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A network meta-analysis of therapies for hyperphosphatemia in CKD based on randomized trials

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To update the efficacy and safety of different drugs for the treatment of patients with hyperphosphatemia in chronic kidney disease, we conducted a network meta-analysis of 22 therapies for the treatment of uncontrolled hyperphosphatemia in patients with chronic kidney disease (CKD). All randomized controlled trials on hyperphosphatemia published from January 2013 to November 2023 were searched from CNKI, VIP database, Wanfang database, PubMed, Scopus, and Cochrane databases. Meta-analysis was used to evaluate the serum phosphorus, calcium levels, total effective rate and adverse events of patients with chronic kidney disease (CKD). Data collection and quality evaluation were carried out by three evaluators, RevMan (5.5.3) and Stata (1.3.0). A total of 71 RCTs, and 22 treatment strategies were included in this NMA. The results showed that all treatment strategies were effective in improving patients' blood phosphorus levels. Among them, SL + CT, CA + CC, SL and TCM had higher overall efficacy, RT, TCM and SL + CT had lower blood phosphorus levels, SL + CT, SL and NAM had lower blood calcium levels, and OAC, CC, NAM and SL had higher safety. Among them, SL + CT seems to be the most recommended treatment strategy. In addition, multidrug combination strategies usually have a higher efficacy and safety profile.

Keywords Hyperphosphatemia, Chronic kidney disease, Serum phosphorus, Serum calcium, Adverse events, Network meta-analysis

Chronic kidney disease (CKD) is one of the most prevalent non-communicable diseases globally, placing a heavy burden on healthcare systems. The incidence, prevalence, mortality and disability-adjusted life years of CKD are estimated to increase significantly globally, with more than 850 million people affected by CKD[1,2]. The ability of CKD patients to excrete phosphate from the body through the kidneys decreases, so the level of phosphate in the blood and body tissue increases with the decline of kidney function[3]. Especially in CKD patients with end-stage kidney disease (ESRD), hyperphosphatemia, a severe complication of CKD, will be widely prevalent. Hyperphosphatemia increases the level of fibroblast growth factor-23 (FGF23) and compensatory phosphate excretion in the kidney, thus increasing the release of parathyroid hormone by calcium-sensing receptors in parathyroid cells[4]. CKD can lead to calcium and phosphate deposits in blood vessels and other tissues, while also damaging bones and worsening kidney failure[5,6].

Hyperphosphatemia is one of the most common complications of CKD. Due to the significant effect of hyperphosphatemia on vascular calcification, resulting in an increase in the number of deaths from various cardiovascular diseases, hyperphosphatemia is often regarded as a "silent killer"[7,8]. Hyperphosphatemia at least partly explained the incidence of complex mineral and bone diseases associated with CKD, as well as hypocalcemia and decreased levels of 1–25 (OH) 2 vitamin D[9]. Specifically, the clinical management of hyperphosphatemia is a daily challenge for nephrologists because the phosphate overload in the diet is mainly due to phosphate "hidden" in food additives[10]. Hyperphosphatemia leads to increased FGF23 levels, compensatory renal phosphate excretion, inhibition of 1–25 (OH) 2 vitamin D production, and increased catabolism. However, further decline in renal function leads to an increased risk of hypocalcemia and hyperphosphatemia, which increases the release of parathyroid hormone through calcium-sensing receptors in parathyroid cells[4]. The management of hyperphosphatemia in CKD has evolved significantly over recent decades. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines initially established systematic recommendations for phosphate management in CKD patients, emphasizing the importance of maintaining serum phosphorus within target ranges. The recently updated 2024 KDIGO guidelines have introduced a more comprehensive "3D" approach (Diet, Drugs, and Dialysis), providing evidence-based recommendations that extend beyond traditional

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phosphate binder therapy. These guidelines emphasize individualized treatment strategies, considering factors such as dietary phosphate sources, various phosphate-binding agents, and other therapeutic interventions based on patient-specific characteristics.

Studies suggested that appropriate phosphorus reduction is considered to play an essential role in the health and longevity of patients with CKD, and traditional treatments for hyperphosphatemia include dietary restrictions and hemodialysis[11]. At present, the treatment of hyperphosphatemia in CKD patients depends on non-calcium-based binders or calcium-based agents, as well as some iron-containing binders and phosphate transport inhibitors[12–14]. At the same time, in China and other parts of Asia, some traditional Chinese medicine prescriptions are being used[15]. Currently, therapeutic agents exist for hyperphosphatemia that can effectively reduce serum phosphorus levels. However, safety issues need to be considered and discussed during the selection of drugs to be administered, mainly due to the lack of randomized controlled trials (RCTs) for hard endpoints. This review addresses the differences between available phosphate binding agents, novel compounds, and therapeutic approaches and the circumstances under which phosphate reduction in the CKD phase should be initiated and maintained. We surveyed 22 commonly used and effective clinical strategies for the treatment of hyperphosphatemia, including 14 drugs, including Traditional Chinese Medicine (TCM), calcium carbonate (CC), lanthanum phosphate (LC), and ferric citrate (FC), sucrose iron oxyhydroxide (PA21), magnesium carbonate (CM), Bixalomer (BL), Calcitonin (CT), Colistin (CL), Sevelamer (SL), calcium acetate (CA), Tenapanor (TP), Oral activated charcoal (OAC), and Nicotinamide (NAM).

Results

Patient characteristics

A total of 2518 potentially relevant articles were screened for inclusion in the meta-analysis, of which 2447 were excluded due to meta-analysis or review articles, duplication of results, and. The remaining 71 RCTs with a total of 14,429 patients were included in this meta-analysis, and these studies were not subject to any language restrictions[16–87]. The literature search and study selection process is shown in Fig. 1A. This study involved a total of 22 treatment strategies. The number of men and women was approximately equal, and the average age was around 57 (Supplementary Table S1). In addition, 12 studies clearly reported the type of blinding used. We assessed the quality of included studies according to the Cochrane risk of bias tool. Each assessment principle was categorized as "high risk," "low risk," and "unclear". This showed that the included studies were not at high risk (Fig. 1B). All patients were diagnosed with hyperphosphatemia according to clear diagnostic criteria in regular hospitals.

Efficacy outcomes

To further explore which treatment strategy was most effective, our study abstracted Surface Under the Cumulative Ranking Curve (SUCAR) to additionally rank the primary outcome improvements of treatment strategies in aggregate (Fig. 2A). The results showed that SL + CT (80.4), CA + CC (69.2), SL (58.9) and TCM (58.6) were ranked in the top four of the treatment strategies and among them SL and TCM seemed to show the same therapeutic effect. However, CC (18.7) and CA (28.2) were less effective treatment strategies. Since the combined ORs for each treatment strategy were derived from direct and indirect comparisons between treatment strategies, to further validate the accuracy of the results of this study, a sensitivity analysis of this result was performed using the TRIM and FILL methods (Fig. 2B). It was found that filling blank samples had no significant effect on OR values, and therefore the results of this study were stable.

Major serum biochemical parameters

As shown in Fig. 3A, we found 51 RCTs that reported on blood phosphorus levels, including 18 treatment strategies. In the assessment of blood phosphorus levels, the results showed that almost all treatment strategies, except placebo, reduced serum phosphorus levels. SUCAR results showed that RT (76.5), TCM (74.5) and SL + CT (73.6) were significantly superior to other treatment strategies in reducing serum phosphorus (Fig. 3B). We plotted a funnel plot of different treatment strategies to test for publication bias, and the distribution of scatter points in the plot was slightly uneven, suggesting some publication bias (Fig. 3C). RT (OR, 0.39; 95% CrI 0.02–0.75), TCM (OR, 0.42; 95% CrI 0.08–0.76) and SL + CT (OR, 0.19; 95% CrI −0.27 to 0.65) significantly reduced serum phosphorus levels compared with placebo (Supplementary Table S2). In the assessment of serum calcium levels, there were considerable differences among the 17 treatment strategies (Fig. 4A). The results showed that SL + CT (87.1), SL (74.3) and NAM (67.8) were significantly superior to other treatment strategies in reducing serum calcium (Fig. 4B). SL + CT (OR, 0.51; 95% CrI −0.19 to 1.21), SL (OR, 0.42; 95% CrI 0.08–0.77) and NAM (OR, 0.21; 95% CrI −0.49 to 0.91) significantly lowered serum calcium levels compared with placebo (Supplementary Table S3). In contrast, MCT had slightly worse results for serum calcium levels. The distribution of scatter points in the funnel plot is slightly uneven, suggesting some publication bias (Fig. 4C).

Adverse reaction rate

Seventy-one studies reported this indicator, with the main adverse reactions included nausea, vomiting, constipation, and diarrhea (Fig. 5A). As shown in supplementary Table S4, we use Stata (13.0) to compare all treatment strategies and gain the advantages of each treatment strategy over other treatment strategies. Then we draw SUCAR to further rank the secondary outcomes of treatment strategies to further explore which treatment strategy is the best (Fig. 5B). All treatment strategies were evaluated according to the SUCRA method. The analysis found that the OAC (21.9), CC (27.8), NAM (34.7) and SL (39.9) treatments exhibited the lowest incidence of adverse events. Conversely, the PA21 (70.3), CA + CC (67.8), and BL (67.1) treatments demonstrated a heightened risk of adverse events compared to the other treatment modalities. We performed a sensitivity

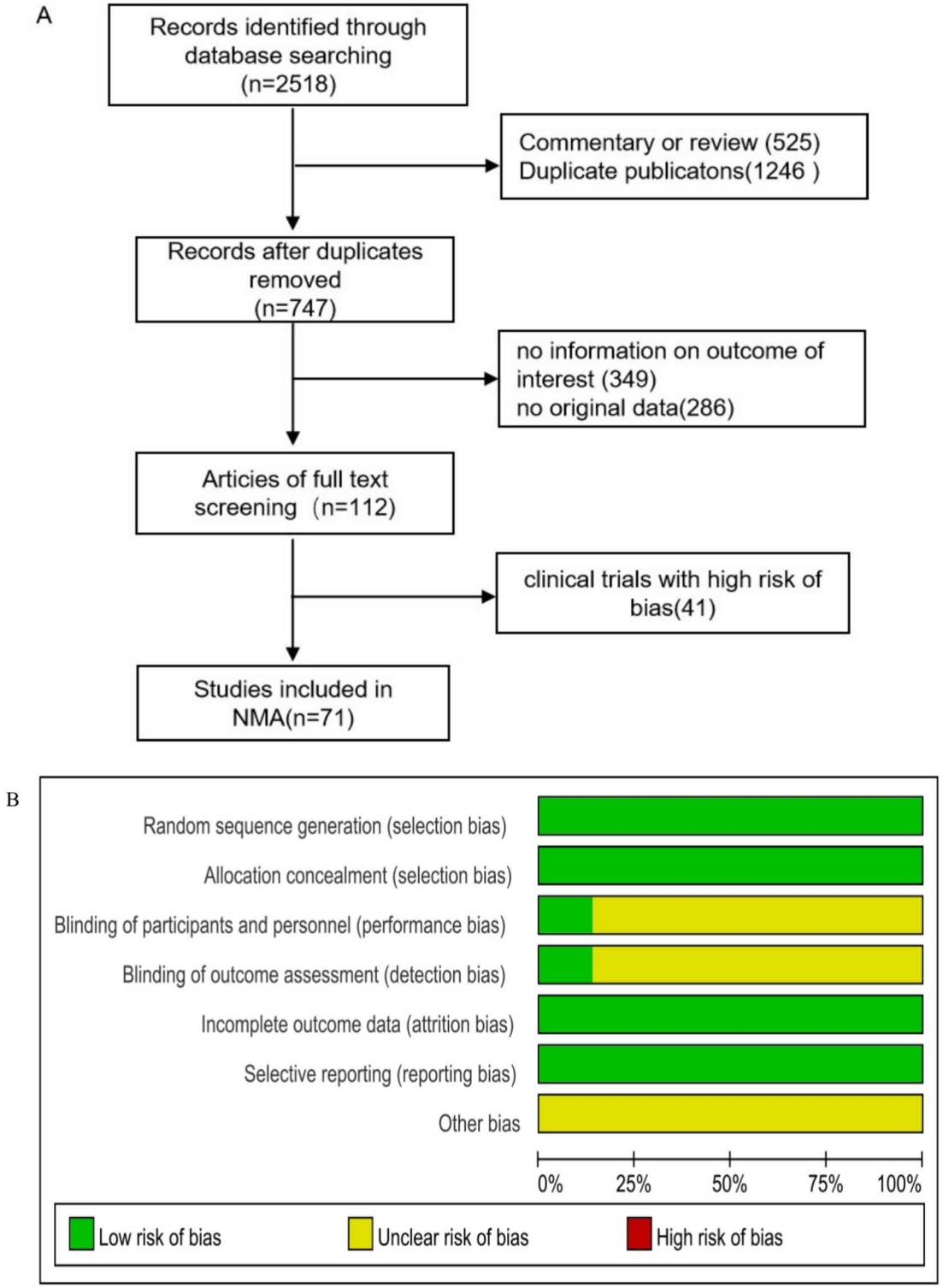
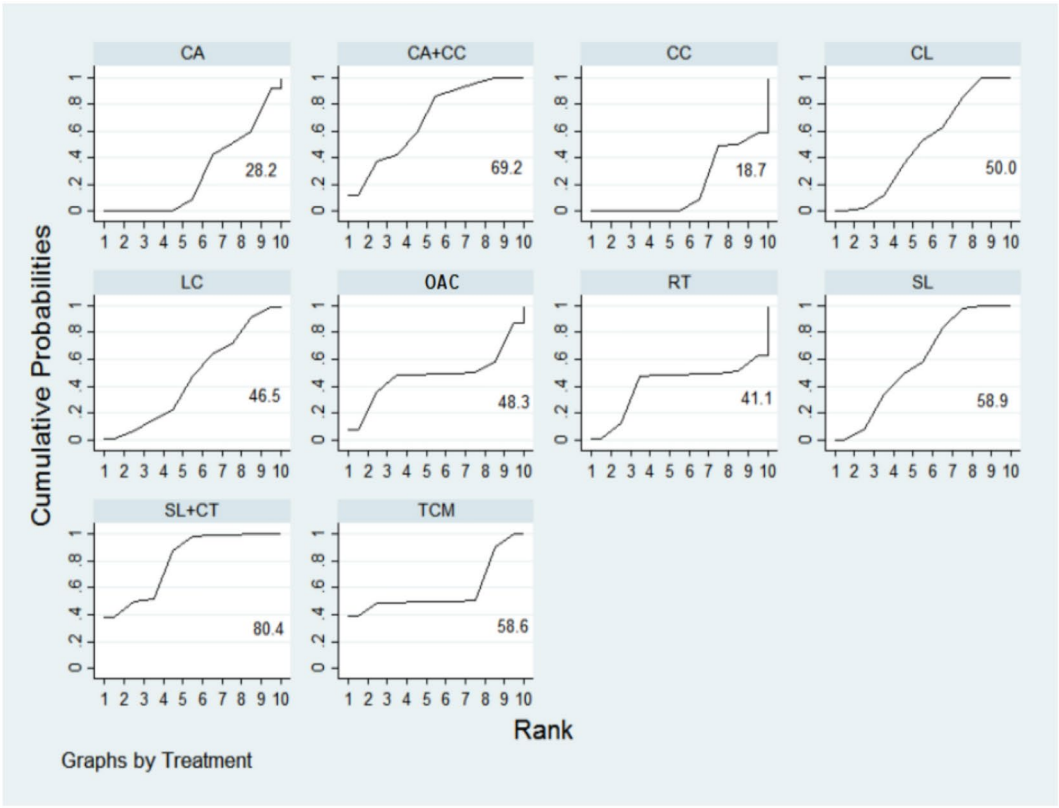


Fig. 1. (**A**) Study selection flowchart search results flowchart and selection of included studies; (**B**) Methodological quality assessment of risk of bias of included studies.

analysis of this result using the TRIM and FILL methods (Fig. 5C). It was found that filling the blank samples had no significant effect on the OR values and therefore the results of this study were stable.

Discussion

Hyperphosphatemia is one of the most common complications of chronic kidney disease (CKD) and is widely found in patients with CKD stages 3–5, especially in maintenance hemodialysis patients[14,88]. Hyperphosphatemia



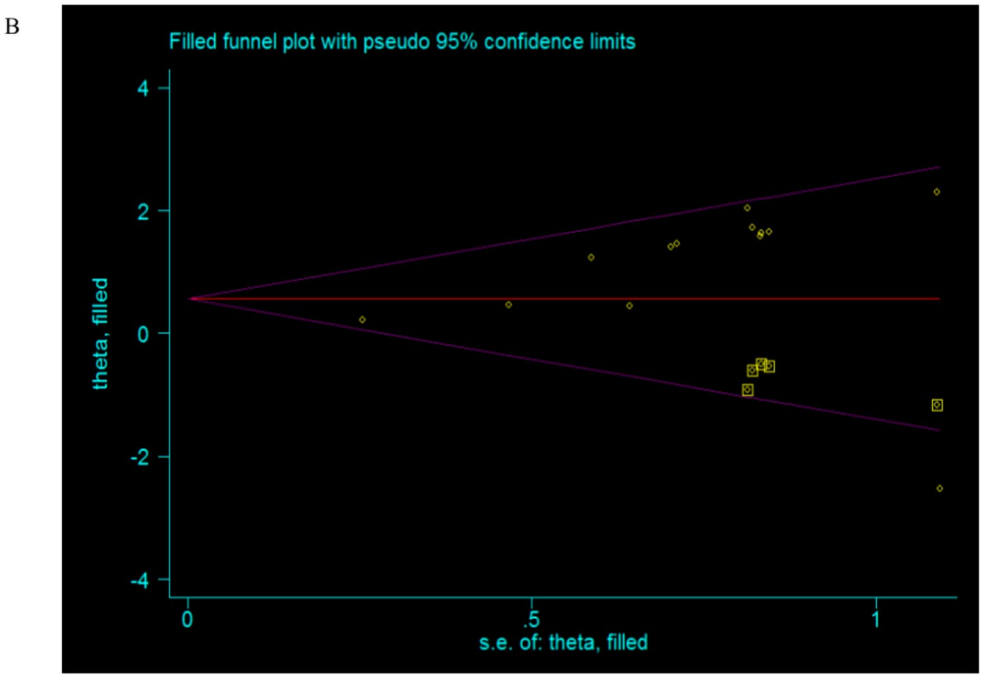


Fig. 2. (**A**) Efficacy ranking of treatment strategies; (**B**) Sensitivity analysis of this study.

can promote the progression of cardiovascular disease in patients with CKD and is closely associated with increased mortality in patients with advanced CKD, where blood phosphorus regulation is metabolically in compensated, and blood phosphorus is significantly elevated[3,89]. However, drugs commonly used to treat hyperphosphatemia have been shown to improve patients' blood phosphorus levels while producing a variety of adverse effects, including nausea and vomiting[90,91].

This study provides a total of 71 studies in this updated review analyzing the safety and efficacy of 22 commonly used clinical hyperphosphatemia therapies versus placebo for treating patients with hyperphosphatemia in CKD.

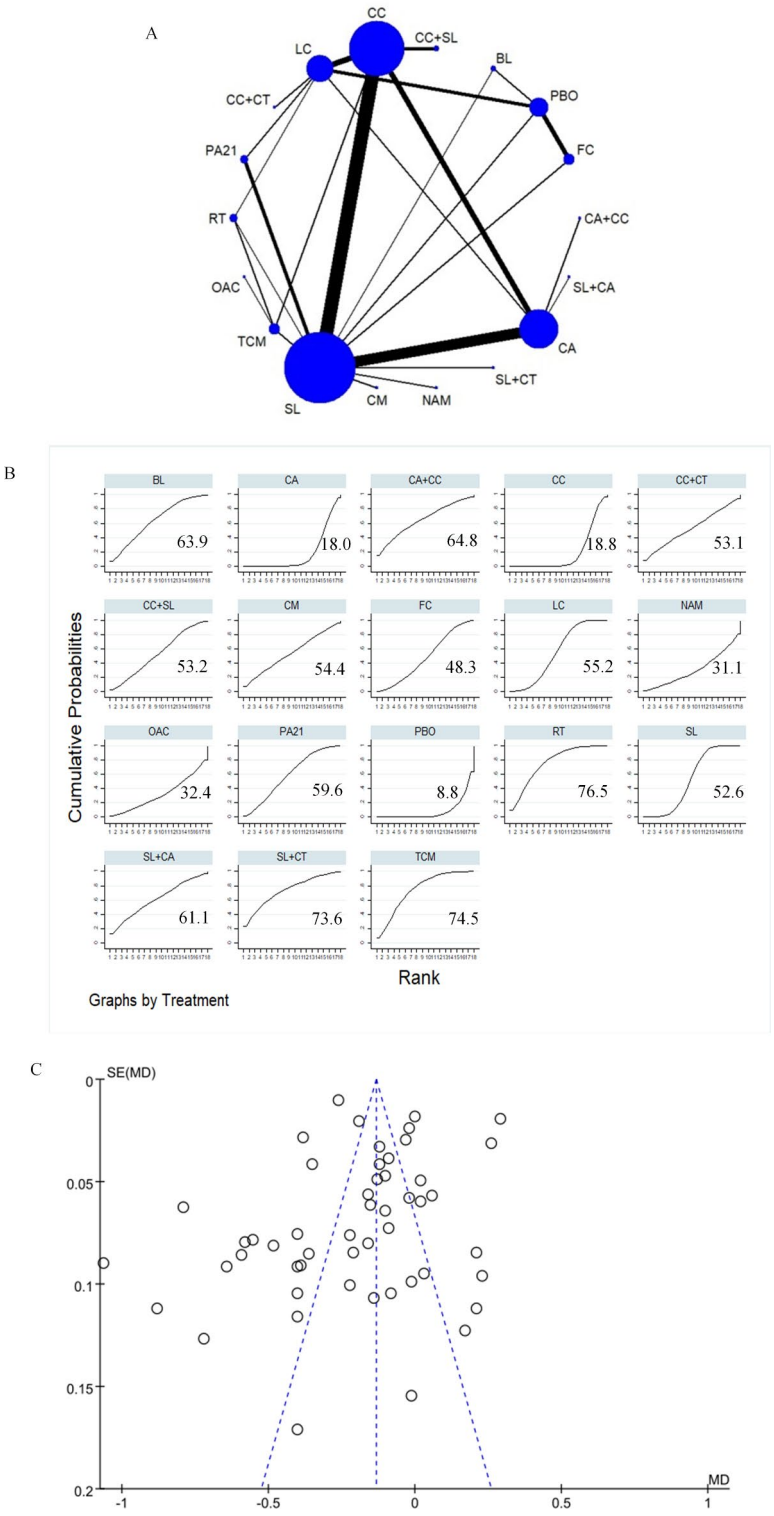


Fig. 3. (**A**) Comparison network included in the analysis; (**B**) ranking of blood phosphorus levels for the 18 treatment strategies; (**C**) publication bias of this study.

This meta-analysis showed that SL + CT, CA + CC, SL and TCM were the highest ranked effective therapeutic strategies in CKD patients with hyperphosphatemia, respectively. The report showed that RT, TCM and SL + CT reduced serum phosphorus and SL + CT, SL and NAM reduced serum calcium. However, the effect of the use of non-calcium-based phosphate binders on other biochemical parameters of mineral metabolism (e.g., PTH or FGF 23) is uncertain. We report an increased risk of adverse effects with PA21, CA + CC, and BL compared with placebo. Clinical outcome and mortality data have been reported in fewer trials, and the effect on cardiovascular

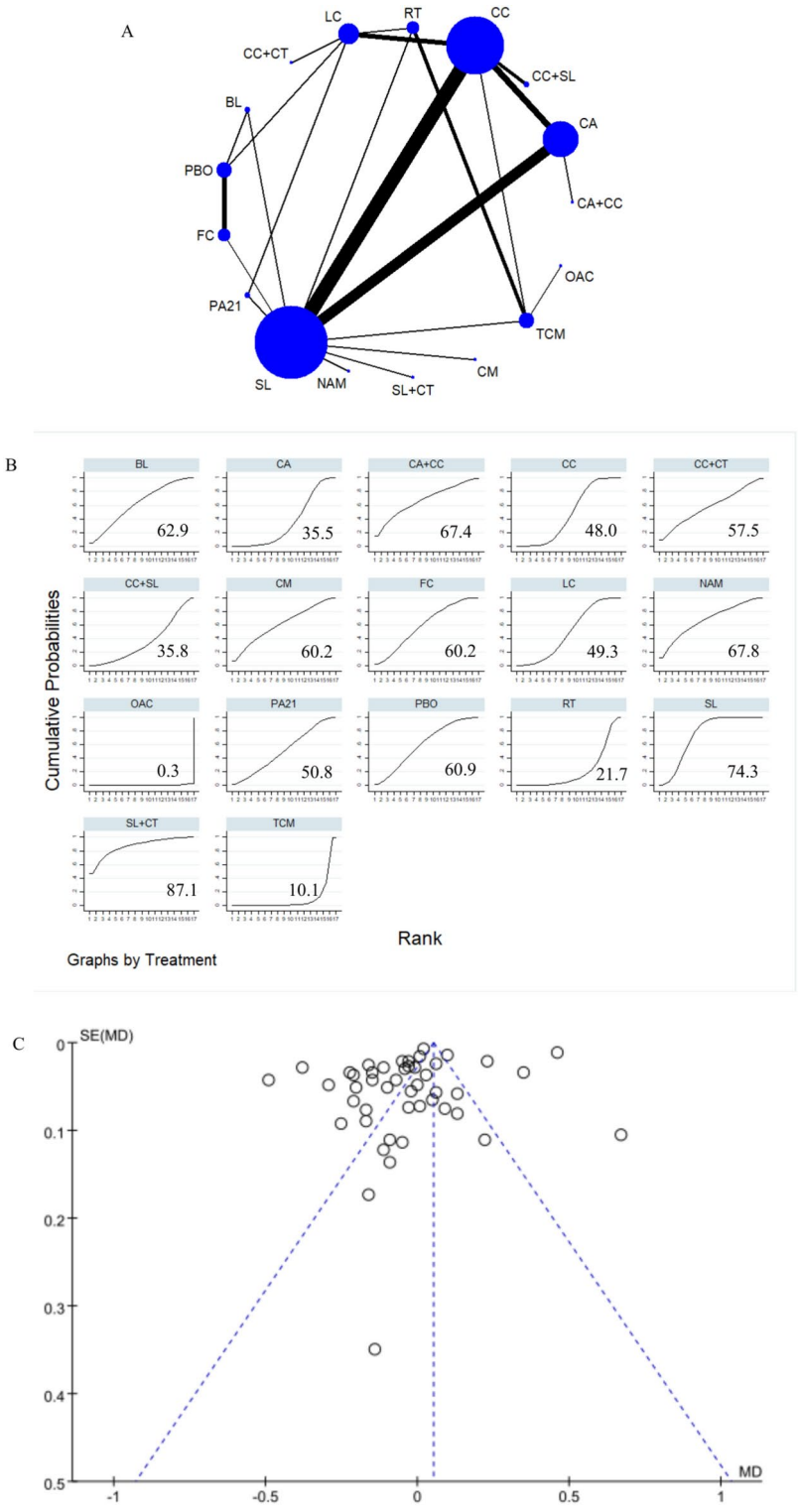


Fig. 4. (**A**) Comparison network included in the analysis; (**B**) ranking of blood calcium levels for the 17 treatment strategies; (**C**) publication bias of this study.

events or all-cause mortality is uncertain. In addition, this study also observed the bias and stability of each outcome, and no significant bias or instability was found, which also improved the accuracy of the results of this study. However, we constructed funnel plots for different treatment strategies to examine the presence of publication bias. The scatter of points displayed slight asymmetry, indicating a potential degree of publication bias. Methods such as the trim-and-fill approach could be considered to adjust for this bias; however, further analysis is needed to identify the specific causes. Furthermore, it is worth noting that the SUCRA values for the

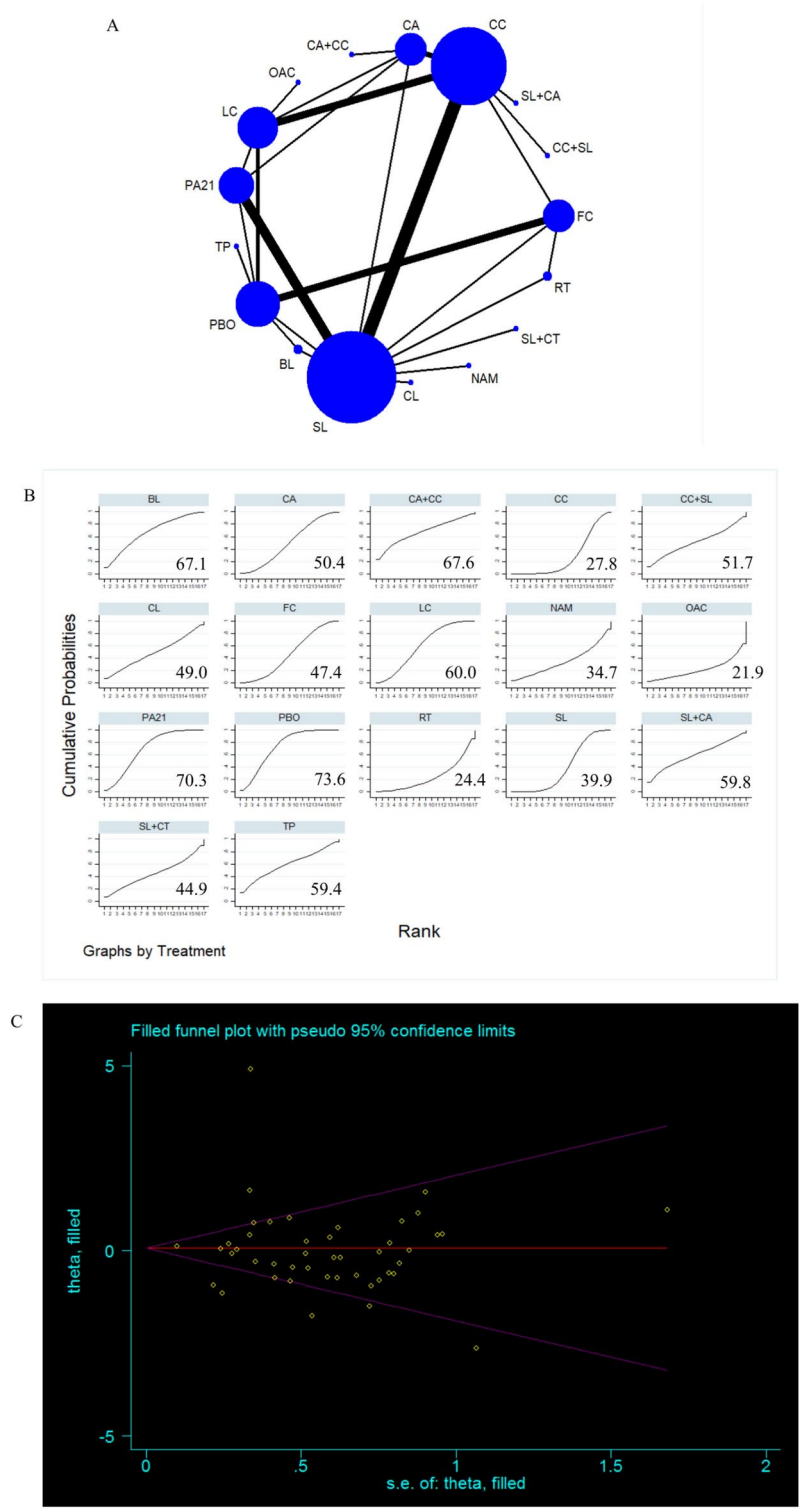


Fig. 5. (**A**) Comparison network included in the analysis; (**B**) ranking of adverse effects of the 17 treatment strategies; (**C**) publication bias of this study.

first three treatment strategies were very close in the two results of this study. Therefore, although they have significant advantages over other treatment strategies, they do not represent the advantages and disadvantages of the three treatment strategies.

SL, as a broad-spectrum drug for hyperphosphatemia, is currently the most used clinically[4,92–95]. It has good efficacy in reducing blood phosphorus levels, but common adverse effects are constipation, abdominal discomfort, nausea, and dyspepsia, with an overall incidence of 25.6%[88,96,97]. Yang et al.[98] compared the effects

of iron-based phosphate binders, calcium-based phosphate binders, and placebo using network mate analysis. It was concluded that iron-based phosphate binders were the more desirable drug, followed by calcium-based phosphate binders, while balancing efficacy and safety. In a Meta-analysis using randomized controlled trials, Patel et al.[99] found that Sevelamer had a lower all-cause mortality rate than calcium-based phosphate binders in patients with CKD stages 3–5D. Habbous et al.[100] found that patients taking Sevelamer had lower blood calcium levels were much lower in patients taking Sevelamer than in those taking calcium-based binders. However, the lack of indirect evidence in previous meta-analyses prevents these studies from drawing comprehensive conclusions about which treatment is most recommended when more than three or two combinations are available. In addition, some direct comparisons could not be found in previous meta-analyses. For example, there were no studies comparing iron-based and magnesium-based phosphate binding agents, as well as TCM. The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 clinical practice guideline has made significant updates in the management of hyperphosphatemia for CKD patients (stages 3a to 5D). The new guideline introduces a comprehensive "3D" approach (Diet, Drugs, and Dialysis) instead of focusing solely on phosphate binders. For dietary management, the 2024 guideline provides more specific recommendations compared to the 2009 version, emphasizing the importance of phosphorus sources: plant-based phosphorus is less bioavailable than animal-based phosphorus, and inorganic phosphorus additives in processed foods should be restricted. While the guideline strongly recommends individualized dietary phosphorus restriction combined with other treatments, it acknowledges that current evidence supporting hard clinical outcomes remains limited, highlighting the need for further research in this area[101]. In this context, our study comprehensively evaluated various therapeutic interventions through multiple dimensions, including treatment efficiency, key serum indicators, and adverse effects. Our findings demonstrated that all investigated drugs exhibited superior or comparable efficacy in phosphorus reduction compared to placebo. Furthermore, through the Surface Under the Cumulative Ranking Curve (SUCRA) analysis, we established a comprehensive ranking of all interventions across different outcomes, providing valuable insights for clinical decision-making.

Conclusion

This paper shows that SL + CT, CA + CC, SL and TCM have higher overall efficacy, RT, TCM and SL + CT have lower blood phosphorus levels, SL + CT, SL and NAM have lower blood calcium levels, and OAC, CC, NAM and SL have lower incidence of adverse events. SL + CT seems to be the most recommended intervention. In addition, multiple drug combinations are usually more efficacious and drug combinations have greater potential to improve the efficacy and safety of blood phosphorus level disorders. Finally, we were unable to calculate the overall effectiveness of all treatments because most studies did not provide data on overall effectiveness. Overall, this NMA provides clinicians with very valuable information on common treatment strategies.

Methods

Search strategy and selection criteria

Our study protocol was registered with Prospero (https://www.crd.york.ac.uk/PROSPERO/) and approved on December 31, 2021. The registration number is CRD42021291021. We searched databases, including China National Knowledge Infrastructure (CNKI), Wanfang database, VIP Medical Information System, PubMed, Embase, and Cochrane Library, which were searched from January 1, 2013 (at the end of the previous systematic review) to November 1, 2023. There were no language restrictions. The search terms were ((chronic kidney disease) AND (hyperphosphatemia)) AND (randomized controlled trials) (title/abstract), respectively. We included parallel-group randomized clinical trials with four weeks or longer follow-up in which patients with CKD were assigned to phosphate binders, Traditional Chinese Medicine, or routine treatment.

Data extraction and study selection

Two reviewers (Yuanyuan Chen and Congyang Zheng) independently screened the titles and abstracts of citations and reviewed the full text of all citations that were considered to be eligible. Record the basic information included in the study (including the name of the study, the number of patients, treatment strategy, mode of administration, dose, duration, results, etc.). Because experimental researchers generally do not report changes in the values of continuous variables from the beginning to the end of treatment, we only consider the values at the end of treatment. In the absence of sufficient detailed data on the published results, the author contacted the test investigators by e-mail or standard email to request more information. The reviewer resolved any differences through discussion. Two judges (Tao Wang and Haiyang Hu) reviewed the data extraction. The inclusion criteria for RCTs were as follows: (1) Patients with CKD diagnosed with hyperphosphatemia, including those on peritoneal dialysis or hemodialysis; (2) All patients with hyperphosphatemia were diagnosed with blood phosphorus levels > 1.45 mmol/L; (3) the sex and age of the patients are not restricted; (4) there is no restriction on literary language. The exclusion criteria are as follows: (1) repeatedly published studies; (2) incomplete or incorrect data; (3) Animal experiments and literature review. The bias risk in the included study was strictly evaluated by using the Cochrane bias risk tool.

Statistical analysis

Our treatment strategy network was conducted using Revman (5.3) and Stata (13.0). We conducted the study using a random effects model and an inconsistency model to make the results more accurate. This study used mean differences (MDs) and corresponding 95% confidence intervals (CrIs) to evaluate continuous prognoses, such as serum phosphate and calcium. For dichotomous variables, we calculated the odds ratios (ORs) and described them with 95% confidence intervals. For all primary and secondary outcomes, we also used contour funnel plots to detect publication bias and assessed the stability of the results using the trim-and-fill method.

In this study, we utilized the SUCRA methodology to provide a systematic ranking of treatment efficacy, which aids in distilling complex network meta-analysis results into more comprehensible insights. Additionally, the TRIM and FILL method was used for sensitivity analyses to detect and correct for potential publication bias by hypothesizing the existence of unpublished studies with negative results. This approach adjusts the analysis to ensure more robust and reliable conclusions. Finally, we completed the NMA within a frequency domain framework. The funder did not intervene in study design, data collection, data analysis, data interpretation, or article writing.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Author contributions
C.Y.Z. and Y.Y.C. devised the project and guided all steps. C.Y.Z., J.L. and T.W. conducted rigorous data analysis. C.Y.Z. and Y.Y.C. carried out the writing of the article. Y.Y.C. and H.Y.H. participated in the revision of the article. All authors participated in the discussion of the manuscript and agreed to submit it.

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Declarations

Competing interests
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