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Original Research

What is Polypharmacy in Patients with Chronic Kidney Disease? A Systematic Review

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ABSTRACT

Purpose: Polypharmacy presents an increasing therapeutic challenge for physicians managing patients with chronic kidney disease (CKD). However, there is a lack of consensus regarding the specific medication count threshold that defines polypharmacy in this population. The objective of this review is to establish a unified definition of polypharmacy in the CKD population by examining the diverse definitions used in previously published studies.

Methods: A comprehensive search was conducted in relevant databases (PubMed, SCOPUS, Cochrane, and disease-specific databases) from 2000 to May 2022 to identify studies with polypharmacy threshold definitions in patients with CKD. Studies meeting the inclusion criteria were included in this review, and their methodologic quality was assessed.

Findings: Following the screening of the search results, duplicate records and studies that did not meet the inclusion criteria were removed, resulting in a total of 18 studies included in this review. Among these, 61.1% specified the polypharmacy definition to be a threshold of ≥5 medications. In addition, 22.2% specified a high polypharmacy definition at a threshold of ≥10 medications. However, none of the studies reported on the dichotomy between kidney-related and non-kidney-related polypharmacy.

Implications: This review indicates that a numerical threshold of ≥5 medications is commonly used to define polypharmacy in patients with CKD. Nevertheless, it remains uncertain whether a kidney-related polypharmacy definition or a high polypharmacy definition would better identify patients with CKD at risk for polypharmacy-related complications.

Introduction

Polypharmacy is a term that refers to the regular use of multiple medications per patient. Although the general threshold for polypharmacy has been established to be 5 or more medications,[1,2] specific definitions for disease-specific polypharmacy, such as in the case of chronic kidney disease (CKD), have yet to be examined. This is particularly important because the standard treatment of some comorbid diseases, such as CKD,does already involves rising number of medications. Additionally, these patients may sometimes require further medications to address other comorbid or acute illnesses, which poses significant risks. The numerous negative consequences encompass the possibility of medications interacting with each other in various ways and/or the potential for negative reactions (adverse effects) occurring as a result of taking the different medications.[3] Other nontherapeutic effects of polypharmacy include an increased risk of hospitalization,[4] decreased physical and cognitive capabilities, and even an increased risk of death.[5]

In the general population, diabetes and hypertension are the primary causes of CKD,[6] and managing these conditions often requires the use of multiple medications, contributing to the occurrence and persistence of polypharmacy in patients with CKD.[3] On average, patients with CKD not requiring dialysis use 6 to 12 medications,[7] with those receiving dialysis possibly requiring even more medications tailored to their needs. Moreover, as CKD progresses and glomerular filtration rate decreases, medication levels in the blood and tissue may accumulate, increasing the risk of dose-related adverse events and drug-drug interactions.[7]

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Despite extensive research on polypharmacy, no studies have examined its prevalence and burden specifically in patients with CKD. Establishing a consensus on the threshold for polypharmacy in this patient population would be valuable for clinical decision-making, medication reconciliation, and the design of prospective studies in this area.[8,9] This review represents the first systematic examination of the medication counts that define polypharmacy in patients with CKD. Although there is a scarcity of studies reporting on medication thresholds in this patient population, a pooled analysis of the available studies would help identify the medication counts and the threshold-defining polypharmacy in patients with CKD.

Methods

Literature Review

A comprehensive literature search strategy was implemented to conduct a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] Relevant English-language literature databases, including PubMed, SCOPUS, Cochrane, as well as databases of systematic reviews and disease-specific data, were searched for articles and clinical trials published from 2000 to May 2022 that pertained to polypharmacy in patients aged ≥18 years or above with CKD. The search terms used were *polypharmacy* [TIAB] AND *kidney* [MeSH] OR *CKD* OR *chronic kidney disease* [MeSH]. Additionally, grey literature was examined for analogous articles not captured in the primary databases mentioned above. Studies that failed to provide a definition for polypharmacy in CKD populations were excluded, as were those with non-systematic designs (such as narrative reviews, case series, and case reports), renal transplant patient cohorts, and studies exploring medication counts in patients undergoing any form of renal replacement therapy.

Data Selection

The assessment of studies for inclusion in the review was conducted by 2 independent reviewers (M.K. and A.A.-K.) who screened the titles and abstracts of retrieved search records to determine eligibility. In the event of any disagreement between the independent reviewers regarding the eligibility of a particular study, consensus was typically reached through a discussion and detailed assessment of the study in question. If consensus could not be reached, a third reviewer was consulted (M.I.D.) to adjudicate. Studies that did not meet the predefined eligibility criteria were excluded.

Data Extraction

To ensure the accuracy of patient data extraction, 2 reviewers (M.K. and A.A.-K.) conducted a preliminary trial of extraction using 5 randomly selected studies. After a successful pilot phase, the reviewers proceeded to extract pertinent information from the included studies. This information encompasses the authors' last names, year of publication, study design, location of the study, country of origin, study population, age range, gender distribution, sample size, the proportion of patients with CKD and polypharmacy, any variations in polypharmacy definitions used, and duration of the study.

Quality Assessment

The risk of bias in assessing the methodologic quality of the included studies was performed using the Loney criteria.[11] This scale incorporates various domains, including study design, sampling methods, data collection techniques, statistical analysis, and interpretation of results. By evaluating these domains, the quality and validity of the studies can be assessed, and potential biases or limitations can be identified. In observational studies, these criteria help researchers determine whether a causal relationship exists between an exposure and an outcome. The Loney criteria algorithm categorizes studies into 3 groups based on the risk of bias: 7 to 8 indicates a likely unbiased study, 5 to 6 suggests some risk of bias, and <4 indicates a substantial risk of bias.[11]

Results

Figure 1 presents the PRISMA chart illustrating the search strategy used, along with a summary of the study selection process. Initially, a total of 487 studies were identified through the literature search. Following a thorough review and removal of duplicates, only 18 studies were deemed suitable for inclusion in this systematic review. These 18 studies included a total of 815,524 patients, of whom 22,413 met the criteria for polypharmacy. The mean (SD) age of the study population was 68.8 (12.76) years, and there was a relatively equal proportion of males and females. The mean duration of follow-up in the included studies varied, with an overall mean of 28.87 months. Moreover, among the included studies, 5 had a cross-sectional design, whereas 5 used a cohort. The study cohorts range from community-based registries to multicenter, prospective hospital cohorts.

Kidney- and Non–Kidney-Related Polypharmacy

No studies reported on dichotomy between kidney- and non–kidney-related polypharmacy. In addition, of the 18 students, only 3 studies had not reported the proportions of their CKD populations.

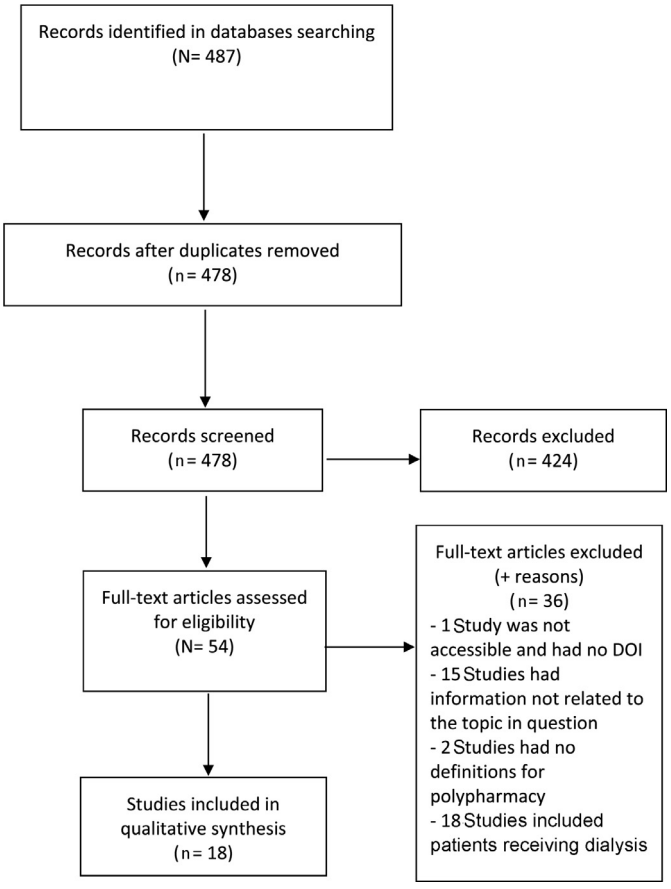

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing inclusion and exclusion of studies from the review.

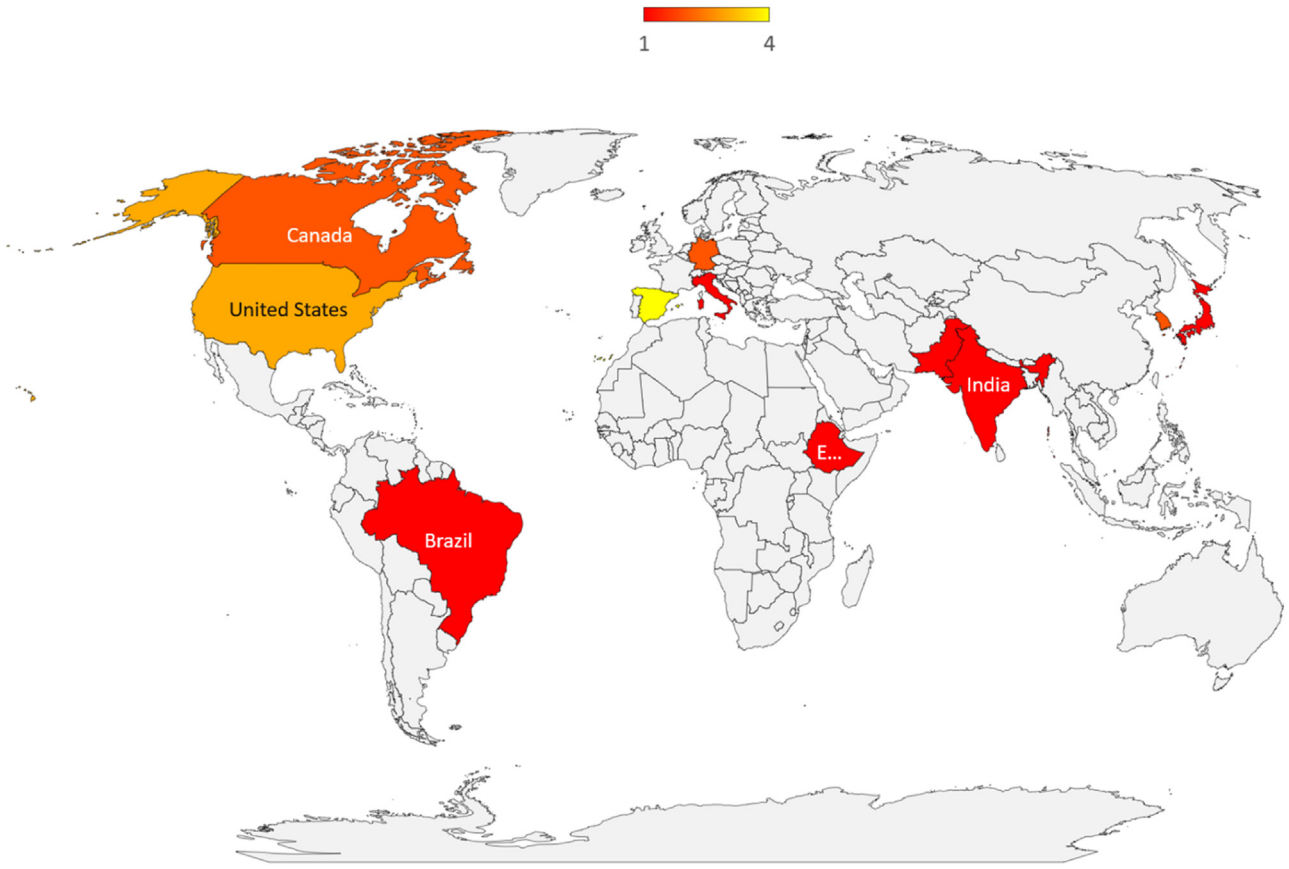

Figure 2. Distribution of the reviewed studies by geographic location.

Disposition of Polypharmacy Phenotypes by Primary Data Source

The review cohort is comprised of 11 studies from various countries and jurisdictions. Figure 2 illustrates the geographic distribution of the reviewed studies. The publication years for these studies range from 2013 to 2021, primarily reporting from North America and Europe. Studies included in this review used polypharmacy definitions that spanned across 5 different groups, with 2 studies having 2 different definitions of polypharmacy. As shown in Table 1, these numerical groups started at definitions as low as ≥5 medications, extending up to ≥11 medications. Of the 18 studies, 11 (61.1%) utilised a definition of polypharmacy as the threshold of ≥5 regular medications per patient. However, there was another notable peak of 4 studies (22.2%) using the definitions of polypharmacy at ≥10 medications, with 2 of these studies providing specific named definitions for this threshold.[12,13] In addition to numerical definitions, 2 studies also provided descriptive definitions of polypharmacy.[14,15] Lobos-Bejarano et al[15] defined polypharmacy as intake of ≥7 medications, excluding anti–vitamin K, whereas Yameen et al[14] had a different iteration of polypharmacy defined as intake of ≥5 medications, excluding supplements.

Table 1
Broad classification of polypharmacy by the reviewed studies.

No. of Medications	No. of studies	Reference
≥5	11	12–14,16–23
≥6	2	24,25
≥7	2	15,26
≥8		
≥9		
≥10*	4	1,13,27,28
>11	1	

* Dubbed excessive polypharmacy[17] or hyperpolypharmacy.[13]

Risk of Bias

A risk of bias assessment was conducted on the 18 included studies using the Loney risk of bias assessment algorithm.[11] None of the studies received a score of ≤5, indicating a high risk of methodologic bias. Among these studies, 16 had a score of 6 to 7, indicating a moderate risk of methodologic bias. Additionally, 2 studies[15,26] obtained a score of 8, indicating a sound methodologic quality.

Discussion

Through a systematicliterature search, this review carried out a pooled synthesis of the various studies reporting on the definitions of polypharmacy in patients with CKD. The included studies provided a working consensus that the regular intake of ≥5 medications serves as the diagnostic threshold for the definition of polypharmacy in this population. This finding has tremendous potential implications for medication reconciliation among intervention strategies in this therapeutically vulnerable cohort of patients.[29] For instance, recent reports from South Korea using a nested case-control design have highlighted the morbidity associated with polypharmacy in patients with CKD, including the unfortunate risk of avoidable mortality.[12,30] Despite this increasing burden, systematic studies that primarily explore polypharmacy in patients with CKD are lacking. Therefore, establishing a numerical threshold of ≥5 medications can help foster therapeutic consensus among clinicians as well as among policymakers when addressing the issue of polypharmacy in patients with CKD.

Moreover, therapeutic morbidity due to polypharmacy is increasing within the general population, particularly in the setting of multimorbidity and subsequent inevitable polypharmacy: such as heart failure, HIV, and chronic liver disease, etc.[31] Given the pivotal roles played by the liver and the kidneys in drug metabolism, these organs are susceptible to the downstream consequences of polypharmacy, including bidirectional interactions, pharmacogenetic interactions, and adverse medication reactions.

It remains uncertain whether the characterization of polypharmacy into kidney- and non–kidney-related categories in patients with CKD will more robustly identify vulnerable patients at risk. Reports on other patient populations, such as people living with HIV,[31] suggest that organ-specific polypharmacy thresholds are more likely to identify polypharmacy patients in need of interventions, such as medication reconciliation. However, in certain communities, as seen in recent report from rural Ethiopia, for example,[32] an increasing medication count may lead to potential misunderstanding of medication instructions. Therefore, future pharmacoepidemiologic studies in patients with CKD should explore polypharmacy within the framework of excess kidney-related medications rather than focusing solely on the number of medications individual patients are taking.

Furthermore, the recent survival advances observed in patients with CKD are primarily attributed to new pharmacotherapy, irrespective of the number or treatment regimen of medications. Therefore, taking multiple organ-specific medications that provide increased survival benefit is not necessarily detrimental. It is therefore necessary to further explore the implications of kidney-related polypharmacy on overall patient outcomes through future systematic studies.

Duration of Polypharmacy

None of the reviewed studies reported the duration of polypharmacy among their respective patient population. However, based on published reports in the general population and patients with specific organ morbidities, the suggested duration of exposure that constitutes polypharmacy is typically 4 months,[1,31] although the exact duration may vary. Understanding the duration of medication exposure is crucial to understand the impact it has on patients through both the pharmacokinetic and pharmacodynamic properties of these medications.[33] For instance, patients with specific organ morbidities, such as CKD, may inevitably experience nonspecific musculoskeletal pain, diarrheal illness, or generalized body fatigue, most of which require symptomatic pharmacotherapy, such as simple analgesia, for a few days. These medications, which are taken for a short duration and serve a specific purpose, may not be considered in the overall numerical count of medications that constitute polypharmacy. Therefore, the 4-month duration reported from previous studies seems reasonable, although it remains a topic open for debate.

Strengths and Weaknesses

The principal strength of this review lies in its novelty at examining the numerical threshold of polypharmacy in the distinct group of patients with CKD. This contribution will undoubtedly support current and future efforts to comprehensively characterize the pattern and clinical phenotypes of polypharmacy in this patient population. Furthermore, it will help address any lingering uncertainties regarding the communication of polypharmacy outcome measures between colleagues and between policy statements.

However, a limitation of this review is the paucity of studies specifically examining kidney-related polypharmacy. Nevertheless, even in light of the above, it is unlikely that these limitations will have a significant impact on the final point estimates of polypharmacy definitions. Moving forward, this review recommends incorporating this definition across national and international CKD guidelines. Additionally, further exploration of the determinative value of assessing kidney- and non–kidney-related polypharmacy from a prospectively collected patient cohort is suggested.

Conclusions

This extensive examination of identified published studies suggests that a numerical threshold of ≥5 medications be used to define polypharmacy in patients with CKD. The utility of alternative definitions of polypharmacy to more robustly identify patients with CKD at risk is uncertain. However, a numerical value of ≥10 medications taken regularly is suggested as a threshold for high polypharmacy.

Authors Contribution

All authors read and approved the manuscript. M.I Danjuma was involved in review conceptualization and as its custodian. A. Al-Khulaifi, M. Khatib, E. Ali, and M.Y. Ali were involved in independent reviews and as third adjudication reviewers. and M.I. Danjuma, A. Al-Khulaifi and M. Khatib were involved in data extraction and analysis. A. Al-Khulaifi, M. Khatib, and M. I Danjuma were involved in intial manuscript dafts. M. Khatib, A. Al-Khulaifi, and M I Danjuma were involved in completing the final manuscript draft.

Declaration of Competing Interest

None.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2023.08.007.

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