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Polypharmacy in Patients with Chronic Kidney Disease with Cardiovascular Disease Comorbidities. A Systematic Review

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ABSTRACT

Polypharmacy has often been defined as the concomitant use of five or more drugs, and has been acknowledged as a significant threat to public health globally. Factors, including multi-morbidity and age, have been identified as the major drivers underlying polypharmacy, and have also been associated with a wider array of adverse health outcomes, alongside mortality. Particularly, chronic kidney disease (CKD) patients are at higher risk of polypharmacy. In addition to using potentially inappropriate drugs, there are several CKD risk factors and associated complications. As such, the objective of this systematic review is to evaluate polypharmacy in individuals with CKD and identify the adverse cardiovascular effects within this population. To achieve this objective, this systematic review will entail an in-depth search on various empirical databases, including Google Scholar, Embase, MEDLINE, CINAHL, Web of Science, and Cochrane Library, as well as existent grey literature drawn from commencement onwards for the various observational studies that reported on polypharmacy in adults

with CKD. All the full-text articles, extracted data, and citations were independently assessed by two reviewers, and the potential conflicts were resolved through consultations and discussions. The appraisal of the study methodological quality was further conducted using apt tools. The primary outcome for this systematic review will be the prevalence of polypharmacy in patients with CKD while the secondary outcome will be the adverse effects of polypharmacy on cardiovascular diseases. Random effects meta-analysis of the observational data may be conducted to effectively summarize polypharmacy pooled prevalence, and the existing correlation between polypharmacy and the adverse consequences. To approximate statistical heterogeneity, both Cochrane's Q and I^2 index will be utilized. Further analysis will be carried out with the objective of exploring the possible heterogeneity sources, including multi-morbidity, kidney replacement therapy, and sex/gender.

Keywords: Polypharmacy; Chronic kidney disease; Cardiovascular disease; Glomerular filtration rate; Drug-drug interaction

INTRODUCTION

Globally, cardiovascular diseases are the leading cause of morbidity and mortality, with more that 50% of individuals affected during their lifetime[1]. Disorders of the heart and blood vessels are referred to as cardiovascular diseases (CVD)[2]. These include: cerebrovascular disease, coronary heart disease, hypertension and heart failure. In the US, the incidence of cardiovascular disease among individuals 60 to79 years of age and 80 years and above of age is 75% and 86% respectively[2].

About 16% of the world's population suffer from CKD, which is linked to poor health outcomes such as cardiovascular diseases[3]. Chronic kidney disease is defined as a decrease in glomerular filtration rate (GFR) of <60 ml/min per 1.73 m square for a duration of at least 3 months[4]. Albuminuria, abnormalities in electrolyte imbalance, urine sediments, anemia, mineral and bone disorders, acid-base abnormalities, sexual dysfunction, and hypertension are some markers associated with CKD[4]. CKD has been linked to adverse health outcomes, including poor life quality, adverse cardiovascular disease (CVD) events, significant morbidity and all-cause mortality[5]. As such, to prevent and slow down CKD progression and offer effective treatment approaches for managing every clinical symptom, various treatment guidelines have been developed[6]. Owing to advancements in treatments, following better comprehension of the extant pathophysiology, the overall number of medications used by a patient has considerably increased, thereby making polypharmacy and its several consequences widespread within this patient cohort.

Polypharmacy has garnered a lot of attention in the medical community. Despite this attention, it's still common among patients, especially the elderly population. Polypharmacy is when someone uses five or more medications on daily bases[5]. Combination of prescriptions and over the counter (OTC) drugs increase the probability of adverse drug reactions (ADRs) and drug-drug interactions (DDIs), which are leading causes of increased risk of hospitalization and death[6]. Polypharmacy has been acknowledged to have a definite risk for medication non-compliance, negative drug events, increased visits to the emergency department, problematic interactions between drugs, drugs and food, and pharmacogenetics, lengthy hospitalizations, and at times, avoidable mortality[7,8]. However, it is still unclear if such polypharmacy is apt, given that regardless of the burden of medication in patients with CKD (that might be up to 30 different medications for every patient), both the mortality and

morbidity rates have remained higher, and this has led to several concerns in relation to the efficiency of such medications[9]. Moreover, the changed pharmacokinetic and pharmacodynamic parameters within the unique renal insufficiency milieu has made the situation increasingly complex, given that cessation of and adjustments to specific medications and treatments may be necessary[10]. Even though the fast-growing polypharmacy epidemic has raised concerns within the medical community, addressing the issue remains a major challenge owing to the existence of uncertainty with regard to the precise polypharmacy prevalence in CKD patients alongside the various socio-demographic aspects influencing the global CKD trends. The comprehension of the polypharmacy burden and adverse effects on patients with CKD, as well as the identification of the susceptible population is likely to enable healthcare professionals and physicians to develop and subsequently execute interventions, including de-prescribing, with the objective of mitigating polypharmacy and its associated adverse outcomes. Therefore, given that polypharmacy is commonly seen among CVD patients, this systematic review seeks to help identify those medications that have an adverse effect on the kidneys, thus leading to CKD which may have significant poor health outcomes among CVD patients.

MATERIALS AND METHODOLOGIES

This present systematic review and meta-analysis has strictly followed the various recommendations offered by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Therefore, to attain the objectives of this study, the researchers have conducted an in-depth search on various electronic medical databases and search engines from January 2000 to January 2024. The electronic databases searched include Scopus, PubMed, Embase, Google Scholar, and Cochrane Database of Systematic Reviews (CDSR). The literature search process entailed the cross-referencing of the papers selected and included. The selection of the above electronic databases and search engines as the key areas of literature search for this systematic review was mainly founded on the observation that they have been validated and verified as key repositories for the most current and appropriate medical literature, as well as their ongoing renewal and update of the literature. To identify the appropriate literature, the researchers employed the following search terms; CKD, CKD and Polypharmacy. Further, the researchers searched grey literature for comparable literature that the above-mentioned databases did not capture. The literature search was restricted to Human Species studies and English language.

INCLUSION AND EXCLUSION CRITERIA

This systematic review and meta-analysis examined studies of patient populations with CKD whose medication counts were considered as polypharmacy and also reported that way. The major outcome regards the pooled approximate of the period of polypharmacy prevalence in the selected studies. Nevertheless, it is worth noting that this systematic review does not involve any novel investigational drug product, and for that reason does not have any plausible requirement for any intervention alongside comparator arms.

Therefore, studies were included if they satisfied the following set criteria; (a) included patients with CKD; (b) had numerical data reports on polypharmacy in the study population; (c) study participants included were aged ≥18 years, and the study was published in English language. Furthermore, the researchers included studies despite what the various authors regarded as polypharmacy diagnosis threshold, for instance ≥5 or ≥10 drugs. Moreover, case series, reviews and case reports were excluded, along with studies that only included participants with

polypharmacy, with those with CKD without polypharmacy being excluded, implying the lack of the denominator or control, which prevents the calculation of polypharmacy prevalence

Selection of the Studies

The studies that were retrieved were exported to EndNote 20® (2021 Clarivate) with the objective of removing the duplicates prior to the remaining papers being imported to the Rayyan Qatar Computing Research Institute (QCRI) software. The selected studies' titles, abstracts and full texts were screened by two independent reviewers to determine inclusion eligibility. Potential disagreements with regard to the reviews were mainly resolved through consultations and consensus discussions with a fourth reviewer.

Data Extraction

For the data extraction, the two independent reviewers initially tried the sample data collection sheet on seven randomly chosen studies to establish this sheet's robustness in relation to patient data abstracting. As a result, the researchers were able to extract the following variables from the selected studies: author names, publication year, study design used, study location/country, study population demographics such as age and gender distribution, study sample size, percentage of CKD patients with polypharmacy, polypharmacy iteration definition (where made accessible), and the study duration.

Assessment of Study Quality

The included study's' risk of bias' was conducted through the use of the Loney's criteria. The appraisal tool's exhaustive description has been carried out elsewhere[11]. In summary, the appraisal tool is made up of eight key domains with an overall score of eight for literature that has an optimal methodology quality. The quality of the methodology was independently assessed by the two reviewers and the potential disagreements resolved through consensus and involvement of a third reviewer.

Synthesis of the Data

For this systematic review, the presentation of the continuous variables was mainly in the form of means (± standard deviation [SD]) or median (interquartile range [IQR]), as determined by the researchers to be appropriate, even as the presentation of the categorical variables took the form of numbers (percentages). Subsequently, the pooled polypharmacy prevalence approximate rates were quantified using a random effects model in patients with CKD, and through the use of the double arcsine transformation. No continuity correction was employed, as the transformation did not require any. So as to aptly ascertain sources of significant heterogeneity within the various included studies, the researchers conducted a sub-group analysis with the objective of evaluating factors such as gender, age, primary data source, and the risk of bias score of each study reviewed. Both I2 statistics and $\tau 2$ statistics were used in the assessment of heterogeneity between the different included studies [Higgins et al., 2003]. The I2 thresholds of 25%, 50%, and 75% were representative of the low, moderate, and high heterogeneity in relation to the study variances, concurrently [Quintana, 2015]. Additionally, the researchers used Doi and funnel plots in the visualization of the smaller-study effects and existing publication biases [Furuya-Kanamori et al., 2018]. Lastly, a sensitivity analysis was conducted, with the objective of ascertaining the study's effect on overall

polypharmacy prevalence in CKD patients. The statistical analyses conducted in the presented study were mainly carried out using Meta XL, v5.3 (EpiGear International, Queensland, Australia).

RESULTS

The literature search led to the retrieval of a total of 764 citations. Following the removal of duplications (n = 749), screening was performed on the titles and abstracts of the remaining articles. As a result, 15 studies were included in this systematic review and meta-analysis as indicated in (Figure 1) below. The most widespread underlying reason for exclusion of the articles were the absence of data to enable the approximation of polypharmacy prevalence and determine the adverse effects of polypharmacy.

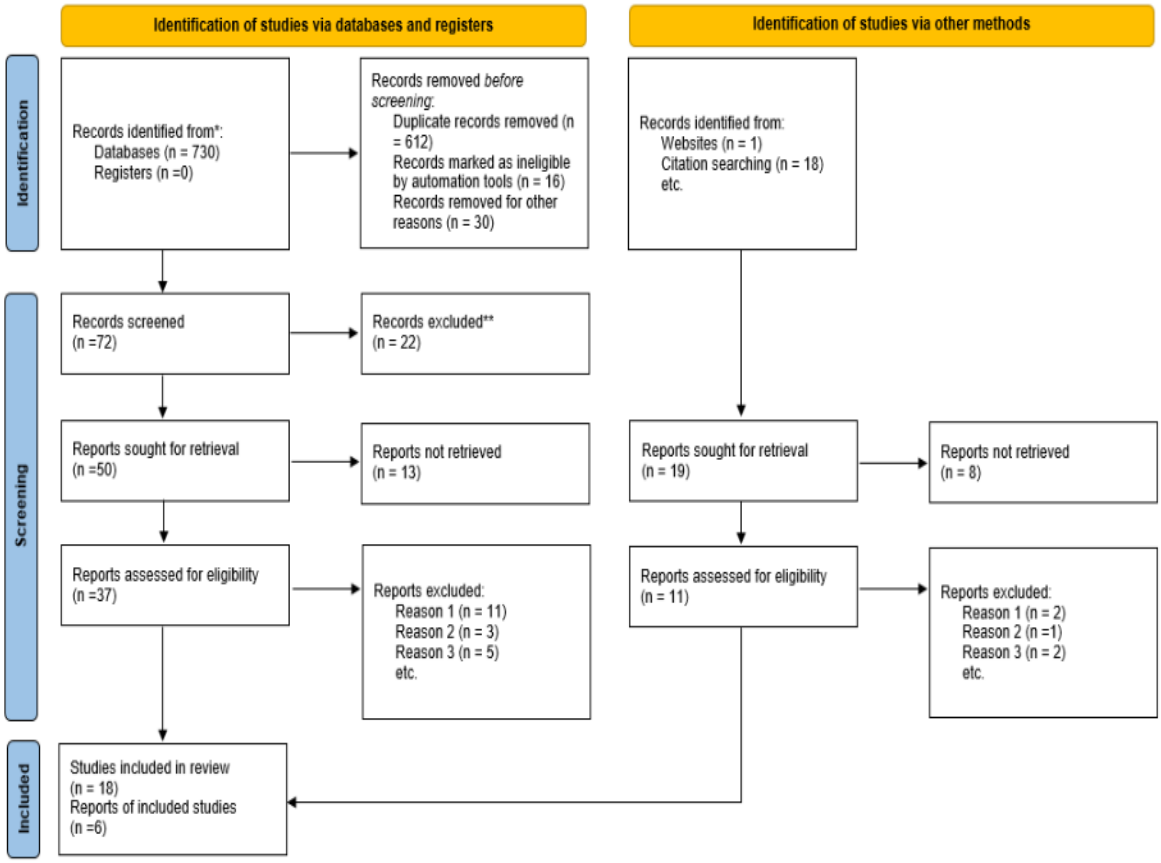

Figure 1: PRISMA Flow Diagram indicating the study selection and inclusion process

DISCUSSION

Polypharmacy, which refers to the concurrent use of multiple medications, is widespread among elderly persons as a result of multiple, concomitant severe health conditions, and has remained a subject of great concern. Though polypharmacy has been defined as the concurrent use of 5 and above medications, hyper-polypharmacy has been defined as the use of 10 and above medications concurrently[1]. Polypharmacy prevalence tends to vary with populations, even as it increases with age. For instance, a larger cohort study with 1,742,336 older adult participants reported a polypharmacy prevalence rate of 44%[12], even as the Scottish Polypharmacy Guidance reported that nearly 11% of the unplanned hospitalizations were mainly as a result of polypharmacy-related harm,

and that nearly 50% of the cases were preventable[2]. Moreover, polypharmacy prevalence varies broadly based on factors such as the definition used, age group, and geographical and healthcare contexts of the study[3]. For instance, in the US, the polypharmacy prevalence was reported to occur in 26% of all adults, with 61% of them being aged 65 years and above and having two or more chronic illnesses[4]. Comparably, in Korea and Sweden polypharmacy prevalence in elderly adults was reported to be 86.4% and 44%, respectively[13,14]. Moreover, in a recent study, polypharmacy prevalence was found to be 95% while hyper-polypharmacy prevalence was found to be 65%[12]. Cardiovascular disease, old age, and number of comorbidities have been significantly linked to polypharmacy and hyper-polypharmacy occurrence in different studies. This might clarify the increasing numbers seen in studies involving older participants with CVD, and who had an average of 6 comorbidities[15,16].

Still, a prospective study conducted in Spain and with a study cohort comprising 5052 older adults reported that the risk of mortality increased by approximately 1.8 times as a result of polypharmacy[12]. Even though the use of additional medication is often clinically significant and is meant to enhance the health of the patient, it might put the patient at elevated risk of experiencing adverse effects of potential drug-drug interactions (DDI), as well as the effects of drug-disease interactions. In most instances, the clinically significant DDIs appear in the form of a decline in the medication's therapeutic effects, increments in the occurrence of the adverse drug reaction events, as well as the compromise of the treatment outcomes[12]. Chronic potential DDIs include life-threatening adverse events and those requiring medical interventions and treatment to either prevent or minimize the adverse effects. In studying the types of drugs/medications that are commonly used by CKD patients and their correlations to CVD and polypharmacy, Morin et al. identified the combination of various prescriptions and over the counter (OTC) medications with the increased likelihood of adverse drug-drug interactions (DDIs) and drug reactions (ADRs), and capable of being the major causes of increased risk of hospitalization and mortality[13]. Thus, DDIs' prevalence rates in CKD patients have been estimated between 56.9% and 89.1%, probably because polypharmacy itself is necessary for the management of this complex condition.

Previously reported prevalence estimates in studies conducted by Danjuma et al. and Veehof et al. are significantly higher compared to the general population, including the different cohorts at higher risk of polypharmacy like the elderly, chronic liver disease patients, and persons with HIV[17,18]. Nevertheless, the approximations were similar to those of populations acknowledged to be increasingly exposed to polypharmacy, including CVD patients and those with heart failure[19]. The noticeably higher prevalence rates are alarming, especially in patients with CKD, given that they are representative of an increasingly challenging and therapeutically susceptible populace; mainly as a result of the vital role played by the kidneys in drug metabolism, and including the pharmacokinetic and pharmacodynamic aspects[10]. As such, this poses a higher risk of adverse drug reactions (ADR) and their related complications/sequela on CKD patients with CVD[10].

With respect to the existing association between heart disease and CKD (prevalence of heart disease and CKD) and the common drugs used by these patients and their interactions, it is noteworthy that variations in pharmacokinetic (PK) and pharmacodynamic (PD) parameters in CKD patients tends to further exacerbate the pathological condition[20]. CKD patients are often affected by an increased number of comorbidities, including underlying conditions along with the reduced renal functionality consequences, including cardiovascular disease,

diabetes, hypertension, mineral and bone disease, and anemia[21,22]. These conditions require multiple medications to ameliorate patients' symptoms and slow the progression of the disease, increasing, however, the risk for the development of drug interactions. Thus, it has been acknowledged that the kidneys play a vital role in handling medications, and more importantly in the excretion of the medications. Among the notable consequences of CKD on pharmacokinetics entails the reductions in renal clearance as a result of the decrease in GFR. The renal impairment effect on PK is, nonetheless, not restricted to the reduced ability to effectively eliminate drugs excreted through the kidneys. A correlation exists between CKD and multiple physiological changes, and, as a result, might influence the various extra-renal pharmacokinetic processes, including the absorption of drugs, as well as the distribution and metabolism of the medications used, which have the ability to increase the risk of toxicity[22]. Consequently, CKD patients are at a higher risk of altered medication exposure and toxic/adverse effects compared to persons with normal kidney function[7]. Therefore, studies using the experimental CKD models have shown altered expressions alongside intestinal and hepatic drug transporters activities that impact the hepatic uptake and intestinal absorption, and also the drug metabolism.

Additionally, CVD prevalence has been observed to be higher in individuals with CKD, which makes them increasingly vulnerable to both polypharmacy and multimorbidity[9,23,24]. Earlier studies have also shown polypharmacy prevalence to range between 62% and 86% in patients with CKD[9,25]. Still, pharmacodynamics and pharmacokinetics may be altered as a result of the dysfunction of the kidney among the elderly persons[10,26], and, as a result, drug adverse events and drug-drug interactions can be intensified in the elderly populations with CKD[10,27]. At present, evidence regarding health outcomes and polypharmacy in elderly persons with CKD remains infrequent. A number of cohort studies have shown that polypharmacy is linked to an increase in the risk of CKD, CVD events, fragility fracture, as well as all-cause mortality in persons with CKD, regardless of the individual CKD status[28-30]. Still, in their study, Wang, et al. observed that in elderly patients with CKD, compared to individuals who did not have polypharmacy, those with polypharmacy had a CVD mortality and an all-cause mortality risk of 1.39 times and 1.27 times, respectively[31]. The study also reported that elderly persons with CKD and polypharmacy presented the highest mortality risk[31]. An early cohort study conducted in the United States,comprising adults aged 45 years and above and with a 5-year follow-up disclosed that only polypharmacy involving 8 or more medications was correlated to an increase in mortality rates, as opposed to minor polypharmacy involving 6 to 7 medications in individuals with CKD, even as no evidence indicating the modification of the association by individual CKD status[29]. A study conducted in Japan and comprising 1,117 participants found that polypharmacy involving 5 to 9 medications and hyper-polypharmacy involving over 10 medications was linked to CKD, including kidney failure, with only hyper-polypharmacy being linked to all-cause mortality[32]. The sensitivity analysis conducted by Wang, et al. has, to this end, indicated that even minor polypharmacy considerably increased mortality rates in older persons with CKD[31]. A recent study has disclosed that extant medication deprescribing interventions often offer minor reductions with regard to mortality rates, but do not offer any considerable effects on falls, hospitalizations, and health-related quality of life in individuals aged 65 years and above[33].

The potential DDIs prevalence in CKD patients have been reported to range between 27.5% and 89.1%[34,35]. The broader DDIs probability range is unusual and several factors may be attributable, including pre-existing

complications and comorbidities, the types and number of medications prescribed to each patient, as well as the CKD stage[30]. Further, the potential DDIs may be identified and subsequently categorized using diverse methodologies, such as virtual software that include the Medscape drug reference database system®, DrugReax®, LexiComp®, and Thomson Reuters Micromedex®, that have been known to offer data regarding the type, mechanism, and risk of DDI, alongside the proposals on effective management of the DDIs. In particular, the Medscape drug reference database system® is categorized the DDIs into 5 key classes on the basis of the degree of clinical significance[36]. For instance, according to the software, Type A DDI classification has no known interactions, while Type B classification entails mild or minor interactions. Thus, in Type A and B, the simultaneous use has diminutive or no indication of clinical concerns. Further, Type C involves significant or modest interactions of the drugs, and their concomitant usage requires a proper monitoring plan to identify possible adverse effects. Type D category involves serious and major interactions, and their concomitant use must be critically evaluated. Lastly, Type X category involves contraindication as the medications might interact with each other in a way that is clinically significant.

Earlier researches carried out on CKD patient' cohorts with regard to polytherapy regimen disclosed that most of the reported clinically significant DDIs were Type C, consisting of moderate severity, followed by Type B, comprising mild and minor DDIs, with major Type D DDIs found to be infrequent, same as Type X DDI, which was attributable to nearly 0.1–1% of all the reported DDIs[36,37]. Also, the potential DDIs may be categorized into pharmacokinetic, in instances where the drug disposition has been changed through co-administration of another medication, thereby adversely affecting the absorption, distribution, plasmatic-proteins binding, and the process of metabolism and excretion, or even pharmacodynamic, in instances where the effect of the medication gets altered at the action site through the existence of a second medication, thereby adversely affecting several physiological mechanisms. Lastly, drug interactions are common, even though under-recognized, and mainly happen in instances where more than one medication is administered intravenously, simultaneously[38, 39]. The drug compounds injected often react and display physicochemical discordancy in the infused solution, resulting in medication inactivity, inflammatory reactions, catheter occlusion, and embolism[40]. A number of studies have evaluated potential DDIs patents in individuals with CKD, and the most common cardiac and kidney medications, as well as DDIs have been listed in (Tables 1, 2 and 3) below.

Table 1: The most commonly prescribed cardiac and kidney medications

Medication Class	**Medications**
Cardiovascular Medications	Diuretics
	Calcium channel blockers
	Alfa blocker
	Ace inhibitor
	Angiotensin receptor blocker
	Beta blocker
	Alfa 2 Agonist

Antibiotics	Ceftriaxone
	Cefoperazone
	Levofloxacin
Gastrointestinal Medications	Proton pump inhibitors
	H2 Blockers
Vitamins and Minerals	Calcitriol
	Vitamin D
	Multiminerals and Multivitamins
Phosphate Binders	Calcium carbonate
	Sevelamer
	Lanthanum
	Calcium acetate
Antidiabetics	Insulin
Hematopoietics	Iron
	Folate
	Erythropoietin
	Darbepoietin

Table 2: the potential DDIs per prescription in patients with CKD

Number of medications per prescription	Number of interactions (range)	Number of interactions (IQR)
A (1-5)	-	-
B (6-10)	0 to 5	2 (1 to 2)
C (11-15)	0 to 7	2 (1 to 4)
D (16-20)	2 to 8	3.5 (2 to 4)

Table 3: The most common DDIs based on the analyses of numerous studies on the potential DDIs patterns in patients with CKD, highlighting the most common and pertinent ones

Study	Type of Study	Number of drugs	Most frequent medication	Most frequent DDI	Severe DDIs (%)
Al-Ramahi et al., 2016	Observational – retrospective cohort study	7.87 ± 2.44	$CaCO_3$ Alpha Calcidol OFS Folic Acid Aspirin	$CaCO_3$ – Amlodipine $CaCO_3$ – Aspirin Aspirin – Furosemide Aspirin – Enoxaparin Aspirin – Insulin	8.4
Fasipe et al., 2018	Retrospective study	10.28 ± 3.85	Furosemide Heparin Lisinopril	$CaCO_3$ – OFS Folic acid – Furosemide Alpha Calcidol - $CaCO_3$	2.7

			$CaCO_3$ Alpha Calcidol	OFS + Vitamin E $CaCO_3$ – Furosemide	
Rama et al., 2012	Prospective, observational study	12.08 ± 6.3	NA	Ascorbic acid – Cyanocobalamine Clonidine – Metoprolol Amlodipine – Metoprolol Insulin – Metoprolol	20
Sgnaolin et al., 2014	Cross-sectional, observational study	6.3 ± 3.1	$CaCO_3$ Erythropoietin Sodium citrate Omeprazole Calcitriole	Atenolol - $CaCO_3$ $CaCO_3$ – OFS $CaCO_3$ – Ticlopidine Enalapril – Erythropoietin Amiodarone – Prednisone	27.6
Marquito et al., 2014	Cross-sectional, observational study	5.6 ± 3.2	Furosemide Simvastatin Losartan Aspirin Captopril	Furosemide – Aspirin Enalapril – Furosemide Captopril – Furosemide Enalapril – Losartan Allopurinol – Captopril	16.8
Adibe et al., 2017	Retrospective study	6.15 ± 1.96	Furosemide Lisinopril Amlodipine Ranitidine Hydrochlorothiazide	Lisinopril – Furosemide Furosemide - $CaCO_3$ $CaCO_3$ – Lisinopril Aspirin – Furosemide Furosemide - Hydrochlorothiazide	3.87
Okoro and Farate, 2019	Cross-sectional study	5.8 ± 1.5	NA	$CaCO_3$ – OFS Lisinopril – Furosemide Captopril – Furosemide Captopril – Spironolactone OFS – Omeprazole/Pantoprazole	0.4
Hegde et al., 2015	Cross-sectional, observational study	9.4 ± 3.9	NA	Sodium bicarbonate – OFS $CaCO_3$ – OFS Aspirin – Carvedilol Sodium bicarbonate – Allopurinol Pantoprazole – OFS	16.41
Saleem et al., 2017	Retrospective study	NA	NA	OFS – Omeprazole Calcium/Vitamin D – Ciprofloxacin Captopril – Furosemide	27.8

				Calcium gluconate – Ceftriaxone Ciprofloxacin – OFS	
Santos-Díaz et al., 2020	Observational cross-sectional study	8.6 ± 3.4	Omeprazole Acetaminophen Aspirin Bisprolol Furosemide	Acenocoumarol – Omeprazole OFS – Omeprazole Metformin – Aspirin Levothyroxine – Omeprazole	11.4

STRENGTHS AND LIMITATIONS

The major strength of the present systematic review can be found in the study's novelty at approximating the prevalence of polypharmacy in CKD patients with CVD comorbidities. Thus, this seeks to allow policy makers and clinicians/physicians, as well as other healthcare stakeholders to effectively estimate the polypharmacy burden and aptly allot the necessary interventional strategies to mitigate the various downstream effects that include the adverse effects of polypharmacy, drug reactions and bidirectional interactions. This systematic review has additionally entailed the in-depth and comprehensive search of several medical databases through the use of established methodologies and subsequently reported using standardized methods. Regardless of these strengths, a number of limitations have been identified in this study. For instance, the researchers only included literature published in English, which not only excluded qualified studies published in other languages but also limited its generalizability. Additionally, the other potential limitation of the present study might be the non-uniform reporting of the adverse outcomes and their correlations to polypharmacy. This might, therefore, make it increasingly challenging to identify the adverse effects related to the use of medications in CKD patient populations. The other notable limitation is the view that some of the identified literatures were not of standard quality, which might negatively impact the reporting of this study's findings. Regardless of these limitations, we anticipate that this systematic review's findings will inform the guidelines of physician practice, medication education, and different quality improvement interventions and initiatives aimed at addressing polypharmacy.

CONCLUSION

In conclusion, the findings of this systematic review underscore first, the gravity of the growing challenge of polypharmacy among CKD patients and highlights the important requirement to execute several the interventions proposed as a means of reducing the challenge of polypharmacy within the general population. This entails deprescribing algorithms, clinical pharmacists led interventions, comprehensive review of medications, screening tools for potentially inappropriate medication (PIM). Thus, it is worth observing that such interventions are uncommon, even as studies on efficiency of the strategies on clinically significant outcomes is limited. Hence, future research efforts should focus on measuring the effectiveness of these interventions. Furthermore, there is a need for experts to make efforts towards development of multifaceted theory-founded interventions customized for patients with CKD. The approach is likely to yield positive results, given that other existing interventions and

approaches, including pragmatic approach, have been found to be checkered, with a number portraying undesirable outcomes without any benefit.

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