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Original Article

Rituximab versus tacrolimus as corticosteroid-sparing therapy for children with steroid-dependent nephrotic syndrome: A systematic review and meta-analysis of randomized and nonrandomized controlled trials

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Abstract

Objectives: Prolonged use of corticosteroids induced complicated course in children with steroid-dependent nephrotic syndrome (SDNS), and the use of tacrolimus, a first-line alternative calcineurin inhibitor (CNI) agent was related to some unwanted adverse effects. Rituximab, a second alternative treatment has been proven to reliably reduce the number of relapses within 12 months with minimal adverse effects. **Materials and Methods:** Our review follows Preferred Reporting Items for Systematic Review and Meta-analysis guidelines. All the databases were derived from MEDLINE, Proquest, EBSCOhost, Wiley, and Google Scholar within the past 11 years. The risk of bias was evaluated using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) and Risk of Bias in Non-Randomized Studies of Interventions. Meta-analysis used Review Manager (version 5.4) with a random effect model to obtain a pooled mean difference (MD) and odds ratio with 95% confidence intervals (CIs). **Results:** Four studies were included based on our eligibility criteria, and only three were included in the quantitative analysis. Three studies had low and one study had a moderate risk of bias. Pooled data results indicated that Rituximab was superior to tacrolimus in reducing the number of patients with 1–2 relapses (MD = 0.44, [95% CI: 0.21–0.91]) and had higher eGFR values (MD = 6.67; [CI − 2.92–10.61]). However, Rituximab showed insignificant superiority compared to tacrolimus in reducing the number of patients with 3 relapses, sustained remission, cumulative steroid use, serum cholesterol, and serum albumin concentrations. **Conclusion:** Rituximab exhibits more advantages in treating SDNS compared to tacrolimus, although the treatment options are highly individualized. Both regimens must also be weighed against their potential side effects to achieve a better overall health status.

Keywords: *Children, Rituximab, Steroid-dependent Nephrotic syndrome, Tacrolimus*

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Introduction

Nephrotic syndrome (NS) has become one of the serious problems affecting children worldwide, approximately 2–16 per 100,000 children per year [1]. Initial development of the NS can be preceded by a viral illness or allergy. Common clinical manifestations included generalized edema, massive proteinuria, and hypoalbuminemia. It occurred in children regardless of ethnicity, with South Asian children experiencing the highest global incidence. Higher relapse risk has been associated with male sex, European race, and children under five [2].

Corticosteroid has become the mainstay therapy for children with NS. The use of prednisolone for 4–6 weeks has been responsible for a resolution of proteinuria within 80% of children with NS. However, 20% of children have failed to show some positive clinical responses regarding the use of corticosteroids, together with nephrotoxicity as one of its significant side effects [3]. These conditions lead to a higher chance of developing kidney failure in young adulthood. Therefore, early diagnosis and prompt treatment are crucially needed.

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According to the kidney disease, Improving Global Outcomes (KDIGO) [4,5], relapses were classified according to their frequency per year and were considered common if occurred twice in 6 months or four times in a year. Steroid-dependent nephrotic syndrome (SDNS) is defined by the number of relapses that happened when prednisolone doses were tapered down or during the absence of its use for 2-weeks period [6]. Children with SDNS require the use of second-line therapy, such as calcineurin inhibitors (CNI) and monoclonal antibodies to achieve complete or partial remission of the NS [7,8]. Otherwise, the disease will progress into end-stage disease.

Tacrolimus, a CNI, has demonstrated efficacy in SDNS by providing steroid-sparing effects. Tacrolimus belongs to the macrolide lactone class of immunosuppressive drugs. It acts by binding to the FK506-binding protein (FKBP12), forming a complex that inhibits the activity of calcineurin [9]. Through this mechanism, tacrolimus suppresses the production of cytokines, particularly interleukin-2, along with impairs activation and proliferation of T-cells [10]. Tacrolimus offers several advantages in the management of SDNS. First, it could minimize the long-term complications associated with corticosteroid therapy. Furthermore, it has demonstrated efficacy in patients who have failed or are intolerant to other immunosuppressive agents [11]. However, despite its efficacy, tacrolimus was associated with certain disadvantages and cautions regarding its interactions with the CYP3A4 enzyme system. Adverse events including nephrotoxicity, neurotoxicity, and gastrointestinal disturbances may occur [12,13], requiring close blood concentration monitoring due to its narrow therapeutic index.

A new potent drug belonging to the class of chimeric monoclonal antibodies, rituximab has shown a robust clinical significance in SDNS by specifically targeting the CD20 antigen [14]. By binding to CD20, rituximab mediates B-cell depletion through various mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis. The reduction in B cells leads to modulation of the immune response and attenuation of the inflammatory process. Rituximab offers several advantages in the management of SDNS. It provides a targeted therapy of B cells, thereby reducing the production of pathogenic antibodies. Rituximab is generally well-tolerated and has a favorable safety profile compared to traditional immunosuppressive agents [15]. Despite its efficacy, rituximab demonstrated certain disadvantages including hypersensitivity as a result of infusion-related reactions, that occur during or shortly after administration [16]. However, these side effects were mild and only required symptomatic therapies.

Prior studies have shown various results regarding the potency of rituximab versus tacrolimus in reducing the number of relapses in SDNS patients. Some studies show that rituximab therapy was superior to 12-month treatment with tacrolimus in maintaining remission, and some reported otherwise. Therefore, this systematic review and meta-analysis aimed to depict the efficacy of both regimens to control the relapse frequency and another kidney parameter in SDNS, thus helping clinicians in choosing the appropriate treatment regimens.

Materials and methods

This systematic review was designed and conducted under the guidelines based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 statement [17].

Registration of the review protocol

This review was registered in PROSPERO on March 12th, 2023, with the registration number CRD42023404102.

Variable of interest and aim of the study

Our study aimed to evaluate the efficacy of tacrolimus versus rituximab in reducing the frequency of relapses along with other kidney and biochemical parameters in children with SDNS.

Eligibility criteria

Types of studies

This systematic review included all published and unpublished randomized-controlled trials that investigated the efficacy of tacrolimus versus rituximab in patients with SDNS. Conversely, reviews, cross-sectional, cohort studies, case reports, case series, conferences, abstracts, book sections, commentaries/editorials, and non-human studies were excluded. Articles with unavailability of full-text and irrelevant topics were also omitted.

Participants

All patients aged ≤18 years old with primary NS were included in this study. Diagnosis of NS was based on KDIGO and the *Management of Steroid Sensitive NS: Revised Guidelines By Indian Academy of Pediatrics*. NS was defined as proteinuria and either hypoalbuminemia (<3 g/dL) or edema (KDIGO 2021). SDNS was defined as two consecutive relapses when on alternate-day steroids or within 14 days of its discontinuation. There was no limitation for gender, race, or ethnicity. Exclusion criteria were patients with previous use of corticosteroid-sparing agents, who suffered from secondary NS, and had an active infection.

Outcome of interest

Outcomes of interest in this study were the number of relapses, number of patients with 1–2 relapses, 3 relapses, number of patients with sustained remission, cumulative steroid use, estimated glomerular filtration rate (eGFR), serum cholesterol, and serum albumin after the use of tacrolimus versus rituximab as a corticosteroid-sparing agent within 6 months and 12 months.

Search strategy and study selection

We used the electronic databases from MEDLINE, EBSCO-Host, Wiley, ProQuest, and Google Scholar dating up to 2023 for literature search. Studies were identified using the following keywords by three independent authors:

(Children [MeSH Term] AND (nephrotic syndrome [MeSH Term] AND (Rituximab [MeSH Term] AND (Tacrolimus [MeSH Term] AND one-year relapse-free [MeSH Term])))

Each study was imported to the Mendeley reference manager program. All studies were checked for duplicates; then titles and abstracts were independently reviewed by all authors and excluded when unsuitable for the aim of this review. Using the eligibility criteria outlined above, selected studies underwent in-depth full-text evaluation before being included in this review. Any disagreements were settled by the review team.

Data collection process

The following information was extracted from the included studies: authors, country of origin, study design, sample size, age and gender of participants, SDNS diagnostic criteria, tacrolimus and rituximab administration protocol, frequency of relapse, number of patients with 1–2 and 3 relapses, number of patients with sustained remission, cumulative of steroid use, eGFR, serum cholesterol, and serum albumin. The data extraction was performed by all authors.

Summary measures

Data from patients in the tacrolimus and rituximab group were extracted either as proportional or continuous data. Proportional data were shown as several affected patients per number of total populations. Continuous data with normally distributed were shown as mean ± standard deviation, whereas nonnormally distributed data were shown as median (interquartile range). For each item, a *P* value and 95% confidence intervals (CI) were also included to show the significance of results. The data summary was constructed independently by all authors.

Assessment of risk bias/quality assessment

The Cochrane Risk of Bias Tool 2.0 (RoB 2) for randomized controlled trials was used to evaluate each study. The tool is divided into seven major categories: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and staff; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective reporting; and (g) other sources of bias. The likelihood of bias was rated as low, high, or of considerable concern for each domain. For non-randomized controlled trials, we perform the quality assessment using Randomized 2 and Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) checklist, comprised of seven domains: (A) bias due to confounding, (B) bias in selection of participants into the study, (C) bias in classification of interventions, (D) bias due to deviations from intended interventions, (E) bias due to missing data, (F) bias in measurement of outcomes, and (G) bias in selection of the reported result. Based on the amount of bias present, each trial's overall quality was split into three categories: (1) low risk of bias (low risk of bias across all domains), (2) high risk of bias (high risk of bias across multiple domains or some worries), and (3) some concerns (some concerns across at least one domain). Each paper was reviewed by two authors independently, and any discrepancies were then discussed among the whole review team until a consensus was reached.

Synthesis of results and statistical analysis

For all continuous outcomes, we calculated the mean differences (MDs) and 95% CIs based on the data at the end of the study period (12 months of follow-up) from both treatment groups. For noncontinuous variables (proportion), we used the number of incidences from each group to determine the Odd Ratios (ORs) as the measure of effect size. Statistical analyses were done for between-group comparison. We used Review Manager 5.4 to conduct the meta-analysis. The results of quantitative synthesis were shown in a forest plot. The power of each study was depicted by its weight, calculated from the sample size, ORs, and the CIs. The accumulation diagram of the final weight is shown in a rhombus shape, whereas a square shape indicates a weight for each study.

Some studies reported primary outcomes using different evaluation or calculation methods, therefore the meta-analyses were conducted with a random effects model. This model presupposes that the treatment impact will be distributed over certain populations and gives each study a more equal weighting. The combined effect measures of the direct comparisons from an individual intervention were compared by the inverse variance method, whereas the proportion data were compared using the Mantel–Haenszel method.

Heterogeneity across trials was assessed using the I^2 statistic. An I^2 value of <25% is considered low heterogeneity, between 25% and 50% indicates moderate to substantial heterogeneity, and more than 50% is considered high heterogeneity. When heterogeneity was present, possible causes were investigated through sensitivity analyses. A $P < 0.05$ was considered statistically significant. A funnel plot could not be generated due to an insufficient number of studies, thus publication bias was assessed qualitatively. The results synthesis and statistical analysis were executed by all authors.

Results

Preferred Reporting Items for Systematic Reviews and Meta-analysis

A flow chart of the research selection process and its results are summarized in Figure 1. The search strategy yielded 617 potentially relevant studies. According to the selection criteria, 210 studies were identified for further full-text assessment, of which 88 articles had the same study center, 64 articles included adult patients for the population of interest, and 73 articles had limited access to full text. Finally, four studies were included in the systematic review and extracted in the meta-analysis. All studies were published between 2012 and 2023.

Quality assessment

Overall four studies were assessed using ROB-2 and ROBINS-I for evaluating the risk of bias, three studies by Wang *et al*. [18], Sinha *et al*. [19], and Mathew *et al*. [20], had a low risk of bias, meanwhile, one study by Basu *et al*. [21], showed a moderate risk. All predicates were summarized based on the total score from each study, as shown in Figures 2 and 3. Each risk of bias scores for RCTs and nonrandomized study is summarized in Supplementary Tables 1 and 2, respectively.

Characteristics of included study

Characteristics of the included studies are shown in Table 1. Studies were designed as RCTs or nonrandom interventions. The participants were female and male children from 1 month

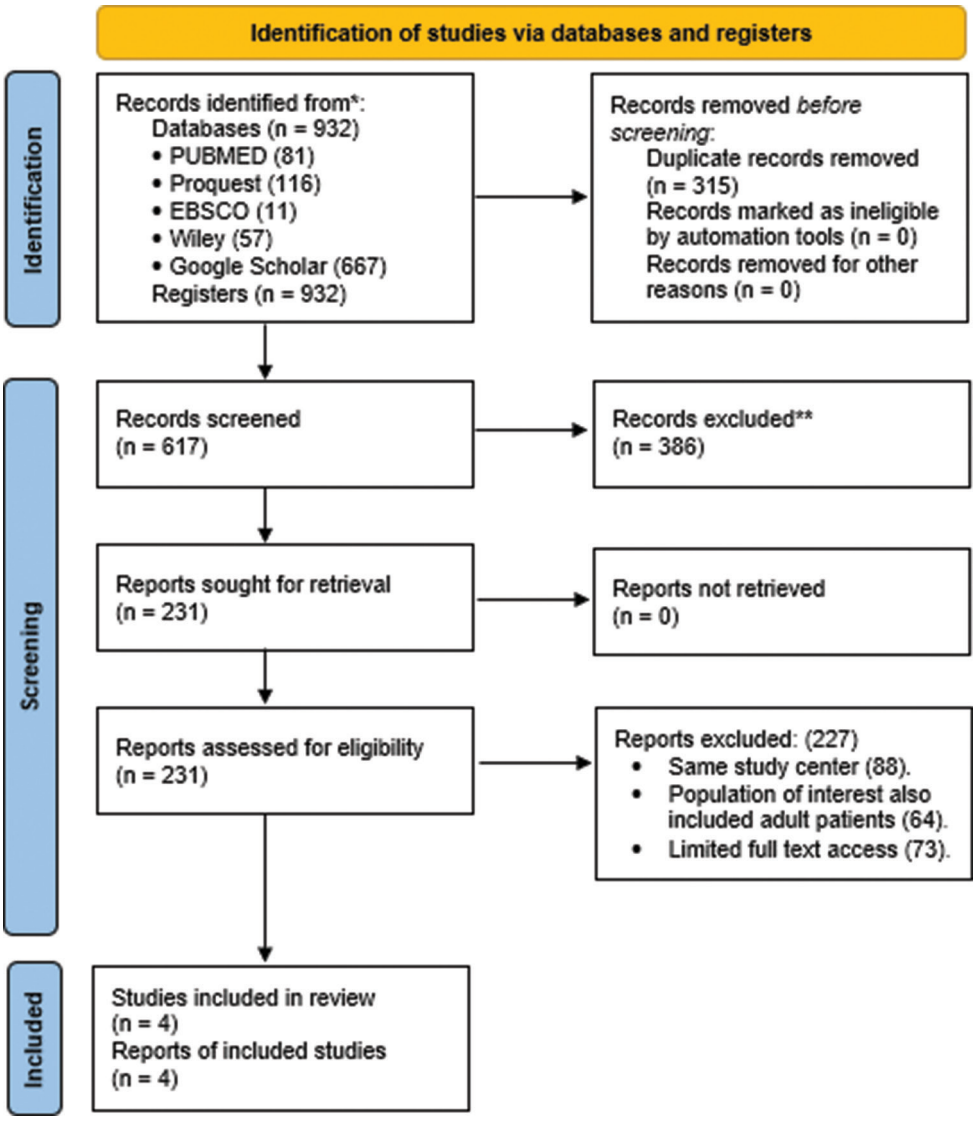

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 flow diagram of included studies

to 18 years old. Children diagnosed with NS are based on KDIGO criteria. All children included were those treated with either tacrolimus or rituximab. The studies included were in the 2017–2022 range. The outcome of interest was measured during 1 year of follow-up. Three out of four studies reported a higher incidence of adverse event-related treatment in the tacrolimus group. The most reported side effects were upper and lower respiratory tract infection, skin infection, diarrhea, gastritis, and hyperglycemia, although no deaths or other serious adverse events were described [18,20,21].

Final results

All four studies included in the quantitative synthesis showed that frequency of relapses, number of patients with 1–2 and 3 relapses, number of patients with sustained remission, cumulative steroid use, eGFR, serum cholesterol, and serum albumin were varied among studies, as shown in Table 2. The result of the Grading of Recommendations, Assessment, Development, and Evaluations assessment presenting the summaries of evidence in this systematic review is shown in Table 3.

Meta-analysis results

The results of a meta-analysis of the four included studies were presented in a forest plot [Figure 4a-h]. The accumulation diagrams of forest plots show the MDs and ORs from each study and the obtained final effect size. In this Figure, the final weight of the combined value is shown in a rhombus shape, whereas a square shape indicates a weight for each study. The size of each square is determined by the weight of that study in the meta-analysis, which is calculated based on the study population samples. Two significant outcomes were found in several patients with 1–2 relapses favoring rituximab (P = 0.03, 95% CI: 0.21–0.91) and estimated GFR which was lower in tacrolimus compared to rituximab groups (P = 0.0006, 95% CI: 2.92–10.61).

Discussion

After a 12-month follow-up, children with SDNS and treated with rituximab have significantly lower odds of experiencing 1–2 relapses compared to tacrolimus (P = 0.03, 95% CI: 0.21–0.91), besides having nonsignificant differences

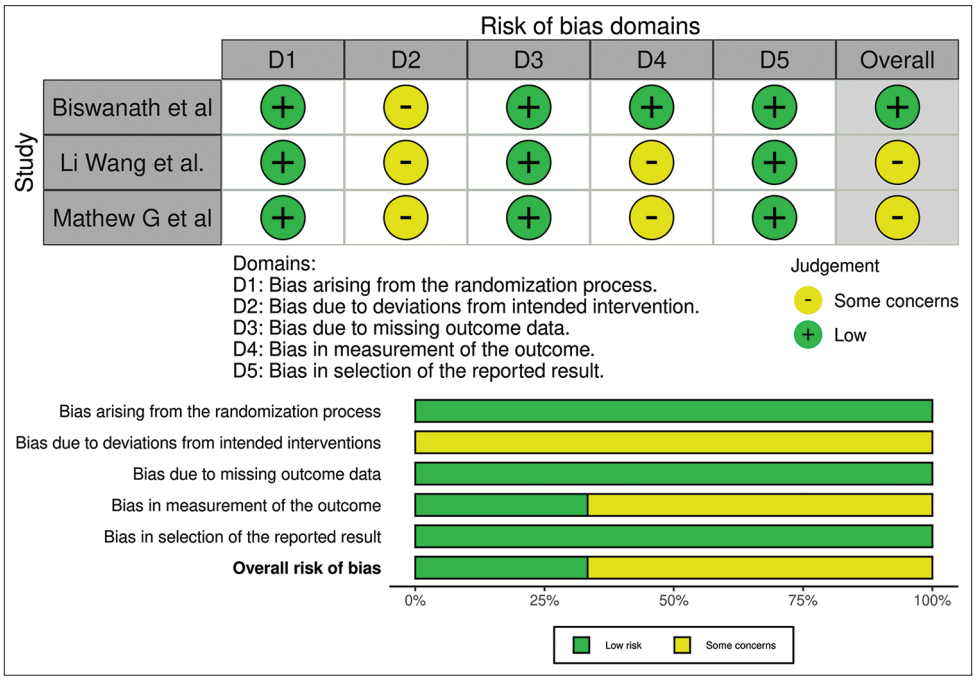

Figure 2: Results of study quality assessment for randomized controlled trials

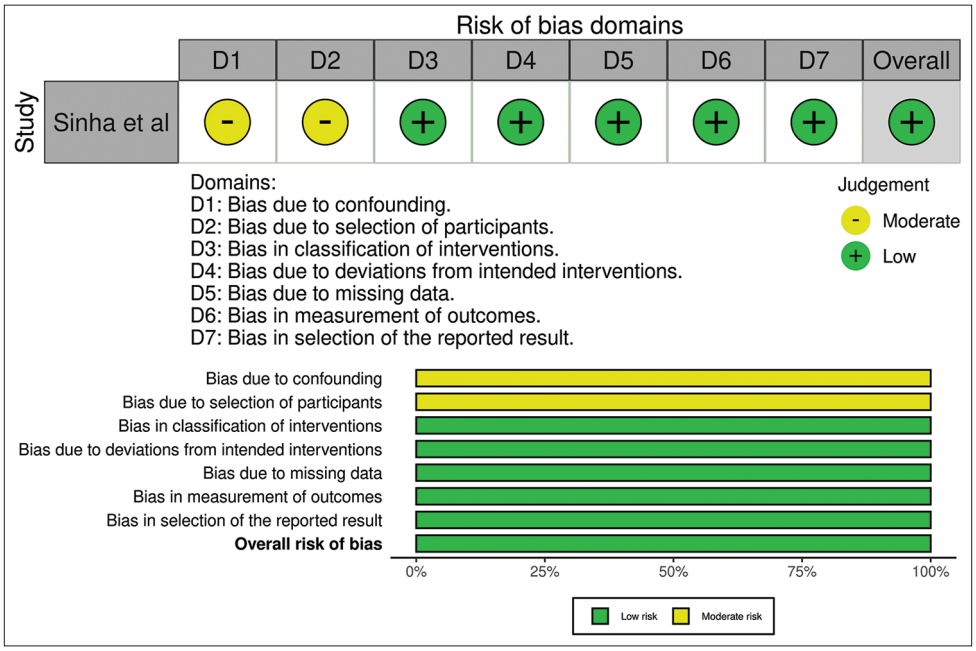

Figure 3: Results of study quality assessment for non-randomized trials

in experiencing three relapses (P = 0.20, 95% CI: 0.04–0.91). Moreover, in a long-term manner, the difference in sustained remission rates between rituximab and tacrolimus is also not statistically significant (P = 0.24, 95% CI: 0.63–6.39). This may suggest that rituximab is more effective at preventing early recurrences or initial relapses. The findings are in line with a study by Basu *et al*. [21], which found that Rituximab's superior therapeutic effect in SDNS disappears during the 2nd year following exposure [11]. It is possible that the treatment's effectiveness plateaus after a certain point in time.

Rituximab is administered intravenously and undergoes elimination through proteolytic clearance by the reticuloendothelial system. The primary pharmacodynamic effect of rituximab is the depletion of CD20-positive B cells. This reduction in B cell numbers leads to decreased production of pathogenic antibodies, modulation of immune responses, and restoration of immune tolerance in SDNS. B-cell activity is a major factor contributing to the initial relapses through the action of B-cell memory [22], hence rituximab may have a more pronounced effect compared to tacrolimus. However,

Table 1: Study characteristic

Author, publication year, country	Types of study	Population					
		n		Age		Sex (*n*)	
		Tacrolimus, *n* (%)	Rituximab, *n* (%)	Tacrolimus	Rituximab	Tacrolimus	Rituximab
Basu *et al*., 2018, India [21]	Randomized clinical trial	60	60	7.2±2.8	7.1±2.8	Male (32) Female (28)	Male (32) Female (28)
Sinha *et al*., 2012, India [19]	Nonrandom intervention	13	10	12.3±3.0	12.2±2.3	Female (3) Male (10)	Female (2) Male (8)
Wang *et al*., 2022, China [18]	Prospective randomized study	17 (33.33)	17 (33.33)	Not stated explicitly Age 2–4 (*n*=11) (21.56) Age 5–7 (*n*=19) (37.25) Age 8–12 (*n*=17) (33.33) Age 13–18 (*n*=4) (7.84)		Not stated	
Mathew *et al*., 2022, India [20]	Randomized controlled trial	20 (48.78)	21 (51.22)	120 months (87.5, 170.5)	109 months (85, 130)	Male (15) Female (5)	Male (19) Girls (2)

Author, publication year, country	SDNS diagnostic criteria	Dosage and duration of therapy		Reported side effects (or treatment-related adverse events)	
		Tacrolimus	Rituximab	Tacrolimus	Rituximab
Basu *et al*., 2018, India [21]	N/A	0.2 mg/kg/day for 12 months (oral)	375 mg/m^2 with maximum dose of 500 mg for 12 months (infusion)	145 AEs (most common: pneumonitis, upper respiratory tract infection, skin infection, infectious diarrhea, gastritis, and hyperglycemia) Serious AE (−)	123 AEs (most common: Pneumonitis and upper respiratory tract infection) Serious AE (−)
Sinha *et al*., 2012, India [19]	SDNS defined as the occurrence of two consecutive relapses while the patient was receiving prednisolone on alternate days or within 15 days of its discontinuation	0.1–0.2 mg/kg/day in two divided dose for 12 months	375 mg/m^2/week for 12 months	Reversible nephrotoxicity No serious AEs	Infusion reactions in the form of chills, myalgia and temporary skin rash No serious AEs
Wang *et al*., 2022, China [18]	SDNS defined as a patients who has a relapse on a reducing course of prednisolone or within 2 weeks of stopping steroids	0.1–0.15 mg/kg/day in 2 divided doses for 6 months	375 mg/m^2 (maximum of 500 mg) for 6 months	34 AEs Infection rate of 1.6±1.0 No serious AEs	24 AEs Infection rate of 1.1±0.7 No serious AEs
Mathew *et al*., 2022, India [20]	SDNS was defined if each of the following criteria was met Frequent relapses (≥2 replases in 6 months or ≥3 relapses per year) or steroid dependence Failure of ≥2 strategies (alternate-day prednisolone, levamisole, cyclophosphamide, MMF) Corticosteroid toxicity (cataract, galucoma, short stature with low growth velocity), or obesity	at 0.1–0.1 mg/kg daily in two divided dose for 1 year	375 mg/m^2 twice, one week apart for 1 year	181 AEs Most common: Upper respiratory tract infections (47), skin and dental infections (14), gastritis (55), cytopenias (7), headache (9) No serious AEs	133 AEs Most common: Upper respiratory tract infections (64), skin and dental infections (15), infusion reactions (12), gastroenteritis (5) No serious AEs

AEs: Adverse events, SDNS: Steroid-dependent nephrotic syndrome, N/A: Not available, MMF: Mycophenolate mofetil

in our results, rituximab failed to depict a long-term protective effect on three relapses and prevented further remissions. These phenomena were caused by the presence of several additional immune cells spared by Rituximab, for instance autoreactive T cells may stimulate newly developed B cells or any presence of autoreactive B cells [23,24].

All three studies field agreed to the use of Rituximab as a superior corticosteroid-sparing agent by reducing the cumulative dose of steroid use compared to tacrolimus for children with SDNS [18,19,21]. The limited toxicity of Rituximab and its potential benefits of maintaining disease remission, together with avoiding the use of steroids and CNI support the use of Rituximab to attain 6 months of steroid-free periods. It was proven that the use of Rituximab can lower the remission rate by three times compared to the single-use or corticosteroid alone in maintaining remission. Meanwhile, one study by Mathew *et al*. [20], stated that both rituximab and tacrolimus had a similar cumulative dose of steroid use. Unfortunately, the overall results suggested that the difference between the two agents was not significant (P = 0.10, 95% CI: −70.84–5.78).

Table 2: Results of studies included in the meta-analysis for frequency of relapses, cumulative steroid dose, number of patients with 1–2 relapses, number of patients with 3 relapses, number of patients with sustained remission, estimated glomerular filtration rate, serum cholesterol, and serum albumin in children with steroid-dependent nephrotic syndrome after 12 months of follow up (at the end of the study period)

Parameter	Basu *et al.*, 2018 [21]					Sinha *et al.*, 2012 [19]				
	Rituximab	Tacrolimus	*P*	MD	95% CI (upper–lower)	Rituximab	Tacrolimus	*P*	MD	95% CI (upper–lower)
Frequency of relapses**	0.60±0.927	0.136±0.43	<0.001	N/A	N/A	0.8±1.0	0.9±1.1	0.92	N/A	N/A
Cumulative steroid dose**	25.8±27.8	86.3±58.0	N/A	−60.5	−77.1–−43.9	46.1±42.1	70.9±26.3	0.11	N/A	N/A
Parameter	**Basu *et al.*, 2018 [21]**					**Sinha *et al.*, 2012 [19]**				
	Rituximab	**Tacrolimus**	***P***	**MD**	**95% CI (upper–lower)**	**Rituximab**	**Tacrolimus**	***P***	**MD**	**95% CI (upper–lower)**
Number of patients with 1–2 relapses*	6 (60)	17 (60)	N/A	N/A	N/A	4 (10)	5 (13)	0.93	N/A	N/A
Number of patients with 3 relapses*	0 (60)	4 (60)	N/A	N/A	N/A	1 (10)	2 (13)	0.93	N/A	N/A
Number of patients with sustained remission*	54 (60)	38 (60)	N/A	5.21	1.93–14.07	5 (10)	6 (13)	0.93	N/A	N/A
eGFR**	118.4±11	111.8±11	N/A	6.6	2.5–10.7	97.2±31.96	93.7±23.80	0.80	N/A	N/A
Serum cholesterol**	79.6±22.1	98.4±16.1	N/A	−18.8	−25.8–−11.7	199±64.1	194.1±71.4	0.87	N/A	N/A
Serum albumin**	5.63±0.99	4.87±0.78	N/A	0.76	0.43–1.09	3.8±0.6	3.4±1.3	0.33	N/A	N/A
Parameter	**Wang *et al.*, 2022 [18]**					**Matthew *et al.*, 2022 [20]**				
	Rituximab	**Tacrolimus**	***P***	**Mean difference**	**95% CI (upper–lower)**	**Rituximab**	**Tacrolimus**	***P***	**MD**	**95% CI (upper–lower)**
Frequency of relapses**	0.5±0.6	1.1±0.9	0.03	N/A	N/A	1.59±1.38	0.65±0.84	N/A	N/A	N/A
Cumulative steroid dose**	53.2±33.2	101.7±72.5	<0.05	N/A	N/A	0.1352±0.1516	0.1136±0.1197	0.15	–0.08	N/A
Parameter	**Matthew G *et al.*, 2022[20]**									
	Rituximab		**Tacrolimus**			***P***	**MD**	**95% CI (upper–lower)**		
Number of patients with 1–2 relapses*	9 (20)		9 (15)			N/A	N/A	N/A		
Number of patients with 3 relapses*	N/A		N/A			N/A	N/A	N/A		
Number of patients with sustained remission*	11 (20)		11 (20)			0.50	0.00	−30.83–30.83		
eGFR**	136.4274±48.1101		117.3103±40.2912			0.14	N/A	N/A		
Serum cholesterol**	154.3483±23.8556		148.8233±50.2643			0.22	N/A	N/A		
Serum albumin**	3.9482±0.8776		4.372±0.4787			0.22	N/A	N/A		

*Data presented as number of patients (total population), **Data presented as mean±SD. Significant at $P<0.05$. SD: Standard deviation, CI: Confidence interval, MD: Mean differences, N/A: Not available

In addition, based on our meta-analysis results, tacrolimus was a less preferable corticosteroid-sparing therapy than rituximab in the context of its undesirable nephrotoxic side effects. The estimated eGFR was lower in tacrolimus compared to the rituximab groups and the difference between the two was significant (P = 0.0006, 95% CI: 2.92–10.61). In concordance with the study by Basu *et al*. [21], rituximab tends to be a safer therapeutic option in children with SDNS to maintain an adequate eGFR rate compared to tacrolimus. Moreover, the minimum eGFR values to start rituximab therapy were considerably low at 60 mL/min per 1.73 m^2 [25,26], thus demonstrating a better therapeutic window. The successful administration of rituximab as a safer and more effective corticosteroid-sparing therapy has raised a question of whether and when anti-B-cell therapy should be considered as the first-line regimen, to minimize corticosteroid exposure and avoid the nephrotoxic effects exerted by the CNI. After 12 months of treatment using both medications, the increase of eGFR value from the baseline to the 12-month was higher in the Rituximab group (MD = 6.6; 95% CI, 2.5–10.7). The results showed that rituximab not only preserved a good renal function but also gradually improved it.

Two studies by Sinha *et al*. and Mathew *et al*. [19,20] stated that tacrolimus gave rise to the value of total serum cholesterol in patients with SDNS, meanwhile, one study by Basu *et al*. [21], signified that rituximab was more influential than tacrolimus. Tacrolimus lowered the synthesis of lipoprotein lipase thus resulting in an elevated propensity for decreased TG clearance, leading to hyperlipidemia states [27]. On the other hand, the exact mechanism of how Rituximab caused changes in the lipid profile remains unknown. A study by Kostoglou-Athanassiou *et al*., in patients with rheumatoid arthritis receiving Rituximab, found that total cholesterol levels rose along with HDL and LDL levels, whereas triglyceride levels dropped. The unfavorable effect on total cholesterol levels following rituximab treatment may be counterbalanced by a concurrent rise in HDL, thus providing patients with a benefit from a lower cardiovascular risk [28]. A study by Fernández-Nebro *et al*. [29], in systemic lupus erythematosus patients who are resistant to conventional therapy, showed that Rituximab may help improve long-term lipid profile indirectly by lowering the inflammatory activity. Hence, overall results concluded that rituximab caused a higher increase in total serum cholesterol, but may be manageable

Table 3: Grade assessment profile of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome children

Outcome	Number of participants	Quality assessment						Summary findings	
		ROB 2	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	OR total or MD total	95% CI (upper, lower)
Frequency of relapses	4 studies	Not serious	Serious[a]	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Low certainty	−0.19	−0.90–0.52
Number of patients with 1–2 relapses	3 studies	Not serious	Not serious	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Moderate certainty	0.44	0.21–0.91
Number of patients with 3 relapses	2 studies	Not serious	Not serious	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Moderate certainty	0.29	0.04–1.97
Number of patients with sustained remission	3 studies	Not serious	Moderate[b]	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Moderate certainty	2.01	0.63–6.39
Cumulative of steroid use	4 studies	Not serious	Serious[a]	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Low certainty	−32.53	−70.84–5.78
eGFR	3 studies	Not serious	Not serious	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Moderate certainty	6.76	2.92–10.61
Serum cholesterol	3 studies	Not serious	Moderate[b]	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Moderate certainty	−8.83	−27.94–10.29
Serum albumin	3 studies	Not serious	Serious[a]	Moderate indirectness[c]	No serious imprecision	No serious publication bias	Low certainty	0.26	−0.55–1.07

[a]I^2 results >75% are considered as high heterogeneity, [b]I^2 results: 50%–75% are considered as moderate heterogeneity, [c]Population only came from Asian ethnicities (India and China), hence decreasing the likelihood to be applied to the broader population. eGFR: Estimated glomerular filtration rate, ROB2: Risk of bias 2, OR: Odds ratio, CI: Confidence interval, MD: Mean differences

and more tolerable over the long course of therapy compared to tacrolimus (P = 0.37, 95% CI: −27.94–10.29).

Serum albumin had comparable results in the rituximab and tacrolimus groups, with two [19,21] studies showing lower albumin levels in the tacrolimus groups and one study [20] reporting otherwise in the rituximab group. The overall results demonstrated a MD of 0.26 favoring tacrolimus, although it was not significant (95% CI: −0.55, 1.07, P = 0.53). Reduced serum albumin concentrations in NS were mainly driven by an increased urine excretion of albumin and other serum proteins, resulting from damaged kidney function. Tacrolimus and rituximab were found to have a protective effect on the kidney, by suppressing the immune response thus restoring its capability to maintain albumin levels. rituximab, which binds to albumin, can be eliminated in the urine of nephrotic individuals; as a result, rituximab is present in the blood more briefly in these people. These findings suggested that Rituximab levels were lower in case of higher proteinuria. A study by Yin *et al*., also supports the evidence that there are no differences in serum albumin levels between rituximab and control groups (SMD = 0.06, 95% CI: −0.32–0.44, P > 0.05) [30]. On the other hand, a Study by Butani and Ramsamooj [31], showed a significant increment of serum albumin from 1.5 to 3.8 mg/dL in children with steroid-resistant NS receiving tacrolimus of 0.1 (0.05–0.2) mg/kg per day for 22 months (P < 0.005). The same results were also reported by Liang *et al*. [32], which found an increment of serum albumin from 26.5 ± 6.2 g/L to 36.9 ± 8.2 g/L in adult patients receiving tacrolimus of 0.05–0.1 mg/kg/day for 12 months.

All studies revealed a higher incidence of adverse events in the tacrolimus group, with upper and lower respiratory infections, skin infection, diarrhea, gastritis, and hyperglycemia accounting as the most reported side effects. The underlying mechanisms might be explained by tacrolimus-induced suppression in human T follicular helper cells, resulting in reduced immune response and increased susceptibility to opportunistic infection [33]. This finding is supported by Loeffler *et al*., which reported one case of anemia, seizure, and five cases of new-onset hypertension related to tacrolimus therapy in children with resistant NS [34].

A high dose and long-term duration of tacrolimus treatment could produce tubular toxicity [35] through its action in interfering with phosphoenolpyruvate carboxyl kinase-1 (PCK-1) [36]. Tacrolimus may increase oxidative stress by reducing the amount of total cell glutathione, along with affecting cell energy metabolism by upregulating PCK-1, the most important enzyme in gluconeogenesis and acid-base balance regulation, thus resulting in hyperglycemia [37]. Moreover, tacrolimus may downregulate the Krebs cycle intermediates such as citrate, aconitate, and fumarate, hence may lead to metabolic changes in the renal tubular epithelium [38]. Notwithstanding, the study reported that Tacrolimus had a complete remission rate of 81% and a partial remission rate of 13% (totaling 94%) in children with resistant NS [34]. On the other hand, Rituximab had a very low and typically well-tolerated incidence of major side effects. A study by Gao *et al*., in children with frequently relapsing NS reported that rituximab groups had minor and less severe adverse events compared to the control group [39]. Therefore, the potential benefits of both regimens must be weighed against their potential side effects.

The substantial representation of studies from Asian countries in our analysis, notably India and China, warrants careful consideration of the potential influence of ethnicity on the observed outcomes. Ethnicity is recognized as a multifaceted variable that encompasses genetic, environmental, and socio-cultural factors, all of which can impact the

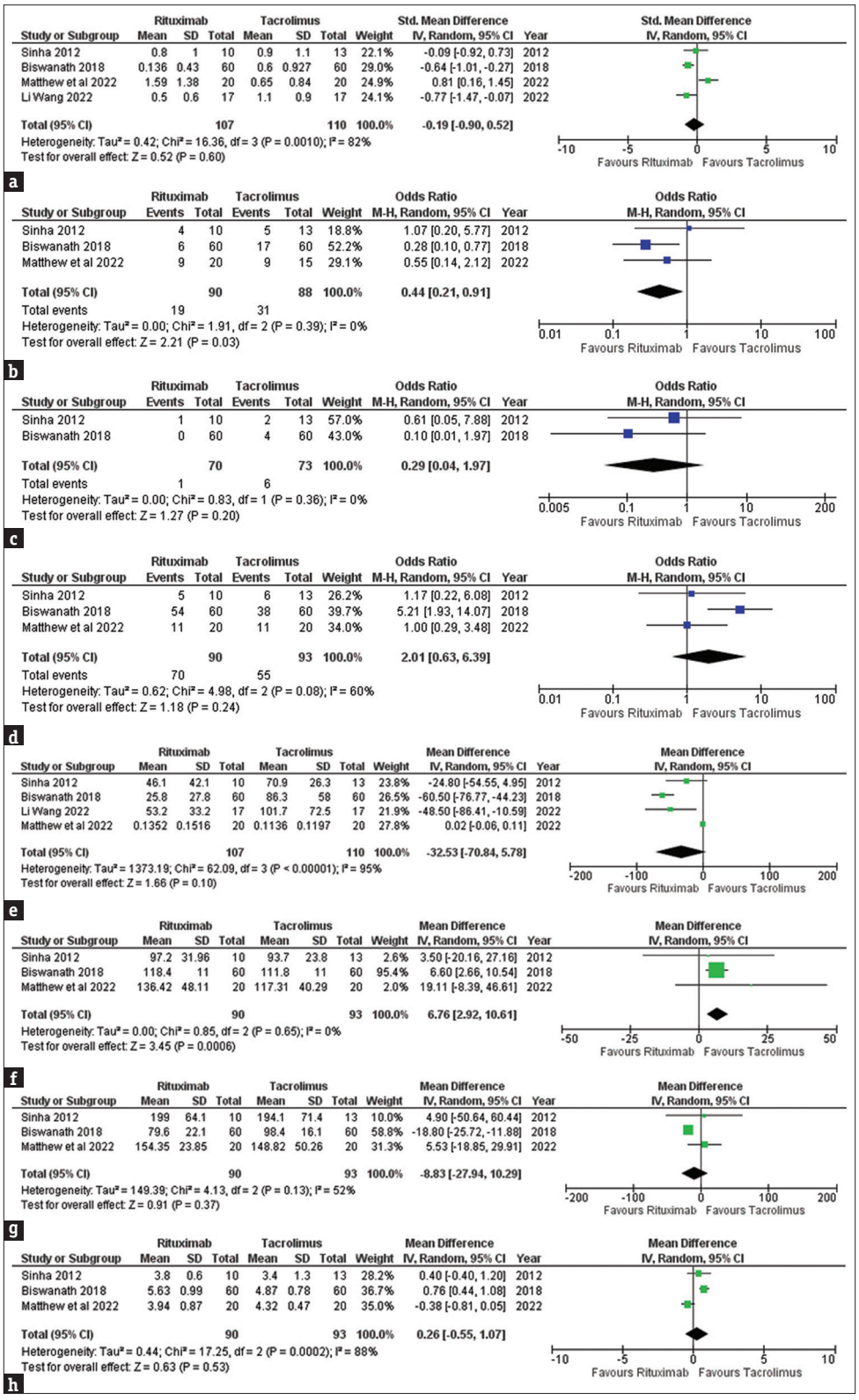

Figure 4: Meta-Analysis results (forest plot) for (a) Frequency of relapses, (b) Number of patients with 1–2 relapses, (c) Number of patients with 3 relapses, (d) Number of patients with sustained remission, (e) Cumulative steroid dose, (f) Estimated glomerular filtration rate, (g) Serum cholesterol, and (h) Serum albumin in children with steroid dependent nephrotic syndrome after 12 months of follow up (at the end of the study period)

presentation and course of various medical conditions, including SDNS [40]. In the context of SDNS, previous research has suggested that genetic predispositions may contribute to the pathogenesis of the condition. While specific genetic markers have not been unequivocally identified, there is a growing body of evidence indicating that certain

genetic variations may play a role in susceptibility to steroid resistance and relapse in NS. Moreover, polymorphisms in genes associated with immune regulation have been implicated in modulating disease severity and response to treatment, potentially contributing to the varying outcomes observed across different ethnic groups [41].

Heterogeneity analysis

The heterogeneity results of frequency of relapses, number of patients with sustained remission, cumulative steroid dose, serum cholesterol, and serum albumin showed an I^2 test value of 82%, 60%, 95%, 52%, and 88% respectively, which could be classified as "*represent moderate heterogeneity*" [42]. The heterogeneity of these results could be observed from clinical, methodological, or statistical perspectives. From a clinical perspective, the differences in number of participants could lead to high levels of heterogeneity. This study involved 23–120 children as participants. The larger the sample, the more likely or unlikely the ES to occur. From a methodological perspective, the differences in study design and population matching could lead to high heterogeneity. In our review, three studies were RCT and one study was nonrandomized intervention. However, considering the possibility of controlling the confounding factors at the beginning of the study, heterogeneity from methodological perspectives was unlikely. Ultimately, from a statistical perspective, variation in intervention effects or results contributed to increased heterogeneity. Despite the various reporting results, all studies were calculated using MDs or ORs as the effect sizes in meta-analysis, thus minimizing the statistical heterogeneity.

Strengths and limitations of the study

This systematic review and meta-analysis, to the best of our knowledge, was the first to compare tacrolimus and rituximab in children with SDNS. However, since most of the studies were conducted in Asia, it is assumed that other ethnic groups cannot be represented by the findings. One study was nonrandomized, indicated that there could be a slight bias that affects the outcomes [19]. The longer corticosteroid coadministration in the tacrolimus arm in some studies may have led to an underestimation of the inherent differences between tacrolimus and Rituximab's efficacy [20]. Forby, the majority of studies only provide a follow-up period of 12 months.

Future directions

Future research should prioritize longer follow-up periods, ethnically diverse populations, and more RCTs using single regimens of tacrolimus and rituximab.

Conclusion

In summary, two significant outcomes were found in a number of patients experiencing 1-2 relapses favoring rituximab and eGFR values which were lower in the tacrolimus groups. It is important to note that the choice of treatment for SDNS is highly individualized and should be based on a thorough assessment by a pediatric nephrologist or a health-care professional familiar with the specific case. The potential benefits of both regimens must be weighed against their potential side effects to achieve a better overall health status. In addition, close monitoring is essential to ensure the treatment is effective and well-tolerated either in short- or long-term manner.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

There are no conflicts of interest.

References

1. Esezobor CI, Solarin AU, Gbadegesin R. Changing epidemiology of nephrotic syndrome in Nigerian children: A cross-sectional study. PLoS One 2020;15:e0239300.
2. Tamura H. Trends in pediatric nephrotic syndrome. World J Nephrol 2021;10:88-100.
3. Park SJ, Shin JI. Complications of nephrotic syndrome. Korean J Pediatr 2011;54:322-8.
4. Nishi S, Ubara Y, Utsunomiya Y, Okada K, Obata Y, Kai H, et al. Evidence-based clinical practice guidelines for nephrotic syndrome 2014. Clin Exp Nephrol 2016;20:342-70.
5. Menon S. Acute kidney injury in nephrotic syndrome. Front Pediatr 2018;6:428.
6. Abdel-Hafez MA, Abou-El-Hana NM, Erfan AA, El-Gamasy M, Abdel-Nabi H. Predictive risk factors of steroid dependent nephrotic syndrome in children. J Nephropathol 2017;6:180-6.
7. Bagga A. Revised guidelines for management of steroid-sensitive nephrotic syndrome. Indian J Nephrol 2008;18:31-9.
8. Kim J, Patnaik N, Chorny N, Frank R, Infante L, Sethna C. Second-line immunosuppressive treatment of childhood nephrotic syndrome: A single-center experience. Nephron Extra 2014;4:8-17.
9. Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol 2016;31:15-39.
10. Shen J, Liu C, Yan P, Wang M, Guo L, Liu S, et al. Helper T cell ($CD4^+$) targeted tacrolimus delivery mediates precise suppression of allogeneic humoral immunity. Research (Wash D C) 2022;2022:9794235.
11. Chin HJ, Chae DW, Kim YC, An WS, Ihm C, Jin DC, et al. Comparison of the efficacy and safety of tacrolimus and low-dose corticosteroid with high-dose corticosteroid for minimal change nephrotic syndrome in adults. J Am Soc Nephrol 2021;32:199-210.
12. Campagne O, Mager DE, Brazeau D, Venuto RC, Tornatore KM. The impact of tacrolimus exposure on extrarenal adverse effects in adult renal transplant recipients. Br J Clin Pharmacol 2019;85:516-29.
13. Meera M, Manikandan S, Parameswaran S. Adverse effects of tacrolimus and its associated risk factors in renal transplant recipients. Exp Clin Transplant 2023;21:22-7.
14. Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: A multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014;384:1273-81.
15. Iijima K, Sako M, Nozu K. Rituximab for nephrotic syndrome in

children. Clin Exp Nephrol 2017;21:193-202.

16. Ravani P, Rossi R, Bonanni A, Quinn RR, Sica F, Bodria M, et al. Rituximab in children with steroid-dependent nephrotic syndrome: A multicenter, open-label, noninferiority, randomized controlled trial. J Am Soc Nephrol 2015;26:2259-66.
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.
18. Wang L, Zhu J, Xia M, Hua R, Deng F. Comparison of rituximab, cyclophosphamide, and tacrolimus as first steroid-sparing agents for complicated relapsing/steroid-dependent nephrotic syndrome in children: An evaluation of the health-related quality of life. Arch Med Sci 2022;18:275-8.
19. Sinha A, Bagga A, Gulati A, Hari P. Short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome. Pediatr Nephrol 2012;27:235-41.
20. Mathew G, Sinha A, Ahmed A, Grewal N, Khandelwal P, Hari P, et al. Efficacy of rituximab versus tacrolimus in difficult-to-treat steroid-sensitive nephrotic syndrome: An open-label pilot randomized controlled trial. Pediatr Nephrol 2022;37:3117-26.
21. Basu B, Sander A, Roy B, Preussler S, Barua S, Mahapatra TK, et al. Efficacy of rituximab versus tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: A randomized clinical trial. JAMA Pediatr 2018;172:757-64.
22. Colucci M, Angeletti A, Zotta F, Carsetti R, Lugani F, Ravà L, et al. Age and memory B cells at baseline are associated with risk of relapse and memory B-cell reappearance following anti-CD20 treatment in pediatric frequently-relapsing/steroid-dependent nephrotic syndrome. Kidney Int 2023;104:577-86.
23. Rehnberg M, Amu S, Tarkowski A, Bokarewa MI, Brisslert M. Short- and long-term effects of anti-CD20 treatment on B cell ontogeny in bone marrow of patients with rheumatoid arthritis. Arthritis Res Ther 2009;11:R123.
24. Emer JJ, Claire W. Rituximab: A review of dermatological applications. J Clin Aesthet Dermatol 2009;2:29-37.
25. Gulati A, Sinha A, Jordan SC, Hari P, Dinda AK, Sharma S, et al. Efficacy and safety of treatment with rituximab for difficult steroid-resistant and -dependent nephrotic syndrome: Multicentric report. Clin J Am Soc Nephrol 2010;5:2207-12.
26. Evans R, Salama AD. Update on rituximab: An established treatment for all immune-mediated kidney diseases? Nephron Clin Pract 2014;126:97-109.
27. Li HY, Li B, Wei YG, Yan LN, Wen TF, Zhao JC, et al. Higher tacrolimus blood concentration is related to hyperlipidemia in living donor liver transplantation recipients. Dig Dis Sci 2012;57:204-9.
28. Kostoglou-Athanassiou I, Tzanavari A, Basdragianni D, Papadaki A, Dadiras N, Athanassiou P. FRI0238 The effect of rituximab on lipid levels in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:454.
29. Fernández-Nebro A, Marenco JL, López-Longo F, Galindo M, Hernández-Cruz BE, Narváez J, et al. The effects of rituximab on the lipid profile of patients with active systemic lupus erythematosus: Results from a nationwide cohort in Spain (LESIMAB). Lupus 2014;23:1014-22.
30. Yin S, He T, Li Y, Wang J, Zeng W, Tang S, et al. Rituximab shows no effect on remission in patients with refractory nephrotic syndrome: A MOOSE-compliant meta-analysis. Medicine (Baltimore) 2016;95:e5320.
31. Butani L, Ramsamooj R. Experience with tacrolimus in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2009;24:1517-23.
32. Liang Q, Li H, Xie X, Qu F, Li X, Chen J. The efficacy and safety of tacrolimus monotherapy in adult-onset nephrotic syndrome caused by idiopathic membranous nephropathy. Ren Fail 2017;39:512-8.
33. Wallin EF, Hill DL, Linterman MA, Wood KJ. The calcineurin inhibitor tacrolimus specifically suppresses human T follicular helper cells. Front Immunol 2018;9:1184.
34. Loeffler K, Gowrishankar M, Yiu V. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol 2004;19:281-7.
35. Mo X, Chen X, Ieong C, Gao X, Li Y, Liao X, et al. Early prediction of tacrolimus-induced tubular toxicity in pediatric refractory nephrotic syndrome using machine learning. Front Pharmacol 2021;12:638724.
36. Yu S, Meng S, Xiang M, Ma H. Phosphoenolpyruvate carboxykinase in cell metabolism: Roles and mechanisms beyond gluconeogenesis. Mol Metab 2021;53:101257.
37. Aouad H, Faucher Q, Sauvage FL, Pinault E, Barrot CC, Arnion H, et al. A multi-omics investigation of tacrolimus off-target effects on a proximal tubule cell-line. Pharmacol Res 2023;192:106794.
38. Joncquel M, Labasque J, Demaret J, Bout MA, Hamroun A, Hennart B, et al. Targeted metabolomics analysis suggests that tacrolimus alters protection against oxidative stress. Antioxidants (Basel) 2023;12:1412.
39. Gao X, Wang Y, Xu Z, Deng H, Yang H, Zhong F. Systematic review and meta-analysis of rituximab for steroid-dependent or frequently relapsing nephrotic syndrome in children. Front Pediatr 2021;9:626323.
40. Banh TH, Hussain-Shamsy N, Patel V, Vasilevska-Ristovska J, Borges K, Sibbald C, et al. Ethnic differences in incidence and outcomes of childhood nephrotic syndrome. Clin J Am Soc Nephrol 2016;11:1760-8.
41. Varner JD, Matory A, Gbadegesin RA. Genetic basis of health disparity in childhood nephrotic syndrome. Am J Kidney Dis 2018;72:S22-5.
42. van Doorn J, van den Bergh D, Böhm U, Dablander F, Derks K, Draws T, et al. The JASP guidelines for conducting and reporting a Bayesian analysis. Psychon Bull Rev 2021;28:813-26.

Supplementary Material

Supplementary Table 1: Risk of bias results for randomized controlled trials

ROB 2	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall ROB judgement
Basu *et al*., [21]	0	1	0	0	0	Low risk
Wang *et al*., [18]	0	1	0	1	0	Low risk
Mathew *et al*., [20]	0	1	0	1	0	Moderate risk

Domain 1: ROB arising from the randomization process, Domain 2: ROB due to deviations from the intended interventions (effect of assignment to intervention, Domain 3: ROB due to missing outcome data, Domain 4: ROB in the measurement of the outcome, Domain 5: ROB in the selection of the reported result. Total score 0: Low ROB, 1: Moderate, 2: Serious, 3: Critical, 4: No information. ROB: Risk of bias

Supplementary Table 2: Risk of bias results for nonrandomized trials

ROBINS-I	Bias due to cofounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Conclusion
Sinha *et al*., [19]	1	1	0	0	0	0	0	Low risk

ROBINS-I: Risk of bias in nonrandomized studies of interventions