Post-transplant recurrence of focal segmental glomerular sclerosis: consensus statements

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Focal segmental glomerular sclerosis (FSGS) is 1 of the primary causes of nephrotic syndrome in both pediatric and adult patients, which can lead to end-stage kidney disease. Recurrence of FSGS after kidney transplantation significantly increases allograft loss, leading to morbidity and mortality. Currently, there are no consensus guidelines for identifying those patients who are at risk for recurrence or for the management of recurrent FSGS. Our work group performed a literature search on PubMed/Medline, Embase, and Cochrane, and recommendations were proposed and graded for strength of evidence. Of the 614 initially identified studies, 221 were found suitable to formulate consensus guidelines for recurrent FSGS. These guidelines focus on the definition, epidemiology, risk factors, pathogenesis, and management of recurrent FSGS. We conclude that additional studies are required to strengthen the recommendations proposed in this review.

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SUMMARY OF RECOMMENDATIONS

Diagnosis recommendations

- We recommend that the diagnosis of recurrent focal segmental glomerular sclerosis (FSGS) in the transplanted

kidney be made in patients with history of primary FSGS in native kidneys, both children and adults, who show:
  - Nephrotic-range proteinuria > 3.5 g/24 h or protein-to-creatinine ratio > 3g/g (>300 mg/mmol) in adults, and first morning or 24-hour protein-to-creatinine ratio >2 g/g (>200 mg/mmol) or > 3+ on urine dipstick in children, AND hypoalbuminemia (serum albumin <3.0 g/dl) (1A). (Supplementary Table S1 explains the grading system for the recommendations.)
  - Allograft biopsy showing FSGS pattern of injury and widespread podocyte effacement (1A).
- We recommend that all patients with FSGS undergoing kidney transplantation be monitored for recurrent FSGS. Patients may be monitored for proteinuria and serum creatinine daily for 1 week, twice weekly in week 2, weekly for 4 weeks, monthly for the first year, and every 3 months thereafter; preferably with use of a first morning void urine sample (1B).

Risk assessment

- We recommend that if the recipient is known to possess a causal pathogenic variant associated with FSGS, potential living-related donors should undergo genetic testing before being accepted as kidney donors, to preclude the donor from a risk of chronic kidney disease, and although uncommon, to assess the risk of development of FSGS in transplanted kidney (1A).
- We recommend kidney transplantation in patients with primary FSGS after the risk of recurrence is discussed with the recipient (2C).
- Recurrent FSGS leading to loss of a prior allograft is associated with a high risk of recurrence in a subsequent allograft. In such a situation, candidacy for a subsequent kidney transplant (especially a living donor transplant) should be carefully considered.

Treatment recommendations

- We recommend prompt initial therapy of recurrent FSGS with plasmapheresis (2A).
- We recommend not providing prophylactic plasmapheresis or rituximab before the kidney transplant (2C).

SECTION 1: INTRODUCTION

Focal segmental glomerular sclerosis (FSGS) is a leading cause of corticosteroid-resistant nephrotic syndrome in children and adults. FSGS is a term that was coined to reflect the histopathologic findings where the glomeruli show hyalinosis, sclerosis, and scarring and can result from several underlying pathophysiological mechanisms. The condition may progress to end-stage kidney disease (ESKD), especially in patients who are treatment resistant.[1]

FSGS may recur in the kidney allograft and is a notable cause of post-transplant morbidity and mortality. Recurrent FSGS (rFSGS) refers to the development of primary FSGS (pFSGS) in the transplanted kidney of patients who had ESKD secondary to pFSGS in their native kidney. Rarely, recurrence of proteinuria may be seen with certain types of genetic FSGS.

The incidence of post-transplant rFSGS ranges from 6% to 57%,[1–3] and various predisposing factors have been identified. There is a large variability in the incidence rate; this can be attributed to the fact that rFSGS is rare and most incidence rates come from studies with a small sample size and limited power. rFSGS is typically diagnosed when transplant recipients manifest nephrotic-range proteinuria with hypoalbuminemia and with or without edema. If rFSGS is suspected, allograft biopsy is necessary to confirm the diagnosis and rule out other causes of allograft injury. Studies have reported varying success with various treatment regimens for rFSGS, including the use of plasmapheresis, immunoadsorption, and immunosuppression.[4]

Familial FSGS has a low risk of recurrence.[5,6] It is hypothesized that a circulating factor, possibly of immune origin, may be responsible for other nongenetic forms of FSGS through podocyte injury.[7,8] Studies have attempted to isolate this circulating factor, and some of the potential candidates include interleukins, tumor necrosis factor, cardiotrophin-like cytokine-1, and soluble urokinase receptor.[9–15] However, none of these contenders has been consistently shown to be the permeability factor in rFSGS.

In this systematic review, we performed a literature search for data pertaining to risk factors, pathogenesis, and management of rFSGS to formulate graded recommendations for management of rFSGS in adult and pediatric patients.

1.1 METHODS

Data searches and sources

This study was registered in the International Prospective Register for Systematic Reviews (2019). To find potential studies, a database search using PubMed/Medline, Embase, and Cochrane was performed to include publications on rFSGS in the adults and children from January 1974 to October 2019. Medical subject headings used in the creation of the search strategy included focal glomerulosclerosis, recurrence, *kidney transplantation, post renal transplant, postoperative complications, graft rejection, and delayed graft function. An asterisk (*) was used to denote when a term was "exploded" to search for all related terms on the familial hierarchy. The search strategy was limited to the English language. Two reviewers (PV and SJ) assessed each title, abstract, and the full-text article. Case reports, case-control studies, and retrospective observational studies, performed among the pediatric and adult population, pertaining to rFSGS were assessed. A third reviewer (RR) reconciled incongruent reviews and assessed for similar data. A population, intervention, comparator, outcome, and study design table was constructed to illustrate the inclusion and exclusion criteria. Our search yielded 614 studies, of which 159 duplicates (studies published in >1 database) were deleted. Next, systematic reviews, meta-analyses, and abstracts were excluded; 221 eligible studies were chosen, and their methods and quality were analyzed. A Preferred Reporting Items for Systematic Reviews and

Meta-Analyses flow diagram of the complete selection process is depicted in Supplementary Figure S1. The methods, search strategy, and population, intervention, comparator, outcome, and study design/Delphi methods[16] are summarized in Supplementary Appendix S1 and Supplementary Figure S2.

Data extraction and statistical analysis

The following data were extracted from transplant recipients: age, sex, ethnicity of patient, type of donor, number of acute rejection episodes, and 5-year graft survival rates. Outcomes (with 95% confidence interval [CI]) were the incidence of rFSGS, episodes of acute rejection, and 5-year graft survival. A meta-analysis of these outcomes was conducted. The degree of between-study heterogeneity was assessed using the I^2 test; $I^2 \geq 50\%$ indicated high heterogeneity. Pooled estimate was calculated with random-effects model for high heterogeneity and fixed-effects model for low heterogeneity. Forest plot was used to visualize outcomes in each study, with estimate of combined outcomes. Publication bias was assessed graphically using funnel plots; $P \leq 0.05$ was considered statistically significant. Statistical analyses were performed with R software, version 3.1.0.

Data were extracted to evaluate the efficacy of rituximab in therapy of rFSGS. Data on 58 patients across 23 studies were collected as follows: age and sex of patient, concurrent treatment, and use of rituximab within 2 weeks of onset of rFSGS. Continuous variables were compared using Mann-Whitney *U* test, whereas association of categorical variables with remission was analyzed by χ^2 or Fisher exact test.

FSGS is a pattern of histologic glomerular injury where "focal segments" of glomeruli are subject to hyalinosis, sclerosis, and scarring. pFSGS is diagnosed when all other causes of the biopsy-proven FSGS have been ruled out. rFSGS was diagnosed when transplant recipients experienced recurrence of massive proteinuria (>40 mg/m^2 per day in children and >1g/L in adults), hypoalbuminemia (<2.5 g/dl) following transplantation,[8] and biopsy showing FSGS pattern of injury in the allograft.

Supplementary Appendix S2 provides a comprehensive overview on the diagnosis and classifications of FSGS. Supplementary Appendix S3 shows a practice algorithm for diagnosis and treatment. A recent study of the Australian and New Zealand Dialysis and Transplant Registry defined recurrence as histologically proven rFSGS and defined date of onset of recurrent disease as either clinically by the onset of nephrotic-range proteinuria with a decrease in serum albumin or as the date of histologic confirmation on tissue biopsy. With this strict definition, they revealed that only 10.3% patients (51 adults and 25 children) showed signs of recurrence occurring within the first 2 years of transplantation.[17]

SECTION 2: DIAGNOSIS AND CLINICAL PRESENTATION

- We recommend that the diagnosis of rFSGS in the transplanted kidney be made in patients with a history of pFSGS in native kidneys, both children and adults, who show:
  - Nephrotic-range proteinuria > 3.5 g/24 h or protein-to-creatinine ratio > 3 g/g (>300 mg/mmol) in adults, and first morning or 24-hour protein-to-creatinine ratio >2 g/g (>200 mg/mmol) or > 3+ on urine dipstick in children, AND hypoalbuminemia (serum albumin <3.0 g/dl) (1A).
  - Allograft biopsy showing FSGS pattern of injury and widespread podocyte effacement (1A).
- We recommend that all patients with FSGS undergoing kidney transplantation be monitored for rFSGS. Patients may be monitored for proteinuria and serum creatinine daily for 1 week, twice weekly in week 2, weekly for 4 weeks, monthly for the first year, and every 3 months thereafter, preferably with use of a first-morning void urine sample (1B).

rFSGS is suspected when a patient with biopsy-proven FSGS in the native kidney develops significant proteinuria (albuminuria ≥ 3+) following transplantation. The diagnosis may be confirmed by an allograft biopsy, which may be normal by light microscopy in the initial stages, with only electron microscopy showing extensive fusion of podocyte foot processes. The treatment of recurrent nephrotic syndrome in patients with pFSGS should not be delayed in such circumstance because the typical focal segmental sclerosis lesions recognizable by routine[18,19] microscopy can take several weeks to develop. The term "focal" is a misnomer because ultrastructural examination shows a diffuse distribution of podocyte injury in all glomeruli. Furthermore, FSGS lesions are more prevalent in deeper (i.e., juxtamedullary) sections rather than the superficial cortex and may not always be sampled by needle biopsy.[20]

The timing of FSGS recurrence may vary: early recurrence (within 48 hours; typically seen in children); infrequent and insidious late recurrence (≥1 month); or intermediate recurrence (2 days to 1 month).[4] Clinical and laboratory changes precede the histologic change by 10 days to 2 months. Three histologic stages are visualized: normal appearing glomeruli; early segmental lesions with foam cell change, endocapillary cellularity, or podocyte hyperplasia; and late focal sclerosing lesions characteristic of late-onset disease defined by some as occurring after 3 months.[21,22] In patients with either acute tubular necrosis or delayed graft function, proteinuria may be missed because of the initial oliguria/anuria.

Late recurrence takes an indolent course, with proteinuria typically appearing at least 3 months after transplantation.[23] Some authors suggest that an adequate biopsy sample should comprise ≥8 glomeruli and examination of 12 to 15 serial sections.[20] However, this issue is best viewed as a statistical problem of estimating a probability. It has been calculated that >25 glomeruli need to be present in a biopsy if one is to confidently detect a lesion that affects 10% of glomeruli.[24] The number of glomeruli required would be larger if a smaller proportion of the glomeruli were diseased or if it is desired that a specific subtype of FSGS be reliably identified.

An important issue is to distinguish between recurrence of pFSGS and *de novo* occurrence of secondary forms of the disease. The latter include chronic T-cell or antibody-mediated rejection, calcineurin inhibitor toxicity with arteriolar hyalinosis, recurrent glomerulonephritis, renal artery stenosis, atheroembolism, thrombotic microangiopathy, reflux nephropathy, viral infections (HIV, parvovirus, cytomegalovirus, or coronavirus disease 2019 [COVID-19]), drug-induced injury (interferon, lithium, or pamidronate), and light chain podocytopathies.[25]

Adaptive FSGS is a unique cause of FSGS that results from excessive nephron stress brought on by a lowered nephron capacity, an increase in body mass, or isolated glomerular

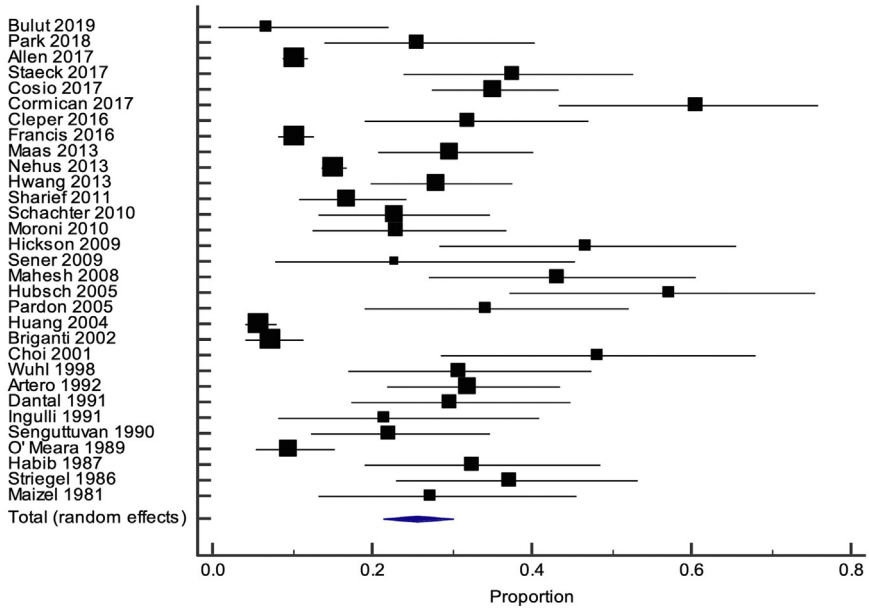

Figure 1 | Forest plot of the meta-analysis of recurrent focal segmental glomerular sclerosis incidence among kidney transplant recipients. The lower diamond in the graph represents the pooled estimate.[S1–S31]

hyperfiltration linked to particular disorders. It is distinguished by a more gradual onset of proteinuria, the lack of hypoalbuminemia, and a less severe fusion of the foot processes of the podocyte.[26] In seeking to distinguish primary from adaptive FSGS by electron microscopy, examination should focus on nonsclerotic glomeruli that do not show ischemic changes. Clinical correlation is of paramount importance because some forms of secondary disease, such as HIV-associated collapsing glomerulopathy and drug-induced injury, can result in extensive podocyte injury. Another caveat is that biopsies taken in the resolving phase of disease, possibly after therapy has been started, may show only mild changes.

SECTION 3: EPIDEMIOLOGY

3.1 Incidence

Determining the precise incidence of rFSGS and its contribution to graft failure is challenging. Thus, it may be difficult to differentiate between donor transmitted, *de novo*, secondary, and recurrent disease.[27,28] Proteinuria occurring early in the post-transplant course is usually indicative of rFSGS. Lesions of FSGS may be incidentally present in transplanted kidneys with good function, even in the absence of proteinuria, and may not always progress to allograft failure.[29,30] Chronic allograft nephropathy and nephrotoxicity due to calcineurin inhibitors may be associated with FSGS lesions in allograft recipients.

The systematic review showed that the pooled incidence of rFSGS in adults was 16.6% (95% CI, 7.5%–28.3%; Supplementary Table S8).[26,31–34] The reported pooled incidence of rFSGS in our systematic review among children was 39.6% (95% CI, 7.5%–49.9%).[26,31–34] Overall, an odds ratio (OR) for rFSGS in children compared with adults was 4.52 (95% CI, 1.82-11.28; Figure 1 and Supplementary Table S9), with younger age (6–10 years) of onset being an important determinant of rFSGS (Supplementary Table S10).[35–37] The pooled incidence of subgroup analysis based on sample size and study design was observed to be within the 95% CI of the OR, indicating that the results of this meta-analysis are robust enough. Also, no publication bias was observed on the basis of the Egger test ($P = 0.98$). We hypothesize that the variability in the reported incidence in individual studies may be attributable to confounding factors, such as cause of FSGS, patients' race, and donor graft characteristics.

3.2 Race

Although pFSGS is more common in African Americans,[38–43] our review shows that rFSGS is more common in patients of European descent (27.98% [range, 17.27%–40.14%]) than non-European patients (14.0% [range, 12.2%–15.9%]), with total fixed-effect OR of Caucasian to non-Caucasian incidence of 1.48 (95% CI, 2.29–1.84; Figure 2 and Supplementary Table S11).[1,31,33,36,37,44] The pooled incidence of subgroup analysis based on sample size and study design was observed to be within the 95% CI of the OR, indicating that the results of this meta-analysis are robust enough. Also, no publication bias was observed on the basis of the Egger test ($P = 0.10$).

3.3 Survival of allografts with rFSGS recurrence

According to an analysis of the European Renal Association–European Dialysis and Transplant Association database, recurrent glomerular disease accounts for 3% of primary graft loss and 48% of secondary graft losses.[45] In the United

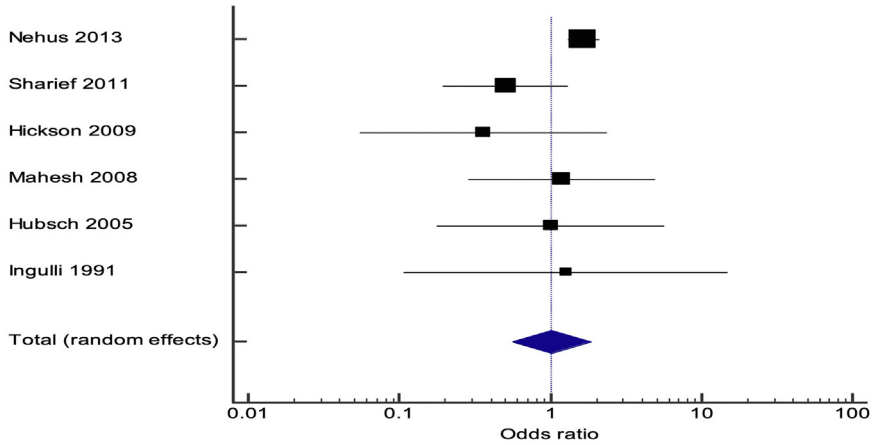

Figure 2| Forest plot of the meta-analysis of recurrent focal segmental glomerular sclerosis incidence among Caucasian and non-Caucasian kidney transplant recipients across different studies. The lower diamond in the graph represents the pooled estimate.[S11,S14,S16,S17,S25,S30]

Network of Organ Sharing registry, 1.8% of graft losses were attributed to recurrent glomerular disease.[46] Of the various glomerular diseases, rFSGS poses the highest risk of graft failure, with a relative risk of 2.25.[25,47,48] The highest risk of recurrence and graft loss is during the first 2 years after transplantation.

Among all causes of graft loss in patients with rFSGS, recurrence is implicated in the failure of >6% of primary transplant and 12% of secondary transplant.[42,49] In adult patients with rFSGS in our systematic review, recurrence confers a 5-year graft survival rate of 52.59% (95% CI, 50.09%–62.00%; n = 116) compared with a rate of 82.77% (95% CI, 79.76%–85.30%; n = 749) without recurrence (Supplementary Table S12). The pooled odds of 5-year graft survival were significantly higher among those without rFSGS versus those with rFSGS (OR, 4.24; 95% CI, 2.77–6.48; $P < 0.001$), as shown in Figure 3. There was no evidence of publication bias on the basis of the Egger test ($P = 0.11$). In a retrospective study in the pediatric population, graft survival in patients with rFSGS was 68% after a minimum follow-up of 4 years, whereas a 93% graft survival was observed in patients with other causes of ESKD.[17] Supplementary Table S13 summarizes the outcomes of kidney transplantation in patients with rFSGS included in our systematic review.

SECTION 4: RISK FACTORS

4.1 Histology

Patients with the mesangial proliferation subtype have been shown to have a higher risk of post-transplant recurrence.[50] However, the Columbia University histologic classification of FSGS does not recognize a mesangioproliferative form of the disease, although it recognizes a cellular variant with endocapillary hypercellularity. Two studies using the Columbia classification did not show a higher risk of recurrence with any subtype,[51,52] but additional studies are needed to address the recurrence rate of the relatively uncommon cellular and collapsing variants.

4.2 Progression to ESKD

A progression to ESKD in pFSGS (within 3 years from FSGS diagnosis)[32,53,54] or rFSGS in a prior kidney allograft increases the risk for rFSGS after subsequent transplantation.[6] Sex, duration of dialysis, and choice of post-transplant therapy did not influence the recurrence of FSGS.[4,55,56] Supplementary Table S14 highlights the various risk factors for rFSGS.

4.3 Genetic factors

- We recommend that if the recipient is known to possess a causal pathogenic variant associated with FSGS, potential living-related donors should undergo genetic testing before being accepted as kidney donors, to preclude the donor from a risk of chronic kidney disease, and in the recipient, to assess the risk of development of FSGS in transplanted kidney (1A).

A study evaluated steroid-resistant nephrotic syndrome in 101 pediatric patients followed up for a median of 58.5 months with age >9 years and at least 1 human leukocyte antigen-AB match and found that there were independent risk factors for disease recurrence. Notably, the patients with genetic steroid-resistant nephrotic syndrome experienced no recurrence.[57]

There are also various syndromic and nonsyndromic forms of genetic FSGS that have been described. Syndromic forms include Alport, Fabry, Frasier, Leigh, Nail-Patella, and Renal-Coloboma-Oligomeganephronia syndromes. Nonsyndromic forms of FSGS are associated with pathogenic variants in podocyte genes, such as *NPHS1*, *NPHS2*, *WT1*, α-actin-4, *CDAP*, *TRP6*, *ACTN4*, *PLCE1*, and *INF2*, which have been associated with FSGS.[58] Inheritance patterns include autosomal recessive (e.g., *NPHS1*, *NPHS2*) or autosomal dominant (e.g., *ACTN4*). Morphologically, patients with genetic forms of FSGS are indistinguishable from those with nongenetic FSGS. Mitochondrial genetic variants may also be associated with FSGS with dysmorphic mitochondria on electron microscopy.[59] The risk of recurrent proteinuria in genetic forms of FSGS is generally low. However, some

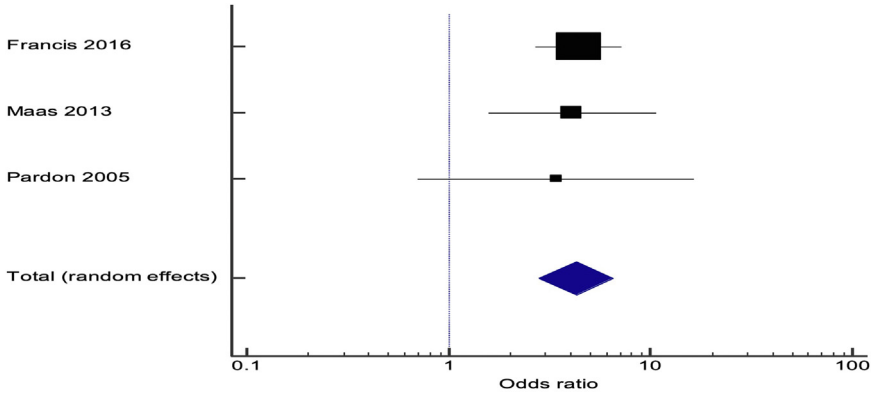

Figure 3 | Forest plot of the meta-analysis of 5-year graft survival among recurrent and nonrecurrent focal segmental glomerular sclerosis kidney transplant recipients across different studies. The lower diamond in the graph represents the pooled estimate.[S7,S8,S18]

patients with NPHS1 pathogenic variants (especially with a homozygous truncating variant, leading to total absence of nephrin) may develop anti-nephrin antibodies, resulting in nephrotic-range proteinuria.[60,61] In the kidney biopsy, the immunofluorescence staining for nephrin in podocytes occurs in an irregular pattern along the glomerular basement membranes.[62] Plasma exchange in combination with cyclophosphamide or anti–CD-20 antibody treatment is generally successful in treating these episodes. Although rFSGS has been reported in association with *NPHS2* gene variants, the response to immunosuppression/plasmapheresis in these patients occurred at rates comparable to pFSGS. This suggests that the pathomechanism of rFSGS was similar to that of pFSGS.[63] It is important to screen prospective family donors of recipients, who should be excluded if they exhibit similar risk genotype as the recipient.

Bertelli *et al.* observed that the recurrence of FSGS associated with the *NPHS2* gene variants is unlikely to recur in the kidney allograft, thus demonstrating that genetic forms of FSGS have a lower risk of recurrence.[64]

Morello *et al.* conducted a meta-analysis to investigate the role of genetic factors and corticosteroid sensitivity in post-transplant recurrence FSGS. The children with a genetic mutation experienced an exclusion of recurrence compared with recurrence seen in 61% of patients with no genetic mutations. Sensitivity to initial corticosteroid therapy in children was associated with significantly higher rates of recurrence after transplant. In a total of 7 studies included with a total cohort of 135 genetic patients, there was no recurrence reported. On the contrary, 129 children (negative genetic test) from 6 studies showed 61% recurrence rate with no heterogeneity.[65] In Supplementary Appendix S4 and Supplementary Table S15, some biomarkers associated with rFSGS have been discussed.

4.4 Impact of kidney donor type on rFSGS

- We recommend kidney transplantation in patients with primary FSGS after the risk of recurrence is discussed with the recipient (2C).
- Recurrent FSGS leading to loss of a prior allograft is associated with a high risk of recurrence in a subsequent allograft. In such a situation, candidacy for a subsequent kidney transplant (especially a living donor transplant) should be carefully considered (2A).
- We suggest that the choice between deceased donor (DD) and living donor (LD) kidney transplantation should be based on availability of grafts from DDs and complications from ongoing chronic dialysis therapy. We suggest the use of LD grafts in individuals with low risk for rFSGS because this confers potential benefits of shorter waiting times (2C).

The recommendation for LD versus DD transplantation grafts in patients with FSGS is controversial. In other forms of ESKD, LD grafts are typically associated with improved graft outcomes compared with DD kidneys. In recessive forms of FSGS (e.g., NPHS2-associated FSGS), allografts from LDs who are heterozygous were observed to have a better graft survival compared with those from DDs.[58] Physicians have avoided using LD grafts in patients with primary FSGS because of the risk of disease recurrence and lack of adequate treatment options.[66]

Data from the North American Pediatric Renal Trials and Collaborative Studies showed that, in the setting of rFSGS, the expected advantage in graft survival for kidneys arising from living donation was lost.[49,53] Along these lines, a review of the US Renal Data System database suggested that rFSGS accounted for more graft losses in the LD group with rFSGS than the DD group with rFSGS (18.7% vs. 7.8%).[67] By contrast, studies from the United Network of Organ Sharing and the Renal Allograft Disease Registries did not show a difference in frequency of disease recurrence between LD and DD recipients after correcting for confounding factors.[26,36,67] Conversely, analysis of the Australian and New Zealand Dialysis and Transplant registry revealed better 5-year LD graft survival (85% vs. 76% in adults; 80% vs. 46% in children), with a median graft survival advantage of 2.7 years.[17]

In our analysis, the pooled incidence of rFSGS was 22.9% (range, 17.6%–28.6%) in LD recipients and 21.8% (range, 15.3%–29.3%; n = 2492) in DD recipients (Supplementary

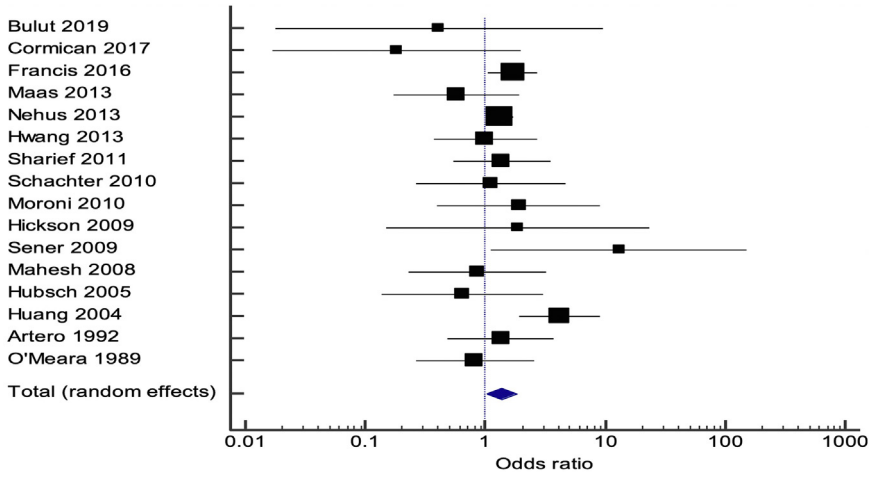

Figure 4| Forest plot of the meta-analysis of recurrent focal segmental glomerular sclerosis among living and deceased donor kidney transplant recipients across different studies. The lower diamond in the graph represents the pooled estimate.[S1,S5,S7,S8 S10–S17,S19,S23,S30,S31]

Table S16).[1,17,31–34,36,44,66,68–73] Our analysis found that DDs may have lower risk of rFSGS than LDs. We propose that genetic testing should be done for donors whose family members have genetic FSGS, presuming that genetic studies should have been done pretransplant in all children with FSGS.

The pooled odds of rFSGS were significantly higher among LDs when compared with DDs (OR, 1.39; 95% CI, 1.17–1.66; $P < 0.001$), as shown in Figure 4. The pooled incidence of subgroup analysis based on sample size, study design, and setting (single center/multicenter) was observed to be within the 95% CI of the OR, indicating that the results of this meta-analysis are robust enough. Also, no publication bias was observed on the basis of the Egger test ($P = 0.57$). However, the data are not adjusted for recipient race, recipient age, and genetic basis of FSGS in the native kidneys. After lengthy discussions, there still is insufficient data to make a definitive recommendation on whether DD offers a lower risk of rFSGS compared with LD.

4.5 Effect of induction therapy on rFSGS

Data on the effects of induction therapy are derived from observation studies with a wide variation in reported incidence of rFSGS (Supplementary Table S17). Raafat *et al.* were the first to analyze the effect of induction therapy on rFSGS.[74] Induction with antilymphocyte globulin and antithymocyte globulin was compared with controls with no induction. The antithymocyte globulin group had 88% recurrence as opposed to 43% recurrence in the antilymphocyte globulin group. In contrast, Pascual *et al.* demonstrated that there were no major differences in the incidence of recurrence following induction therapy with alemtuzumab, interleukin 2 receptor antagonists, or antithymocyte globulin group. At this time, it is unclear if specific induction therapy has an effect on rFSGS.[74–76]

4.6 Effect of nephrectomy

A survey done on the current practice regarding FSGS recurrence after pediatric kidney transplantation found that 37% of patients underwent unilateral or bilateral nephrectomy before transplant.[77] The literature search did not reveal any evidence for or against native kidney nephrectomy. Thus, bilateral native kidney nephrectomy before kidney transplantation as a preventive measure of recurrence cannot be recommended.

4.7 The role of autoantibodies

The role of anti-nephrin antibodies in nongenetic recurrent FSGS is being actively investigated. Circulating anti-actin and anti-ATP synthase antibodies were reported in 8 of 60 children with nongenetic idiopathic nephrotic syndrome.[78] In a single case of rFSGS, anti-angiotensin-1 receptor antibody was found, with improvement of symptoms with plasmapheresis, i.v. Ign therapy, and losartan therapy.[79] A panel of seven Abs (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) were found to predict post-transplant FSGS recurrence with 92% accuracy.[80] Anti-nephrin antibodies were first implicated in minimal change disease.[81] Pretransplant anti-nephrin antibody was reported in 1 patient who presented with early post-transplant recurrence of FSGS.[82] In a recent study of 22 Japanese pediatric kidney transplant recipients with nongenetic FSGS, 11 experienced post-transplant recurrence. Elevated levels of anti-nephrin antibodies were noted in these patients, with punctate IgG deposition observed in graft biopsies. Biopsies after remission showed no IgG staining and a normal nephrin expression pattern. Anti-nephrin antibody levels decreased after remission. In contrast, patients with genetic FSGS and those with nongenetic FSGS without recurrence showed comparable anti-nephrin antibody levels to control individuals, with normal graft biopsy results. The role of autoantibodies needs to be further validated in larger cohorts.

SECTION 5: TREATMENT OF RECURRENT FSGS

5.1 Overview of treatment of rFSGS

Because of the paucity of well-designed randomized trials, the management of rFSGS has not been standardized. Multiple

treatments have been prescribed, making it difficult to analyze the specific outcomes associated with any 1 particular therapy. Current treatment options include plasmapheresis or immunoadsorption therapy, immunosuppressive therapy with a calcineurin inhibitor and use of anti-CD20 monoclonal antibodies for B-cell depletion, and management of concomitant modifiable risk factors (Supplementary Appendix S5). Supplementary Appendix S6 highlights the current ongoing trials. Pulse methylprednisolone therapy has been shown to be effective in a few studies but warrants more investigation.[22,83]

- We recommend prompt initial therapy of rFSGS with intensive plasmapheresis (1C).
- We recommend not providing prophylactic plasmapheresis or rituximab before the kidney transplant (2C).

5.1A Plasmapheresis

Therapeutic plasma exchange (TPE), or plasmapheresis, has been considered as a treatment for rFSGS because of the underlying putative pathogenic role of a circulating factor.[57,84] This was demonstrated with resolution of urinary albumin excretion in rats following plasmapheresis.[85] Subsequent clinical use and efficacy of intermittent TPE in the post-transplant period has been evaluated and shows promising results (Supplementary Table S18).

The probability of achieving remission is dependent on the time of initiation of TPE.[86] Early initiation of TPE for patients with rFSGS is associated with higher remission rates.[87] One commonly used regimen includes 1.5 times plasma volume exchanges for 3 consecutive days, followed by every other day for a total of 2 weeks.[88] The regimen is combined with standard anti-rejection medications, including cyclosporine, mycophenolate mofetil, and corticosteroids.[89] In a study by Restropo *et al.*, of 17 patients with rFSGS, 12 achieved remission after treatment with plasmapheresis while on corticosteroid-based immunosuppression.[90] Demir *et al.* also demonstrated remission in patients with rFSGS after the administration of plasma exchange and i.v. cyclosporine.[91] A case study by Ino *et al.* followed the case of a 29-year-old female patient with rFSGS who achieved remission after plasmapheresis along with maintenance therapy with rituximab.[92] Hansrivjit *et al.* conducted a meta-analysis that showed combination therapy of plasmapheresis and rituximab achieved remission in 72.7% of patients (n = 85), thus indicating its success in treating patients with rFSGS.[92]

The use of preemptive TPE in the perioperative period has also been considered in high-risk patients (those who had rapid progression to ESKD or had rFSGS in their first transplant) for prophylaxis against rFSGS. In 1 study, high-risk patients were perioperatively treated with 8 sessions of TPE. None of the patients experienced recurrence, and 50% of patients with rFSGS in their first transplant experienced recurrence following their second transplant.[89] However the beneficial effect of prophylactic plasmapheresis was not corroborated by subsequent studies.[33] Vallianou *et al.* conducted a study with 26 patients. Sixteen of these patients underwent plasmapheresis, thereby achieving remission in all of those patients.[93]

Clinical practice guidelines

- We suggest that treatment be initiated promptly in a patient with a clinical diagnosis of rFSGS while kidney biopsy confirmation is awaited.
- The suggested regimen for plasmapheresis in rFSGS includes daily plasmapheresis for 3 days and then 3 times a week for 2 weeks. Exchanges of 1 to 1.5 plasma volumes, using citrate or heparin anticoagulation, with replacement by human albumin or hemofiltration solution should be targeted; fresh frozen plasma should be used as replacement fluid if plasma fibrinogen is low. Plasmapheresis may be terminated after reduction of proteinuria (<1 g/d).

5.1B Immunoadsorption

In our systematic review, 5 case series (n = 23) considered the efficacy of immunoadsorption (IA) in the treatment of rFSGS, reporting that ≈91% achieved complete or partial remission (Supplementary Table S13). Allard *et al.* observed 12 patients between the ages of 2 and 13 years who were started on IA.[94] They received a median of 4.2 IA sessions during the first week and 2.5 sessions during the second week. Two of the 12 patients (17%) achieved complete remission, and 8 of the 12 patients (66%) had partial remission, with no graft losses reported. In addition, various studies have also assessed the use of IA in combination with plasmapheresis[86,95] (Supplementary Table S19). Because of the absence of randomized trials with this combination therapy, we recommend against combined therapy (immunoadsorption and plasmapheresis) and believe the therapeutic choice between plasmapheresis or IA should depend on local availability, cost, and experience.[86,96]

IA is a selective procedure that mitigates some of the potential adverse effects observed with TPE, such as postoperative bleeding due to loss of coagulation factors.[97] Nonetheless, IA poses its own set of adverse effects. Citrate toxicity has been reported because of the use of citrate as a systemic or regional anticoagulant in the plasma circuit. Depression of humoral immunity can cause acute bacterial infections (urinary tract infections, pneumonia, and bronchitis), fungal infections, or viral infections. Reactivation of hepatitis B virus has also been reported. When the indications for Ig supplementation are met, they should be meticulously followed to avoid the risk of life-threatening anaphylaxis and transmission of blood-borne viruses.[98] In highly dependent patients, the frequency of IA sessions can potentially impact the quality of life.[94] In a study by Neciri *et al.*, treatment with immunoadsorption showed remission in 5 of 7 patients. Of these patients, 4 had LD transplant, whereas 3 had DD transplant.[99]

Clinical practice guidelines

- Immunoadsorption should initially be conducted with 2.5 to 3 plasma volumes and should be performed every day for

1 week, followed by alternate-day treatments for 2more weeks, and then twice weekly for another 2 weeks.
- We suggest that either plasmapheresis or immunoadsorption be reinstituted in patients who successfully respond to initial sessions of plasmapheresis but later relapse (2C).

5.1C Calcineurin inhibitors and corticosteroids

In our systematic review, 3 case series (n = 21) evaluated the efficacy of cyclosporine A (CsA) in patients with rFSGS and showed that ≈81% (17 of 21) of patients achieved complete or partial remission. All the patients were treated with CsA in these case series. Canaud *et al.* described 10 patients with rFSGS who received high-dose oral corticosteroids (1 mg/kg per day, tapered to 10 mg/d over 8–12 weeks), i.v. CsA (for 14 days, to achieve 2-hour CsA levels of 1200–1400 ng/ml), and prolonged plasmapheresis (6–9 months) supplemented with angiotensin pathway blockers once remission was achieved. All patients achieved complete remission, with 90% able to maintain a sustained remission compared with only 27% achieving long-term remission in controls.[88] There are limited data on high-dose tacrolimus in children or adults with rFSGS. Given the widespread use of tacrolimus, and its potential early benefit in transplant recipients, most centers prefer to continue tacrolimus instead of switching to CsA. The aim is to target tacrolimus levels around the higher recommended limit.[100,101] Shishido *et al.* demonstrated that a course of i.v. pulse methylprednisone infusions combined with high-dose oral CsA therapy can lead to complete remission in up to 70% of pediatric patients within 18 months of beginning treatment.[83] The participants received infusions of methylprednisolone on 3 consecutive days during weeks 1, 3, and 5, then monthly until 6 months after transplant. At this point, if they were in complete or partial remission, pulse therapy was continued for an additional 18 months. CsA dose was titrated on the basis of area under the curve of 0 to 4 (Supplementary Table S20).

Clinical practice guidelines

- We suggest consideration of the use of calcineurin inhibitors with concomitant high-dose corticosteroids and apheresis in selected patients with rFSGS (2B).

5.1D Low-density lipoprotein apheresis

Low-density lipoprotein apheresis, which removes potential nephrotoxic lipids, may prevent kidney injury and improve nephrotic symptoms.[102–106] A 47-year-old man with rFSGS resistant to therapy with methylprednisolone and TPE experienced partial remission with low-density lipoprotein apheresis, resulting in a decrease in proteinuria from 9.6 to 2.0 g/d.[107] A case series conducted among pediatric patients showed that 9 weeks of low-density lipoprotein apheresis therapy combined with pulse methylprednisolone produced either complete or partial remission of rFSGS proteinuria in all 7 participants.[108] Low-density lipoprotein apheresis may be considered in patients who are resistant to TPE and IA; however, more studies are warranted in evaluating the efficacy of this procedure and its use.

Clinical practice guideline

- Low-density lipid apheresis may be considered in patients who are refractory to plasmapheresis and immunoadsorption.

5.1E Rituximab

Several case reports have been published detailing the efficacy of rituximab in treating rFSGS, with variable conclusions.[109–118]

We conducted a meta-analysis of 58 patients across 23 studies and found a total remission rate of 63.8%, a complete remission rate of 48.3%, and a partial remission rate of 15.5%. On performing a subgroup analysis, we noted that age ($P = 0.24$) and rituximab ($P = 0.70$) were not significantly associated with remission. The various doses used in these 23 studies are illustrated in Supplementary Table S21. We analyzed the OR for sex (the term *sex*is used as the biological classification of individuals as males, females, or intersex) (1.66; 95% CI, 0.39–7.07; $P = 0.73$) and for starting rituximab within 2 weeks of recurrence (2.44; 95% CI, 0.80–7.50; $P = 0.11$) and noted that these 2 factors were not significantly associated with remission. The various studies on the efficacy of rituximab are shown in Supplementary Table S21. Our analysis is concurrent with a previously conducted systematic review by Araya *et al.*, who also showed similar remission rates.[119] They noted that fewer rituximab infusions and normal serum albumin at the time of recurrence were associated with higher response. Contrary to our analysis, on multivariate analysis, they found that male sex and shorter initiation time of rituximab following relapse was associated with response.

Rituximab has demonstrated a 50% remission rate in patients who did not respond to plasma exchange and i.v. cyclosporine.[120] A large group study done in kidney transplant recipients showed that rituximab can be recommended as a rescue treatment in cases refractory to initial therapy or in those who failed weaning from plasmapheresis.[118] Bharati *et al.* observed 6 patients who were treated with TPE (3 sessions per week for a total of 7–10 sessions) and single-dose rituximab (375 mg/m^2) after completion of TPE.[121] Of the 6 patients, 5 (83.3%) achieved remission in proteinuria, with the other patient requiring ongoing plasma exchange. On the other hand, El Khashab *et al.* observed 8 patients (aged 17–36 years) who were treated with a single dose of rituximab (375 mg/m^2) post-transplant, with no patients having graft loss and 1 patient developing proteinuria after 4 months.[122] Koutroutsos *et al.* conducted a study and demonstrated that combination of rituximab and plasmapheresis helped achieved remission in 9 of 10 patients with rFSGS.[123]

Rituximab as preemptive therapy. Case reports and small case series have reported on the role of rituximab for patients with a history of rFSGS post-transplant for recurrence prophylaxis in a subsequent kidney transplant (Supplementary

Table S22). A study by Boonpheng *et al.* assessed the risk of FSGS recurrence by the use of rituximab with or without plasmapheresis in patients after kidney transplantation.[124] As per this analysis, there was no difference in recurrence in patients receiving rituximab, with a pooled risk ratio of 0.82. There is no strong evidence to suggest the preemptive role of rituximab in prevention of FSGS recurrence.

Clinical practice guidelines

- Therapy with rituximab should be considered in patients with rFSGS who have contraindications to plasmapheresis, or who fail to improve despite treatment with plasmapheresis or immunoadsorption. Rituximab doses ranged from 75 to 3375 mg (median dose, 1500 mg/m^2) (2B).
- Plasmapheresis/immunoadsorption should be withheld for 48 hours following any rituximab infusion to prevent immediate drug removal.

5.1F Abatacept and belatacept

Few studies have investigated the efficacy of abatacept or belatacept (Supplementary Table S23). Yu *et al.* described resolution of proteinuria in 4 patients with rituximab-resistant rFSGS and 1 patient with primary FSGS who received abatacept at 250 or 500 mg per day.[125] Similar encouraging results were reported by Sprenger-Mähr *et al.* and Shah *et al.*[125–127]

Of concern, combination therapy with plasmapheresis and abatacept has been associated with severe sepsis.[125] Delville *et al.* prospectively treated 9 patients with rFSGS using either abatacept or belatacept but failed to induce remission or detect B7-1 in the patient biopsies.[128]

5.1G Cyclophosphamide

Cyclophosphamide has been reported to be associated with varying response rates in the treatment of rFSGS. Used as induction therapy, Kershaw *et al.* reported a complete remission in 2 of 3 patients and partial remission in 1 of 3 patients.[129] Two studies used cyclophosphamide as a substitute for an antimetabolite medication post-transplant concurrently with TPE and pulse corticosteroids, and this led to sustained rFSGS remission in all 3 patients in 1 study but only 33% of 16 children in the other study.[129,130] In another report, cyclophosphamide and TPE alone produced a sustained remission in 7 of 11 patients.[4]

5.1H Renin-angiotensin system blockade

Increased expression of nuclear factor-κB and the angiotensinogen gene has been observed in patients with rFSGS.[131] This is consistent with mouse models, where it was hypothesized that angiotensin II may contribute to rFSGS by causing preferential constriction of the afferent arteriole and associated increased intraglomerular pressure.[132]

Recently, various case series have reported the antiproteinuric efficacy of renin-angiotensin system blockers in rFSGS.[121,133,134] A study by Abuzeineh *et al.* found an association of angiotensin II type 1 receptors and rFSGS, leading to worse allograft outcome.[133]

Clinical practice guidelines

- We suggest therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with persistent proteinuria in the absence of contraindications, with close monitoring of kidney function (2C).

5.1I Newer therapies

Novel anti-CD20 antibodies. Ofatumumab has been used in rFSGS. Data are limited to case reports and small case series, and responses include complete or partial remission or no effect on proteinuria or kidney function. The positive results with the combination of obinutuzumab and the anti-CD38 (plasma cell) antibody daratumumab in patients with multidrug-resistant minimal change disease offers a future consideration for the treatment of rFSGS.[135–140]

Anti–tumor necrosis factor-α. Leroy *et al.* reported the successful treatment of a case of biopsy-proven rFSGS with only prior partial response to plasma exchange using bimonthly infliximab at a dose of 3 mg/kg along with high-dose corticosteroids (60 mg/1.73 m^2 per day).[141] During several periods when treatment was discontinued, relapses ensued that were not controlled by high-dose corticosteroids (3 methylprednisolone pulses, followed by 60 mg/1.73 m^2 per day) or etanercept (25 mg biweekly) provided alone, suggesting a synergistic action of dual concomitant therapy. In fact, when the relapses were treated with a combination of therapies again, remission was achieved.

Mesenchymal stem cell. Belingheri *et al.* proposed an innovative treatment with mesenchymal stem cells (MSCs) in a 13-year-old boy with rFSGS dependent on chronic plasma exchange. MSCs were administered in 6 doses, divided into 3 cycles of 2 infusions (1×10^6 cells/kg per dose). After the first MSC cycle, the patient did not need plasma exchange for 50 days. In view of worsening proteinuria, the patient was treated with a second and a third MSC dose at 3 and 7 months, respectively. Notably, after MSC dosing, there was a sustained decrease in the number of circulating inflammatory factors (CD40L, EN-RAGE, eotaxin-3, interleukin 16, migration inhibitory factor, myeloperoxidase [MPO], N-terminal pro–B-type natriuretic peptide [NT-proBNP], plasminogen activator inhibit [PAI-1], and thrombospondin-1). Epidermal growth factor receptor ligands (amphiregulin, epidermal growth factor, heparin-binding epidermal growth factor, and transforming growth factor-α), which are upregulated in experimental models of FSGS and in mesangial cell proliferation, were also found at significantly lower levels following MSC treatment in this patient. MSCs could potentially exert a paracrine effect, modulating the microenvironment or stimulating native kidney stem cells.[142]

RECENT STUDIES

A total of 7 studies reported the data on remission among subjects with recurrent FSGS on treatment.[18,90,91,93,99,123,133] The total sample size among these studies was 134, with the median age of the subjects ranging from 3.2 to 51 years (male, 56%; female, 44%; LD, 63%; DD, 37%; Hispanic, 16.8%; Caucasian, 42.6%; Black, 14.9%; Asian, 18.8%; others, 6.9%).

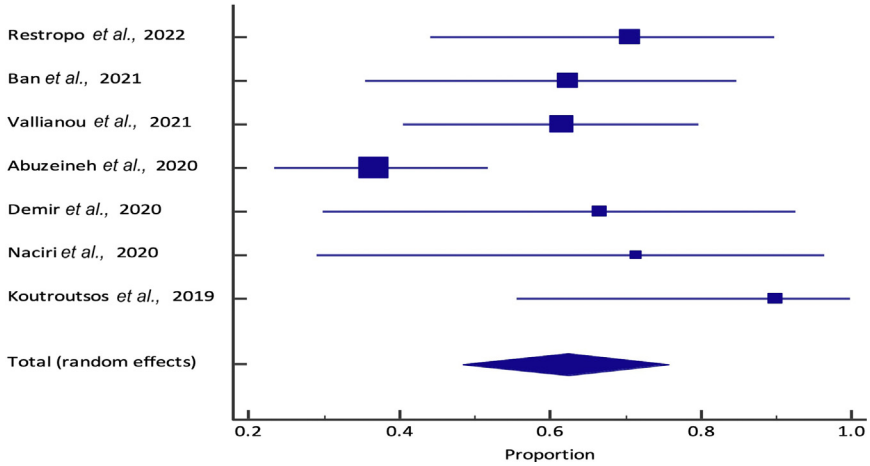

Figure 5 | Forest plot of the meta-analysis of remission among subjects with recurrent focal segmental glomerular sclerosis on treatment. The lower diamond in the graph represents the pooled estimate.[S115–S121]

The different treatments included plasmapheresis, thymoglobulin, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors, cyclophosphamide, immunoadsorption, and rituximab. The pooled proportion of remission among subjects with recurrent FSGS on these treatments was 62.51% (95% CI, 48.38%–75.61%) (I^2 = 61.57%; range, 12.28%–83.16%; $P = 0.016$; $df = 6$; random effects; 7 studies; Supplementary Table S24; Figure 5). A publication bias was observed on the basis of the Egger test ($P = 0.0174$).

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Appendix S1. Methods.
Supplementary Appendix S2. Diagnosis, clinical presentation, and classifications of focal segmental glomerular sclerosis (FSGS).
Supplementary Appendix S3. Practice algorithms.
Supplementary Appendix S4. Biomarkers.
Supplementary Appendix S5. Current treatment options for recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Appendix S6. Ongoing trials on recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Figure S1. PRISMA chart of included and excluded studies.
Supplementary Figure S2. Delphi method.
Supplementary Table S1. Grading the quality of evidence and strength of the recommendation.
Supplementary Table S2. Complete search strategy.
Supplementary Table S3. Population, intervention, comparator, outcome, and study design (PICOS) table.
Supplementary Table S4. The Joanna Briggs risk-of-bias tool.
Supplementary Table S5. Time line of guideline creation.
Supplementary Table S6. Delphi round results for guideline and practice points.
Supplementary Table S7. AMSTAR checklist.
Supplementary Table S8. Meta-analysis of recurrent focal segmental glomerular sclerosis (FSGS) incidence among kidney transplant recipients across different studies.
Supplementary Table S9. Meta-analysis of recurrent focal segmental glomerular sclerosis (FSGS) incidence among pediatric and adult kidney transplant recipients across different studies.
Supplementary Table S10. Incidence of recurrent focal segmental glomerular sclerosis (FSGS) among pediatric kidney transplant recipients stratified by age groups across different studies.
Supplementary Table S11. Recurrent focal segmental glomerular sclerosis (FSGS) incidence among Caucasian and non-Caucasian kidney transplant recipients.
Supplementary Table S12. Meta-analysis of 5-year graft survival among recurrent and nonrecurrent focal segmental glomerular sclerosis (FSGS) kidney transplant recipients across different studies.
Supplementary Table S13. Studies on efficacy of immunoadsorption in the treatment of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S14. Factors affecting the risk of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S15. Biomarker candidates for recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S16. Meta-analysis of recurrent focal segmental glomerular sclerosis (FSGS) among living and deceased donor kidney transplant recipients across different studies.
Supplementary Table S17. The effects of induction therapy on focal segmental glomerular sclerosis (FSGS) recurrence.
Supplementary Table S18. The use of prophylactic plasmapheresis to prevent recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S19. Studies on efficacy of the combined use of immunoadsorption with plasmapheresis and other modalities in the treatment of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S20. Studies on efficacy of cyclosporine in the treatment of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S21. Studies on efficacy of rituximab in the treatment of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S22. Studies on efficacy of prophylactic rituximab in recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S23. Studies on efficacy of abatacept/belatacept in the treatment of recurrent focal segmental glomerular sclerosis (rFSGS).
Supplementary Table S24. Data of remission among subjects with recurrent focal segmental glomerular sclerosis (FSGS) on treatment across different studies from year 2020 to 2022.
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