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Systematic Review
Impact of Tacrolimus Versus Cyclosporine on Overall Response, Complete Remission and Relapse in Nephrotic Syndrome: A Systematic Review and Meta-Analysis

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Abstract

Background and Objective: Nephrotic syndrome requires effective treatment to reduce symptoms and prevent recurrence. As immunosuppressants, tacrolimus and cyclosporine are commonly used, although research on their efficacy and outcomes is continuing. Patients diagnosed with nephrotic syndrome were included in this meta-analysis to determine the impact that immunosuppressants such as tacrolimus and cyclosporine have on the overall response, full remission and recurrence of the condition. **Materials and Methods:** The Embase, PubMed and Cochrane Library databases were searched to do this systematic review and meta-analysis. Using predefined criteria, records were screened for relevance, the risk of bias was assessed with Cochrane and Newcastle-Ottawa tools and data was extracted for meta-analysis. The included studies were limited to those comparing tacrolimus with cyclosporine in nephrotic syndrome patients regarding overall response, complete remission and relapse rates. **Results:** The qualitative and quantitative synthesis comprised 8 investigations. The meta-analysis of the overall response, complete remission and relapse yielded no statistically significant difference between tacrolimus and cyclosporine. The relative risk (RR) for overall response was 1.03 (95% CI [0.97, 1.10], p = 0.34; for complete remission, 1.1057 (95% CI [0.9986, 1.2244], p = 0.05) and for relapse was 1.17 (95% CI [0.79, 1.74], p = 0.43). The entire response data displayed a minimal probability of publication bias, as indicated by the funnel plot. **Conclusion:** This examination found no significant difference in nephrotic syndrome response, complete remission or recurrence rates between tacrolimus and cyclosporine. These findings suggest that patient environment and clinical factors may affect drug choice. Investigating these outcomes requires further research and high-quality investigations.

Key words: Nephrotic syndrome, tacrolimus, cyclosporine, relative risk, complete remission, relapse rates

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

A group of medical disorders known as nephrotic syndrome includes proteinuria, hyperlipidemia, hypoalbuminemia and edema[1]. This glomerular disease affects both adults and children, with significant variability in its cause, pathology and response to therapy[2]. The syndrome's management is pivotal, not only to alleviate symptoms but also to prevent complications such as infections, thrombosis and progressive kidney damage leading to chronic kidney disease[3]. Immunosuppressive agents are central to the therapeutic approach, which aims to reduce the immune system's activity, thus ameliorating proteinuria and improving renal function[4].

Tacrolimus and cyclosporine are two immunosuppressants that are essential to the nephrotic syndrome therapy paradigm[5]. These calcineurin inhibitors operate by suppressing T-cell activation, but their specific impacts on the disease course and patient outcomes have been a focus of clinical investigation[6]. Despite the widespread use of these agents, the medical community continues to grapple with questions regarding their comparative effectiveness in achieving overall response, complete remission and rates of relapse[7].

Historically, cyclosporine held a prominent place in treatment regimens due to its earlier introduction and initial evidence of efficacy[8]. However, subsequent studies have highlighted the potential of tacrolimus as a viable alternative, with some suggesting a more favorable side-effect profile and possibly greater effectiveness in inducing remission[9]. Yet, these findings are not unequivocal and variability in study designs, patient populations and treatment protocols has resulted in a landscape of evidence that is heterogeneous and often conflicting[10].

The uncertainty surrounding the relative benefits and drawbacks of tacrolimus versus cyclosporine in nephrotic syndrome has led to a need for a thorough synthesis of the available literature. In order to address that need, this research presents a comprehensive review and meta-analysis of the relevant literature with the goal of elucidating how different medications affect the overall response, full remission and recurrence rates in this patient population.

Previous studies by Lombel *et al.*[11] have laid the groundwork for understanding the intricacies of treatment response in nephrotic syndrome. Case series and observational studies have given way to more complex Randomised Controlled Trials (RCTs), which offer a higher degree of evidence, in the literature. Nevertheless, results across studies have been disparate at times, necessitating a comprehensive approach to data synthesis. For instance, some RCTs and observational studies have suggested that tacrolimus may be superior in inducing complete remission, while others have reported no significant differences between the two drugs[9,12]. These conflicting results underscore the complexity of treating nephrotic syndrome and the multifaceted nature of the disease's response to immunosuppression.

Although there are several immunosuppressants, tacrolimus and cyclosporine are among those that are most commonly prescribed. However, research on the effectiveness and effects of these medications is still ongoing. According to the findings of this systematic review and meta-analysis, there was no significant difference between tacrolimus and cyclosporine in terms of the overall response, rates of complete remission or recurrence in patients who were diagnosed with nephrotic syndrome. By conducting an extensive search of databases such as PubMed, Embase and the Cochrane Library and employing rigorous criteria for including studies, this paper seeks to overcome the limitations of individual studies[13]. Utilising reliable instruments to evaluate the possibility of bias, such as the Cochrane and Newcastle-Ottawa tools, enhances the validity of the results[14,15].

Hence, this comprehensive research was undertaken to evaluate the influence of immunosuppressants such as tacrolimus and cyclosporine on the overall response, complete remission and recurrence of patients with nephrotic syndrome.

MATERIALS AND METHODS

Search strategy and criteria for selection: The present study was performed in the Second Affiliated Hospital of Zhejiang University School of Medicine, China from August to November, 2023. Three internet databases-Embase, PubMed and Cochrane Library (Trials)-were thoroughly searched to find research comparing the effects of tacrolimus and cyclosporine on nephrotic syndrome. To guarantee that the most recent research was included, the search was extended until April 25, 2024. Table 1 provides a thorough search technique that is specific to each database. A combination of free-text keywords and Medical Subject Headings (MeSH) phrases about tacrolimus, cyclosporine and nephrotic syndrome was included in the search. To combine search words the Boolean operators "AND" and "OR were utilised". There were no publication date limitations and the search was restricted to English-language publications only.

Criteria for eligibility: All studies that satisfied the following predetermined requirements were taken into consideration for inclusion: (1) They had to be RCTs, cohort studies or case-control studies; (2) They had to compare the effectiveness of cyclosporine and tacrolimus in treating patients with nephrotic syndrome and (3) They had to report on at least one of the outcomes listed below: Overall response, relapse rates or complete remission. Studies were excluded based on pre-established criteria: Animal studies, case reports, irrelevant topics, meta-analyses, non-English publications, protocols, reviews, inaccessible full texts or a lack of reported efficacy indicators. Duplicate publications reporting the same patient population and outcomes were also excluded.

Study selection: The titles and abstracts of the retrieved records were reviewed for possible relevancy by two separate reviewers. All potentially relevant studies' full texts were acquired and they were then further examined to make sure they met the requirements for inclusion and exclusion. Conflicts among reviewers were settled by conversation or if required, by seeking advice from a third reviewer.

Data extraction: Using a standardised data extraction form, two independent reviewers extracted data for every study that was included. The data that was retrieved contained research characteristics like nation, study design, pathologic type, follow-up duration, intervention details, sample size, demographic information (number of males/females, age) and outcomes about the overall response, complete remission and relapse rates. If further information or clarification is needed When any additional information or explanation, approach the authors of the study.

Bias assessment risk: Using the proper instruments, the included studies' quality was evaluated. The Cochrane Collaboration's technique for evaluating bias risk was used to examine randomized controlled trials. Random allocation concealment, sequence generation, participant and staff blinding, outcome assessment blinding, insufficient outcome data, selective reporting and other biases are the seven particular areas that this instrument evaluates. Every domain received a risk of bias rating of low, uncertain or high. The Newcastle-Ottawa Scale, which assesses research group selection, group comparability and exposure or outcome determination, was used to evaluate observational studies. A maximum of nine stars were given to studies for each quality item. Two writers independently examined each paper and disagreements were settled by conversation or by seeking the opinion of a third reviewer.

Statistical analysis: Review Manager (RevMan) version 5.4.1 was utilized to conduct the meta-analyses. The effect sizes were shown as 95% confidence intervals (CIs) around risk ratios (RRs) for recurrence, total response and full remission. The I^2 statistic and the Chi-squared test were used to measure the heterogeneity among the studies; I^2 values of 25, 50 and 75%, accordingly, indicated low, moderate and high heterogeneity. When heterogeneity was low to moderate (I^2 <50%), a fixed-effect model (Mantel-Haenszel technique) was employed for meta-analysis; otherwise, a random-effects model was utilised. Using funnel plots, where each study was displayed according to the effect magnitude and its standard error, publication bias was evaluated. To assess the possible risk of bias across the studies reflecting on each outcome, symmetry across the vertical line was employed. Set to $p<0.05$, the level of statistical significance was maintained.

RESULTS

Search strategy and study selection: A comprehensive overview of the search methodology used in the three main databases, such as PubMed, Embase and the Cochrane Library. The search strategies were tailored to each database to ensure comprehensive retrieval of relevant studies. The Keywords such as "tacrolimus", "cyclosporine" and "nephrotic syndrome" were used in various combinations with Boolean operators AND and OR to filter the studies related to the research question. Similarly, in Embase and Cochrane Library, the search strategies were adapted according to the taxonomy and indexing terms used in these databases, ensuring a robust search framework aimed at capturing a wide array of pertinent research.

The flow diagram for the study selection procedure used in this systematic review and meta-analysis was shown in Fig. 1. Initially, database searches turned up a total of 639 entries. After duplicates were eliminated, 611 entries were screened using the title and abstract; this process resulted in the elimination of 599 records due to factors including lack of relevance to the topic, language barriers and inappropriate study design or publication type. The remaining 12 articles underwent full-text assessment for eligibility, resulting in the exclusion of four articles due to accessibility issues or lack of relevant efficacy indicators. Consequently, eight studies were deemed suitable for inclusion and were subjected to both qualitative and quantitative synthesis. The results of this systematic review are more valid since only high-quality and pertinent papers were included in the meta-analysis thanks to this rigorous selection approach.

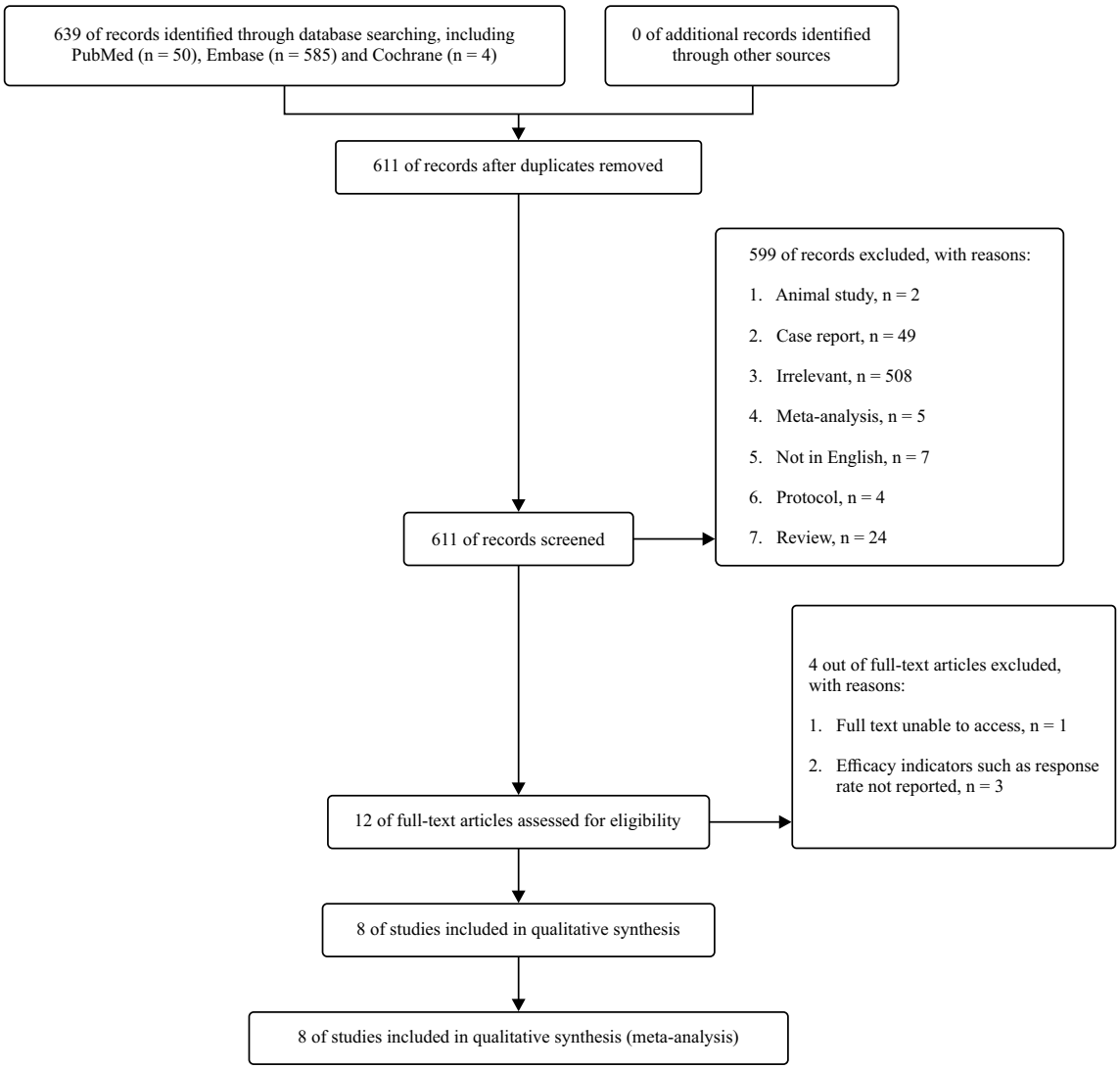

Fig. 1: Study selection process flow diagram

Included study characteristics: In the study, eight papers[16-23] were considered appropriate for inclusion and underwent both qualitative and quantitative synthesis. The primary features of the eight research that make up this systematic review and meta-analysis were displayed in Table 1, encompassing a diverse range of study designs, pathologic types of nephrotic syndrome and varying follow-up periods. The geographic spread of the studies covered countries like China, India and Pakistan, which provided insights into the potential regional variations in treatment response. A thorough comparison of the effects of tacrolimus and cyclosporine was made possible by the use of prospective cohort studies, retrospective cohort studies and Randomised Controlled Trials (RCTs).

The majority of pathologic categories reported in these investigations were IgM Nephropathy (IgMN), Mesangioproliferative Glomerulonephritis (MsPGN), Focal Segmental Glomerulosclerosis (FSGS) and minimal change disease (MCD). Follow-up periods across studies varied significantly, ranging from as short as 6 months to as long as 74 months. Such variability provided an opportunity to assess the short-term and long-term impacts of the interventions.

The studies compared the administration of tacrolimus and cyclosporine across a total sample size of 487 patients. The distribution of interventions indicated that a considerable number of participants received either tacrolimus or cyclosporine, with sample sizes ranging from 11 to 50 for tacrolimus and 12 to 60 for cyclosporine. The studies did not uniformly report the gender distribution (M/F) or provide complete information, indicating a need for caution when interpreting gender-specific responses to the treatment.

The age of participants varied widely from infants as young as approximately 1 year to adults up to 33.8 years, suggesting that the findings could be relevant to a broad age spectrum of patients with nephrotic syndrome. However, the mean ages differed within and between studies, which may influence the treatment outcomes. All things considered, the included studies provide a wealth of data to compare the effects of cyclosporine and tacrolimus on nephrotic syndrome patients, though the heterogeneity in study designs, population characteristics and follow-up times necessitated a careful approach to data synthesis and analysis.

Evaluation of the bias risk in the included studies: The Cochrane risk of bias method was used to assess the risk of bias for the RCTs that were included in the systematic review, as shown in Table 2. Chin *et al.*[21] and Choudhry *et al.*[22] showed little chance of bias in the domains of allocation concealment, random sequence creation, partial outcome data and selective reporting, indicating that these areas had sound scientific practices. Regarding the blinding of outcome evaluation, both investigations indicated an unknown risk of bias. This lack of clarity in blinding could potentially influence the detection biases. However, the overall impact on the study outcomes appears mitigated by robust procedures in other areas of bias assessment.

The Newcastle-Ottawa Scale is used to summarise the risk of bias evaluations for the cohort studies in Table 3. This assessment focuses on three dimensions: The research cohorts' selection, comparability and outcome. All six cohort studies scored consistently across the selection, comparability and outcome domains, suggesting a reliable ascertainment of outcome assessment. They proved that the cohorts were equivalent based on design or analysis and that the desired outcomes were absent at the beginning of the trials. Nonetheless, a prevalent constraint observed in every cohort study was in the 'adequacy of follow up of cohorts' category, when zero points were obtained. This indicates potential issues related to how well these studies monitored participants over time, which could influence the reliability of the reported outcomes, particularly concerning longer-term effects.

Comparative efficacy of tacrolimus versus cyclosporine on nephrotic syndrome outcomes: Figure 2a illustrated the comparative effects of tacrolimus and cyclosporine on the overall response rate in patients with nephrotic syndrome. The Mantel-Haenszel fixed-effect model analysis of the combined data from eight research yields a relative risk (RR) of 1.03 with 95% confidence intervals (CIs) spanning from 0.97 to 1.10. A low to moderate level of heterogeneity across the included studies is indicated by an I-squared value of 31%, which also indicates a rather consistent impact size across study contexts. The p-value of 0.34 indicates that the difference in overall response rates between tacrolimus and cyclosporine is not statistically significant, suggesting comparable efficacy of the two immunosuppressants in inducing a response in patients with nephrotic syndrome.

In Fig. 2b, data from six studies are synthesized to evaluate the impact of tacrolimus compared to cyclosporine on achieving complete remission in nephrotic syndrome. The Mantel-Haenszel fixed-effect model yields an RR of 1.1057 with 95% CIs closely straddling the threshold of statistical significance ([0.9986, 1.2244]). An I-squared score of 29% indicates low to moderate heterogeneity amongst the research, which lends credence to the usefulness of pooling the data. Despite the point estimate suggesting a trend towards higher remission rates with tacrolimus, the p-value of 0.05 implies that the difference does not reach conventional levels of statistical significance and thus, no definitive conclusion can be drawn regarding the superiority of tacrolimus over cyclosporine for complete remission.

The likelihood of recurrence in individuals receiving tacrolimus or cyclosporine treatment was shown in Fig. 2c. The forest plot includes data from four studies, with an RR of 1.17 and 95% CIs between 0.79 and 1.74, as analyzed by the Mantel-Haenszel fixed-effect model. The dependability of the pooled estimate is supported by an I-squared value of 0%, which indicates no heterogeneity across the trials. However, the p-value of 0.43 indicates that the observed difference in relapse rates between the two treatments is not statistically significant. This finding suggests that when it comes to the likelihood of a recurrence of the disease in nephrotic syndrome individuals, tacrolimus and cyclosporine have comparable profiles.

Evaluation of publication bias: For the papers included in the meta-analysis reporting on overall rates of response to tacrolimus versus cyclosporine in nephrotic syndrome, Fig. 3a shows a funnel plot evaluating publication bias. The plot positions each study as a point in a scatter plot based on the effect size (RR) and the standard error (SE) of the log-transformed RR. Visual examination of the funnel plot exhibits symmetry about the vertical line, which represents the aggregate effect size. This symmetry implies that the reported total response rates are not likely to be impacted by publication bias. The even distribution of studies on either side of the mean effect size indicates that smaller studies with negative or inconclusive results are just as likely to be published as larger studies or those with positive results.

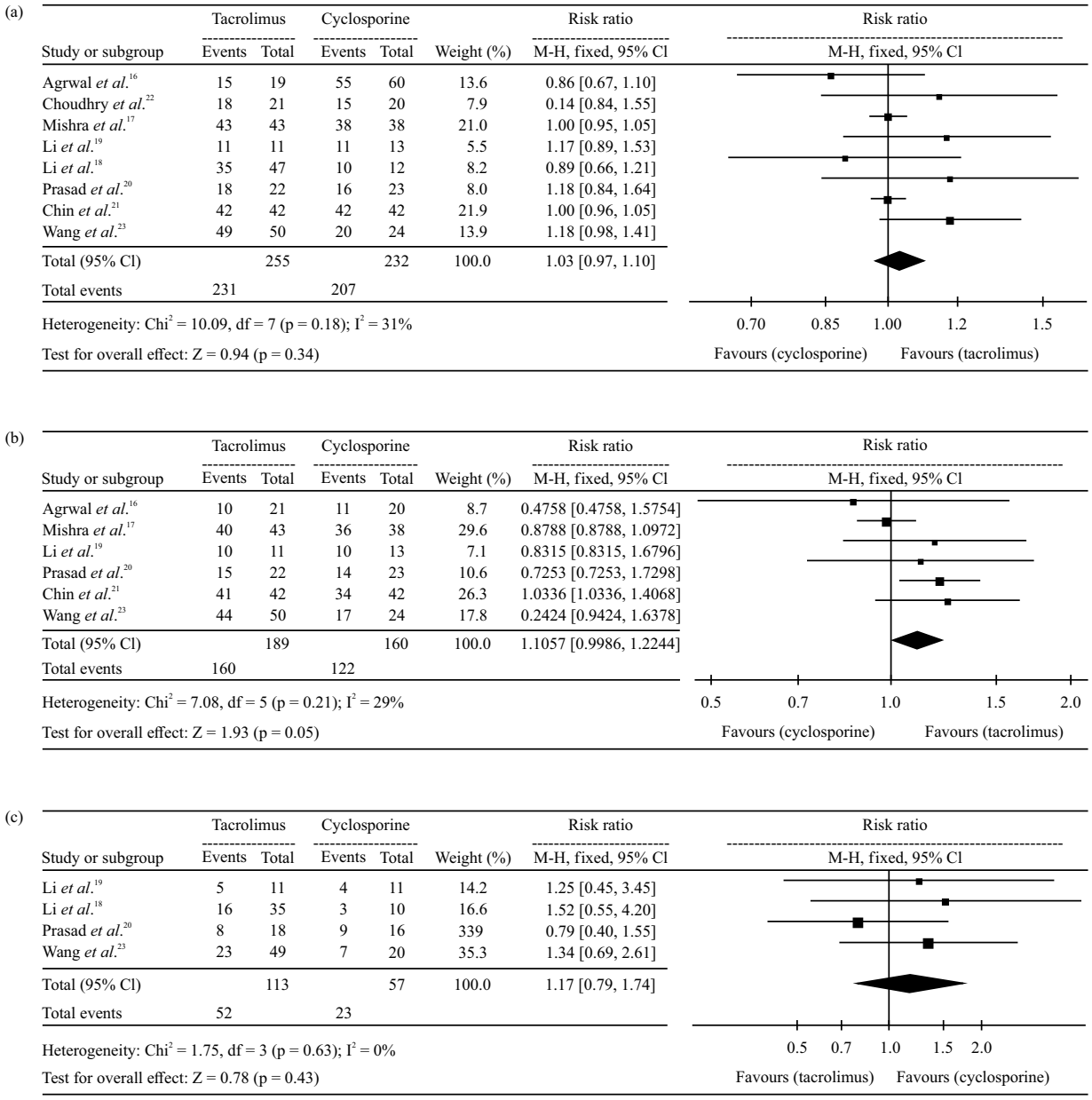

Fig. 2(a-c): Forest plots comparing tacrolimus impact versus cyclosporine on response outcomes in nephrotic syndrome sufferers, (a) Comparative effects of tacrolimus and cyclosporine, (b) Impact of tacrolimus compared to cyclosporine and (c) Likelihood of recurrence in individuals receiving tacrolimus or cyclosporine

The funnel plot in Fig. 3b examines publication bias within the studies that provide data on complete remission rates for tacrolimus versus cyclosporine. Similar to the previous plot, studies are mapped based on their effect size and the precision of the estimate. The distribution of studies in the funnel plot appears relatively balanced, due to the smaller number of research that contributed to this result, any asymmetry cannot be completely ruled out. Nonetheless, there are no clear indications of publication bias, as the studies are reasonably distributed across different levels of precision and effect sizes.

The funnel plot used to evaluate publication bias in studies reporting relapse rates after tacrolimus or cyclosporine therapy was shown in Fig. 3c. The effect sizes are plotted against the matching SEs of the log-transformed RR in the figure. The funnel plot is sparser since there are fewer studies in this outcome analysis.

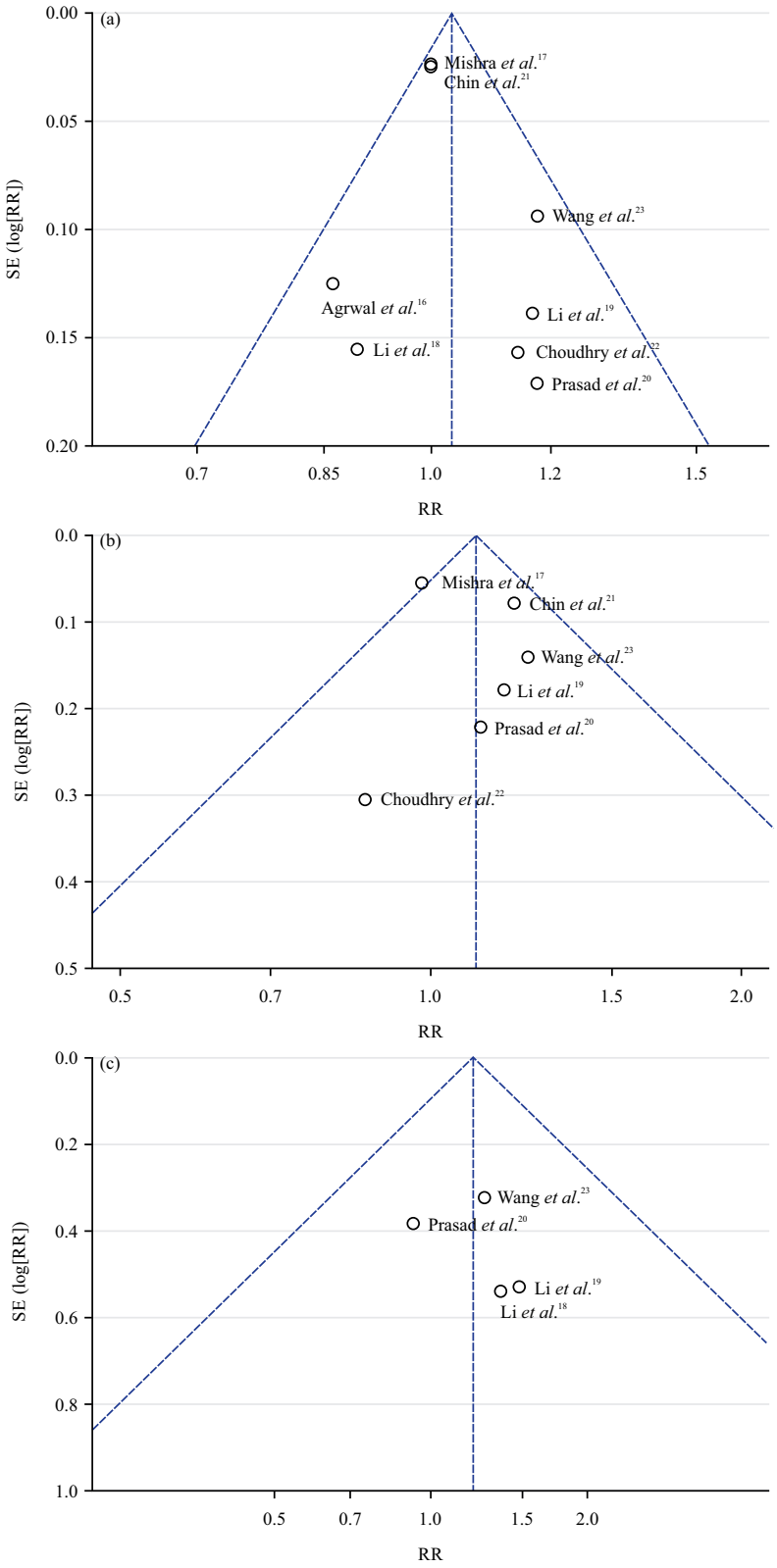

Fig. 3(a-c): Funnel plots of comparison between tacrolimus and cyclosporine for overall response, complete remission and relapse in nephrotic syndrome, (a) Funnel plot evaluating publication bias, (b) Funnel plot shows the data on complete remission rates for tacrolimus versus cyclosporine and (c) Funnel plot shows relapse rates after tacrolimus or cyclosporine therapy

Table 1: Main characteristics of the included studies

Study	Country	Study design	Pathologic type	Follow up (months)	Intervention	Sample size	M/F	Age (years)
Agrwal *et al.*[16]	India	Retrospective cohort study	FSGS/MCD/MsPGN	12~60	Tacrolimus	19	NA	13 (9~15)
					Cyclosporine	60	NA	
Mishra *et al.*[17]	India	Prospective cohort study	FSGS/MCD/MsPGN	6	Tacrolimus	43	NA	1.08~12.00
					Cyclosporine	38	NA	
Li *et al.*[18]	China	Retrospective cohort study	FSGS/MCD/MsPGN	40	Tacrolimus	47	29/18	6.3±3.8
					Cyclosporine	12	11/1	4.6±2.7
Li *et al.*[19]	China	Prospective cohort study	MCD	21	Tacrolimus	11	NA	25.0±10.5
					Cyclosporine	13	NA	33.8±12.1
Prasad *et al.*[20]	India	Prospective cohort study	MCD/FSGS	72	Tacrolimus	22	21/1	11.18±4.08
					Cyclosporine	23	22/1	10.85±4.79
Chin *et al.*[21]	China	RCT	FSGS/MCD/MsPGN	6	Tacrolimus	42	27/15	1.25~12.00
					Cyclosporine	42	22/20	
Choudhry *et al.*[22]	India	RCT	FSGS/MCD/MsPGN	6~12	Tacrolimus	21	14/7	1~15.5
					Cyclosporine	20	11/9	1.67~12
Wang *et al.*[23]	China	Prospective cohort study	FSGS/MCD/MsPGN/IgMN	6	Tacrolimus	50	NA	8.6±5.8
					Cyclosporine	24	NA	7.7±5.0

Table 2: Assessment of risk of bias in RCTs using the Cochrane risk of bias tool

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Choudhry *et al.*[22]	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Chin *et al.*[21]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table 3: Assessment of risk of bias in cohort studies using the Newcastle-Ottawa scale

	Selection				Comparability	Outcome		
Study	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Li *et al.*[19]	1	1	1	1	1	1	1	0
Wang *et al.*[22]	1	1	1	1	1	1	1	0
Mishra *et al.*[17]	1	1	1	1	1	1	1	0
Li *et al.*[18]	1	1	1	1	1	1	1	0
Prasad *et al.*[20]	1	1	1	1	1	1	1	0
Agrwal *et al.*[16]	1	1	1	1	1	1	1	0

DISCUSSION

In the study, the validity of the findings from this systematic review is enhanced due to the inclusion of only high-quality and relevant publications in the meta-analysis, which was achieved by a rigorous selection process. In treating nephrotic syndrome, the effectiveness of tacrolimus and cyclosporine was evaluated in this systematic review and meta-analysis. In terms of overall response (RR = 1.03, 95% CI [0.97, 1.10], p = 0.34), complete remission (RR = 1.1057, 95% CI [0.9986, 1.2244], p = 0.05) and relapse rates (RR = 1.17, 95% CI [0.79, 1.74], p = 0.43), the pooled analysis of eight studies, which included both RCTs and cohort studies, did not find any statistically significant difference between the two calcineurin inhibitors.

Based on patient preference, side effect profile and cost, the decision between tacrolimus and cyclosporine may be influenced. These results implied that both medications are similarly effective in treating nephrotic syndrome.

With a decreased frequency of cosmetic side effects such hypertrichosis and gum hyperplasia, tacrolimus may have a more favourable side effect profile than cyclosporine, according to earlier research by Prasad *et al.*[20]. As opposed to cyclosporine, tacrolimus has been linked to an increased incidence of New-Onset Diabetes after Transplantation (NODAT)[24].

The thorough literature searches, the incorporation of cohort studies and RCTs and the evaluation of several effectiveness outcomes are among the systematic review and meta-analysis's strong points. The low to moderate heterogeneity observed among the included studies for overall response and complete remission rates and the absence of heterogeneity for relapse rates, further strengthen the reliability of the findings. Furthermore, the funnel plots indicate that in this meta-analysis and systematic review of tacrolimus versus cyclosporine in the management of nephrotic syndrome, publication bias is not a significant problem. The symmetry of the plots in overall response outcomes indicates that the meta-analysis results reflect a balanced representation of the available evidence without apparent skewness due to unpublished data. It is important, however, to remain cautious about the interpretation of funnel plot symmetry, particularly when the number of studies is limited, as other factors could influence the distribution of studies in the analysis[25].

This study does, however, have many shortcomings. First, different follow-up times for the included studies might have affected how long-term outcomes like recurrence rates were evaluated. Second, the heterogeneity seen in the meta-analyses may have been influenced by the different pathologic forms of nephrotic syndrome seen in the included studies. Third, because the included trials utilised varied treatment regimens, it is unclear what the ideal dosage and length of tacrolimus and cyclosporine therapy should be for nephrotic syndrome. Finally, while RCTs showed robustness in several critical areas, the unclear risk associated with blinding could introduce performance or detection biases, albeit the extent of this impact is uncertain. On the other hand, the group studies, despite their strong performance in selection and outcome assessment, were potentially compromised by inadequate follow-up procedures[26]. These factors need to be carefully considered when weighing the evidence derived from these studies, as they might affect the validity and generalizability of the conclusions regarding the effects of tacrolimus versus cyclosporine on nephrotic syndrome consequences.

CONCLUSION

As a result, there was not a significant distinction between tacrolimus and cyclosporine in terms of the overall response, rates of full remission or recurrence in nephrotic syndrome individuals, according to this systematic review and meta-analysis. The two calcineurin inhibitors seem to work just as well together to treat this illness. Nevertheless, more well-planned, large-scale RCTs with longer follow-up periods are required to validate these results and evaluate the long-term safety and efficacy of these medications in the treatment of nephrotic syndrome. Future studies should also aim to identify the optimal dosage and duration of treatment with tacrolimus and cyclosporine, as well as to evaluate their efficacy in specific pathologic types of nephrotic syndrome.

SIGNIFICANCE STATEMENT

This comprehensive review and meta-analysis found no significant difference between tacrolimus and cyclosporine in overall response, complete remission or recurrence in nephrotic syndrome patients. This sickness seems to be treated equally effectively by the two calcineurin inhibitors. However, larger, well-planned RCTs with longer follow-up periods are needed to confirm these findings and assess the long-term safety and effectiveness of these nephrotic syndrome drugs. Future research should determine the best tacrolimus and cyclosporine dose and duration and assess their effectiveness in various pathologic forms of nephrotic syndrome.

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