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Review

Pharmacist-led intervention in pre-dialysis chronic kidney disease: A systematic review and meta-analysis

[Intervención dirigida por farmacéuticos en la enfermedad renal crónica predialítica: una revisión sistemática y un metaanálisis]

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Abstract

Context: Chronic kidney disease (CKD) imposes a significant global healthcare burden. Pharmacist-led interventions have been proposed to improve pre-dialysis CKD management, yet comprehensive quantitative evidence remains limited.

Aims: To evaluate the effects of pharmacist-led interventions on clinical outcomes, medication adherence, patient knowledge, and drug-related problems (DRPs) in adults with pre-dialysis CKD.

Methods: A systematic search of PubMed, Scopus, Web of Science, and Crossref (2010–2024) was conducted in accordance with preferred reporting items for systematic reviews and a meta-analysis (PRISMA) guideline. Eligible randomized controlled trials (RCTs) and quasi-experimental studies were included. Meta-analysis was performed using RevMan 5.4.1.

Results: Twelve studies (4,945 patients) were included. Pharmacist-led interventions significantly reduced DRPs (mean difference: -0.23; 95% CI: -0.37 to -0.08; p=0.002) and improved patient knowledge (mean difference: 0.80; 95% CI: 0.64–0.95; p<0.001). No significant changes were observed in estimated glomerular filtration rate, blood pressure, or medication adherence.

Conclusions: Pharmacist-led interventions reduced drug-related problems and improved patient knowledge in pre-dialysis CKD. However, no significant changes were observed in eGFR, blood pressure, or medication adherence. Clinically, pharmacists help prevent adverse events and enhance adherence, supporting long-term care quality. Future studies should examine whether combined interventions, including lifestyle and dietary support, can translate these benefits into measurable clinical outcomes.

Keywords: chronic kidney disease; drug-related problems; medication adherence; patient knowledge; pharmacist intervention; systematic review.

Resumen

Contexto: La enfermedad renal crónica (ERC) supone una importante carga para los sistemas de salud a nivel mundial. Se han propuesto intervenciones dirigidas por farmacéuticos para mejorar el manejo de la ERC en la etapa predialítica; sin embargo, la evidencia cuantitativa exhaustiva sigue siendo limitada.

Objetivos: Evaluar los efectos de las intervenciones dirigidas por farmacéuticos sobre los resultados clínicos, la adherencia al tratamiento, el conocimiento del paciente y los problemas relacionados con los medicamentos (PRM) en adultos con ERC en etapa predialítica.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science y Crossref (2010-2024) siguiendo la guía PRISMA (Preferred Reporting Items for Systematic Reviews and a Meta-Analyses). Se incluyeron ensayos controlados aleatorizados (ECA) y estudios cuasiexperimentales elegibles. El metaanálisis se realizó con RevMan 5.4.1.

Resultados: Se incluyeron doce estudios (4945 pacientes). Las intervenciones dirigidas por farmacéuticos redujeron significativamente los problemas relacionados con la medicación (diferencia media: -0,23; IC del 95%: -0,37 a -0,08; p=0,002) y mejoraron el conocimiento del paciente (diferencia media: 0,80; IC del 95%: 0,64–0,95; p<0,001). No se observaron cambios significativos en la tasa de filtración glomerular estimada, la presión arterial ni la adherencia al tratamiento.

Conclusiones: Las intervenciones dirigidas por farmacéuticos redujeron los problemas relacionados con la medicación y mejoraron el conocimiento del paciente en la enfermedad renal crónica en prediálisis. Sin embargo, no se observaron cambios significativos en la TFG, la presión arterial ni la adherencia al tratamiento. Clínicamente, los farmacéuticos ayudan a prevenir eventos adversos y a mejorar la adherencia, lo que contribuye a la calidad de la atención a largo plazo. Futuros estudios deberían examinar si las intervenciones combinadas, que incluyan apoyo en el estilo de vida y la dieta, pueden traducir estos beneficios en resultados clínicos medibles.

Palabras Clave: enfermedad renal crónica; problemas relacionados con la medicación; adherencia al tratamiento; conocimiento del paciente; intervención farmacéutica; revisión sistemática.

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Abbreviations: CKD: Chronic Kidney Disease; DRPs: Drug Related Problems; PRISMA: Preferred Reporting Items for Systematic Reviews and a Meta-Analysis; CV: cardiovascular diseases; RAAS: Renin-Angiotensin-Aldosterone System; KDIGO: Kidney Disease Improving Global Outcome; ESRD: End-Stage Renal Disease; eGFR: Estimated Glomerular Filtration Rate; PROSPERO: Prospective Register of Systematic Reviews; RCT: Randomized Controlled Trial; MeSH: Medical Subject Headings; BUN: Blood Urea Nitrogen; BP: Blood Pressure; QoL: Quality of Life.

INTRODUCTION

Chronic kidney disease (CKD) affects approximately 10% of the global population and is a leading cause of mortality worldwide. Progression from early-stage CKD to end-stage renal disease (ESRD) increases the risk of cardiovascular complications, hospitalizations, and reduced quality of life (Kefale et al., 2019). Lifestyle modification, blood pressure control, antihypertensive medication, and lipid management are advised to reduce the risk of renal failure, since CKD is associated with several comorbidities, including obesity, diabetes, and hypertension (Kidney Disease Improving Global Outcome, 2024). These interventions are particularly significant given that, despite being asymptomatic, most patients with mild-to-moderate CKD face an increased risk of cardiovascular disease, anemia, metabolic bone disease, or progression to ESRD requiring hemodialysis (Francis et al., 2024; Kovesdy, 2022).

CKD and ESRD are linked to heightened mortality risk, elevated hospitalization rates, and reduced life expectancy. The advancement from early to late stages of CKD often leads to the emergence of more symptoms and associated consequences (Erfanpoor et al., 2021). Early intervention in the pre-dialysis stages (CKD stages 1–4) is crucial to slow disease progression and manage comorbidities. In this environment, comprehensive and multidisciplinary strategies for CKD care are widely acknowledged as vital (Mallamaci & Tripepi, 2024; Ruiz-Ortega et al., 2020).

Pharmacists, as integral members of multidisciplinary teams, play a critical role in medication optimization, patient education, and prevention of drug-related problems (DRPs) (Jha et al., 2013; Seng et al., 2020). In pre-dialysis CKD, characterized by polypharmacy and complex medication regimens, pharmacist-led interventions can substantially improve clinical outcomes, including blood pressure regulation, glycemic control, anemia management, reduced drug-related complications, and slowing of estimated glomerular filtration rate (eGFR) decline (Qaseem et al., 2013). However, the extent to which pharmacist-led interventions influence clinical outcomes in pre-dialysis CKD remains unclear.

Numerous independent studies have shown favorable outcomes associated with pharmacist participation in CKD management, including enhanced medication adherence, greater attainment of therapeutic objectives, and lower hospitalization rates (Khokhar et al., 2020). The diversity in intervention methods, patient demographics, and outcome metrics among these studies complicates the capacity to formulate broad generalizations. A comprehensive review of current evidence is needed to assess the overall effectiveness and identify key components of pharmacist-led interventions in pre-dialysis CKD.

To the best of current knowledge, there is a lack of pooled quantitative data comparing the effects of such interventions by pharmacists, especially among patients with pre-dialysis CKD. This review is a quantitative, up-to-date analysis of data from randomized controlled trials and quasi-experimental studies evaluating a variety of interventions for pre-dialysis CKD patients. This review aims to evaluate the effect of pharmacist-led interventions on clinical outcomes in patients with pre-dialysis CKD. This review aimed to synthesize data from various studies to provide evidence-based insights into the significance of pharmacist participation in early chronic kidney disease management, thereby guiding future healthcare policies, clinical practices, and research priorities to optimize care for this at-risk population. The measured outcomes focus on improvements in kidney function parameters, drug-related problems, patients' knowledge, adherence to therapy, and patients' quality of life. Numerous prior studies have examined the impact of pharmacist intervention on CKD using diverse research methodologies, there has yet to be a review focused on pre-dialysis CKD patients (Ardavani et al., 2023; Jasińska-Stroschein, 2022; Stemer & Lemmens-Gruber, 2011). This review employs a comprehensive search strategy encompassing a wide range of outcomes to deliver an in-depth assessment of pharmacist interventions in pre-dialysis CKD.

MATERIAL AND METHODS

Review methodology

The systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021) and a literature search across various databases from 2010 to 2024. Registration on the International Prospective Register of Systematic Reviews (PROSPERO) was carried out to prevent the risk of study duplication (CRD420251058067). The literature search, study selection, quality assessment, and data extraction procedure were conducted by two reviewers (BLN and MKAJ). The articles were evaluated and discussed

with other reviewers (BS and AT) in order to resolve any disagreements. The final decision was made by consensus of all reviewers.

Information sources and literature search strategy

The following databases were searched for relevant literature: PubMed (MEDLINE), Crossref, Scopus, and Web of Science through the Publish or Perish (PoP) from https://harzing.com/resources/publish-or-perish. The search process used Medical Subject Headings (MeSH) for keywords: "pharmacist intervention" or "pharmacy service" or "clinical pharmacist service", "chronic kidney disease" or "pre-dialysis" or "non-dialysis" and "knowledge" and "kidney function" and "medication adherence" and "drug related problems" and "quality of life". The Boolean operators "OR" and "AND" were used in the search. In addition to searching databases, we used online tools such as Google Scholar and analyzed the citations of the chosen research and review papers in both directions. The full search strategy is presented in Supplementary Table S1.

Eligibility criteria

The screening process began with assessing the titles and abstracts of the publications. For studies with full-text access, screening continued by reviewing the entire article. Eligibility criteria were established based on the PICOs framework, which included: 1) Population: adults with pre-dialysis CKD (stages 1–4); 2) Intervention: pharmacist-led interventions; 3) Comparison: standard care, usual care, or no pharmacist involvement; 4) Outcomes: kidney function parameters, drug-related problems, patient knowledge, therapy adherence, and quality of life; 5) Study design: randomized controlled trials, prospective analytical studies, pre-post intervention studies, and quasi-experimental studies. Studies were excluded if they: 1) involved dialysis or transplant patients; 2) included children or adolescents under 18 years old or animals; 3) were published in languages other than English.

Study selection and data collection process

Two reviewers independently conducted the study selection process. Any disagreements were addressed until the third independent reviewer agreed on a course of action. Study selection and data collection procedures are summarized in the PRISMA diagram, and articles were extracted from databases using the Rayyan electronic instrument from http://rayyan.qcri.org to assist the author in the identification and selection process (Ouzzani et al., 2016). A detailed description of the procedures used to assess whether each study met the review's inclusion criteria was provided. This included specifying the number of reviewers who evaluated each record and full-text article, noting whether they conducted the assessment independently, and, if applicable, outlining any automation tools utilized during the process. The care model assessed in the studies had to be capable of delivering an intervention specifically designed for disease management. Each eligible study was required to include at least one control group receiving usual care and one intervention group receiving services from a clinical pharmacist, either independently or in collaboration with other healthcare professionals. Information on baseline characteristics and study outcomes was also considered. Studies failing to meet the criteria for population, intervention, control, or outcomes were excluded.

Data extraction

The collected data comprised the first author's name, year of publication, study location, design, population, sample size, intervention, comparator, delivery format, and assessed outcomes. This information was subsequently organized into a data extraction table (Table 1).

Data items (outcomes)

The data to be extracted included sociodemographic information and clinical parameters; detailed descriptions of the intervention and control groups, including sample sizes, intervention types, and durations; primary and secondary outcomes; and the authors' key conclusions. In addition, information was collected on the resources available to pharmacists for providing care and the specific procedures they employ.

Data were extracted on kidney function (e.g., creatinine, eGFR, blood urea nitrogen/BUN, BP, phosphorus, urine albumin/creatinine ratio, proteinuria, and glycated hemoglobin), humanistic outcomes (e.g., knowledge, medication adherence, and QoL), and drug-related problems/DRPs. If at least two articles discuss an outcome, it advanced to the meta-analysis stage.

Study of risk of bias assessment

The revised Cochrane Collaboration's 'Risk of Bias' instrument (RoB 2) was used to assess risk of bias in a randomized study (Sterne et al., 2019). A quasi-experimental study, with the risk of bias assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies (QES) (Munn et al., 2019).

Table 1. Characteristics of included studies.

No	Author, year/ location	Design	Sample size	Intervention	Delivery format	Measured outcomes	Main finding
1	Ghimirey et al. (2013). Lalitpur, Nepal	The prospective, pre–post study	Intervention: 32. Control: 32	Patients counseling	Leaflet	The actual KAP (knowledge, attitude, and practice) regarding CKD	After the intervention, there was a significant improvement in KAP scores; these values were modified to 13.75 ± 3.510, 38.78 ± 3.035, and 6.91 ± 0.777, respectively ($p<0.05$).
2	Cabello-Muriel et al. (2014). Murcia, Spain	A prospective, open, quasi-experimental	Intervention: 125. Control: 124.	Patients counseling	Face-to-face	The renal function (CrCl)	Significant differences were observed in CrCl between discharge and admission in the intervention groups (5.1 ± 0.9 vs. 6.4 ± 1.0, $p<0.01$).
3	Cooney et al. (2015). USA	Randomized control trial	Intervention: 1070. Usual care: 1129.	A phone−based pharmacist intervention.	By phone and face-to-face	Systolic BP, Parathyroid hormone (PTH), phosphorus, urine albumin/creatinine ratio, medication adherence, and quality of life.	Participants in the intervention group were significantly more likely to have a PTH measurement during the study period (46.9% vs. 16.1% in the control group; $p<0.001$).
4	Chang et al. (2016). USA	A pragmatic, cluster-randomized trial	Intervention: 24. Control: 23.	Pharmacist-led Medication Therapy	Face-to-face and phone	Proteinuria and blood pressure	The pharmacist MTM intervention did not significantly enhance total proteinuria screening at the population level (OR 2.6, 95% CI: 0.5–14.0; $p = 0.3$).
5	Lalonde et al. (2017). Canada	Multicenter, cluster-randomized, controlled trial.	1.143	ProFiL pharmacists	Web-training program	eGFR, BP, glycated hemoglobin, drug-related problems, and knowledge.	Reduction of drug-related problems and improvements in knowledge, but no significant differences in clinical attributes were observed across the groups.
6	Chandrasekhar et al. (2018). Malabar region of South India	The prospective interventional study	163	Patient counseling and patient information leaflets	Counseling, leaflets, and a telephonic interview	Medication adherence	After intervention, there is a significant improvement in medication adherence ($p<0.001$).
7	Khokar et al. (2020). Pakistan	This multi-arm pre-post prospective study	Intervention: 60. Control: 60.	The pharmacist's intervention	Counseling and Telephonic interview	eGFR, SCr, BUN, uric acid, knowledge, and medication adherence	The intervention significantly enhances knowledge scores (19.10 ± 3.65 vs. 17.57 ± 3.55, $p = 0.022$). The medication adherence score in the intervention group improved significantly compared with the control group ($p<0.05$). The other outcomes do not provide substantial enhancement impacts.

Table 1. Characteristics of included studies (continued...)

No	Author, year/ location	Design	Sample size	Intervention	Delivery format	Measured outcomes	Main finding
8	Song et al. (2021). South Korea	A prospective, randomized, parallel, controlled clinical trial	Intervention: 50. Control: 50.	Drug therapy evaluation and management (DrugTEAM)	Face-to-face	DRPs and medication adherence.	The incidence of DRPs is decreased was 0.94 ± 1.03 ($p<0.001$). The medication adherence score post-discharge was greater in the intervention group (5.2 ± 1.0); however, this difference was not statistically significant ($p = 0.205$).
9	Pehlivanli et al. (2023). Turkey	This was a prospective interventional study	Intervention: 269	Pharmacist interventions	Real-time face-to-face	Drug-related problems	The incidence of DRPs is decreased, respectively. ($p<0.05$).
10	Vu et al. (2023). Los Angeles	Pre- and post-intervention	Intervention: 20	Pharmacist-led intervention: "Positive Kidney Health"	Face-to-face	UACR and eGFR	Improved patients' kidney test results and ordered UACR screening, but not significantly.
11	Alam et al. (2024). Malaysia	A single-arm, pre- and post-intervention study design	Intervention: 370	Medication-related concerns	Face-to-face	Drug-related problems	The significant impact of clinical pharmacist intervention on drug-related problems (DRPs). The primary kind of drug-related problem (DRP) was drug interaction statistically significant change ($p = 0.032$). A prevalent DRP identified was that inadequate compliance substantially decreased ($p = 0.042$). Untreated indications after pharmacist intervention demonstrated a statistically significant difference ($p = 0.004$).
12	Wickramasinghe et al. (2024). Sri Lanka	A randomized controlled clinical trial	Intervention: 101. Control: 100.	Patients counseling	Booklet	Knowledge of CKD	Drug and disease knowledge at 12 months in the intervention group is better than in the control group ($p<0.05$).

Statistical analysis

The included studies were synthesized into a narrative, organized by intervention type, target population characteristics, and outcome measures. Review Manager (RevMan Version 5.4.1) software (The Cochrane Collaboration) was used to analyze data in cases where applicable (e.g., comparable outcomes across studies). Continuous data were reported as a mean difference (MD) for outcomes measured on the same scale, or as a standardized mean difference (SMD) when different measurement instruments were used, each accompanied by a 95% confidence interval. Heterogeneity across studies was assessed using the Q test and the I^2 statistic. A fixed-effect model was applied when heterogeneity was low ($I^2 < 50\%$), while a random-effects model was used if substantial heterogeneity was present ($I^2 \geq 50\%$). Additionally, the significance threshold was established at $p<0.05$. Variability was identified, and potential explanations, including clinical and/or methodological differences, were examined. If heterogeneity remained unexplained, a narrative synthesis was undertaken rather than a meta-analysis. Subgroup analysis was conducted to further investigate sources of heterogeneity.

Forest plots were generated to visually present the pooled effect sizes and their confidence intervals, while funnel plots were used to explore potential publication bias. Publication bias was also evaluated quantitatively using Egger's test; a $p<0.05$ indicated significant bias. Sensitivity analysis was performed by removing studies with potential bias and subsequently reanalyzing the data to determine the robustness of the findings. For missing or incomplete data, attempts were made to contact study authors; if data remained unavailable, analyses were conducted using the best available information without imputation.

RESULTS

Search results and characterization of included studies

The study search was conducted on four major databases, namely PubMed, Web of Science, Scopus, and Crossref, and screened 2,185 studies. After removing records prior to screening, 125 studies remained. Screening of titles and abstracts identified 74 papers relevant to the review question. We eliminated 62 of these articles based on the qualifying criteria. The PRISMA flow map (Fig. 1) shows that the final collection comprised 12 papers (Page et al., 2021).

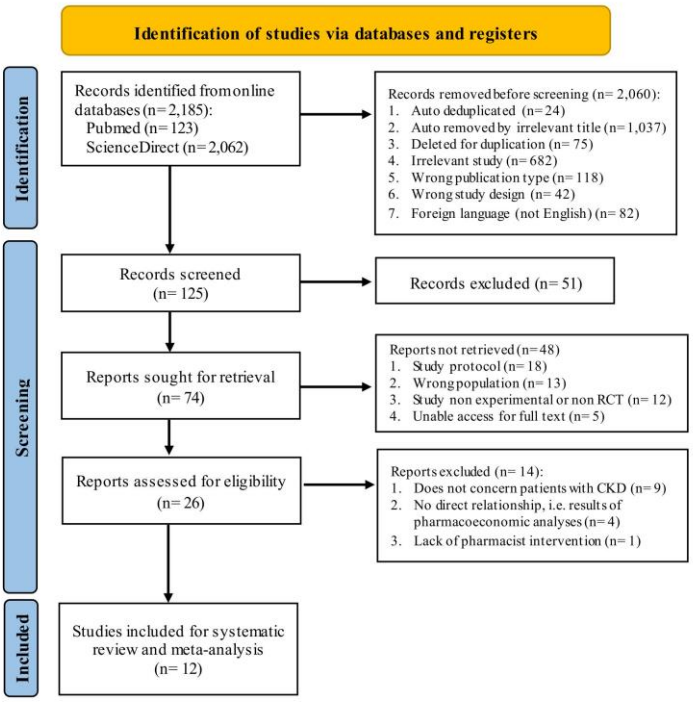

Figure 1. PRISMA 2020 flow diagram template for systematic reviews.

The grey boxes should be completed only if applicable; otherwise, they should be removed from the flow diagram. Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information.
https://journals.plos.org/plosmedicine/article/figure?id=10.1371/journal.pmed.1003583.g001

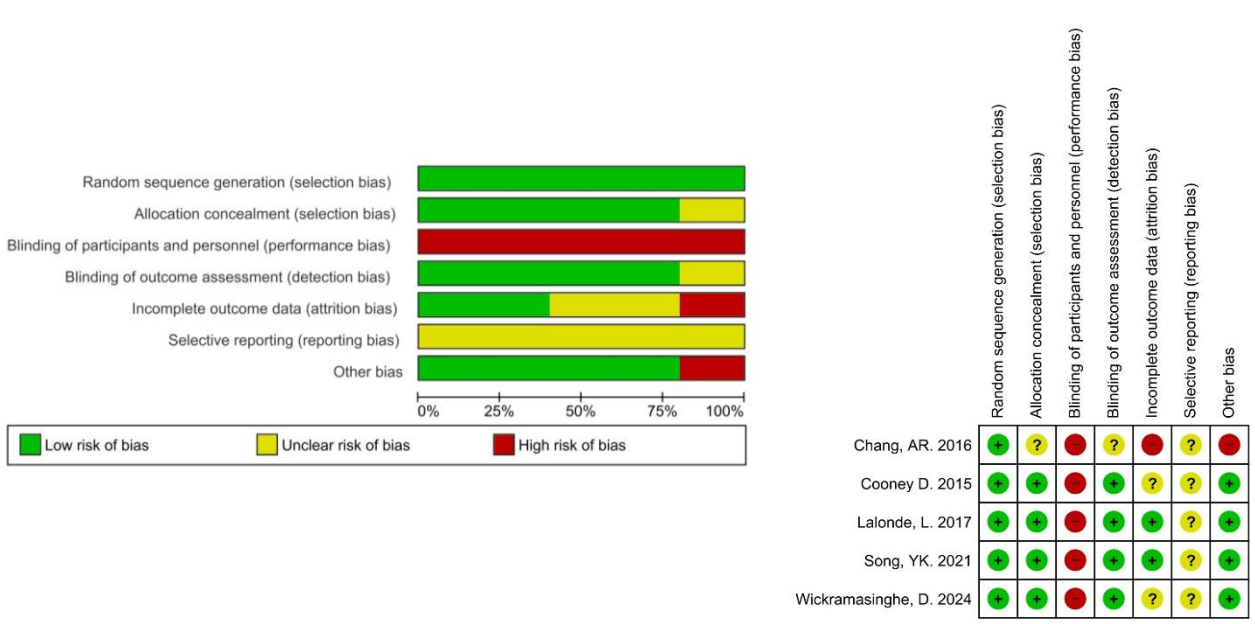

Figure 2. Risk of bias summary for the included randomized controlled trials, assessed using the Cochrane Risk of Bias (RoB 2) tool.

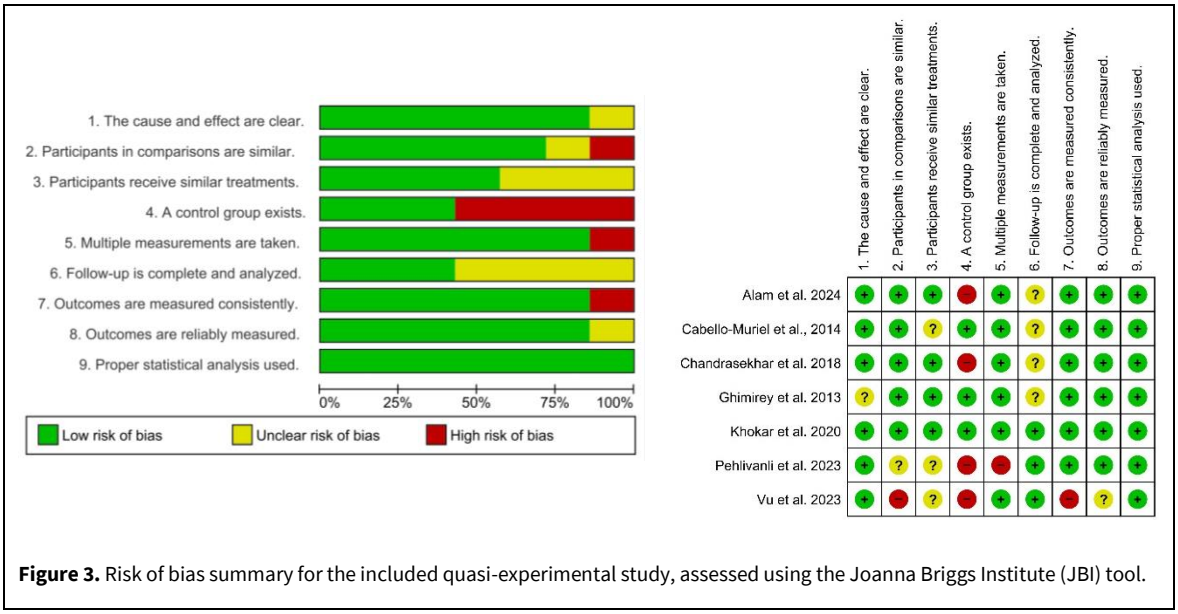

Figure 3. Risk of bias summary for the included quasi-experimental study, assessed using the Joanna Briggs Institute (JBI) tool.

Risk of bias in studies

A quality assessment of the included articles was performed. Assessment criteria were applied independently by four reviewers for randomized control trials (RCTs) and quasi-experimental studies. The criteria for ranking risk of bias were defined as follows: ≤49% indicates high risk, 50% to 69% indicates moderate risk, and >70% indicates low risk. Among the 12 articles, five were randomized controlled trials (RCTs), and seven were quasi-experimental studies. The findings of the study quality assessment are illustrated in Figs. 2 and 3.

Fig. 2 shows the results of the study bias analysis included in the analysis for the Randomized Control Trial (RCT) study design. An analysis of the risk of bias across studies identifies multiple areas of concern. Random sequence generation and allocation concealment are generally well managed, as evidenced by most studies demonstrating a low risk of bias in these areas, suggesting that the randomization process was adequate. Blinding participants and personnel pose considerable challenges. Assessments indicated a substantial risk of bias in this domain, potentially affecting the objectivity of the results due to performance bias. The blinding of outcome assessments showed

variability, with some studies demonstrating a low risk and others presenting an unclear risk, thereby increasing the risk of detection bias. The risk of bias related to incomplete outcome data and selective reporting was ambiguous in the majority of studies.

The risk of bias assessment for the non-randomized experimental study, as indicated in Fig. 3 above, appears predominantly low to moderate. The graphic summary indicates that the research incorporated in the analysis exhibited robust methodology. The majority of the evaluated criteria, including clarity of causation, participant homogeneity, and uniformity of outcome measurements, demonstrated a little risk of bias among the studies included. These results indicate that essential elements of study design and execution were effectively managed, hence enhancing the dependability of the results.

The bias analysis results indicated "unclear risk" and "high risk" criteria. This finding indicates that some studies exhibited shortcomings in specific domains. The existence of a control group (criterion 4) and the thoroughness and evaluation of follow-up data (criterion 6) appeared to introduce a certain level of bias in the specific research. Some of these problems may relate to insufficient data reporting, methodological deficiencies, or inadequate control measures. These should be emphasized when analyzing the study results.

In assessing the methodological quality of the included studies, several domains were judged as having an unclear risk of bias due to insufficient or incomplete reporting. These uncertainties limit the ability to determine whether the studies adequately minimized potential sources of bias. A summary of the domains with unclear risk of bias across the included studies is presented in Table 2.

Study characteristics

Table 1 presents the characteristics of the included studies. In 12 papers, 100% of patients had CKD (non-dialysis). Sample sizes ranged from 64 to 1,070 patients. In total, 4,945 patients were involved in this review. The results were likely representative of the population as the sample size increases. Based on Table 2, five studies were randomised controlled trials (Chang et al., 2016; Cooney et al., 2015; Lalonde et al., 2017; Song et al., 2021; Wickramasinghe et al., 2024). One study was later categorized as a quasi-experimental study for quality assessment (Cabello-Muriel et al., 2014). Six studies were prospective pre–post study (Alam et al., 2024; Chandrasekhar et al., 2018; Ghimirey et al., 2013; Khokhar et al., 2020; Pehlivanli et al., 2023; Vu et al., 2023) among the included research. Among 12 studies, 100% of the intervention was delivered by pharmacists. Most frequently in 12 studies, pharmacists assessed the primary clinical outcomes (e.g., eGFR, BP, phosphorus, urine albumin/creatinine ratio, proteinuria, glycated hemoglobin), drug-related problems, patient knowledge, medication adherence, and quality of life. The follow-up durations varied from 1 to 17 months, with a median of 8.5 months. Delivery of interventions includes in-person counseling, informational brochures and booklets, online training programs, and telephone follow-up. The full characteristics of the included studies are presented in Supplementary Table S2.

Results of syntheses

Description of pharmacist-led interventions

Table 2 summarizes the pharmacist-led interventions in CKD patients. Pharmacist-led interventions in patients with chronic kidney disease (CKD) encompass a wide range of clinical strategies to optimize therapy and improve outcomes. These interventions included patient counseling on CKD, medication use, diet, and lifestyle, as well as communication with physicians regarding drugs that required dose adjustment or posed nephrotoxic risks (Cabello-Muriel et al., 2014; Chandrasekhar et al., 2018; Cooney et al., 2015; Ghimirey et al., 2013; Khokhar et al., 2020). Structured programs, such as Medication Therapy Management (MTM), were implemented to enhance proteinuria screening and CKD treatment within health systems (Chang et al., 2016). Other models, including ProFiL training, incorporated a 90-minute interactive web-based session focused on drug use in CKD (Lalonde et al., 2017), while the DrugTEAM approach encompassed medication reconciliation, medication evaluation and management, and discharge pharmaceutical care transitions (Song et al., 2021). Pharmacists also addressed medication-related difficulties, including poor adherence, drug–drug interactions, inappropriate dosing frequency, and adverse drug reactions (Alam et al., 2024; Pehlivanli et al., 2023). Furthermore, initiatives such as the “Positive Kidney Health” program supported the identification of candidates for renoprotective therapies and the use of collaborative practice agreements to increase uptake of evidence-based treatments to prevent CKD progression (Vu et al., 2023). In addition, the preparation of educational resources, such as a drug and disease information booklet developed in collaboration with nephrologists, further enhanced patient knowledge and understanding of CKD management (Wickramasinghe et al., 2024).

Table 2. Summary of unclear bias domains in included studies.

Study included (author, year)	Study design	Bias domains (unclear)	Justification (from peer review process)	Quality
Chang et al. (2016)	RCT (RoB2)	1. Allocation concealment. 2. Blinding of outcome assessment. 3. Selective reporting.	1. Randomization was performed by computer, but allocation concealment was not described. 2. The primary outcome was proteinuria screening from EHR and chart review, but the blinding of data extractors was unclear. 3. Without a protocol or preregistration, selective reporting could not be assessed.	Fair
Cooney et al. (2015)	RCT (RoB2)	1. Selective reporting. 2. Other Bias.	1. The study was registered (NCT01290614), but the consistency of reported versus prespecified outcomes was unclear. 2. Participants were informed by letter with an option to opt out by phone.	Good
Lalonde et al. (2017)	RCT (RoB2)	Selective reporting.	Selective reporting can only be judged by comparing reported outcomes with a prespecified protocol.	Very Good
Song et al. (2021)	RCT (RoB2)	Selective reporting.	Without the study protocol, it is unclear whether all prespecified outcomes were reported.	Very Good
Wickramasinghe et al. (2024)	RCT (RoB2)	1. Incomplete outcome data. 2. Selective reporting	1. From 256 patients screened, attrition occurred (death, dialysis, default). Attrition differed between groups, making the risk of bias unclear. 2. Without a protocol or preregistration, it is unclear whether all prespecified outcomes were reported.	Good
Alam et al. (2024)	QES (JBI)	Follow-up is complete and analyzed.	The study mentions potential dropouts and justifies increasing the sample size. It is not clear whether follow-up was complete, or if differences in follow-up were described or analyzed.	Very Good
Chandrasekhar et al. (2018)	QES (JBI)	Follow-up is complete and analyzed.	The study mentions selecting 163 patients from 950, but doesn't explicitly discuss dropouts or any analysis of incomplete follow-up. It's unclear if all 163 patients completed the entire study.	Very Good
Ghimirey et al. (2013)	QES (JBI)	1. The cause and effect are clear. 2. Follow-up is complete and analyzed.	1. The effect of pharmacist-provided counseling on knowledge, attitude, and practice regarding chronic kidney disease is unclear. 2. The study does not explicitly state whether the follow-up was complete for all participants. There is no mention of dropouts or loss to follow-up.	Very Good
Khokar et al. (2020)	QES (JBI)	None	None	Excellent
Cabello-Muriel et al. (2014)	QES (JBI)	1. Participants receive similar treatments. 2. Follow-up is complete and analyzed.	1. Both groups received care in the IM department, but it is unclear if treatments were standardized. The control group received usual care without pharmacist input. 2. The study does not report on follow-up or dropouts, only the final number of participants per group.	Very Good
Pehlivanli et al. (2023)	QES (JBI)	1. Participants in comparisons are similar. 2. Participants receive similar treatments.	1. The study lacks a control group and only includes the intervention group. It's difficult to assess similarity without a point of comparison. While the patients' demographics are detailed, there's no comparison with a group not receiving the intervention. The only within-group comparison is between patients with and without DRPs. 2. No control group; effect unclear.	Good
Vu et al. (2023)	QES (JBI)	1. Participants receive similar treatments. 2. Outcomes are reliably measured.	1. Not applicable. 2. The study uses a previously validated Kidney Knowledge Survey, which supports reliability. However, it does not mention any reliability assessment of the study-specific survey items or the chart review process.	Fair

Collectively, these findings emphasize the multifaceted role of pharmacists in improving medication safety, supporting patient self-management, and facilitating collaborative care in CKD.

Pharmacist-led interventions impact the clinical outcomes of patients with CKD

The efficacy of an intervention can be assessed by evaluating its quantifiable results. The details of the impact on clinical outcomes in patients with CKD across all studies are presented in Supplementary Table S3. Most studies in this review divide outcomes into primary and secondary. The most widely used primary outcome (found in six studies) is kidney function using the following parameters: creatinine, creatinine clearance (CrCl), estimated glomerular filtration ratee (GFR), blood urea nitrogen (BUN), blood pressure, parathyroid hormone (PTH), urine albumin-creatinine (UAC) ratio, proteinuria, glycated hemoglobin, uric acid, and phosphorus. This review found that pharmacist-led interventions produced significant benefits in reducing drug-related problems and improving patient knowledge, highlighting their value in optimizing medication use and supporting patient engagement. However, no significant improvements were observed in clinical parameters such as eGFR and blood pressure, suggesting that longer follow-up periods or more intensive strategies may be necessary to achieve measurable clinical outcomes.

Several studies reported changes in kidney function markers following intervention. One study found a non-significant reduction in creatinine ($p>0.05$; 95% CI = -0.32 to 0.39) (Khokhar et al., 2020), while CrCl significantly improved between admission and discharge (5.1 ± 0.9 vs. 6.4 ± 1.0; $p<0.01$) (Cabello-Muriel et al., 2014). Improvements in eGFR and blood pressure were observed in five studies each, but not significantly ($p>0.05$) (Chang et al., 2016; Cooney et al., 2015; Khokhar et al., 2020; Lalonde et al., 2017; Vu et al., 2023). For the UAC ratio, Cooney et al. (2015) reported a significant decrease ($p<0.001$), whereas Vu et al. (2023) did not ($p>0.05$). Other outcomes included non-significant changes in BUN, proteinuria, HbA1c, and uric acid ($p>0.05$), while PTH and phosphorus showed significant reductions ($p<0.001$) (Chang et al., 2016; Cooney et al., 2015; Khokhar et al., 2020; Lalonde et al., 2017).

Four trials examined the benefits of pharmacist-led interventions for medication adherence in pre-dialysis CKD patients. Alongside the findings from the analyzed continuous or dichotomous data (refer to Table 2), which indicated alterations in medication adherence scores, three studies noted improved adherence to antihypertensive therapy, antidiabetic treatment, and anti-ischemic heart disease at the conclusion of the intervention, although not significantly ($p>0.05$) (Cooney et al., 2015; Khokhar et al., 2020; Song et al., 2021), one study reported better adherence significantly at the end of intervention ($p<0.001$) (Chandrasekhar et al., 2018).

The impact of pharmacist-led interventions on patients' knowledge prior to dialysis with CKD was reported in four studies. Three studies reported substantially improved knowledge at the conclusion of the intervention ($p<0.05$), in addition to the results from polled analysis of continuous or dichotomous data (see Table 1), which revealed changes in knowledge score (Ghimirey et al., 2013; Khokhar et al., 2020; Wickramasinghe et al., 2024), one study reported better knowledge at the end of intervention but the significance data was not available (Lalonde et al., 2017).

One study examined the effect of a pharmacist-led intervention on quality of life in pre-dialysis patients with chronic kidney disease (CKD). Owing to the disparate scales: Short-Form 12 (SF-12) and Kidney Disease Quality of Life (KDQoL), only one study reporting the quality of life, a combined meta-analysis was not conducted. The results from the intervention group compared with usual care showed an improvement in patients' quality of life, but it was not significant ($p>0.05$) (Cooney et al., 2015).

In addition to the continuous data on DRPs per patient that was included in the meta-analysis (see Table 2). Across the included studies, pharmacist-led interventions were consistently associated with reductions in drug-related problems (DRPs) among patients with chronic kidney disease (CKD). Lalonde et al. (2017) reported a decline in DRPs among ProFiL patients (2.16 to 1.60), compared with minimal change in controls (1.70 to 1.62), with a greater effect observed at higher baseline DRPs (–0.51 vs. –0.32 DRPs per patient; $\beta = -0.11$; $p = 0.6$). Similarly, Song et al. (2021) identified 182 DRPs among CKD inpatients, with all intervention patients presenting ≥1 DRP (median 3.5; IQR 2–5). The most common categories were indication without prescription (35.7%) and inappropriate dosage/administration (31.9%). The mean number of DRPs per patient was significantly lower in the intervention group compared with controls (0.94 ± 1.03 vs. 1.96 ± 1.25; $p<0.001$), with 51.1% of intervention-group DRPs fully resolved by discharge (Song et al., 2021). Pehlivanli et al. (2023) found that 48.7% of patients experienced at least one DRP (mean 0.8 ± 1.0 per patient), totaling 205 cases, predominantly related to treatment effectiveness (50.7%) and safety (43.9%), with drug and dose selection being the main causes. Of these, 71.7% were resolved, 23.4% remained unresolved, and 2.9% were indeterminate; DRPs were more frequent among females and were associated with longer hospital stays and

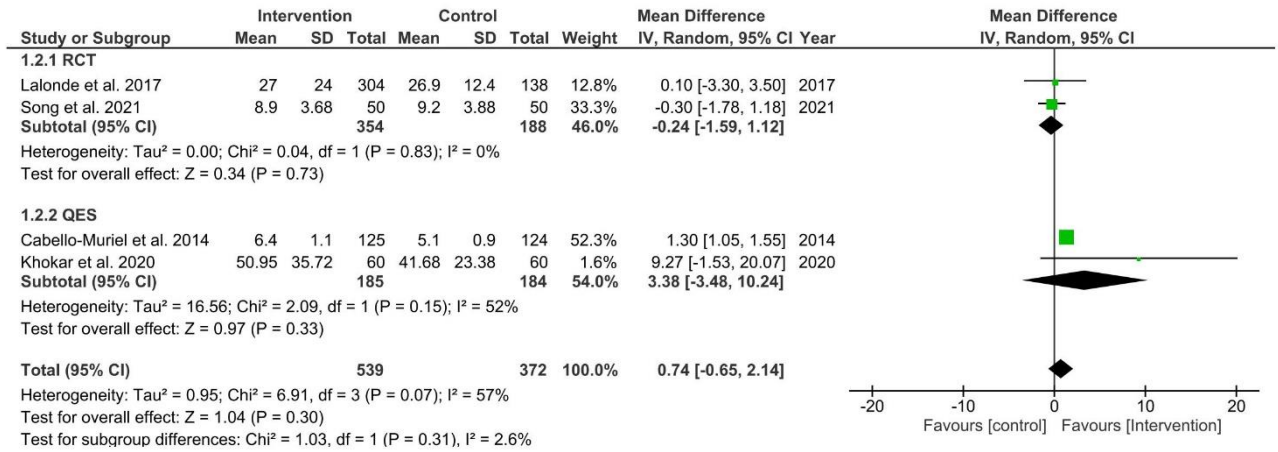

Figure 4. Forest plot of the effect of pharmacist intervention on the outcome of patients' estimated glomerular filtration rate (eGFR).

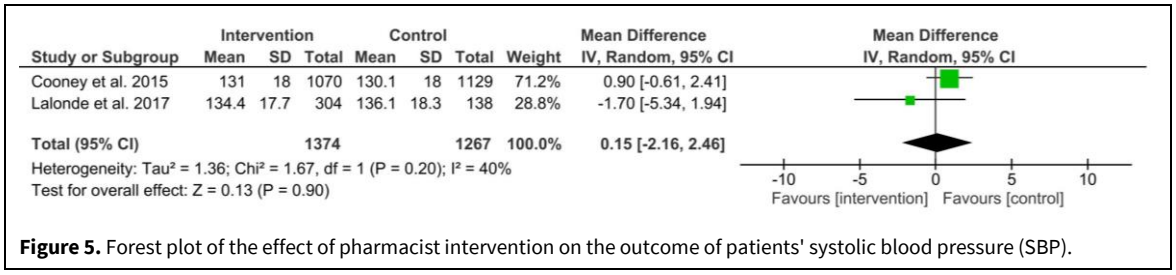

Figure 5. Forest plot of the effect of pharmacist intervention on the outcome of patients' systolic blood pressure (SBP).

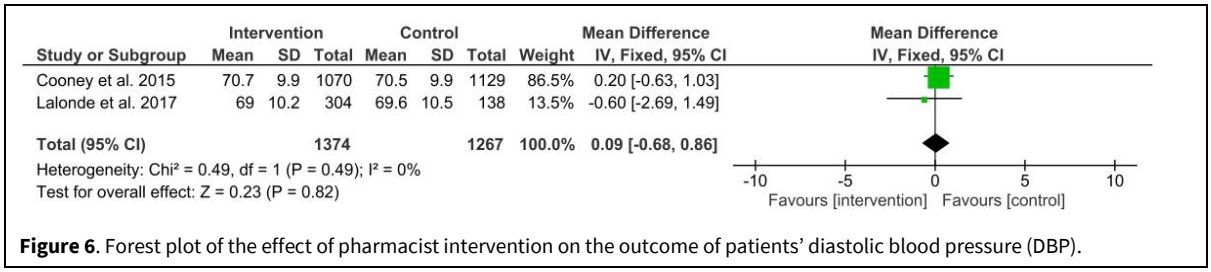

Figure 6. Forest plot of the effect of pharmacist intervention on the outcome of patients' diastolic blood pressure (DBP).

higher medication use (p<0.05). More recently, Alam et al. (2024) observed that all patients presented with at least one DRP (mean 2.90 ± 1.15; range 1–7), with significant reductions following pharmacist intervention. Inappropriate medication selection, duplicate therapy, stoppable medications, contraindicated drugs, drug interactions, medicine non-receipt, non-compliance, and untreated indications all decreased significantly (p<0.05), while overdose, subtherapeutic levels, undertreated indications, and adverse drug reactions showed nonsignificant downward trends.

Forest plot analysis of the clinical outcomes of patients with chronic kidney disease (CKD) who received intervention from pharmacists

According to the data extraction results, six clinical outcomes of CKD patients influenced by pharmacist intervention were incorporated into the meta-analysis. The results included alterations in estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), diastolic blood pressure (DBP), patient medication adherence, patient drug-related problems (DRPs), and patient knowledge of disease and medication. The results of the meta-analysis are shown in the following forest plot. Fig. 4 presents the findings of a meta-analysis encompassing four experimental trials. The pharmacist-led intervention did not have a direct effect on enhancing eGFR values in patients with CKD. The pooled mean difference was 0.74 (95% CI: -0.65 to 2.14), indicating no statistically significant disparity between the intervention and control groups (p=0.30). The diamond at the bottom signifies the aggregated estimate, which intersects zero, so affirming the absence of a substantial overall effect.

The forest plot findings of pharmacist-led interventions on systolic (SBP) and diastolic (DBP) blood pressure outcomes are illustrated in Figs. 5 and 6. The findings indicate that blood pressure in patients with chronic kidney disease did not exhibit substantial alterations following pharmacist intervention. Fig. 5

indicates that the analysis encompasses data from two investigations, yielding a total combined sample size of 1,374 participants. The intervention group had 131 people with a mean score of 130.1 (SD 18), whereas the control group included 1129 persons with a mean score of 136.1 (SD 13). The aggregated mean difference between the intervention and control groups is 0.52, with a 95% confidence interval of -0.87 to 1.91. The inclusion of 0 in the confidence interval indicates that there is no statistically significant difference between the intervention and control groups overall. The studies exhibit moderate heterogeneity, indicated by a Chi² value of 1.67, a p-value of 0.20, and an I² statistic of 40%, suggesting some variability that is not statistically significant. The Z-test for the total effect yields a value of 0.73 and a p-value of 0.46, reinforcing the absence of meaningful evidence for a difference between the intervention and control groups in these investigations.

Fig. 6 shows that the overall pooled mean difference between the intervention and control groups is 0.09, with a 95% confidence interval of -0.68 to 0.86. As this interval includes 0, there is no statistically significant difference between the groups.

The heterogeneity metrics indicate a Chi² value of 0.49, a p-value of 0.49, and an I² of 0%, indicating minimal heterogeneity and consistent results. The Z-test for the overall effect is 0.23, with a p-value of 0.82, indicating no statistically significant difference between the intervention and the control.

Fig. 7 shows that the role of pharmacists in individuals with chronic kidney disease did not markedly improve medication adherence. This meta-analysis pooled the findings of three investigations, encompassing 1180 people in the intervention groups and 1239 participants in the control groups. The individual research outcomes revealed comparable mean scores in both groups, whereas the pooled analysis indicated an overall mean difference of around -0.07. The confidence interval ranged from -0.15 to 0.01, encompassing zero, indicating no statistically meaningful difference between the intervention and control groups overall. Nonetheless, the studies exhibited significant heterogeneity, evidenced by a Chi² value of 6.95 and an I² of 71%, suggesting considerable variability in the outcomes potentially attributable to variations in study populations, therapies, or other factors. The overall effect test yielded a Z-value of 1.68 and a p-value of 0.09, approaching but not attaining conventional statistical significance. This finding suggests a trend indicating a disparity across groups; however, the evidence is insufficient to establish a statistically significant effect.

The meta-analysis results indicated that pharmacist-led interventions significantly decreased drug-related problems (DRPs) in patients with chronic kidney disease (CKD) (Fig. 8). This study involves three studies, with 483 individuals in the intervention group and 323 in the control group. The various studies present comparable mean scores: Lalonde et al. (2017) reported 1.6 (SD 1.79) compared to 1.62 (SD 1.79), Song et al. (2021) reported 0.9 (SD 1) compared to 1.43 (SD 1), and Pehlivani et al. (2023) reported 0.49 (SD 1) compared to 0.8 (SD 1). The overall mean difference is -0.23, with a 95% confidence interval from -0.37 to -0.08, indicating a statistically significant advantage for the control group, as the interval excludes zero. The studies exhibit considerable heterogeneity, as indicated by an I² of 87% and a Chi-squared value of 15.75, suggesting significant variability presumably attributable to differences in study designs, demographics, or interventions. The Z-test for the total effect produces a value of 3.08 and a p-value of 0.002, indicating that the difference between groups is statistically significant. The analysis demonstrates a consistent advantage for the control group across trials; however, the significant heterogeneity suggests variability in the results that must be taken into account when interpreting these findings.

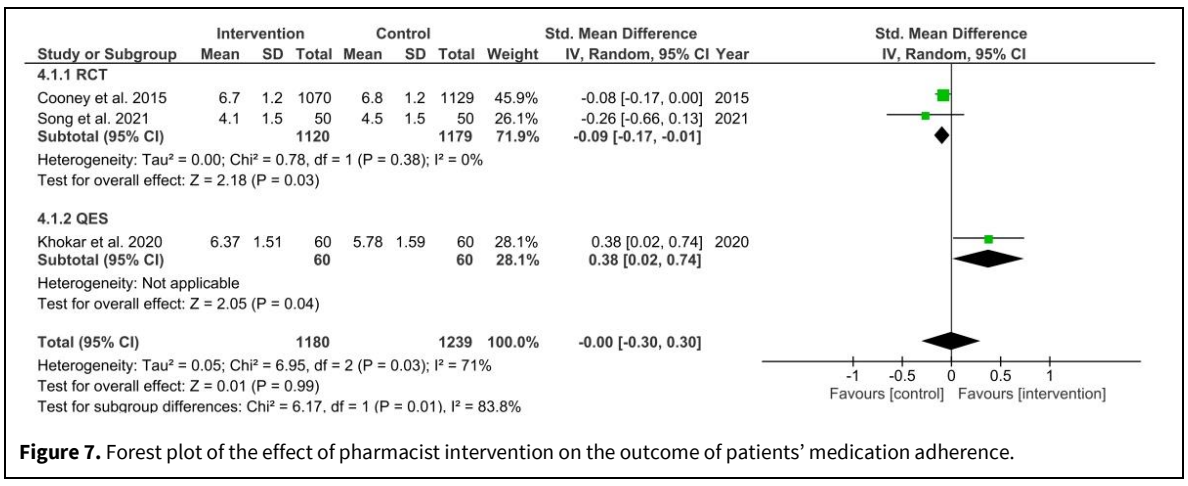

Figure 7. Forest plot of the effect of pharmacist intervention on the outcome of patients' medication adherence.

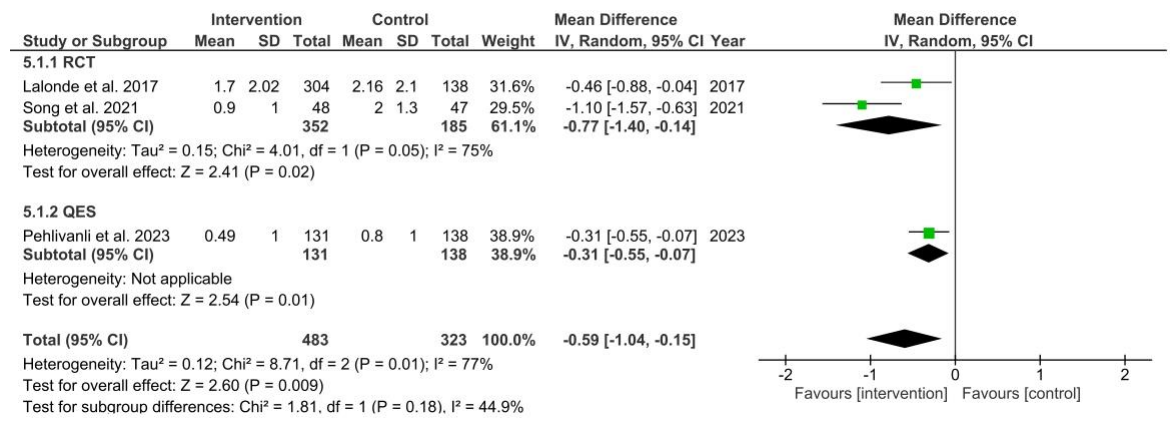

Figure 8. Forest plot of the effect of pharmacist intervention on the outcome of patients' drug-related problems (DRP).

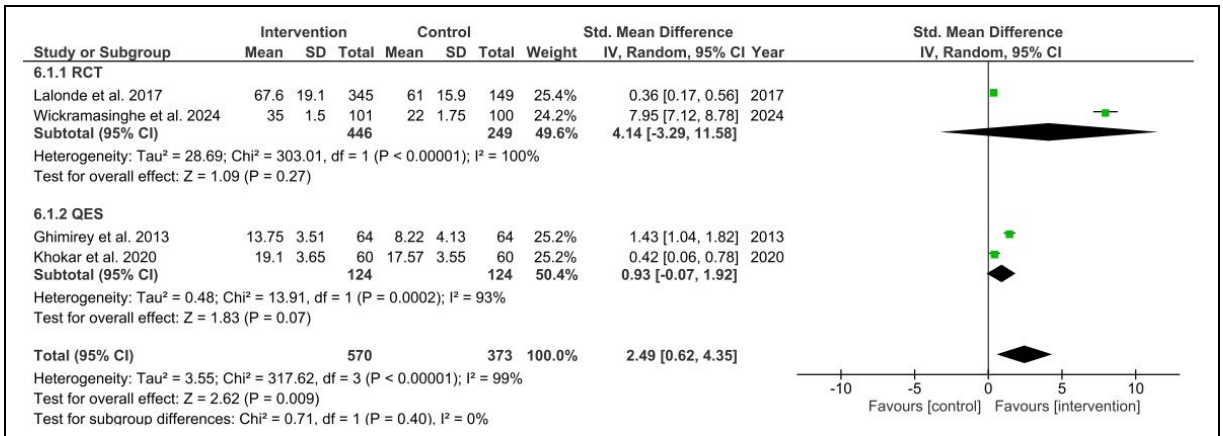

Figure 9. Forest plot of the effect of pharmacist intervention on the outcome of patients' knowledge of disease and medication.

Comparable results were also observed in patients' knowledge outcomes (Fig. 9). Patients with chronic kidney disease demonstrate greater understanding of the condition and its pharmacotherapy following pharmacist intervention. The meta-analysis synthesized data from four trials involving 570 participants, including 373 in the control group. The intervention group's mean scores varied from 13.75 (SD 3.51) to 67.6 (SD 19.1), whereas the control group's scores ranged from 4.13 (SD 4.13) to 61 (SD 15). The aggregated mean difference is 0.80, with a 95% confidence interval ranging from 0.64 to 0.95. A positive effect size, in conjunction with the exclusion of zero from the confidence interval, indicates a statistically significant difference in favor of the intervention group. The studies exhibit significant heterogeneity, indicated by an I^2 of 99% and a Chi-squared value of 317.62. This finding implies considerable variation in outcomes, potentially attributable to differences in study populations, intervention types, or other factors. The Z-test for the overall effect yielded a value of 10.18, with a p-value of 0.0001 or less, indicating that the observed effect is statistically significant. The data indicate that the intervention has a positive impact compared with the control; however, significant heterogeneity suggests considerable variability in results across trials.

Pharmacist-led interventions resulted in substantial decreases in drug-related issues and improvements in patient knowledge regarding CKD and drugs. Interventions demonstrated minimal or statistically insignificant improvements in clinical metrics such as eGFR, blood pressure, and medication adherence, suggesting a need for targeted initiatives in these domains. Significant heterogeneity within research likely results from variations in intervention designs, methods of pharmacist involvement, varied patient demographics, and diverse healthcare environments. This variability indicates the need for caution when generalizing these results, underscoring the need for more standardized interventions and outcome metrics in subsequent research.

Funnel plot reporting biases in meta-analysis

Meta-analysis uses funnel plots to show the relationship between study size or precision and effect magnitude. Each point represents a study, with the effect size on the x-axis and an accuracy measure, such

as standard error, on the y-axis. A funnel plot's symmetry helps identify publication and reporting biases. Asymmetric funnels show study heterogeneity, while symmetrical funnels indicate no bias. It helps academics assess the robustness and validity of meta-analysis results. In this study, six meta-analyses were conducted on outcomes, resulting in six funnel plot analyses, as shown in Fig. 10.

Marked as "SE (SMD)" on the y-axis, this denotes the Standard Error of the Standardized Mean Difference. The scale ranges from 0 at the top to 0.5 at the bottom. Lower values on this axis indicate greater precision due to a smaller standard error. Studies positioned at the top are typically larger than those situated at the bottom. Marked as "SMD," the x-axis denotes the Standardized Mean Difference. The scale spans from roughly -5 to +5. The Standardized Mean Difference (SMD) quantifies impact size, reflecting both the degree and direction of the disparity between the groups under investigation. A value of 0 signifies no effect, positive values denote a beneficial effect, and negative values represent a detrimental effect.

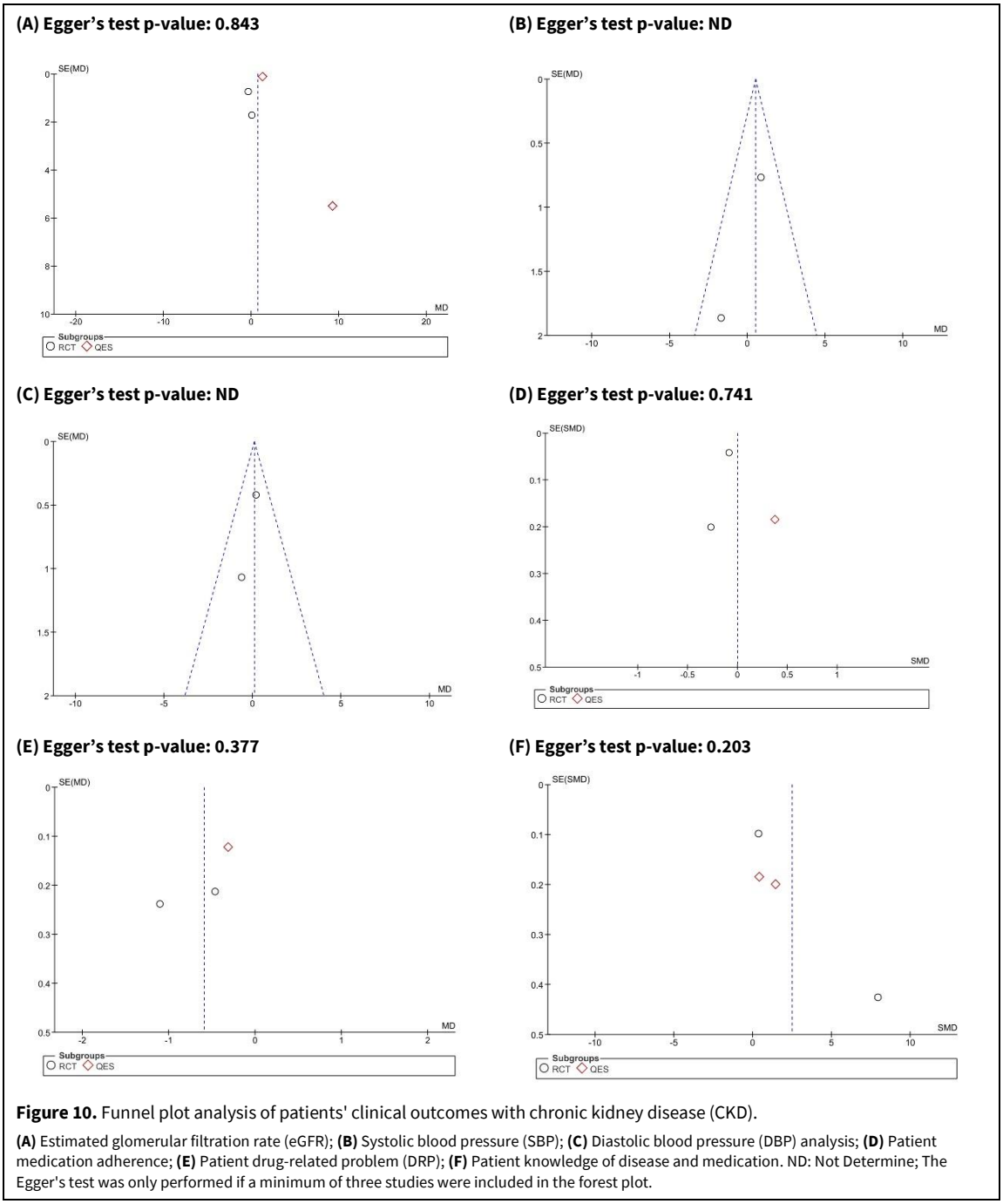

Figure 10. Funnel plot analysis of patients' clinical outcomes with chronic kidney disease (CKD).

(A) Estimated glomerular filtration rate (eGFR); **(B)** Systolic blood pressure (SBP); **(C)** Diastolic blood pressure (DBP) analysis; **(D)** Patient medication adherence; **(E)** Patient drug-related problem (DRP); **(F)** Patient knowledge of disease and medication. ND: Not Determine; The Egger's test was only performed if a minimum of three studies were included in the forest plot.

The prevalence of studies with minimal effect sizes near zero and high precision in this study indicates that, in general, a substantial effect may be absent. The outlier study reveals one study with a significant beneficial effect; however, its diminished precision results in reduced weight. The possible asymmetry in the funnel plot raises concerns about publication bias. Studies yielding poor results or modest favorable outcomes may be underrepresented. This bias may exaggerate the perceived effect size. This funnel plot suggests potential publication bias and warrants further inquiry. Although certain research suggests a minimal impact, an anomalous study indicates a significant, favorable effect. The possible imbalance, however, necessitates prudence in interpreting the overall results.

Funnel plot inspection and Egger's tests did not suggest major publication bias ($p>0.05$), although the small number of studies per outcome limited statistical power. Overall, pharmacist-led interventions consistently improved knowledge and reduced DRPs, while effects on clinical outcomes and adherence remained inconsistent.

DISCUSSION

This systematic review and meta-analysis highlight the significant role of pharmacist-led interventions in enhancing patient knowledge among pre-dialysis CKD patients. The observed improvement in knowledge reflects the effectiveness of structured counseling and disease-specific education, consistent with prior research reporting that pharmacist involvement enhances health literacy and promotes self-management behaviors. The critical role of pharmacists in promoting medication literacy is further emphasized by the improved patient knowledge achieved through pharmacist education, which has the potential to enhance self-management capabilities and long-term adherence to therapy. The prospective study conducted by Ghimirey et al. (2013) reported that the mean knowledge score in the case group after pharmacist counseling was significantly higher than before the intervention. It is hypothesized that early-stage patient education contributes to the deceleration of CKD development. One prospective comparative study by Khokhar et al. (2020) found a substantial difference in knowledge scores between the intervention and control groups at follow-up. In accordance with prior research, the pharmacist intervention paradigm demonstrated efficacy in enhancing patient disease knowledge (Choi & Lee, 2012).

The improvement in knowledge among pre-dialysis CKD patients following pharmacist-led interventions is largely attributed to the pharmacist's expertise in pharmacotherapy, medication safety, and chronic disease management, which enables complex medical information to be delivered in a clear, patient-centered manner. Unlike physician consultations, which are often time-limited, pharmacist-led education emphasizes treatment goals, self-management, and ongoing patient support (Khokhar et al., 2020). The use of multimodal strategies such as individualized counseling, written resources, and visual aids has also been shown to improve comprehension and knowledge retention (Ghimirey et al., 2013). Repeated interactions further enable clarification, correction of misconceptions, and reinforcement of adherence behaviors, contributing to sustained knowledge gains (Alam et al., 2024). Nonetheless, some studies have reported limited or non-significant effects, which may be explained by differences in intervention design, patient baseline knowledge, and contextual factors such as health literacy or healthcare infrastructure (Choi & Lee, 2012). These findings suggest that while pharmacist-led education is generally effective, its impact is influenced by patient characteristics and the setting in which it is implemented.

From a practical perspective, these findings emphasize the critical role of integrating pharmacists into multidisciplinary CKD care teams. Pharmacists can complement the roles of physicians and nurses by ensuring patients receive structured, continuous education on disease progression, medication management, and lifestyle modifications. Standardizing educational protocols and tailoring them to patient literacy levels and cultural backgrounds may further enhance outcomes. In addition, implementing pharmacist-led educational programs as part of routine CKD management in outpatient clinics could improve patient knowledge, reduce preventable complications, and ultimately support better long-term clinical outcomes.

This systematic review and meta-analysis also highlight the significant role of pharmacist-led interventions in reducing DRPs among pre-dialysis CKD patients. Likewise, the reduction in DRPs highlights the pharmacist's role in reviewing prescriptions, detecting potential drug-related risks, and adjusting medication regimens according to renal function, findings that align with earlier studies in CKD and other chronic conditions. The complex medication regimens that are typically prescribed for CKD patients, which frequently increase the risk of medication errors and adverse events, render the substantial decrease in DRPs observed to be particularly significant. Pharmacists' contributions to the safer use of medications are evident in their identification and resolution of inappropriate medications, titration errors, and potential drug interactions.

This analysis shows that pharmacists primarily provided patient education and motivation while reviewing prescriptions to identify DRPs. In advanced

healthcare settings, nephrology-focused pharmacists focus on managing drug interactions and adjusting doses based on renal function (Thanapongsatorn et al., 2021; Theeranut et al., 2021; Tuttle et al., 2018). Pharmacist-led interventions have proven effective in reducing DRPs, as their expertise in pharmacotherapy and medication safety enables systematic reviews, detection of inappropriate prescribing, and identification of interactions or dosing errors. Such interventions are particularly important in polypharmacy populations, where DRP risk is markedly higher (Song et al., 2021). Beyond pharmacotherapy optimization, pharmacist-led interventions include patient education and counseling, which enhance adherence, promote self-management, and reduce DRPs by empowering patients to recognize and report adverse events. Evidence shows these strategies improve patient safety, while the high acceptance of pharmacist recommendations, such as dose adjustments and therapeutic substitutions, highlights their value in interprofessional collaboration and clinical decision-making (Alam et al., 2024).

The consistent reduction of DRPs across studies demonstrates that pharmacist involvement yields systematic and reproducible benefits rather than incidental effects. Integrating pharmacists into multidisciplinary teams is particularly vital in chronic disease management, where polypharmacy and limited consultation time increase patient vulnerability. Standardized pharmacist-led interventions such as medication reviews, patient counseling, and collaborative therapeutic decision-making have been shown to reduce DRPs and improve outcomes in pre-dialysis CKD. Moreover, from an economic perspective, these interventions prevent costly hospitalizations and complications, with accumulated savings surpassing implementation costs, thereby establishing their clinical relevance and economic sustainability (Pehlivanli et al., 2023).

Only one study reported the impact of pharmacist-led interventions on quality of life, another important measure for CKD patients. This study demonstrated a high degree of heterogeneity and a variety of scales. Nevertheless, four of the studies indicated that the activities performed exhibited benefits for role-emotional, mental health, social functioning, and/or general health measures. While pharmacist-led interventions have shown clear benefits in improving adherence, reducing drug-related problems, and optimizing therapy, their impact on patients' quality of life remains underexplored. Most studies emphasize clinical outcomes, overlooking patient-reported measures that reflect physical, psychological, and social well-being. This methodological gap risks underestimating the holistic value of pharmacists' contributions to patient-centered care (Cooney et al., 2015). Future research should integrate validated quality-of-life instruments, such as SF-36 or EQ-5D, alongside clinical indicators to provide a more comprehensive evaluation of outcomes and better demonstrate pharmacists' role in enhancing overall well-being.

Although this evaluation did not show significant improvements in clinical parameters such as blood pressure and eGFR, it contrasts with notable improvements in medication-related outcomes, highlighting the complexity of CKD progression and the potential need for more intensive interventions or longer follow-up to detect clinical changes. Pharmacist interventions appear to have a greater impact on medication management and patient education than on physiological parameters, which are influenced by multiple factors. Unlike Nakanishi et al. (2021), who found home-based blood pressure telemonitoring particularly effective, Kamath et al. (2020) reported improved hypertension management mainly through primary care physician interventions, with limited pharmacist involvement. Other systematic reviews indicated pharmacist involvement positively affected clinical outcomes, including BUN, BP, phosphorus, urine albumin/creatinine ratio, proteinuria, HbA1c, and creatinine clearance or eGFR (Al Raiisi et al., 2019; Hsu et al., 2021; Nicoll et al., 2018). Ardavani et al. (2025) found significant improvements in systolic BP and hemoglobin, but not in diastolic BP, eGFR, creatinine, or LDL. Pharmacist interventions did not improve kidney function (Tuttle et al., 2018). Nevertheless, they consistently achieved a clinically meaningful reduction in systolic BP of about 6 mmHg, crucial for CKD management. This effect is likely mediated through enhanced medication management, drug history review, pharmacological recommendations, and patient counseling to improve adherence (Habas et al., 2022; Qudah et al., 2016). The lack of statistically significant improvements in blood pressure and eGFR following pharmacist-led interventions may be attributed to the inherently progressive nature of CKD and the limited duration of most interventional studies. Although pharmacist-led initiatives demonstrably enhance medication adherence, optimize pharmacotherapy, and reduce drug-related problems, translating these benefits into measurable clinical outcomes often requires sustained, long-term management alongside multidisciplinary care. Furthermore, individual patient characteristics, comorbid conditions, and intrinsic physiological variability may attenuate the immediate impact on blood pressure and renal function, suggesting that clinically meaningful changes may emerge only over extended follow-up.

In this review, medication adherence in individuals with pre-dialysis CKD was not significantly influenced by the pharmacist interventions. In more than 70% of

studies, pharmacist-led patient interventions included activities such as patient-centered medication education (e.g., therapeutic objectives, potential adverse effects, and/or contraindications), disease management, lifestyle modifications, and nutrition. Nevertheless, medication adherence in individuals with CKD appears to be a persistent challenge, despite numerous educational initiatives. Findings showed a mixed effect of pharmacist interventions. Furthermore, other systematic assessments revealed that various instructional methods had an ambiguous effect on medication adherence in other chronic illnesses, including hypertension, chronic renal disease, heart failure, and diabetes (Greer et al., 2016; Ha Dinh et al., 2016; Tan et al., 2019). In contrast, Chisholm-Burns et al. (2013) demonstrated improved medication adherence among those who received a 1-year behavioral contract intervention delivered by a clinical pharmacist. Despite the implementation of pharmacist-led interventions to improve medication adherence, the results did not show a significant change in patients' adherence. Several factors may explain this outcome. First, medication adherence is influenced by complex, multifactorial determinants, including patients' beliefs, socioeconomic status, disease perception, and psychological factors, which may not be fully addressed by standard pharmacist interventions. Second, the duration and intensity of the intervention might have been insufficient to produce measurable changes, particularly in patients with long-standing habits or chronic conditions. Third, external factors such as polypharmacy, side effects, or lack of social support could have continued to hinder adherence despite educational or counseling efforts. These findings suggest that while pharmacist interventions are crucial for promoting proper medication use, achieving significant improvements in adherence may require more personalized, intensive, or multidisciplinary strategies over a longer period.

Despite generally positive findings, several limitations should be acknowledged, including small sample sizes, heterogeneity in study designs, restricted healthcare settings, and inconsistent evaluation of long-term outcomes, all of which constrain the generalizability of the results. Pharmacist-led interventions consistently enhanced medication safety; however, the modest effects observed on clinical parameters such as eGFR and blood pressure indicate that outcomes are influenced by patient characteristics, disease stage, and intervention intensity. This review benefits from rigorous bias assessment and the inclusion of both randomized controlled trials and quasi-experimental studies, yet heterogeneity, potential publication bias, and the limited number of high-quality RCTs further restrict the strength of conclusions. Collectively, these findings underscore the pivotal role of pharmacists in CKD management while highlighting existing evidence gaps. Addressing these gaps through larger, multicenter, long-term studies with standardized interventions is essential to fully elucidate the clinical and economic impact of pharmacist-led care and to support their effective integration into multidisciplinary CKD management.

Strengths and limitations

This systematic review has several strengths. It focused exclusively on pre-dialysis CKD, a stage where early interventions are most impactful, ensuring clinical relevance. The review followed PRISMA guidelines, was prospectively registered, and included both RCTs and quasi-experimental studies, thereby capturing a broad spectrum of evidence. A rigorous risk-of-bias assessment was performed using RoB 2 and the JBI QES checklist, increasing the reliability of findings. Furthermore, meta-analyses were conducted for multiple key outcomes to enhance quantitative synthesis, while narrative synthesis was used when pooling was not appropriate, thereby improving methodological transparency.

Nonetheless, some limitations must be acknowledged. Considerable heterogeneity was observed across studies in terms of intervention type, duration, and outcome measurement, particularly for medication adherence and patient knowledge. The majority of studies had relatively short follow-up periods (<12 months), limiting the ability to detect long-term changes in slow-progressing outcomes such as eGFR. Most included studies originated in Asia and upper–middle–income countries, which may limit generalizability to other healthcare settings. Although funnel plots and Egger's tests were conducted, the small number of studies per outcome limited the power to detect publication bias. Variability in adherence assessment tools and quality-of-life measures further constrained comparability across studies. In addition, due to the limited number and diversity of studies, we were unable to conduct meta-regression or sensitivity analyses based on CKD stage, intervention duration, or healthcare setting, which may have provided deeper insight into sources of heterogeneity.

CONCLUSION

Pharmacist-led interventions in pre-dialysis CKD patients effectively reduce drug-related problems and improve patient knowledge, but show no significant impact on clinical outcomes such as eGFR or blood pressure. These findings underscore the value of including pharmacists in multidisciplinary CKD care teams to optimize medication use and empower patients in self-management. Pharmacists play a key role in ensuring safe and effective pharmacotherapy and in empowering patients to engage in self-care. Their

involvement may prevent adverse events and improve adherence, contributing to long-term care quality even without immediate clinical improvements. Further studies with larger cohorts and longer follow-up are needed to assess whether pharmacist interventions can influence CKD progression or clinical endpoints. Research should also explore integrated approaches combining pharmacist support with lifestyle and dietary counseling to maximize both clinical and patient-centered outcomes.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

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GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, writing, or editing of this manuscript. All content was developed solely by the authors, who take full responsibility for its accuracy and integrity.

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AUTHOR CONTRIBUTION:

Contribution	Nopitasari BL	Suprapti B	Tjempakasari A	Jaya MKA
Concepts or ideas	x	x	x	
Design	x	x	x	x
Definition of intellectual content	x	x	x	x
Literature search	x	x	x	x
Experimental studies				
Data acquisition	x	x	x	x
Data analysis	x	x	x	x
Statistical analysis			x	x
Manuscript preparation	x	x	x	x
Manuscript editing	x	x		x
Manuscript review	x	x	x	x

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Supplementary data

Table S1. Search strategy.

Database	Keyword
PubMed	#1 “Pharmacist intervention” OR “Pharmacy service” OR “Clinical pharmacist service”
	#2 “Chronic kidney disease” OR “chronic kidney disease pre-dialysis” OR “chronic kidney disease non-dialysis”
	#3 “Kidney Function” OR “estimated Glomerular Filtration Rate” OR “eGFR”
	#4 “Medication adherence” OR “Drug adherence” OR “Patient adherence”
	#5 “Knowledge” OR “Patient knowledge”
	#6 “Drug related problems” AND “Quality of life”
	#7 (#1 OR #2) AND #3 AND #4 AND #5 AND #6
Web of Science	#1 Pharmacist intervention OR Pharmacy service OR Clinical pharmacist service
	#2 Chronic kidney disease OR chronic kidney disease pre-dialysis OR chronic kidney disease non-dialysis
	#3 Kidney Function OR estimated Glomerular Filtration Rate OR eGFR
	#4 Medication adherence OR Drug adherence OR Patient adherence
	#5 Knowledge OR Patient knowledge
	#6 Drug related problems AND Quality of life
	#7 (#1 OR #2) AND #3 AND #4 AND #5 AND #6
Scopus	#1 “Pharmacist intervention” OR “Pharmacy service” OR “Clinical pharmacist service”
	#2 “Chronic kidney disease” OR “chronic kidney disease pre-dialysis” OR “chronic kidney disease non-dialysis”
	#3 “Kidney Function” OR “estimated Glomerular Filtration Rate” OR “eGFR”
	#4 “Medication adherence” OR “Drug adherence” OR “Patient adherence”
	#5 “Knowledge” OR “Patient knowledge”
	#6 “Drug related problems” AND “Quality of life”
	#7 (#1 OR #2) AND #3 AND #4 AND #5 AND #6
Crossref	#1 “Pharmacist intervention” OR “Pharmacy service” OR “Clinical pharmacist service”
	#2 “Chronic kidney disease” OR “chronic kidney disease pre-dialysis” OR “chronic kidney disease non-dialysis”
	#3 “Kidney Function” OR “estimated Glomerular Filtration Rate” OR “eGFR”
	#4 “Medication adherence” OR “Drug adherence” OR “Patient adherence”
	#5 “Knowledge” OR “Patient knowledge”
	#6 “Drug related problems” AND “Quality of life”
	#7 (#1 OR #2) AND #3 AND #4 AND #5 AND #6

Table S2. Full characteristics of the included studies**.**

No	Author, year	Design	Population	Sample size	Intervention	Comparator	Duration	Delivery format	Measured outcomes
1	Ghimirey et al. (2013).	The prospective, pre–post study	CKD patients aged 18–75 years who were ready to give informed consent to collect data for the study were included in the study	Intervention: 32. Control: 32	Case group patients were counseled regarding chronic kidney disease, their medication, diet, and lifestyle, and they were also provided with an informative leaflet	Control group patients, the pharmacist did not intervene	1 month	Leaflet	The actual KAP (knowledge, attitude, and practice) regarding CKD
2	Muriel et al. (2014).	A prospective, open, quasi-experimental, controlled study with parallel groups	All patients admitted to the IM department over 18 years of age, with CKD, which is defined as the presence of creatinine clearance (CrCl) in the last 3 months, 60 mL/min/1.73 m^2, with at least one nephrotoxic drug in the pharmacological treatment	Intervention (125, age: 82). Control (124, age: 81)	For patients in the intervention group, the pharmacist informed the physician about potentially nephrotoxic drugs that were not appropriately adjusted for patients' renal function, at which time the pharmacist proposed a recommended dose adjustment.	Control group (usual clinical practice)	7 months	Face-to-face	The renal function (Creatinine Clearance/CrCl)
3	Cooney et al. (2015).	Randomized control trial	Moderate to severe CKD is defined by the most recent estimated glomerular filtration rate (eGFR), calculated using the 4-variable MDRD equation, < 45 mL/min/1.73 m^2	Intervention (1070, age: 75.6. Usual care (1129, age: 75.5)	Multifactorial intervention: a phone−based pharmacist intervention, pharmacist−physician collaboration, patient education (informational pamphlet), and a CKD registry. The pharmacists reviewed medications and lifestyle modifications with the patients, ordered the KDOQI-recommended labs, and arranged nephrology consults for patients with severe CKD (eGFR <30 mL/min/1.73 m^2)	Control group (usual care)	12 months	By phone and face-to-face	The primary clinical outcome (systolic BP). The primary process outcome (PTH). Secondary clinical outcomes (BP, phosphorus, and urine albumin/creatinine ratio). Secondary process measures (medication adherence). Secondary clinical outcomes (quality of life).
4	Chang et al. (2016).	A pragmatic, cluster-randomized trial	Patient with stage 3A CKD	Intervention (24.64). Control (23, 70.6).	Pharmacist MTM to improve proteinuria screening and CKD management in a large, integrated health system	Control group (did not receive any additional care)	17 months	Face-to-face and phone	The primary study outcome was proteinuria and blood pressure
5	Lalonde et al. (2017).	Multicenter, cluster-randomized, controlled trial.	Patients with CKD stage 3a, 3b, or 4 from 6 CKD clinics (Quebec, Canada) and their community pharmacies	207 community pharmacies, 494 pharmacists,	ProFiL pharmacists completed a 90-minute An interactive web-based training program on the use of medications	Control group	12 months	Web-training program	Renal function test (eGFR, BP, glycated hemoglobin). Primary outcome

Table S2. Full characteristics of the included studies**.**

No	Author, year	Design	Population	Sample size	Intervention	Comparator	Duration	Delivery format	Measured outcomes
				and 442 patients with CKD participated	in CKD and received a clinical guide, patients' clinical summaries, and facilitated access to the CKD clinic.				(drug-related problems), knowledge.
6	Chandrasekhar et al. (2018).	The prospective interventional study	Nephrology outpatients who underwent the treatment of chronic kidney disease, both male and female patients, who are willing to participate in the study	163 patients were selected based on inclusion-exclusion criteria, and informed consent was taken	Pharmaceutical interventions like patient counseling and patient information leaflets containing a general outline of information about CKD and the importance of medicines	NA	12 months	Counseling, leaflets, and a telephonic interview	Medication adherence
7	Khokar et al. (2020).	This multi-arm pre-post prospective study	All patients visiting the nephrology outpatient department with an established diagnosis of CKD stage 2 to 4 (GFR between 15- 89 mL/min per 1.73 m^2) according to K/DOQI guidelines of the National Kidney Foundation (NKF) were enrolled in the current study	Intervention (60, age: 53.30). Control (60, age: 58.47).	The pharmacist intervention model was structured into the educational brochure and the information materials provided to the patients. The primary components of the educational material were knowledge of disease and medication adherence. The disease knowledge included the introduction of CKD with prior information on normal functions and the role of the kidney in the human body, dietary modification to slow down the disease progression, and improving medication adherence behavior	The control group only received the usual care	3 months	A 45-minute session was held in the nephrology outpatient clinic. A telephonic follow-up was designed to encourage patients about medication adherence	The outcomes measured were: eGFR, renal function tests (SCr, BUN, Uric acid), knowledge, and medication adherence
8	Song et al. (2021).	A prospective, randomized, parallel, controlled clinical trial	Patients were eligible if they were (1) new admissions in the nephrology ward, (2) over 18 years of age, (3) diagnosed with CKD by their nephrologist previously, (4) confirmed to have either an eGFR of less than 60 mL/min/1.73 m^2 or kidney damage, as shown by laboratory results	Intervention (50, 51 years). Control (50, 54 years)	Drug therapy evaluation and management (DrugTEAM) included a (1) medication reconciliation (MR) service, (2) medication evaluation and management (MEM) service, (3) discharge pharmaceutical care transition (dPCT) service.	The control group received usual care	3 months	Face-to-face	The primary outcome was the average number of DRPs per patient at discharge. Secondary outcomes were medication adherence

Table S2. Full characteristics of the included studies**.**

No	Author, year	Design	Population	Sample size	Intervention	Comparator	Duration	Delivery format	Measured outcomes
9	Pehlivanli et al. (2023).	This was a prospective interventional study	Eighteen years and older, Predialysis patients (Stage 1–5 CKD), considering KDIGO classification, with or without comorbidity	Intervention: 269; age: 53.6	Interventions for each identified DRP were discussed with the prescriber, and appropriate recommendations were suggested to resolve the problem	NA	5 months	Real-time face-to-face	Drug-related problems
10	Vu et al. (2023)	Pre- and post-intervention	NA	Intervention: 20	Pharmacist-led intervention: “Positive Kidney Health”	NA	12 months	Face-to-face informed consent and receive the educational workbook	Progression of chronic kidney disease: UACR, eGFR
11	Alam et al. (2024).	A single-arm, pre- and post-intervention study design	Patients included were adults aged 18 years and older diagnosed with CKD (non-dialysis), receiving treatment at the outpatient nephrology department	Intervention: 370	Medication-related problems such as compliance, drug-drug interaction, frequency issues, such as administration problems or adverse drug reactions	NA	6 months	Face-to-face	Drug-related problems
12	Wickramasinghe et al. (2024).	A randomized controlled clinical trial	Patients attending the predialysis renal clinics and diagnosed by a consultant nephrologist to be in CKD Stages 4 or 5, were recruited	Intervention: 101; Control: 100	The drug and disease knowledge questionnaire was administered, and a "drug and disease information booklet"	Drug and disease knowledge questionnaire	12 months	Booklet	Knowledge of CKD

Table S3. The details of the impact on the clinical outcomes of patients with CKD.

No	Author, Year	Kidney function	Medication adherence	Drug related problems	Knowledge	Quality of life
		Results	**Results**	**Results**	**Results**	**Results**
1	Ghimirey et al. (2013)	NA	NA	NA	1. Knowledge = Diff +5.53 (p = 0.000) sig 2. Attitude = Diff +0.75 (p = 0.325) not sig 3. Practice = Diff +0.32 (p = 0.083) not sig	NA
2	Cabello-Muriel et al. (2014)	1. Stage 3 (mild) a. CrCl improvement = Diff. -0.9 (not sig) b. CrCl relative = Diff. -2.1 (not sig) 2. Stage 4-5 (severe and predialysis) a. CrCl improvement = Diff. +4.8 (p<0.05) sig. b. CrCl relative = Diff. +20.5 (p<0.05) sig.	NA	NA	NA	NA
3	Cooney et al. (2015)	1. Primary clinical outcome Systolic blood pressure (mmHg) among participants with baseline BP >130/80 mmHg = Diff +0.7 (p = 0.57) not sig. 2. Primary process measure PTH measured during study period = Diff +320 (p<0.001) sig. 3. Secondary clinical outcomes a. Blood pressure < 130/80 mmHg = Diff +8/12 (p = 0.84) not sig. b. Phosphorus = Diff +153 (p<0.001) sig. c. Ualb/Cr ratio = Diff +167 (p<0.001) sig.	1. Secondary process measures Medication Adherence = Diff -0.1 (p = 0.70) not sig.	NA	NA	1. Secondary clinical outcomes Quality of life = Diff +2.5 (p = 0.15) not sig.
4	Chang et al. (2016)	1. Proteinuria screening = Diff +4 (p = 0.05) not sig. 2. Achieved BP goal = Diff 0 (p = 0.9) not sig.	NA	NA	NA	NA
5	Lalonde et al. (2017)	1. eGFR = Diff +0.1 (sig NA) 2. Blood pressure a. Systolic = Diff -1.8 (sig NA) b. Diastolic = Diff -0.6 (sig NA)	NA	1. Total DRPs = Diff -0.02 (sig NA)	1. Knowledge = Diff +9.2 (sig NA)	NA

Table S3. The details of the impact on the clinical outcomes of patients with CKD.

No	Author, Year	Kidney function	Medication adherence	Drug related problems	Knowledge	Quality of life
		Results	**Results**	**Results**	**Results**	**Results**
		3. Glycated hemoglobin = Diff +0.1 (sig NA)				
6	Chandrasekhar et al. (2018)	NA	1. CKD stage 3 a. High = Diff +16 patients (p<0.001) sig b. Medium = Diff -16 patients (p<0.001) sig c. Low = Diff 0 (p<0.001) sig 2. CKD stage 4 a. High = Diff +25 patients (p<0.001) sig b. Medium = Diff -13 patients (p<0.001) sig c. Low = Diff -12 patients (p<0.001) sig 3. CKD stage 5 a. High = Diff +15 patients (p<0.001) sig b. Medium = Diff -12 patients (p<0.001) sig c. Low = Diff -3 patients (p<0.001) sig	NA	NA	NA
7	Khokar et al. (2020)	1. Creatinine (md/dL) = Diff -0.12 (p = 0.617) not sig 2. BUN (mg/dL) = Diff +0.98 (p = 0.799) not sig 3. Uric acid (mg/dL) = Diff -1.23 (p = 0.225) not sig 4. eGFR-EPI (mL/min/1.73 m^2) = Diff +9.27 (p = 0.096) not sig	1. Medication adherence = Diff -0.59 (p =0.042) sig.	NA	1. Knowledge = Diff -1.53 (p =0.022) sig.	NA
8	Song et al. (2021)	NA	1. Medication adherence = Diff -9 patients (p = 0.057) not sig.	1. Total number of DRPs at discharge = Diff +47 patients (p<0.001) sig.	NA	NA
9	Pehlivanli et al. (2023)	NA	NA	1. Total number of patients with DRPs and without DRPs = Diff +7 patients (p = 0.034) sig.	NA	NA

Table S3. The details of the impact on the clinical outcomes of patients with CKD.

No	Author, Year	Kidney function	Medication adherence	Drug related problems	Knowledge	Quality of life
		Results	**Results**	**Results**	**Results**	**Results**
10	Vu et al. (2023)	2. Kidney test results (eGFR, UACR) = Diff +30% (sig NA)	NA	NA	NA	NA
11	Alam et al. (2024)	NA	NA	1. Improper drug selection: a. Prescribing the wrong drug = Diff -68 patients (p =0.055) not sig b. Duplication of drug with similar effect = Diff -55 patients (p =0.001) sig c. Administration of stoppable drug = Diff -65 patients (p =0.005) sig d. Contraindication of drugs = Diff -26 patients (p =0.020) sig 2. Drug interaction = Diff -91 patients (p =0.032) sig 3. Failure to receive drugs = Diff -69 patients (p =0.012) sig 4. Overdose = Diff -65 patients (p =0.052) not sig 5. Subtherapeutic = Diff -51 patients (p =0.110) not sig 6. Poor compliance issues = Diff -64 patients (p =0.042) sig 7. Untreated indication = Diff -110 patients (p =0.004) sig 8. Drugs without indication (under-treated indication) = Diff -72 patients (p =0.072) not sig 9. Presence of adverse drug reactions = Diff -77 patients (p =0.062) not sig	NA	NA
12	Wickramasinghe et al. (2024).	NA	NA	NA	Initial (at 6 months) 1. Knowledge regarding the disease = Diff +1.00 (p = 0.421) not sig 2. Knowledge regarding drugs = Diff +1.00 (p =0.054) not sig	NA

Table S3. The details of the impact on the clinical outcomes of patients with CKD.

No	Author, Year	Kidney function	Medication adherence	Drug related problems	Knowledge	Quality of life
		Results	**Results**	**Results**	**Results**	**Results**
					3. Knowledge regarding food and beverages = Diff 0 (p =0.326) not sig 4. Knowledge regarding risk factors = Diff 0 (p =0.325) not sig At 12 months 1. Knowledge regarding the disease = Diff +3.00 (p<0.050) sig 2. Knowledge regarding drugs = Diff +3.00 (p<0.050) sig 3. Knowledge regarding food and beverages = Diff +6.00 (p<0.050) sig 4. Knowledge on risk factors = Diff +2.00 (p<0.050) sig	