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NEPHROLOGY - REVIEW

Factors affecting medication adherence among pre-dialysis chronic kidney disease patients: a systematic review and meta-analysis of literature

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Abstract

Background Medication adherence plays an essential role in slowing the progression of chronic kidney disease (CKD). This review aims to summarise factors affecting medication adherence among these pre-dialysis CKD patients.

Methods A systematic review of the literature was performed in Medline®, Embase®, SCOPUS® and CINAHL®. Peer-reviewed, English language articles which evaluated factors associated with medication adherence among pre-dialysis CKD patients were included. Meta-analysis was performed to assess the pooled medication adherence rates across studies. Factors identified were categorised using the World Health Organization's five dimensions of medication adherence (condition, patient, therapy, health-system, and socio-economic domains).

Results Of the 3727 articles reviewed, 18 articles were included. The pooled adherence rate across studies was 67.4% (95% CI 61.4–73.3%). The most studied medication class was anti-hypertensives (55.6%). A total of 19 factors and 95 sub-factors related to medication adherence were identified. Among condition-related factors, advanced CKD was associated with poorer medication adherence. Patient-related factors that were associated with lower medication adherence included misconceptions about medication and lack of perceived self-efficacy in medication use. Therapy-related factors which were associated with poorer medication adherence included polypharmacy while health system-based factors included loss of confidence in the physician. Socioeconomic factors such as poor social support and lower education levels were associated with poorer medication adherence.

Conclusion Factors associated with poor medication adherence among pre-dialysis CKD patients were highlighted in this review. This will aid clinicians in designing interventions to optimise medication adherence among pre-dialysis CKD patients.

Keywords Pre-dialysis · Non-dialysis · Chronic kidney disease · Medication adherence · Patient compliance

Introduction

Chronic kidney disease (CKD) is a growing health problem which is associated with increased risk of cardiovascular mortality, morbidity and reduced quality of life [1–4]. For CKD patients, pharmacological therapy plays an important role in slowing down disease progression and addressing symptoms arising from disease-related complications such as anaemia [5].

Medication adherence, defined as 'the extent to which the patient's behaviour matches agreed recommendation from the prescriber' [6], forms the cornerstone for effective management of CKD. However, non-adherence to medication is highly prevalent among CKD patients, affecting up to 80% of patients according to a review by Schmid et al. [7]. Importantly, medication non-adherence has been shown to be associated with adverse clinical outcomes such as increased risk of CKD progression and mortality, as seen in the recent Chronic Renal Insufficiency Cohort (CRIC) study [8].

There exists a multitude of factors and barriers which affects medication adherence among pre-dialysis patients. However, information from different studies appears to be

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conflicting, which confounds the ability of policymakers and physicians to design efficacious interventions to optimise outcomes for pre-dialysis CKD patients. For example, Smita et al. showed that increased number of comorbidities was associated with poorer medication adherence among both dialysis and non-dialysis CKD patients [9]. However, a cohort study by Tangkiatkumjai et al. found that having comorbidities such as hypertension and dyslipidemia was not associated with poorer medication adherence in pre-dialysis patients [10].

To our best knowledge, there is no review which has summarised factors impacting medication adherence specifically in pre-dialysis CKD patients. Hence, this review aims to identify and highlight factors influencing medication adherence among pre-dialysis CKD patients.

Materials and methods

We performed a literature search among major online databases which comprised of Medline®, Embase®, SCOPUS® and CINAHL® in accordance to the PRISMA checklist. The search terms utilised were (chronic renal insufficiency or chronic renal failure or chronic kidney disease or chronic kidney insufficiency or pre-dialysis or non-dialysis) and (drug or medication or treatment or therapeutics or medicine or therapy) and (compliance or adherence or non-compliance or persistence or non-adherence) and (factors or barriers). For the searches performed in Medline®, medical subject headings (MeSH) terms were employed and details of the full search strategy are listed in supplementary file 1. The search terms utilised were adapted from systematic reviews which examined medication adherence factors in other patient populations such as osteoporosis and rheumatological diseases [6, 11]. We also performed finger-searches of references listed in included articles. There were no restrictions of articles' start dates and the review is current as of 17 February 2020.

The independent evaluation and inclusion of articles were conducted by two reviewers (JYT and JJBS) and they discussed where discrepancies occurred. In situations where discrepancies could not be rectified, further discussion was made with a third independent reviewer (CTY).

Full-text, English language articles which evaluated medication adherence in adult, pre-dialysis CKD patients were included. Meta-analyses, case reports, case series as well as other systematic reviews were excluded. Additionally, articles which included patients on any mode of renal replacement therapy such as dialysis or kidney transplant were excluded.

The quality assessment of included studies was performed by two reviewers (JYT and JJBS). For cross-sectional and observational cohort studies, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by National Health, Lung and Blood institute was used [12]. For qualitative studies, the Critical Appraisal Skills Programme checklist for qualitative research was utilised [13].

The medication adherence rates at the end of each study's follow-up were reported as the proportion with 95% confidence intervals, if available. I^2 statistic was utilised to evaluate heterogeneity and where significant heterogeneity (> 50%) was detected, random-effects model was used. Otherwise, the fixed-effects model was utilised. Subgroup analyses for medication adherence were stratified by study design (retrospective or prospective data collection), the main classes of medication studied and the continents where the studies were conducted in. In view of the statistical, methodological and clinical heterogeneity expected from included studies, we did not perform a quantitative analysis of factors associated with medication adherence. Instead, a narrative summary of factors that affected medication adherence was provided.

Medication adherence factors that were identified were then classified into domains in accordance with World Health Organization (WHO) recommendations [14]. The five domains were therapy-related, patient-related, condition-related, health system-related and socioeconomic-related factors. A kidney model for medication adherence among pre-dialysis CKD patients was also suggested to help physicians in better visualising these domains that affected medication adherence (supplementary file 4).

Results

The flowchart for the selection and inclusion of articles is shown in Fig. 1. Of the 3727 initial articles shortlisted, 18 articles were included in the final analyses after excluding duplicated and irrelevant articles.

The details of included studies were shown in supplementary file 2. The studies were mainly conducted in North America ($n = 9$, 50%) and in tertiary healthcare settings such as hospitals ($n = 17$, 94.4%). Majority of the studies included fewer than 500 patients ($n = 12$, 66.7%) and only five studies recruited over 1000 patients (27.8%). The most common class of medication studied across studies was anti-hypertensives ($n = 10$, 55.6%), with four studies specifically evaluating patients' adherence to anti-hypertensives only. Medication adherence was self-reported by patients during interviews or focused group discussions in seven (38.9%) studies while medication adherence measures which include medication possession ratio (MPR) and proportion of days covered (PDC) were utilised in three (16.7%) studies. The most common instrument used for assessment of medication adherence was the Eight-item Morisky Medication Adherence Scale (MMAS) ($n = 2$, 11.1%), while the remaining

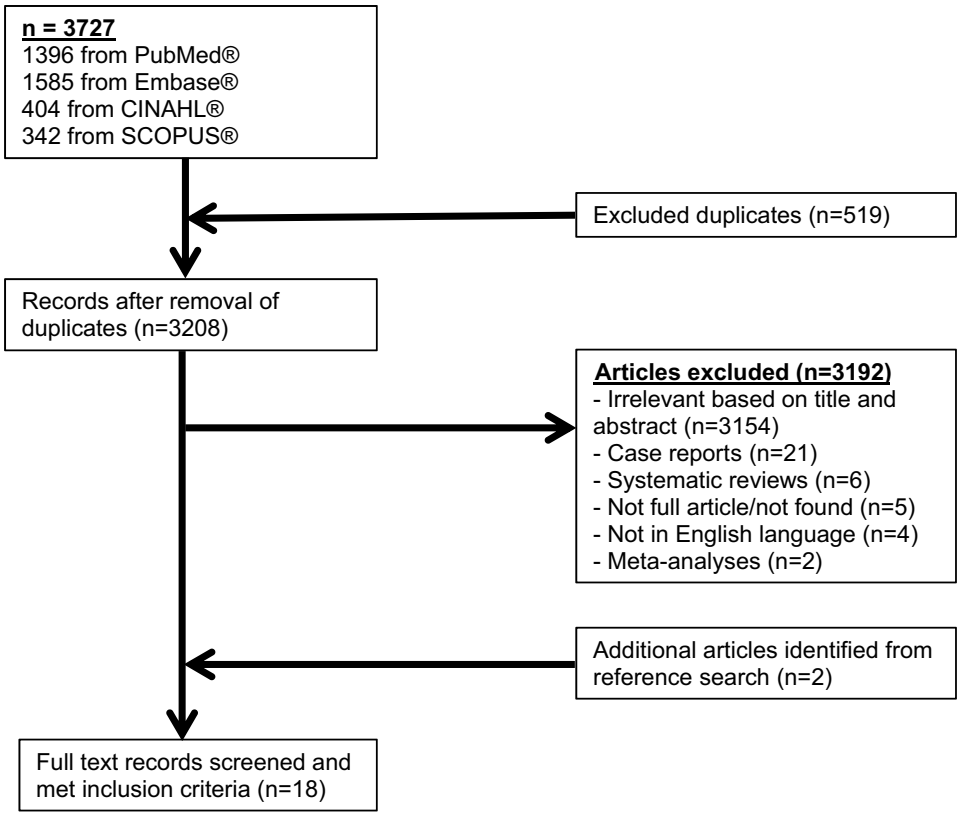

Fig. 1 Flow chart for the inclusion of articles for review

studies utilised structured questionnaires comprising of a varying number of questions.

The medication adherence rates were reported in 13 studies and ranged from 33.0 to 87.7%. Meta-analysis of these studies comprising of 54,652 patients showed a pooled medication adherence rate of 67.4% (95% confidence interval (CI) 61.4–73.3%) (Fig. 2). The prevalence of medication adherence among pre-dialysis CKD patients was similar between prospective and retrospective studies [(68.8%; 95% CI 61.1–76.6%) vs (65.8%; 95% CI 57.0–74.6%)] (Fig. 2). Comparing studies which examined medication adherence for anti-hypertensives only with other classes of medication, there were no significant differences in the prevalence of medication non-adherence [(64.3%; 95% CI 48.4–80.3%) vs (68.9%; 63.9–74.0%)] (Fig. 3). Likewise, the prevalence of medication adherence was comparable between studies conducted in North America and other continents [(64.3%; 95% CI 56.4–72.2%) vs (71.5%; 95% CI 63.9–79.1%)] (Fig. 4).

Details pertaining to the risk of bias assessment in the studies were reported in supplementary file 3. The risk of bias was low in 16 (88.9%) studies and moderate in 2 (11.1%) studies.

Overall, we identified 19 factors with 95 sub-factors which were subsequently classified using WHO's five dimensions of adherence. Studies that supported or disputed individual sub-factor were presented in Tables 1, 2, 3, 4 and 5. A sunburst chart was used to show the frequency of sub-factors evaluated in the included studies (Fig. 5). The most commonly studied domain was condition-related domain (32%), followed by patient-related domain (28%) and therapy-related domain (20%). Details pertaining to the characteristics of included studies were reported in Supplementary Table 1.

Condition-related factors

Table 1 shows condition-related factors which affected medication adherence. A total of 3 factors with 32 sub-factors were noted, which were "CKD related," "comorbidities related," and "laboratory parameters" (Table 1). More severe CKD was linked with poorer medication adherence [8, 15–18]. Comorbidity factors which were associated with low medication adherence included having metabolic diseases such as hypertension [8, 19, 20], and psychiatric conditions such as depression [8, 19, 21]. Cardiovascular diseases e.g. coronary heart disease [16, 21, 22] and hyperlipidemia [15, 22] was associated with better medication adherence. Finally, under laboratory parameters, hypoalbuminemia was associated with poorer medical adherence [8, 15, 21].

Patient-related factors

Table 2 lists patient-related factors which affected medication adherence. Four main factors with 20 sub-factors were

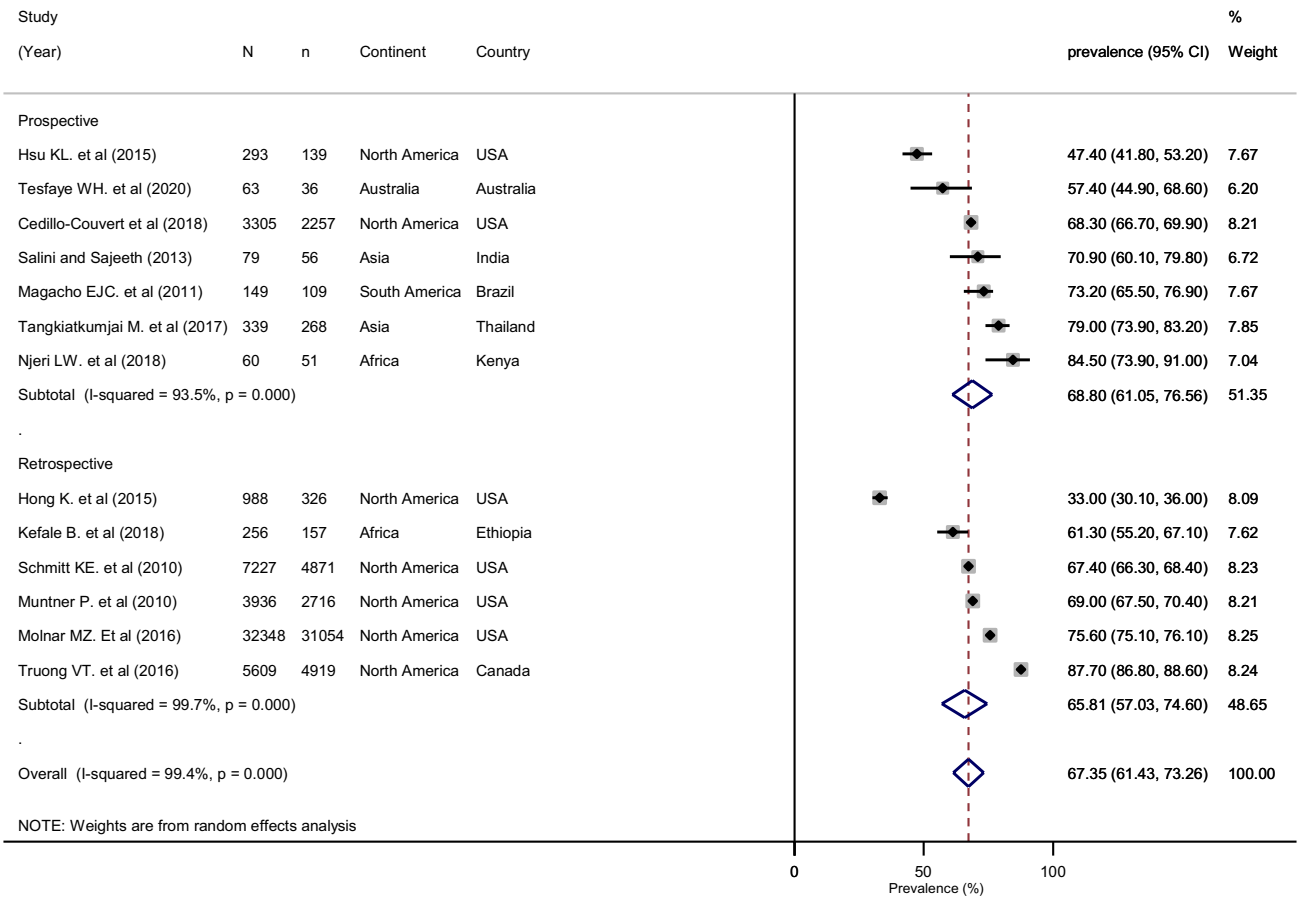

Fig. 2 Forest plot for meta-analyses of medication adherence rates stratified by study design. *N* number of patients in the study, *n* number of patients who were adherent in the study

noted, which included "patient demographics," "physical and mental function," "disease and treatment perceptions," and "others" (Table 2). Demographical factors linked with poorer medication adherence included higher body mass index [8, 19, 23], male gender [8, 22, 23] and ethnicity/race [8, 19, 21]. Conversely, higher age was associated with better medication adherence [8, 10, 19–22]. Among factors related to physical and mental functions, forgetfulness was the most common sub-factor associated with poor medication adherence [10, 17, 19, 24, 25]. For "disease and treatment perceptions" related factors, misconceptions about medication use [10, 17, 19, 25], lack of perceived self-efficacy in medication use or disease management [18, 24–26] and poor attitude towards treatment [17, 25, 27] were associated with poorer medication compliance.

Therapy-related factors

Table 3 lists therapy-related factors which affected medication adherence. Five therapy-related factors with 18 sub-factors were identified, including "medication dosing regimen," "medication side effects," "type of medication," "medication administration," and "others." For dosing regimen factors, high pill burden [16, 24, 28] and taking more types of medication [8, 15, 17] were the most common subfactors that reduced medication adherence. Similarly, developing medication-related side effects [10, 24, 25, 27] and fear of medication adverse effects [17, 25] were associated with poorer medication adherence. Among classes of medication, the use of anti-hypertensives [15, 21, 22] was associated with better medication adherence. Self-administration of medication [16, 28] and use of medication aids or devices [17, 25] were associated with better medication adherence. Higher medication cost was associated with poorer medication adherence [24, 25].

Health-based system factors

Table 4 lists health system-based factors which affected medication adherence. 3 health system-based factors with 12 sub-factors were noted, which were "healthcare provider factors", "communication and support from healthcare

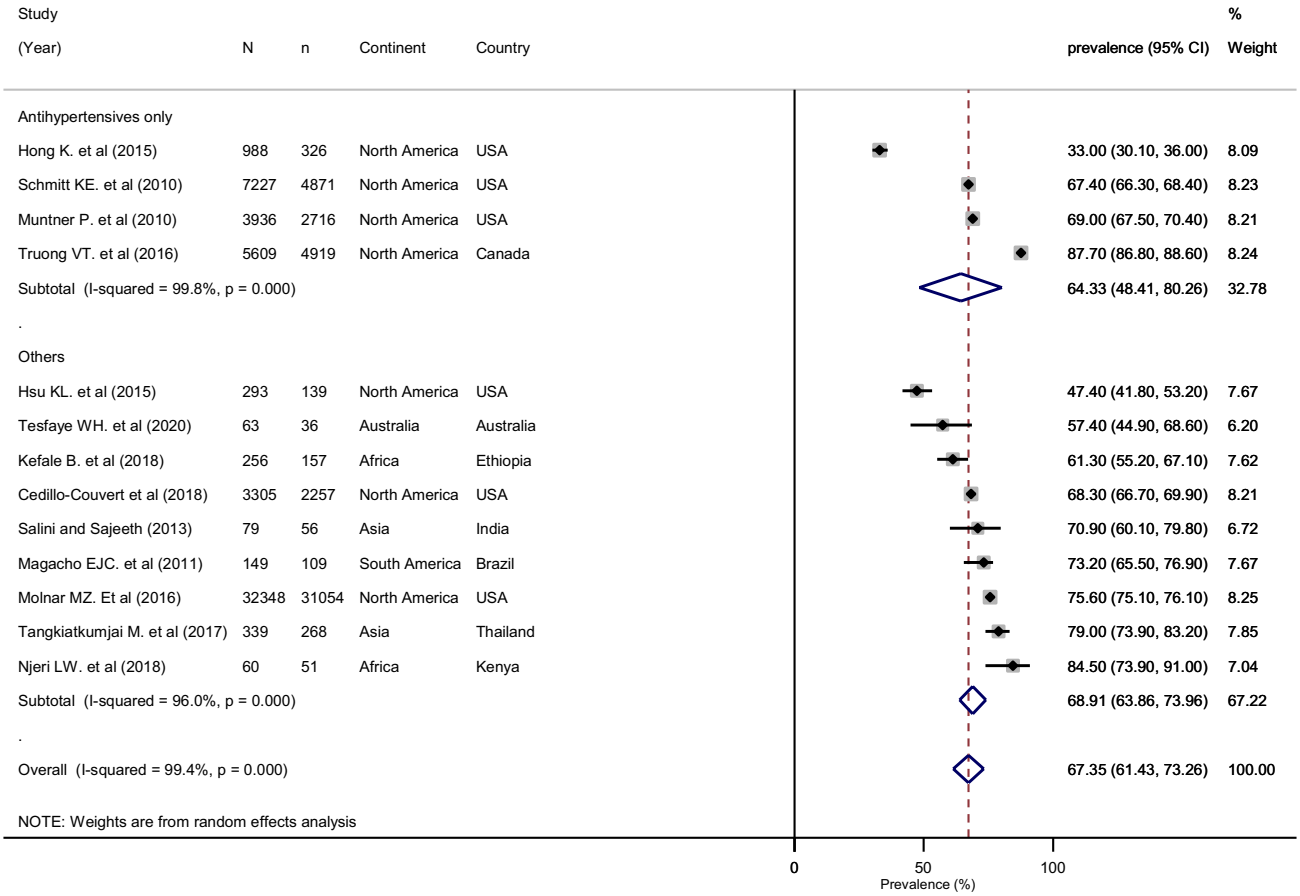

Fig. 3 Forest plot for meta-analyses of medication adherence rates stratified by medication class. *N* number of patients in the study, *n* number of patients who were adherent in the study. "Others" included studies which examined multiple drugs or if the classes of medication examined were not specified in the methodology

providers" and "healthcare facilities factors". Healthcare provider factors that were linked with poorer medication adherence consisted of loss of trust and/or confidence in physician [17, 24, 25]. Among "communication and support from healthcare providers" factors, the lack of patient education [25] and support from healthcare professionals [26] were linked with low medication adherence, while patient empowerment [26] was associated with better medication compliance. Finally, poor accessibility to healthcare facilities was associated with lower medication adherence [25].

Social-economic factors

Table 5 lists social-economic factors which affected medication adherence. Four socio-economic factors with 13 sub-factors were noted, namely "social," "economic", "lifestyle" and "media-related" factors. Under social factors, poor family or social support [17, 26] and lower education [8, 19] were associated with poorer medication adherence. Economic factors such as lower-income level were associated with poorer medication adherence [19, 24]. For lifestyle factors, alcohol consumption was associated with poorer medication adherence [19, 25, 29]. Finally, media reports of adverse events and perceived disagreements between physicians [27] were associated with poorer medication adherence.

Kidney model for medication adherence among pre-dialysis CKD patients

Due to the complexity of factors affecting medication adherence among pre-dialysis CKD patients, we propose the use of a kidney model of medication adherence to aid physicians in retaining these factors and implementing it in their practice (supplementary file 4). Each segment in the model represents one of the five WHO domains of medication adherence.

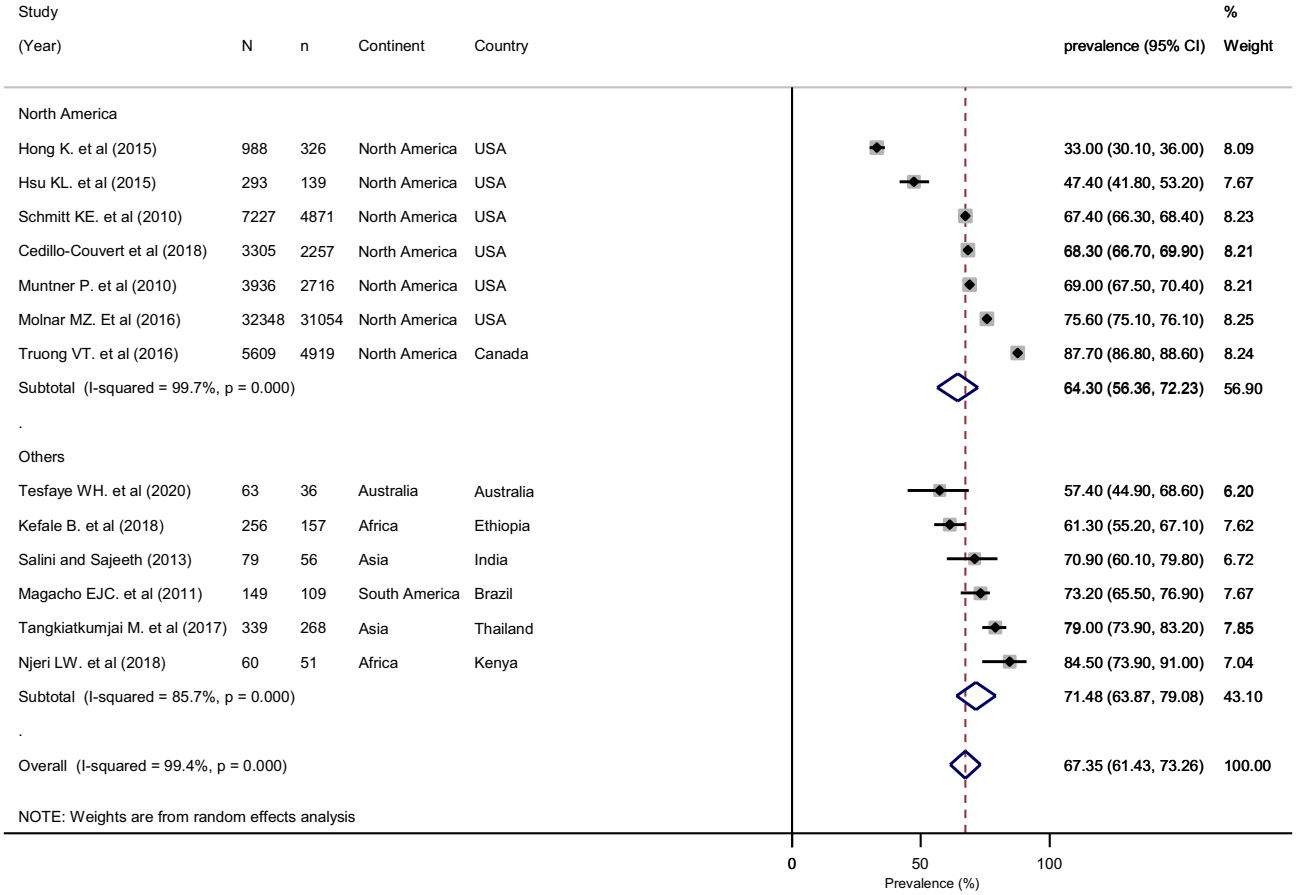

Fig. 4 Forest plot for meta-analyses of medication adherence rates stratified by continents. *N* number of patients in the study, *n* number of patients who were adherent in the study

Discussions

Overall, this review has summarised factors that influence medication adherence in pre-dialysis CKD patients. The pooled medication adherence rate across studies was 68%. This was comparable to that in hemodialysis patients, where a review by Ghmire et al. found that the medication non-adherence rates ranged from 12.5 to 98.6% [30]. A potential explanation for this variability could be due to disparities in the characteristics of patient populations, class of medication studied and the tools used for assessing adherence. Research has consistently demonstrated that cross-cultural differences exist and shape an individual's belief about effective disease and medication self-management [31]. A common example would be the use of complementary and alternative medication where its usage ranges from 10 to 40% in the United States and Australia to more than 50% in countries such as Germany and South Korea [32]. Of note, the majority of included studies were conducted in North America in this review. While no significant differences were found with regards to medication rates observed in studies conducted within and outside of North America, our findings may be limited by the scarcity of studies conducted among continents especially Europe, Africa and South America. Hence, more studies are required to characterise and understand the cross-cultural factors that affect medication adherence among pre-dialysis CKD patients in countries outside North America.

In addition, chronic kidney disease often entails complications such as anaemia, and mineral and bone disorders (CKD-MBD) which require treatment with iron supplements, phosphate binders and vitamin D analogues [33]. While the adherence rates to medication therapies for CKD-related complications such as phosphate binders are generally well-studied in hemodialysis patients [7, 34], our review showed that this is less well-studied among pre-dialysis CKD patients. Given the association of CKD-MBD with complications such as poorer cardiovascular outcomes and increased risk of bone fractures [35] and that therapies such as phosphate binders constitute the majority of the pill burden for CKD patients [36], future studies should consider

Table 1 Condition-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Types of studies	No. of studies that disagree	Type of studies
Chronic kidney disease related				
More advanced stages of chronic kidney disease	5	C [16], CS [18], O [8, 15], MSM [17]	2	C [20], CS [19]
Presence of vascular access (e.g. arteriovenous fistula)			1	O [21]
Comorbidities related				
Hypertension	3	C [20], CS [19], O [8]		
Psychiatric conditions (depression)	3	CS [19], O [8, 21]		
Diabetes	2	O [8], CS [61]	2	C [23], O [21]
Hepatic disease	2	O [15, 21]		
Higher number of comorbidities	2	C [20, 29]	1	C [23]
Symptomatic from comorbidities	1	Q [26]	1	DEQ [25]
Higher number of hospitalisation episodes related to comorbidities	1	O [15]		
Cardiovascular diseases (e.g. coronary heart disease, myocardial infarction)	1	CS [61]	3	C [16, 22], O [21]
Neurological diseases (e.g. Dementia)	1	O [21]	1	C [22]
AIDS/HIV	1	O [21]		
Chronic pulmonary diseases	1	O [21]		
Peptic ulcer disease	1	O [21]		
Hyperlipidemia			2	C [22], O [15]
Cerebrovascular diseases			1	O [21]
Connective tissue diseases			1	O [21]
Malignancies			1	O [21]
Number of physician visits			1	C [22]
Laboratory parameters				
Hypoalbuminemia	3	O [8, 15, 21]	1	CS [19]
Lower haemoglobin level	3	O [8, 15, 21]		
Higher total cholesterol	2	O [15, 21]		
Higher serum calcium			2	O [8, 21]
Lower phosphate level			2	O [8, 21]
Higher alkaline phosphatase	1	O [21]		
Higher blood urea nitrogen	1	O [15]		
Higher Hba1c	1	O [21]		
Higher parathyroid hormone level	1	O [21]		
Higher urine albumin to creatinine ratio	1	O [21]		
Lower bicarbonate level	1	O [21]		
Lower white blood cells level	1	O [21]		
More severe proteinuria	1	O [8]		

C cohort study, *CS* cross-sectional study, *O* observational study, *Q* qualitative study, *MSM* mixed study method, *DEQ* descriptive exploratory qualitative

evaluating the medication adherence rate of pre-dialysis CKD patients to these medication classes.

In this review, the tools used for assessment for medication adherence varied significantly across studies, ranging from medication adherences indices e.g. MPR derived from medication claim records to self-reported medication adherence questionnaires. While there is a multitude of tools available for the evaluation of medication adherence, there is no single measure that is regarded as the "gold standard" due to each instrument's inherent limitations [37]. For example, while utilising MPR or PDC from secondary databases permits for the assessment of multi-drug adherence, these indices do not take into account partial adherence, prescriptions that are missed out and incomplete records arising from discontinuation of medication that was conveyed verbally to patients [38]. Likewise, one of the key limitations of

Table 2 Patient-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Types of studies	No. of studies that disagree	Type of studies
Patient demographics				
Older age	2	C [16, 23]	6	C [10, 20, 22], CS [19], O [8, 21]
Male gender	3	C [22, 23], O [8]	2	CS [19], O [21]
Higher body mass index	3	C [23], CS [19], O [8]	2	O [15, 21]
Ethnicity/race (non-Hispanic black or Hispanic vs others, African-Americans vs others, African Americans vs White)	3	CS [19], O [8, 21]		
Marital status (single vs married)	2	O [8, 21]	1	CS [19]
Physical and mental function				
Increased forgetfulness	5	C [10], CS [19, 24], MSM [17], DEQ [25]		
Fatigue	1	MSM [17]		
Poor vision	1	DEQ [25]		
Poor physical function	1	CS [18]		
Disease and treatment perceptions				
Misconceptions about medication use	4	C [10], CS [19], MSM [17], DEQ [25]		
Lack of perceived self-efficacy in medication use or disease management	4	CS [18, 24], Q [26], DEQ [25]		
Poor attitude towards treatment	3	Q [27], MSM [17], DEQ [25]		
Misconceptions about chronic kidney disease	3	C [10], Q [26], DEQ [25]		
Inappropriate prioritisation of medication importance by patients	2	MSM [17], DEQ [25]		
Lack of knowledge of CKD and its management	1	Q [27]		
Self-responsibility towards their health			1	MSM [17]
Greater patient interest in shared decision making	1	C [23]		
Non-compliance with physician follow-up visits	1	CS [61]		
Others				
Difficulty in maintaining and safekeeping medication prescription	1	DEQ [25]		
Poor physical health-related quality of life	1	C [23]		

C cohort study, *CS* cross-sectional study, *O* observational study, *Q* qualitative study, *MSM* mixed study method, *DEQ* descriptive exploratory qualitative

using self-reported questionnaires and scales e.g. MMAS-8 for medication adherence assessment is that they suffer from biases related to social desirability and patient recall [38]. Given the complexity of comorbidities and medication therapies that CKD patients face, accurate assessment of patients' medication adherence is important and future studies should explore designing a medication adherence assessment tool tailored for CKD patients which can effectively evaluate their adherence to medication. In the meantime, ongoing studies which are evaluating medication adherence among pre-dialysis CKD patients may wish to consider adopting a multi-measure approach, which encompasses using two or more medication adherence measures that complement each other's strength and weaknesses [38]. This approach has been shown to have high predictive power for medication adherence. For example, a study by Liu et al. which evaluated showed that a composite adherence score derived from electronic medication packaging (EMP) devices, pill counts and clinician interview had the strongest predictive relationship with anti-retroviral medication adherence when compared to the separate usage of individual measures [39].

Among condition-related factors, more severe CKD was unsurprisingly associated with poorer medication adherence. Progressive CKD disease often portends complications such as anaemia which require additional therapy such as erythropoiesis-stimulating agents and iron supplementation. The greater propensity of these patients to require higher pill burden and more complex medication regimens often contribute to poorer medication adherence among CKD patients [40]. As such, physicians should be cognizant and evaluate

Table 3 Therapy-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Types of studies	No. of studies that disagree	Type of studies
Medication dosing regimen				
High pill burden	5	C [16, 23], CS [24, 61], O [28]		
More types of medication	4	CS [29], O [8, 15], MSM [17]		
Frequent changes in medication regimen	3	DEQ [25], Q [27], MSM [17]		
Complex medication regimen	2	CS [24], MSM [17]		
High dosing frequency	2	C [10], MSM [17]		
Medication side effects				
Presence of medication side effects	4	C [10], CS [24], Q [27], DEQ [25]		
Fear of medication adverse effects	2	MSM [17], DEQ [25]		
Type of medication				
Use of anti-hypertensives			3	C [22], O [15, 21]
Use of antiplatelet agent	1	O [21]	1	O [8]
Use of statins			2	O [8, 21]
Use of phosphate binders	1	O [21]		
Use of vitamin D analogues			1	O [21]
Medication administration				
Drug administration (Caregiver/third party vs self-administration)	2	C [16], O [28]		
Use of medication assist devices or aids			2	MSM [17], DEQ [25]
Others				
Higher medication cost	2	CS [24], DEQ [25]		
Presence of multiple brand names for same medication	1	DEQ [25]		
Use of multiple packaging for medication	1	DEQ [25]		
Adverse size, taste and texture of some medicines	1	MSM [17]		

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for medication non-adherence especially in patients with more severe CKD. Psychiatric conditions such as depression were also associated with poorer medication adherence. Of note, a review by Palmer et al. estimated the prevalence of depression among Stage 1 to 5 non-dialysis CKD patients at 21.4% [41], which is significantly higher than both diabetic (11%) [42] and congestive cardiac failure patients (14%) [43]. Another study also showed that the prevalence of depression did not differ among patients with different stages of CKD [44]. As mental illnesses are often under-recognised among CKD patients [44], there is a need for greater vigilance in screening for such illnesses, especially among non-compliant, pre-dialysis patients to optimise their medication adherence.

Among patient-related factors, older age was interestingly not associated with poorer medication adherence, when compared to studies in dialysis patients [45]. Elderly patients with chronic diseases have been shown to have poor health literacy and limited comprehension of the repercussions of medication non-adherence, which perpetuates their non-adherence to medication [46, 47]. Our findings were, however, similar to a review performed in peritoneal dialysis patients which showed that poor medication adherence was more prevalent among younger patients [48]. A postulated reason could be the impact of age being attenuated by patient's ability for self-care or having a caregiver [48]. Another suggested hypothesis is the greater fear of worsening their health among older individuals, especially as CKD progression often culminates in dialysis. This, in turn, makes them more motivated to adhere to their medications [49]. It was also noted that increased patient forgetfulness and medication prioritisation was associated with poorer medication adherence. The utilisation of memory aids and specialised dosette boxes may be helpful in improving adherence with complex dosing regimens and should be considered for patients with forgetfulness [50]. Pertaining to medication prioritisation, a study by Parker et al. conducted among both dialysis and non-dialysis patients found that it was closely tied to medication understanding [40]. Medication that was poorly understood or perceived to be less important in

Table 4 Health system-related factors and their association with poorer adherence/persistence/compliance to medication therapy

Factors	No. of supporting studies	Types of studies	No. of studies that disagree	Type of studies
Healthcare provider factors				
Loss of confidence in physician	3	CS [24], MSM [17], DEQ [25]		
Lack of patient-physician communication	2	Q [26], MSM [17]		
Higher frequency of scheduled clinic visits			2	C [20, 22]
Coordination of care across different settings (retaining copies of repeat prescription by pharmacists, refilling dosette boxes by pharmacists, provision of bridging medicine while waiting for current prescription)			2	Q [26], DEQ [25]
Inconsistent advice provided by physician	1	DEQ [25]		
Unclear treatment goals and regimen	1	Q [26]		
Prioritisation of health condition by physician			1	Q [26]
Specialty of physicians (General Practitioners vs. specialists)			1	DEQ [25]
Communication and support from healthcare providers				
Lack of patient education	1	DEQ [25]		
Lack of support from healthcare professionals	1	Q [26]		
Patient empowerment by healthcare providers			1	Q [26]
Healthcare facilities factors				
Poor accessibility to medication, medical facilities or pharmacies	1	DEQ [25]		

C cohort study, *CS* cross-sectional study, *O* observational study, *Q* qualitative study, *MSM* mixed study method, *DEQ* descriptive exploratory qualitative

Table 5 Social-economic factors and their association with poorer adherence/persistence/compliance with medication therapy

Factors	No. of supporting studies	Types of studies	No. of studies that disagree	Type of studies
Social factors				
Poor family/social support	2	Q [26], MSM [17]		
Lower education	2	CS [19], O [8]		
Low socioeconomic status	1	O [8]	1	C [22]
Live alone	1	DEQ [25]		
Work commitments that require frequent movement	1	DEQ [25]		
Location of residence (stroke buckle versus non-belt regions)			1	CS [19]
Economic factors				
Lower income level	2	CS [19, 24]		
Lack of/limited insurance coverage	2	C [20], O [8]		
Types of occupation (e.g. students, driver, teacher working in private school vs. farmers)			1	CS [24]
Lifestyle factors				
Alcohol consumption	3	CS [19, 29], DEQ [25]		
Current smoker	2	C [20], CS [19]		
Previous smoking history			1	C [20]
Media-related				
Media reports of adverse events and perceived disagreements between physicians	1	Q [27]		

C cohort study, *CS* cross-sectional study, *O* observational study, *Q* qualitative study, *MSM* mixed study method, *DEQ* descriptive exploratory qualitative

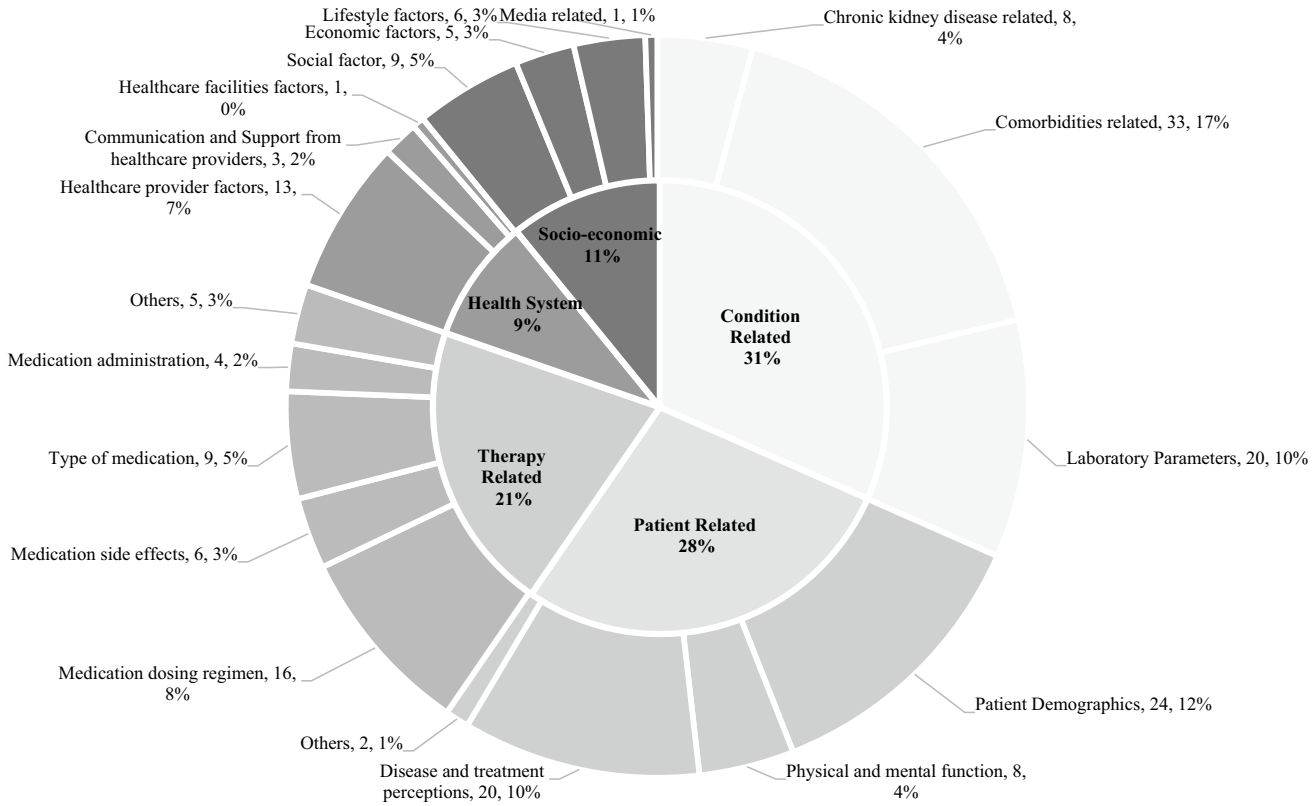

Fig. 5 Sunburst chart showing the frequencies of sub-factors affecting medication adherence investigated in studies

providing symptomatic relief tended to receive lower priority and consequently, poorer medication adherence [40]. Healthcare professionals such as doctors and pharmacists should endeavour to clarify any of such misconceptions if detected during the consultation.

For therapy-related factors, high pill burden was associated with poorer medication adherence. A study by Wee et al. that high pill burden was independently associated with impaired health-related quality of life (HrQoL) among pre-dialysis patients after adjustment for CKD associated complications e.g. anaemia and mineral and bone disorder [3]. Likewise, high pill burden has been linked with poorer medication compliance as well as lower mental and physical HrQoL among hemodialysis patients [36]. With the increasing importance of HrQoL as an outcome measure of health and CKD patients being one of the patient groups with the highest pill burden (average of eight types of medication per day) [51], reducing pill burden via de-prescribing of non-essential medications and optimisation of medication dosing regimens may be a reasonable approach to improve patients' adherence to medication therapy. Of note, de-prescribing, which entails the step-wise process of selecting and discontinuing medication where existing risks outweigh the benefits of [52], has been shown to reduce risk of medication adverse effects and improve medication adherence [53].

Among health system-related factors, the lack of patient trust in physicians and poor patient-physician communication was associated with lower medication adherence. The quality of patient-physician relationship forms the central cornerstone of effective healthcare delivery, where it can facilitate or hinder medication adherence [54]. Specifically, patient-physician communication has been highlighted as a modifiable factor that has a positive impact on patient outcomes [54]. While shared decision making and being patient-centric has been shown to improve adherence among patients with chronic diseases [54], physicians should also be aware that patient preferences may change with time [55] and hence should actively solicit this information from patients. Overall, the provision of care to patients and the extent of patient involvement in shared decision making should be individualised according to each patient's needs.

Among socioeconomic factors, poor social support and low-income levels were associated with poorer medication adherence. Social support comprises of two major components, which are namely instrumental and emotional domains [56]. The instrumental domain reflects the ease of obtaining help from others pertaining to activities of daily

life and practical situations. On the other hand, the emotional component consists of behaviours from others e.g. keeping company, which aid in ensuring one's overall psychosocial well-being [56]. In patients with end-stage kidney disease, improving the social support of patients has been shown to improve their quality of life and health-related outcomes e.g. medication adherence and mortality [57]. With regards to low-income levels, a qualitative study performed by Ghimire et al. among end-stage renal failure disease patients showed that financial difficulties were the leading contributory factor that impeded patients' access to medication [30]. For example, medications e.g. over-the-counter vitamin D supplements that were not covered by health insurance/governmental subsidy schemes were regarded by patients to be "relatively more unaffordable", which led to increased non-compliance. As such, for patients with limited financial capacities and poor social support, physicians should consider referring them to medical social services or other relevant government agencies for assistance. We also found that media reports of medication-related adverse events and perceived disagreements between physicians were also associated with poorer medication adherence. With the internet becoming an increasingly important conduit for health education [58] and rising internet health consumption among patients [59], more is needed to understand the impact of media and internet on healthcare and medication adherence patterns. Of note, Baker et al. found that approximately 15% of chronic disease patients altered their health treatment regimen without professional advice after searching for information from the internet. Another study by Weaver et al. noted that self-discontinuation of medication therapy occurred in ~ 11.2% of patients with greater internet health-seeking behaviours [60]. Physicians should be vigilant and address any misconceptions or inaccuracies during consultations with patients, especially among those with suspected non-adherence.

This review is not without its limitations. Although a total of 92 sub-factors associated with medication adherence were found, the aggregate magnitude of individual factors on medication adherence in pre-dialysis CKD patients was not evaluated due to the heterogeneity of the studies. This may be assessed in a future meta-analysis when data from more studies are available. In addition, while we utilised a relatively comprehensive search strategy, there remained the possibility of omitting potentially relevant articles. To mitigate this, we did not restrict the search period for this review and conducted finger-searching of references among included articles. Lastly, a significant proportion of the included studies only evaluated patients' compliance to a single class of medication i.e. anti-hypertensives. Consequently, this may lead to over-estimation of the overall adherence rate of pre-dialysis CKD patients to their medications, especially as polypharmacy is highly prevalent among these patients due to their multiple comorbidities. While our meta-analyses did not show significant differences in medication adherence rates between studies that examined usage of anti-hypertensives only and multiple drug classes, more studies are required to evaluate if there are medication class-specific differences in non-compliance rates among pre-dialysis CKD patients and their overall medication adherence rates.

Conclusion

Overall, this systematic review has identified factors which were associated with poorer medication adherence among pre-dialysis CKD patients. Given the important role that medication adherence plays in slowing the progression of CKD, it is imperative that physicians and healthcare providers be aware of the complexity of factors that impair patients' adherence to medication. Additionally, the findings from this review will guide researchers, clinicians and policymakers in channelling future research resources to evaluate less well-studied medication adherence factors and also design interventions to optimise health outcomes for patients with chronic kidney disease.

Authors' contributions JJBS was the principal investigator of the study while JYT, CTY, HH, WYM Foo were the co-investigators. JJBS, JYT and CTY were involved in literature review for the inclusion of articles. All authors were involved in the analysis of data. The first draft of the manuscript was prepared by JJBS and JYT. All authors revised the draft critically for important intellectual content and agreed to the final submission.

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