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NEPHROLOGY - ORIGINAL PAPER

Combined rituximab and plasmapheresis or plasma exchange for focal segmental glomerulosclerosis in adult kidney transplant recipients: a meta-analysis

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Abstract

Purpose To demonstrate the efficacy of combined rituximab and plasmapheresis (PP)/plasma exchange (PE) therapy for focal segmental glomerulosclerosis in transplanted kidneys (ptFSGS).

Methods We searched MEDLINE, SCOPUS, and Cochrane Library for eligible publications. Only observational studies or clinical trials containing patients' age > 18 years were included for full-text extraction.

Results A total of eight observational studies ($n = 85$) were included in meta-analyses. With a median follow-up of 18 months (IQR 4.4), combination therapy of RTX-PP/PE in patients with ptFSGS resulted in overall remission rate of 72.7% (95% CI 52.3–86.6%) with a significant reduction of proteinuria and serum creatinine levels. Complete remission was 41.0%, while partial remission was 31.7%. The mean difference of serum creatinine levels between pre- and post-treatment was −0.65 mg/dL (95% CI −1.15 to −0.14). The mean difference of the degree of proteinuria between pre- and post-treatment was −4.79 g/day (95% CI −7.02 to −2.56). Subgroup analyses were performed after adjusted for study year, type of intervention, and primary pre-transplant lesion. Patients with recurrent FSGS tended have lesser reduction in the degree of proteinuria compared to patients with de novo FSGS. Incidence of serious adverse events with combined RTX-PP/PE therapy was 0.12 event/year.

Conclusion We conclude that combined RTX-PP/PE therapy may be considered as an alternative treatment of ptFSGS in achieving remission by lowering proteinuria and serum creatinine levels. However, the efficacy of combined RTX-PP/PE therapy must be confirmed in randomized-controlled trials.

Keywords Rituximab · Plasmapheresis · Plasma exchange · Immunoadsorption · Focal segmental glomerulosclerosis · Kidney transplant · Nephrotic syndrome

Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in adults [1]. The incidence of end-stage kidney disease (ESKD) due to FSGS in the United States has dramatically increased in the past decades, from 0.2% in 1980 to 2.3% in 2000 [2]. This increase in incidence is likely multifactorial as FSGS can develop following numerous secondary causes [3]. Interestingly, recurrence of FSGS in renal allografts occurs in 30–50% and is associated with reduced graft survival [4]. The treatment for recurrent FSGS in kidney transplant recipients is difficult, since these patients are already on immunosuppressants, such as calcineurin inhibitors (CNI).

Steroids have been the mainstream therapy for FSGS in adults, but approximately one-half of patients achieved remission [5]. Moreover, partial remission is more

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common than complete remission for FSGS. Moreover, a large proportion of patients relapse and later become steroid resistant [6]. The use of other immunosuppressive agents, such as CNI, has been shown to induce remission in resistant or steroid-dependent FSGS [6]. Nonetheless, the use of steroids and CNI can be limited in some patients due to their both short-term and long-term side effects. Rituximab (RTX), an anti-CD20 antibodies, has been introduced for treatment of FSGS in children [7]. However, clinical evidence is limited to establish its role in adults. Likewise, plasmapheresis (PP) has been shown to be effective in treatment of recurrent FSGS post-transplant with reported 50–60% remission rate in most studies [8, 9]. However, relapses are common after discontinuing PP. These data suggested that recurrent FSGS in renal allografts is difficult to treat with the current treatment regimens.

In 2011, Damodar et al. were among the first researchers to introduce the use of combined rituximab and plasmapheresis (RTX-PP) in the treatment of post-transplant FSGS (ptFSGS) [10]. In this study, combined RTX-PP resulted in reduction of serum creatinine levels and degree of proteinuria in all patients. Later, several groups of researchers have attempted to demonstrate the efficacy of combined rituximab and plasmapheresis as well as plasma exchange for ptFSGS. The sample size, however, was small and the results were inconclusive across studies. Thus, we conducted this meta-analysis to elaborate the treatment outcomes of combined RTX-PP/PE therapy for ptFSGS in adults. The knowledge obtained from this study would help guide the design of randomized-controlled trial and support the treatment decision for patients who develop FSGS in renal allografts.

Materials and methods

Information sources and search strategy

The protocol of this systematic review is registered with ResearchRegistry.com (registration number: reviewregistry843). We conducted a systematic literature search on Ovid MEDLINE, SCOPUS, and the Cochrane Library from database inception through September 2019. The literature search was conducted by two independent authors (P.H. and N.G.) using the following search approach: "focal segmental glomerulosclerosis" OR "minimal change disease" AND "rituximab". The search strategy for each database is elaborated in Supplemental Document 1. Additional articles were obtained through manual reference search of the included studies. This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [11].

Study selection

Only articles available in English were included for further screening. Other inclusion criteria include clinical trials, or observational studies that enrolled patients age ≥ 18 years with post-kidney transplant FSGS who were treated with combined rituximab-plasmapheresis/plasma exchange therapy. Studies containing secondary FSGS were excluded. Case reports or studies demonstrating either rituximab or plasmapheresis/plasma exchange alone were excluded. Eligible studies needed to provide the following outcomes: degree of proteinuria, serum creatinine levels, remissions, and relapses. Moreover, this systematic review and meta-analysis is limited to patients who developed FSGS after kidney transplantation regardless of pre-transplant primary lesions. Retrieved articles were independently examined for eligibility by two authors (P.H. and N.G.). Conflicts were resolved by consensus between the authors or by consulting the third physician or a biostatistician. All references were managed through Endnote X9.2 software (Clarivate Analytics, Philadelphia, PA, USA).

Data collection process

A structured data collecting form was developed to gather the following data from each included study: title, name of authors, publication year, and country where the study was conducted, type of study, patients' diagnosis, sample size, intervention, total dosage of rituximab, treatment outcomes, follow-up duration, CD19/20 depletion rate, and serious adverse events. Complete remission is defined by a reduction in proteinuria to less than 1 g/g upon completion of treatment course. Partial remission is defined by a reduction in proteinuria > 50% from peak proteinuria level, but still above 1 g/g upon completion of treatment. Risk of bias was assessed using ROBINS-I tool for non-randomized studies of interventions [12] with the following category; participants, intervention(s), comparator, co-intervention(s), and outcome(s). Quality of studies fulfilled inclusion criteria which was rated as low, moderate, or high risk of bias.

Sensitivity analysis and publication bias

Sensitivity analyses and subgroup analyses were performed to minimize the heterogeneity between studies. Sensitivity analyses were performed by removing one study at a time. Subgroup analyses were preformed based on the study date (prior to 2015 vs. after 2015), and type of intervention (rituximab–plasmapheresis vs. rituximab–plasma exchange). Publication bias was analysed by

Egger's regression intercept and Funnel plot if the number of included studies is greater than 10 [13].

Statistical analysis

We used the Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc, Englewood, NJ, USA) to conduct meta-analyses and SPSS version 23.0 (IBM Corp., Armonk, NY, USA) for descriptive analyses. Study with immunoadsorption will be presented in the systematic review table, but will not be included in the meta-analysis. Statistical heterogeneity of studies was assessed using Cochran's Q test and I^2 ($\leq 25\%$, insignificant heterogeneity; 26–50%, low heterogeneity; 51–75%, moderate heterogeneity; and $\geq 75\%$, high heterogeneity) [14]. Note that I^2 reported in this study was derived from fixed-effects model of analysis. We analysed the results using random-effects model or mixed-effects to minimize the heterogeneity or between-study variance. For descriptive analyses, continuous data were reported in mean ± standard deviation (SD) or median ± interquartile range (IQR), depending on data distribution. P value less than 0.05 is considered statistically significant.

Results

Study characteristics

A total of 699 potential articles were identified from our literature search. Exclusion criteria were applied to limit only studies elaborating the effect of RTX-PP/PE combination therapy in patients with post-transplant FSGS. The flowchart of systematic literature search and review is demonstrated in Fig. 1. A total of eight studies were included in the systematic review. Alachkar, 2018 comprised of both retrospective and prospective cohort. All included studies were observational studies. Four of eight cohorts were in prospective design. The treatment outcomes (degree of proteinuria and serum creatinine levels) were available in all cohorts to be included for meta-analyses. Overall remission was reported in six studies. The median follow-up duration was 18 months (IQR 4.4). Note that 81/89 (91%) patients had the primary lesion of FSGS while 8/89 (9%) had primary disease other than FSGS, including hypertension, diabetes, or unknown. Mean pre-treatment and post-treatment serum creatinine level were 2.37 ± 0.48 mg/dL and 1.86 ± 0.45 mg/dL, respectively. Mean pre-treatment and post-treatment urine protein were 7.96 ± 3.40 g/g and 3.53 ± 2.39 g/g, respectively. Study characteristics are illustrated in Table 1.

Combined RTX-PP/PE therapy on overall remission

Overall remission was analysed from six studies ($n = 51$). We demonstrated that the overall remission rate of ptFSGS was 72.7% (95% CI 52.3–86.6%; $I^2 = 28.6\%$) following combined RTX-PP/PE therapy. Event rates for complete remission and partial remission are similar. Complete remission was achieved in 41.0%, while partial remission was achieved in 31.7%. Figure 2 illustrates the Forest plot of the meta-analysis for overall remission rate.

Combined RTX-PP/PE therapy on proteinuria

Of 85 patients, combined RTX-PP/PE therapy resulted in a significant reduction of proteinuria in post-transplant FSGS. The mean difference of the degree of proteinuria between pre- and post-treatment is − 4.43 g/day (95% CI − 6.81 to − 2.04; $I^2 = 98.7\%$). The Forest plot of combined RTX-PP/PE therapy on the degree of proteinuria is illustrated in Fig. 3.

Combined RTX-PP/PE therapy on serum creatinine levels

RTX-PP/PE combination therapy resulted in a significant reduction of serum creatinine levels in post-transplant FSGS. The mean difference of serum creatinine levels between pre- and post-therapy was − 0.49 mg/dL (95% CI − 0.84 to − 0.14; $I^2 = 0\%$). The Forest plot of combined RTX-PP/PE therapy on serum creatinine levels is illustrated in Fig. 4.

Subgroup analyses

Subgroup analyses were performed based on study date (prior to 2015 vs. year 2015 and later), type of intervention (rituximab plus plasmapheresis vs. rituximab plus plasma exchange), and pre-transplant disease (FSGS vs. non-FSGS). One study with immunoadsorption was excluded from the meta-analysis. There were no significant differences in the degree of proteinuria ($Q = 1.44$, mixed-effects; $p = 0.23$) as well as serum creatinine levels ($Q = 0.55$, mixed-effects; $p = 0.46$) between studies prior to 2015 vs. after 2015. After adjusted for type of intervention, the reduction of proteinuria and serum creatinine level was similar between RTX-PP and RTX-PE groups ($Q = 1.19$, mixed effect; $p = 0.28$ for proteinuria and $Q = 0.21$, mixed effect; $p = 0.65$ for serum creatinine). Our subgroup analysis showed that the reduction of proteinuria was significantly greater among patients who had non-FSGS in pre-transplant lesion (− 8.13 g/day; 95% CI − 9.60 to − 6.65) compared to patients who had FSGS pre-transplant (− 2.52 g/day; 95% CI − 3.09 to − 1.95) ($Q = 48.35$, mixed-effects; $p < 0.001$). Nonetheless, there was no significant

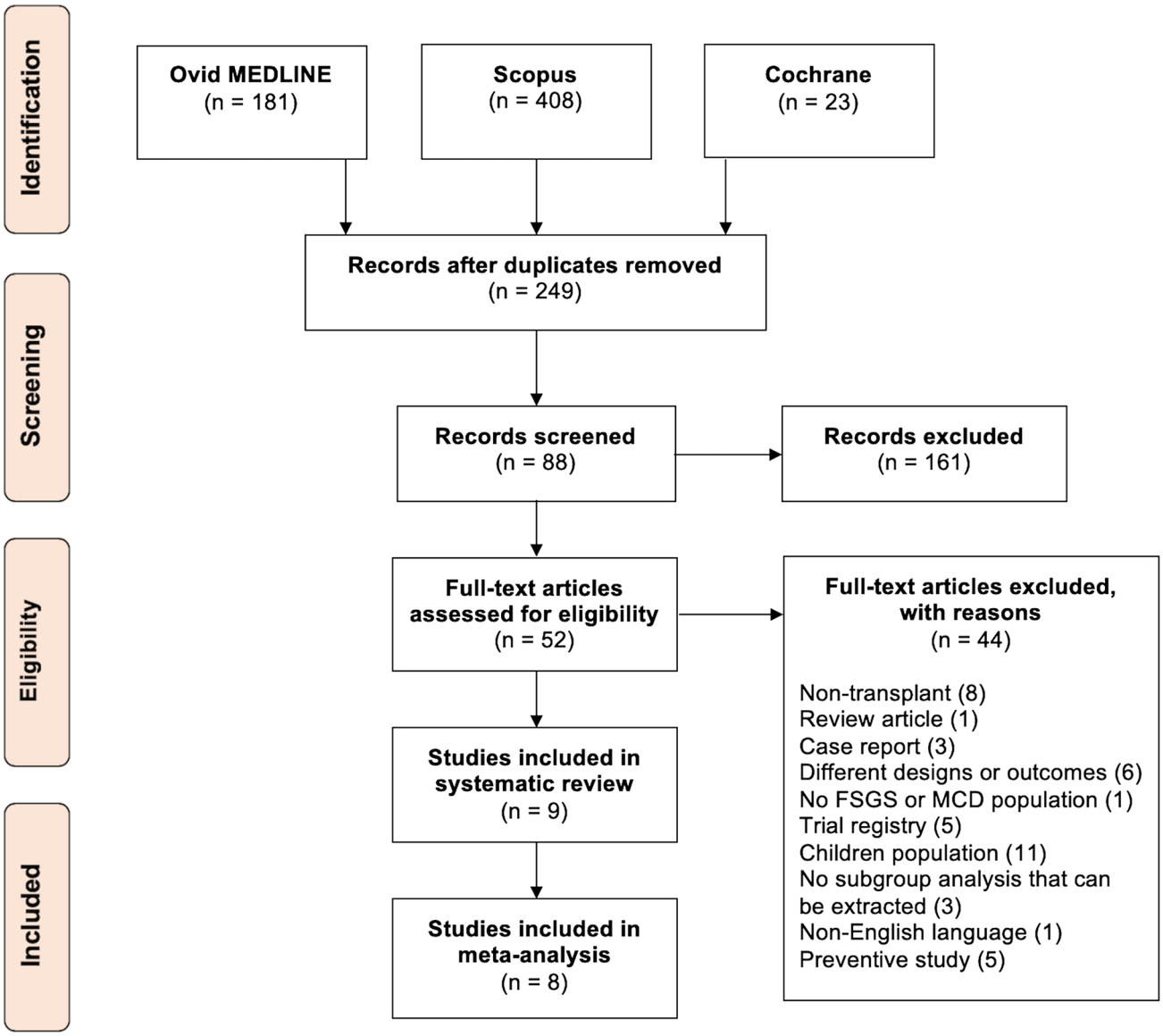

Fig. 1 Flowchart of systematic literature search from all databases. Inclusion criteria include observational studies or clinical trials, age > 18 years; treatment is combined RTX with either plasmapheresis or plasma exchange or immunoadsorption, post-kidney transplant FSGS, and in English language

difference in serum creatinine reduction after adjusted for pre-transplant lesion ($Q = 1.55$, mixed-effects; $p = 0.21$).

Adverse events

Only two studies reported serious adverse effect from RTX-PP/PE combination therapy. One study stated that sepsis occurred in 20% of patients, while the other study reported severe infection in up to 73% of patients. From our analysis, the incidence of serious adverse events following combined RTX-PP/PE therapy was 0.12 event per year.

Sensitivity analysis and publication bias

Sensitivity analyses were performed by removing one study at a time for both meta-analyses of overall remission, proteinuria, and serum creatinine levels. We found that overall remission, reductions in both proteinuria and serum creatinine levels remained statistically significant in all sensitivity analyses. Publication bias was evaluated by Egger's regression intercept. The Funnel plots for publications cannot be performed as the number of included studies is less than 10. Egger's regression intercept for overall remission, difference in mean proteinuria, and mean serum

Table 1 Characteristics of included studies

Study	Year	Country	Type of study	Patients	Primary lesion	Number	Intervention	Concurrent regimen	Mean RTX dose mg/m^2 (median ± IQR)	Outcomes	CD19/20 depletion rate	Study follow-up time	Serious adverse events
Rodriguez-Ferrero et al. [28]	2009	Spain	Observational (prospective)	Recurrent FSGS post-transplant	FSGS	3	RTX + PP	MMF, TAC, PRED	1500	Remission: 0% SCr: 4.09, 1.26, 2.1 (pre) vs. 4.3, 1.91, 1.66 (post) Proteinuria: 4.97, 7.22, 6.16 (pre) vs. 3.13, 3.99, 7.38 (post)	CD19 depleted 100%	29.7 months (21–35)	None
Damodar et al. [10]	2011	USA	Observational (retrospective)	Post-transplant FSGS	1 FSGS, 2 unknown	3	RTX + PP	MMF, TAC, PRED	875 (375–1125)	Remission: 100% (33% CR, 67% PR) SCr: 2.8, 3.4, 2.1 (pre) vs. 2.0, 2.5, 1.0 (post) eGFR: 25, 20, 37 (pre) vs. 37, 29, 82 (post) Proteinuria: 11, 12,—(pre) vs. 0.7, 1, 2 (post)	N/A	9 months	None
Tsagalis et al. [29]	2011	Greece	Observational (prospective)	Recurrent FSGS post-KT	FSGS	4	RTX + PP	MMF, TAC, PRED	2 g total	Remission: 100% (50% CR, 50% PR) Proteinuria: 9.7 ± 7.1 (pre) vs. 1.05 ± 0.7 (post) SCr: 1.5 ± 0.6 (pre) vs. 1.3 ± 0.5 (post) eGFR: 40.5 ± 15.4 (pre) vs. 52.6 ± 20.4 (post) Median follow-up time 30 months (18–60 months)	B-cell depleted 25%	34.5 months (18–60)	None

Table 1 (continued)

Study	Year	Country	Type of study	Patients	Primary lesion	Number	Intervention	Concurrent regimen	Mean RTX dose mg/m^2 (median ± IQR)	Outcomes	CD19/20 depletion rate	Study follow-up time	Serious adverse events
Alachkar et al. [30]	2013	USA	Observational (retrospective)	Recurrent FSGS post-KT	FSGS	12	RTX + TPE	MMF, TAC, PRED	375–750	Remission: 76% (36% CR, 40% PR) Proteinuria*: mean 12.2 ± 13.3 (pre) vs. 6.8 ± 13.3 (post) SCr: median 2.3 (1.5–3.0) (pre) vs. 1.9 (1.3–3.0) (post) eGFR: median 32.9 (24.1–49.2) (pre) vs. 36.3 (27.1–65.5) (post)	N/A	15.6 ± 10.6 months	N/A
Lionaki et al. [31]	2015	Greece	Observational (retrospective)	Recurrent FSGS post-KT	FSGS	4	RTX + IA	CNI, PRED	N/A	Complete remission: 2/4 (50%) Partial remission: 2/4 (50%) Proteinuria*: mean 9.08 ± 1.37 (pre) vs. 1.80 ± 1.68 (post)	N/A	48.3 months	None
Garrouste et al. [32]	2017	France	Observational (retrospective)	Recurrent FSGS post-KT	FSGS	19	RTX + TPE	CNI, PRED	750 (375–1500)	Complete remission: 9/19 (47.4%) Partial remission: 3/19 (15.8%) 5-year graft survival rate*: 100% (responders) vs. 36.5% (non-responders)	N/A	18 ± 39 months	Severe infection (73%)
Alachkar et al. [33]	2018	USA	Observational (retrospective)	Recurrent FSGS post-KT	FSGS	19	RTX + TPE	MMF, TAC, PRED	N/A	Remission: not reported Proteinuria*: mean 4.84 ± 0.76 g/g (pre) vs. 2.06 ± 0.47 (post) SCr*: median 2.5 (1.7, 3.5) mg/dL (pre) vs. 1.8 (post)	N/A	N/A	None

Table 1 (continued)

Study	Year	Country	Type of study	Patients	Primary lesion	Number	Intervention	Concurrent regimen	Mean RTX dose mg/m^2 (median ± IQR)	Outcomes	CD19/20 depletion rate	Study follow-up time	Serious adverse events
Alachkar et al. [33]	2018	USA	Observational (prospective)	Recurrent FSGS post-KT	FSGS	15	RTX + TPE	MMF, TAC, PRED	N/A	Remission: not reported Proteinuria*: mean 4.19 ± 1.14 g/g (pre) vs. 2.07 ± 0.75 (post) SCr: median 1.5 (1.3, 2.4) mg/dL (pre) vs. N/A	N/A	N/A	None
Koutroutsos et al. [34]	2019	UK	Observational (prospective)	Post-transplant FSGS	4 FSGS, 2 unknown, 1 HTN, 3 DM	10	RTX + TPE	TAC	2 g total	Complete remission: 4/10 (40%) Partial remission: 5/10 (50%) No response: 1/10 (10%) Relapse: 1/9 (11.1%) Proteinuria*: mean UPCR 517.4 ± 524.2 mg/mmol (pre) vs. 87 ± 121.6 mg/mmol (post) eGFR: mean 39 ± 24.6 (pre) vs. 59 ± 12.5 (post)	B-cell depleted 100%	20 ± 9.3 months	Sepsis (20%)

CNI calcineurin inhibitors, *CR* complete remission, *DM* diabetes mellitus, *FSGS* focal segmental glomerulosclerosis, *HTN* hypertension, *IA* immunoadsorption, *KT* kidney transplant, *MMF* mycophenolate mofetil, *PP* plasmapheresis, *PR* partial remission, *PRED* prednisone, *RTX* rituximab, *SCr* serum creatinine, *TAC* tacrolimus, *TPE* therapeutic plasma exchange, *UPCR* urine protein/creatinine ratio

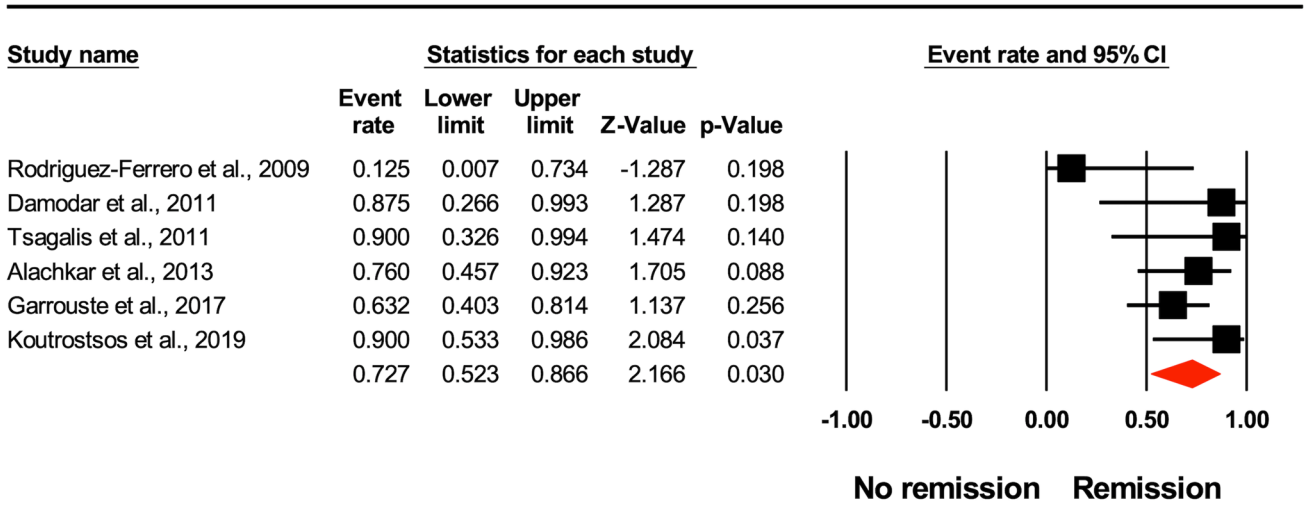

Fig. 2 Forest plot demonstrating a meta-analysis of overall remission following combined rituximab and plasmapheresis/plasma exchange therapy using random-effects model analysis

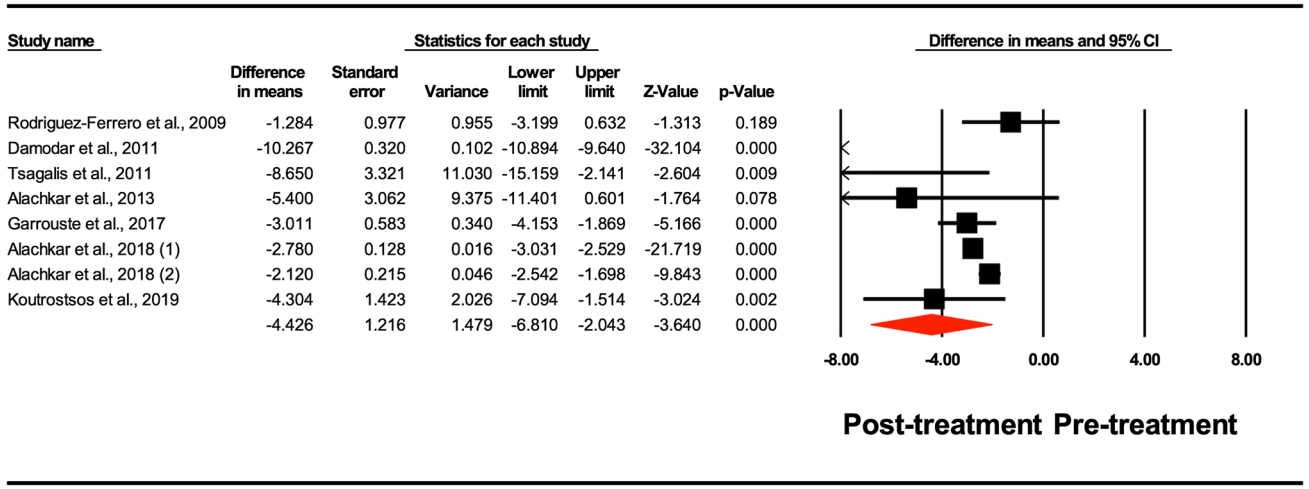

Fig. 3 Forest plot demonstrating a meta-analysis of the differences in mean proteinuria between pre- and post-treatment using random-effects model analysis

creatinine did not indicate the possibility of publication bias ($p = 0.354$, $p = 0.438$ and $p = 0.205$, respectively).

Discussion

Up to 70% of patients with ptFSGS achieved remission with a significant reduction of proteinuria (− 4.4 g/day) and serum creatinine (− 0.49 mg/dL) following combined RTX-PP/PE therapy. A systematic review of case reports and case series of patients with ptFSGS ($n = 77$) treated with PP alone showed that the remission was achieved in 71% [15]. This review, however, contained mixed adult and pediatric population and lack of control group which limit the conclusions on causality. Additional study showed that relapses were common in patients treated with PP and those who responded to treatment were likely PP-dependent [16]. Our study suggested that adding rituximab to plasmapheresis/plasma exchange treatment resulted in a significant lower serum creatinine and proteinuria leading to disease remission.

Recent progress in the pathophysiology of recurrent FSGS suggested that glomerular permeability to albumin was associated with some plasma-borne factors, known as circulating permeability factors [17]. Examples of these factors include cardiotrophin-like cytokine 1 (CLC-1)

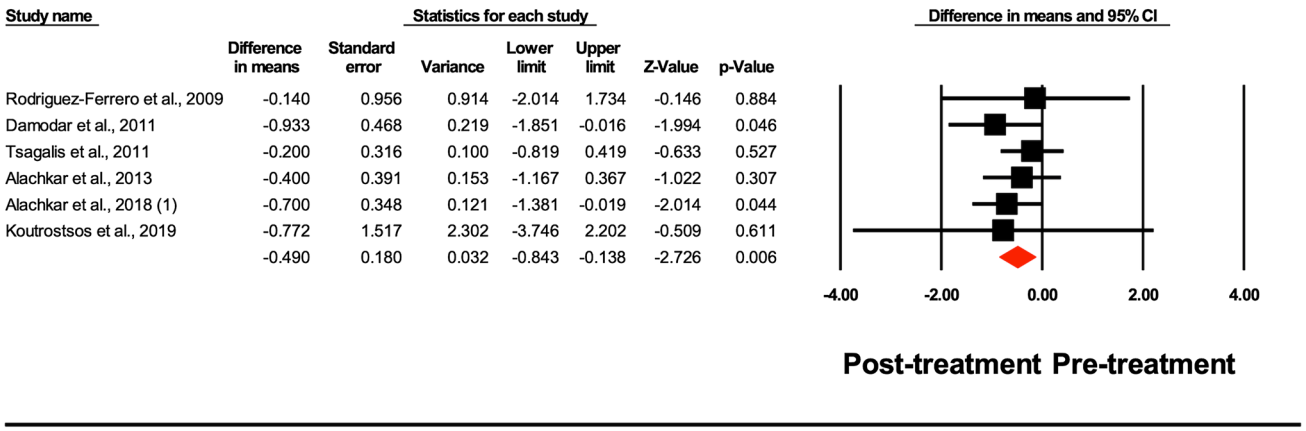

Fig. 4 Forest plot demonstrating a meta-analysis of the differences in mean serum creatinine levels between pre- and post-treatment using random-effects model analysis

and soluble urokinase receptor (suPAR). Dysregulation of these substances leads to podocyte injury and increased permeability [18, 19]. Thus, it has been proposed that plasmapheresis or plasma exchange therapy helps to eliminate circulatory permeability factors as the treatment of primary FSGS. Rituximab is a monoclonal antibody directed against CD20-positive lymphocytes. Histological study in transplanted kidneys affected by FSGS recurrence revealed some degrees of lymphocytic infiltration [20]. This finding might suggest that FSGS is an antibody-mediated disease. Thus, the rationale of adding rituximab to plasmapheresis/plasma exchange in the treatment of FSGS is to inhibit antibody production as well as to eliminate circulatory permeability factors and disease-mediated antibodies.

From subgroup analyses, the reduction of proteinuria was significantly greater in patients who had non-FSGS in pre-transplant lesion compared to patients who had recurrent FSGS. Although, this could be secondary to selection bias as patients with recurrent FSGS tended to have greater proteinuria at baseline; however, there are emerging evidence that recurrent FSGS is associated with poorer treatment outcomes and graft outcomes in comparison to de novo FSGS [21]. The treatment outcomes of either RTX-PP or RTX-PE were similar. It is widely reported that recurrent FSGS is associated with an increased risk of allograft loss up to 18.7% [22]. Autoantibodies directed against actin, angiotensin II type 1 receptor, adenosine triphosphate synthase, nephrin, and Thy1 have been implicated in the pathogenesis of FSGS recurrence [22]. However, it is not fully understood if primary FSGS and recurrent FSGS share a common pathophysiology. Furthermore, it is also possible that recurrent FSGS is usually resistant to treatment as most patients already underwent and completed the standard treatment. Bench research and clinical studies are needed to conclude the underlying mechanism of recurrent FSGS as opposed to primary FSGS.

We found that the incidence of serious adverse effects from combined RTX-PP/PE therapy was relatively low compared to what previously described in the literature. World Apheresis Registry reported the extent of side effects during apheresis to be approximately 5% [23]. One explanation is patients with post-transplant FSGS received cumulative dose of plasma with shorter duration of treatment compared to patients with the other diagnoses. Malignancies, neurological disorders, and haematological disorders are the most common indications for plasmapheresis/plasma exchange [24]. These patients generally required a higher dose of replaced plasma and longer duration of treatment. However, it is worth noting that our finding might be underpowered given its relatively small pooled sample size and only two studies reported adverse events. We advised interpreting our finding with caution.

There are some limitations to our study. First, all included studies were observation studies without comparative control group making it difficult to draw a conclusion. Second, the pooled sample size remains small with moderate heterogeneity. We encouraged the audience to apply the findings from our study with caution. Third, relapses were not reported in all studies. Having missing data could underpower the analyses. Fourth, the subtype of FSGS was not identified in all studies. As suggested by D'Agati [25], the response to treatment of FSGS is dependent on its subtype from the biopsy. Fifth, the use of pre-transplant plasmapheresis to prevent recurrence of ptFSGS was demonstrated in several studies to date; however, it is beyond the scope of this research [26, 27]. Sixth, our results could be subjected to possible confounders, such as immunosuppressive therapy, pre-transplant

prophylactic PP/PE, and ABO incompatibility of kidney transplantation. These factors, however, will be eliminated by randomization in future clinical trials. Finally, data from unpublished studies or studies in non-English language were not reviewed. However, we identified no potential publication bias in our analyses. In spite of these limitations, this is the first meta-analysis supporting a randomized-controlled trial comparing the treatment outcomes of combination therapy of RTX and PP/PE versus rituximab or PP/PE alone for ptFSGS.

Post-transplant FSGS is a disease entity that is difficult to treat. In this meta-analysis, we showed that combined RTX-PP/PE therapy resulted in a significant reduction in proteinuria and serum creatinine levels leading to remissions. However, the data are still immature in preventing relapses after treatment.

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Author contributions PH and NG performed literature search, citation screening, and data collection. PH analysed the data and drafted the manuscript. PH and NG revised and edited the manuscript for submission.

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Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interest.

Ethics approval This study does not involve human participants and/or animals. Thus, ethical approval is not required.

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