5)	84(7.2)	7 (6.5)	77 (7.3)
Diseases of the nervous system	61 (12.7)	1 (4.3)	60 (13.1)	148 (12.8)	15 (14.0)	133 (12.6)
Diseases of the eye and adnexa	75 (15.6)	5 (21.7)	70 (15.3)	153 (13.2)	15 (14.0)	138 (13.1)
Diseases of the ear and mastoid process	9 (1.9)	0 (0.0)	9 (2.0)	17 (1.5)	1 (0.9)	16 (1.5)
Diseases of the circulatory system	374 (77.8)	19 (82.6)	355 (77.5)	887 (76.5)	98 (91.6)	789 (75.0)
Diseases of the respiratory system	142 (29.5)	3 (13.0)	139 (30.3)	337 (29.1)	20 (18.7)	317 (30.1)
Diseases of the digestive system	251 (52.2)	10 (43.5)	241 (52.6)	592 (51.1)	68 (63.6)	524 (49.8)
Diseases of the skin and subcutaneous tissue	41 (8.5)	1 (4.3)	40 (8.7)	93 (8.0)	4 (3.7)	89 (8.5)
Diseases of the musculoskeletal system and connective tissue	91 (18.9)	5 (21.7)	86 (18.8)	224 (19.3)	20 (18.7)	204 (19.4)
Diseases of the genitourinary system	137 (28.5)	6 (26.1)	131 (28.6)	342 (29.5)	40 (37.4)	302 (28.7)
Pregnancy, childbirth and the puerperium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)
Certain conditions originating in the perinatal period	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital malformations, deformations and chromosomal abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	18 (4.3)	1 (4.3)	37 (3.7)	37 (3.2)	5 (4.7)	32 (3.0)
Injury, poisoning and certain other consequences of external causes	60 (52.2)	12 (52.2)	138 (10.5)	138 (11.9)	23 (21.5)	115 (10.9)

BCJ, the Beers Criteria Japanese version; GMTSE-2015, "Guidelines for medical treatment and its safety in the elderly 2015".

6,009 euros, 3,857–4,656 euros, and 2,250 euros (771,134 yen, 494,968–597,504 yen, 288,743 yen, respectively) (Carrasco-Garrido et al., 2010; Leendertse et al., 2011; Rottenkolber et al., 2011). Although this study's result is slightly similar to that of these previous studies, it is higher than that of the German report, probably because the latter was limited to internal

TABLE 7 | Direct costs of avoidable adverse drug events in older adults.

A. Outpatients

	Patients using drugs listed in BCJ	Patients using drugs listed in GMTSE-2015
The direct costs per patient who was older adults using the drugs listed regardless of the visit reasons (yen)	3,212 (≅25 euros) [$C_{out,\ targ,\ BCJ}$]	3,341 (≅26 euros) [$C_{out,\ targ,\ GMTSE}$]
The direct cost in the whole country (yen/year)	23.06 billion (≅180 million euros) [$C_{out,\ nat,\ BCJ}$]	48.30 billion (≅376 million euros) [$C_{out,\ nat,\ GMTSE}$]

B. Inpatients

	Patients using drugs listed in BCJ	Patients using drugs listed in GMTSE-2015
The direct costs per patient who was older adults using the drugs listed regardless of the hospitalization reasons (yen)	55,548 (≅433 euros) [$C_{in,\ targ,\ BCJ}$]	80,246 (≅625 euros) [$C_{out,\ targ,\ GMTSE}$]
The direct cost in the whole country (yen/year)	60.37 billion (≅470 million euros) [$C_{in,\ nat,\ BCJ}$]	210.14 billion (≅1,637 million euros) [$C_{in,\ nat,\ GMTSE}$]

BCJ, the Beers Criteria Japanese version; GMTSE-2015, "Guidelines for medical treatment and its safety in the elderly 2015".

medicine inpatients. In addition, the methods for calculating hospitalization cost in Japan differ from those in other countries.

In this study, which combined inpatients and outpatients, the direct costs of managing adverse drug events were 804.53 billion yen (6,269 million euros) per year for all ages in Japan. In the Netherlands, the direct cost of managing adverse drug events in inpatients was about 94 million euros (12 billion yen) annually in 2011(Leendertse et al., 2011). In Spain, this annual cost was about 226–273 million euros (29–35 billion yen) for inpatients in 2010 (Carrasco-Garrido et al., 2010), while in Germany it was 816 million euros (105 billion yen) for outpatients in 2011 (Stark et al., 2011). Because the medical and technical fee differs in each country, the calculated costs cannot be accurately compared each other. However, the cost in Japan in this study was slightly high compared with those countries when the costs were corrected according to total population of those countries. That would be due to a larger population of older people in Japan than in those countries.

Older people are more likely to experience adverse drug events due to decreased physiological function (Mangoni and Jackson, 2004). Risk factors for adverse drug events in older adults include polypharmacy, dementia, reduced visual acuity, renal damage, and liver damage (The Japan Geriatrics Society, 2015). In particular, polypharmacy is an important risk factor of adverse drug events resulting in outpatient visits and hospitalization (Matsuyama et al., 2021). To prevent adverse drug events, the BCJ and GMTSE-2015 have begun to be used to suggest appropriate prescription drugs, reduce the use of drugs with a high risk of adverse events, and propose alternative drugs with lower risk. In this study, we calculated the direct cost of avoidable adverse drug events using the BCJ and GMTSE-2015 as references.

For the patients using drugs listed in the BCJ and GMTSE-2015, the direct costs of managing adverse drug events per patient were 3,212–3,341 and 55,548–80,246 yen (25–26 and 433–625 euros) for outpatients and inpatients, respectively. Meanwhile, the direct costs for the entire country per year were 23.06–48.30 and 60.37–210.14 billion yen (180–376 and 470–1,637 million euros) for outpatients and inpatients, respectively. A previous study of patients who used the drugs listed in the BCJ and GMTSE-2015 showed that the direct cost of managing adverse drug events per patient was 497–798 and 1,109–13,371 yen (4–6 and 9–104 euros) for outpatients and inpatients, respectively, and the direct costs for the whole country per year were 267.87–381.42 and 2.18–79.42 billion yen (2,087–2,972 and 17–619 million euros) for outpatients and inpatients, respectively (Tachi et al., 2019).

Medical costs for older adults are 25,127.6 billion yen (196 billion euros) per year in Japan (Ministry of Health, Labour and Welfare in Japan, 2015), while the direct costs of managing adverse drug events in older adults were 804.53 billion yen (6,269 million euros) for all ages, suggesting that the direct costs account for a certain proportion of the medical cost in Japan.

The proportion of the direct costs in the whole country for patients with adverse drug events due to drugs listed in the BCJ and GMTSE-2015 to those due to all kinds of drugs was 14.0% (83.43/597.19) to 43.3% (258.44/597.19) in older adults (outpatients and inpatients). A previous study in Japan indicates that polypharmacy is an induction risk factor of adverse drug events resulting in outpatient visits and hospitalization (Matsuyama et al., 2021). Therefore, adverse drug events resulting in outpatient visits and hospitalization should be avoided through prescription optimization and changing, reducing, and discontinuing the BCJ- and GMTSE-2015-listed drugs as needed. Of course, not all calculated costs of the adverse events through the BCJ and GMTSE-2015 would be reduced in actuality because other costs such as the lack of therapy and other adverse events caused by substitute drugs might occur due to the changed, reduced or discontinued prescription. Cost reduction based on the prevention of

adverse drug events in older adults through the BCJ and GMTSE-2015 would be one of practical approach to reduce the costs of adverse drug events and eventually, reduce overall medical costs.

This study's limitation is that it is a retrospective survey using electronic medical records that was conducted at only one general hospital in one region. The number of patients included in this study was small compared to that in the study using dataset of health insurance and claims. However, the smaller sample included detailed background of patients and adverse drug events, which are not available in the dataset of health insurance and claims. In addition, in this study, the extrapolation of the cost in the sample to the national cost was rough. To resolve the ensuring problems, Slight et al. reported a better and more defendable approach, which involves estimating the population-adjusted costs per patient and population-adjusted adverse drug events nationally, followed by an extrapolation (Slight et al., 2018). In Japan, the public medical insurance system covers the medical care of the whole nation and the Japanese government does not publicize the dataset of attributes of outpatients and inpatients of the whole nation. Therefore, we could not adjust extrapolation, for example, through multi-variate analysis. However, we consider the unadjusted extrapolation acceptable in this study for the three reasons below. First, from the patient survey in 2014 (Ministry of Health, Labour and Welfare in Japan, 2014), there are few differences of attributes in the data in this study and the whole nation. Second, the whole nation in Japan can receive the same quality of medical care with the same fee. Third, the hospital in this study is a representative hospital in Japan because it has almost all medical departments and gives both primary and secondary medical cares.

CONCLUSION

We found that, in Japan, high medical costs are often due to managing adverse drug events, and that the costs of avoidable adverse drug events—based on the BCJ and GMTSE-2015—in older adults account for a substantial proportion of overall medical costs. By using BCJ and GMTSE-2015 as references for medicines that should not be prescribed to older adults, it may be possible to avoid adverse drug events and reduce medical costs may be possible.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Gifu Municipal Hospital (approval number: 349) and the ethics committee of Gifu Pharmaceutical University (approval number: 28-8). Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: Based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Ministry of Health, Labour and Welfare of Japan), obtaining written informed consent from patients was not required because this study was a retrospective analysis of routinely collected data and did not require any interventions or interactions with patients.

AUTHOR CONTRIBUTIONS

All authors designed the study and contributed to data collection, statistical analyses, and interpretation of results, with complete access to the study data. TT, SA, TO, and MY collected the data, while HK, TM, and MS analyzed it. HK drafted the manuscript and TT revised it. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.761607/full#supplementary-material

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Prevalence of Chronic Polypharmacy in Community-Dwelling Elderly People in Poland: Analysis of National Real-World Database Helps to Identify High Risk Group

Przemysław Kardas[1]*, *Aneta Lichwierowicz*[2], *Filip Urbański*[2], *Ewa Chudzyńska*[2], *Marcin Czech*[3] and *Grzegorz Kardas*[4]

[1]Department of Family Medicine, Medical University of Lodz, Łódź, Poland, [2]National Health Fund, Warsaw, Poland, [3]Department of Pharmacoeconomics, Institute of Mother and Child, Warsaw, Poland, [4]Department of Internal Diseases, Asthma and Allergy, Medical University of Lodz, Łódź, Poland

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***Correspondence:**
Przemysław Kardas
pkardas@csk.am.lodz.pl

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Introduction: Multimorbidity often comes with age, making elderly people particularly prone to polypharmacy. Polypharmacy, in turn, is a risk factor for adverse drug reactions, drug-drug interactions, non-adherence to medication, negative health outcomes, and increased healthcare services utilization. The longer the exposure to polypharmacy is, the higher the risk of these consequences is. Therefore, a detailed assessment of the prevalence and drivers of chronic polypharmacy in the elderly is particularly important.

Aim of study: To find out the prevalence of chronic polypharmacy in the elderly population of Poland, and to characterize the subgroup with the highest risk of this problem, using real-world data.

Methodology: A retrospective analysis of data on dispensation and healthcare services utilization held by the national payer organization for the year 2018. Chronic polypharmacy was defined as possession, as a result of dispensation, of five or more prescribed drugs within 80% of each of the consecutive 6 months.

Results: Chronic polypharmacy was found in 554.1 thousand patients, i.e. in 19.1% of the national 65+ cohort. On average, those patients were 76 years old, and 49.3% of them were female. The vast majority (68.6%) continued their polypharmacy for the period of the whole year. There was a marked variation in geographical distribution of chronic polypharmacy with the highest value of 1.7 thousand per 100,000 inhabitants in the Łódź Voivodeship. Patients exposed to chronic polypharmacy filled prescriptions from 4.5±2.36 healthcare professionals. The average number of drugs they used was 8.3±3.84 DDD per patient per day. The most often prescribed drugs were Metformin, Atorvastatin and Pantoprazole. The average annual hospitalisation rate in those patients was 1.03±2.4.

Conclusion: This study was the first of this kind involving a nationwide assessment of chronic polypharmacy in Polish elderly people. We found that this problem affected one fifth of Polish older adults and it remains stable due to its direct relation to chronic

conditions. Thus, our results confirm that this phenomenon is highly important for the national health policy and requires relevant interventions. The planned introduction of pharmaceutical care in Poland is expected to help in solving the problem.

Keywords: polypharmacy, potentially inappropriate prescribing, drug safety, elderly, pharmacoepidemiology, real-word data, healthcare services utilization, Poland

INTRODUCTION

Twenty-first century medicine is witnessing an unprecedented paradox. On the one hand, achievements of modern medicine and pharmacy, along with a boost in global economy, led to a new scenario offering billions of human beings access to medications they need. On the other hand, multiple medicines used by a lot of individuals not only add to the spiral rise of healthcare costs but also entail additional risks. Thus, a positive concept of 'access to drugs in case of need' is slowly evolving into an unfavourable phenomenon of "polypharmacy", which becomes a chronic problem, particularly among the elderly and constitutes one of the major concerns of the public health worldwide.

Polypharmacy lacks a standard consensual definition. Nevertheless, its paradoxical nature is reflected in terminology. In general, polypharmacy describes a scenario in which multiple medicines are used by the same patient. In practical terms, polypharmacy is most often defined as a concurrent use of five or more drugs, whereas the use of ten or more drugs is usually regarded as 'excessive polypharmacy' (World Health Organization, 2019). However, these numbers are used for pragmatic reasons only as there is no firm evidence based on which a sound threshold could be created, dichotomizing the number of drugs used concurrently to be either acceptable or too high (Masnoon et al., 2017).

Risks associated with polypharmacy are multiple and include potentially inappropriate prescribing, adverse drug reactions, drug-drug interactions and decreased adherence to medication, which all lead to further negative health consequences, such as reduced quality of life, negative health outcomes and increased healthcare services utilisation (Khezrian et al., 2020; Lee et al., 2020). The longer the exposure to polypharmacy is, the more probable and more pronounced all of these negative consequences are.

The significance of the challenge created by polypharmacy has been increasing, especially due to its escalating prevalence. Particularly in Europe, recent years have seen a growing trend for this phenomenon, e.g., in Sweden the prevalence of polypharmacy increased between 2006 and 2014, from 16.9 to 19.0% (Zhang et al., 2020).

While polypharmacy might be temporal among younger patients (e.g. due to infection), it is usually chronic in the elderly. The possibility of long-term multidrug therapies increases with age and related multimorbidity. These interlinked factors are undoubtedly the major drivers of the recent rise in polypharmacy prevalence in Europe. Data collected in the UK showed that 20.8% of patients with two clinical conditions were prescribed four to nine medicines, whereas in those with six or more comorbidities, the relevant percentage was 47.7%. At the same time, statistics show that more than 50% of people aged over 65 years are diagnosed with two or more diseases, and the older they get, the more diseases they suffer from (Barnett et al., 2012).

Therefore it should come as no surprise that the problem of polypharmacy in elderly people is already widespread in Europe. A nationwide cohort study conducted in Sweden among individuals aged ≥65 years found prevalence of polypharmacy in 44.0% of the group, and the prevalence of excessive polypharmacy in 11.7% (Morin et al., 2018). In this country, the existence of these scenarios strictly correlates with age and peaks up to 79.6 and 36.4% in individuals aged 90 years and over, respectively (Zhang et al., 2020). Scottish data provide evidence that around 35% of those aged 85 years and over receive more than ten medicines (Stewart et al., 2017). A recent analysis of a large European cohort found polypharmacy to occur in 32.1% of citizens aged 65 years or above, ranging from 26.3 to 39.9% across 18 of the studied countries (Midão et al., 2018).

The observed rise in polypharmacy prevalence is particularly pronounced in the elderly (Hovstadius et al., 2010). Over the period of 15 years, the prevalence of polypharmacy in this group of patients grew fourfold in Ireland, from 17.8 to 60.4% (Moriarty et al., 2015). Currently those aged over 65 years account for 19.2% of the European Union population, and this proportion is expected to reach 29.1% by 2080, whereas in the case of those aged over 80 years, relevant percentage rates will change from the present 5.4–12.7% (Eurostat, 2020). If these predictions prove to be true, the burden of polypharmacy is expected to rise dramatically in Europe in the upcoming decades.

In Poland, neither prevalence nor characteristics of polypharmacy have been studied extensively so far. Nevertheless, there are good arguments to believe that its significance might particularly result from high use of prescription medications in the country. In the European health interview survey (EHIS), the collected data indicated a slightly higher use of such medications in Poland, as compared to the EU-28. That tendency, however, was particularly pronounced in the elderly–use of prescription medications was reported by 83.6% of those aged 65–74 years, and 92.8% of those aged 75 years and over in Poland, whereas the European average in these groups was 78.1%, and 87.1%, respectively (Eurostat, 2021). Moreover, a very high prevalence of polypharmacy (78.6%) was observed among Polish patients provided with palliative care (Grądalski, 2019).

Moreover, the Polish population is ageing fast (Leszko et al., 2015). Consequently, polypharmacy has become a serious medical, social and economic threat, exerting a major impact on the sustainability of the national healthcare system. From this perspective, an objective assessment of polypharmacy rates in

elderly citizens is of utmost importance for the national health policy. What is of particular interest, however, is the identification of the most vulnerable group of patients being at high risk of chronic polypharmacy.

The aim of our study was to estimate the prevalence of chronic polypharmacy in the elderly (65+) population in Poland, using databases of the National Health Fund (NHF, Polish: *Narodowy Fundusz Zdrowia*). NHF is the sole public payer organization in the Polish healthcare system with a nationwide coverage. The NHF databases collect information on dispensation of reimbursed drugs, as well as on utilization of healthcare services. Based on an analysis of the data, we wanted to characterise the subgroup of elderly patients with the highest risk of chronic polypharmacy.

METHODOLOGY

Data and Study Design

This was a retrospective analysis of data on drug dispensation and healthcare services utilization recorded in NHF databases for 2018.

The NHF databases register full information on dispensation of all drugs which are subject to reimbursement, regardless of whether a particular prescription was issued by a public or a private healthcare provider. Thus, according to availability of data, we studied prevalence of polypharmacy caused by dispensation of reimbursed drugs only. Data available for the analysis of healthcare services utilization included the type and number of both hospitalisations as well as ambulatory services, along with their principal diagnoses.

In order to avoid a bias of short-term therapies of no importance for chronic treatment, the analysis excluded medications from the following Anatomical Therapeutic Chemical (ATC) groups: A01 - Stomatological preparations, A06 - Drugs for constipation, D–Dermatologicals, J01 - Antibacterials for systemic use, J02 - Antimycotics for systemic use, J05 - Antivirals for systemic use, J06 - Immune sera and immunoglobulins, J07–Vaccines, P03 - Ectoparasiticides, including scabicides, insecticides and repellents and V–Various.

Definition of Polypharmacy

For the purpose of this study, polypharmacy was operationalised as taking five or more prescribed medications at the same time, according to the most common approach, as suggested by the WHO report (World Health Organization, 2019). A 6-month period was adopted a basic framework for the analysis. Accordingly, relevant numbers of drugs were calculated according to the number of reimbursed drugs dispensed within 6 months from the first dispensation in the calendar year.

Chronic polypharmacy was operationalised as "possession, as a result of dispensation, of five or more prescribed drugs within each of consecutive 6 months" where "possession" meant at least 80% of a period covered by dispensed drug supply. For calculation of daily doses, the WHO standard daily defined doses (DDDs) were used.

Statistical Analyses

In descriptive statistics, both original numbers, means, medians and standard deviations, as well as the percentage rates calculated out of the total number of identified polypharmacy cases were presented, unless otherwise stated. For calculation purposes, the national population of Poland in 2018 was assumed to be 38,411,148, and a number of citizens aged over 65 years to be 6,732,360, according to public statistics (Statistics Poland, 2019).

Ethics

Analyses of aggregated anonymised dispensation data and health services utilisation do not involve ethical issues. Therefore, according to the policy of the Ethical Commission of the Medical University of Lodz, those analyses were not subject to the ethical approval procedure.

RESULTS

Prevalence of Polypharmacy in the Elderly

Among all Polish citizens who satisfied our operational definition of polypharmacy (i.e. were dispensed ≥5 reimbursed drugs within 6 months from their first dispensation in 2018, 4.507M in total), those aged over 65 years accounted for 2.899M, i.e. 64.3%. It means that 43.1% of Polish elderly people were subject to polypharmacy in 2018.

The number of elderly patients on polypharmacy who had five or more prescribed drugs for at least 80% of days in a month varied over the time, being the highest in December 2018, and the lowest in January 2018 (**Figure 1**).

Within the group, 554.1 thousand individuals used ≥5 reimbursed drugs for at least 80% of days in half-year horizon, satisfying our definition of chronic polypharmacy. Those individuals accounted for 1.4% of the total national population, and 19.1% of the national cohort of those aged over 65 years.

Characteristics of Elderly on Chronic Polypharmacy

Detailed characteristics of a group of elderly patients on chronic polypharmacy are presented in **Table 1**. On average, those patients were 76 years old, and 49.3% of them were female. The proportion of men on chronic polypharmacy was highest for those aged 84 years (16.5%), whereas in women it was generally lower, with the peak for the age of 83–84 years (9.0%) (for details, see **Figure 2**).

There was a marked variation in geographical distribution of chronic polypharmacy among Polish elderly people. First of all, patients affected by this phenomenon lived either in Poland's capital city, Warsaw (30,0 k, 5.4%), or in the third most populated Polish city, i.e. Łódź (14,8 k, 2.7%). Per 1,000 inhabitants of the county (Polish: powiat), the highest percentage of patients was observed in Sosnowiec county - 23 per 1,000 inhabitants, and in Łódź county - 22 per 1,000 inhabitants, whereas the lowest one was found in the Leżajsk county - 6.5 per 1,000 inhabitants. In terms of the number of inhabitants of the Voivodeship, the

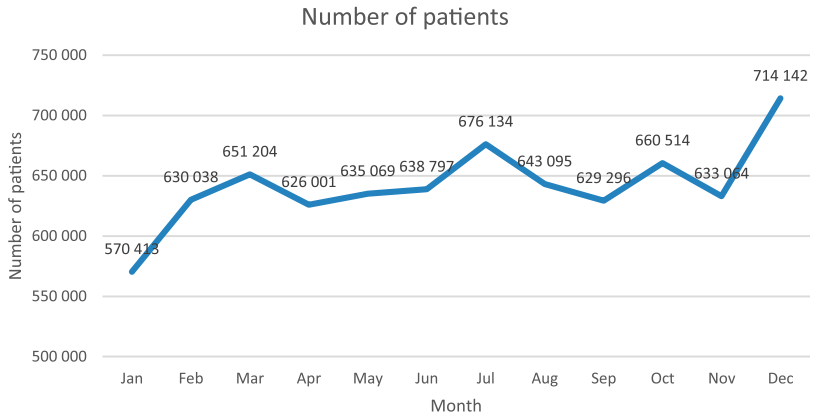

FIGURE 1 | Number of Polish elderly patients who during at least 80% of days within a specific month of year 2018 were on five or more drugs.

TABLE 1 | Detailed characteristics of a group of Polish elderly patients who were identified to be a subject of chronic polypharmacy in 2018.

Parameter		N	%
Elderly people on chronic polypharmacy		554,085	100.0
Individuals alive as of December 31, 2018		532,218	96.1
Gender	Male	272,922	49.3
	Female	259,263	46.8
	Missing data	33	0.0
Age (years)	65–69	116,091	21.0
	70–74	132,378	23.9
	75–79	113,440	20.5
	80–84	99,269	17.9
	85–89	54,077	49.3
	90–94	15,006	46.8
	95+	1 957	0.0

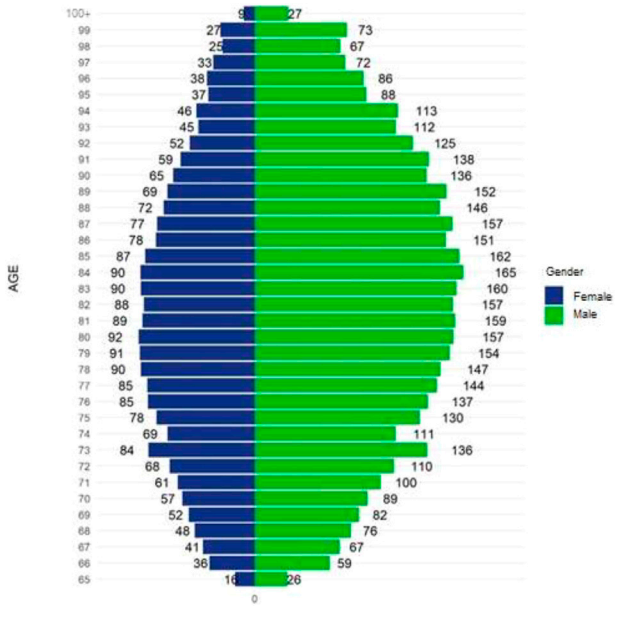

FIGURE 2 | Number of elderly patients on chronic polypharmacy in Poland in 2018 per 1,000 of inhabitants by age and gender.

greatest number of people with chronic polypharmacy was observed in the Łódź Voivodeship - 1.7 thousand per 100 thousand inhabitants, and the lowest one in the Podkarpackie Voivodeship - 1.0 thousand per 100 thousand inhabitants (**Figure 3**).

Out of the total number of elderly patients on chronic polypharmacy, the vast majority (0.380M, i.e. 68.6%) continued their polypharmacy for the period of the whole year.

Prescriptions Contributing to Chronic Polypharmacy

Patients exposed to chronic polypharmacy filled prescriptions on average from median 4 (mean: 4.5±2.36) healthcare professionals (**Figure 4**) issued at 14 (mean 14.7 ±6.61) medical encounters in the year 2018 (**Figure 5**). Almost 30% (28.9% - 160.2 thousand) of patients on chronic polypharmacy in 2018 filled prescriptions from six or more prescribers (another prescriber every 2 months, on average). Approximately, 1% of this group (5.6 k) filled their prescriptions from another prescriber each month, on average.

During the year, the average number of medical institutions in which a prescription was issued for them was 2.6±1.39 (**Figure 6**). In the group of the analysed patients, 23% (127.7 thousand) filled prescriptions from over three service providers, and 1% (7.3 thousand) filled prescriptions from seven or more service providers in 2018. The maximum number of healthcare providers issuing prescriptions per patient per year was 32.

Patients on chronic polypharmacy were dispensed 13.6 million prescriptions (9.1% of all prescriptions for ready-made drugs) for 49.0 million packages of drugs (12.1% of all packages). The average annual number of dispensed prescriptions per patient was 24.6 (+/−10.3), the average number of dispensed drug packs per patient – 88.4 (+/–

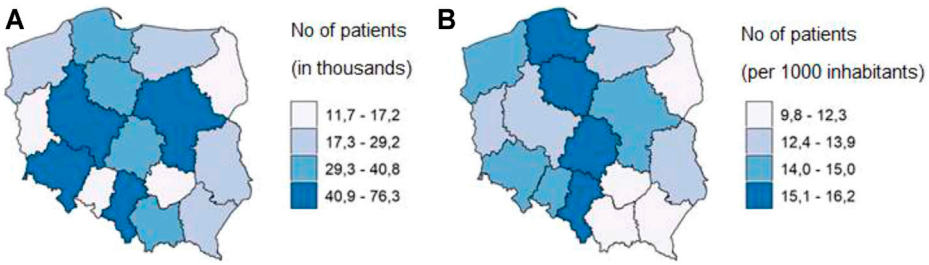

FIGURE 3 | Number of elderly patients on chronic polypharmacy in Poland in 2018 by Voivodeship **(A)**, and per 1,000 inhabitants of Voivodeship **(B)**.

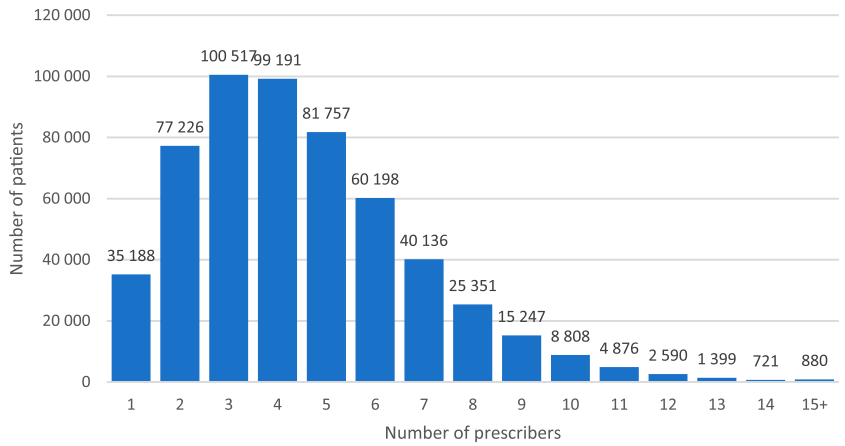

FIGURE 4 | Number of elderly patients on chronic polypharmacy in Poland in 2018 by number of prescribers who issued their prescriptions.

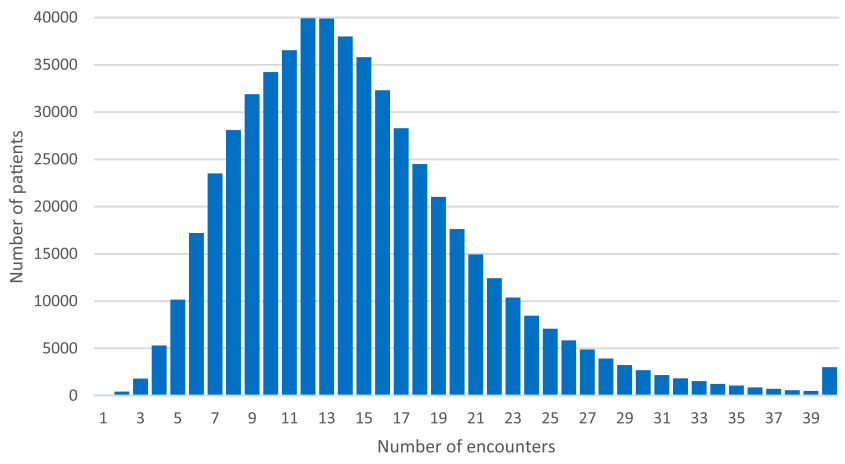

FIGURE 5 | Number of elderly patients on chronic polypharmacy in Poland in 2018 by number of encounters during which their prescriptions were issued.

31.6). The average number of DDD was 2 784±1,401 per patient per year, i.e. 8.3±3.84 DDD per patient per day. Out of the total number of patients on chronic polypharmacy, 25% (130,968) took an average of ten or more DDD per day, and 1% (5 164) took 24 or more doses per day.

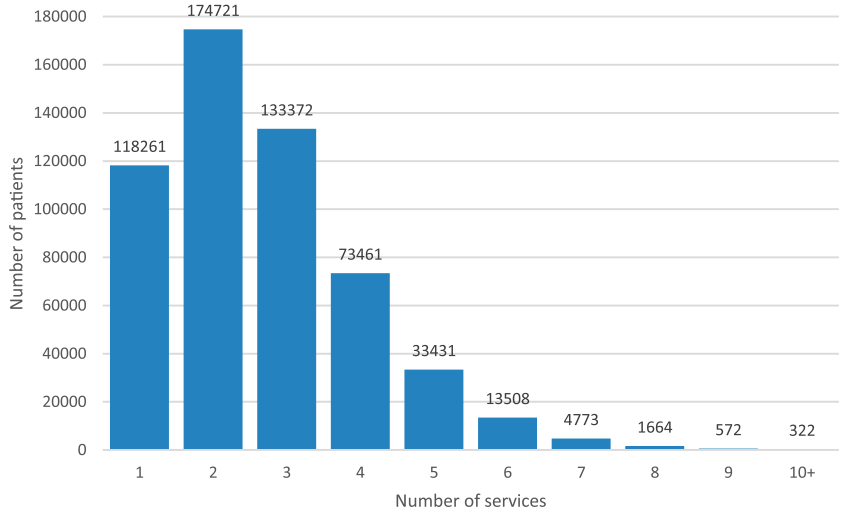

FIGURE 6 | Number of elderly patients on chronic polypharmacy in Poland in 2018 by number of healthcare services in which their prescriptions were issued.

TABLE 2 | Top-20 drugs prescribed to elderly patients with chronic polypharmacy.

No	Medication	% Of patients prescribed particular drug (N = 554,085)	% Of prescriptions (N = 13,607,512)
1	Metformin	50.3	13.1
2	Atorvastatin	46.7	11.4
3	Pantoprazole	38.0	7.1
4	Ramipril	35.3	9.0
5	Amlodipine	33.2	8.0
6	Furosemide	27.2	6.4
7	Allopurinol	25.8	5.5
8	Rosuvastatin	25.3	5.9
9	Tamsulosin	24.7	5.1
10	Nebivolol	23.9	6.0
11	Tramadol + Paracetamol	23.3	3.1
12	Indapamide	23.3	5.6
13	Potassium Chloride	21.9	4.0
14	Finasteride	21.1	4.2
15	Spironolactone	18.5	3.3
16	Omeprazole	18.1	3.4
17	Levothyroxine	16.7	2.9
18	Doxazosin	16.5	3.7
19	Gliclazide	15.9	3.9
20	Glimepiride	14.4	3.8

Drugs Contributing to Chronic Polypharmacy in Elderly People

Among 20 most common drugs contributing to chronic polypharmacy, the most prevalent were cardiovascular agents (seven purely cardiovascular drugs, as well as doxazosin used in both hypertension and benign prostate hyperplasia (BPH)), oral antidiabetic agents (three 3 drugs), drugs used in BPH (two agents indicated specifically for BPH + doxazosin, see comment above), and lipid lowering drugs (two agents). The most frequently prescribed drugs among those patients were as follows: Metformin (50.3% patients, 13.1% prescriptions), Atorvastatin (46.7% patients, 11.4% prescriptions), Pantoprazole (38.0% patients, 7.1% prescriptions), Ramipril (35,3% patients, 9.0% prescriptions) and Amlodipine (33.2% patients, 8.0% prescriptions) (for details, see **Table 2**).

Healthcare Services Utilisation by Elderly People on Chronic Polypharmacy

Among patients on chronic polypharmacy, 98.7% used primary care services and 86.3% used ambulatory specialist consultations. The number of primary healthcare consultations was 7.1 million

TABLE 3 | Healthcare services utilization by elderly patients on chronic polypharmacy.

Health service	No. of patients utilizing particular healthcare service	% Of patients on chronic polypharmacy utilizing particular healthcare service (N = 554,085)
Primary healthcare	544,934	98.7
Outpatient specialist services	476,681	86.3
Hospital treatment	284,798	51.6
Medical rehabilitation	122,950	22.3
Emergency medical services	118,065	21.4
Psychiatric care and addiction treatment	39,279	7.1
Services contracted separately	14,948	2.7
Palliative and hospice care	8 651	1.6
Nursing and care services	7,749	1.4
Pilot programs	3,008	0.5

TABLE 4 | Top-20 principal diagnoses in selected patients on chronic polypharmacy in 2018 by healthcare services other than hospitalisation.

No	Diagnosis	No. of patients	% Of elderly patients on chronic polypharmacy
1	Repeat prescriptions	316,721	57.2
2	Primary hypertension	282,855	51.0
3	Non-insulin dependent diabetes mellitus	196,833	35.5
4	Prostatic hyperplasia	120,116	21.7
5	Persons encountering health services in other specified circumstances	119,322	21.5
6	Chronic ischemic heart disease	112,948	20.4
7	Persons consulting on behalf of another person	78,269	14.1
8	Heart failure	76,304	13.8
9	Atrial fibrillation and flutter	69,165	12.5
10	Encounter for medical observation for suspected diseases and conditions ruled out	68,894	12.4
11	Degenerative changes of the spine	67,930	12.3
12	Chronic obstructive pulmonary disease	64,994	11.7
13	Acute infection of the upper respiratory tract, multiple or undefined	63,840	11.5
14	Polyosteoarthritis	57,674	10.4
15	Hypertensive disease involving the heart	56,209	10.1
16	Bronchial asthma	53,326	9.6
17	People contacting the health service for consultation and advice other than classified elsewhere	50,564	9.1
18	Disorders of the spinal nerve roots and nerve plexuses	49,639	9.0
19	General medical examination of people without ailments and without disease diagnosis	47,747	8.6
20	Acute bronchitis	46,699	8.4

(i.e. 12.8 per patient, on average), and in outpatient specialist care - 4.2 million (7.6 per patient). On average, in 2018 patients received care from 2.6±1.39 different types of healthcare services (**Table 3**).

After the technical code 'Appointment for issue of a repeat prescription' (ICD-10 code: Z76.0), the most frequent diagnosis made in these patients in outpatient settings were primary hypertension (51.0%) and type 2 diabetes (35.5%) (for details, see **Table 4**).

Out of the entire group, 51.6% patients were hospitalized, mainly due to heart failure (3.9% of patients) (**Table 5**). The total number of hospitalisations in this group of patients in 2018 was 0.569M, making the average annual hospitalization rate 1.03 ± 2,4 (mean±SD), whereas in the general population of elderly citizens, the relevant number was 0,55± 1,42.

DISCUSSION

To the best of the authors' knowledge, this is the first study to describe chronic polypharmacy in Polish elderly people. It provides detailed characteristics of the subgroup of patients who are most likely to be affected by this phenomenon. Our findings show that chronic polypharmacy is a frequent problem among Polish older adults. On average, over 40% of Polish elderly citizens were on polypharmacy in 2018, and every fifth was on chronic polypharmacy. Considering the fact that the population of Poland is aging fast, and the number of elderly citizens is continuously rising, these findings are crucial for the national health policy, and definitely, deserve a lot of attention.

Despite diverse definitions of polypharmacy and methodologies employed in individual studies, recent

TABLE 5 | Principal diagnoses of hospitalisations in elderly people on chronic polypharmacy in 2018.

No	Principal diagnosis	No	% Of hospitalisations of elderly patients on chronic polypharmacy (N = 0.569M)	% Of elderly patients on chronic polypharmacy (N = 0.554M)
1	Heart failure, unspecified	21,524	3.8	3.9
2	Complicated cataract	16,775	2.9	3.0
3	Congestive heart failure	16,018	2.8	2.9
4	Atrial fibrillation and flutter	10,752	1.9	1.9
5	Other forms of age-related cataracts	9,508	1.7	1.7
6	Heart and blood vessel disease in the course of atherosclerosis	8 831	1.6	1.6
7	Left ventricular heart failure	6,294	1.1	1.1
8	Spontaneous (primary) hypertension	6,146	1.1	1.1
9	Cancer chemotherapy cycles	6,103	1.1	1.1
10	Acute subendocardial infarction	6,034	1.1	1.1
11	Atherosclerosis of the extremities	4,900	0.9	0.9
12	Unstable angina	4,503	0.8	0.8
13	Age-related nuclear cataract	3,948	0.7	0.7
14	Acute kidney failure, unspecified	3,734	0.7	0.7
15	Chronic ischemic heart disease, unspecified	3,703	0.7	0.7
16	Heart disease in the course of atherosclerosis	3,327	0.6	0.6
17	Acute myocardial infarction, unspecified	3,302	0.6	0.6
18	Non-insulin dependent diabetes mellitus (with renal complications)	3,221	0.6	0.6
19	Unspecified chronic obstructive pulmonary disease in exacerbation	3,092	0.5	0.6
20	Chest pain, unspecified	3,060	0.5	0.6

European data are also alarming when it comes to the prevalence of polypharmacy in the elderly. In the last years, the prevalence of this phenomenon among older people has risen even further in Europe (Carmona-Torres et al., 2018). Polypharmacy was observed in 21.9% of community-dwelling Spanish elderly people (Carmona-Torres et al., 2018), 39.4% of Italian elderly citizens (Slabaugh et al., 2010), 41.2% of Swiss older adults (Blozik et al., 2013), and 51% of Danish individuals aged over 75 years (Kornholt and Christensen, 2020). Based on the data collected in the Sixth Wave of SHARE survey, completed in November 2015, polypharmacy was identified in 32.1% of elderly Europeans, on average, whereas in Poland, this ratio was higher and amounted to approximately 33.8% (Midão et al., 2018).

Due to its natural background related to multimorbidity which is usually composed of chronic diseases, polypharmacy in older age is in most cases a chronic condition (Muth et al., 2019). This, however, does not mean that its long-term nature is well-studied. One of the few exceptions is a longitudinal nationwide cohort study including all older Swedish adults (aged 65 years and over) with five or more prescription drugs in October 2010. The proportion of individuals who remained exposed to polypharmacy after 6 months, 12 months and until the end of this over 3-years-long study was 82, 74 and 55%, respectively (Wastesson et al., 2019). Our own observations of two thirds of chronic polypharmacy patients who maintain this status for the period of the whole year suggests that once an elderly person is prescribed a high number of drugs, the chances for reducing this number are very low. Another study covered an even longer period of 10 years (between 2000 and 2010) and analysed data of nearly two million patients aged 65–94 years living in Lombardy (Northern Italy). The overall prevalence of chronic polypharmacy, defined as administration of five or more drugs during 1 month for at least six (consecutive or not) months in a year, rose from 1.33% in 2000 to 3.34% in 2005 and 7.10% in 2010 (Franchi et al., 2013). In a Dutch study which included 45,731 patients aged 55 years or over with at least one prescribed medication, 27% were found to experience polypharmacy. The number of medications used in the polypharmacy group was on average 11.2 of which 6.9 was used chronically (Sinnige et al., 2016).

Our findings indicate that with similar absolute numbers, chronic polypharmacy was much more prevalent in Polish elderly men than in women. This is an unexpected result as in the studies performed in other countries, polypharmacy in the elderly was found to be associated with female gender. Other known drivers of polypharmacy in the elderly include age, being separated/divorced/widowed, lack of education, higher body mass index, being bedridden and self-medication (Carmona-Torres et al., 2018). Factors associated with chronic polypharmacy involve similar characteristics, i.e., a more advanced age, female sex, living in an institution, chronic multimorbidity and multidose dispensing (Wastesson et al., 2019).

Among the factors contributing to polypharmacy, age is a particularly important one as polypharmacy prevalence rises dramatically with years of life. A clear example of such a correlation are the results of a nationwide Swedish study. Among those aged <60, 60–69, 70–79, 80–89 and over 90 years, polypharmacy was present in 8.5, 35.9, 54.8, 73.0 and 79.6%, respectively, with excessive polypharmacy peaking up to 36.4% in individuals aged 90 years and over (Zhang et al., 2020). Our observation of a mean age of 76 years among elderly patients on chronic polypharmacy in Poland corresponds well with this tendency.

A marked variation in geographical distribution of chronic polypharmacy among Polish elderly citizens was also an interesting finding of our analysis. No matter which administrative unit of the country is considered, Łódź appears to be the epicentre of chronic polypharmacy. There are other data proving that the health parameters in this region deviate negatively from national averages (World Health Organization, 2012). Perhaps the variation of polypharmacy prevalence in the elderly is not only a Polish specificity since similar findings were reported in Italy and the Netherlands (Franchi et al., 2013; Sinnige et al., 2016). Nevertheless, uneven distribution of chronic polypharmacy density across various regions should be taken into account when drawing up regional health plans.

Elderly patients on chronic polypharmacy characterised in our analysis were provided with care by multiple health professionals. This is certainly a reflection of their poor health and the need to obtain necessary health service. Nevertheless, these findings also indirectly point to a lack of coordinated care and imperfect communication between various prescribers and healthcare institutions, which leads to chronic polypharmacy in the elderly. So far, only several health conditions (e.g., myocardial infarction) have been covered by coordinated care in Poland, and when it comes to communication, the major innovative enabler ensuring it, i.e., the nationwide electronic health record, has not been fully introduced yet. Fortunately, both these solutions are included in short-term development plans of the National Health Fund and the Polish Ministry of Health. Therefore, it may be expected that this situation will change for better.

Not surprisingly, our cohort of the elderly people on chronic polypharmacy was found to be hospitalised twice more often than the general Polish population of citizens aged 65 years or over. Perhaps this correlation between polypharmacy and hospitalisations in elderly patients is not surprising as those with poorer health may not only need more drugs but also more frequent hospitalisations. However, it seems that hospitalisation is an independent risk factor for polypharmacy in general, and inappropriate polypharmacy in particular. In an Irish study conducted among older people admitted to hospital, the likelihood of potentially inappropriate prescriptions after admission was higher than prior to it (adjusted odds ratio 1.72), regardless of patients' characteristics (Pérez et al., 2018).

A specific local factor that may certainly have an impact on the rate of polypharmacy in Polish elderly people is the availability of basic drugs free of charge offered to this group of citizens. Starting from September 1, 2016, "*Program Leki 75+*" ("Drugs 75+ Program") was initiated. It enabled those aged 75 years and above to obtain these drugs at no co-payment. The overall idea of the program was to ensure access to necessary medications to those at the highest risk of multimorbidity since, in general, the prescribed drugs are subject to co-payment by patients in Poland, which varies both across and within specific drug classes. This, however, might be an incentive to overprescribe both for prescribers and their patients rather than to look for other non-pharmacological options of addressing health problems. So far, this problem has not been extensively studied and dedicated research is required.

Finally, it needs to be emphasized that the analysed medicines that contribute to chronic polypharmacy are the drugs used typically for management of chronic conditions. Among the top five ones, four were indicated for lifelong treatment, i.e., 1. Metformin (mostly recommended for diabetes), 2. Atorvastatin (hyperlipidaemia, coronary artery disease), 4. Ramipril (hypertension, chronic heart failure and other cardiovascular conditions), and 5. Amlodipine (hypertension and other cardiovascular conditions). This list, undoubtedly grouping highly indicated drugs, differs considerably from the one including the most prevalent potentially inappropriate ATC codes identified in the Swiss elderly, of which the top five were Zolpidem, Estradiol, Acemetacin, Amiodarone and Trimipramine (Blozik et al., 2013). Thus, it might not be an easy task to discontinue such treatments in elderly patients in Poland without causing a serious disruption of their care.

Our findings also deserve practical solutions. A recent WHO report on polypharmacy urges countries to put polypharmacy high on their agendas in order to reduce its prevalence by implementing dedicated programs (World Health Organization, 2019). Quite often, however, it is still not the case in Europe. A search for polypharmacy management programs, undertaken within the framework of the SIMPATHY project, revealed such initiatives in five out of nine assessed countries only (McIntosh et al., 2018). Regrettably, no such official program was identified in Poland (Stewart et al., 2017), nor introduced to the date of this publication.

To be safe, effective and cost-effective, any program that attempts to deal with the complexities of prescribing medications in elderly people should be patient-centred, clinically robust, multidisciplinary and designed to fit into the healthcare system in which it is delivered (Stewart et al., 2017). Such a program may be based on one or multiple interventions. So far, various solutions have been proposed to reduce inappropriate prescribing and subsequent polypharmacy in older adults, ranging from comprehensive geriatric assessment, shared decision-making, medication reviews performed by either pharmacists or physicians, training of healthcare staff, use of various guidelines, checklists, up to different forms of computer and/or artificial intelligence-assisted clinical decision support systems (Lee et al., 2020).

Comprehensive approaches work well, e.g., dedicated palliative consultations resulted in a decrease in the number of drugs used in complex palliative patients in Poland (Grądalski, 2019). However, they also impose serious limitations related to their time-consuming nature, as well as a need for highly experienced staff. Unfortunately, with a very limited number of practicing geriatricians and absence of clinical pharmacists working in outpatient care, scaling up of such results has not been possible in Poland so far.

Considering the above, it seems to be much more realistic to implement simpler, explicit criteria-based interventions aimed at deprescribing, such as drug reviews using validated tools (e.g. STOPP/START or Beers criteria) (Kurczewska-Michalak et al., 2021). Such interventions may be further developed by dedicated applications or computer-assisted decision support systems, in order to promote their applicability. However, these approaches are still time-consuming, which makes their implementation a considerable

challenge for busy clinicians who sometimes, unfortunately, do not pay much attention to the problem of polypharmacy.

In such circumstances, it may be expected that another intervention to be introduced soon will help prevention and management of polypharmacy in elderly patients in Poland. The Polish Act on the Profession of Pharmacists (Dziennik Ustaw, 2021) became effective in april 2021. Among innovations codified by this Act, there is a new service provided within pharmaceutical care which was not available in Poland before. Under the ministerial document specifying the scope of the service, it will cover identification, management and prevention of drug problems in general, and it will also include reviews of drugs which will most probably be reimbursed (Ministerstwo Zdrowia, 2021). Thus, access to professional drug reviews may be soon widely available in Poland, with obvious benefits for elderly people facing the risk of inappropriate polypharmacy.

This study has several limitations. One of them is that we were not able to correlate an individual exposure to polypharmacy with either the kind or number of conditions that an individual patient was diagnosed with. Similarly, we could not assess whether the identified cases met the criteria for either 'appropriate' or "inappropriate polypharmacy". All that was not possible due to the fact that the nationwide electronic health record system has not yet been launched in Poland, which made comparisons between clinical and dispensation data very difficult and limited them to the reports on hospital stays or some outpatient services. Thus, we could only hypothesize that multimorbidity must have had an effect on polypharmacy prevalence in the studied population. There exists evidence proving that the greater the number of conditions an elderly patient is diagnosed with, the higher the probability of polypharmacy (Slabaugh et al., 2010).

Another limitation of our study is related to the scope of the analysed drugs which was narrowed down to reimbursed prescription medications only. In fact, polypharmacy is a problem that may be caused by various sorts of remedies, including non-reimbursed prescription drugs, as well as over-the-counter (OTC) drugs and dietary supplements which are often overused in Poland (Bochenek et al., 2016). Thus, our findings should be accepted as conservative estimates. A survey-based study assessing older (70+) primary care patients in Germany found that 26.7% of them were on prescribed polypharmacy, however, the percentage increased to 53.6% when OTC drugs were included as well (Junius-Walker Uet al, 2007). On the other hand, this is a natural disadvantage of analyses based on pharmacy claims data since they do not capture dispensation of OTC drugs or drug-similar products. However, the alternative approach, which is based on surveying and thus makes it possible to identify the use of non-prescription products, is subject to a large recall bias, and considerable underreporting.

Finally, our analysis covered only 1 year. In order to better understand the prevalence of polypharmacy in the elderly, and in particular, to observe its dynamics over time, the longitudinal analyses are warranted.

Nevertheless, this study has also a number of strengths. It was based on a nationwide database, with only a few drug groups of minor importance excluded from the analysis for practical reasons. Moreover, our analysis was based on dispensation, and not prescription data, which allowed us to avoid a considerable bias. Due to various reasons, a large number of prescriptions is never filled. We found this proportion to reach as many as 20.8% of all prescriptions issued in Poland (Kardas et al., 2020).

CONCLUSION

This study was the first of this kind involving a nationwide assessment of chronic polypharmacy in Polish elderly people. We found that this problem affected one fifth of Polish older adults and it remains stable due to its direct relation to chronic conditions. We also observed a marked variation in geographical distribution of chronic polypharmacy in Polish elderly citizens, peaking in the Łódź Voivodeship. The medicines that contributed most to chronic polypharmacy in our analysis were the drugs used typically for management of chronic conditions. It is noteworthy, however, that our analysis did not cover OTC drugs which could impact polypharmacy even more. Considering the fact that the population of Poland is aging fast, and the number of elderly citizens is continuously increasing, one may expect a further rise in chronic polypharmacy among Polish elderly citizens in the upcoming decades. Therefore, our results confirm that this phenomenon is highly important for the national health policy and requires relevant interventions. The planned introduction of pharmaceutical care in Poland may be expected to provide a practical solution that will help to address this problem properly.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data that support the study findings are made available by the authors with the permission of NHF (data owner). Restrictions apply to the availability of the data which were used under the license for this study. Requests to access these datasets should be directed to przemyslaw.kardas@umed.lodz.pl.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Study concept and design: AL, EC, FU, GK, MC, and PK. Analysis: AL, GK, and PK. Manuscript text: PK and GK. All the authors participated in the interpretation of the results, drafting and reviewing of the manuscript, and approved the final version.

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SYSTEMATIC REVIEW
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Polypharmacy Management in the Older Adults: A Scoping Review of Available Interventions

M. Kurczewska-Michalak[1], P. Lewek[1], B. Jankowska-Polańska[2], A. Giardini[3], N. Granata[4], M. Maffoni[4], E. Costa[5], L. Midão[5] and P. Kardas[1]*

[1]Department of Family Medicine, Medical University of Lodz, Lodz, Poland, [2]Department of Clinical Nursing, Faculty of Health Science, Wroclaw Medical University, Wroclaw, Poland, [3]IT Department, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy, [4]Psychology Unit, Istituti Clinici Scientifici Maugeri IRCCS, Montescano Institute, Pavia, Italy, [5]UCIBIO/REQUIMTE, Faculty of Pharmacy and Porto4Ageing, University of Porto, Porto, Portugal

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***Correspondence:**
M. Kurczewska-Michalak
m.kurczewska@o2.pl

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Background: Polypharmacy paves the way for non-adherence, adverse drug reactions, negative health outcomes, increased use of healthcare services and rising costs. Since it is most prevalent in the older adults, there is an urgent need for introducing effective strategies to prevent and manage the problem in this age group.

Purpose: To perform a scoping review critically analysing the available literature referring to the issue of polypharmacy management in the older adults and provide narrative summary.

Data sources: Articles published between January 2010–March 2018 indexed in CINHAL, EMBASE and PubMed addressing polypharmacy management in the older adults.

Results: Our search identified 49 papers. Among the identified interventions, the most often recommended ones involved various types of drug reviews based on either implicit or explicit criteria. Implicit criteria-based approaches are used infrequently due to their subjectivity, and limited implementability. Most of the publications advocate the use of explicit criteria, such as e.g. STOPP/START, Beers and Medication Appropriateness Index (MAI). However, their applicability is also limited due to long lists of potentially inappropriate medications covered. To overcome this obstacle, such instruments are often embedded in computerised clinical decision support systems.

Conclusion: Multiple approaches towards polypharmacy management are advised in current literature. They vary in terms of their complexity, applicability and usability, and no "gold standard" is identifiable. For practical reasons, explicit criteria-based drug reviews seem to be advisable. Having in mind that in general, polypharmacy management in the older adults is underused, both individual stakeholders, as well as policymakers should strengthen their efforts to promote these activities more strongly.

Keywords: polypharmacy, elderly, older adults, adverse drug event, adverse drug reaction, explicit criteria, inappropriate prescribing, multimorbidity

INTRODUCTION

Recently, polypharmacy (also called polytherapy or polypragmasy) became an important public health problem due to its far-reaching consequences, such as possible negative effects on individual health, as well as increased use of healthcare services and costs (Fried et al., 2014). In particular, polypharmacy is known to cause a higher risk of adverse drug events and drug-drug interactions. It also often leads to medication non-adherence. All these provide negative health outcomes as well as increased risk of geriatric syndromes (e.g., cognitive impairment, or falls). This, in turn, leads to increased risk of hospitalization and institutionalization, as well as much greater health care expenditures (Maher et al., 2014). Therefore, polypharmacy is considered to be "one of the greatest prescribing challenges" (Payne and Avery, 2011).

Obviously, polypharmacy is not limited to older adults. Nevertheless, the highest prevalence of this scenario comes with older age. A nationwide cohort study in Sweden among individuals aged ≥65 has found prevalence of polypharmacy reaching 44%, and prevalence of extreme polypharmacy (defined as taking ten drugs or more) of 11.7% (Morin et al., 2018). Data from the United Kingdom highlight that 20.8% of individuals with two clinical conditions have been prescribed four to nine medicines, whereas 10.1% of them—ten or more medicines. In patients with six or more comorbidities, relevant values were 47.7 and 41.7%, respectively, and these figures increased with age (Barnett et al., 2012). In Poland, polypharmacy has been observed among 55.0% of the citizens aged 80+ (Kardas et al., 2021). Scottish data show that around 35% of those aged 85 years and above receive more than ten medicines (Stewart et al., 2017a). A recent analysis of a large European cohort has found polypharmacy (defined as concurrent use of five or more medications) to be present in 32.1% of citizens aged 65 years or above, ranging from 26.3 to 39.9% across the studied countries (Midão et al., 2018). High prevalence of polypharmacy in the older adults has also been observed outside Europe, e.g., in countries such as Brazil (Pereira et al., 2017) and United States (Quinn and Shah, 2017).

Thus, the burden of polypharmacy is a direct consequence of demographic challenge which, though observed worldwide, is particularly pronounced in Europe. According to Eurostat data, currently those aged 65 years or above, account for 19.2% of the European Union's population, and this proportion is expected to rise up to 29.1% by 2080, whereas percentage of those aged over 80 years, is expected to increase even more dramatically—from the present 5.4–12.7% (Eurostat (2015). People i, 2015).

The longer citizens live, the higher are the chances of multimorbidity which is defined by the World Health Organization as "the co-occurrence of two or more chronic medical conditions in one person" (World Health Organization, 2008). Prolonged life expectancy, the privilege of people living in the 21st century, means much longer years lived with chronic conditions the number of which grows even more with age. Current statistics estimate that over 70% of people aged over 65 years are affected by multimorbidity (National Guideline Centre, 2016). It has a major impact on healthcare systems, e.g., primary care physicians in England care for patients with multimorbidity in 78% of their consultations (Salisbury et al., 2011), whilst in several other settings, e.g., geriatrics, this percentage may reach 100%.

Ageing and multimorbidity, i.e., two interlinked factors mentioned above, are to a large extent responsible for the observed rapid rise in global prevalence of polypharmacy (Guthrie et al., 2015). However, the current paradigm of healthcare seriously increases the chances of polypharmacy in the older adults as well. Undoubtedly, it is a consequence of single-disease oriented guidelines promoting pharmacotherapy as a routine solution. This approach leads to undesirable effects, such as difficulties in integrating care in multimorbidity cases, poor communication between patients, carers and their multiple care providers, and a lack of patient-focused (rather than condition-focused) care plans (Boyd et al., 2005; May et al., 2009). Unfortunately, the guidelines only seldom tend to address the complex nature of multimorbidity trying to address it from the patient's perspective in order to prioritize certain conditions or treatments over the other ones, thus reducing the burden of prescribed drugs (Montori et al., 2013; Farmer et al., 2016). Similarly, "defensive medicine" makes the initiation of therapy easy and always correct, contrary to a more conservative approach which accepts that not every condition is automatically the reason for taking a medication, thus giving both the prescriber and the patient more freedom in making their choices based on accepted priorities (Austad et al., 2016).

Despite the significance of the problems created by polypharmacy in the older adults, this subject is only seldom tackled in European countries in a systematic way. An extensive search for polypharmacy guidance documents (both published in peer-reviewed journals and made available as grey literature) performed recently across Europe has identified only five European countries that actually have such documents targeting older patients (Stewart et al., 2017a).

There is a variety of tools aimed at reduction of inappropriate polypharmacy using either implicit (judgement-based) or explicit (item list-based) criteria (Kaufmann et al., 2014). Unfortunately, their practical implementation in older adults care is very limited. Recent research shows that healthcare professionals (HCPs) are often either unaware of such tools or disregard them as not being user-friendly (Mc Namara et al., 2017). For example, the use of various forms of drug reviews has been reported in half of 32 studied European countries only (Bulajeva et al., 2014).

Under such circumstances, healthcare professionals should be supported and motivated to implement polypharmacy targeting interventions. Therefore, the overall aim of this paper was to summarize available information on the methods to prevent and manage polypharmacy in the older adults. Accepting the perspective of practical approach and pragmatic guidance to polypharmacy management, the objective of this scoping review was to map available interventions and more complex strategies, and discuss their implementability. The rationale behind the approach was a common belief that there is no "one-size-fits-all" solution for polypharmacy management in the older adults. Therefore, in order to help HCPs select an approach that would satisfy their requirements best and increase

overall application of polypharmacy management, the literature search strategy was designed to identify the scientific publications detailing a broad spectrum of interventions available for polypharmacy management in the older adults. In order to reflect the state-of-the-art findings, the literature search was limited to items published from 2010 onward.

MATERIALS AND METHODS

Search Strategy

In this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Moher et al., 2009). The electronic databases, i.e., CINHAL, EMBASE and PubMed, were systematically searched in accordance with the predefined literature search strategy based on a various combination of keywords including "polypharmacy" and its equivalents, terms corresponding to a systematic approach to polypharmacy management, such as "intervention" etc., and various identifiers of older age. The **Supplementary Online Material S1** provides the combination of search terms that were used to identify relevant publications.

Inclusion Criteria

Publications were included if: (A) they outlined interventions addressing polypharmacy (however, not implementation of guidelines) in the older adults in any of the following settings: 1) clinical practice, 2) health care systems, 3) scientific research; and (B) they were published in the years between 2010 and 2018. What is noteworthy is that the definition of an "intervention" was not explicit in order to allow for a broad spectrum of search results that could be of potential interest to the readers. Similarly, we accepted various definitions of the "elderly" used by the authors, not limited to the traditional convention defining the "elderly" as those aged 65 years or above. (Orimo, 2006).

Exclusion Criteria

Articles were excluded if they: 1) were not peer-reviewed; 2) were written in a language other than English; 3) were not devoted to interventions addressing polypharmacy; or 4); did not present intervention descriptions in full details (e.g., letters, comments, conference proceedings, editorials, erratum, etc., as opposed to original articles, reviews, systematic reviews, randomized controlled trials and guidelines).

Study Selection

Studies meeting the inclusion criteria were initially selected, based on screening the titles and abstracts by one researcher (PL). Copies of full-text papers considered as potentially relevant after the first screening were then fully analysed independently by two researchers (out of the three: BJ-P, MK-M, and PL). In the case of different opinions on possible inclusion of an article into the study, the third author (PK) was consulted to reach a consensus.

Data Extraction Process and Analysis

The data was extracted from each eligible paper according to the predefined framework which included the source, year of publication, country of origin, type of the publication, definitions of polypharmacy used by the authors, target for intervention (i.e., multimorbidity or individual disease typical for elderly people), characteristics of intervention, settings, healthcare professionals involved in/suggested to deliver the intervention, and results of intervention implementation (for publications assessing implementation of interventions only). The extracted data are presented in the **Supplementary Online Material S2**. Further elaboration of the extracted data involved grouping according to the predefined criteria and a statistical analysis with descriptive statistics. The final analysis of the extracted data took the form of a narrative, descriptive summary and synthesis.

RESULTS

Characteristics of Selected Studies

The literature search included 244 publications. Subsequently, 127 duplicates were removed, and the titles and abstracts of the remaining 117 articles were reviewed, which resulted in elimination of 67 papers that did not meet the inclusion criteria. A further detailed review of the full-text articles led to elimination of another paper. A final set of 49 articles that met the inclusion criteria was accepted for synthesis. For details of article screening and the exclusion process, see the PRISMA flow chart in **Figure 1**. The identified publications originated from a variety of European as well as non-European countries and included original articles, reviews, systematic reviews, randomized controlled trials and guidelines. A few papers were focused on one specific disease characteristic for older people [e.g., diabetes (Dunning, 2017), hip fracture (Komagamine and Hagane, 2017), etc.], whereas a majority of the publications did not define the type of disease. One study was focused on the patients with multimorbidity (Bokhof and Junius-Walker, 2016). All the reviewed studies were focused on elderly patients.

Aims of Identified Interventions

Across the reviewed literature, some attention is paid to prevention of polypharmacy. Optimal or appropriate prescribing was advised as a general method of polypharmacy prevention (Kaufman, 2011; Nobili et al., 2011; Cadogan et al., 2015; Cadogan et al., 2016; Cadogan et al., 2017). This recommendation, however, was not necessarily followed by detailed practical guidance. Only one publication provides recommendations on how to prevent polypharmacy in very specific patients, i.e., critically ill older adults who, when staying at an intensive care unit, are at risk of developing delirium (Garpestad and Devlin, 2017). In fact, strategies of polypharmacy management identified in our search predominantly target correction of polypharmacy. Specific aims of relevant interventions include one or several out of the below-listed ones:

1. Reduction of polypharmacy (lowering the number of drugs prescribed and/or used)
2. Increasing the use of a recommended medication

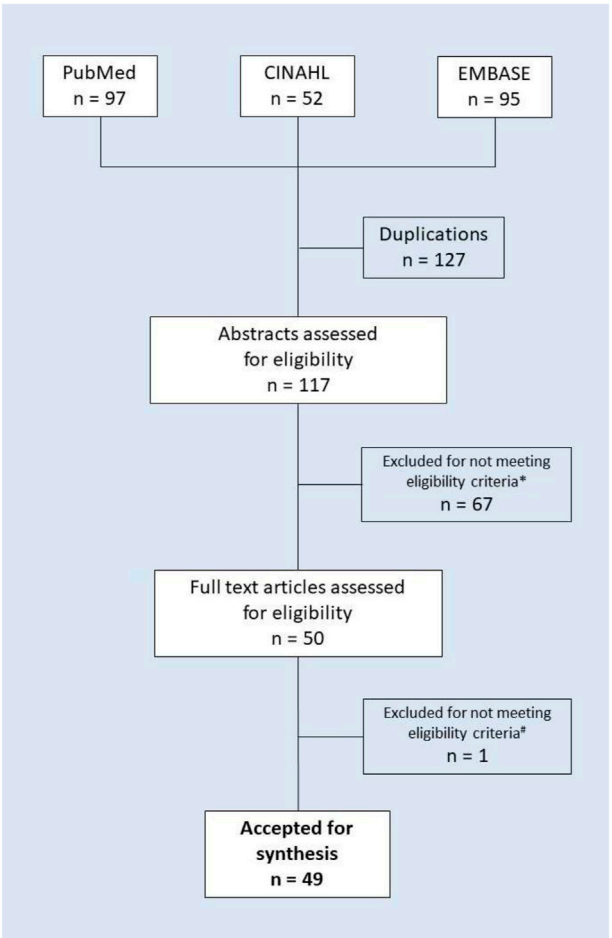

FIGURE 1 | PRISMA flow chart of the literature search and study selection. Note: * Excluded due to not detailing interventions to manage polypharmacy (56 items) or not meeting other eligibility criteria (e.g., not providing the details of the intervention, 11 items in total); # excluded for not meeting eligibility criteria (non-English-language publication).

3. Lowering the costs (drug costs, and/or overall healthcare system expenditures)
4. Enhancing patient adherence to medication
5. Increasing effectiveness of drug therapy (e.g., avoidance of hospitalisations, etc.)
6. Securing patient safety (e.g., avoidance of adverse drug reactions)

Targets of Identified Interventions

Although the role of patients is emphasized, and relevant recommendations include better patients' health literacy and awareness of their complex multiple medication regimens (Bokhof and Junius-Walker, 2016), patients are not perceived as those who actively initiate any formalised action against polypharmacy. In fact, it is also suggested that general practitioners (GPs) might support patients by "inviting" their contribution to polypharmacy and medication safety, as their awareness of the significance of their active role in addressing polypharmacy is currently very low (Schöpf et al., 2017).

Thus, the reviewed literature supports the use of interventions targeting polypharmacy which are initiated by healthcare professionals. A suggested trigger to employ such an intervention is just presence of polypharmacy in an older adult. This advice, however, is not easy to implement due to current lack of common standard definition of polypharmacy. In fact, the authors adopted various existing definitions, as illustrated in **Table 1**. Among them, the most commonly used definition of polypharmacy was taking concurrently five or more medications. However, in some publications other threshold values were also used, ranging from 1 to >9. Moreover, in several papers a qualitative approach to polypharmacy definition was preferred and the most common one was the imprecise definition describing it as "the use of a number of different medicines possibly prescribed by different doctors and often filled in different pharmacies, by a patient who may have one or several health problems" (Kaufman, 2011; Nobili et al., 2011; Clyne et al., 2016; Dunning, 2017; Lin et al., 2018). Finally, in nine papers the operational definition of polypharmacy was not precisely detailed (Planton and Edlund, 2010; Sergi et al., 2011; Mansur et al., 2012; Van der Linden et al., 2014; Yamanouchi et al., 2014; Cadogan et al., 2016; Garpestad and Devlin, 2017; Heaton et al., 2017; McNicholl et al., 2017) leaving it open to individual interpretation.

Who Should Provide a Polypharmacy Management Intervention

The reviewed literature pointed to a range of healthcare professionals who may or should provide polypharmacy addressing intervention. The most common setting in which polypharmacy management interventions were most successful was primary care and they were implemented either by GPs, or by primary healthcare team (Kaufman, 2011; Nobili et al., 2011; Sabzwari et al., 2013; Bergert et al., 2014; Kann et al., 2015; Bokhof and Junius-Walker, 2016; Cadogan et al., 2016; Clyne et al., 2016; Sinnige et al., 2016; Cadogan et al., 2017; Franco et al., 2017; Schöpf et al., 2017; Tommelein et al., 2017). However, some interventions were provided at community or hospital pharmacies, by pharmacists alone, in the form of pharmaceutical care, or in cooperation with a physician, e.g., under an umbrella of collaborative physician-pharmacist medication therapy management (MTM) program (Mansur et al., 2012; Patterson et al., 2012; Doan et al., 2013; Cooper et al., 2015; Jódar-Sánchez et al., 2015; Wilson et al., 2015; Cadogan et al., 2016; Chau et al., 2016; Jokanovic et al., 2017; Komagamine and Hagane, 2017; Malet-Larrea et al., 2017; McNicholl et al., 2017; McNicholl et al., 2017; Tommelein et al., 2017; Lin et al., 2018). Specialists who are perfectly prepared to take care of polypharmacy in the older adults are geriatricians, thus relevant interventions could be included in the geriatric consultation (Eyigor and Kutsal, 2012; Kojima et al., 2014; Van der Linden et al., 2014). Finally, other settings also allow for polypharmacy interventions which have been successfully provided in various hospital settings such as

TABLE 1 | Definition of polypharmacy used in reviewed publications.

Definition of polypharmacy			
Type of definition	**—**	**—**	**References**
Numerical	**Number of medications**	**Number of studies**	**—**
	1	1	Bokhof and Junius-Walker, (2016)
	>3	1	Zelko et al. (2016)
	≥4	7	Kaufman. (2011); Patterson et al. (2012); Patterson et al. (2014); Cooper et al. (2015); Stewart et al. (2017b); Cadogan et al. (2017); Patton et al. (2017)
	>5	2	Doan et al. (2013); Kim and Parish. (2017)
	≥5	17	Clyne et al. (2012); Eyigor and Kutsal (2012); Sabzwari et al. (2013); Bergert et al. (2014); Jódar-Sánchez et al. (2015); Kann et al. (2015); Chau et al. (2016); Sharma et al. (2016); Sinnige et al. (2016); Urfer et al. (2016); Franco et al. (2017); Kaufman. (2017); Komagamine and Hagane. (2017); Malet-Larrea et al. (2017); Schöpf et al. (2017); Tommelein et al. (2017); Lin et al. (2018)
	5–9	1	Harugeri et al. (2010)
	≥9	2	(Kojima et al. (2014); Jokanovic et al. (2017))
Qualitative	**Definition**	**Number of studies**	**References**
	1. The use of a number of different medicines possibly prescribed by different doctors and often filled in different pharmacies, by a patient who may have one or several health problems	5	Kaufman. (2011); Nobili et al. (2011); Clyne et al. (2016); Dunning. (2017); Lin et al. (2018)
	2. The use of multiple medicines and/or more medicines than clinically indicated	4	Patterson et al. (2014); Wilson et al. (2015); Rodrigues and Oliveira. (2016); Levy. (2017)
	3. Prescribing of multiple medicines (this includes "inappropriate polypharmacy" and "appropriate polypharmacy")	1	Stewart et al. (2017a)
	4. At risk of inappropriate prescribing and adverse drug events	1	Hughes et al. (2016)

teaching hospitals (Harugeri et al., 2010; Urfer et al., 2016; Lin et al., 2018), acute care hospitals (Komagamine and Hagane, 2017), acute geriatric wards (Mansur et al., 2012; Van der Linden et al., 2014). It is worth emphasizing that such interventions are also advisable in the case of residential aged care facilities (Kojima et al., 2014; Jokanovic et al., 2017). Some studies highlight the need for an interdisciplinary approach, e.g., in order to execute Comprehensive Geriatric Assessment (CGA), the authors suggest an interdisciplinary team comprising nurses, occupational and physical therapists, social workers, general practitioners and geriatricians (Sergi et al., 2011).

How Often Should an Intervention Be Provided

The available literature does not pay much attention to the question of how often interventions targeting polypharmacy should be repeated. According to one publication included in our review, GPs should scrutinize senior people's medications on each consultation whenever a patient meets the criteria of polypharmacy (Dunning, 2017). The recently published WHO report on medication safety in polypharmacy generally recommends that "appropriate polypharmacy should be considered at every point of initiation of a new treatment for the patient, and when the patient moves across different health care settings." (World Health Organization, 2019) As for residents of care homes, the NICE guidelines advise that an interval in medication reviews "should be no more than 1 year" and that many residents may require reviews more often. (National Institute for Health and Clinical Excellence, 2015) Obviously, practical implementation of relevant interventions is limited by many factors, such as the availability of qualified staff, a paradigm of the local healthcare system, reimbursement of the intervention, etc.

Details of Identified Interventions

Full list of all types of interventions identified in the reviewed studies is presented in **Table 2.**

For obvious reasons, effective management of polypharmacy should start with its prevention. Appropriate prescribing is the method that undoubtedly satisfies this expectation. Thus, a thorough risk–benefit analysis of each medicine should be made whenever any drug is prescribed (Kaufman, 2011; Nobili et al., 2011; Bokhof and Junius-Walker, 2016; Cadogan et al., 2016; Cadogan et al., 2017). If, however, polypharmacy is already in place, deprescribing is another logical step to be taken, as suggested by several publications (Bokhof and Junius-Walker, 2016; Sharma et al., 2016; Urfer et al., 2016; Jokanovic et al., 2017; Kaufman, 2017; Komagamine and Hagane, 2017; Schöpf et al., 2017). Although not limited to, the concept, aims, and practice of deprescribing overlap much with polypharmacy management. One of its definitions describes it as "the process of withdrawal of an inappropriate medication, supervised by a health professional with the goal of managing polypharmacy and improving outcomes" (Reeve et al., 2015). This broad concept has been supported by specific guidance, e.g., patient-centred deprescribing strategy, proposed in one of the publications (Kaufman, 2017). The strategy includes five steps: 1.

TABLE 2 | Polypharmacy interventions identified in reviewed publications.

Intervention		Number of publications	References
Optimal/appropriate prescribing		5	Kaufman (2011); Nobili et al. (2011); Cadogan et al. (2015); Cadogan et al. (2016); Cadogan et al. (2017)
Deprescribing		7	Bokhof and Junius-Walker (2016); Sharma et al. (2016); Urfer et al. (2016); Jokanovic et al. (2017); Kaufman (2017); Komagamine and Hagane (2017); Schöpf et al. (2017)
Drug review		18	Planton and Edlund (2010); Kaufman, (2011); Nobili et al. (2011); Sergi et al. (2011); Kojima et al. (2014); Wilson et al. (2015); Chau et al. (2016); Hughes et al. (2016); Sharma et al. (2016); Urfer et al. (2016); Stewart et al. (2017b); Cadogan et al. (2017); Dunning (2017); Jokanovic et al. (2017); Kaufman (2017); Komagamine and Hagane (2017); Levy (2017); McNicholl et al. (2017)
Medication review with follow-up (MRF)		2	Jódar-Sánchez et al. (2015); Malet-Larrea et al. (2017)
Comprehensive program of polypharmacy management		1	Kaufman, (2017)
Pharmaceutical care		3	Patterson et al. (2012); Cooper et al. (2015); Tommelein et al. (2017)
Collaborative physician—pharmacist medication therapy management (MTM)		1	Lin et al. (2018)
Comprehensive Geriatric Assessment		4	Sergi et al. (2011); Eyigor and Kutsal (2012); Sharma et al. (2016); Pazan and Wehling (2017)
Validated screening tools			
	STOPP/START	19	Nobili et al. (2011); Sergi et al. (2011); Eyigor and Kutsal (2012); Patterson et al. (2012); Bergert et al. (2014); Patterson et al. (2014); Cooper et al. (2015); Chau et al. (2016); Clyne et al. (2016); Hughes et al. (2016); Rodrigues and Oliveira (2016); Sharma et al. (2016); Urfer et al. (2016); Cadogan et al. (2017); Franco et al. (2017); Kim and Parish (2017); Komagamine and Hagane (2017); Levy (2017); McNicholl et al. (2017)
	Beers criteria	17	Planton and Edlund (2010); Nobili et al. (2011); Sergi et al. (2011); Eyigor and Kutsal (2012); Patterson et al. (2012); Sabzwari et al. (2013); Kojima et al. (2014); Patterson et al. (2014); Cooper et al. (2015); Clyne et al. (2016); Hughes et al. (2016); Rodrigues and Oliveira (2016); Sharma et al. (2016); Kim and Parish (2017); Komagamine and Hagane (2017); Levy (2017); McNicholl et al. (2017)
	MAI	11	Sergi et al. (2011); Barnett et al. (2012); Eyigor and Kutsal (2012); Patterson et al. (2012); Bergert et al. (2014); Patterson et al. (2014); Cooper et al. (2015); Rodrigues and Oliveira (2016); Sharma et al. (2016); Cadogan et al. (2017); Patton et al. (2017)
	NORGEP	3	Nobili et al. (2011); Hughes et al. (2016); Rodrigues and Oliveira (2016)
	IPET	1	Eyigor and Kutsal, (2012)
	McLeod	4	Nobili et al. (2011); Patterson et al. (2012); Patterson et al. (2014); Cooper et al. (2015)
	PIM	5	Nobili et al. (2011); Kojima et al. (2014); Van der Linden et al. (2014); Sharma et al. (2016); Levy (2017)
	PIP	5	Stewart et al. (2017b); Franco et al. (2017); Kaufman (2017); McNicholl et al. (2017); Tommelein et al. (2017)
	PRISCUS	2	Bergert et al. (2014); Hughes et al. (2016)
	MRCI	2	Mansur et al. (2012); Cadogan et al. (2017)
	ARMOR	2	Planton and Edlund (2010); Levy (2017)
New screening tool			
	RASP 2.0	1	Van der Linden et al. (2014)
	GheOPS tool	1	Tommelein et al. (2017)
	multidrug cytochrome-specific software program	1	Doan et al. (2013)
Computerised decision support		6	Eyigor and Kutsal (2012); Patterson et al. (2012); Patterson et al. (2014); Cooper et al. (2015); Bokhof and Junius-Walker (2016); Sinnige et al. (2016)

Note: STOPP–Screening Tool of Older Persons' Potentially Inappropriate Prescriptions; START–Screening Tool to alert Doctors to the Right Treatment; MAI–Medication Appropriateness Index; IPET–Inappropriate Prescribing in the Elderly Tool; NORGEP–The Norwegian General Practice criteria; McLeod–McLeod criteria; PIM–Potentially Inappropriate Medication; PIP–Potentially Inappropriate Prescribing; PIM–Potentially Inappropriate Medications; EMR–Electronic Medical Record; MRCI–Medication Regimen Complexity Index; PRISCUS–PhaRmaCotheRaPy In eldeRly PatIentS; ARMOR–Assess, Review, Minimize, Optimize, Reassess.

comprehensive medication history; 2. identification of potentially inappropriate medications; 3. determination if medication can be ceased and prioritisation; 4. planning and executing withdrawal; and finally, 5. monitoring, support and documentation.

A practical implementation of the deprescribing process in older adults may be guided by four crucial questions as proposed by Page et al. (2016), i.e.:

1. Is it an inappropriate prescription (e.g., a case without clear indication, obvious contraindications, or a consequence of "prescribing cascade")?
2. Does the drug lead to adverse effects or interactions that outweigh symptomatic effects or potential future benefits?
3. Are drugs taken for symptom relief but the symptoms are stable?

4. Is drug intended to prevent serious future events but the potential benefit is unlikely to be realised due to limited life expectancy?

If the answer to any of these questions is positive, then the medication should be considered for deprescribing.

No matter whether deprescribing comes under its own name, or not, it is the major aim of corrective polypharmacy addressing interventions. Perhaps, the most well-known and crucial part of this process is a drug review.

Indeed, various forms of drug reviews and identification of potentially inappropriate medications were the most often suggested procedures according to our literature review (see **Table 2**). Drug reviews might be stand-alone procedures. However, they might be also embedded in more complex programs, being the core item of e.g., Comprehensive Geriatric Assessment (Sergi et al., 2011; Eyigor and Kutsal, 2012; Sharma et al., 2016; Pazan and Wehling, 2017), pharmaceutical care (Patterson et al., 2012; Cooper et al., 2015; Tommelein et al., 2017), and collaborative physician—pharmacist medication therapy management (Lin et al., 2018).

Effective polypharmacy management with drugs reviews may require that several additional factors are taken into consideration, such as:

- Settings: hospital vs. outpatient, in the latter case: primary care vs. specialised care (e.g., outpatient geriatric clinic).
- A healthcare professional to perform drug review (e.g., a physician, pharmacist, nurse, other)
- The purpose and related scope of the drug review
- Criteria to guide drug review (implicit vs. explicit)
- A tool to base drug review on (comprehensive vs. limited in scope; validated vs. non-validated)
- A method used for drug review (manual vs. supported by a computerised clinical decision system)

Depending on their purpose, drug reviews may have a different scope. Therefore, current literature distinguishes three types of such reviews (Shaw and Seal, 2015; Clyne et al., 2008):

- Type 1—Prescription review, performed often without the patient, addressing technical issues relating to the prescription (e.g., duplications, possible drug-drug interactions etc.)
- Type 2—Concordance and compliance review, performed most often in the patient's presence, addressing issues relating to their medicine-taking behaviour
- Type 3—Clinical medication review, requiring the patient's presence, addressing issues relating to their use of medicines in the context of their clinical conditions

Drug reviews are advised to be undertaken by all physicians and particularly frequently by GPs (Kaufman, 2011). Pharmacists seem to be competent to carry out drug reviews as well. The medication review with follow-up (MRF) performed by pharmacists in community pharmacies provided a decreased number of prescribed medicines, reduction of emergency department visits and hospitalizations, improvement of quality of life of patients, and it also lowered the mean daily cost of prescribed medication (Jódar-Sánchez et al., 2015; Malet-Larrea et al., 2017). In Spanish study, the cost analysis showed that MRF saved the national health system € 97 per patient in 6 months. It was calculated that for every 1 euro invested in MRF a service returned a benefit of € 3.3 to € 6.2 (Malet-Larrea et al., 2017).

In practical terms, drug reviews are usually formalised, and driven by either implicit (judgement-based), or explicit criteria. Due to their usefulness, explicit criteria-based screening tools are used most often to help systematic assessment of drug safety and appropriateness. In publications covered by this review, the tools most often recommended for use in clinical practice were the ones based on such criteria, i.e., STOPP/START criteria, Beers Criteria and MAI index. A short overview of these three instruments is presented below.

Beers Criteria

In 1991, a geriatrician Mark H. Beers published criteria on potentially inappropriate use of medication in the older adults agreed by experts (Beers, 1997). After a few updates, the last version in 2019 (stewarded by the American Geriatrics Society) included not only evidence-based recommendations on drugs to be avoided, but also guidance on which medication should be used with caution, expected to cause significant drug-drug interactions or be reduced depending on the kidney function in seniors. (By the 2019 American Geri, 2019) These are the longest running explicit criteria for potentially inappropriate medication for older patients with five updates since the first publication. They are useful as a clinical, educational and public health tool developed to be used in conjunction with healthcare providers. However, the main disadvantage of Beers criteria is the fact that two large European studies have shown a lack of their association with adverse drug reactions (Onder et al., 2005; Laroche et al., 2007). Due to a large number of presented drugs, it is a challenge to create a simple checklist using these criteria. Also, additional software is required to take full advantage of its potential (Levy, 2017). It should be emphasized that being of American origin, Beers criteria may include or miss medications used or not in Europe (O'Mahony, 2019).

STOPP/START Criteria

Proposed for the first time in 2008 by an Irish geriatrician Denis O'Mahony and his colleagues, it is a list of potential prescribing omissions (underprescribed drugs) and potentially inappropriate medications for seniors. In its second version published in 2015, the list included revised criteria included in the first version divided into groups depending on the body systems approved by 19 experts from 13 European countries. (O'Mahony et al., 2015). Its definite advantage is the evidence for correlation with reduction of adverse drug events. (Hamilton et al., 2011). They are endorsed and used by several European societies including the National Institute for Clinical Excellence (NICE) and the United Kingdom Royal College of General Practitioners (O'Mahony, 2019). However, these criteria (currently planned for 5-year periods) (O'Mahony, 2019) need updating, and just

like other explicit criteria (e.g., Beers) they cannot evaluate drug therapy omission, adherence, life expectancy, issues related to comorbidities or patient preferences. Some studies show that they ignore a majority of drug-related problems in seniors (Verdoorn et al., 2015).

Medication Appropriateness Index

In 1992, a clinical pharmacist Joseph Hanlon and a geriatrician Kenneth Schmader proposed criteria in a form of ten questions enabling assessment of drugs taken by a patient. (Hanlon et al., 1992) By providing an answer to each question based on a three-point scale ("A" being appropriate, "B" being marginally appropriate, and "C" being inappropriate), appropriateness index can be calculated for each drug. A weighting system for each MAI question has also been developed. In order to obtain a total MAI score per person, the scores for individual drugs were summed up (Hanlon et al., 1992). This method was quite easy to perform; therefore, it was employed in multiple studies. It also considered drug-drug or drug-disease interactions. However, its main disadvantage was the time needed for answering the questions. It took 10 minutes per drug, which (Hanlon et al., 1992) made it impossible to use MAI in a busy outpatient clinic without application of computer software. Moreover, patient medication adherence was not included. The MAI score did not help the clinician to prioritize which drugs should be changed, neither did it provide assistance in how to modify drug regimens to avoid adverse drug withdrawal events that could occur in older adults. (Hanlon and Schmader, 2013).

Along with the validated reliable instruments, we have identified three studies based on the development and/or testing of new screening tools (Doan et al., 2013; Van der Linden et al., 2014; Tommelein et al., 2017). One of them was focused on development and validation of RASP checklist to systematically identify Potentially Inappropriate Medications (PIMs) in the older adults (Van der Linden et al., 2014). The second study used GheOP^{3}S tool for identification of potentially inappropriate prescribing (PIP) in community-dwelling older people on polypharmacy (Tommelein et al., 2017). The third one analysed CYP-mediated patients' drug-drug interactions (Doan et al., 2013). Detailed characteristics of these studies are provided in the **Supplementary Online Material S3**.

Implicit criteria-based approaches are usually employed by more complex strategies, such as comprehensive geriatric assessment (CGA). Typically, CGA includes a drug review, performed with the involvement of interdisciplinary team comprising nurses, occupational and physical therapists, social workers, general practitioners and geriatricians (Sergi et al., 2011). With the use of several evaluation tools exploring cognitive, clinical, nutritional, functional and social parameters, the team conducts a global assessment of an older adult with the primary aim of drug therapy optimisation and correction of medications used for untreated or under-treated conditions (Sergi et al., 2011).

It is noteworthy that some publications advised concurrent use of more than one screening tool. For example, one review (Planton and Edlund, 2010) suggested the use of both ARMOR (Assess, Review, Minimize, Optimize, Reassess) and Beers criteria, along with the recommendation to avoid drugs covering side effects of other drugs (i.e., the so-called "prescribing cascade"), whereas another one suggested the use of two explicit-based approaches, i.e., Beers and STOPP criteria (Levy, 2017).

Drug reviews can be further facilitated by implementing specific computerised decision support systems and mobile applications which most often use one or many validated screening tools, at first those based on explicit criteria. Such an approach proved to be an effective element of primary care and pharmaceutical care, leading to reductions in inappropriate prescribing (Patterson et al., 2012; Cooper et al., 2015). Multidimensional geriatric assessment could be also improved by dedicated IT solutions providing on-line access to information on patients, alerts indicating inappropriate drugs prescribed, assessment of the effects of accompanying diseases, reviewing potential drug-drug interactions, etc. (Eyigor and Kutsal, 2012).

Comprehensive Strategies

Our search revealed comprehensive strategies described in dedicated guidelines. One of these, focused on geriatric patients on multimedication (Bergert et al., 2014), was designed especially for GPs. They identified eight key steps as components of appropriate prescription process:

Step 1. Patient evaluation and collecting information
Step 2. Medication review
Step 3. Agreeing with patients on treatment objectives
Step 4. Prescription decision
Step 5. Communication and obtaining patient agreement
Step 6. Drug dispensing
Step 7. Medication usage
Step 8. Monitoring and assessment

As for medication review in Step 2, these guidelines suggest the use of several instruments, including MAI, STOPP/START and PRISCUS. It is noteworthy that, in Step 3, after agreeing overall objectives of the treatment with the patient, along with their expectations for a pharmaceutical treatment, a GP is supposed to prescribe a drug (Step 4), communicate this to the patient, and obtain their agreement (Step 5).

Being one of only very few well-organized polypharmacy management programs in Europe (Stewart et al., 2017a), the NHS Scotland Polypharmacy Guidance (Wilson et al., 2015) offers probably the most complete guidance to polypharmacy management, as evaluated by our search. This guidance accepts a patient-centred approach to ensuring safe and appropriate use of medicines in polypharmacy. Therefore, it advocates a drug review process that should be focused on the patient as a whole rather than a jigsaw of conditions. The updated third edition of the guidance, published in 2018, provides a holistic model of care based on a comprehensive approach to medication review and provides healthcare professionals with practical tips to improve prescribing in polypharmacy and make it less problematic (Scottish Government Polyp, 2018). This approach may be easily adopted to the need of polypharmacy management in the older adults (Wilson et al., 2015). It recommends that

TABLE 3 | An overview of key considerations of 7 Steps of NHS Scotland Polypharmacy Guidance, 3rd edition [from (Wilson et al., 2015), with modifications].

Domain	Steps	Process
Aims	1. Identify objectives of drug therapy	Review diagnoses and identify therapeutic objectives with respect to • Management of existing health problems • Prevention of future health problems
Need	2. Identify essential drug therapy	Identify essential drugs (not to be stopped without specialist advice) • Drugs that have essential replacement functions (e.g., thyroxine) • Drugs to prevent rapid symptomatic decline (e.g., drugs for Parkinson's disease, heart failure)
	3. Does the patient take unnecessary drug therapy	Identify and review the (continued) need for drugs • with temporary indications • with higher than usual maintenance doses • with limited benefit in general or the indication they are used for • with limited benefit in the patient under review
Effectiveness	4. Are therapeutic objectives being achieved?	Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives • to achieve symptom control • to achieve biochemical/clinical targets • to prevent disease progression/exacerbation
Safety	5. Does the patient have adverse drug reactions or is at risk of adverse drug reactions?	Identify patient safety risks by checking for • drug-disease interactions • drug-drug interactions • robustness of monitoring mechanisms for high-risk drugs and for high-risk drug-drug and drug-disease interactions • risk of accidental overdosing Identify adverse drug effects by checking for • specific symptoms/laboratory markers • cumulative adverse drug effects • drugs that may be used to treat ADRs caused by other drugs
Costeffectiveness	6. Is drug therapy costeffective?	Identify unnecessarily costly drug therapy by • Considering more cost-effective alternatives (but balance against effectiveness, safety, convenience)
Adherence/ Patientcenteredness	7. Is the patient willing and able to take drug therapy as intended?	Identify risks to patient non-adherence by considering • Is the medicine in a form that the patient can take? • Is the dosing schedule convenient? • Is the patient able to take medicines as intended? • Is the patient's pharmacist informed of changes to regimen? Ensure drug therapy changes are tailored to patient preferences by • Discuss with the patient/carer/or welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/carer/or welfare proxies what medicines have an effect of sufficient magnitude to consider continuation/discontinuation

clinicians step back from the usual process of chronic condition management to specifically consider the challenges of multimorbidity. They should realize that patients need a "multimorbidity focus" and initiate a process that enables patients to prioritize their own care needs.

In practical terms, the guidance is composed of seven steps to follow (see **Table 3**). It starts with establishing treatment objectives in cooperation with the patient (Step 1), and it is followed by identification of essential (Step 2) and unnecessary drugs (Step 3). Then, it is checked whether therapeutic objectives have been achieved (Step 4), which is followed by identification of potential or actual adverse drug reactions (Step 5). At the end of the process it is verified whether therapy costs can be minimized (Step 6) and checked if the patient is willing and able to receive drug therapy as planned (Step 7). This model provides a cohesive structure for a polypharmacy management process that is holistic, patient-centred and applicable to older adults across a range of health care settings. It should be emphasized that this model is not based on any specific explicit criteria-based tools. Instead, it uses its own set of potentially unnecessary drugs.

This approach is well-designed and based on strong evidence, however, it is also time—consuming. List of medications that should be considered by healthcare professionals following Steps from 2 to 7 includes almost 100 drugs, groups of drugs and scenarios. This might be a serious disadvantage, especially in primary care settings. Busy practitioners may not necessarily be able to manage that big load of data. To overcome this limitation, in Scotland, since 2013 pharmacists have been funded to work in general practice and support appropriate polypharmacy management (Mair et al., 2019). Recently, an application has also been made available for clinicians to help practical realization of this process, along with a toolkit for patients taking multiple medicines, as well as their carers to support self-management and shared decision-making during

consultation and medicine reviews (The Scottish Government Polypharmacy, 2018).

It is noteworthy that from the interventions described above, several ones were analysed and checked in order to confirm their effectiveness in clinical outcomes in randomized controlled trials, interventional or prospective studies. They included several interventions, e.g., assessment of appropriateness of polypharmacy (Komagamine and Hagane, 2017; Lin et al., 2018), drug reviews (Jódar-Sánchez et al., 2015; Malet-Larrea et al., 2017; McNicholl et al., 2017) or checklists improving quality of drug prescription (Urfer et al., 2016). A complex intervention to be used in a nursing home (covering a drug list review, identification of potentially inappropriate medications using the Beers criteria, potential drug-drug interactions and contraindicated medications using the Epocrates online drug-drug interaction program) has been assessed in a prospective study which demonstrated a decrease in potentially inappropriate medications, contraindicated drugs, and medication costs. (Kojima et al., 2014) Characteristics of the studies providing evidence of effectiveness for selected interventions that have been identified in our search are presented in the **Supplementary Online Material S4**.

DISCUSSION

Our review clearly shows that current scientific literature devotes a lot of attention to polypharmacy, not only in its general aspect, but particularly focusing on older adults. Consequently, various potentially useful approaches to polypharmacy management have been described, ranging from narrow-focused screening tools up to comprehensive programs and complex strategies. This large variety of solutions enables healthcare professionals to adopt polypharmacy-addressing interventions that suit their needs and preferences, taking into account specificity of the clinical scenario. On the other hand, it may lead to obvious confusion in less experienced medical staff who, in their busy daily practice, may not find enough time or motivation to learn and implement a new service which might be certainly time-consuming. Indeed, there is evidence that the uptake of available strategies is more than limited (Mc Namara et al., 2017).

Theoretically, the most effective polypharmacy strategy could be appropriate prescribing. If each and every drug initiated in a patient satisfied the criteria of appropriate prescribing, the multidrug therapies could be avoided, and the prevalence of polypharmacy would reduce. Unfortunately, the current fragmented architecture of the healthcare systems, and single disease-oriented clinical guidelines do not help practical implementation of this concept (Farmer et al., 2016). Instruments designed to promote appropriate prescribing are mostly based on implicit criteria and thus not easy to implement, particularly in the digital version.

A very interesting finding of our review was that current literature does not perceive the patients as those who take care of their therapies in terms of initiating activities aimed at reduction of inappropriate polypharmacy. Apart from the NHS Scotland Polypharmacy Guidance, which takes the patient's perspective into account along the whole cycle of polypharmacy management, most of other publications reserve a much less important role for the patient making them an object rather than a subject of relevant interventions. In the light of current limited use of available tools by healthcare professionals, this paradigm perhaps needs to be changed. Being provided with necessary knowledge, even an older adult may be an important ally for HCPs in adoption of polypharmacy management interventions.

In absence of patients' pressure to get involved in polypharmacy issues, healthcare professionals are expected to self-initiate relevant activities. Here again, available literature does not help much, not providing a clear message on when to consider such an activity, and how often to include it in routine care. Perhaps, the most frustrating problem is current lack of uniform definition of polypharmacy, which not only hinders implementation of available interventions, but also makes their benchmarking much more elusive (Masnoon et al., 2017).

The most common operational definitions of polypharmacy, applied in the reviewed publications, were based on the number of concurrently prescribed and/or used drugs, with five and more being the most frequent option. This, however, deserves a comment. Although polypharmacy has numerous negative consequences, in some cases is desirable. Perhaps, for every patient there is an optimal number of drugs to be used (e.g., for hypertension to be controlled according to certain recommended levels, often two or more medications are required). It results from a rational compromise between the benefits of providing evidence-based therapies for particular conditions, and the negative consequences of using too many drugs at the same time. Thus, "appropriate polypharmacy" or "optimal polypharmacy" should be distinguished from inappropriate one (Rankin et al., 2018). Unfortunately, this distinction is subject to case-by-case approach. Therefore, it may cause confusion, as it cannot be concluded with a simple uniform threshold that would be suitable for everyone, which dichotomizes the number of drugs used concurrently to be either acceptable or too high (Masnoon et al., 2017).

Our findings undoubtedly show that available interventions might be successfully implemented by a range of healthcare professionals, first of all GPs, pharmacists, and geriatricians. Some tools are dedicated or are most suitable for each out of these groups [e.g., recommendations for treating adult and geriatric patients on multimedication designed by and for GPs (Bergert et al., 2014)], whereas others are much more generic, and might be implemented across different settings [e.g. STOPP/START (O'Mahony et al., 2015)].

Our results show that various forms of drug reviews are particularly often used for polypharmacy management in the older adults. However, despite an obvious value of drug reviews, they are not necessarily employed routinely in clinical practice. On the contrary, in Europe, various forms of these reviews were reported in only 16 out of 32 studied countries (Bulajeva et al., 2014). Most often, medication reviews were reported to be carried out in hospital settings (14 countries), followed by 13 countries reporting implementation of such a procedure in community settings, and only six in nursing homes. In community settings, those were mostly reviews targeting prescription and verifications

of patients' medicine-taking behaviours (reported in nine and 11 countries, respectively), and much less often, medication reviews in the context of patients' clinical conditions (reported in six countries only). Another important question is which approach to choose to guide the drug review. A systematic review of tools to assess potentially inappropriate prescribing found that out of 46 different instruments identified, 39 did not have any validation in clinical settings (Kaufmann et al., 2014).

From a practical point of view, the core assumption on a strategy used for drug review is very important. According to the applied criteria, approaches may be divided into two different categories, i.e., those based on implicit and explicit criteria. Strategies based on implicit criteria involve highly individualized clinicians' assessments relying mostly on their experience. These strategies are designed usually as protocols, algorithms or concepts examples of which are ARMOR (Haque, 2009) or the Prescribing Optimization Method (Drenth-van Maanen et al., 2009). Implicit criteria are usually short and concise. However, since they depend on clinicians' knowledge and experience, they are highly subjective and thus, of limited applicability across patient populations, or in benchmarking (Levy, 2017). Last but not least, implementation of these strategies is very limited by the fact that they are extremely time-consuming. For example, comprehensive geriatric assessment has proved effective in reducing the number of prescriptions and daily drug doses (Sergi et al., 2011). On the other hand, it takes a lot of time, particularly when performed face-to-face with the patient (Martin-Khan et al., 2016). For all these reasons, this approach is not often used in clinical practice.

The other type of strategies aimed at reducing polypharmacy is based on explicit criteria. These are much easier to use, straightforward criteria which allow for objective elimination of inappropriate drugs, consisting mostly of lists of medications to be excluded from a patient's treatment regimen. Most well-known examples of such an approach illustrated by our review are Beers (By the 2019 American Geri, 2019) and STOPP/START criteria (O'Mahony et al., 2015). It is noteworthy that explicit criteria are those which can be particularly well embedded in computer decision support systems and relevant applications. Interestingly, our findings show that explicit STOPP/START and Beers criteria are the validated tools most often used in polypharmacy management in the older adults. However, even these criteria are not generally accepted as a "golden standard". On the contrary, they are criticized for not listing a relevant number of drug-related problems (Verdoorn et al., 2015) and a limited clinical value (Parekh et al., 2019). Some authors suggest that they should be used in a complementary fashion to improve detection of adverse drug reactions (Brown et al., 2016). Actually, some decision support systems use both these sets of criteria in parallel (Monteiro et al., 20192019). Moreover, practical use of these criteria might be difficult. A recent systematic review on identifying potentially inappropriate prescribing in older people with dementia found that out of 15 studies using the Beers criteria, as many as 13 did not use the full tool (Hukins et al., 2019). Due to the large number of potentially contraindicated medications listed (114 recommendations in the START/STOPP and 90 in the Beers), the use of these criteria is particularly limited in primary care (Croke, 2020).

Complex and time-consuming nature of polypharmacy management encourages the use of various decision-support systems. Indeed, a rising number of computer decision-support systems and dedicated applications is available to help clinicians manage polytherapy in real life conditions of busy practice (Eyigor and Kutsal, 2012; Patterson et al., 2012; Patterson et al., 2014; Cooper et al., 2015; Bokhof and Junius-Walker, 2016; Sinnige et al., 2016). Of course, such solutions possess some disadvantages also: they produce dozens of alerts, of which some are of low clinical usefulness, and therefore, subject to overriding (Knight et al., 2019).

Unfortunately, even the availability of such enablers does not guarantee frequent implementation of polypharmacy management mechanisms. A good illustration of the problem is the case of the German FORTA ("Fit fOR The Aged") guidelines. Originally released in Germany in 2008 as a tool for aiding physicians in screening for unnecessary, inappropriate or harmful medications and drug omissions in older patients in an everyday clinical setting (Wehling, 2009), it was validated in a clinical trial (Wehling et al., 2016), and turned into the application (Pazan and Wehling, 2017). However, a study conducted in 2018 in general practitioners in Baden-Württemberg, Germany revealed that out of 872 surveyed GPs, 39 knew the FORTA list, and 15 declared to use the FORTA App only (Meyer and Wehling, 2020).

This scoping review possesses several limitations. First of all, it was limited to English language publications, and thus, articles published in other languages were excluded. Moreover, among a number of approaches available for polypharmacy management, we were not able to prioritise one over the other, due to the lack of objective benchmarking criteria. Nevertheless, we believe that comprehensive review of available methods provided in this paper will help interested stakeholders make their own choices, and thus, meet the aim of this exercise.

CONCLUSION

This scoping review showed a variety of approaches being suggested for and/or employed for the management of polypharmacy in the older adults. These approaches vary in their replicability, complexity, and applicability. The most often recommended ones were various types of drug reviews, guided by either implicit or explicit criteria. Of these, implicit criteria based approaches are used infrequently due to their subjectivity, and limited practical implementability. To the contrary, most of the reviewed publications advocated the use of explicit criteria-based approaches. However, their practical applicability is somehow limited due to very long lists of potentially inappropriate medications covered. To overcome this, that sort of criteria are often embedded in clinical decision support systems.

Our results show that currently, no gold standard exists for polypharmacy management in older adults, and various approaches are used in parallel. Depending on the purpose of drug review, its settings, and available time, the users are free to

employ one of existing interventions and/or tools. For practical purposes, employing a drug review based on one of the available explicit criteria seem to be the best choice. Having in mind that in general, polypharmacy management in the older adults is underused, both individual stakeholders, as well as policymakers should strengthen their efforts to promote these activities more strongly.

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

Contribution of each author is equal regarding preparing the manuscript. BJ-P, PK, MK-M and PL performed the search of the literature.

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SUPPLEMENTARY MATERIAL

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Predictors of Polypharmacy Among Elderly Patients in China: The Role of Decision Involvement, Depression, and Taking Chinese Medicine Behavior

*Chaoyi Chen[1], Zhanchun Feng[1], Qian Fu[1], Jia Wang[2], Zehao Zheng[2], Hao Chen[3] and Da Feng[2]**

[1]School of Medicine and Health Management, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, [2]School of Pharmacy, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, [3]Second People's Hospital of Yichang City, Yichang, China

Introduction: The prevalence of polypharmacy is gradually increasing in geriatrics, which may contribute to adverse effects, such as potential drug–drug and drug–disease interactions. These side effects remain an important challenge in patient safety, which has a significant impact on mortality and incidence rate.

Aims: Therefore, this study aims to understand the epidemiology of polypharmacy and identify factors that have an impact on the management of potentially inappropriate prescribing.

Methods: This study is a cross-sectional study, analyzing the prescription data from 720 hospitalized patients aged 50+ with a random cluster sampling method. We used inverse probability treatment weighting (IPTW) method to group and match polypharmacy and non-polypharmacy patients, and logistic regression was conducted to explore the factors associated with polypharmacy.

Results: The prevalence of polypharmacy accounted for 50.14% among the old patients in this study. Female patients (67.34%) have more polypharmacy than male patients, and key predictors associated with polypharmacy in the logistic regression model included the following: domicile (AOR = 0.63, 95% CI 0.42–0.95), annual income (AOR = 0.38, 95% CI 0.20–0.70), the number of chronic diseases (AOR = 3.68, 95% CI 2.69–5.06), taking Chinese medicine (AOR = 1.70, 95% CI 1.22–2.36), decision involvement (AOR = 1.49 95% CI 1.10–2.03), and depression (AOR = 1.42, 95% CI 1.03–1.96).

Conclusion: Polypharmacy is common among the participants with chronic diseases in Hubei province, China. The study emphasizes that gerontology practitioners should be prudent in applying clinical guidelines to provide personalized, comprehensive assessment of decision making of prescriptions, especially in socioeconomically deprived areas.

Keywords: polypharmacy, multimorbidity, chronic diseae, multiple medication, older patient

Abbreviations: AVE, average variance extracted; CESD, Center for Epidemiological Studies-Depression Scale; CI, confidence interval; CNY, Chinese Yuan; OR, odds ratio.

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****Correspondence:***
Da Feng
fengda@hust.edu.cn

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INTRODUCTION

Multimorbidity, commonly defined as the coexistence of two or more chronic diseases in a single individual (Diederichs et al., 2011), has become a global concern following the health expectation increase among chronic disease patients. Some studies revealed that the prevalence of multimorbidity among the middle-aged and elderly people in China has ranged from 57.0 to 74.0% (Shuaishuai et al., 2021), which is higher than 59.4% in Canada (ranged from 16.9 to 59.4%) and 36.6% in European countries (Nguyen and Jeannie, 2019; Laires et al., 2020). In particular, among the older patients with multimorbidity, multiple medication regimens under the treatment of concurrent chronic diseases also increased the polypharmacy risks (Hajjar et al., 2007; Nguyen and Jeannie, 2019).

Polypharmacy is generally defined as the concurrent use of five or more medications (Lee et al., 2020). It has been widely reported that for the elderly patients there exists big health risk caused by polypharmacy (Cadogan et al., 2016). For example, due to the frail elderly patient's declined renal and hepatic function with long-term use of multiple medicines, they cannot be metabolized in their body, which may cause further damage to their organs (Venturini et al., 2011; Masnoon et al., 2017; Wastesson et al., 2018). Polypharmacy was linked to adverse events and poor health outcomes including falls, adverse drug effects, even increasing the rate of hospital admission, and mortality (Scott et al., 2015; Masnoon et al., 2017; Wastesson et al., 2018).

Seriously, patient safety is one of the most crucial targets of the health system, which is essential to achieve Universal Health Coverage (UHC) (Organization, 2019). However, polypharmacy is a typical and widespread public health problem among the older population in China (Lai et al., 2018). Therefore, well-understood epidemic characteristics of polypharmacy and identifying the impact factors of how physicians and elder patients manage their potentially inappropriate prescription behaviors were necessary. Recently, many pieces of evidence confirmed that polypharmacy is associated with basic demographic characteristics, comorbidity, multiple specialist diagnosis, and patients' self-medication knowledge and driven by a lower level of shared decision-making behaviors (Halli-Tierney et al., 2019; Khezrian et al., 2020; Liau et al., 2021), but the fields of polypharmacy and its relationship with taking Chinese medicine behavior and depression symptoms require in-depth research.

To address this gap, we conducted this study by the inverse probability treatment weighting method, which could be used to reflect the polypharmacy status and update insights on the prevalence of multiple medications in China, and then explored the factors influencing patients' polypharmacy. Meanwhile, the evidenced strategies could be provided to improve the elderly patients' rational drug use and their health outcomes.

METHODS

Participants and Procedure

This study was conducted from March to May 2021. We first selected eight administrative regions (including Jianghan District, Jiang'an District, Qiaokou District, Hongshan District, Wuchang District, Hanyang District, Caidian District, and Jiangxia District) from 13 administrative regions in Wuhan, Hubei province, China, and then randomly selected from the administrative regions in eight tertiary hospitals. Patients (≥age 18) having at least one chronic disease (such as hypertension, heart disease, and diabetes) and routine daily medication for 3 months or more were recruited to participate in the survey. Potential participants were invited by trained investigators. Before beginning the investigation, each patient needs to fill in an informed consent or orally agree to participate in the survey.

MEASURES

Dependent Variable

We assessed polypharmacy medication by using this single question: how many kinds of drugs have you taken to treat your chronic diseases in the last 3 months? According to previous studies consider taking of 5 or more drugs at the same time to be multi-drugs (Charlesworth et al., 2015; Onder et al., 2005). This study regards taking five or more drugs simultaneously as polypharmacy. In our study, we divided this behavior into two categories: taking 0–4 drugs is regarded as non-polypharmacy, while taking five or more drugs is interpreted as polypharmacy.

Instrument Development

To explore the factors that influenced the patients' polypharmacy and their participation in the medication decision-making process, we designed a self-developed survey tool, which included four parts: the basic demographic information (age, domicile, gender, and income), treatment decision involvement of patients, risk perception, self-care-related health information, and emotional status.

Response Variables

1) Decision involvement. The shared decision-making tool (SDM-Q-9) (Kriston et al., 2010) mainly includes three dimensions (nine measurement items): 1) information exchanges (the doctor communicated with me about the medication regimen; the doctor talked with me about which medication treatment is more appropriate; I had plenty of time to communicate with the doctor); 2) participation (in the selection of medication, the doctor ever asked my advice; I asked the doctor about the pros and cons; the doctor encouraged me to participate in the choice of the medication regimen); 3) reaching an agreement (I weighed the pros and cons of different medication regimens

TABLE 1 | Reliability and validity of the survey instrument.

Variables	Cronbach's alpha	Composite reliability	Average variance extracted
Decision involvement	0.876	0.904	0.613
CES-D10	0.750	0.818	0.517
Risk perception	0.785	0.786	0.453

with professionals finally; I made the final medication treatment decision together with the doctor; I agreed with the doctor on which medication regimen to use). Responses are provided with a 5-item Likert scale, from 1 (completely disagree) to 5 (completely agree), and the total score is 45. This section was divided into two grades: 1) the total score is ≥29 (average score), regarded as high decision involvement; 2) the total score is less than the average score, which is perceived to be at a low level. In addition, the Cronbach's alpha coefficient was 0.876, which means that it has high reliability. To assess the instrument's validity, average variance extracted validity (AVE) is used (**Table 1**). Its value is 0.613, which is greater than 0.5, indicating that the SDM tool has good validity (Yang and Zhang, 2014).

2) Depression scale. This dimension was measured by the 10-item Center for Epidemiological Studies-Depression Scale (CES-D10) (Verger et al., 2009). The answers for CES-D10 are on a four-scale metrics coding from 0 to 3 (0 = less than 1 day; 1 = 1, 2 days; 2 = 3, 4 days; 3 = 5–7 days). The total score of the scale ranged from 0 to 30, with the higher score indicating more depressive symptoms, and CES-D10 has been used in previous studies and it showed good internal reliability and validity (Andresen et al., 1994).
3) Risk perception. It comprises 10 items for evaluating the individual's perspective of economic burden risk, psychology risk, health risk, and time risk with a 5-item Likert scale from 1 (totally disagree) to 5 (totally agree) during medication. The standardized Cronbach's α coefficient was 0.785, and AVE was 0.453 (**Table 1**).
4) Health related items. They include the number of chronic diseases, whether taking traditional Chinese medicine or not, and have you ever had any adverse drug reactions during the medication?

Statistical Analysis

Descriptive statistics were reported as frequency and percentage. The patients with chronic diseases of polypharmacy were regarded as the treatment group, and the patients of non-polypharmacy were regarded as the control group. χ^2 tests were used to examine the factors associated with polypharmacy. For retaining the sample complete information and controlling the bias of the estimation results caused by the selection bias and endogenous problems, we used an inverse probability treatment weighting (IPTW) method to group and match dependent variables, and then a balance weighted test of covariates was conducted by verifying the matching effect, and propensity value weighted regression analysis was carried out to further predict the impact of the vital factors and pathway on the polypharmacy of the elderly patients. In this study, p-values of <0.05 were considered to be statistically significant. Statistical analyses and plot forest were performed by R3.6.0 software and Graph-Pad Prism 9.0.

TABLE 2 | Descriptive characteristics of the study population.

Characteristics	Respondents (N = 720)	Proportion (%)
Gender		
Male	303	42.08
Female	417	57.92
Age		
<60	184	25.55
60–70	284	39.45
>70	252	35.00
Education		
Junior high school and below	417	57.92
High school	188	26.11
College and above	115	15.97
Domicile		
City	556	77.30
Rural	164	22.70
Living status		
Alone	179	24.86
Not alone	541	75.14
Annual individual income		
<16,400 Yuan	80	11.11
16,400–28,399 Yuan	63	8.70
28,400–37,599 Yuan	117	16.25
≥37,600 Yuan	460	63.94
Medical insurance		
Purchased	522	72.50
None	198	27.50

RESULTS

Characteristics of the Study Population

A total of 720 respondents participated in this study, and 536 people were ≥60 years old, accounting for 74.45%. In the sample, the average age was 73.56 years (ranging from 50 to 101 years), 42.08% (n = 303) were male, 77.30% resided in urban cities, 179 people were reported to live alone, 57.92% (n = 417) have obtained junior high school and below degrees, 63.94% reported annual individual income ≥37,600 Chinese Yuan (CNY), and 72.50% had urban medical insurance (**Table 2**).

Polypharmacy Among the Elderly Patients

Overall, the results show that 361 people took five or more drugs (polypharmacy), accounting for 50.14%, and 359 have been identified as non-polypharmacy. This study found a significantly higher percentage of polypharmacy among the older adults who were suffering from three or more chronic diseases (69.53%); in

TABLE 3 | Characteristics of polypharmacy and non-polypharmacy among the participants.

Characteristic	Polypharmacy		Non-polypharmacy		
	Frequency	Percentage (%)	Frequency	Percentage (%)	*p*
Age (years)					0.638
<60	87	24.10	97	27.02	
60–70	147	40.72	137	38.16	
>70	127	35.18	125	34.82	
Domicile					0.029
Urban	292	80.89	264	73.54	
Rural	69	19.11	95	26.46	
Gender					0.753
Male	154	42.66	148	41.23	
Female	207	57.34	211	58.77	
Level of education					
Junior high school and below	201	55.68	215	59.89	0.435
High school	102	28.25	87	24.23	
College and above	58	16.07	57	15.88	
Annual Individual income/Yuan					
<16,400 Yuan	42	11.63	38	10.58	
16,400–28399Yuan	31	8.59	32	8.91	
28,400–37,599 Yuan	42	11.63	75	20.89	0.008
≥37,600 Yuan	246	68.14	214	59.61	
Medical insurance for urban residents					0.838
None	101	27.98	97	27.02	
Have	260	72.02	262	72.98	
Living status					0.131
No	80	22.16	98	27.30	
Yes	281	77.84	261	72.70	
Number of diseases					0.013
0–2	110	30.47	215	59.89	
>3	251	69.53	144	40.11	
Medical institution visited					
Primary medical institution	21	5.82	24	6.69	0.171
Non-primary medical institution	298	82.55	277	77.16	
Uncertain medical institution	42	11.63	58	16.16	
Risk perception					0.944
High	191	52.91	188	52.37	
Low	170	47.09	171	47.63	
Depression					0.001
High	198	54.85	150	41.78	
Low	163	45.15	209	58.22	
Adverse drug reaction					0.361
No	74	20.50	63	17.55	
Yes	287	79.50	296	82.45	
Decision involvement					0.020
High	180	49.87	148	41.23	
Low	181	50.13	211	58.77	
Taking Chinese medicine					0.000
No	172	47.65	239	66.57	
Yes	189	52.35	120	33.43	

addition, female patients (N = 207, 57.34%) have more multiple medications than male patients (N = 154, 42.66%), and urban residents (N = 292, 80.89%) had a higher prevalence of polypharmacy. Furthermore, the individuals who took Chinese medicine (52.35%) recently and who showed higher levels of depression (54.85%) tend to take multiple medications (**Table 3**).

Logistic Regression Analysis Results Before Propensity Score Weight Matching

The adjusted OR (AOR) and 95% CI from binary logistic regression analysis (before matching) are displayed in **Figure 1**. The results showed that respondents who have more than two chronic diseases (OR = 3.18, 95% CI = 2.66–3.70) and rural households (OR = 0.61, 95% CI = 0.18–0.84) are less prone to polypharmacy than the urban. Patients who take traditional Chinese medicine (OR = 1.65, 95% CI = 1.32–1.98) are more likely to exhibit polypharmacy than those who do not take. In addition, patients with the annual income in the second interval of 28,400–37,600 Yuan (OR = 0.39, 95% CI = 0.26–0.75) had a significant association with polypharmacy. Patients with severe depression (OR = 1.64, 95%CI = 1.30–1.97) are more likely to have multiple medications.

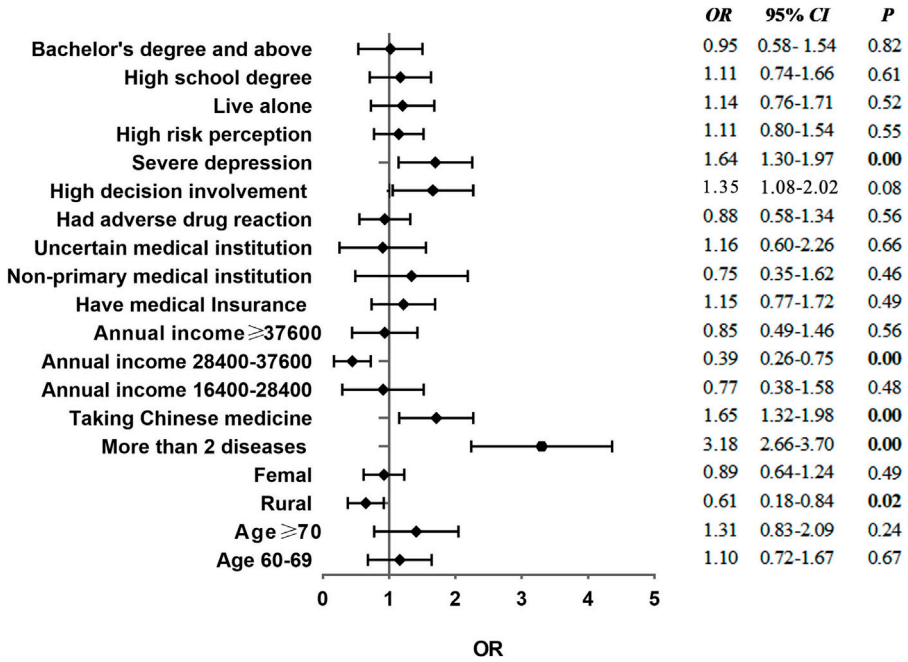

FIGURE 1 | Forest plot of logistic regression analysis results of polypharmacy before matching.

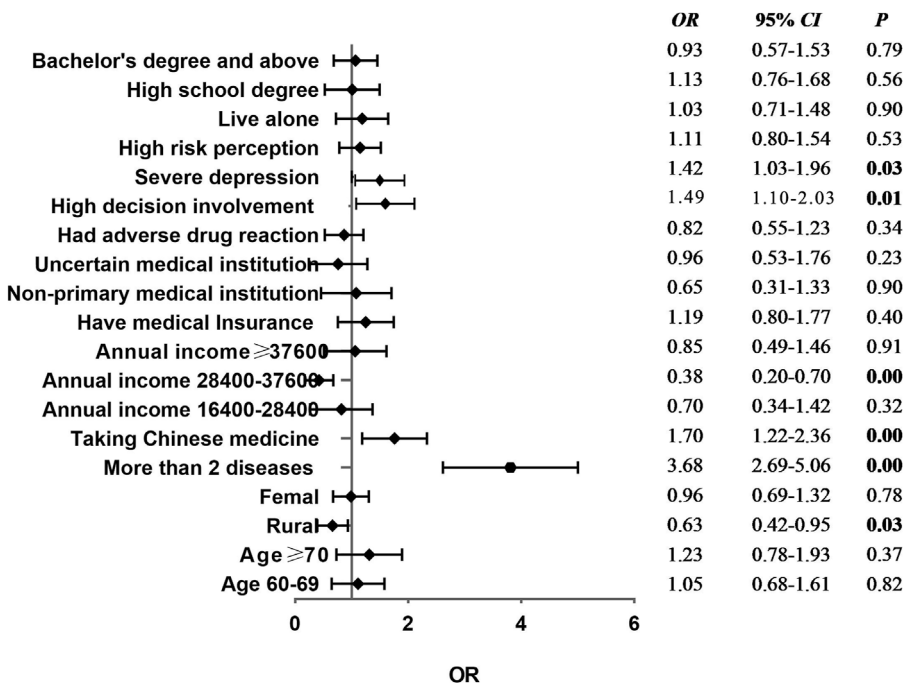

FIGURE 2 | Forest plot of logistic regression analysis results of polypharmacy after matching.

Logistic Regression Analysis Results After Propensity Score Weight Matching

By using the propensity score weighted (PSW) matching method for adjusted effect evaluation in the logistic regression analysis results of polypharmacy, it was found that the regression coefficient of the model increased from 0.46 to 0.63, which indicated that the predictive effect of the pair was enhanced. **Figure 2** shows that adjusted OR results and relationship between decision-making involvement, the type of domicile, whether to take traditional Chinese medicine, annual income, depression degree, and the number of diseases were remaining statistically significant ($p < 0.05$), compared with the unmatched results. After verification and analysis, it indicated this empirical model has a certain degree of robustness.

DISCUSSION

This study was performed to describe the prevalence of polypharmacy among the elderly patients in China. We found that the rate of polypharmacy was high as nearly 50.14% elder patients with chronic diseases were prescribed five or more medications. Similar rates (44.90–83.50%) were reported in the previous literature (Chan et al., 2009; Kim et al., 2014). As expected, the likelihood of polypharmacy was correlated with main factors: the type of domicile, annual individual income, the number of chronic diseases, taking Chinese medicine behavior, depression symptoms, and decision involvement.

In the cohort of patients who were reported to live in rural areas (AOR = 0.63, 95% CI 0.42–0.95), there was weakening of the association with polypharmacy. It is likely that they have poor access and availability of various chronic medicines in the region they live. As community-level medical institutions can only provide essential medicines in the township (Rixiang et al., 2018; Yuanzheng, 2018), to some degree, the range of medicines supplied by primary medical institutions was limited. It can discount excessive medicine usage. In addition, compared with urban residents, the rural have a lower household income, which cannot afford redundant medical and health expenditure; as a result, they rely on several common medications (nifedipine, simvastatin, and metformin) for general therapy of hypertension and diabetes. Therefore, the probability of combination of other medications in this group is relatively small.

Compared with the low-income group, the middle-income group (28,400–37,600 Yuan) was more inclined to go to primary-level medical institutions for medical treatment (Hongme et al., 2020). The physicians of the community health service institute as the "public health gatekeeper" only undertake the function of diagnosis and treat symptoms, but if a large number of drugs are prescribed to the patients in the local area, it cannot be accepted by the local residents. Conversely, high-income groups are more willing to use health services in municipal/provincial general hospitals with higher convenience and accessibility. In this clinical scenario, they could approach more medicines from multiple prescribers, which increase the risk of multiple medication use. Furthermore, it leads to a prolonged hospital stay in which the "prescribing cascades" are identified and corrected (Schenker et al., 2019).

The proportion of elderly patients taking traditional Chinese medicine was high, and a previous study highlighted the potentially high impact of traditional Chinese medicine on polypharmacy in Chinese populations (Chan et al., 2015). This is in line with our study; the participants who tend to take traditional Chinese medicine were more likely to take multiple medications (Lai et al., 2018). One explanation was based on the construal level theory (McCrea et al., 2012; Lermer et al., 2016); the lower-level construal group indicated that the elderly people with health problems mainly focus on immediate goals and not the long-term health needs. Under these circumstances, obtaining traditional Chinese medicine will become a process to fill the psychological gap. It simply proposes that the psychological distance of medication behavior decision making is acceptable compared with physical examination and hospitalization. Besides, according to previous interviews with the respondents in this survey, we noticed that for the people who tend to take Chinese medicine, it may be due to their low medical knowledge literacy and insufficient information about adverse outcomes and harm of various medicines, and they mistakenly believe that the direct way to control the disease is to take different kinds of medicines to treat the disease, which result in polypharmacy correspondingly.

We found that polypharmacy is mostly a consequence of multiple chronic diseases; this is consistent with studies from Mina Khezrian and Yuxin Liu, and coexistence of multiple chronic diseases is prevalent in frail people, resulting in a decline in the cognitive status and increased probability of taking multiple medications (Khezrian et al., 2020; Zhang et al., 2020; Liu et al., 2021). Another explanation is that the physicians need to make complicated and long-term therapy to achieve the desired health outcomes for individual patients (Ellis et al., 2020). Thereby, more medication regimens were used in treatment, which would also cause prescribing cascades (Alwhaibi et al., 2018). Furthermore, the residents of the survey area have a low level of health information literacy (Shilong et al., 2015); they could ignore and underestimate the potential health risks of polypharmacy.

Noteworthy surveys have proved that depression was a significant independent predictive factor for polypharmacy in elderly (Marengoni et al., 2011; Yavuzer et al., 2017), and we also found that people who were reported to have high depression symptoms were more likely to exhibit polypharmacy. Psychological problems would increase the general susceptibility of having functional disability or cognitive impairment (Burnier et al., 2020). In addition, it distressed patients' adherence to drug therapy, which caused polypharmacy for reducing their self-concerns about health problems. In the absence of practice guidelines and external medication supervision, taking a large number of medications was regarded as the psychological protection of chronic physical disorders (Smith et al., 2014). Therefore, severe depression may contribute to excessive polypharmacy.

Patients who tend to make joint decisions between physicians and patients are less likely to take multiple medications; increasing clinical evidence indicates that patients' involvement

in medical decision making improves health care outcomes (Alden et al., 2014). In short, if a patient has been fully involved in the decision as an equal collaborator, they can understand the critical issues and share information provided by physicians and make a rational treatment choice (Rostoft et al., 2020). Before finalizing the medication regimen, clinicians should balance the benefits and risks with polypharmacy (Zhang et al., 2020). Indeed, appropriate communication of medicine regimens contributes to preventing polypharmacy and negative health outcomes among frail patients (Kutner et al., 2015; Wastesson et al., 2018; Ozavci et al., 2020).

CONCLUSION

Polypharmacy is common among the participants with chronic diseases in Hubei province, China. Given that several factors influencing multi-medication use were identified in this study, we suggest that health care professionals should broaden the knowledge of rational medication and improve the residents' medication literacy. Besides, in clinical practice, physicians should be prudent in applying clinical guidelines and encourage patients to participate in decision making of prescriptions and reduce patients' internal psychological burden. In the community, family doctors' monitoring and assessment of patients' use of medication have a significant impact on appropriate adherence to their prescribed drug regime.

Limitations

Our study has several limitations. Various definitions of polypharmacy existed in the literature, and we only considered the number of drugs used, namely, ≥5 drugs as polypharmacy, so it is difficult to make a distinction between the necessary prescribing and polypharmacy medication. Second, we used the CES-D10 scale in this study, which could only screen for the presence of depressive symptoms or negative emotion. A complete diagnostic assessment of clinical depression would be conducted in the future. Third, we did not put the medication duration and medication adherence factors into our design section for providing a valuable tool, and we will continue to improve the questionnaire in subsequent research.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restriction: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to fengda@hust.edu.cn.

ETHICS STATEMENT

This 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). All participants gave written informed consent to participate in this study. All methods were carried out in accordance with our college's guidelines and regulations.

AUTHOR CONTRIBUTIONS

DF, JW, and ZF contributed to conceptualization and methodology; CC and JW contributed to analysis and interpretation of data; then, CC wrote the original draft; ZZ contributed to data collection; and QF contributed to raising many useful amendments of this article. All the authors contributed to implementation and revision of the manuscript.

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Cost-Related Medication Nonadherence (CRN) on Healthcare Utilization and Patient-Reported Outcomes: Considerations in Managing Medicare Beneficiaries on Antidepressants

Abdulrahman A. Alnijadi[1,2†], Jing Yuan[3†], Jun Wu[4], Minghui Li[5] and Z. Kevin Lu[1]**

[1]Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina, Columbia, SC, United States, [2]Department of Pharmacy Practice, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, Saudi Arabia, [3]Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy, Fudan University, Shanghai, China, [4]Department of Pharmaceutical and Administrative Sciences, Presbyterian College, Clinton, SC, United States, [5]Department of Clinical Pharmacy and Translational Science, University of Tennessee Health Science Center, Memphis, TN, United States

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James Zhang,
University of Chicago, United States

***Correspondence:**
Minghui Li
mli54@uthsc.edu
Z. Kevin Lu
lu32@email.sc.edu

†These authors have contributed equally to this work

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Background: Many patients face a financial burden due to their medications, which may lead to poor health outcomes. The behaviors of non-adherence due to financial difficulties, known as cost-related medication non-adherence (CRN), include taking smaller doses of drugs, skipping doses to make prescriptions last longer, or delaying prescriptions. To date, the prevalence of CRN remains unknown, and there are few studies about the association of CRN on self-reported healthcare utilization (Emergency room (ER) visits and outpatient visits) and self-reported health outcomes (health status and disability status) among older adults taking antidepressants.

Objectives: The objectives were to 1) examine the CRN prevalence, and 2) determine the association of CRN on self-reported healthcare utilization and self-reported health outcomes.

Methods: This study was a cross-sectional study of a sample of older adults from the Medicare Current Beneficiary Survey (MCBS) who reported having used antidepressants in 2017. Four logistic regressions were implemented to evaluate the association of CRN, and self-reported healthcare utilization and self-reported health outcomes.

Results: The study identified 602 participants who were Medicare beneficiaries on antidepressants. The prevalence of CRN among antidepressant users was (16.61%). After controlling for covariates, CRN was associated with poorer self-reported outcomes but not statistically significant: general health status [odds ratio (OR): 0.67; 95% confidence interval (CI): 0.39–1.16] and disability status (OR: 1.34; 95% CI: 0.83–2.14). In addition, CRN was associated with increased outpatient visits (OR: 1.89; 95% CI: 1.19–3.02), but not associated with ER visits (OR: 1.10; 95% CI: 0.69–1.76).

Conclusion: For Medicare beneficiaries on antidepressants, CRN prevalence was high and contributed to more outpatient visits. The healthcare provider needs to define the reasoning for CRN and provide solutions to reduce the financial burden on the affected patient. Also, health care providers need to consider the factors that may enhance patient health status and healthcare efficiency.

Keywords: cost-related medication nonadherence, healthcare utilization, patient reported outcomes, older adults, medicare beneficiaries, antidepressants

1 BACKGROUND

Antidepressant drugs aim to relieve the symptoms of depression and are also used for many conditions of mental well-being and long-term pain management (NHS Choices, 2021). Antidepressants act by resolving neurotransmitter's chemical imbalance in the brain (Andrade and Rao, 2010). The chemical imbalances in the brain contribute to changes in the patient's behavior and mood (Harvard Health, 2019). Examples of these neurotransmitters are serotonin, dopamine and noradrenaline, and norepinephrine (Khushboo and Sharma, 2017). There are many antidepressant drug classes available to help with the chemical imbalance in the brain. The most commonly prescribed classes are Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and Atypical Antidepressants (Antidepressants, 2021; Ogbru, 2021). Approximately 20% of older adults use antidepressants in a month, according to the National Center for Health Statistics (NCHS) (Products Data Briefs Number, 2020).

Older adults are prone to financial burden and increased health care expenditures linked to polypharmacy and comorbidities (Nobili et al., 2011). Psychiatric drugs are among the most expensive drugs (Bartels, 2003). Medications are priced differently based on whether they are generic, brand-name, or mail-order, and they are divided into five tiers (Behring, 2020). When a drug is placed in a higher tier, the patient will pay a higher copayment or coinsurance (Medicare, 2021). The difference in prices will be applicable for all medications, including antidepressant prescriptions. Many patients face a serious financial burden due to medications, contributing to medication non-adherence to save money. In addition, there is significant data on how Medicare Part D and the coverage gap impact utilization and out-of-pocket expenditures (Park and Martin, 2016).

Antidepressants are the third among prescription drugs and the fourth most commonly sold drug in the United States, with up to 10% of adults taking at least one prescription (Pratt et al., 2011; Davey and Chanen, 2016). It is critical to determine the extent of non-adherence with these drugs. Non-adherence happens when patients skip 20% or higher of the antidepressant drug (ten Doesschate et al., 2009). It is believed that comorbid conditions, patient characteristics, patient behaviors, and patient education can be significant factors that may influence medication adherence (Pampallona et al., 2002; Prukkanone et al., 2010). Non-adherence with medication may pose a higher risk to older adults, resulting in poorer outcomes compared to younger populations (Hughes, 2004; Banning, 2008). For antidepressant drugs, there is a clear association between non-adherence and deterioration of patient clinical and economic outcomes (Ho et al., 2016). In addition, medication non-adherence may lead to health complications that result in an economic strain on the health care system, and it is more problematic, particularly for patients with chronic disorders such as psychiatric illnesses like depression (Dunbar-Jacob and Mortimer-Stephens, 2001; Weiden et al., 2004).

Non-adherence behavior caused by financial challenges is referred to as cost-related medication non-adherence (CRN) (Lee et al., 2018). The Medicare Part D introduced in 2006 was fairly successful in lowering CRN levels. Nevertheless, CRN was not completely solved, and CRN was reported among Medicare beneficiaries in subsequent years (Madden, 2008; Kennedy et al., 2011). Cost is the major cause of non-adherence for those taking antidepressants (Piette et al., 2004). Even though numerous policies (for example, Part D) have been implemented to reduce CRN, the CRN of the older adults using antidepressants remains unclear. Also, we have limited knowledge of how CRN influences individuals with varying socioeconomic factors. Acknowledging the contributing factors associated with CRN among Medicare beneficiaries on antidepressants will assist stakeholders and health care providers in order to assess CRN rates in older adults. The assessment will allow for better CRN management to overcome this issue. In addition, consider the factors that may enhance patient health status and healthcare efficiency. Therefore, the objectives of this study were to 1) examine the CRN prevalence, and 2) determine the association of CRN on healthcare utilization and self-reported health outcomes.

2 METHODS

2.1 Data Source

We used the data from the Medicare Current Beneficiaries Survey (MCBS) in 2017. The MCBS is a longitudinal rotating panel survey funded by the Centers for Medicare and Medicaid Services (CMS). Medicare beneficiaries were surveyed for twelve rounds, three data collection periods per year, and followed up to 4 years. The MCBS data is ideal for this analysis, as it covers almost all applications in healthcare for eligible patients in all areas of healthcare services. In particular, the MCBS provides information on health status, access to healthcare, insurance coverage, out-of-pocket expenses, financial resources, and

socio-economic and demographic characteristics of the entire beneficiary of Medicare (MCBS Methodology Report, 2016).

2.2 Study Population

The survey respondents were included in the study if they were 65 years or older and used antidepressants based on Medicare Part D claims. Participants were excluded from the study if they were eligible for Medicare due to End-Stage Renal Disease (ESRD) or if they were enrolled in Health Maintenance Organization (HMO) plans.

The cost of healthcare for individuals with impairments such as ESRD is more than twice as expensive as those with temporary or no disabilities (Pumkam et al., 2013). Individuals with ESRD will be sicker than included participants, which may result in a higher financial burden and more hospital visits. Excluding these people prevents extreme or outlier observations from influencing the regression result. HMO members had no data from claims on various health problems in the MCBS survey data (Raghunathan et al., 2020). Thus, they must be excluded from the study.

2.3 Measurements

2.3.1 Dependent Variables

Self-reported health outcomes were related to the quality-of-life metrics reported in the MCBS, including health status (Excellent, Very good, Good, Fair and Poor) and disability status (No disability, One disability, Two or more disabilities) (Medicare Current Beneficiary Survey, 2017). We used binary outcomes for health status (Great health status and Poor health status) and disability status (No disability and one or more disability). In MCBS, we have included four related disability indicators: any difficulties with concentration/remembering/deciding, walking/climbing stairs, dressing/bathing, and difficulties in doing errands (Medicare Current Beneficiary Survey, 2017). Self-reported healthcare utilizations were defined as ER and hospital outpatient visits (Yes or No), as reported through the MCBS survey.

2.3.2 Independent Variables

CRN was calculated based on Yes or No responses to any of these four survey questions: taking smaller doses of drugs, skipping doses to make medications last longer, delaying prescriptions because of cost, and not getting prescriptions because they cost too much (Pierre-Jacques et al., 2008; Zivin et al., 2009). Survey participants' characteristics, including gender, age, race/ethnicity, marital status, census region, residence, income, and education. We also calculated the Charlson comorbidity index (CCI) for the number of comorbidities.

2.4 Statistical Analysis

We conducted four models of logistic regression, two models for the association of CRN on self-reported healthcare utilization and two models for the association of CRN on self-reported health outcomes. For all four models, the covariates were the same (demographics, socioeconomic status, and health status). The key independent variable was the same for both objectives: CRN. The key dependent variables were different depending on the objectives, including whether health outcomes (health status and disability status) or patient healthcare utilization (ER visits and outpatient visits) were used.

All the data analyses were carried out by using version 9.4 of Statistical Analysis Systems (SAS) Software.

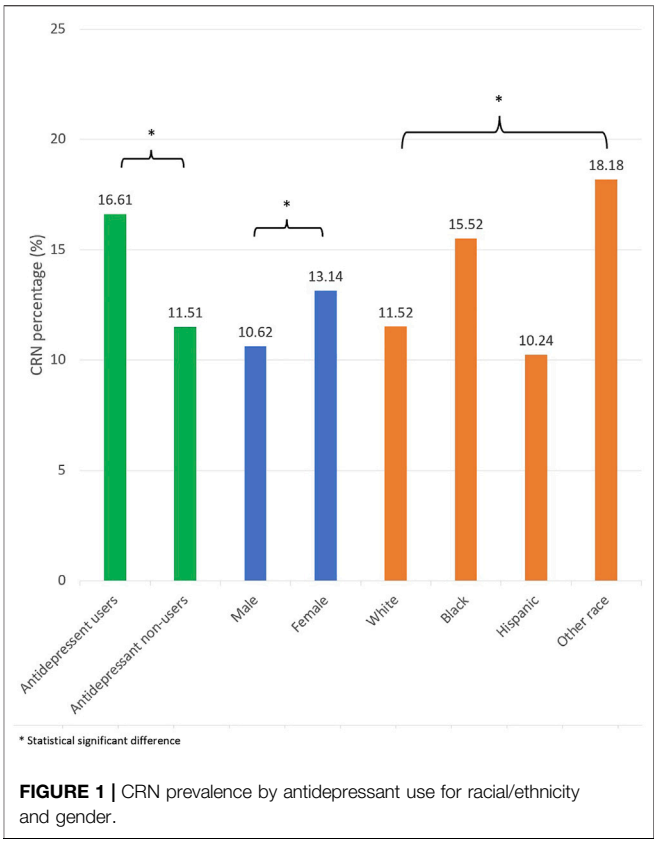

FIGURE 1 | CRN prevalence by antidepressant use for racial/ethnicity and gender.

3 RESULTS

The study identified 602 participants who were Medicare beneficiaries on antidepressants. For the CRN prevalence by antidepressant use, there were 16.61% of participants reported CRN. Females reported CRN more than males (13.14 vs. 10.62%). For the prevalence by racial/ethnicity, 15.52% were African American, 11.52% were White, 10.24% were Hispanic, and 18.18% other races (**Figure 1**).

Table 1 described the characteristics of the study sample. For the self-reported health outcomes, 78.24% of participants reported superior general health status, and 50.66% reported no disability. For patient healthcare utilization, 43.19% of participants visited outpatient and 41.53% visited ER. For the demographic characteristic, 45.18% of the participants were age between 75 and 84 years old; 73.42% were female; 89.04% were White; 6.48% were African American; 2.99% were Hispanic; 41.69% were single; 40.70% of participants lived in the South; 74.92% were in metropolitan residence. Regarding socioeconomic status, 66.95% were income higher than $20,000 US dollars; 44.35% attended some college or possessed a degree. For the health status characteristics, 43.52% of

TABLE 1 | Baseline characteristic of the study sample.

Characteristics	Antidepressant users (*n* = 602)	
	n	%
CRN		
Yes	100	16.61
No	502	83.39
General health status		
Great health status	471	78.24
Poor health status	131	21.76
Disability status		
No	305	50.66
one or more	297	49.34
Outpatient visit		
Yes	260	43.19
No	342	56.81
ER visit		
Yes	250	41.53
No	352	58.47
Age group		
65–74	222	36.88
75–84	272	45.18
85+	108	17.94
Gender		
Female	442	73.42
Male	160	26.58
Race/ethnicity		
Non-Hispanic White	536	89.04
Non-Hispanic Black	39	6.48
Hispanic	18	2.99
Others	—	—
Education		
Less than high school	199	33.06
High school graduate	136	22.59
Some college degree	93	15.45
College graduate	174	28.90
Marital status		
Single	251	41.69
Married	124	21.10
Widowed	224	37.21
Family income per year (US$)		
<10,000 per year	54	8.97
10,001–20,000 per year	145	24.09
20,001–40,000 per year	173	28.74
≥40,001 per year	230	38.21
Census region		
Northeast	102	16.94
Midwest	148	24.58
South	245	40.70
West	107	17.77
Residence		
Non-metropolitan	151	25.08
Metropolitan	451	74.92
CCI		
0	89	14.78
1	61	10.13
2+	201	33.39
Unknown	251	41.69
Antidepressant class		
SSRIs	351	58.31
SNRIs	87	14.45
TCAs	36	5.98
MAOIs	—	—
Other classes	128	21.26

CRN, cost-related medication nonadherence; CC, charlson comorbidity index; ER, emergency room; SSRIs, selective serotonin reuptake Inhibitors; SNRIs, serotonin and noradrenaline reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors.

participants have reported one or more comorbidities. For the antidepressant classes, 58.31% were SSRI users, 14.45% were SNRI users, 5.98% were TCAs users, and 31.26% used other antidepressants.

The factors associated with general health status, after adjusting for possible confounders, we discovered that Medicare beneficiaries with antidepressants who had some college degree [odds ratio (OR): 2.48; 95% confidence interval (CI): 1.23–5.02], had a graduate degree (OR: 3.01; 95% CI: 1.57–5.78), had an income of $10,001-$20,000 per year (OR: 1.09; 95% CI: 0.52–2.28), had an income of $20,001-$40,000 per year (OR: 1.90; 95% CI: 0.85–4.25), and had income more than $40,000 per year (OR: 3.01; 95% CI: 1.22–7.42), and were in the South region (OR: 2.01; 95% CI: 1.08–3.75) were more likely to report a superior general health status (**Table 2**). On the contrary, among antidepressant users who were male (OR: 0.50; 95% CI: 0.30–0.83), were Africans Americans (OR: 0.46; 95% CI: 0.22–0.97), had less than a high school of education (OR: 0.86; 95% CI: 0.49–1.50), had one comorbidity (OR: 0.34; 95% CI: 0.13–0.87), and had two or more comorbidities (OR: 0.32; 95% CI: 0.14–0.72) were more likely to report an inferior general health status. Furthermore, the factors associated with disability status, antidepressant users who had some college degree (OR: 0.60; 95% CI: 0.35–1.02), had a graduate degree (OR: 0.61; 95% CI: 0.38–0.97), had an income of $10,001-$20,000 per year (OR: 0.93; 95% CI: 0.44–1.96), had an income of $20,001-$40,000 per year (OR: 0.50; 95% CI: 0.23–1.06), had an income of $40,000 or more (OR: 0.40; 95% CI: 0.18–0.89) were less likely to report a disability (**Table 2**). On the other hand, antidepressant users who were 85 + years of age (OR: 1.98; 95% CI: 1.14–3.45), and had two or more comorbidities (OR: 2.02; 95% CI: 1.16–3.55) were more likely to report a disability.

After controlling for other covariates, CRN was statistically associated with outpatient visits (OR: 1.89; 95% CI: 1.19–3.02) but not statistically associated with ER visits (OR: 1.10; 95% CI: 0.69–1.76) (**Table 3**). The factors associated with outpatient visits, antidepressant users with an income of $10,001-$20,000 per year (OR: 2.28; 95% CI: 1.07–4.84), an income of $20,001-$40,000 per year (OR: 2.62; 95% CI: 1.20–5.74), an income of more than $40,000 per year (OR: 2.66; 95% CI: 1.15–6.15), had two or more comorbidities (OR: 2.06; 95% CI: 1.18–3.60) were more likely to visit the outpatient department. On the other hand, antidepressant users who were age 85+ (OR: 0.56; 95% CI: 0.32–0.99), were living in the South region (OR: 0.54; 95% CI: 0.32–0.89), were metropolitan residence (OR: 0.41; 95% CI: 0.27–0.63) and had one comorbidity (OR: 0.99; 95% CI: 0.48–2.04) were less likely to visit outpatient department. Moreover, the factors associated with ER visits, antidepressant users were age 85+ (OR: 1.99; 95% CI: 1.16–3.42) were more likely to visit ER. By contrast, antidepressant users who had an income of $20,001-$40,000 per year (OR: 0.30; 95% CI: 0.14–0.62), or an income of more than $40,000 per year (OR: 0.37; 95% CI: 0.17–0.80) were less likely to visit ER.

4 DISCUSSION

This study found that the prevalence of CRN was high among antidepressant users. The prevalence of CRN in antidepressant

TABLE 2 | The association of CRN on patients' reported health outcomes.

	General health status			Disability status		
	OR	**95% (CI)**		**OR**	**95% (CI)**	
CRN						
No	(Ref)			(Ref)		
Yes	0.67	0.39	1.16	1.34	0.83	2.14
Age group						
65–74	(Ref)			(Ref)		
75–84	1.19	0.72	1.95	1.34	0.90	2.00
85+	1.62	0.83	3.17	1.98	1.14	3.45
Gender						
Female	(Ref)			(Ref)		
Male	0.50	0.30	0.83	1.21	0.79	1.84
Race						
Non-Hispanic White	(Ref)			(Ref)		
Non-Hispanic Black	0.46	0.22	0.97	1.65	0.77	3.54
Hispanic	1.05	0.34	3.31	1.66	0.52	5.35
Others	5.77	0.64	52.12	2.21	0.43	11.40
Education						
Less than high school	0.86	0.49	1.50	1.15	0.69	1.93
High school graduate	(Ref)			(Ref)		
Some college degree	2.48	1.23	5.02	0.60	0.35	1.02
College graduate	3.01	1.57	5.78	0.61	0.38	0.97
Marital status						
Single	0.95	0.50	1.81	0.98	0.58	1.66
Married	(Ref)	—	—	(Ref)		
Widowed	0.91	0.51	1.63	1.46	0.92	2.32
Income (US$)						
<10,000 per year	(Ref)	—	—	(Ref)		
10,001–20,000 per year	1.09	0.52	2.28	0.93	0.44	1.96
20,001–40,000 per year	1.90	0.85	4.25	0.50	0.23	1.06
≥40,001 per year	3.01	1.22	7.42	0.40	0.18	0.89
Census region						
Northeast	(Ref)			(Ref)		
Midwest	1.21	0.63	2.32	0.96	0.55	1.67
South	2.01	1.08	3.75	0.76	0.46	1.27
West	1.21	0.59	2.50	0.94	0.52	1.70
Residence						
Non-metropolitan	(Ref)			(Ref)		
Metropolitan	0.81	0.49	1.33	1.07	0.71	1.63
CCI						
0	(Ref)			(Ref)		
1	0.34	0.13	0.87	1.31	0.64	2.67
2+	0.32	0.14	0.72	2.02	1.16	3.55
Unknown	0.61	0.27	1.33	1.38	0.79	2.39

CRN, cost-related medication nonadherence; CCI, charlson comorbidity index.

users is not well documented in the literature. Many studies reported the prevalence of CRN among individuals with depression, and it was relatively over 20% (Bambauer et al., 2007; Zivin et al., 2009; Gu and Shen, 2020). From the literature, gender was not typically associated with CRN. However, our study and other studies reported that females were more likely to experience CRN than males (Heisler et al., 2005; Briesacher et al., 2007; Zivin et al., 2010).

We found that CRN was not associated with general health status and disability status for self-reported health outcomes. In comparison to other studies, De Avila et al. reported a higher risk of persistent CRN was linked to worse self-reported health and depression (De Avila et al., 2021). Bambauer et al. indicated that CRN was worsened by poor health among both older adults and beneficiaries with disabilities (Bambauer et al., 2007). Furthermore, for self-reported healthcare utilization, CRN was associated with increased outpatient visits. The reason for increased outpatient visits may be related to the deterioration of the patient's clinical outcome. There was a clear relationship between non-adherence and worsening patient clinical outcomes among individuals with antidepressant drugs (Ho et al., 2016). Also, our study found there was no association for ER visits and CRN. In comparison to other studies, Blanchard et al. indicated a statistically significant link between severe CRN and ER visits (Blanchard et al., 2013). Individuals who reported CRN were more likely to visit ER at least once and had a greater overall mean number of visits than those who did not report CRN (Blanchard et al., 2013).

Many sociodemographic characteristics were factors and played a major role in the association of self-reported

TABLE 3 | The association of CRN on patients' healthcare Utilization.

	Outpatient visit			ER visit		
	OR	**95% (CI)**		**OR**	**95% (CI)**	
CRN						
No	(Ref)			(Ref)		
Yes	1.89	1.19	3.02	1.10	0.69	1.76
Age Group						
65–74	(Ref)			(Ref)		
75–84	0.92	0.62	1.36	1.36	0.91	2.03
85+	0.58	0.33	1.02	1.99	1.16	3.42
Gender						
Female	(Ref)			(Ref)		
Male	0.71	0.47	1.07	1.49	0.99	2.24
Race						
Non-Hispanic White	(Ref)			(Ref)		
Non-Hispanic Black	1.63	0.79	3.36	1.72	0.85	3.51
Hispanic	0.85	0.26	2.73	0.51	0.18	1.48
Others	1.31	0.31	5.47	0.48	0.11	2.12
Education						
Less than high school	1.32	0.79	2.21	0.71	0.43	1.17
High school graduate	(Ref)			(Ref)		
Some college degree	1.17	0.69	1.98	0.67	0.39	1.14
College graduate	1.07	0.66	1.72	0.73	0.45	1.17
Marital Status						
Single	0.86	0.51	1.45	0.87	0.51	1.46
Married	(Ref)			(Ref)		
Widowed	0.84	0.53	1.34	0.79	0.50	1.26
Income (US$)						
<10,000 per year	(Ref)			(Ref)		
10,001–20,000 per year	2.28	1.07	4.84	0.59	0.30	1.18
20,001–40,000 per year	2.62	1.20	5.74	0.30	0.14	0.62
≥40,001 per year	2.66	1.15	6.15	0.37	0.17	0.80
Census Region						
Northeast	(Ref)			(Ref)		
Midwest	0.97	0.57	1.67	0.89	0.52	1.53
South	0.54	0.32	0.89	0.68	0.41	1.12
West	0.82	0.46	1.46	0.92	0.52	1.64
Residence						
Non-metropolitan	(Ref)			(Ref)		
Metropolitan	0.41	0.27	0.63	1.04	0.69	1.58
CCI						
0	(Ref)			(Ref)		
1	0.99	0.48	2.04	0.65	0.31	1.36
2+	2.06	1.18	3.60	1.65	0.96	2.85
Unknown	1.95	1.13	3.37	1.20	0.70	2.06

CRN, Cost-related medication nonadherence; CCI, charlson comorbidity index; ER, emergency room.

healthcare utilization and self-reported health outcomes. Gender, education, income, and comorbidities were all factors of self-reported health status. Age, education, and income were all factors of self-reported disability status. Region, residence, and comorbidities were all factors of outpatient visits. Age, income, and comorbidities were all factors of ER visits. Healthcare providers need to consider these factors to enhance patient health status and healthcare efficiency.

Healthcare providers play a major role in influencing patients' medication adherence. Medication adherence improves patient outcomes, and better patient outcomes are associated with close physician-patient relationships (Johnson, 2019). According to the patients, their healthcare provider is the most credible source of information about their current health condition and prescription regimen (Brundisini et al., 2015). Healthcare providers must pay close recognition to Medicare beneficiaries using antidepressants, in order to detect possible financial obstacles to adherence. Also, to support individuals in seeking other treatment options of antidepressants by identifying the causes of CRN and providing solutions to alleviate the financial burden on those impacted individuals. Solutions include offering less costly generic comparable drugs, drug-discount programs, and pharmaceutical and savings assistance programs (Bussell et al., 2017). Furthermore, interventions like medication therapy management (MTM) are necessary to avoid CRN in older adults since MTM assure that patients receive the best possible treatment. Patients with numerous chronic illnesses, complex drug regimens, high prescription prices, and multiple prescribers benefit the most from MTM (Community pharmacists and medication, 2021).

This study is the first of its kind to assess the association of CRN on self-reported healthcare utilization (ER visits and outpatient visits) and self-reported health outcomes (health status and disability status) among Medicare beneficiaries on antidepressants. In addition, this study uses the MCBS data, which has rich information about patients compared to using claims data only. The claims data has limited variables and is not rich in information. The MCBS data provides rich information on health status, access to services, insurance benefits, out-of-pocket costs, financial resources, socioeconomic information, and demographic information of Medicare beneficiaries.

There are three limitations of this study. First, this research did not distinguish between the various classes of antidepressants. The analysis did not include a subgroup analysis of antidepressant classes due to the small sample size of antidepressant users. Second, the causal relationship cannot be determined due to the nature of the cross-sectional study design. Exposure and outcome are both determined at the same time in cross-sectional studies (Kramer, 1988). We cannot assume that exposure happened before the outcome since exposure is assessed concurrently with the outcome (Kramer, 1988). Future studies using a longitudinal research design are required to establish cause-effect relationships. Finally, since MCBS was a self-reported survey, some of the assessments may be vulnerable to social desirability bias and recall bias – especially for CRN. However, MCBS surveyed Medicare beneficiaries three times a year to minimize recall bias (The Medicare Current Beneficiary Survey, 2021). Also, MCBS uses proxy measures if the respondent is unable to answer. Therefore, the use of self-reports is unlikely to result in significant recall bias.

5 CONCLUSION

For Medicare beneficiaries on antidepressants, CRN prevalence was high. Also, CRN contributed to more outpatient visits. The healthcare provider needs to define the reasoning for CRN and provide solutions to reduce the financial burden on the affected patient. Also, health care providers need to consider the factors that may enhance patient health status and healthcare efficiency.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data will not be made readily available for the privacy of the participants. Requests to access these datasets should be directed to https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

AA and ZL contributed to the conception and design of the study. AA, JW, and ML took part in the literature review and critical draft writing. AA and ML did data analysis. JW, JY, ML, and ZL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.764697/full#supplementary-material

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Comparative Efficacy of Pharmacotherapy for Macular Edema Secondary to Retinal Vein Occlusion: A Network Meta-analysis

Sheng Gao[1,2], *Yun Zhang*[1,2], *Xun Li*[1,2], *Ge Ge*[1,2], *Jianan Duan*[1,2], *Chunyan Lei*[1,2], *Yue Zeng*[1,2], *Zhaolun Cai*[3]* and *Meixia Zhang*[1,2]*

[1]*Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China,* [2]*Research Laboratory of Macular Disease, West China Hospital, Sichuan University, Chengdu, China,* [3]*Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China*

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***Correspondence:**
Zhaolun Cai
caizhaolun@foxmail.com
Meixia Zhang
zhangmeixia@scu.edu.cn

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Purpose: This network meta-analysis was conducted to obtain the relative effectiveness of different pharmacotherapy of macular edema secondary to retinal vein occlusion (RVO) by summarizing all available evidences.

Methods: PubMed, Embase, and Cochrane Library databases were searched for all relevant randomized controlled trials. The outcomes were estimated through a network meta-analysis, including the mean change in best-corrected visual acuity (BCVA) from baseline, the proportion of patients who gained ≥15 letters in BCVA from baseline, the mean change in central retinal thickness (CRT).

Results: We identified 15 randomized controlled trials (RCTs) involving 3,431 patients with RVO in our study. Different therapeutic regimens were compared including three anti-vascular endothelial growth factor (VEGF) agents (ranibizumab, bevacizumab, and aflibercept), ranibizumab with laser, dexamethasone intravitreal implant, and laser. For branch RVO, ranibizumab 0.5 mg monthly [weighted mean difference (WMD) = 11, 95% confidence intervals (CrI) 3.6 to 19], ranibizumab 0.5 mg 3 + pro re nata (WMD = 9.4, 95% CrI 0.43–18) is most effective in terms of changes of BCVA and 15 letters or more of BCVA improvement. For central RVO, three anti-VEGF regimens can improve visual acuity and there is no significant difference of efficacy among ranibizumab, bevacizumab and aflibercept ($p > 0.05$). Ranibizumab 0.5 mg monthly could achieve additional efficacy in CRT reduction in eyes with branch RVO or central RVO (WMD = -130, 95% CrI -400 to 140 or WMD = -280, 95% CrI -590 to 16)). Dexamethasone intravitreal implant (WMD = 1.7, 95% CrI -4.2 to 7.1 or WMD = 0.38, 95% CrI -9.8 to 8.8)) did not show a significant improvement in visual acuity at the end of 6 months follow-up in eyes with branch RVO or central RVO.

Conclusion: In summary, this network meta-analysis demonstrated several anti-VEGF agents had equivalent effects on mean visual acuity changes and anatomical recovery in 6 months in eyes with branch or central RVO. Only one injection of dexamethasone

intravitreal implant in 6 months could not maintain the visual benefit. Patients and clinicians could choose pharmacotherapies with further consideration toward personal factors.

Keywords: retinal vein occlusion (RVO), macular edema (ME), anti-VEGF (vascular endothelial growth factor) agents, dexamethasone intravitreal implant, retinal laser photocoagulation, efficacy and safety, network meta-analysis

1 INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disease which threatens visual acuity (VA) through macular edema and neovascularization. The general prevalence rate of RVO was approximately 0.52% in 2008 and its rate increased with age (Rogers et al., 2010). RVO is classified into the branch RVO (BRVO) and the central RVO (CRVO) according to the partial or complete occlusion caused by occlusive location. Several studies have confirmed the efficacy of pharmacotherapy for RVO secondary macular edema including anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids intravitreal injection (Brown et al., 2011; Campochiaro et al., 2011). The published guidelines highlight several therapeutic strategies as recommendable treatment for patients with macular edema secondary to RVO(Schmidt-Erfurth et al., 2019; Flaxel et al., 2020). Several meta-analyses were performed on the therapies of RVO. However, it is still limited to an incomplete comparison of pharmacotherapy, or only one of the BRVO or CRVO has been analyzed (Ford et al., 2014; Regnier et al., 2015; Sermsiri et al., 2018). The network meta-analysis overcomes the limitation of traditional meta-analysis and a shortage of head-to-head trials (Rücker, 2012).

To address the knowledge gap, we have conducted a Bayesian network meta-analysis that included both direct and indirect comparisons simultaneously to obtain the comparative effectiveness of different pharmacotherapy of macular edema secondary RVO(Dias et al., 2013).

2 METHODS

2.1 Protocol and Registration

The study protocol is registered in INPLASY (INPLASY202070012). The study was structured based on the PRISMA guidelines for Network Meta-analyses (Hutton et al., 2015). The protocol for this network meta-analysis had been published on Medicine (Zhang et al., 2020). The study aims to evaluate the efficacy and safety of intravitreal pharmacotherapies to obtain a comprehensive treatment recommendation for macular edema secondary to RVO.

2.2 Information Sources and Search Strategy

We systematically searched the electronic PubMed, Embase, and Cochrane Library databases (last updated on October 1, 2020). The detailed search strategies were presented in the **Supplementary Table S1**.

2.3 Eligibility Criteria

We summarized the detailed eligibility criteria according to the PICOS approach (patient, intervention, comparison, outcome, study design type) (Guyatt et al., 2011).

2.3.1 Patients and Comparison of Interventions

The randomized controlled trials (RCTs) that compared two or more of the following treatment strategies (different anti-VEGF monotherapy regimens, anti-VEGF agent combined with laser photocoagulation, intravitreal corticosteroid monotherapy, and sham-controlled group (only the patients who received the sham injections for 6 months)) for patients with BRVO or CRVO were included in our analysis. We only analysed the agent dose that was approved or recommended by the guidelines to maximize the clinical significance for our study, including ranibizumab 0.5 mg, bevacizumab 1.25 mg, aflibercept 2 mg, conbercept 0.5 mg, dexamethasone intravitreal implant 0.7 mg, and triamcinolone acetonide 1 mg. Both laser photocoagulation and anti-VEGF combined with laser therapy were included in our analysis to provide more indirect data.

2.3.2 Outcomes

Trials included should contain at least one of the outcomes in BRVO or CRVO. The outcomes included the mean change in BCVA from baseline (only the ETDRS results used for visual acuity were included in analysis), the proportion of patients who gained ≥15 letters in BCVA from baseline, and the mean change in CRT from baseline.

All the outcomes were analyzed at 6 months.

2.4 Study Selection and Data Collection

The studies were screened and selected independently by two reviewers and the relevant data were extracted from the included studies. The two reviewers (SG and YZ) summarized all study characteristics using the same standardized collection form. Any disagreement was resolved in discussion with another reviewer (CL) to reach a consensus.

2.5 Risk of Bias

The risk of bias of individual studies was assessed by the Cochrane Collaboration's method. Studies were evaluated based on sequence generation, allocation concealment, blinding, selective reporting, incomplete outcome data, and other kinds of bias (Higgins et al., 2011). Disagreements were resolved by discussion with another reviewer (ZC) as an arbitrator to reach a consensus.

2.6 Data Synthesis and Statistical Analysis

The network meta-analyses were implemented within a Bayesian framework using Stata 14 (Stata Corp, College Station, TX,

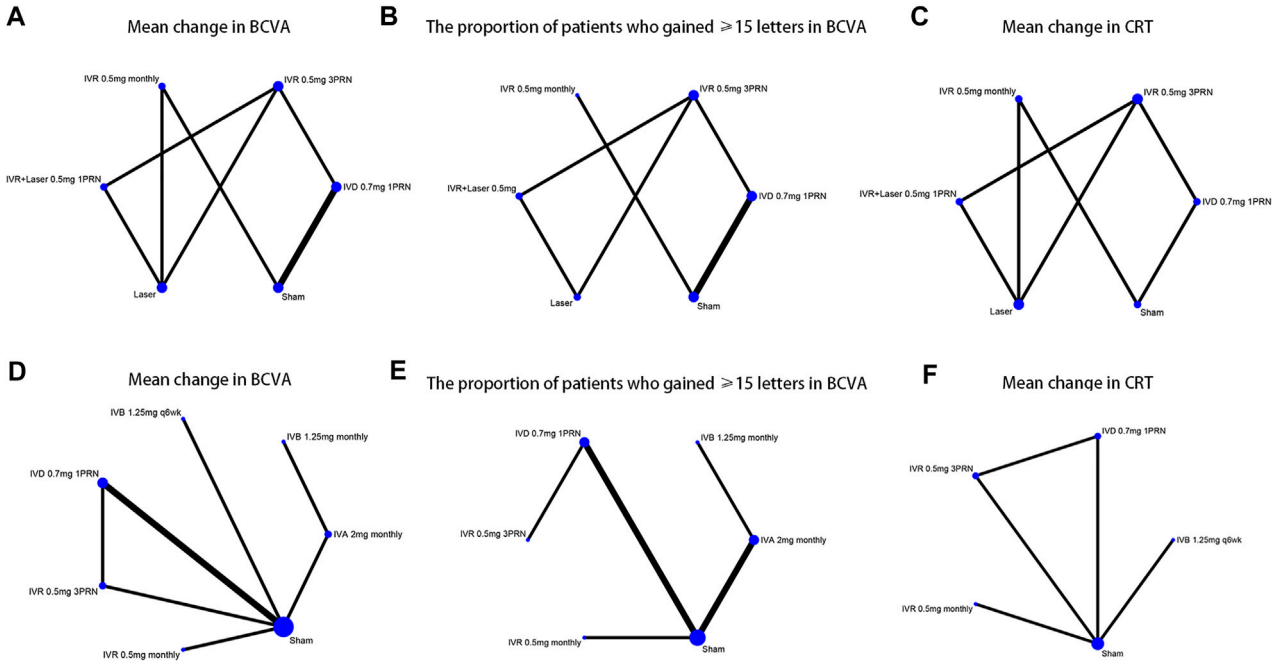

FIGURE 1 | Network of the comparisons for the Bayesian network meta-analysis **(A–C)** The efficacy outcomes of macular edema secondary to branch retinal vein occlusion **(D–F)** The efficacy outcomes of macular edema secondary to central retinal vein occlusion.

United States), JAGS, and R (version x64 3.5.1). Random-effects models were used to evaluate the heterogeneity (Rücker and Schwarzer, 2015). The preferred outcome measures were reported as the relative risk (RR) with its 95% confidence intervals (CrI) and weighted mean difference (WMD) with its 95% CrI for dichotomous data and continuous data, respectively. To estimate the consistency between direct and indirect comparisons, we used the node-splitting method to calculate the inconsistency of the model. The inconsistency was reported by Bayesian p-value. A p-value < 0.05 indicated a significant inconsistency (Dias et al., 2010). We estimated the treatments for each outcome base on potential ranking probabilities which were calculated by the surface under the cumulative ranking curve (SUCRA) for each intervention (Salanti et al., 2011). The SUCRA value ranged from 0 to 1, the higher SUCRA value represented the better efficacy of treatment (Valk et al., 2009). To ensure the feasibility of our network meta-analysis, we drew the network plots to illustrate the comparisons of interventions across trials. Trials were excluded if the investigated treatment lacked the network connective nodes.

3 RESULTS

3.1 Study Selection and Characteristics of Included Studies

We identified 1,044 potentially relevant studies. Fifteen RCTs that conformed to the inclusion criteria were contained in the network analysis, including six RCTs for BRVO(Haller et al., 2010; Campochiaro et al., 2011; Tan et al., 2014; Li X. et al., 2017; Tadayoni et al., 2017; Hattenbach et al., 2018) and nine RCTs for CRVO(Brown et al., 2010a; Haller et al., 2010; Kinge et al., 2010; Boyer et al., 2012; Epstein et al., 2012; Holz et al., 2013; Hoerauf et al., 2016; Scott et al., 2017a; Li X. et al., 2017). Overall, a total of 3,431 patients with macular edema secondary to RVO were involved in the study. The included trials compared the following eight interventions: intravitreal ranibizumab (IVR) 0.5 mg as needed after three initial monthly injections (3PRN); IVR 0.5 mg monthly; IVR with laser as soon as indicated by the investigators (IVR with the laser); dexamethasone intravitreal implant (DEX implant) 0.7 mg; intravitreal aflibercept (IVA) 2 mg monthly; intravitreal bevacizumab (IVB) 1.25 mg monthly; IVB 1.25 mg every 6 weeks (q6wk); laser therapy alone; and sham-controlled. Triamcinolone acetonide and conbercept were excluded for the absence of data and shortage of trials that connects the network nodes (Ramezani et al., 2012; Li F. et al., 2017; Sun et al., 2017). The network plots of all analytical comparisons are shown in **Figure 1**. The characteristics of the included trials are summarized in **Table 1**. The literature screening and selection process is shown in **Supplementary Figure S1**.

3.2 BRVO

3.2.1 Mean Change in BCVA From Baseline

Six trials comparing six interventions in terms of mean change in BCVA at 6 months from baseline were examined (Haller et al., 2010; Campochiaro et al., 2011; Tan et al., 2014; Li X. et al., 2017; Tadayoni et al., 2017; Hattenbach et al., 2018). **Figure 1A** and **Figure 2** showed separately the network plots and the results based on a Bayesian network meta-analysis that combines direct

TABLE 1 | Study and patient population characteristics of included studies.

Author, year	Treatment	Dose	Therapeutic regimen	Sample size	Mean age	Efficacy outcomes
BRVO						
Hattenbach, L. O., et al. 2018	IVR	0.5 mg	3PRN	126	NR	①②③
	IVD	0.7 mg	1	118		
Li, X., et al. 2017	IVD	0.7 mg	1	63	54.6	①②③
	Sham	—	—	65	53.0	
Tadayoni, R., et al. 2016	IVR	0.5 mg	3PRN	183	64.7	①②③
	IVR + laser	0.5 mg + laser	3PRN	180	67.3	
		—	—	92	67.7	
Tan, M. H., et al. 2014	IVR	0.5 mg	Monthly	15	69.6	①③
	Laser	—	—	21	66.7	
Haller, J. A., et al. 2010	IVD	0.7 mg	1	291	64.7	①②
	Sham	-	1	279	63.9	
Campochiaro, P. A., et al. 2011	IVR	0.5 mg	Monthly	131	67.5	①②③
	Sham	—	—	132	65.2	
CRVO						
Scott, I. U., et al. 2017	IVA	2 mg	Monthly	180	69	①②
	IVB	1.25 mg	Monthly	182	69	
Li, X., et al. 2017	IVD	0.7 mg	1	66	54.6	①②③
	Sham	—	—	65	53.0	
Hoerauf H, et al. 2016	IVR	0.5 mg	3PRN	124	65.3	①②③
	IVD	0.7 mg	1	119	66.9	
Holz, F. G., et al. 2013	IVA	2 mg	Monthly	106	59.9	①②
	Sham	-	Monthly	71	63.8	
Epstein, D. L., et al. 2012	IVB	1.25 mg	Q6w	30	70.6	①③
	Sham	-	-	30	70.4	
Boyer, D., et al. 2012	IVA	2 mg	Monthly	114	65.5	①②
	Sham	—	—	73	67.5	
Kinge, B., et al. 2010	IVR	0.5 mg	3PRN	16	72	①③
	Sham	—	—	16	72	
Haller, J. A., et al. 2010	IVD	0.7 mg	1	136	64.7	①②
	Sham	—	1	147	63.9	
Brown, D. M., et al. 2010	IVR	0.5 mg	Monthly	130	67.6	①②③
	Sham	—	—	130	65.4	

Efficacy outcome: ①Mean change in BCVA; ②The proportion of patients who gained ≥15 letters in BCVA from baseline; ③Mean change in CRT from baseline; Abbreviations: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVD, intravitreal dexamethasone implant; IVR, intravitreal ranibizumab; NR, not reported; PRN, pro re nata; Q6w, every six weeks.

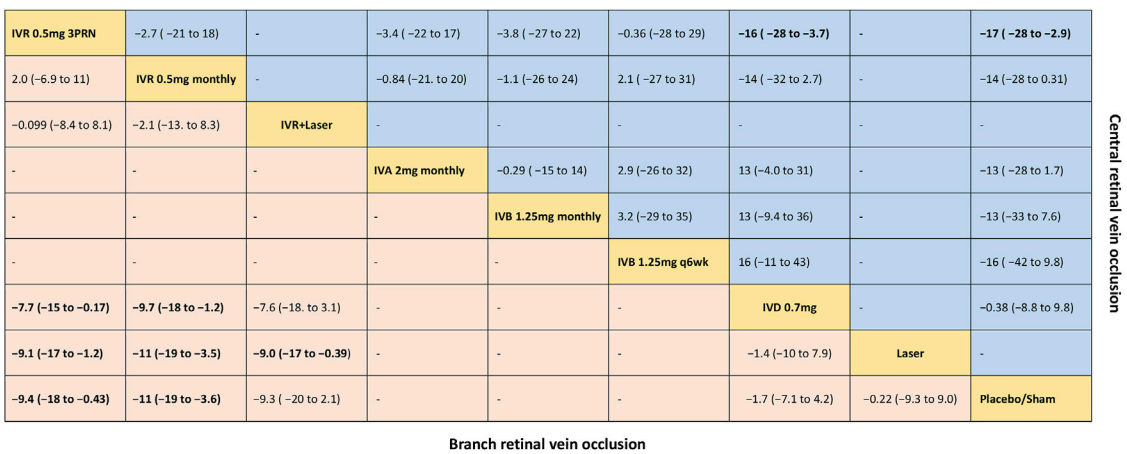

FIGURE 2 | Comparative effectiveness of pharmacotherapies in terms of the mean change in BCVA for macular edema secondary to retinal vein occlusion in network meta-analysis. Weighted mean difference (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. Bold cells are significant. For branch retinal vein occlusion, weighted mean difference <0 favors row-defining treatment. For central retinal vein occlusion, weighted mean difference <0 favors column-defining treatment.

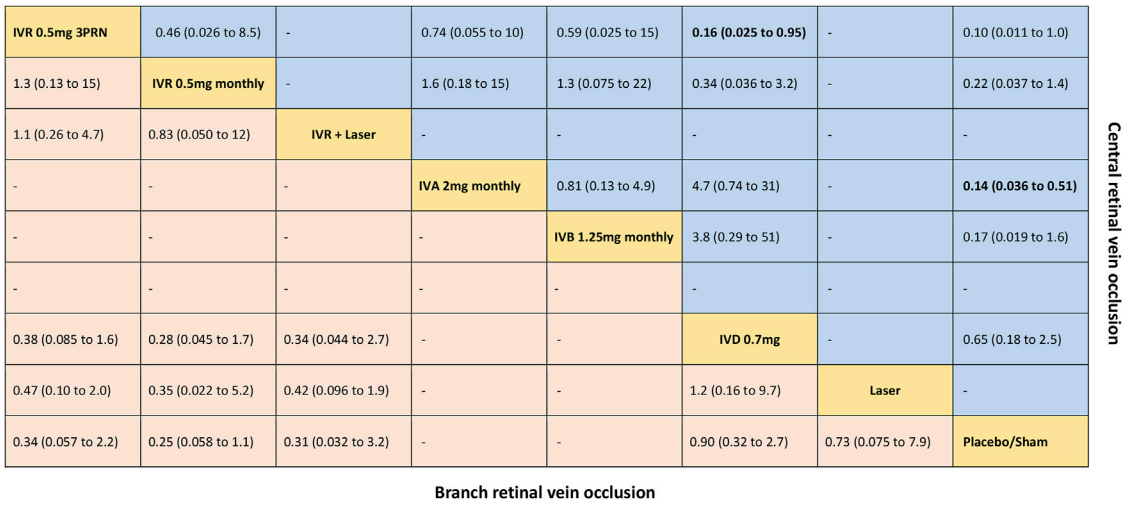

FIGURE 3 | Comparative effectiveness of pharmacotherapies in terms of the proportion of patients who gained ≥15 letters in BCVA for macular edema secondary to retinal vein occlusion in network meta-analysis. Relative risk (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. Bold cells are significant. For branch retinal vein occlusion, relative risk <1 favors row-defining treatment. For central retinal vein occlusion, relative risk <1 favors column-defining treatment.

and indirect comparisons. Both IVR 0.5 mg monthly and 3PRN showed a statistically significant mean change in BCVA compared with sham-controlled. IVR with laser therapy showed a statistically nonsignificant trend toward meaningful change in BCVA compared with sham-controlled. However, both DEX implant, the laser alone, and sham-controlled were not superior to the other. The mean change in BCVA at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg monthly [WMD = 11 with 95% CrI (3.6, 19), SUCRA = 88%], IVR 0.5 mg 3PRN [WMD = 9.4 with 95% CrI (0.43, 18), SUCRA = 74%], IVR with laser [WMD = 9.3 with 95% CrI (-2.1, 20), SUCRA = 73%], DEX implant 0.7 mg [WMD = 1.7 with 95% CrI (-4.2, 7.1), SUCRA = 31%], and laser alone therapy [WMD = 0.22 with 95% CrI: (-9.0, 9.3), SUCRA = 18%].

3.2.2 The Proportion of Patients Who Gained ≥15 Letters in BCVA

Five trials comparing six interventions contributed to the analysis of the proportion of patients who gained ≥15 letters in BCVA (Haller et al., 2010; Campochiaro et al., 2011; Tadayoni et al., 2016; Li X. et al., 2017; Hattenbach et al., 2018). **Figure 1B** and **Figure 3** showed individually the network plots and the results of the network meta-analysis. Both IVR 0.5 mg monthly, IVR 0.5 mg 3PRN, and IVR with laser therapy showed a statistically nonsignificant trend toward improved the proportion of patients who gained ≥15 letters in BCVA. Both DEX implant, the laser alone, and sham-controlled were not clearly superior to the other. The proportion of patients who gained ≥15 letters in BCVA at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg monthly [RR = 3.9 with 95% CrI (0.91, 17), SUCRA = 80%], IVR with laser [RR = 3.3 with 95% CrI (0.31, 31), SUCRA = 75%], IVR 0.5 mg 3PRN [RR = 3 with 95% CrI (0.46, 17), SUCRA = 70%], laser alone therapy [RR = 1.4 with 95% CrI (0.13, 13), SUCRA = 32%], and DEX implant 0.7 mg [RR = 1.1 with 95% CrI: (0.37, 3.1), SUCRA = 24%].

3.2.3 Mean Change in Central Retinal Thickness From Baseline

Five trials comparing six interventions in terms of mean change in CRT were evaluated (Campochiaro et al., 2011; Tan et al., 2014; Tadayoni et al., 2016; Li X. et al., 2017; Hattenbach et al., 2018). **Figure 1C** and **Figure 4** showed separately the network plots and the results of the network meta-analysis. IVR 0.5 mg monthly showed a statistically nonsignificant trend toward improved central retinal thickness. Both IVR 0.5 mg 3PRN, IVR with laser therapy, DEX implant, the laser alone, and sham-controlled were not superior to the other. The mean change in central retinal thickness at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg monthly [WMD = -130 with 95% CrI (-400, 140), SUCRA = 88%], DEX implant 0.7 mg [WMD = 11 with 95% CrI (-260, 270), SUCRA = 54%], IVR with laser [WMD = 26 with 95% CrI (-370, 420), SUCRA = 50%], IVR 0.5 mg 3PRN [WMD = 70 with 95% CrI (-260, 390), SUCRA = 36%], and laser alone therapy [WMD = 150 with 95% CrI: (-190, 470), SUCRA = 15%].

3.3 CRVO

3.3.1 Mean Change in BCVA From Baseline

Nine trials comparing seven interventions in terms of mean change in BCVA at 6 months from baseline were evaluated (Brown et al., 2010a; Haller et al., 2010; Kinge et al., 2010; Boyer et al., 2012; Epstein et al., 2012; Holz et al., 2013; Hoerauf et al., 2016; Scott et al., 2017a; Li X. et al., 2017). **Figure 1D** and **Figure 2** showed separately the network plots and the results of the network meta-analysis. The mean change in

IVR 0.5mg 3PRN	−91 (−500 to 290)	-	160 (−250 to 530)	190 (−67 to 430)	-	190 (−79 to 440)
−200 (−520 to 130)	**IVR 0.5mg monthly**	-	250 (−170 to 670)	280 (−100 to 670)	-	280 (−16 to 590)
−45 (−330 to 240)	160 (−220 to 520)	**IVR+Laser**	-	-	-	-
-	-	-	**IVB 1.25mg q6wk**	−28 (−430 to 350)	-	36 (−260 to 340)
−59 (−320 to 200)	140 (−190 to 470)	−14 (−380 to 360)	-	**IVD 0.7mg**	-	7.4 (−250 to 240)
78 (−190 to 340)	**280 (1.8 to 540)**	120 (−170 to 410)	-	140 (−190 to 460)	**Laser**	-
−70 (−390 to 260)	130 (−140 to 400)	−26 (−420 to 370)	-	−11 (−270 to 260)	−150 (−470 to 190)	**Placebo/Sham**

Central retinal vein occlusion

Branch retinal vein occlusion

FIGURE 4 | Comparative effectiveness of pharmacotherapies in term of the mean change in central retinal thickness for macular edema secondary to retinal vein occlusion in network meta-analysis. Weighted mean difference (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. Bold cells are significant. For branch retinal vein occlusion, weighted mean difference <0 favors row-defining treatment. For central retinal vein occlusion, weighted mean difference <0 favors column-defining treatment.

BCVA at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg 3PRN [WMD = 17 with 95% CrI (2.9, 28), SUCRA = 76%], IVB 1.25 mg q6wk [WMD = 16 with 95% CrI (-9.8, 42), SUCRA = 67%], IVR 0.5 mg monthly [WMD = 14 with 95% CrI (-0.31, 28), SUCRA = 64%], IVA 2 mg monthly [WMD = 13 with 95% CrI (-1.7, 28), SUCRA = 60%], IVB 1.25 mg monthly [WMD = 13 with 95% CrI (-7.6, 33), SUCRA = 58%], DEX implant 0.7 mg [WMD = 0.38 with 95% CrI: (-9.8, 8.8), SUCRA = 14%].

3.3.2 The Proportion of Patients Who Gained ≥15 Letters in BCVA

Seven trials comparing six interventions contributed to the analysis of the proportion of patients who gained ≥15 letters in BCVA (Brown et al., 2010a; Haller et al., 2010; Boyer et al., 2012; Holz et al., 2013; Hoerauf et al., 2016; Scott et al., 2017a; Li X. et al., 2017). **Figure 1E** and **Figure 3** showed separately the network plots and the results of the network meta-analysis. IVA 2 mg monthly showed a statistically significant gained ≥15 letters in BCVA compared with sham-controlled. The proportion of patients who gained ≥15 letters in BCVA at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg 3PRN [RR = 9.8 with 95% CrI (1.0, 89), SUCRA = 82%], IVA 2 mg monthly [RR = 7.2 with 95% CrI (2.0, 28), SUCRA = 75%], IVB 1.25 mg monthly [RR = 5.8 with 95% CrI (0.62, 53), SUCRA = 62%], IVR 0.5 mg monthly [RR = 4.6 with 95% CrI (0.74, 27), SUCRA = 54%], DEX implant 0.7 mg [RR = 1.5 with 95% CrI: (0.40, 5.7), SUCRA = 21%].

3.3.3 Mean Change in Central Retinal Thickness From Baseline

Five trials comparing five interventions in terms of mean change in CRT were examined (Brown et al., 2010a; Kinge et al., 2010; Epstein et al., 2012; Hoerauf et al., 2016; Li X. et al., 2017). **Figure 1F** and **Figure 4** shows separately the network plots and the results of the network meta-analysis. The mean change in central retinal thickness at 6 months from baseline, ordered from the most to least effective therapies based on the SUCRA values, were as follows: IVR 0.5 mg monthly [WMD = -280 with 95% CrI (-590, 16), SUCRA = 91%], IVR 0.5 mg 3PRN [WMD = -190 with 95% CrI (-440, 79), SUCRA = 74%], IVB 1.25 mg monthly [WMD = -36 with 95% CrI (-340, 260), SUCRA = 38%], DEX implant 0.7 mg [WMD = -7.4 with 95% CrI: (-240, 250), SUCRA = 26%].

3.4 Quality of Evidence

The bias assessment for eligible RCTs included in the network meta-analysis is shown in **Figure 5** according to the Cochrane risk-of -bias tool, suggesting no severe risk of bias. The results of node-splitting analysis and their *p*-value were larger than 0.05 which demonstrated no statistical inconsistency between direct and indirect comparisons among all outcomes in any closed loops.

4 DISCUSSION

In the network meta-analysis, we compared the efficacy of different pharmacotherapies for BRVO or CRVO comprehensively. Anti-VEGF agents can improve visual acuity and recover retinal anatomical structure in patients with both BRVO and CRVO at 6 months. DEX implant and laser alone did not show a significant improvement in visual acuity at the end of 6 months follow-up both in BRVO and CRVO. For BRVO, anti-VEGF combined with laser therapy showed no statistically significant difference in improving vision or reducing CRT at 6 months compared with anti-VEGF monotherapy. In general,

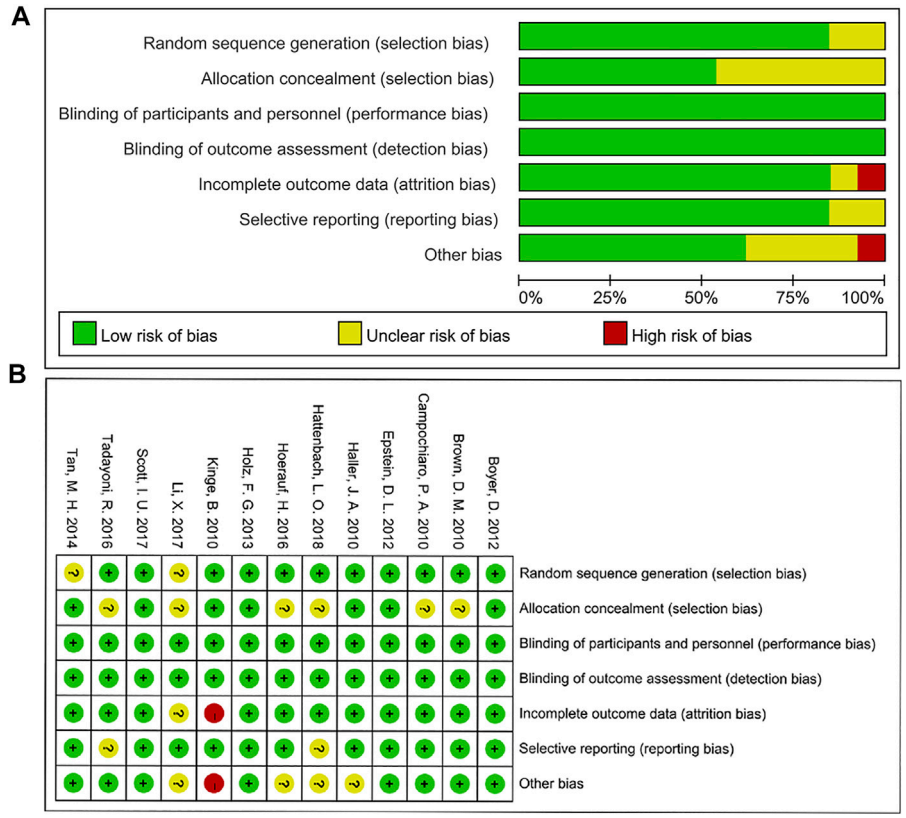

FIGURE 5 | Risk of bias graph **(A)** and summary **(B)**.

our result confirmed the results of head-to-head RCTs including the VIBRANT, BRIGHTER, RABAMES, GALILEO, CRUISE, and COPERNICUS trials, which was expanded and consistent with the previous meta-analysis (Brown et al., 2010b; Boyer et al., 2012; Holz et al., 2013; Campochiaro et al., 2015; Pielen et al., 2015; Tadayoni et al., 2016).

In the analysis of the mean change of BCVA and visual benefits, all the anti-VEGF agents with different therapeutic regimens within our evaluation system showed better clinical benefit for visual acuity at 6 months. Patients and clinicians could make decisions in conjunction with other factors, such as personal preference, cost, the intravitreal injection frequency, and follow-up burden (Justis et al., 2017). It is worth noting that the baseline VA is the important predictor for final VA like the final vision was lower in those with poor baseline BCVA even with a relatively higher mean change of BCVA (Boyer et al., 2007; Gupta, 2008; Bressler and Susan, 2012). The baseline characteristics of baseline VA are similar between the CRUISE study and COMRADE-C study, while the time between diagnosis and randomization is longer in the CRUISE study (3.3 months) than in the COMRADE-C study (about 1.5 months) (Brown et al., 2010b; Hoerauf et al., 2016). At the end of 6 months follow-up, even if the injection number is more in CRUISE study with a monthly therapeutic regimen, the mean change of BCVA is lower in the CRUISE study (14.9 letters) compared with the COMRADE-C study (16.9 letters), like the proportion of patients gained ≥15 letters are 47.7 versus 58.9%.

In terms of reducing CRT and recovering the retinal anatomical structure, except for the IVR 0.5 mg monthly in BRVO and 0.5 mg monthly or 3PRN in CRVO showed a statistically nonsignificant trend toward decreased CRT, the other treatments were not clearly superior to the sham-controlled group at month 6. This might be related to the natural course of disorders that macular edema might persist or resolve itself over time (Scott et al., 2017b). The CRT represented a rapid decline then relative stability with anti-VEGF agents. When using DEX implant, it showed a rapid decline to bottom around month two then reoccurring increase without retreatment (Haller et al., 2010; Li X. et al., 2017). As the absence of data about aflibercept and the shortage of trails that connect the network nodes, the trials investigating the CRT decline in aflibercept were excluded (Boyer et al., 2012; Holz et al., 2013). In the SCORE2 study, although there was no statistically significant between aflibercept and bevacizumab in mean change of CRT, the complete resolution of fluid was significantly higher in the aflibercept group compared with the bevacizumab group in post hoc analyses (Scott et al., 2017a). The effectiveness of aflibercept on functional and anatomic outcomes deserves attention.

For DEX implant both in BRVO and CRVO, the results of trials we included were consistent, and all DEX implant groups

received a single DEX implant injection followed by sham injections in 6 months (Haller et al., 2010; Hoerauf et al., 2016; Li X. et al., 2017). In the GENEVA study, the mean BCVA achieved an apex of about 10 letters at month two in all RVO, while this value decreased progressively and reached approximately 7 letters in BRVO and baseline level in CRVO at month 6. As well as the proportion of patients who gained ≥15 letters, it was significantly greater in DEX implant groups than a sham group in the first 3 months, but the difference between two groups was no longer statistically significant at month 6 both in BRVO and CRVO(Haller et al., 2010). Similar variation trends of BCVA and visual benefits were observed in the COMRADE-C study and Li, X.'s study (Hoerauf et al., 2016; Li X. et al., 2017). Hence, the BCVA improvements brought by a single DEX implant approximately continue for 3 months. The subsequently persistent decline suggests that patients need extra treatment within 6 months. The other study which gave another injection of DEX implant when BCVA decreased and macular edema increased around month four showed no significant difference between DEX implant and bevacizumab in mean change of BCVA and CRT at the end of 6 months follow-up (Gado and Macky, 2014). Therefore, additional RCTs of DEX implant with a shorter retreatment period would be needed to assess the efficacy of DEX implant, which might relatively reduce the advantage of anti-VEGF agents in our network meta-analysis.

The value of laser photocoagulation alone therapy for macular edema secondary to BRVO remains evaluated. Our network meta-analysis showed there is no significant difference between the laser group and sham-controlled group both in vision and anatomic outcomes. Meanwhile, the effectiveness of laser combined with ranibizumab is not superior to the anti-VEGF monotherapy. In the 6 months results of the BRIGHTER study, the number of anti-VEGF injections was 4.5 ± 1.2 in a combined group which was similar to the ranibizumab monotherapy (4.8 ± 1.0 injections) (Tadayoni et al., 2016). Prolonging to 24 months study, the mean number of ranibizumab injections was no different in combined arm and ranibizumab monotherapy either. The addition of laser did not obtain better functional outcomes or less treatment (Tadayoni et al., 2017).

The safety analysis was not included in our work for network connection failure caused by the absence of data. In general, the anti-VEGF agents both ranibizumab, bevacizumab, and aflibercept have a low incidence of increased intraocular pressure (IOP) and cataract. The adverse events and serious adverse events were no new safety events and were consistent with those reported in previous studies of age-related macular degeneration (Rosenfeld et al., 2006; Brown et al., 2009; Heier et al., 2012; Tadayoni et al., 2016). In terms of DEX implant, the treatment-related IOP increase is a well-known risk of intravitreal corticosteroid therapy (Yannuzzi et al., 2014; Aref et al., 2015). Ocular hypertension occurred significantly more frequently in the DEX implant group. The changes in IOP peaked around month two and declined progressively with no statistical difference from sham-controlled at month 6. The overall incidence of ocular adverse events was significantly higher in the DEX implant group. But the occurrence of cataracts and serious adverse events were no significant between DEX implant and sham-controlled group (Haller et al., 2010; Hoerauf et al., 2016).

In the analysis of the number of injections, there is no statistical significance between monthly injection and PRN regimen as similar functional outcomes and anatomical outcomes. It suggested that an individualized PRN regimen could reduce the treatment need and treatment burden both cost and follow-up monitoring. The treat-and-extend regimen was excluded for a shortage of trials that connects the network nodes. A recent RCT showed a significantly less number of injections with IVA T&E regimen compared with IVR T&E regimen, and no difference between two groups regarding vision and CRT(Casselholm De Salles et al., 2019). Although the DEX implant gradually released the drug over several months, the 6 months retreatment period seems too long to keep the vision and retinal structure. The studies of optimal retreatment period still need to be verified.

Several limitations in our present work merit further discussion. The limitations of the difficulty of investigations of potential heterogenicity, such as regional, ethnic, economic, and medical differences, were caused by the meta-analysis of aggregate data rather than individual patient data. Due to the obvious influence of initial VA and duration of disease on final vision, although the inclusion criteria were basic matching, they might also have a certain impact on our meta-analysis. Owing to the absence of data and shortage of trials that connects the network nodes, the trials including aflibercept in BRVO, triamcinolone acetonide, and conbercept were excluded from our work, which causes the types of pharmacotherapies included in our work less than the actual agents available in the clinic.

Despite the above-mentioned limitations, our study has several strengths. To the best of our knowledge, this is the first network meta-analysis to quantitatively review the effectiveness of anti-VEGF therapy and DEX implant for BRVO and CRVO comprehensively. Second, we had strict inclusion criteria and separated all the different therapeutic regimens to avoid potential differences caused by individual clinical intervals. Third, the lack of statistically significant inconsistency in our work confirms the accuracy of the results.

In conclusion, our results show that multiple pharmacotherapies would be effective treatments for macular edema secondary to RVO. Three anti-VEGF agents cause significant VA improvement and have equivalent effects on mean VA changes, vision benefits, and anatomical outcomes. In particular, ranibizumab 0.5 mg monthly shows relatively excellent performance. Only one injection of dexamethasone intravitreal implant in 6 months could not maintain the visual benefit, but it might improve the speed and incidence of visual improvement in the short term. While the ocular adverse events and optimal long-term dosing schedule still need attentions. Patients and clinicians could choose drugs with further consideration toward personal factors such as patient preference, individual treatment response, convenience of dosing, financial constraints, and evolving regulatory standards.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: SG, MZ Searched the databases: YZ and JD. Study inclusion: XL and GG Data collection: SG, YZ, CL, and YZ Analyzed the data: SG, YZ, and ZC Wrote the paper: SG and YZ Critical revision of the manuscript for important intellectual content: MZ and ZC.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.752048/full#supplementary-material

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Non-Vitamin K Oral Anticoagulant After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

Dongxu Li[1†], *Xiaofang Ma*[2†], *Xu Zhou*[3] *and Yongjun Qian*[1,4*]

[1]Department of Cardiovascular Surgery, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Emergency Medicine, Emergency Medical Laboratory, West China Hospital, Sichuan University, Chengdu, China, [3]Evidence-based Medicine Research Center, Jiangxi University of Traditional Chinese Medicine, Nanchang, China, [4]National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China

Objective: We aimed to compare non-vitamin K oral anticoagulants (NOACs) with a traditional antithrombotic such as vitamin K antagonist (VKA) and antiplatelet agents in patients after transcatheter aortic valve replacement (TAVR).

Methods: We conducted a search in PubMed, EMBASE, and the Cochrane Library until November 2021 for studies involving comparisons of any type of NOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban, with VKA or antiplatelet agents after TAVR. A comparison of NOACs versus VKA was performed in patients with an indication for oral anticoagulation. In addition, we compared NOACs versus antiplatelet in patients without such indication. We calculated the hazard ratios with 95% confidence intervals (CIs) to determine long-term outcomes. The primary outcome was a combined endpoint consisting of all-cause mortality, stroke, major bleeding, or any related clinical adverse events. Secondary outcomes were all-cause mortality, major bleeding, and stroke, respectively.

Results: A total of 10 studies including 10,563 patients after TAVR were included in this meta-analysis. There were no significant differences in any of the long-term outcomes between the NOAC and VKA groups. Although there were no significant differences in the combined endpoint, major bleeding, or stroke, a significant difference was observed in the all-cause mortality (HR 1.74, 95% CI 1.25–2.43, p = 0.001) between the NOAC and antiplatelet groups.

Conclusion: For patients with an indication for oral anticoagulation after TAVR, NOACs seem to be associated with noninferior outcomes compared with VKA therapy. However, for patients without an indication for oral anticoagulation, NOACs appear to be associated with a higher risk of all-cause death as compared with antiplatelet treatment.

Systematic Review Registration: https://clinicaltrials.gov/, identifier CRD42020155122.

Keywords: transcatheter aortic valve replacement, non-vitamin K oral anticoagulant, mortality, bleeding, stroke

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***Correspondence:**
Yongjun Qian
qianyongjun@scu.edu.cn

[†]*These authors have contributed equally to this work*

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INTRODUCTION

Since the introduction of transcatheter aortic valve replacement (TAVR) in 2002, it has been widely used in high-risk patients with aortic stenosis (Cribier et al., 2002; Hamm et al., 2016). In addition, the consequent antithrombotic therapy after TAVR has remained an important issue (Sun et al., 2009; Guedeney et al., 2019). Since thrombosis may originate from the valved stent, bioprosthetic valve, or other related diseases (Trepels et al., 2009; Tay et al., 2011; De Marchena et al., 2015; Piayda et al., 2018; Mangieri et al., 2019; Ranasinghe et al., 2019), there are currently two main antithrombotic strategies, namely, antiplatelet therapy and anticoagulation therapy (Sherwood and Vora, 2018; Lugo et al., 2020).

In patients with valvular heart disease, the main indications for anticoagulation include chronic or paroxysmal atrial fibrillation, lung embolism, deep vein thrombosis, poor left ventricular ejection fraction (including left ventricle aneurysms), and extensive arterial vascular disease (Chesebro et al., 1986; Figini et al., 2013; Nijenhuis et al., 2020). Thus, recent guidelines from the American College of Cardiology (ACC) and European Society of Cardiology (ESC) have divided patients who have undergone TAVR into those who have an indication for oral anticoagulation and those who do not have an indication (Falk et al., 2017; Otto et al., 2021).

For patients without an indication, the ACC (Otto et al., 2021) recommends "aspirin 75–100 mg daily is reasonable in the absence of other indication for oral anticoagulants (moderate recommendation); or dual antiplatelet therapy with aspirin 75–100 mg and clopidogrel 75 mg may be reasonable for 3–6 months (weak recommendation); or anticoagulation with a VKA to achieve an INR of 2.5 in patients at low risk of bleeding for at least 3 months (weak recommendation)," whereas the ESC (Falk et al., 2017) recommends "dual antiplatelet for the first 3–6 months followed by lifelong single antiplatelet, or single antiplatelet in the case of high bleeding risk." For patients with an indication, no specific recommendation is found in the ACC guideline, whereas the ESC recommends lifelong oral anticoagulation therapy. Aside from the consensus on 3-to-6-month dual antiplatelet therapy for TAVR patients who do not need oral anticoagulation, a detailed recommendation of oral anticoagulation for TAVR patients, especially for patients with an indication, remains unclear.

There are currently four non-vitamin K oral anticoagulants (NOACs) approved in clinical therapy, including dabigatran, apixaban, rivaroxaban, and edoxaban (Angiolillo et al., 2018; Levy et al., 2018). Because of the advantages of their shorter half-life, less drug interaction, and no requirement for repeated measurement of the international normalized ratio, NOACs have been used as the first-line drug for patients with nonvalvular atrial fibrillation and deep vein thrombosis

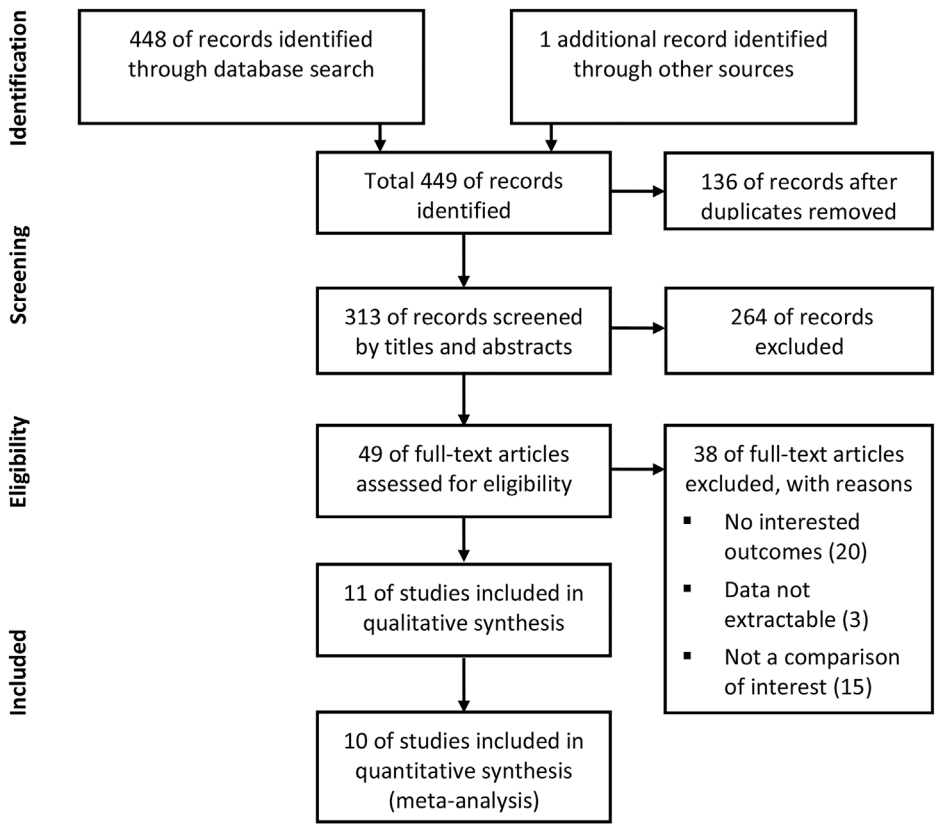

FIGURE 1 | Flow diagram of the literature search and study selection.

TABLE 1 | Characteristics of included studies.

Author	Year	Region	Design	Group	Medication	N	Age, year	Sex, M, %	BMI, kg/m^2	STS score *, %	CHA_2DS_2-VASc score †	Endpoint ‡, n	Mortality, n	Bleeding, n	Stroke, n	Follow-up, months
Seeger et al. (2017)	2017	Germany	PC	NOAC	Api+ 4-week SAPT/DAPT	141	82.1 ± 5.3	49.6	27.2 ± 4.2	7.5 ± 5.2	5.0 ± 1.2	22	19	NA	1	12
				VKA	Warf+ 4-week SAPT/DAPT	131	80.5 ± 6.3	51.9	27.4 ± 5.1	7.9 ± 6.3	4.9 ± 1.1	9	6	NA	1	12
Geis et al. (2018)	2018	Germany	RC	NOAC	Dabi/Riva/Api/Edo	154	83.1 ± 5.3	49.4	26.6 ± 5.3	4.1 ± 1.9	4.6 ± 1.2	17	12	3	5	6
				VKA	Warf	172	83.0 ± 4.9	45.3	27.0 ± 5.3	4.4 ± 2.4	4.8 ± 1.3	14	11	3	2	6
Jochheim et al. (2019)	2019	Germany	PC, PSM	NOAC	Riv/Api/Dabi + less than 3-month SAPT/DAPT	326	81.6 ± 6.7	47.9	26.3 ± 5.2	4.5 ± 1.2	NA	63	47	69	10	12
				VKA	Warf + less than 3-month SAPT/DAPT	636	81.1 ± 6.1	47.3	26.6 ± 4.9	4.5 ± 1.2	NA	87	70	146	13	12
Butt et al. (2021)	2019	Denmark	RC, PSM	NOAC	Dabi/Riva/Api+ 6-month SAPT/DAPT	219	83 ± 1.2	53.9	NA	NA	5.0 ± 1.4	NA	15	11	NA	12 ± 1
				VKA	Warf+ 6-month SAPT/DAPT	516	82 ± 1.3	53.7	NA	NA	4.9 ± 1.3	NA	54	28	NA	27.4 ± 1
Kosmidou et al. (2019)	2019	United States	RC, PSM	NOAC	Dabi+ 6-month SAPT/DAPT	155	82.8 ± 6.7	65.6	28.4 ± 6.1	8.2 ± 4.2	5.6 ± 1.3	39	33	8	12	33.6 ± 3.6
				VKA	Warf+ 6-month SAPT/DAPT	778						234	207	43	41	
Kalogeras et al. (2020)	2019	United Kingdom	RC, PSM	NOAC	Dabi/Riva/Api/Edo+ in-hospital SAPT/DAPT	115	81.9 ± 6.3	59.1	27.3 ± 5.8	NA	NA	13	13	NA	NA	15.1 ± 3.8
				VKA	Warf+ in-hospital SAPT/DAPT	102	82.5 ± 5.8	57.8	25.9 ± 5.8	NA	NA	16	16	NA	NA	15.1 ± 3.8
Kawashima et al. (2020)	2020	Japan	PC, PSM	NOAC	Dabi/Riva/Api/Edo + SAPT/DAPT	227	84.4 ± 4.7	30.4	22.6 ± 3.8	7.7 ± 5.1	5.1 ± 1.0	NA	NA	NA	NA	19 ± 2.5
				VKA	Warf + SAPT/DAPT	176	84.3 ± 4.9	36.9	21.7 ± 3.7	9.5 ± 9.5	5.2 ± 1.1	NA	NA	NA	NA	
Dangas et al. (2020)	2020	Switzerland	RCT, ITT	NOAC	Riva+ 3-month aspirin	826	80.4 ± 7.1	51.6	28.1 ± 5.5	4.0 ± 3.2	4.5 ± 1.3	105	64	46	30	14.3 ± 2.3
				Antiplatelet	Aspirin+ 3-month clopidogrel	818	80.8 ± 6.0	49.5	28.2 ± 5.7	4.3 ± 3.5	4.6 ± 1.2	78	38	31	25	15.8 ± 1.7
Didier et al. (2021)	2021	France	RC, PSM	NOAC	Dabi/Riva/Api/Edo+ in-hospital SAPT/DAPT	1,378	83.4 ± 6.1	52.6	27.1 ± 5.5	NA	NA	NA	161	55	29	13.0 ± 2.4

(Continued on following page)

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

Author	Year	Region	Design	Group	Medication	N	Age, year	Sex, M, %	BMI, kg/m^2	STS score *, %	CHA_2DS_2-VASc score †	Endpoint ‡, n	Mortality, n	Bleeding, n	Stroke, n	Follow-up, months
				VKA	Warf+ in-hospital SAPT/DAPT	1,093	83.5 ± 6.4	51.9	26.9 ± 5.1	NA	NA	NA	263	91	37	21 ± 3.4
Van Mieghem et al. (2021)	2021	Multiple countries	RCT, ITT	NOAC	Edo+ 3-month SAPT/DAPT	713	82.1 ± 5.4	51.3	27.5 ± 5.7	4.8 ± 3.5	4.5 ± 1.4	170	85	98	29	18.5
				VKA	Warf+ 3-month SAPT/DAPT	713	82.1 ± 5.5	53.6	27.9 ± 5.4	5.0 ± 4.1	4.5 ± 1.3	157	93	68	35	17.7
Collet (2021)	2021 (Presentation)	France	RCT, ITT	NOAC	Api	749	81.6 ± 6.1	45.9	27.5 ± 5.5	5.1 ± 5.0	4.4 ± 1.4	64	54	64	28	12
				VKA/ Antiplatelet	Warf/SAPT + DAPT	228/ 523	82.3 ± 6.4	47.9	27.3 ± 5.2	5.1 ± 5.4	4.3 ± 1.4	64	41	64	21	12

*M: male; BMI: body mass index; PC: prospective cohort; RC: retrospective cohort; PSM: propensity score matching; RCT: randomized controlled trial; ITT: intention to treat; NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; Api: apixaban; Warf: warfarin; Dabi: dabigatran; Riva: rivaroxaban; Edo: edoxaban; SAPT: single-antiplatelet therapy; DAPT: dual-antiplatelet therapy; NA: not applicable. * The risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. A score of greater than 8% indicates high risk, 4%–8% intermediate risk, and less than 4% low risk (Dangas et al., 2020; Ishizu et al., 2021). † The CHA2DS2-VASc, is a measure of the risk of stroke among persons with atrial fibrillation. Weighted scores are based on the presence of congestive heart failure, hypertension, diabetes mellitus, or vascular disease; a history of stroke or transient ischemic attacks; an age of 65–74 years or 75 years or older; and sex. 1–2 points refer to low risk, 3–4 to moderate risk, and >5 to high risk (Jacobs et al., 2015; Van Mieghem et al., 2021). ‡ Combined endpoint event was defined as the composite of all-cause mortality, stroke, major bleeding, or any related clinical adverse events including acute kidney injury, coronary obstruction, major vascular complications, and valve dysfunction requiring reintervention.*

(Verheugt and Granger, 2015; Diener et al., 2017; Steffel et al., 2018; Ortel et al., 2020). However, the application of NOACs in patients after TAVR is still controversial (Nijenhuis et al., 2019; Saito et al., 2020). Thus, we aimed to conduct a systematic review and meta-analysis to assess the outcomes of NOACs versus VKA and NOACs versus antiplatelets in patients after TAVR, with the aim of providing some evidence for a clinical treatment strategy.

METHODS

Registration and Study Protocol

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (**Supplementary File S1**) (Moher et al., 2009). The study was registered in the PROSPERO international prospective registry of systematic reviews (CRD42020155122).

Search Strategy

A literature search prior to November 15, 2021, was conducted in PubMed, EMBASE, and the Cochrane Library databases using predefined medical subject heading terms, Boolean operators, and truncation symbols in combination with direct keywords. The detailed search strategies were as follows: "((oral anticoagulant*) OR (DOAC*) OR (NOAC*) OR (Dabigatran) OR (Apixaban) OR (Rivaroxaban) OR (Edoxaban)) AND ((transcatheter aortic valve) OR (TAVR) OR (TAVI))." To ensure a complete search, the reference lists of the identified studies were independently reviewed by two authors (D.X.L. and X.F.M.).

Inclusion and Exclusion Criteria

All included studies were either randomized controlled trials (RCTs) or observational studies that reported the baseline characteristics of patients. The inclusion criteria were as follows: 1) studies assessing at least one kind of NOAC, such as dabigatran, apixaban, rivaroxaban, and edoxaban; 2) studies comparing the effects of NOACs with vitamin K antagonist (VKA) or antiplatelets in patients who had undergone TAVR; and 3) studies reporting at least one of the following variables after agent administration: any kind of endpoint event, death, bleeding, or stroke. Abstracts with complete information were also included. In addition, we excluded animal studies, case reports, and articles for which the full text was not available in English.

Risk of Bias Assessment

A risk of bias assessment was conducted for all included studies. The Cochrane risk of bias tool was used for RCTs, and the risk of bias in non-randomized studies-of interventions (ROBINS-I) tool was used for non-RCTs (Higgins et al., 2011; Sterne et al., 2016). Both tools were evaluated with eight categories, respectively. Each domain was judged as high, low, or unclear risk of bias with the overall assessment of each study graded as low risk of bias (when more than five domains were low risk of bias), high risk of bias (at least three domains were high risk of bias), or medium risk of bias (otherwise).

TABLE 2 | Related disease history of included patients.

Author	Group	N	Atrial fibrillation, %	Hypertension, %	Diabetes mellitus, %	Renal disease, %	Coronary artery disease, %	Stroke or intracerebral bleeding, %	Permanent pacemaker, %
Seeger et al. (2017)	NOAC	141	100	NA	32.6	44.7	66	11.3	16.3
	VKA	131	100	NA	32	48.9	58.8	14.5	13.7
Geis et al. (2018)	NOAC	154	94.2	95.5	30.5	NA	51.9	15.6	NA
	VKA	172	93.6	91.9	33.1	NA	51.2	14.5	NA
Jochheim et al. (2019)	NOAC	326	99.1	89.9	28.8	53.3	56.9	18.4	NA
	VKA	636	99.1	89.5	34.1	44.3	55.4	16.5	NA
Butt et al. (2021)	NOAC	219	100	87.2	17.8	5.9	54.3	34.8	NA
	VKA	516	100	88.6	24.2	14.2	54.5	25.2	NA
Kosmidou et al. (2019)	NOAC	155	100	91.7	35.3	8.9	76.3	22	NA
	VKA	778							
Kalogeras et al. (2020)	NOAC	115	68.7	NA	24.3	NA	13.8	NA	13
	VKA	102	59.8	NA	26.8	NA	15.2	NA	17.6
Kawashima et al. (2020)	NOAC	227	100	75.8	24.2	74.4	26	10.6	8.4
	VKA	176	100	76.7	24.4	77.8	35.2	19.3	10.2
Dangas et al. (2020)	NOAC	826	0	87.2	28.6	NA	39.3	6.2	9.7
	Antiplatelet	818	0	85.2	28.7	NA	37.3	4.3	9.8
Didier et al. (2021)	NOAC	1,378	70	NA	24.2	48.6	37.2	11.5	15.9
	VKA	1,093	70	NA	21.7	51.5	33.1	13.2	15.7
Van Mieghem et al. (2021)	NOAC	713	100	90.7	37.9	NA	41.1	17.3	NA
	VKA	713	100	92.1	36	NA	41.7	16.3	NA
Collet (2021)	NOAC	749	28.3	80.9	29.5	NA	52.3	10.4	NA
	VKA/ Antiplatelet	228/ 523	26.5	80	28.5	NA	49.6	11.9	NA

NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; NA: not applicable.

Data Extraction and Outcomes of Interest

Full texts of all included studies were reviewed, and data extraction was performed by two independent authors (D.X.L. and X.F.M.), with disagreement resolved by a consensus among all authors. The characteristics of the studies included publication year, study region, study design, sample size, age, sex, body mass index, any kind of risk score for cardiovascular surgery such as the Society of Thoracic Surgeons (STS) score, the risk score for stroke for anticoagulation such as the CHA_2DS_2-VASc score, type of bioprosthetic valve, related medication, and follow-up period. In addition, previously related diseases in the patients included atrial fibrillation, hypertension, diabetes mellitus, renal dysfunction, coronary artery disease, stroke, intracerebral bleeding, and arrhythmia that required a permanent pacemaker. In the STS score system, 0%–4% refers to low risk, 4–8% to moderate risk, and >8% to high risk (Ishizu et al., 2021). In the CHA_2DS_2-VASc score, 1–2 points indicate low risk, 3–4 points moderate risk, and >5 points high risk (Jacobs et al., 2015). The main outcome was the combined endpoint event (a composite of all-cause mortality, stroke, major bleeding, or any related clinical adverse events including acute kidney injury, coronary obstruction, major vascular complications, and valve dysfunction requiring reintervention). Additional outcomes were all-cause mortality, major bleeding (including life-threatening and disabling bleeding), and stroke, respectively. All of the above-mentioned outcomes were long-term outcomes with follow-up time and were extracted as time-to-event data.

Statistical Analysis and Meta-analysis

We compared NOACs versus VKA and NOACs versus antiplatelets according to whether the patient had an indication or not for oral anticoagulation, separately. Subgroup analyses were stratified by the research type. The outcomes of interest were extracted directly from original studies as the hazard ratio (HR) accompanied by the 95% confidence interval (CI) and were pooled by the inverse variance method with a random-effects model (DerSimonian and Kacker, 2007). Statistical heterogeneity was tested using the chi-square test and I^2 test. If the result of an analysis resulted in $p < 0.05$ or $I^2 > 50\%$, the studies were considered to be heterogeneous. To explore the source of heterogeneity, if necessary, sensitivity analysis was conducted. When more than 10 studies were included in the meta-analysis, a funnel plot with Egger's regression test was performed to detect any potential publication bias (Higgins and Green, 2011). All statistical analyses were performed assuming a two-sided test at 5% level of significance, using Review Manager software (version 5.4.1; Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Search Results and Study Characteristics

According to the inclusion and exclusion criteria, 11 studies were included in the qualitative analysis (Seeger et al., 2017; Geis et al.,

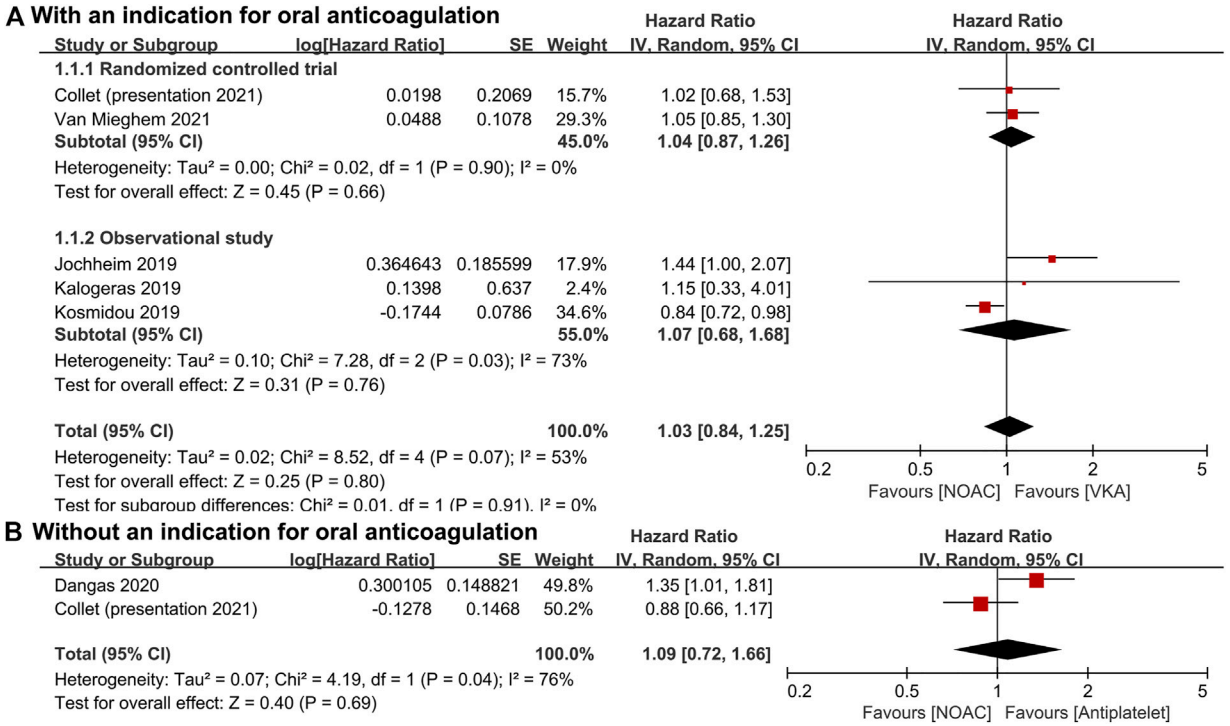

FIGURE 2 | Forest plots for combined endpoint. **(A)**: a comparison of NOAC versus VKA in TAVR patients with an indication for oral anticoagulation; **(B)**: a comparison of NOAC versus antiplatelet in TAVR patients without an indication; NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; SE: standard error; CI: confidence interval.

2018; Jochheim et al., 2019; Kosmidou et al., 2019; Dangas et al., 2020; Kalogeras et al., 2020; Kawashima et al., 2020; Butt et al., 2021; Collet, 2021; Didier et al., 2021; Van Mieghem et al., 2021). Because one study did not report outcomes of interest as the HRs we needed, 10 studies consisting of 10,563 patients who underwent TAVR were included in the meta-analysis. The detailed steps of the literature search are presented in the flow diagram in **Figure 1**. **Table 1** shows the characteristics of the included studies and patient baseline characteristics. Ten studies included the comparison of NOACs versus VKA in TAVR patients with an indication for oral anticoagulation. Two studies included the comparison of NOACs versus antiplatelet in patients without an indication.

Ten studies were published between 2017 and 2021, and one study was presented at the ACC Session in 2021. Among them, three were RCTs, three were prospective cohort studies, and the other five were retrospective cohort studies. Eight studies were conducted in Europe, one in Japan, one in the United States, and one from multiple countries. The range of the follow-up period was from 6 to 33.6 months.

Four studies included patients who were administered only a single kind of NOAC, and the remaining studies included patients administered various NOACs. The mean STS risk score ranged from 4.1 to 8.8, which indicates that most of the included patients were of moderate-to-high risk for cardiac surgery. The mean CHA_2DS_2-VASc score ranged from 4.6 to 5.6, also indicating that most patients were of moderate-to-high risk for stroke. Meanwhile, most of the included TAVR patients had various related diseases (**Table 2**).

In addition, the results of the risk of bias are demonstrated in **Supplementary File S2**. According to the Cochrane risk-of-bias tool for RCTs and the ROBINS-I tool for non-RCTs, only one observational study included in the meta-analysis was categorized as a moderate risk of bias; the others (consisting of three RCTs) were of a low risk of bias. For the three RCTs, randomized assignment with intention-to-treat analysis was used to lower the risk of bias in patient baseline characteristics such as age, sex, body mass index, valve type, risk score, and a history of related disease, as shown in **Tables 1**, **2**. For the other six observational studies, the adjustment by propensity score matching was used in the analyses to prevent potential bias in the comparison of patient groups induced by confounders, as mentioned above (Kalogeras et al., 2020).

Results of the Meta-analysis

For patients with an indication for oral anticoagulation, there were no significant differences between the NOAC and the VKA groups in the total outcomes of the combined endpoint (HR 1.03, 95% CI 0.84–1.25, $p = 0.80$; **Figure 2A**), all-cause mortality (HR 0.87, 95% CI 0.71–1.07, $p = 0.20$; **Figure 3A**), major bleeding (HR 0.92, 95% CI 0.67–1.25, $p = 0.58$; **Figure 4A**), or stroke (HR 0.99, 95% CI 0.65–1.52, $p = 0.97$; **Figure 5A**). In addition, the results of the subgroup analyses by RCTs and observational studies were consistent with the above total outcomes.

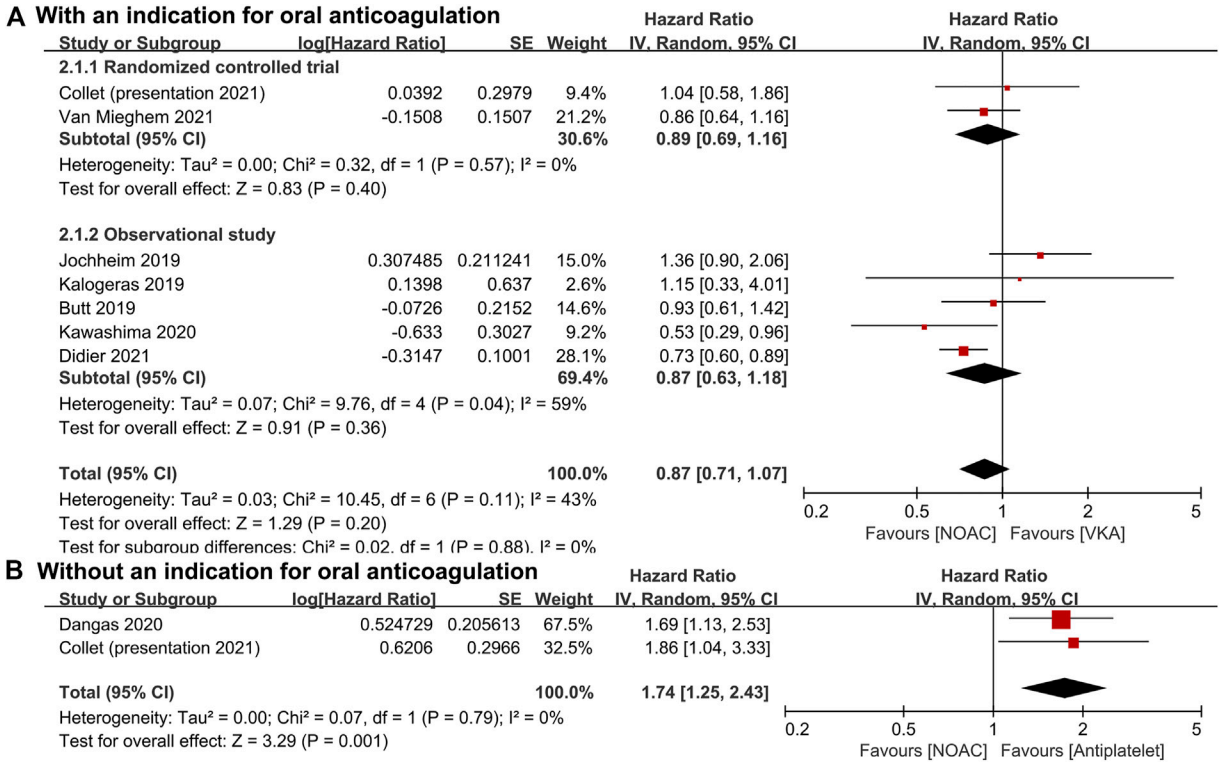

FIGURE 3 | Forest plots for all-cause mortality. **(A)**: a comparison of NOAC versus VKA in TAVR patients with an indication for oral anticoagulation; **(B)**: a comparison of NOAC versus antiplatelet in TAVR patients without an indication; NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; SE: standard error; CI: confidence interval.

For patients without an indication for oral anticoagulation, the pooled estimates of all-cause mortality (HR 1.74, 95% CI 1.25–2.43, $p < 0.05$; **Figure 3B**) favored antiplatelet rather than NOAC administration. In addition, the pooled estimates of the combined endpoint (HR 1.09, 95% CI 0.72–1.66, $p = 0.69$; **Figure 2B**), major bleeding (HR 1.28, 95% CI 0.93–1.77, $p = 0.14$; **Figure 4B**), and stroke (HR 1.20, 95% CI 0.71–2.04, $p = 0.50$; **Figure 5B**) showed no significant differences between the two groups. Because both included studies were RCTs, there was no subgroup analysis in the comparison.

Sensitivity Analysis and Publication Bias

We conducted sensitivity analyses to ascertain the primary origin of heterogeneity. After temporarily omitting one study (Kosmidou et al., 2019; Kosmidou et al., 2019; Didier et al., 2021) from the combined analyses, we found that the pooled estimates of endpoint (HR 1.12, 95% CI 0.95–1.32, $p = 0.19$, $I^2 = 0\%$), major bleeding (HR 1.06, 95% CI 0.82–1.36, $p = 0.67$, $I^2 = 30\%$), and stroke (HR 0.77, 95% CI 0.56–1.08, $p = 0.13$, $I^2 = 0\%$) were still consistent with the former values (HR 1.03, 95% CI 0.84–1.25, $p = 0.80$, $I^2 = 53\%$, HR 0.92, 95% CI 0.67–1.25, $p = 0.58$, $I^2 = 66\%$, HR 0.99, 95% CI 0.65–1.52, $p = 0.97$, $I^2 = 61\%$, respectively). Therefore, we could consider these synthetic results stable and convincible. We planned to conduct a funnel plot with Egger's regression test to detect the publication bias across the studies; however, none of the outcomes met the criteria of including a minimum of 10 studies.

DISCUSSION

This meta-analysis included RCTs and non-RCTs for the evaluation of comparisons of NOACs with VKA or antiplatelets in the long-term outcomes of patients undergoing TAVR with or without an indication for oral anticoagulation. We found no significant differences between the NOAC and the VKA groups in the combined endpoint, all-cause mortality, major bleeding, or stroke. However, we did observe significant differences in the all-cause mortality between the NOAC and antiplatelet groups.

We noticed that although Liang et al. (2020) and Ueyama et al. (2020) conducted two meta-analyses that compared NOACs with VKA in patients after TAVR, Liang et al. included seven studies of 5,089 patients for the meta-analysis, and they demonstrated a priority in VKA against NOACs in stroke (risk ratio 1.44, 95% CI 1.05–1.99, $p = 0.02$) (Liang et al., 2020). Ueyama et al. conducted a meta-analysis involving 2,569 patients from five studies and found that all-cause mortality (odds ratio [OR] 1.07, 95% CI 0.73–1.57, $p = 0.72$), major and/or life-threatening bleeding (OR

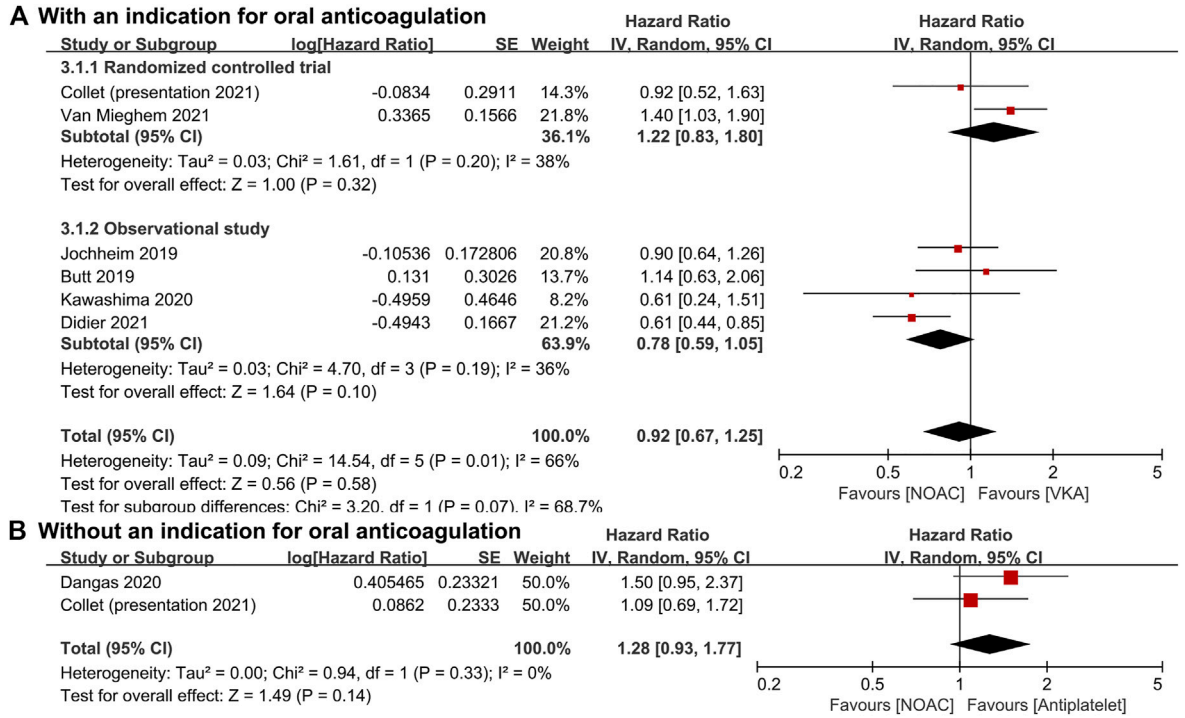

FIGURE 4 | Forest plots for major bleeding. **(A)**: a comparison of NOAC versus VKA in TAVR patients with an indication for oral anticoagulation; **(B)**: a comparison of NOAC versus antiplatelet in TAVR patients without an indication; NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; SE: standard error; CI: confidence interval.

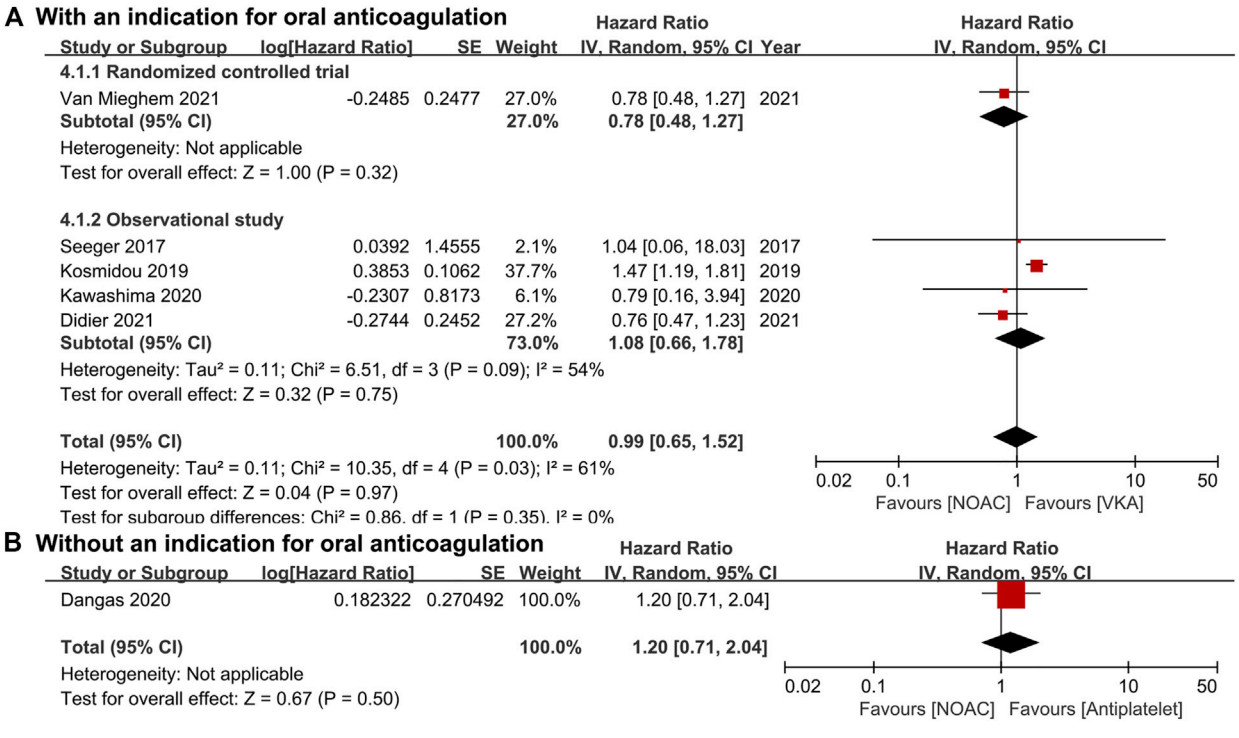

FIGURE 5 | Forest plots for stroke. **(A)**: a comparison of NOAC versus VKA in TAVR patients with an indication for oral anticoagulation; **(B)**: a comparison of NOAC versus antiplatelet in TAVR patients without an indication; NOAC: non-vitamin K oral anticoagulant; VKA: vitamin K antagonist; SE: standard error; CI: confidence interval.

0.85, 95% CI 0.64–1.12, $p = 0.24$), and stroke (OR 1.52, 95% CI 0.93–2.48, $p = 0.09$) were similar between DOACs and VKA in patients undergoing TAVI with concomitant indication for oral anticoagulation.

Two points in our study were different from the above studies. First, to assess the follow-up outcomes related to time, we calculated the time-to-event data as the HR value. Second, we aimed to focus on the effects of NOACs on TAVR patients. Thus, we included studies involving NOAC administration, regardless of whether the patients did or did not have an indication for anticoagulation. As a result, two kinds of comparisons were performed based on whether patients had an indication for oral anticoagulation, respectively, that is, patients with an indication for oral anticoagulation (NOACs versus VKA) and patients without an indication (NOACs versus antiplatelet). Such two points make this study different from the previous ones, and we believe that the results of our study can supplement the conclusions of previous studies and provide evidence for clinical decision-making.

About the risk of bias, because of the utility of intention-to-treat analysis in RCTs and propensity score matching in most observational cohorts, the risks of bias were lowered, and nine of the included studies were of low risk of bias.

As the main outcome, the combined endpoint was mostly defined as the composite of all-cause mortality, stroke, major bleeding, and other critically relevant cerebrovascular events (Jochheim et al., 2019; Butt et al., 2021). The studies by Jochheim et al. (HR 1.44, 95% CI 1.00–2.07, NOAC vs. VKA), Kalogeras et al. (HR 1.15, 95% CI 0.33–4.04, NOAC vs. VKA), Van Mieghem et al. (HR 1.05, 95% CI 0.85–1.31, NOAC vs. VKA), and Collet et al. (HR 0.92, 95% CI 0.73–1.16, apixaban vs. standard of care) all showed that during the follow-up, there were no significant differences in the long-term endpoint between the NOAC and other groups (Jochheim et al., 2019; Kalogeras et al., 2020; Collet, 2021; Van Mieghem et al., 2021). However, Dangas et al. reported a higher risk of death or thromboembolic events (HR 1.35, 95% CI 1.01–1.81) in the rivaroxaban group as compared with the antiplatelet group (Dangas et al., 2020).

With regard to the risk of death, Butt et al. not only compared the all-cause mortality between NOACs and VKA (HR 0.93, 95% CI 0.61–1.40) but also performed subgroup analyses of dabigatran versus VKA, rivaroxaban versus VKA, and apixaban versus VKA and found no significant difference between any of them (Butt et al., 2021). Moreover, Jochheim et al. (HR 1.36, 95% CI 0.90–2.06) and Collet et al. (HR 1.04, 95% CI 0.58–1.86) after 1-year follow-up and Kalogeras et al. (HR 1.15, 95% CI 0.33–4.04) after 2-year follow-up also reported no significant differences in mortality between the NOAC and the VKA groups (Jochheim et al., 2019; Kalogeras et al., 2020; Collet, 2021). However, Kawashima et al. (HR 0.53, 95% CI 0.29–0.96) and Didier et al. (HR 0.73, 95% CI 0.60–0.89) demonstrated that as compared with VKA, NOACs might be associated with lower long-term mortality in TAVR patients with concomitant atrial fibrillation (Kawashima et al., 2020). In patients with nonvalvular atrial fibrillation, NOACs were also reported to be associated with a reduced risk of all-cause mortality as compared with warfarin, especially in Asian patients (Chan et al., 2018; Xue and Zhang, 2019).

Among patients who do not require oral anticoagulation, Dangas et al. reported a total of 64 deaths in the rivaroxaban group and 38 in the antiplatelet group, respectively (HR 1.69, 95% CI 1.13–2.53), indicating a higher mortality rate in the rivaroxaban group (Dangas et al., 2020). Meanwhile, Collet et al. also found a higher risk of all-cause death (HR 1.86, 95% CI 1.04–3.34), especially noncardiovascular death (HR 2.99, 95% CI 1.07–8.35), in the apixaban group compared with the antiplatelet group (Collet, 2021). Most deaths occurred long after the discontinuation of the trial drug and were due to noncardiovascular causes, such as sepsis or acute renal failure (Dangas et al., 2020; Collet, 2021). The mechanism of the higher mortality in the NOAC group remains unclear.

As one of the most important complications, major bleeding (including disabling and life threatening) was also use to assess the safety of NOACs and other antithrombotic agents. Major bleeding occurred in 46 patients in the NOAC group and 31 patients in the antiplatelet group, respectively (HR, 1.50; 95% CI, 0.95–2.37) according to Dangas et al. (Dangas et al., 2020). Although Butt et al. (HR 1.14, 95% CI 0.63–2.06), Jochheim et al. (HR 0.90, 95% CI 0.64–1.26), and Kawashima et al. (HR 0.61, 95% CI 0.25–1.52) also reported no increased risk of long-term major bleeding between the NOAC and the VKA treatments, Van Mieghem et al. (HR 1.40, 95% CI 1.03–1.91) showed higher risk and Didier et al. (HR 0.61, 95% CI 0.44–0.85) showed lower risk in the NOAC group (Jochheim et al., 2019; Kawashima et al., 2020; Butt et al., 2021; Didier et al., 2021; Van Mieghem et al., 2021). In patients with nonvalvular atrial fibrillation, NOACs were suggested with a decreased risk of major bleeding compared with VKA (Caldeira et al., 2015; Chan et al., 2018; Xue and Zhang, 2019). In patients with heart failure, apixaban might be associated with a comparable risk of major bleeding compared with aspirin, while other NOACs might be associated with a higher risk (Huang et al., 2020).

As another important complication after TAVR, stroke might occur due to the thrombosis in patients with low-intensity anticoagulation or no anticoagulation (Hansson et al., 2016; Otto et al., 2021). During the follow-up, incidences of both ischemic (HR 1.28, 95% CI 0.73–2.23) and hemorrhagic (HR 0.67, 95% CI 0.11–3.67) stroke did not differ significantly between the NOAC and antiplatelet groups in patients without an indication (Dangas et al., 2020). Similarly, in patients with an indication, the risks of all strokes were not significantly different between the NOAC and the VKA groups (Seeger et al., 2017; Kawashima et al., 2020; Didier et al., 2021; Van Mieghem et al., 2021). However, NOACs have been shown to be more effective than VKA for reducing the risk of stroke in patients with nonvalvular atrial fibrillation (Granger et al., 2011; Ajam et al., 2020; Diener et al., 2020).

In addition, although rivaroxaban and apixaban are considered to be associated with a lower risk of subclinical valve thrombosis (Dangas et al., 2020; Collet, 2021), because of the unexplained higher mortality, we, for now, cannot suggest

NOACs as a routine antithrombotic therapy in patients who have undergone TAVR who do not require oral anticoagulation.

LIMITATIONS

This study has several limitations. First, because of the limited number of included studies, there might be publication bias in our pooled estimates, and thus the results should be interpreted with caution. Second, the patients included in most studies were administered both anticoagulation and antiplatelet agents in the early term; therefore, the early-term outcomes might be affected by the unknown potential interaction. For this reason, we did not use the early-term but rather the long-term outcomes to assess the safety and efficacy of NOACs in TAVR patients. Third, a different category of NOACs and a different type of implanted bioprosthetic valve might be the origin of the heterogeneity; thus, to make the results more reliable, we performed analyses using a random-effects model. Fourth, although most included TAVR patients were of moderate-to-high risks for cardiac surgery and stroke, original studies did not separate them into two different risk subgroups, respectively. Therefore, this meta-analysis could not specifically check those high-risk patients.

CONCLUSION

For patients with an indication for oral anticoagulation after TAVR, NOACs may be an alternative with noninferior outcomes to VKA. However, for patients with no indication, the use of an antiplatelet appears to be a safer choice, with a lower rate of all-cause mortality as compared with NOACs. Given that some limitations cannot be overcome, more high-quality studies and follow-up data are needed to confirm our findings.

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

DL and XM wrote the manuscript. YQ designed the research. DL, XM and XZ performed the literature search and data analysis. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.755009/full#supplementary-material

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Medication Use and Costs Among Older Adults Aged 90 Years and Older in Italy

Maria Beatrice Zazzara[1], Agnese Cangini[2], Roberto Da Cas[3], Ilaria Ippoliti[3], Alessandra Marengoni[4], Andrea Pierantozzi[2], Elisabetta Poluzzi[5], Simona Zito[2], Graziano Onder[6] and the Italian Working Group on Medication Use in the Elderly*

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [2]Agenzia Italiana Del Farmaco, Rome, Italy, [3]Pharmacoepidemiology Unit, National Centre for Drug Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy, [4]Department of Clinical and Experimental Sciences, Università Degli Studi di Brescia, Brescia, Italy, [5]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [6]Department of Cardiovascular and Endocrine-Metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome, Italy

Older adults are often affected by multiple chronic conditions and experience geriatric syndromes that may affect the risk/benefit profile of medications. Little is known about the use of such medications in the older population. This article describes medication use and costs in Italian adults aged ≥90 years. Data from the 2019 Pharmaceutical Prescriptions database, concerning data on medications reimbursed by the Italian National Health Service, were analyzed in terms of prevalence and amount of use expressed as defined daily dose/1,000 users (DDD/1,000 users/day), accounting for different age-groups and sex. All individuals aged ≥90 years used at least one medication, with a mean number of 3128 DDD/1,000 users/day corresponding to an annual cost of 683 euros per user. Both use and costs linearly decreased with increasing age, with men accounting for a higher amount of DDD/1,000 users and costs than women across all age-groups. Antihypertensives (1330 DDD/1,000 inhabitants), antiplatelet agents (337 DDD/1,000 inhabitants), medications for peptic ulcer and gastroesophageal reflux (328 DDD/1,000 inhabitants), and lipid-lowering agents (166 DDD/1,000 inhabitants) were the most frequently used medications. We observed a progressive decrease in the usage of the majority of medications with increasing age, with the exception of antibiotics and antipsychotics. Individuals aged ≥90 years used a lower DDD/1,000 users, with an associated decrease in annual costs. The persistent use of preventive medications highlights the potential lack of awareness regarding medication rationalization and guidance for optimizing prescriptions. Our findings highlight the need for further initiatives to improve medications' appropriateness in these older age-groups.

Keywords: older adults, medication appropriateness, inappropriate prescribing, centenarians, medication use

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Ria Benko,
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Janet Sultana,
Mater Dei Hospital, Malta
Mario Ulises Pérez-Zepeda,
Dalhousie University, Canada

****Correspondence:***
Maria Beatrice Zazzara
mariabeatrice.zazzara@policlinicogemelli.it

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INTRODUCTION

The proportion of older adults has increased worldwide (United Nations, 2019) and so has the number of medications regularly used by older adults (Onder et al., 2014a; Charlesworth et al., 2015; Gao et al., 2018). Older adults are often affected by multiple chronic conditions, often have complex polypharmacy regimens, and experience geriatric conditions such as cognitive impairment, hearing

and vision impairment, sarcopenia, and frailty that can limit the effectiveness, safety, and ability to use several medications (Cherubini et al., 2012; Poudel et al., 2013; Onder et al., 2014a; Onder et al., 2018).

The use of medications in the oldest old—older adults aged 80 years and older—adds further complexity, due to changes in the risk/benefit profile of pharmacologic treatments (Onder et al., 2014a; Charlesworth et al., 2015; Gao et al., 2018). Treatment adherence might be limited due to the presence of cognitive and functional deficits. Life expectancy may be shorter than the *time until benefit* of medications frequently used for primary or secondary prevention (Onder et al., 2014a; Onder et al., 2018). In addition, the use of multiple medications may trigger the onset of and worsen the symptoms of geriatric syndromes, such as falls (Dhalwani et al., 2017) and delirium (Aloisi et al., 2019), with a significant impact on the quality of life of the oldest old. Furthermore, medication metabolism is often altered by kidney and liver disorders, leading to an increased risk of adverse drug reactions, hospitalization, medication-related morbidity and mortality (Cherubini et al., 2012; Pérez et al., 2018; Fralick et al., 2020; Zazzara et al., 2021), and healthcare costs (Watanabe et al., 2018). Finally, older multimorbid and frail individuals are frequently excluded from clinical trials (Poudel et al., 2013; Aloisi et al., 2019), with scarce evidence and guidelines relevant for this population (Dhalwani et al., 2017; Zazzara et al., 2021).

In the absence of high-quality evidence and recommendations, physicians often face the onerous task of evaluating risks and benefits of pharmacological treatments (Onder et al., 2016). In this study, we aim to outline national characteristics of medication use and relevant annual costs in Italian older adults aged 90 years and older and highlight possible differences and similarities with adults aged 70–79 and 80–89 years. These findings may be relevant for identifying ways to improve the prescribing process and deprescribing and to formulate guidance on pharmacological treatments for older adults.

METHODS

Italian Pharmaceutical Reimbursement System

In Italy, the costs of care for older people are largely covered by the National Health Service [Servizio Sanitario Nazionale (SSN)], based on universal entitlement. The SSN covers costs of pharmacologic treatment for most diseases, providing universal pharmaceutical coverage to the whole population. The conditions of the reimbursement system are established at a national level. Costs of medications are the same all year long and across Italian regions. Reimbursed drugs include essential medications that are proven to be effective for the treatment of acute or chronic diseases (i.e., antihypertensive drugs, antibiotics, hypoglycemic agents, antibiotics, antidepressants, antiplatelet agents, and anticoagulants.). Non-reimbursed drugs include non-essential medications that can be dispensed to citizens with or without a medical prescription and over-the-counter medications (Onder et al., 2014b; The Medicines Utilisation Monitoring Centre, 2021).

Data Analysis

Data were extrapolated from the Pharmaceutical Prescriptions database (also known as the Italian Health Insurance Card database) that includes anonymized patient-level data on medications prescribed and dispensed by community pharmacies and reimbursed by Italian SSN in the Italian population (The Medicines Utilisation Monitoring Centre, 2021). Information on each drug package, identified via package unique identifier codes and the fifth level Anatomical Therapeutic Chemical (ATC) classification (World Health Organization, 2021), was tracked at individual level in an encrypted format. Based on these data from the Pharmaceutical Prescriptions database, the Osservatorio Nazionale sull'Impiego dei Medicinali "OsMed" (Medicines Utilization Monitoring Centre), an organ of the Italian Medicines Agency (AIFA), publishes an annual report on consumption and expenditure of medications supplied by the SSN and changes over time and across different Italian regions (Italian Medicines Agency, 2021; The Medicines Utilisation Monitoring Centre, 2021). This report aims to facilitate the circulation and dissemination of healthcare-related public information. Article number 50 of Italian Law 24 November 2003, n. 326, with regard to the monitoring of healthcare expenditure and appropriateness of medical prescription, ensure the publication of these data (Gazzetta Ufficiale della Repubblica Italiana, 2003).

We conducted a descriptive analysis of data on patients aged 90 years and older, with an overview of differences and similarities with patients aged 70–79 and 80–89 years. Data were analyzed in terms of prevalence and amount of use expressed as defined daily dose per 1,000 users (DDD/1,000 users per day) and reported accounting for different age-groups, sex, and Italian regions, and in terms of both DDD per 1,000 inhabitants per day and prevalence of use for different pharmaceutical classes of medications. The defined daily dose (DDD) is a technical unit of measurement created to address drug consumption with the aim of reducing intraregional and international variabilities and represents the average maintenance dose per day of a certain medication in adult subjects, in relation to the main therapeutic indication of the drug (therefore, it is a standard unit and not the recommended dose for the single patient) (World Health Organization, 2021).

We initially considered the prevalence of medication use across three macro age-groups: 70–79, 80–89, and 90 years and older. Prevalence was calculated by dividing the number of individuals receiving at least one medication in 2019 by the total number of Italian individuals in that age-group according to the Italian National Institute of Statistics in January 2019 [70–79 years, n = 5,928,218 (9.9% of the whole population); 80–89 years, n = 3,530,515 (5.9%); 90 years or older, n = 765,773 (1.3%)] (Istituto Nazionale di Statistica, 2021a). We then focused our analysis on characteristics of use per pharmaceutical class of medications within the age-group of oldest individuals aged 90 years or older, which was further subcategorized into three age-groups: 90–94, 95–99, and ≥100 years. The number of medications was determined by the number of medications prescribed and dispensed in 2019 for each

TABLE 1 | Medication use by sex and age-group (2019).

	Total	Men	Women
70–79 years			
DDD/1,000 users per day	3,189	3,494	2,932
Prevalence of use (%)	97	97	97
Annual cost per user (Euros)	670	733	617
Number of medications (median—25^{th}–75^{th} percentile)	7 (4–10)	7 (4–10)	7 (4–10)
Users with 5+ medications (%)	69	68	70
Users with 10+ medications (%)	29	28	30
80–89 years			
DDD/1,000 users per day	3,677	3,981	3,472
Prevalence of use (%)	100	100	100
Cost per user (Euros)	805	890	748
Number of medications (median—25^{th}–75^{th} percentile)	8 (5–12)	8 (5–12)	8 (5–12)
Users with 5+ medications (%)	79	79	79
Users with 10+ medications (%)	38	38	38
≥90 years			
DDD/1,000 users per day	3,128	3,483	2,984
Prevalence of use (%)	100	100	100
Cost per user (Euros)	683	802	634
Number of medications (median—25^{th}–75^{th} percentile)	8 (5–11)	8 (5–12)	8 (5–11)
Users with 5+ medications (%)	76	79	76
Users with 10+ medications (%)	36	39	35

user using fifth level ATC codes, with each individual receiving at least one prescription in 2019. The mean number of DDD per 1,000 users (inhabitants) per day was calculated by dividing the total number of DDDs prescribed and dispensed during 2019 for individuals in each age-group by the total number of adults in the Italian population in that age-group. Results were then divided by 365 days and reported per 1,000/users (inhabitants)/day. The prevalence of use for each pharmaceutical class of medications was calculated by dividing the number of individuals in 2019 receiving at least one medication within a specific pharmaceutical class of medications by the total number of Italian individuals in that age-group (90–94; 95–99, and ≥100 years).

As additional analysis, we estimated variation in medication use as measured by the mean number of DDDs/1,000 users per day, across the 21 Italian regions and autonomous provinces. The costs were calculated based on gross expenditure on the medication on the Italian market (Italian Medicines Agency, 2021). Annual costs per user were calculated by dividing the overall costs of medications prescribed and dispensed during 2019 in individuals in each age-group by the total number of individuals receiving at least one medication during 2019 in the same age-group.

RESULTS

Data on the trend of medication use in individuals aged 70–79 years, 80–89 years, and 90 years or older are shown in **Table 1**. Individuals aged 90 years or older used at least one medication and received a mean number of 3128 DDD/1,000 users/day corresponding to an annual cost of 683 euros per user. Individuals aged 80–89 years had a similar prevalence of use but used a substantially higher amount of medications (DDD/1,000 users per day = 3,677, +18%) and were responsible for higher annual costs per user, while individuals aged 70–79 years had a slightly lower prevalence of use (97%), used 3189 DDD/1,000 users per day similarly to those aged 90 years and older, and had intermediate annual costs per user. Men had higher usage and were responsible for higher costs than women, across all age-groups. The median number of medications per day was seven in both men and women aged 70–79 years and eight in both men and women aged 80–89 and 90 years and older. The proportion of women use ≥5 or ≥10 medications was higher than that of men in the age-group 70–79 years (70 vs. 68% and 30 vs. 28%, respectively) but lower in those aged 90 years or older (76 vs. 79% and 35 vs. 39%).

Figure 1 shows that among individuals aged ≥90 years, the number of DDD/1,000 users and annual costs linearly decreased with increasing age, with a substantial reduction in medication use and annual costs among centenarians. Differences between men and women were consistent across age-groups, with men taking a higher number of medications per day (3587 DDD/1,000 users in men aged 90–94; 3122 DDD/1,000 in women aged 90–94) and having a higher overall expenditure (829 euro annual cost per male user aged 90–94 versus 667 euro annual cost per female user aged 90–94). In addition, we observed variability across the 21 Italian regions and autonomous provinces in terms of DDD/1,000 users per day, with values ranging from 2849 DDD/1,000 users to 3467 DDD/1,000 users per day with a difference of 32% (**Supplementary Figure S1**).

Consumption of DDD/1,000 inhabitants/day per pharmaceutical class of medications according to the three subcategories of oldest adults aged 90–94, 95–99, and≥100 years and sex is presented in **Table 2**. Antihypertensives were the most frequently used medications (1330 DDD/1,000 inhabitants per day) among Italian older adults aged 90 years and older, followed by antiplatelet agents, medications for peptic ulcer and gastroesophageal reflux disease (GERD), and lipid-lowering agents (ranged between 337 and 166 DDD/1,000 inhabitants per day). With increasing age, we observed a significant reduction in the

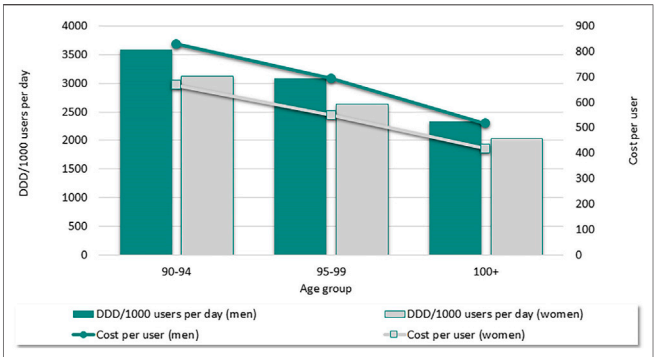

FIGURE 1 | Mean number of DDD/1,000 users per day and cost per user by sex and age-group (2019).

use of most classes of medications analyzed, with the exception of antibiotics and antipsychotics that showed an increase in DDD/1,000 inhabitants per day, especially in the ≥100 years of age-group. We observed a substantial reduction in the use of antihypertensive agents with increasing age (1361 DDD/1,000 inhabitants per day for the 90–94 age-group, 1241 DDD/1,000 inhabitants per day for the 95–99 age-group, and 985 DDD/1,000 users per day for the group aged ≥100). The use of antiplatelet agents was consistent across all age-groups of adults aged ≥90 years with only small differences between men (382 DDD/1,000 inhabitants per day) and women (321 DDD/1,000 inhabitants per day). The use of medications for peptic ulcer and GERD and lipid-lowering agents demonstrated a progressive reduction of usage across the three different age-groups with a higher consumption level in men than in women for both classes of medications. Antiparkinsonian and antidementia medications showed a significant reduction between the three subcategories of older individuals, especially among centenarians. **Table 2** also shows that medications for genito-urinary disorder were used mostly by men (493 DDD/1,000 inhabitants per day in men compared to one DDD/1,000 inhabitants per day in women). Conversely, medications for osteoporosis treatment were more frequently used by women (108 DDD/1,000 inhabitants per day) than men (44 DDD/1,000 inhabitants per day).

The prevalence of use per pharmaceutical class of medications according to subcategories of oldest adults aged (90–94, 95–99, and ≥100 years) and sex is shown in **Supplementary Table S1**.

DISCUSSION

In this study, we showed that among older adults aged 90 years and over, consumption of medications progressively decreases with increasing age, with an associated decrease in overall annual costs. Although the prevalence and median number of medications per day appear comparable to adults aged 80–89 years, the reduction in the amount of medications used (as measured by mean number of DDD/1,000 users per day) was particularly significant, especially among centenarians.

The hypothesis that our results could only be related to a change in the number of users per day, in a country with such high proportions of oldest old as Italy (Istituto Nazionale di Statistica, 2021), seems a bit simplistic and might undermine important nuances of this complex population.

The gradual reduction of medication burden after 90 years of age might be due to physiological changes in pharmacodynamics and pharmacokinetics that occur with aging that require a

TABLE 2 | Consumption (DDD/1,000 inhabitants per day) by sex and age-group (2019) for pharmaceutical classes.

	Men				Women				Total			
	90-94	95-99	100+	Total	90-94	95-99	100+	Total	90-94	95-99	100+	Total
Antihypertensives	1,416	1,293	950	1,391	1,339	1,226	992	1,308	1,361	1,241	985	1,330
Antiplatelet agents	379	398	377	382	319	331	310	321	336	345	320	337
Medications for peptic ulcer and GERD	350	360	329	351	323	313	273	320	331	323	281	328
Lipid-lowering agents	239	148	63	223	162	93	44	145	184	105	47	166
Medications for genito-urinary disorders	496	486	404	493	1	1	1	1	142	106	63	133
Antidepressants	93	87	72	92	139	115	80	133	126	109	79	122
Antidiabetics	146	104	64	138	118	87	61	111	126	91	61	118
Anticoagulants	139	115	84	135	108	95	71	104	117	100	73	112
Medications for per asthma and COPD	162	155	127	160	81	78	67	80	104	95	76	102
Medications for eye disorders	121	116	110	120	85	78	56	83	95	86	64	93
Medications for osteoporosis	44	44	42	44	116	85	55	108	95	76	53	91
Thyroid medications	21	18	13	21	47	37	24	44	39	33	22	38
NSAIDs	33	32	32	33	38	32	25	36	37	32	26	35
Antibiotics	36	44	54	38	28	33	36	29	30	35	39	31
Pain medications	23	21	17	22	34	30	21	33	31	28	20	30
Antiparkinsonian medications	27	17	11	25	17	11	7	16	20	13	7	18
Antiepileptics	16	14	12	16	15	13	9	14	15	13	10	15
Antipsychotics	10	13	13	11	14	17	15	15	13	16	15	14
Antidementia medications	12	5	2	11	14	6	2	12	14	6	2	12

GERD = gastroesophageal reflux disease.
COPD = chronic obstructive pulmonary disease.
NSAIDS = non-steroidal anti-inflammatory drug.

mandatory adjustment of the dosage, determining a decrease in DDD/1,000 users per day (Zazzara et al., 2021). Our observation could relate to a more sophisticated phenomenon referred to as the "*healthier survivor effect*"—the possibility of a natural selection of healthier subjects more resistant to traditional risk factors (Robins, 1986; Evert et al., 2003; Hadley and Rossi, 2005; Hagberg and Samuelsson, 2008; Onder et al., 2016) that might have delayed or eluded the onset of common diseases and fatal illness (Evert et al., 2003).

Furthermore, the reduction in the amount of medications could be explained by a different attitude of physicians toward the prescribing process, with increased attention to avoiding inappropriate prescriptions (Cherubini et al., 2012; Onder et al., 2014b). For example, we have outlined a significant decrease in the use of lipid-lowering medications, probably related to an increased awareness among clinicians of their relatively reduced beneficial effect in primary prevention (Armitage et al., 2019).

However, we observed a frequent use of medicines prescribed for the treatment and primary and secondary prevention of cardiovascular events, such as antihypertensives and antiplatelet agents, whereas the use of preventive treatment in the older population may not always seem appropriate when life expectancy versus time to benefit of the medications is taken into consideration.

If true that inappropriate prescriptions involve both unnecessary or omitted treatments and age alone cannot be a detriment to a new prescription when needed, especially if in the absence of any contraindications (Cherubini et al., 2012), at the same time the use of some specific classes of medications in the very old population raises some concerns. Despite extensive literature addressing the role of acetylsalicylic acid in older adults and suggesting an unbeneficial role in several cases (O'Sullivan, 2019), we still found a high prevalence of antiplatelet agent use, likely prescribed for secondary prevention in the examined population. Particular concern also emerges from the data on GERD medication, the prolonged use of which is associated with important adverse events in older adults (Maes et al., 2017). Concern also derives from the data on the use of medications for osteoporosis treatment. The evidence of benefit versus harm over longer periods of treatment in frail multimorbid individuals is scarce, and therefore, a continuous utilization among centenarians appears inappropriate (National Guideline Centre, 2016; Onder et al., 2018). The persistent use of preventive medications might reflect a lack of awareness of physicians toward medication reconciliation, review, and deprescribing (Crisafulli et al., 2021) in the oldest old. This highlights the need for further guidance to improve appropriate prescribing and identify potentially inappropriate medications and potential omissions, thus avoiding any possible age-related bias (Onder et al., 2018; Zazzara et al., 2021). Furthermore, we highlighted a significant difference in medication use between men and women that likely indicates a higher burden of chronic disease in men at older age (Prince et al., 2015).

Finally, we outlined a regional variability of drug utilization across Italy that could reflect different regional demographics, regional regulations, or different distribution of chronic diseases (Onder et al., 2018; Zazzara et al., 2021). While evaluating reasons for this national variability is behind the scope of this work, it could reflect the lack of precise clinical guidelines on prescribing in this population.

Strengths and Limitations

In this study, we have analyzed data of the entire Italian population aged 90 years and older and provided important insights into medication utilization. Italy is one of the countries with the oldest population worldwide, with more than seven million people aged 75 years and older and 765 thousand aged over 90 in 2019 (Istituto Nazionale di Statistica, 2021b). These data, though not generalizable to populations from other countries, frame a picture of a country with a high proportion of older individuals and reflect the difficulties and issues of constructing precise prescription guidelines for the oldest adults.

Nonetheless, this study has several limitations. We conducted a descriptive analysis on a national database that collects prespecified information, and possible confounders might have been undermined. Due to the nature of the data, we were unable to address differences in medication use according to important geriatric syndromes, such as frailty and cognitive and physical impairment. The analysis relied on data from an administrative database and information on the diagnosis for which medications were dispensed was not available. Eliciting whether the indication for a medication was appropriate is thus not possible. Also, the analysis did not assess data on compliance and actual intake of the medications, particularly important in case of individuals with cognitive impairment or neglected care.

Furthermore, data on reimbursed medications exclude unfilled prescriptions and non-reimbursed medications such as benzodiazepines or phytotherapics or over-the-counter medications. This might have led to an underestimation of the mean number of medications, consumption, and expenditure. Finally, the annual analysis may have included individuals who died within the year and the difference in medication use across the three different macro age-groups (70–79; 80–89; ≥100) might have been influenced by a different mortality rate. Therefore, the reduction of medication utilization in the older decades might be a partial reflection of an increased mortality or a shorter period of observation.

CONCLUSION

In our study, we described characteristics of medication use and related costs in the oldest individuals aged ≥90 years, and with regard to those aged 70–79 and 80–89 years. There are limited data from clinical trials and guidance relevant for these older age-groups. Our study highlights the need for evidence to improve medication use in the oldest old and allow physicians to feel more confident when prescribing for older adults.

A targeted—yearly—review of medication regimens is strongly advised to avoid utilization of medications that can become redundant or even dangerous for the vulnerable older population. The inclusion of older adults in clinical trials will help

generate an evidence base for the use of medications in older adults. Our findings are helpful to plan and implement interventions aimed at improving the appropriateness of medication use, influencing policy makers, and reducing national variability.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Raw data on consumption and expenditure of medications at a national and regional level are published every year in the Open data by the AIFA's Medicines Utilisation Monitoring Centre (OsMed). https://www.aifa.gov.it/en/dati-aifa.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

GO, RD and EP designed and supervised the study. AP, RD and II carried out data analysis. AC, AP, SZ contributed to data collection. MBZ contributed to literature search, the interpretation of results, and writing of the manuscript. GO critically revised the analyses and the interpretation of the findings and contributed to writing of the manuscript. AC, AM, AP, EP, II, RD, SZ and GO critically revised the manuscript. All the co-authors reviewed the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

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Identifying Potential Drug-Related Problems Among Geriatric Patients With Use of an Integrated Clinical Decision Support Tool

Veera Bobrova[1], Daniela Fialová[2,3], Shane Desselle[4], Jyrki Heinämäki[1] and Daisy Volmer[1]*

[1]Faculty of Medicine, Institute of Pharmacy, University of Tartu, Tartu, Estonia, [2]Department of Social and Clinical Pharmacy, Faculty of Pharmacy in Hradec Králové, Charles University, Prague, Czechia, [3]Department of Geriatrics and Gerontology, First Faculty of Medicine, Charles University, Prague, Czechia, [4]Touro University California College of Pharmacy, Vallejo, CA, United States

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****Correspondence:***
Veera Bobrova
veera.bobrova@ut.ee

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Background: Drug-related problems (DRPs) which arise from potentially inappropriate medications (PIMs) are a common problem in older people with multi-morbidity and polypharmacy.

Aim: To develop an integrated PIM clinical decision support tool for identification of DRPs in geriatric multi-morbid polypharmacy patients, using the EU(7)-PIM and EURO-FORTA lists, with a focus on high-risk medications.

Methods: The integrated PIM tool used the information on PIMs in both databases—the EU(7)-PIM and EURO-FORTA. PIMs were classified into four color groups based on risk profile: high-risk PIMs (should be avoided in older patients) as red, moderate-risk PIMs (require dose and/or treatment duration adjustment) as yellow, low-risk PIMs (low DRP risk) as green, and questionable PIMs (incomplete/missing information) as grey.

Results: The summarized list of the high-risk (red and some grey) PIMs contained 81 active substances and medication classes. According to the ATC classification, most of the high-risk PIMs (n = 60, 74.1%) belong to the A, C, and N medication groups and 50.6% (n = 41) of the high-risk PIMs have currently marketing authorization in Estonia. The preliminary list of the moderate- and low-risk (yellow, green, and other grey) PIMs contained 240 active substances and medication classes, but sub-classification of this category into one or another group depends mainly on an individual patient´s clinical characteristics in a concrete analyzed study sample and needs further research.

Conclusion: The integrated clinical decision support tool based on the EU(7)-PIM and EURO-FORTA criteria addresses the need for more efficient identification of DRPs. It can be applied to identify PIMs and geriatric prescribing problems in different health care settings, and also in a context of little clinical information available.

Keywords: drug related problems, Estonia, multi-morbidity, older adults, polypharmacy, potentially inappropriate medications, clinical decision support tool

INTRODUCTION

As the world's population ages, the proportion of older patients in the population potentially vulnerable to multi-morbidity and polypharmacy increases. In addition, various psychosocial problems including lack of social support and economic problems may further exacerbate the risk of poorer health and worsened quality of life (Lau and Dolovich, 2005; Crealey et al., 2012; Alldred et al., 2016; Cheen et al., 2019; Crutzen et al., 2019; Gudi et al., 2019; Šola et al., 2020). Polypharmacy and inappropriate medication use among geriatric populations particularly in Central and Eastern Europe requires more attention in various health care settings and should be specifically recognized and managed at the governmental level (Botev, 2012).

In Estonia, the proportion of older adults (65 years old and older) gradually increases, being at the moment 19.4% (Tuula et al., 2021). By the year 2050, it is expected to increase up to 27.9% (Statistics Estonia: Stati, 2021). After 30 years there will be a relatively high proportion of older people with an expected higher degree of chronic morbidity and potential polypharmacy. The need for geriatric care will increase even more (Sepp et al., 2021).

The e-health system in Estonia is known to be one of the most ambitious and advanced digital solutions in Europe, where more than 95% of the data provided by health care institutions has been digitized (E-Estonia: healthcare, 2020). Yet, there are still many challenges ahead to find new possibilities of integrating innovative solutions focused on specific population groups into the national e-health care system. More attention should be paid to the geriatric population's rational drug prescribing and use, as there is still no universally integrated age-oriented e-health system in Estonia for monitoring potential drug-related problems (DRPs) and for reporting older patients' outcomes.

For the purpose of safe and effective medication prescribing in older adults, several explicit and implicit assessment tools have been created to identify potentially inappropriate medications (PIMs) and drug-drug interactions (DDIs), along with other types of prescribing problems (Bala et al., 2019; Pazan et al., 2019; Reeve, 2020; Rantsi et al., 2021). Over the last few years, the European Union EU(7)-PIM list (Renom-Guiteras et al., 2015) and European "Fit fOR The Aged" (EURO-FORTA) list (Pazan et al., 2018) for older patients, as well as the STOPP/START criteria version 2 (O'Mahony et al., 2015), have been published as the latest (2015, 2018, and 2015, respectively) inappropriate geriatric prescribing evaluation tools more specific for Europe. Recent studies demonstrated that some PIM criteria are less sensitive when used separately (Fialova et al., 2005; Siebert et al., 2013; Elseviers et al., 2014; Reich et al., 2014), and thus the authors suggest integrating at least two PIM screening tools to increase the sensitivity for the identification of DRPs in geriatric patients. The EU(7)-PIM list was created as a screening tool for pharmacoepidemiological applications with minimal clinical information about the individuals concerned. It is also one of the very few PIM checklists that include suggestions for dose adjustments and therapeutic alternatives (Renom-Guiteras et al., 2015; Thummar et al., 2019). However, it does not take into account an important aspect such as the aims of the treatment, and it is mainly focused on the overtreatment of the geriatric patient (Renom-Guiteras et al., 2015). Thus, prescribing appropriateness for PIMs could be additionally addressed by using other criteria, e.g., the EURO-FORTA criteria that strongly relies on 26 main treatment indication groups (Pazan et al., 2018). The EURO-FORTA list addresses aspects of drug selection for diagnoses and both aspects of inappropriate drug treatment in older adults: overtreatment and undertreatment. In addition, the EURO-FORTA criteria contain beneficial medications for certain indications (Pazan et al., 2018; Curtin et al., 2019).

The aim of this study was to develop an integrated PIM clinical decision support tool for identification of DRPs in geriatric multi-morbid patients in Estonia, using the combination of existing European PIM tools: the EU(7)-PIM and EURO-FORTA lists with a special focus on high-risk medications in older patients.

MATERIALS AND METHODS

Tool Selection

In this method study, the EU(7)-PIM (Renom-Guiteras et al., 2015) and EURO-FORTA lists (Pazan et al., 2018) were selected as the basis for preparing an integrated e-health clinical decision support tool for screening adverse drug reactions (ADRs), DDIs, and PIMs in Estonia. The EU(7)-PIM and the EURO-FORTA tools have different approaches to the PIM identification (Renom-Guiteras et al., 2015; Wehling, 2016; Pazan et al., 2018; Pazan et al., 2019), which thus lend well to their being integrated for even greater efficiency and effectiveness (**Table 1**). At the moment, there is no universal concept used in Estonia to evaluate the rationality and safety of drug use targeted specifically to the geriatric population. The EU(7)-PIM and the EURO-FORTA tools were selected, as these are designed to evaluate medicines regularly used in European countries. In the future, this concept may become a substantial part of the primary health care settings in Estonia.

As no clinical trials and animal tests were performed, nor sensitive personal data were used in the present study, it was not necessary to seek the approval of the Ethics Committee.

Definition of the Color Indicators

Based on the risk and severity of potential adverse events described in the EU(7)-PIM and EURO-FORTA lists, the PIMs were suggested to be classified into four general color coding groups:

1) very significant PIMs as red color PIMs: active substances or medication classes that should be avoided in geriatric patients, when possible, and alternative treatment must be strongly considered (*high risk*);
2) significant PIMs as yellow color PIMs: active substances or medication classes that require mostly dose and/or treatment

TABLE 1 | Short comparison of the explicit criteria-based EU(7)-PIM[1] and EURO-FORTA[2] tools.

	The EU(7)-PIM tool	The EURO-FORTA tool
Year	2015	2018
Number of experts; number of countries/regions involved	30; 7	64; 7
Mean Delphi consensus coefficient	0.9	0.9
Target population	older people ≥65 years	older people ≥65 years; or ≥60 years with ≥6 medications, ≥3 diagnoses
Number of active substances or drug classes	282 chemical substances or medication classes from 34 therapeutic groups	264 chemical substances or medication classes organized into 26 categories according to diagnosis or clinical syndrome
PIM identification	Class A: active substance (PIM) should be avoided in older adults	Class A: indispensable medication, clear-cut benefit
	Class B: active substance is PIM in case of certain clinical conditions/co-morbidities or active substance is only considered as PIM	Class B: medication with proven or obvious efficacy in older adults, but limited extent of effect and/or safety concerns
	Combination of class A and B	Class C: medication with questionable efficacy/safety profiles in the older adults which should be avoided or omitted; explore alternatives
		Class D: avoid if at all possible in older adults, omit first and use alternative substance
Specifications	Explicit	Has both implicit and explicit measures[3, 4]
	Drug oriented listing approach	Patient-in-focus listing approach
	Often restricted to doses or treatment duration	Not restricted to doses or treatment duration
	Not related to specific illnesses or conditions (no drug–disease aspect)	Related to specific illnesses or conditions (drug–disease aspect)
	Has suggestions for dose adjustments and therapeutic alternatives	Does not suggest dose adjustments and therapeutic alternatives
	Suitable for pharmacoepidemiological applications	Suitable for pharmacoepidemiological applications

PIM—potentially inappropriate medication.

[1]Renom-Guiteras A, Meyer G, Thürmann, PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015; https://doi.org/10.1007/s00228-015-1860-9.

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duration adjustment according to the patient health status and other medical details (*moderate risk*);

3) non-significant PIMs or non-PIMs as green color PIMs: active substances or medication classes that could be used in case of adequate therapy monitoring, older patients are not at potential high risk of DRPs (*low risk*);
4) questionable PIMs as grey color PIMs: any of the EU(7)-PIM or EURO-FORTA active substances or medication classes are presented whether in the EU(7)-PIM or in EURO-FORTA list only, and more data about the use of the particular PIM must be collected, or other PIM tool should be considered. The grey color PIMs can refer to all three risk profiles (high, moderate, and low). See **Figure 1**; **Table 2** for more details.

The content and structure of the present integrated PIM identification dataset based on the EU(7)-PIM and EURO-FORTA lists were defined in repeated sessions, including evaluation by experts from Estonia and the Czech Republic in the period April 2020 to May 2021. These experts are also contributing to the scientific works on the EUROAGEISM H2020 ESR7 project (2017-2021) entitled "Inappropriate prescribing and availability of medication safety and medication management services in older patients in Europe and other countries".

High-Risk (Red and Some Grey) Potentially Inappropriate Medications

In the present study, the authors focused on the high-risk PIMs: active substances or medication classes that are always (independently on individual clinical conditions) clinically very significant PIMs in older patients. According to the original PIM criteria used, both A-class EU(7)-PIM and D-class EURO-FORTA active substances or medication classes are those that should not be used in geriatric patients in general, as these can often bring potential medication-related harm.

The high-risk PIMs were developed as follows:

- all A-class active substances or medication groups were extracted from the EU(7)-PIM list with additional information about the reasoning of PIM classification and special considerations of use;
- the EURO-FORTA tool was screened for the same active substances or medication groups, and the respective class (A-, B-, C- or D-class) was specified for each PIM; in case of

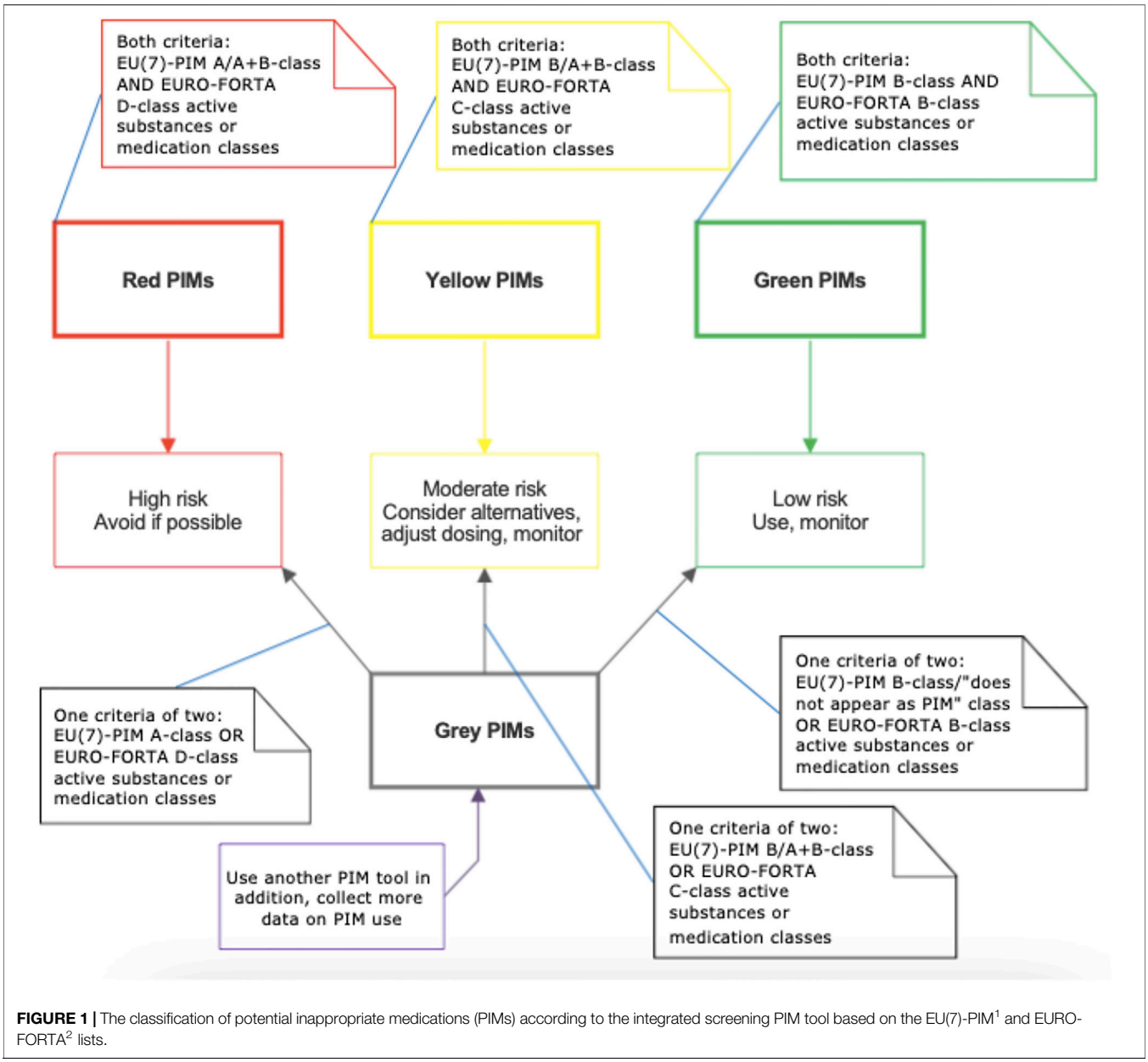

FIGURE 1 | The classification of potential inappropriate medications (PIMs) according to the integrated screening PIM tool based on the EU(7)-PIM[1] and EURO-FORTA[2] lists.

missing data, the EURO-FORTA class of the active substance or medication group was marked as "no information";

- the rest of the EURO-FORTA D-class active substances or medication groups were extracted from the list and compared to the EU(7)-PIM criteria, and the respective class (A-, A + B-, B-class or "does not appear as PIM" class) was specified for each PIM; in case of missing data, the EU(7)-PIM class of the active substance or medication group was marked as "no information";
- if the abovementioned active substances or medication classes are presented in both the EU(7)-PIM and EURO-FORTA criteria, the red color was used to indicate the high risk for the geriatric population. If the active substances or medication classes presented whether in the EU(7)-PIM or in EURO-FORTA list only, the grey color was used to highlight the need to collect more data about the use of these high-risk PIMs in older adults;
- the local (Estonia) and international (European Medicines Agency) Summaries of Product Characteristics (SmPCs)

[1]Renom-Guiteras A, Meyer G, Thürmann, PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015; https://doi.org/10.1007/s00228-015-1860-9.

[2]Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) list: International consensus validation of a clinical tool for improved drug treatment in older people. Drugs Aging. 2018; https://doi.org/10.1007/s40266-017-0514-2.

TABLE 2 | Detailed description of the integrated screening tool based on the EU(7)-PIM[1] and EURO-FORTA[2] lists.

	Type of PIMs	Description	Actions to be undertaken
High risk	Red color	Active substances or medication classes that refer to both the EU(7)-PIM *A-* or *A + B-class* and EURO-FORTA *D-class*	Avoid in older individuals, if possible, monitor patient safety, strongly consider alternative treatment. Only for grey color: collect more data on the PIM use, consider another PIM tool
	Grey color	Active substances or medication classes that refer to only the EU(7)-PIM *A-class* or to the EURO-FORTA *D-class*	
Moderate risk	Yellow color	Active substances or medication classes that refer to both the EU(7)-PIM *B- or A + B-class* and EURO-FORTA *C-class*, for the majority when used in higher doses and/or for longer treatment course than recommended in geriatric patients	Monitor patient safety, collect additional patient health data, consider dose adjustment, consider alternative treatment. Only for grey color: collect more data on the PIM use, consider another PIM tool
	Grey color	Active substances or medication classes that refer to only the EU(7)-PIM *B- or A + B-class* or to the EURO-FORTA *C-class*, for the majority when used in higher doses and/or for longer treatment course than recommended in geriatric patients	
Low risk	Green color	Active substances or medication classes that refer to both the EU(7)-PIM *B-class and EURO*-FORTA *B-class*, those with limited concerns on the effect or safety in geriatric patients or not considered as inappropriate when used in lower doses and/or for short treatment course in geriatric patients	Monitor treatment safety, repeat medication review on regular basis, patient is more likely not at the high risk of DRPs. Only for grey color: collect more data on the PIM use, consider another PIM tool
	Grey color	Active substances or medication classes that refer to only the EU(7)-PIM *B-class or marked as "does not appear as PIM" or to the EURO*-FORTA *B-class*, those with limited concerns on the effect or safety in geriatric patients or not considered as inappropriate when used in lower doses and/or for short treatment course in geriatric patients	

PIM—potentially inappropriate medication; DRP—drug related problem.

[1]*Renom-Guiteras A, Meyer G, Thürmann, PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015; https://doi.org/10.1007/s00228-015-1860-9.*

[2]*Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) list: international consensus validation of a clinical tool for improved drug treatment in older people. Drugs Aging. 2018; https://doi.org/10.1007/s40266-017-0514-2.*

were used to collect any additional information on the use of PIMs in geriatric patients (e.g., dosage and treatment duration adjustment in older adults);
- the PIMs were checked for availability and actual use in Estonia by addressing the official register of medications (2021) (State Agency of Medicines, 2019; State Agency of Medicines, 2020).

Moderate- and Low-Risk (Yellow, Green, and Other Grey) Potentially Inappropriate Medications

The process of identifying the moderate- and low-risk PIMs according to the integrated PIM tool depends directly on individual patient characteristics and many factors concerning the patient´s health status and other clinical issues. For most of the yellow and green PIMs, the clinical relevance of a particular PIM may change depending on the duration of treatment and dosing, treatment indication, and possible DDIs and therapeutic duplications. These PIMs should be considered when the treatment rationality at an individual patient level is assessed in geriatric patients. For this reason, for the moderate- and low-risk PIMs a preliminary list was prepared. The creation of the preliminary list leaves the matter of the moderate- and low-risk PIMs partly open and allows subsequent modifications of the list in the future, if needed. The list of the moderate- and low-risk PIMs was developed as follows:

- all B- and C-class active substances or medication groups (excluding those with the high risk) were extracted from the EURO-FORTA list;
- the EU(7)-PIM tool was screened for the same active substances or medication groups with additional information about reasoning of PIM classification and special considerations of use, and the respective class (A + B- and B-class or "does not appear as PIM" class, excluding A-class referred to the high risk) was specified for each PIM;
- where possible, the risk (moderate or low) and the color (yellow, green, or grey) were established for each individual active substance or medication group according to the integrated method. In addition, the factors that could potentially affect the actual risk for older patient (e.g., adverse events, dosing, duration of treatment, indication, renal functions) were specified based on the EU(7)-PIM and EURO-FORTA criteria;
- the rest of the active substances or medication groups, for which it was difficult to predict the risk due to the missing information in one of the PIM criteria, formed the "Other potential moderate- or low-risk PIMs" group with the need for future research.

By this, the moderate- and low-risk PIMs are all those PIMs mentioned in the EU(7)-PIM and EURO-FORTA lists, that are not treated as high-risk PIMs according to the present study

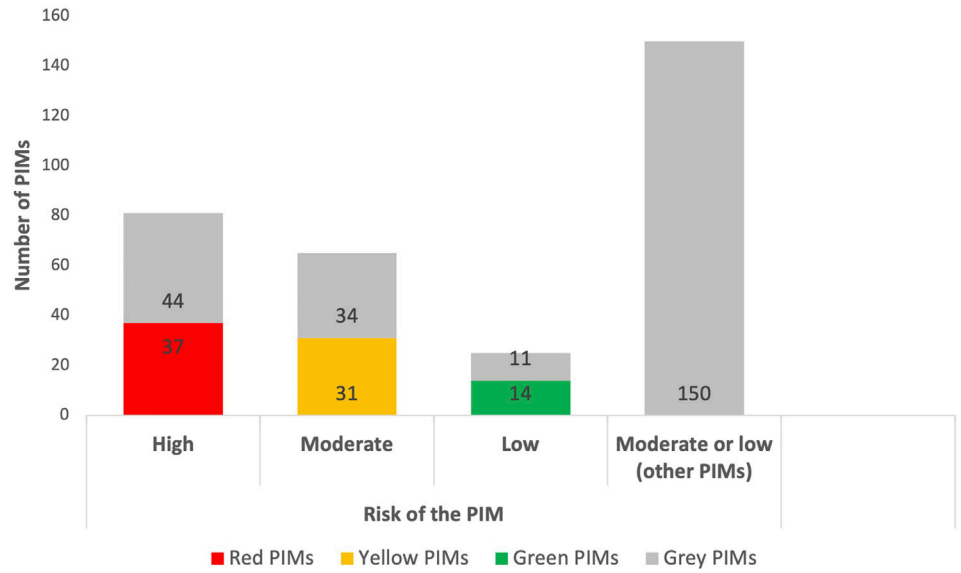

FIGURE 2 | Proportion of the high-, moderate- and low-risk PIMs in the integrated screening tool based on the EU(7)-PIM[1] and EURO-FORTA[2] criteria.

TABLE 3 | High-risk PIMs with and without marketing authorization in Estonia (n = 81, 100%).

	All high-risk PIMs% (n)	High-risk PIMs with marketing authorization in Estonia% (n)	High-risk PIMs not authorized but still marketed in Estonia (ET, RT)% (n)	High-risk PIMs not authorized and not marketed in Estonia% (n)
PIMs listed in the integrated tool	100 (81)	50.6 (41)	16.1 (13)	33.3 (27)
Originally belong to the EU(7)-PIM criteria[1]	75.3 (61)	38.3 (31)	11.1 (9)	25.9 (21)
Originally belong to the EURO-FORTA criteria[2]	75.3 (61)	40.7 (33)	14.8 (12)	19.8 (16)
Originally belong to both criteria at the same time[1,2]	50.6 (41)	28.4 (23)	9.9 (8)	12.3 (10)
Red PIMs	45.7 (37)	26.0 (21)	8.6 (7)	11.1 (9)
Grey PIMs	54.3 (44)	24.7 (20)	7.4 (6)	22.2 (18)
A (alimentary tract and metabolism) ATC group	18.5 (15)	8.65 (7)	1.2 (1)	8.65 (7)
C (cardiovascular system) ATC group	22.2 (18)	8.65 (7)	4.9 (4)	8.65 (7)
G (genito urinary system and sex hormones)	3.7 (3)	3.7 (3)	0	0
J (antiinfectives for systemic use) ATC group	1.2 (1)	1.2 (1)	0	0
L (antineoplastic and immunomodulating agent)	1.2 (1)	1.2 (1)	0	0
M (musculo-skeletal system) ATC group	7.4 (6)	2.5 (2)	1.2 (1)	3.7 (3)
N (nervous system) ATC group	33.3 (27)	18.5 (15)	6.2 (5)	8.6 (7)
R (respiratory system) ATC group	8.8 (7)	3.7 (3)	1.2 (1)	3.7 (3)
V (various)	1.2 (1)	0	1.2 (1)	0
Geriatric information in SmPC was found	49.4 (40)	34.6 (28)	6.2 (5)	8.6 (7)

ATC, Anatomical Therapeutic Chemical (classification); ET (Erialaorganisatsiooni Taotlusega ravimid, est) and RT (Ravimiameti Taotlusega ravimid, est): used by application of specialized physician, hospitals or research institutions; PIM, potentially inappropriate medication; SmPC, Summaries of Product Characteristics.

[1]Renom-Guiteras A, Meyer G, Thürmann, PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015; https://doi.org/10.1007/s00228-015-1860-9.

[2]Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) list: International consensus validation of a clinical tool for improved drug treatment in older people. Drugs Aging. 2018; https://doi.org/10.1007/s40266-017-0514-2.

methodology. The active ingredients or medication classes are categorized as yellow not only because of the active substance itself (like most of the red color PIMs) but in many cases due to the long-term treatment course and high doses being inappropriate for geriatric patients. In contrast, green color PIMs could be mostly appropriate for geriatric patients when used in lower doses and/or for a shorter period of time, as stated in the EU(7)-PIM and EURO-FORTA criteria. Still, there could be always some exceptional cases in clinical practice, e.g., when the green color PIM can become inappropriate or classified as yellow color PIM. Other moderate- or low-risk (grey color) PIMs are those with missing data in the integrated PIM tool that are not possible to classify as yellow or green color PIMs, and the risk (moderate or low) cannot be specified in general. For these PIMs,

there is a need to use additional data sources (e.g., any other PIM list).

RESULTS

High-Risk (Red and Some Grey) Potentially Inappropriate Medications

According to the integrated PIM clinical decision support tool, the total list of the high-risk PIMs contained 81 active substances, including one combination of two medications, eight medication classes and two classes of dietary and other oral **Supplementary Appendix S1**. Of the PIMs identified, there were 37 (45.7%) red and 44 (54.3%) grey color high-risk PIMs in the tool (**Figure 2**).

The study methodology suggests that 61 (75.3%) of the high-risk PIMs originally belonged to the EU(7)-PIM criteria, and the same number of the high-risk PIMs originally belonged to the EURO-FORTA criteria. Half of the high-risk PIMs (n = 41, 50.6%) belonged to both criteria at the same time. Thus, the present integrated PIM tool consists of 41 high-risk PIMs that present in the EU(7)-PIM and EURO-FORTA criteria (coinciding PIMs), 20 high-risk PIMs that present only in the EU(7)-PIM, and 20 high-risk PIMs that present only in the EURO-FORTA. Therefore, the tool enables to identify 20 high-risk PIMs more (81 PIMs) than the EU(7)-PIM (61 PIMs) and EURO-FORTA (61 PIMs) can determine if used separately (**Table 3**).

Most of the high-risk PIMs belonged to the N (nervous system), C (cardiovascular system), and A (alimentary tract and metabolism), medication groups according to the ATC (Anatomical Therapeutic Chemical) classification (**Table 3**). For half (n = 40, 49.4%) of the high-risk PIMs, the authors found specific information in SmPC about use in geriatric patients (**Table 3**; **Supplementary Appendix S1**).

The number of the authorized and marketed high-risk PIMs in Estonia in 2021 was 50.6% ($n = 41$) from the total number of the corresponding PIMs in the developed integrated tool. This type of PIMs was mostly available as prescription (Rx, $n = 30$, 37.0%), but also as over-the-counter (OTC, n = 8, 9.9%) medications or dietary supplements (n = 3, 3.7%) (**Table 3**, **Supplementary Appendix S1**). The list of the high-risk PIMs that are not authorized in Estonia, but still used by the application of specialized physician, hospitals, or research institutions, consists of 13 active substances, which corresponds to 16.1% of the total number of the PIMs in the developed integrated tool. It was found that 27 (33.3%) of the high-risk PIMs were not authorized and not marketed in Estonia in 2021 (**Table 3**, **Supplementary Appendix S1**).

Moderate- and Low-Risk (Yellow, Green, and Other Grey) Potentially Inappropriate Medications

As the identification of the yellow and green PIMs depends directly on an individual patient's clinical characteristics, the authors of the present study prepared the preliminary list of the moderate- and low-risk PIMs, consisting of a total of 240 active substances or medication groups (**Supplementary Appendix S2**). The sub-classification and the proportion of the moderate- and low-risk PIMs in the integrated tool can be found from **Supplementary Appendix S2**; **Figure 2**.

The risk information presented in both EU(7)-PIM and EURO-FORTA tools enabled the authors to presume that 65 PIMs could be classified as moderate-risk PIMs: 31 (47.7%) being classified as yellow, and 34 (52.3%) as grey color PIMs. At the same time, 25 PIMs could be more likely associated with the low risk: 14 (56.0%) classified as green and 11 (44.0%) as grey color PIMs.

All 65 moderate-risk PIMs belong originally to the EURO-FORTA tool B- or C-class, and only 30 (46.2%) to the EU(7)-PIM A + B- and B-class, or to the "does not appear as PIM" class. Analogously, all 25 low-risk PIMs belong originally to the EURO-FORTA tool B-class and only 8 (32.0%) to the EU(7)-PIM B-class or "does not appear as PIM" class.

The rest 150 active substances or medication groups were defined as "other potential moderate- or low-risk PIMs", where 126 (84.0%) PIMs originally belonged to the EU(7)-PIM list and 24 (16%) to the EURO-FORTA criteria (**Supplementary Appendix S2**).

Based on the EU(7)-PIM list, nine moderate-risk, and five low-risk active substances or medication groups were suggested as an alternative to some PIMs, and thus the authors of the present study marked them as "beneficial medications" (**Supplementary Appendix S2**). For this reason, the low-risk beneficial medications have the potential to be excluded from the list of the PIMs in the integrated tool as non-PIMs after validation of the tool. At the same time, the moderate-risk beneficial medications could be transferred to the low-risk PIM group after additional research.

DISCUSSION

This is the first study in Estonia focusing on the use of the EU(7)-PIM and EURO-FORTA criteria jointly to create an integrated PIM clinical decision support tool identifying potentially inappropriate prescribing for geriatric patients. Previous research has demonstrated that it is not sufficient to use only one PIM criteria in the study design, because it may give inconclusive results (Tommelein et al., 2016; Wamil et al., 2019; Johansen et al., 2020). The integrated PIM tool allows for a more specific assessment of the risks of PIMs and therefore enables it to become the convenient instrument to evaluate the complex medication use problems in primary health care settings. During the process of creation of the integrated PIM tool, the authors identified several important considerations that will be addressed and discussed below in the text along with some recommendations for future research.

The integrated PIM tool enabled to list of 25% more high-risk PIMs than the two separate tools (EU(7)-PIM and EURO-FORTA). In addition, a comparison of the two tools provided extended information on moderate- and low-risk PIMs, but also highlighted the lack of data on the use of PIMs in the elderly. In this study, a total of 194 PIMs (150 related to moderate- and low-

risk PIMs) were identified with insufficient information for final classification. In order to identify the actual risk for these particular PIM, it is not sufficient to use the combination of the EU(7)-PIM and EURO-FORTA criteria, but also it is important to know some specific additional information on patients' medication and clinical data, that may vary depending on the PIM being under examination. Future research is needed to identify described discrepancies that may differ depending on the specific country and local drug prescribing traditions and guidelines. At the same time, although the list of the high-risk PIMs and the preliminary list of the moderate- and low-risk PIMs were accepted unanimously by all authors of the present study, the PIMs with insufficient risk information always need additional inspection and consideration by experts in the field. It is conceivable that for these PIMs that could be classified as high-, moderate- or low-risk PIMs only by one of the lists [the EU(7)-PIM or EURO-FORTA list], there should be an even more detailed explanation on how or whether to use them in older adults.

The present study showed that the actual use of some high-risk PIMs in Estonia differs from the concept provided by the EU(7)-PIM and EURO-FORTA lists. For example, use of PIMs in combined medicinal products (dextromethorphan, diphenhydramine, estrogen, magnesium hydroxide); as OTCs and food supplements with different requirements to the patient information (Aloe, Ginkgo folium, magnesium hydroxide, *Senna* glucosides, and St. John's Wort), and in a different pharmaceutical formulation (niacin - nicotinic acid - only as an injection, viscous paraffin, and minoxidil as external products). The study results suggest a need to further explore the problem of combined medicinal products and other discrepancies mentioned above before the integrated PIM tool becomes a widely available instrument for clinical use, and this suggestion is corroborated by the implications discussed in other studies (Sönnerstam et al., 2017; Curtin et al., 2019; Fialová et al., 2019). Another issue that should be addressed in the near future is the urgent need to update the PIM lists on a regular basis by inserting newly identified PIMs or changing the content of already existing PIMs (Wauters et al., 2016; European Monitoring Centr, 2019).

The study showed that the information concerning the rational and safe use of the medications in older adults was found from the SmPCs for only 49.4% (n = 40) of the high-risk PIMs. The additional information concerning safety aspects (e.g., dosage and treatment duration adjustment, or any other recommendations for the geriatric patients) must be collected, including appropriate medication safety studies. There are 16.1% (n = 13) of the high-risk PIMs with no marketing authorization in Estonia but still used in some Estonian patients/groups of patients by application of specialized physician, hospitals, or research institutions. The list of described high-risk PIMs can change many times a year depending on the necessity for the medications that are not presented in the country-specific drug market and thus closer attention should be paid to this group of PIMs. The authors see an urgent need to discover possible new PIMs that are relevant for Estonia and that could be added to the integrated PIM list in the future.

At the moment, the existing international PIM tools are available in Estonia only as original research papers (e.g., PDF documents). This makes their use in everyday clinical practice inconvenient and also reduces awareness and usability among healthcare professionals. The integration of the clinical decision support PIM tool to the e-health system in Estonia is the expected future step. It will help more efficiently identify patients at risk and improve the safety and efficacy of drug prescribing to older adults. Current software packages do not screen geriatric risks of medications. The information available on the implementation of both instruments [the EU(7)-PIM and EURO-FORTA] should be examined in advance and, if necessary, taken into account when applying the integrated PIM tool in real clinical practice. The important aspects that should be carefully considered before applying the integrated PIM list in practice are, for example, the information on how to use the EURO-FORTA list in daily clinical practice based on experiences from clinical trials and the personal experiences ("a use algorithm for FORTA") of the authors of the list (Wehling, 2016), or any relevant information about the practical use of the EU(7)-PIM tool by different research groups (Sönnerstam et al., 2017; Thummar et al., 2019). In addition, it is crucial to investigate the ways to include additional information about the PIMs listed in both criteria in the design of the integrated PIM tool, e.g., "positive" list of active substances or medication classes (A- and B-class medications) for certain indications by EURO-FORTA, as well as suggestions for dose and/or treatment duration adjustments (also in relation to hepatic and renal function), and therapeutic alternatives for PIMs based on the EU(7)-PIM list. Lastly, the authors discuss the future option to include recommendations concerning the use of a similar alternative PIM checklist [e.g., the Ghent Older People's Prescriptions Community Pharmacy Screening (GheOP3S)-Tool Version 2] for identification of the grey PIMs or any other possible discrepancies (Foubert et al., 2021).

As the concept (color coding) of the present integrated tool is intentionally similar to the drug interaction and counter indication decision support software based on the inxbase/riskbase database used in Estonia (Inxbase and Riskbase data, 2020), the tool can become a part of this software. It will be focused more on the older populations' safe and rational medication use, and can also be applied in a context of little clinical information available. In this scenario, access to the integrated PIM tool may be provided in the future to health care employees from different care settings, including doctors, nurses, pharmacists, and others. For similar purposes, it could also be used in other countries which may benefit from applied methodology into the combination of these two internationally, widely recognized tools.

STRENGTHS AND LIMITATIONS

The integrated PIM clinical decision support tool could support the process of detection of high-risk medications for older adults. It could also help to state more specific risks for each PIM compared to the use of either one of the individual PIM lists

[e.g., the EU(7)-PIM or EURO-FORTA]. From both criteria used [e.g., the EU(7)-PIM or EURO-FORTA] as a basis in the design of the present integrated tool, the appropriate information on PIMs was adopted so that it helps to reach a full-fledged examination of DRPs in geriatric patients and to apply this approach in case of patients with limited clinical data. The integrated PIM tool is based on the structured color categorization of the PIMs by risk and severity of using them in older people and has both, drug-oriented and patient-in focus approaches. In addition to high-risk medications, the tool was designed to determine moderate- and low-risk PIMs, but in this case, sufficient patient clinical information will be needed. On the basis of what has been stated above, this is the real patient data that indeed plays a critical role in the process of PIM categorization for moderate- and low-risk PIMs. This situation forced the authors of the present study to abandon the idea to put together the complete list of moderate- and low-risk PIMs. Thus, the preliminary list of this type if PIMs was prepared with a future perspective for additional research in this area. The authors of the present study deem it appropriate to conduct the tool validation with real patients first in order to understand the actual need for the combined tool within healthcare employees in Estonia and to see if the tool and its concept is understandable and practical. Thus, the validation of the tool is the future step that must be undertaken before the tool can be implemented in real clinical practice. Although the tool is not yet validated it indicates the preliminary evidence of it identifying PIMs more germane in this context and shows promise in being piloted as an effective PIM tool in future clinical studies. It must be also acknowledged that the quality of the integrated tool is directly linked to the updating of the original PIM criteria and that this type of tools should be updated on a regular basis. And last but not least, each country or region should adapt the assessment PIM tools according to the medications on the market (including combined drugs) available and the traditions of their clinical use.

CONCLUSION

This study introduces a novel integrated PIM clinical decision support tool based on the two European most widely known and used the EU(7)-PIM and EURO-FORTA criteria to address the need for more efficient identification of DRPs in geriatric, multi-morbid patients. The present integrated tool consists of 321 active ingredients or medication classes. Based on the information in the source instruments, there was the most background information for the classification of high-risk PIMs, enabling to recognize 25% more respective PIMs than with the EU(7)-PIM or EURO-FORTA separately. On the other hand, for detailed classification, approximately half of the high-risk PIMs and the majority of the moderate or low-risk PIMs require further information on the use of medicines in older adults, or the clinical and other characteristics of a particular patient. This result points to a continuing lack of information on the geriatric use of medicines, as well as the need to integrate the use of theoretical tools into everyday medical practice, especially in the context of polypharmacy growth. The validation of the integrated tool is the next step in its development and implementation in clinical practice.

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

VB, DF, and DV—data evaluation, planning and writing the article. SD and JH—useful criticism and suggestions during writing and revision of the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.761787/full#supplementary-material

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The Impact of Age on Propofol Requirement for Inducing Loss of Consciousness in Elderly Surgical Patients

Hua Yang[1†], Hui-Min Deng[2†], Hai-Yan Chen[1†], Shu-Heng Tang[1], Fang Deng[1], Yu-Gang Lu[2] and Jin-Chao Song[1*]*

[1]Department of Anesthesiology, Shidong Hospital Affiliated to University of Shanghai for Science and Technology, Shanghai, China, [2]Department of Anesthesiology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China

It is generally accepted that geriatric patients are more sensitive to propofol than adults; thus, a dose-adjusted propofol is recommended for these patients during the induction of anesthesia. However, for patients aged 75 years and over, established guidelines for propofol induction doses do not provide dose references. To this end, we observed 80 surgical patients (female 39, male 41, American Society of Anesthesiologists physical status score I ~ II) to access the appropriate dose of propofol for inducing loss of consciousness (LOC). Accordingly, patients were subdivided into group A (20 patients, 45–64 years), group B (20 patients, 65–74 years), group C (20 patients, 75–84 years), and group D (20 patients, ≥ 85 years). All patients received propofol (at a rate of 0.3 mg/kg/min) alone for inducing LOC, which was defined by loss of both eyelash reflex and verbal response. Compared with group A, the propofol requirement for LOC in Group B, C and D decreased by 14.8, 25.2 and 38.5%, respectively. Bivariate linear correlation analysis showed that propofol requirement was negatively correlated with age. After adjusting for potential confounders, age was still an independent factor affecting propofol requirement. In conclusion, the propofol requirement for inducing LOC decreased significantly in elderly patients. We demonstrated that age was an independent factor impacting propofol requirement for LOC during the induction of general anesthesia, implying that the propofol dose for anesthesia induction should be further reduced in elderly surgical patients, especially those aged 75 years and over.

Keywords: elderly, anesthetics, propofol, intravenous anaesthesia, loss of consciousness

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***Correspondence:**
Jin-Chao Song
sjch2013@163.com
Yu-Gang Lu
luyugang@tongji.edu.cn

†These authors have contributed equally to this work

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INTRODUCTION

Advances in surgical techniques and improvement of perioperative management have led to a larger proportion of elderly patients presenting to undergo surgical procedures (Aurini and White, 2014). Previous studies have shown that more than half of all surgical procedures were performed on patients over the age of 65 (Yang et al., 2011). With the deepening of global aging, this proportion is expected to further increase in the coming decades. For these patients, anesthesiologists often need to adjust the anesthetic regimen, including medication selection, dosage optimization and so on, to adapt to the elderly physiological changes. However, only limited empirical data on guiding the appropriate dosing of anesthetic induction agents for elderly patients can be referred by the anesthesiologists (Phillips et al., 2015).

Propofol, as an intravenous hypnotic agent, has been widely used for anesthetic induction and maintenance in surgical patients. It can provide quick and smooth anesthesia induction. However, a common side-effect of propofol-based induction is dose-dependent hemodynamic instability (Sahinovic et al., 2018), such as hypotension and bradycardia, especially in elderly patients. Compared with the middle-aged adult, the principles of geriatric physiology are not merely a linear extension (Yang et al., 2011). These elderly patients represent a unique clinical group, in addition, they typically suffer from a number of chronic diseases. Although some studies have recommended that propofol-based induction should be avoided in these elderly individuals (Reich et al., 2005; Phillips et al., 2015), many anesthesiologists still choose to use propofol in clinical anesthesia rather than other drugs which have little effect on hemodynamics.

Based on the fact that elderly patients have increased sensitivity to propofol, anesthesiologists are recommended to reduce the dose of propofol used for induction in patients aged over 65 years from 2 to 2.5 mg/kg to 1–1.5 mg/kg (McEvoy et al., 2008). However, for patients over 75 or even 85 years old, it is unclear whether this recommendation is still applicable and what dose of propofol is appropriate for such patients. To this end, we designed the current study to access the appropriate dose of propofol for these patients, and to analyze the role of age on propofol requirement in the process of loss of consciousness (LOC) induced by propofol.

PATIENTS AND METHODS

Participants

We conducted a cross-sectional study following the Declaration of Helsinki from April to August 2020. The study was approved by the Institutional Research Ethics Committee of Shidong Hospital. Patients aged 45 years and over scheduled for general surgery or orthopedic surgery under general anesthesia were considered eligible. Patients were excluded if they: = 1 * GB3 ① American Society of Anesthesiologists (ASA) physical status score ≥3; = 2 * GB3 ② allergic to propofol; = 3 * GB3 ③ body mass index (BMI) ≤ 20 or ≥30 kg/m^2; = 4 * GB3 ④ taking hypnotics, opioid analgesic or antianxiety agents; = 5 * GB3 ⑤ known or suspected heart failure (ejection fraction <40%), severe respiratory disease, renal or metabolic diseases; = 6 * GB3 ⑥ could not complete the informed consent procedure independently. Written informed consent was obtained from all patients.

Study Protocol

A total of 80 patients who met the inclusion and the exclusion criteria were divided into four groups, Group A (20 patients, 45–64 years), Group B (20 patients, 65–74 years), Group C (20 patients, 75–84 years), and Group D (20 patients, ≥ 85 years), according to age. Noninvasive blood pressure, heart rate, electrocardiogram, pulse oxygen saturation and end-tidal carbon dioxide were monitored continuously throughout the operation. After 5 min of preoxygenation, propofol was pumped at a rate of 0.3 mg/kg/min until the LOC occurred. The LOC was defined by loss of both eyelash reflex and verbal response. The assessment of the loss of eyelash reflex and verbal response was carried out every 10 s after propofol pumping for 1.5 min. An anesthesiologist assistant, who was blinded to the grouping, performed the above reflex assessment and finally determined the end point of titration. Meanwhile, the dose of propofol (Propofol requirement) and the time of reflection disappear (T reflection disappear) for each patient were recorded. After induction of propofol, 0.4–0.6 ug/kg of sufentanil and 0.2 mg/kg of cisatracurium were administered, and endotracheal intubation was performed 3 min later.

Perioperative variables included in the analysis were sex, BMI, albumin (ALB), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), blood urea nitrogen (BUN), glomerular filtration rate (GFR), ejection fraction (EF) and pulse oxygen saturation (SpO2).

Hemodynamic parameters including mean arterial pressure (MAP) and heart rate (HR) at five different time points (T0, before propofol administration; T1, LOC; T2, 3 min after the administration of fentanyl and cisatracurium; T3, 1 min after intubation; T4, 5 min after intubation; T5, 10 min after intubation) were recorded. Hypotension was defined as a MAP <65 mmHg, hypertension was defined as a MAP >90 mmHg, bradycardia was defined as a HR < 45 bpm persisting more than 30 s and was treated with IV atropine 0.5 mg.

Statistical Analysis

Baseline characteristics of patients were described as mean (standard deviation, SD) for continuous variables, frequency (percentage) for categorical variables, or median (interquartile range, IQR) for continuous variables with skewed distribution. One-way analysis of variance, Kruskal–Wallis test and χ^2 test were used to analyze the demographic data and hemodynamic changes in each group, as appropriate. We used the Mantel-Haenszel $\chi 2$ test to explore the trend relationship between categorical variables and age groups, and linear regression between continuous variables and age groups. Pearson correlation coefficients were calculated to assess correlations between propofol requirement and different parameters.

To evaluate the independent association of age with propofol requirement, multiple linear regression models were constructed. Three models were fitted, Model I: unadjusted; Model II: adjusted for gender and BMI; Model III: further adjusted for, ALT, ALB, and GFR. The selection of variables in the model was based on univariate analysis results at p-value < 0.1 and clinical expertise to assess whether variables within the model affected drug metabolism *in vivo*. Furthermore, considering the strong professional relevance of several indicators of liver or kidney function, we selected those that met the clinical value to enter the model. The collinearity diagnostic was used to determine whether the variables in the model were highly interrelated, as determined by the variance inflation factor and tolerance. We also use smooth curve fitting to examine whether the relationship between age and propofol requirement was linear while adjusting for potential confounders above. All statistical analyses were performed using SPSS, version 20.0 (SPSS Inc. Chicago, IL, United States) and R,

TABLE 1 | Baseline characteristics of patients in different age groups.

	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	Group D (n = 20)	*p* Value	*p* Trend
Male, No. (%)	9 (45)	10 (50)	11 (55)	11 (55)	0.908	0.487
BMI, mean (SD), kg/m^2	24.05 (0.61)	24.40 (0.50)	24.05 (0.61)	24.40 (0.50)	0.055	0.224
Liver function						
Albumin, mean (SD), g/L	42.15 (7.08)	41.13 (5.04)	39.32 (4.00)	37.76 (7.74)	0.121	0.016
Bilirubin, median (IQR), μmol/L	11.50 (9.70–15.78)	12.90 (10.25–19.83)	14.85 (12.13–22.45)	15.30 (11.60–23.18)	0.123	0.034
ALT, median (IQR), U/L	18.50 (11.25–26.50)	18.00 (12.00–22.75)	12.50 (11.00–18.25)	14.50 (10.25–24.00)	0.358	0.583
AST, median (IQR), U/L	22.00 (18.00–25.00)	23.00 (16.00–32.00)	21.00 (17.00–28.50)	22.00 (17.25–28.25)	0.958	0.168
Kidney function						
Scr, median (IQR), mg/dl	0.67 (0.55–0.86)	0.80 (0.68–0.92)	0.80 (0.65–1.01)	0.78 (0.62–1.05)	0.126	0.033
BUN, median (IQR), mg/dl	14.57 (11.90–16.95)	15.55 (12.74–19.54)	13.98 (10.99–17.44)	15.69 (11.25–20.02)	0.746	0.761
GFR, mean (SD), mL/min/1.73m^2	136.83 (29.07)	115.41 (26.87)	107.24 (28.67)	111.98 (35.09)	0.014	0.008
EF, mean (SD) %	63.65 (2.37)	62.35 (1.90)	64.05 (3.32)	63.10 (3.16)	0.239	0.986
SpO2, mean (SD) %	97.25 (0.91)	96.60 (0.99)	96.70 (0.98)	96.85 (0.88)	0.146	0.252

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine, BUN, blood urea nitrogen; GFR, glomerular filtration rate; EF, ejection fraction; SpO2, pulse oxygen saturation.

p *value in one-way analysis of variance, Kruskal-Wallis test, or χ2 test;* p *trend in linear regression or Mantel-Haenszel χ2 test.*

TABLE 2 | Comparison of anesthetic effects in different age groups.

	Group A (*n* = 20)	Group B (*n* = 20)	Group C (*n* = 20)	Group D (*n* = 20)	*p* Value	*p* Trend
Propofol requirement, mean (SD), mg/kg	1.35 (0.20)	1.15 (0.20)[a]	1.01 (0.21)[b]	0.83 (0.17)[c,d,e]	< 0.001	< 0.001
T reflection disappear, mean (SD), s	262.50 (36.11)	230.00 (42.43)[a]	200.50 (43.34)[b]	165.00 (32.36)[c,d,e]	< 0.001	< 0.001

[a]*Significant difference between Group A and B.*
[b]*Significant difference between Group A and C.*
[c]*Significant difference between Group A and D.*
[d]*Significant difference between Group B and D.*
[e]*Significant difference between Group C and D.*

version 3.6.3 (R Project for Statistical Computing). A two-side p-value < 0.05 was considered statistically significant.

Sensitivity Analysis

Given the limitations of the study sample size, we observed the robustness of the findings by including different indicators of kidney and liver function into the models separately, and assessed the model fit by R^2 and adjusted R^2. Model I adjusted for gender, BMI, ALT, and GFR; model II adjusted for gender, BMI, ALT, GFR, ALB, and TBIL; model III adjusted for gender, BMI, ALT, GFR, ALB, TBIL, and AST.

RESULTS

The baseline characteristics of patients are presented in **Table 1**. Of the 80 patients (mean age = 74 ± 12 years, range 45–93 years), 39 (48.75%) were female. No differences in BMI, ALT, AST, BUN, EF and SpO2 between age groups. However, GFR was significantly associated with age (p = 0.014) and the mean difference (95%CI) in age between groups A and B was 29.59 (4.60–54.58). Furthermore, GRF and albumin decreased linearly with age, whereas Scr and bilirubin were reversed (all p-trends < 0.05).

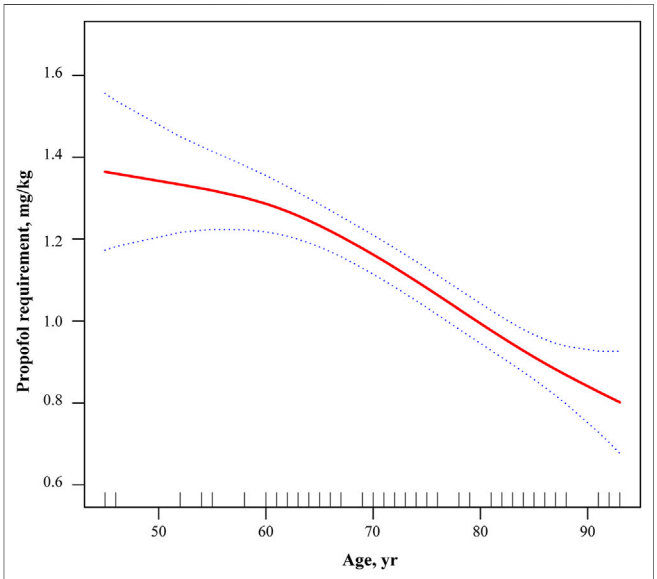

FIGURE 1 | Adjusted dose-response relationship between propofol requirement and age. Adjusted for gender, BMI, ALB, ALT, and GFR. BMI, body mass index; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate.

TABLE 3 | Correlation coefficients between age and propofol requirement.

	Propofol Requirement, Mg/Kg		
	R	95% CI	*p* Value
Age, yr	−0.689	−0.789–0.553	< 0.001
BMI, kg/m^2	−0.214	−0.414–0.006	0.057
Albumin, g/L	0.312	0.099–0.497	0.005
Ln (Bilirubin), μmol/L	−0.169	−0.375–0.052	0.133
Ln (ALT), U/L	0.018	−0.203–0.237	0.875
Ln (AST), U/L	−0.145	−0.353–0.078	0.201
Ln (Scr), mg/dl	−0.173	−0.379–0.048	0.124
Ln (BUN), mg/dl	0.037	−0.184–0.255	0.744
GFR, mL/min/1.73m^2	0.286	0.070–0.476	0.010
EF, %	0.095	−0.127–0.308	0.401

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine, BUN, blood urea nitrogen; GFR, glomerular filtration rate; EF, ejection fraction.

Differences in anesthesia effects between ages were shown in **Table 2**. Propofol requirement and T reflection disappear differed significantly between ages ($p < 0.001$), and all had significant linear decreases with age (P-trend < 0.001). Compared to group A, group B had a mean reduction in propofol requirement of 0.20 mg/kg (95%CI = 0.07–0.33) and a mean reduction in T reflection disappear of 32.50 s (95%CI = 7.28–57.72). Significant differences were consistent across all neighboring groups (all $p < 0.05$). Additionally, to further determine whether the relation between age and propofol requirement was linear, the estimated dose-response curve was fitted. There was a continuous linear decreasing trend and statistical significance between propofol requirement and age after adjusting for gender, BMI, ALB, ALT, and GFR (**Figure 1**).

Bivariate linear correlation analysis showed that propofol requirement was significantly and positively correlated with albumin (r = 0.312; 95% CI = 0.099–0.497; $p = 0.005$) and GRF (r = 0.286; 95%CI = 0.070–0.476; $p = 0.010$), and negatively correlated with age, such that significant decline in propofol requirement with increasing age (r = -0.689; 95%CI = -0.789 ~ -0.553; $p < 0.001$). Other kidney and liver parameters were not significantly correlated with propofol requirements (**Table 3**).

Patient age was an independent and significant factor in propofol requirement. When propofol requirement entered models as a continuous variable, advanced age was associated with lower propofol requirements. In the fully adjusted model, none of the variables included in the model were strongly interrelated by collinearity diagnostic. per 1-SD increase in age was associated with a decrease in propofol requirement of approximately 0.171 ($\beta = -0.167$; 95%CI = −0.218 ~ −0.116; $p < 0.001$). In the unadjusted model, a high level of age (Group D) was strongly associated with a lower propofol requirement ($\beta = -0.525$; 95%CI = −0.648 ~ −0.403; $p < 0.001$). Furthermore, P-trend was calculated using age groups as ordinal variables, and the results showed a linear trend between age and propofol requirement (P-trend < 0.001). The association yielded relatively consistent results after adjusting for gender and BMI [β (95%CI): Group B: 0.185 (−0.310 ~ −0.060), $p = 0.004$; Group C: 0.348 (−0.470 ~ −0.226), $p < 0.001$; Group D: 0.512 (−0.637 ~ −0.387), $p < 0.001$] (Model II). After further adjustment for, ALT, ALB, and GFR, the associations were slightly weakened but still statistically significant, with β values of −0.158 (95%CI = −0.286 ~ −0.029; $p = 0.017$), −0.316 (95%CI = −0.449 ~ −0.182; $p < 0.001$) and −0.459 (95%CI = −0.595 ~ -0.324; $p < 0.001$) for groups B, C, and D, respectively (Model III) (**Table 4**).

Considering the sample size limitation of the study population and to ensure the robustness of the findings, we constructed models for sensitivity analysis by including different number of variables in the models. For example, in model 1, after adjusting for gender, BMI, ALT, and GFR, the change of propofol requirement in Group B, Group C, and Group D compared to Group A was −0.168 (95%CI = −0.297 ~ −0.039; $p = 0.012$), −0.340 (95%CI = −0.471 ~ −0.208; $p < 0.0001$), and -0.490 (95% CI = −0.621 ~ −0.359; $p < 0.0001$). There was a trend relationship between change in propofol requirement and age (p for trend <0.001). There was little change in the other sensitivity analysis results, as shown in the Appendix (**Supplementary tables1-3**). The results of the sensitivity analysis were consistent with the results of the main analysis.

After induction of anesthesia, the MAP and HR of patients in each group began to decrease, especially at T2 (3 min after the administration of fentanyl and cisatracurium). After intubation, MAP and HR rebounded in different degrees and tended to be stable in 5–10 min (**Figure 2**). However, there was no difference in percent changes relative to the baseline between the four groups (MAP: T1, $p = 0.404$; T2, $p = 0.558$; T3, $p = 0.460$; T4, $p = 0.202$; T5, $p = 0.109$; HR: T1, $p = 0.499$; T2, $p = 0.970$; T3, $p = 0.237$; T4, $p = 0.135$; T5, $p = 0.922$).

DISCUSSION

In the present study, we investigated the effective dose of propofol in surgical patients aged 45 years and over for LOC during the induction of general anesthesia. We found that the propofol requirement for LOC decreased significantly with increasing age. Additionally, we demonstrated that patient age was an independent and significant factor in propofol requirement for LOC, implying that the propofol dose for anesthesia induction should be further reduced in elderly surgical patients, especially those aged 75 years and over.

Increasing aging population paired with age-associated coexisting diseases and longer life spans have resulted in an increasing proportion of geriatric surgery. For these elderly patients, age-related changes in physiology, anatomy and cognitive function have a great impact on both the pharmacodynamics and pharmacokinetics of administered anesthetics (Yang et al., 2011; Alamo et al., 2014; Kok and Reynolds, 2017; Lim and Lee, 2020). Anesthesiologists have to tailor the anesthetic scheme to account the changes associated with aging, comorbidities, and patient medications so as to optimize the perioperative prognosis of these elderly patients. However, guiding evidence focusing on geriatric patients remains poor so far. Clinicians tend to adjust the anesthetic regimen according to their own experience. Additionally, a large retrospective cohort study has found that the median (IQR) propofol dose for anesthesia induction in patients aged over 65 years was 1.8 (1.4–2.2) mg/kg, greater than recommended

TABLE 4 | Effects of age on propofol requirement.

Age, yr	Model I		Model II		Model III	
	β (95%CI)	*p* Value	β (95%CI)	*p* Value	β (95%CI)	*p* Value
Per 1 SD	−0.187 (−0.232 ~ −0.143)	< 0.001	−0.185 (−0.230 ~ −0.140)	< 0.001	−0.167 (−0.218 ~ −0.116)	< 0.001
Group A	0.00 [References]	—	0.00 [References]	—	0.00 [References]	—
Group B	−0.201 (−0.323 ~ −0.078)	0.002	−0.185 (−0.310 ~ −0.060)	0.004	−0.158 (−0.286 ~ −0.029)	0.017
Group C	−0.344 (−0.466 ~ −0.221)	< 0.001	−0.348 (−0.470 ~ −0.226)	< 0.001	−0.316 (−0.449 ~ −0.182)	< 0.001
Group D	−0.525 (−0.648 ~ −0.403)	< 0.001	−0.512 (−0.637 ~ −0.387)	< 0.001	−0.459 (−0.595 ~ −0.324)	< 0.001
Trend	< 0.001	< 0.001	< 0.001	—	—	—

Model I: unadjusted; Model II: adjusted for gender and BMI; Model III: further adjusted for, ALT, ALB, and GFR, One SD, is equal to 12.
BMI, body mass index; ALT, alanine aminotransferase; ALB, albumin; GFR, glomerular filtration rate.

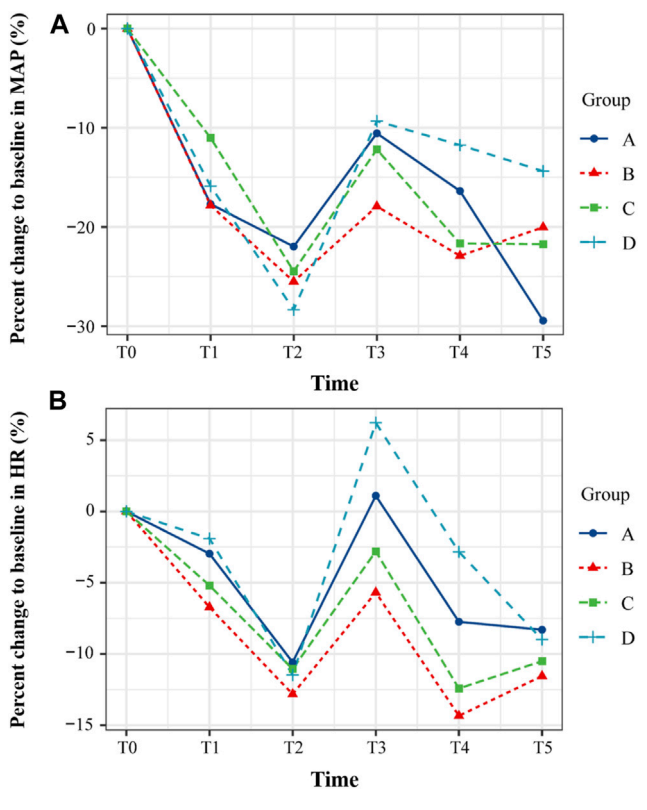

FIGURE 2 | The changes of hemodynamic parameters at five different time points during the induction of anesthesia. **(A)** Mean arterial pressure (MAP). **(B)** Heart rate (HR). The percent changes of MAP and HR relative to the baseline between the four groups were compared. All the values are presented as mean. T0, before propofol administration; T1, LOC; T2, 3 min after the administration of fentanyl and cisatracurium; T3, 1 min after intubation; T4, 5 min after intubation; T5, 10 min after intubation.

doses (1–1.5 mg/kg) (Phillips et al., 2015). In our study, the effective dose of propofol for LOC in patients (65–74 years) was 1.15 mk/kg, which is 14.8% lower than that for patients aged 45–64 years. Our findings are in line with previous studies (Koh et al., 2017; You et al., 2019). Moreover, our results show that propofol requirement for LOC in patients aged 75–84 years and ≥85 years are 25.2 and 38.5% lower than that for patients aged < 65 years, respectively (**Table 2**). Based on age-grouping, we demonstrate that as age increased by decade, the propofol requirement for LOC in elderly reduces dramatically (**Figure 1**). These findings confirm the guideline for minimal administration of propofol and recommend that the dose of propofol for anesthesia induction should be further reduced for patients aged 75 years and over.

One major purpose of this study was to investigate the impact of age on the propofol requirement for LOC in elderly during anesthesia induction. Therefore, we incorporated factors that might have an impact, such as gender, BMI, albumin, bilirubin, ALT, AST, and GFR into the models (**Table 4**). After adjustment for these factors, age was still an independent factor. From the perspective of the increased sensitivity of the elderly to anesthetics, our results do not conflict with previous studies (Akhtar, 2018; Kim et al., 2018; Sahinovic et al., 2018; You et al., 2019). However, unlike previous research paradigms, we focused on elderly surgical population which aged over 65 years, and tried to eliminate the interference caused by concomitant medication, comorbidities and renal insufficiency. Remarkably, this geriatric surgical population represents a special group. They typically suffer from cardiopulmonary dysfunction, metabolic diseases, and nervous system dysfunction, etc. (Yang et al., 2011; Lim and Lee, 2020; Pickering et al., 2020). Increasing age represents the change within senescent process, rather than a sort of pathological condition. Correspondingly, this aging process impedes the ability of the body to maintain homeostasis, especially when the body is under stress (Yang et al., 2011; El Beheiry and Mak, 2013). Meanwhile, studies also have shown that advanced age is an independent risk factor for prognosis of various surgical procedures (Keenan and White, 2005; Pommergaard et al., 2016; Tan et al., 2017; Cammarata et al., 2019). Therefore, clinicians should be more aware of these changes caused by aging, so as to provide the most effective perioperative treatment for these elderly surgical patients.

In the present study, Bivariate linear correlation analysis showed that propofol requirement was positively correlated with serum albumin and GFR. It is well known that propofol binds to plasma proteins, mainly serum albumin, because of its lipophilicity. Normally, about 80% of propofol will be bound to serum albumin after intravenous injection (Shityakov et al., 2020), therefore, serum albumin level will significantly affect

the pharmacologically active concentration of propofol. GFR is the best test to measure the level of kidney function and determine the stage of kidney disease. GFR declines with age, even in people without kidney disease. Kidneys play an important role in the elimination of propofol. Studies have shown that renal metabolic clearance of propofol accounts for almost one-third of total body clearance and is the major contributor to the extrahepatic elimination of propofol (Hiraoka et al., 2005; Takizawa et al., 2005). However, given that the onset time of propofol is very short (one arm-brain circulation) and the elimination half-life of propofol is quite long (4–6 h), the propofol dose for anesthesia induction is unlikely to be affected by GFR.

In this study, the MAP and HR of the patients decreased gradually with the infusion of propofol, and further decreased with the administration of sufentanil and cisatracurium. Endotracheal intubation reversed the decreasing trend of MAP and HR, and both of them stabilized 10 min later. Elder patients are more prone to hemodynamic instability caused by propofol, due to the increased sensitivity to propofol and the decreased initial distribution volume (Gragasin et al., 2012; You et al., 2019). Concerns on hemodynamic depression of propofol in elderly patients have led anesthesiologists to choose alternative drugs (e.g., etomidate) or to combine with other drugs (e.g., midazolam, dexmedetomidine, etc.) for anesthesia induction. However, a recent study indicates that pretreatment with midazolam and remifentanil led to a significant decrease in MAP, compared with propofol alone (You et al., 2019). There was no case of hypotension or bradycardia in our cohort, which may be due to the slow infusion of propofol on the one hand and the absence of other pretreatment induction drugs on the other. Therefore, in addition to the dosage of propofol, we should also pay attention to the infusion rate of propofol and the choice of combined use of drugs for anesthesia induction in elderly surgical patients.

There are several limitations in our study. First, this was a single-center observational study, with potential selection biases including race, type of surgery, propofol infusion rate. Second, our study only included patients with ASAI~II, which could eliminate the interference caused by some comorbidities, such as diabetes or hypertension, but it may also limit the universality of our results. Third, each anesthesiologist has his own induction habit such as pretreating with midazolam or dexmedetomidine, which leads to great differences in anesthesia induction.

In addition, some confounding factors that may influence the results might have been overlooked due to unavailable data, including inflammation and nutritional status. Further studies with larger sample sizes, different drug infusion rates, smaller age intervals (e.g., 5 years) and more diverse elderly surgical patients will be needed to more accurately elucidate the relationship between age and propofol induction dose for elderly surgical patients.

In conclusion, this observation study in surgical patients aged 45 years and over demonstrated that age was an independent and significant factor in propofol requirement for LOC during the induction of general anesthesia. Propofol dosage should be tailored in elderly patients, especially those older than 75 years, which may eventually bring benefit to these individuals. However, due to the limitations of our research design, further studies are needed to validate this conclusion and to verify whether this will improve the perioperative prognosis of patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by. The Institutional Research Ethics Committee of Shidong Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design: J-CS and Y-GL. Data collection: HY and H-MD. Statistical analysis: H-MD. Manuscript drafting: H-MD and YGL. Manuscript modification: Y-GL, H-MD, H-YC, S-HT and FD. Supervision: J-CS. Project administration: J-CS.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.739552/full#supplementary-material

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