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Effect of Rituximab Versus Mycophenolate Mofetil or Cyclophosphamide as Control in Lupus Nephritis: A Meta-Analysis

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Abstract: *Objective:* To evaluate the effects of rituximab versus mycophenolate mofetil or cyclophosphamide as control in lupus nephritis by meta-analysis. *Methods:* A systematic search was carried out up to January 2022, obtaining 7 studies involving 645 participants with lupus nephritis at the commencement of the investigation; 198 of them were treated with rituximab, while 447 were treated with mycophenolate mofetil or cyclophosphamide. We determined the odds ratio (OR) and mean difference (MD) with 95% confidence index (CI) to compare rituximab's efficacy to that of mycophenolate mofetil or cyclophosphamide as control in lupus nephritis using random- or fixed-effects model by dichotomous or continuous techniques. *Results:* The rituximab group showed significantly higher complete renal remission rate (OR = 2.52; 95% CI 1.30–4.91, P = 0.006) and total renal remission rates (OR = 2.22; 95% CI 1.36–3.63, P = 0.001) than the control group. However, there was no significant difference in terms of end Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (MD -1.16; 95% CI -2.88–0.57, P = 0.19), proteinuria (MD -0.31; 95% CI -0.70–0.09, P = 0.013), and serum creatinine (MD 0.01; 95% CI -0.04–0.07, P = 0.64) between the rituximab group and the control. *Conclusion:* Rituximab exhibited significantly greater complete renal remission rate and total renal remission rates, with no significant difference in terms of shorter-end SLEDAI, proteinuria, and serum creatinine, compared with the control in individuals with lupus nephritis.

Keywords: Rituximab; Mycophenolate mofetil; Cyclophosphamide; Lupus nephritis; Complete renal remission rate; Total renal remission rates; End Systemic Lupus Erythematosus Disease Activity Index; Proteinuria; Serum creatinine

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1. Introduction

Lupus nephritis occurs in up to 40% of individuals with systematic lupus erythematosus [1] and is a main contributor to illness and mortality. At present, the suggested treatment for lupus nephritis comprises prednisolone with intravenous cyclophosphamide or oral mycophenolate mofetil [2]. However, these treatments are not always effective, and recurrent relapses would require further continual management. Ultimately, long-term organ damage occurs as a consequence of drug toxicity. B-lymphocyte has a role in the development of systematic lupus erythematosus and lupus nephritis [3]. Rituximab, a monoclonal antibody against CD20, prevents pathogenic B cells from producing autoantibodies and antigens [4]. Rituximab is effective in some individuals with lupus nephritis, whether it is used solely or in combination with other immunosuppressants, comprising those who are unresponsive or with poor response to cyclophosphamide or oral mycophenolate mofetil treatment [2,5,6]. However, current data from a randomized controlled trial in which rituximab or placebo was used as an adjuvant to glucocorticoids and oral mycophenolate mofetil for lupus nephritis reported that rituximab, in comparison with placebo, had no

effect on the improvement of clinical outcomes after one year of follow-up [7]. Hence, we intended to determine the effect of rituximab in comparison with that of mycophenolate mofetil or cyclophosphamide as a control on lupus nephritis in our current study.

2. Methodology

This meta-analysis followed the accepted technique and was organized according to the epidemiology statement [8].

2.1. Study selection

The search was limited to studies in English, and the inclusion criteria were not restricted by the study type or size.

The main goal of the studies was to compare the effect of rituximab to that of mycophenolate mofetil or cyclophosphamide as a control in lupus nephritis, utilizing odds ratios (ORs), mean differences (MDs), frequency rates, or relative risks, with a 95% confidence index (CI). Editorials, review articles, letters, and comments were excluded from the analysis, as they had no correlation. **Figure 1** shows the mode of analysis.

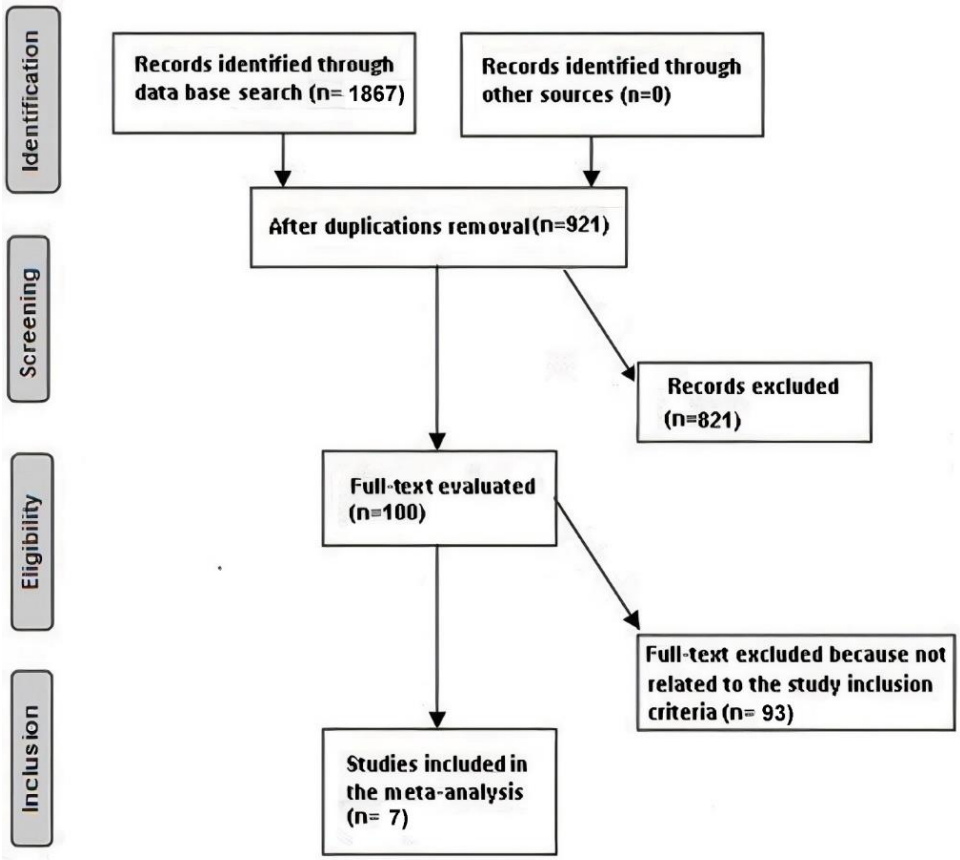

Figure 1. Schematic diagram of the study method

In this meta-analysis, we classified and integrated the inclusion criteria as follows:

(i) prospective study, randomized controlled trial, or retrospective study;
(ii) individuals with lupus nephritis;
(iii) rituximab and control as interventions;
(iv) research work comparing rituximab with mycophenolate mofetil or cyclophosphamide as control in lupus nephritis.

The exclusion criteria were as follows:

(i) research work with management other than rituximab and mycophenolate mofetil or cyclophosphamide as control;
(ii) research work that did not focus on the impact of comparative outcomes;
(iii) research work that did not evaluate the effect of rituximab compared to that of mycophenolate mofetil or cyclophosphamide as control in lupus nephritis.

2.1.1. Identification

The PICOS approach was used. We established the crucial parts of PICOS: P (population), lupus nephritis patients; I (intervention/exposure), rituximab; C (comparison), mycophenolate mofetil or cyclophosphamide as control; O (outcome), complete renal remission rate, total renal remission rates, end SLEDAI, proteinuria, and serum creatinine; S (study design), without limitation [9]. A systematic and quick search on MEDLINE/PubMed, Google Scholar, Embase, OVID, and Cochrane Library up to January 2022 was conducted by using keywords and correlated words, such as rituximab, mycophenolate mofetil, cyclophosphamide, lupus nephritis, complete renal remission rate, total renal remission rates, end SLEDAI, proteinuria, and serum creatinine (**Table 1**). EndNote was used to pool the relevant investigations to eliminate duplication. The gathering of information was done from the remaining studies. A comprehensive evaluation of the title and abstracts was also carried out to rule out any data that did not show any effect of rituximab, in comparison with mycophenolate mofetil or cyclophosphamide as control, on the outcomes investigated in individuals with lupus nephritis.

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 “rituximab” [MeSH Terms] OR “mycophenolate mofetil” [MeSH Terms] OR “cyclophosphamide” [MeSH Terms] OR “lupus nephritis” [All Fields] #2 “complete renal remission rate” [MeSH Terms] OR “proteinuria” [All Fields] OR “serum creatinine” [All Fields] OR “total renal remission rates” [All Fields] OR “end Systemic Lupus Erythematosus Disease Activity Index score” [All Fields] #3 #1 AND #2
Embase	#1 “rituximab”/exp OR “mycophenolate mofetil”/exp OR “cyclophosphamide”/exp OR “lupus nephritis”/exp #2 “complete renal remission rate”/exp OR “proteinuria”/exp OR “serum creatinine”/exp OR “total renal remission rates”/exp OR “end Systemic Lupus Erythematosus Disease Activity Index score”/exp #3 #1 AND #2
Cochrane Library	#1 (rituximab):ti,ab,kw OR (mycophenolate mofetil):ti,ab,kw OR (cyclophosphamide):ti,ab,kw OR (lupus nephritis):ti,ab,kw (word variations have been searched) #2 (complete renal remission rate):ti,ab,kw OR (proteinuria):ti,ab,kw OR (serum creatinine):ti,ab,kw OR (total renal remission rates):ti,ab,kw OR (end Systemic Lupus Erythematosus Disease Activity Index score):ti,ab,kw (word variations have been searched) #3 #1 AND #2

Abbreviations: /exp, explosion; ti,ab,kw, terms in either title, abstract, or keyword fields.

2.1.2. Screening

The data characteristics about the subject and study were collected, categorized, and aggregated into a uniform format. In order to categorize the data in a standardized form, the first author’s surname, length of study/trial, place of practice, study design, subject type, sample size, categories, demography, methods of

treatment, information source, method of evaluation (both qualitative and quantitative), statistical analysis, and primary outcome evaluation were used [10].

In order to assess the methodological quality, the Cochrane risk-of-bias tool from the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 was utilized.

The extent of bias risk was taken into account in the assessment criteria. If all criteria of quality are satisfied, the risk is low; if one of the criteria of quality is not met or is partially met, the risk is moderate; but if one of the criteria of quality is not met or included, the risk is high. Any inconsistencies in the original article were double-checked.

In order to ensure the reliability of methodology, discussions were held to address any disagreement that occurred between the two reviewers while gathering data and, if necessary, by the corresponding author when the inclusion criteria of a study/trial were found to be dependent on previously indicated standards [11]. When several types of data were found in a single study based on the evaluation of relationship, they were extracted independently.

2.1.3. Eligibility

The primary eligibility criterion was the effect of rituximab on lupus nephritis when compared to mycophenolate mofetil or cyclophosphamide as control. In lupus nephritis, the effect of rituximab, compared to mycophenolate mofetil or cyclophosphamide as control, on the complete renal remission rate, total renal remission rates, end SLEDAI, proteinuria, and serum creatinine was evaluated, and the extraction of these data was done.

2.1.4. Inclusion

Studies comparing rituximab's effect on lupus nephritis with that of mycophenolate mofetil or cyclophosphamide as control were included in the sensitivity analysis. The effect of rituximab in comparison with mycophenolate mofetil or cyclophosphamide as control in lupus nephritis was deemed a subgroup of sensitivity analysis.

2.2. Statistical analysis

At a 95% CI, the OR and MD for a fixed-effects or random-effects model were estimated using dichotomous or continuous approaches. The I^2 index ranged from 0 to 100%, with the I^2 index for heterogeneity being defined as no (0%), low (25%), moderate (50%), and high (75%) [10]. The random-effects model was used when $I^2 > 50\%$, whereas the fixed-effects model was used when $I^2 < 50\%$. In sub-group analysis, a significant difference in *P*-value was stated at 0.05 in the initial evaluation of the outcome. By evaluating the funnel plots of the logarithm of ORs compared to their standard errors, publication bias was evaluated objectively and subjectively by Egger's regression test (if $P \geq 0.05$) [10]. All of the *P*-values were two-tailed. Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform statistical analysis and produce graphs.

3. Results

Seven studies (from 2008 to 2022) that met the inclusion criteria were selected from 1,867 different studies [2,5,6, 12-15]. Based on the seven studies, there were 645 participants with lupus nephritis, among which 198 were treated with rituximab, while 447 were treated with mycophenolate mofetil or cyclophosphamide as control for lupus nephritis. All past works evaluated the effect of rituximab in comparison with mycophenolate mofetil or cyclophosphamide as control in lupus nephritis. All seven studies reported data stratified by complete renal remission rates and total renal remission rates, five studies reported data stratified by end SLEDAI, five studies reported data stratified by proteinuria, and five studies reported data

stratified by serum creatinine. At the commencement of investigation, there were between 24 and 222 individuals with lupus nephritis. **Table 2** shows the results of the seven investigations.

Table 2. Characteristics of the selected studies for meta-analysis

Study	Country	Total	Rituximab	Control	Type of control
Moroni, 2012 [6]	Italy	24	10	14	Cyclophosphamide
Rovin, 2012 [13]	USA	144	72	72	Mycophenolate mofetil or cyclophosphamide
Moroni, 2014 [2]	Italy	54	17	37	Mycophenolate mofetil or cyclophosphamide
Zhang, 2015 [5]	China	84	42	42	Cyclophosphamide
Goswami, 2019 [14]	India	222	22	200	Mycophenolate mofetil or cyclophosphamide
Roccatello, 2021 [15]	Italy	60	30	30	Mycophenolate mofetil or cyclophosphamide
Gururani, 2021 [16]	India	57	5	52	Mycophenolate mofetil or cyclophosphamide
	Total	**645**	**198**	**447**	

The rituximab group showed significantly higher complete renal remission rate (OR = 2.52; 95% CI 1.30–4.91, *P* = 0.006), with moderate heterogeneity (I^2 = 50%), and total renal remission rates (OR = 2.22; 95% CI 1.36–3.63, *P* = 0.001), with no heterogeneity (I^2 = 0%), in comparison with the control group, as shown in **Figures 2** and **3**.

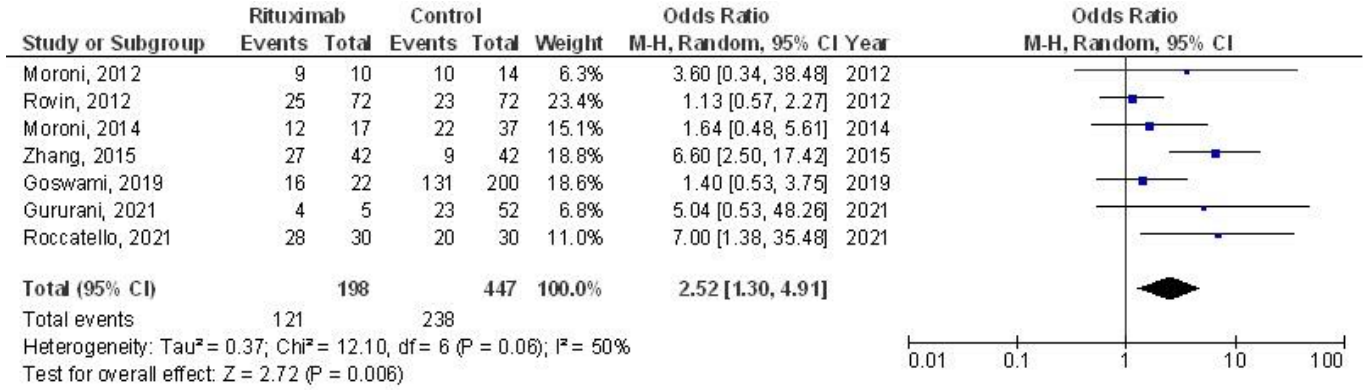

Figure 2. A forest plot showing the complete renal remission rate of rituximab versus control in individuals with lupus nephritis

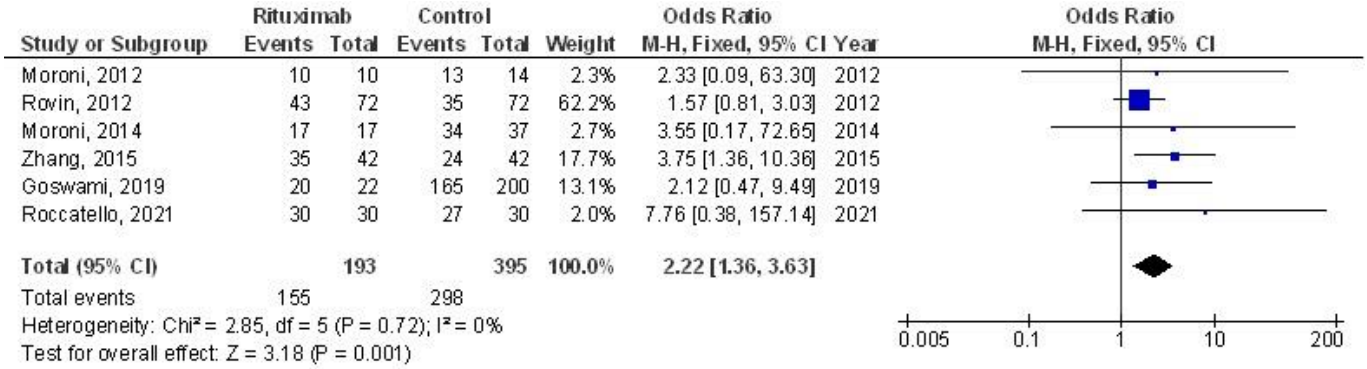

Figure 3. A forest plot showing the total renal remission rates of rituximab versus control in individuals with lupus nephritis

There were no significant differences in terms of end SLEDAI (MD -1.16; 95% CI -2.88– 0.57, *P* = 0.19), with high heterogeneity (I^2 = 83%), proteinuria (MD -0.31; 95% CI -0.70–0.09, *P* = 0.013), with

high heterogeneity (I^2 = 87%), and serum creatinine (MD 0.01; 95% CI -0.04–0.07, P = 0.64), with no heterogeneity (I^2 = 0%), between rituximab and control in individuals with lupus nephritis, as shown in **Figures 4**–**6**.

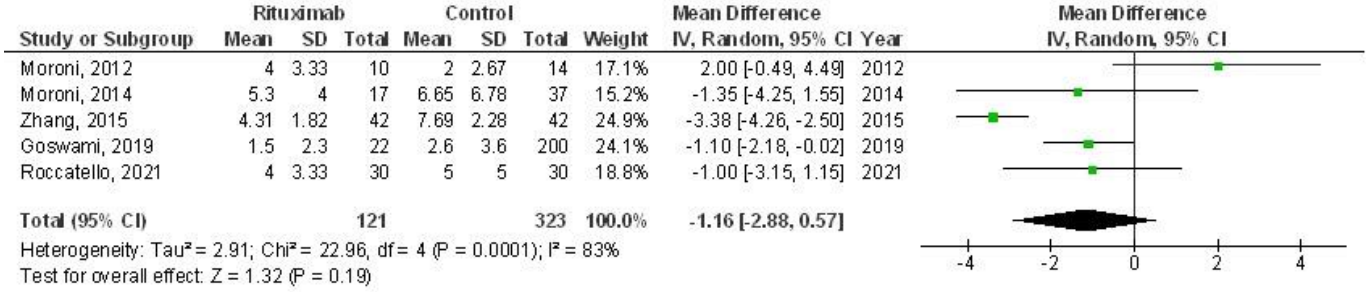

Figure 4. A forest plot showing the end SLEDAI score of the rituximab group versus the control group

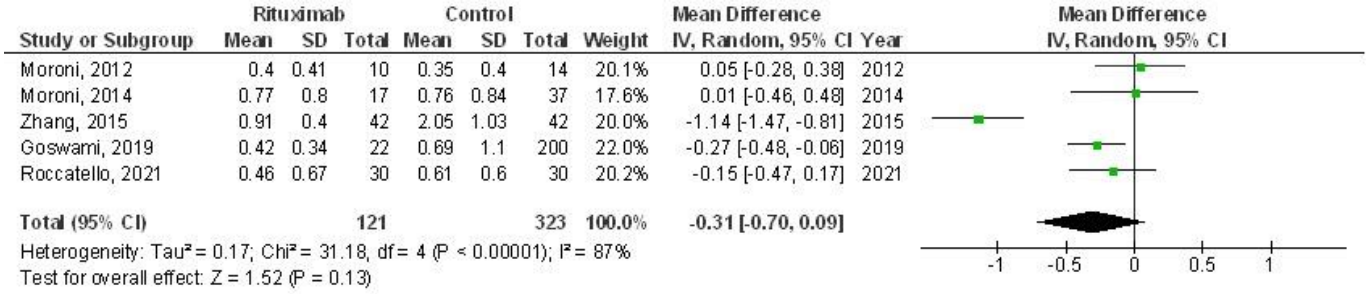

Figure 5. A forest plot showing the proteinuria of the rituximab group versus the control group

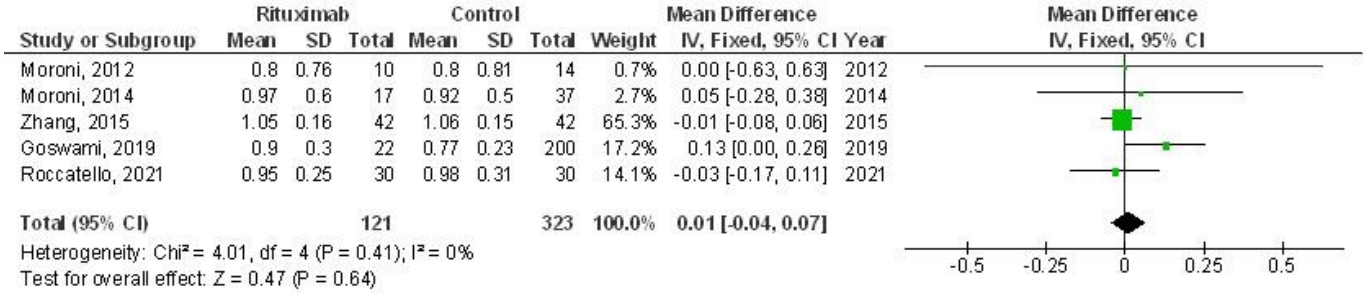

Figure 6. A forest plot showing the serum creatinine of the rituximab group versus the control groups

Since none of the studies adjusted or specified these characteristics, the stratified data did not evaluate age, gender, or ethnicity differences between the two groups. When quantitative measurement was performed via Egger's regression test and the evaluation of the funnel plot, no publication bias (P = 0.87) was found. However, some randomized controlled trials demonstrated poor methodological quality. There was no biased reporting or incomplete data in any of the studies, indicating that they were free of selective reporting bias.

4. Discussion

In the seven studies selected, 645 participants were included in our meta-analysis, among which 198 of them were treated with rituximab at the commencement of the study, while the remaining 447 were treated with mycophenolate mofetil or cyclophosphamide as control for lupus nephritis [2,5,6, 12-15]. The rituximab group showed significantly higher complete renal remission rate and total renal remission rates when compared to the control group. However, there was no significant difference in terms of end SLEDAI,

proteinuria, and serum creatinine between the rituximab group and the control group. The analysis of outcomes ought to be conducted with care in view of the small number of studies selected and the small sample size in more than half of the included studies; 5 out of 7 studies had a sample size of less than 100, suggesting the need for additional research to either validate these findings or perhaps contribute to the confidence in the effect assessment.

Lately, a growing number of studies have revealed that the addition of rituximab appears to be of benefit to the management of lupus nephritis [2,5,6]. Kotagiri *et al*. [16] demonstrated a partial or complete renal response to rituximab therapy in 79% of participants with refractory illness who did not respond to standard treatment (steroids plus cyclophosphamide, mycophenolate, or azathioprine) at a median period of five months. The results from a multicentered observational study in Italy demonstrated that the renal remission rates, both complete and partial response, to rituximab in individuals with systematic lupus erythematosus refractory to standard treatment reached 94.1%, and the complete renal remission rate was 30.9% after a 12-month follow-up period [17]. This meta-analysis supported the effectiveness of rituximab as demonstrated in previous studies. Nevertheless, the lupus nephritis assessment in rituximab research on individuals suffering from active lupus nephritis has reported that the rates of renal remission, either partial or complete response, were not statistically different between the group treated with rituximab and the control group [12]. The reason for this may be the different baseline characteristics of patients in the lupus nephritis assessment with rituximab study. The patients enrolled in the lupus nephritis assessment with rituximab study were individuals with first occurrence of lupus nephritis, as opposed to the participants in our meta-analysis who had been treated with various immunosuppressive drugs and were typically resistant to standard therapy. This inconsistency may have been caused by the substantially greater sample size in our study, which may be another factor. We also pooled further renal outcomes at the end of the follow up, but no significant difference was found between them on which the addition of more studies perhaps could significantly affect the confidence level. A relative improvement in end SLEDAI and proteinuria was observed in individuals treated with rituximab. Lowering proteinuria and serum creatinine is crucial to treating lupus nephritis. However, no significant difference or relative difference in serum creatinine was observed at the end of the follow-up. The possible reason for this inconsistency is that only five studies included information on proteinuria at the end of the follow-up period, whereas the other two did not provide detailed values that might have had an impact on the results. The results indicated that the group treated with rituximab had lower proteinuria at the end of the follow-up period, although the difference was not statistically significant. However, if more cases were recognized and analyzed, rituximab may be effective at reducing proteinuria. Contis *et al*. [18] demonstrated that rituximab contributes to the improvement of proteinuria in individuals with lupus nephritis, from 3 g/24 h at baseline to 0.5 g/24 h after 12 months of follow-up. Hence, greater, properly designed, prospective, and controlled investigations are required to evaluate and assess these influences. The safety of rituximab for induction in individuals with lupus nephritis requires additional assessment.

This meta-analysis demonstrated the association between rituximab and mycophenolate mofetil or cyclophosphamide as control in individuals with lupus nephritis. In order to confirm this potential relationship and obtain outcomes that are clinically significant, additional research is required. Clinically significant outcomes have been indicated in other meta-analyses that demonstrated similar effects [7, 19-22], but a clear justification has yet to be offered to explain these outcomes, thereby necessitating further investigation. Our study did not establish whether these factors are related to the outcomes. Therefore, well-designed clinical trials are needed to evaluate these factors in different age groups, genders, and ethnicities.

5. Limitations

Since many studies were excluded from this meta-analysis, there is a possibility of collection bias. The

eliminated studies did not meet the inclusion criteria of the meta-analysis. Furthermore, we were unable to ascertain if the outcomes were associated with age, gender, or ethnicity. The goal of the study was to see if there is a link between the effect of rituximab and mycophenolate mofetil or cyclophosphamide as control in lupus nephritis on the outcomes of individuals with lupus nephritis. Since the study was based on data from previous studies, it may be bias due to missing details. This meta-analysis was based on seven studies, five of which had small sample size (under 100 participants). In addition, the type of rituximab, mycophenolate mofetil, or cyclophosphamide used in the included studies for lupus nephritis treatment varied. Individual characteristics such as age, gender, obedience, nutritional status, and ethnicity were unlikely to cause bias. As a result of multiple unpublished research and missing data, there could be a pooled influence bias. Various pharmacological drugs, treatment schedules, and dosages in addition to healthcare plans were used. Moreover, the included studies did not provide a sufficient assessment of the hospital expenses covered by the individuals studied.

6. Conclusions

When compared to controls, patients with lupus nephritis treated with rituximab had significantly higher complete and total renal remission rates. However, there was no significant difference in proteinuria, serum creatinine, or SLEDAI score between the rituximab group and the control group. Since more than half of the studies included in our meta-analysis have small sample size, the analysis of outcomes should be performed with care, along with the recommendation of other studies to verify these outcomes and perhaps contribute to the confidence in the effect evaluation.

Disclosure statement

The authors declare no conflict of interest.

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