Response to Steroid and Immunosuppressive Therapies May Predict Post-transplant Recurrence of Focal Segmental Glomerulosclerosis

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Abstract

Recurrence of focal segmental glomerulosclerosis (FSGS) is a major challenge in kidney transplantation. Several clinical factors, including initial steroid sensitivity, have been associated with increased post-transplant FSGS recurrence risk. However, conflicting data have been reported, possibly due to the heterogeneous pathophysiology of FSGS and the lack of genetic testing of FSGS patients. Further, the response to immunosuppressive therapies have not been evaluated. This study aimed to assess the risk factors for post-transplant recurrence in stringently selected patients based on a comprehensive clinicopathological evaluation and genetic testing. Fifty-nine patients aged 1–25 years at FSGS onset who underwent kidney transplantation between 2002 and 2018 were enrolled. Patients with secondary, familial, syndromic, and genetic FSGS and those who did not undergo genetic testing were excluded. Data from 15 kidney transplant recipients were analyzed. Nine (60%) patients experienced post-transplant FSGS recurrence, while six patients did not. The proportion of patients who achieved complete or partial remission with initial steroid and/or additional therapies with immunosuppressive agents and/or plasmapheresis was significantly higher in the FSGS recurrence group than the group without FSGS recurrence (P=0.04). In conclusion, this study suggests that the response to steroid treatment, other immunosuppressive agents, and/or plasmapheresis may predict post-transplant FSGS recurrence.

Introduction

Focal segmental glomerulosclerosis (FSGS) recurrence is a major challenge in kidney transplantation, as it is associated with poor graft survival [1]. Disease recurrence and risk of graft loss have been reported to be 14–50% and 40–60%, respectively [1–3]. The most reliable risk factor of recurrence is previous allograft recurrence, which is associated with an 80–100% risk of recurrence in the second allograft [4–6]. In contrast, patients with genetic forms of FSGS, which have been reported to account for 24–30% of FSGS patients of age 25 years or younger at onset [7, 8], have a very low risk of recurrence [1, 6, 9]. Other clinical factors reported to be associated with increased risk of recurrence include young age [10–13], female sex [12, 13], non-African American recipients [10, 14], mesangial cell proliferation in the native kidneys [15, 16], minimal change disease determined via initial native kidney biopsy [17], rapid progression to end-stage kidney disease [10, 13, 15], pretransplant bilateral nephrectomy [12, 18], and living donor transplantation [19]. However, conflicting results have been reported regarding these factors [6, 20–22], which may be attributed to the heterogeneous pathophysiology of FSGS and the lack of genetic testing.

In 2014, Ding et al. [23] showed that initial steroid sensitivity in children with subsequent steroid-resistant nephrotic syndrome was associated with elevated risk of post-transplant recurrence, but the study lacked a detailed genetic analysis of patients. Subsequently, the same group analyzed the incidence of post-transplant FSGS recurrence in patients that did not possess mutations associated with FSGS and showed that four (80%) of five patients who tested negative for FSGS and were initially steroid-sensitive experienced post-transplant recurrence [24]. However, the sample size was small and other risk factors of recurrence were not evaluated [24]. Therefore, little is known regarding previously reported risk factors of

post-transplant recurrence in genetic-testing-negative patients. Moreover, whether response to additional immunosuppressive agents and/or plasmapheresis therapies after initial steroid resistance is associated with an increased risk for post-transplant FSGS recurrence has not been evaluated. Furthermore, it has been shown that patients with nephrotic syndrome and diffuse foot process effacement on electron micrograph have an increased likelihood of having a diagnosis of primary FSGS or circulating factors (CFs)-mediated FSGS [9, 22, 25]. However, the association between these clinicopathological factors and post-transplant recurrence has not been evaluated.

We conducted a multicenter retrospective study to examine the risk factors of post-transplant FSGS recurrence in patients who did not have known genetic mutations associated with FSGS. We also analyzed whether nephrotic syndrome at FSGS onset, diffuse foot process effacement in native kidney biopsy specimens, and treatment responses to immunosuppressive agents and plasmapheresis are associated with increased risk of post-transplant recurrence.

Results

Comparison of clinical characteristics of patients with and without post-transplant recurrence

Data from a total of 15 patients were analyzed (Fig. 1). Of the total number of patients included, nine (60%) had post-transplant FSGS recurrence, whereas six did not experience FSGS recurrence during the observational periods of more than 2 years. The median time from transplantation to recurrence was 1 day (range, 0–3 days). All of 9 patients with FSGS recurrence presented with nephrotic range proteinuria, and 6 of them were confirmed by allograft biopsy. Clinical characteristics of recurrent and non-recurrent patients are compared in Table 1. No significant differences between patients with recurrent and non-recurrent FSGS were observed regarding sex, age at onset, histological diagnosis based on initial native kidney biopsy specimens, initial steroid sensitivity, time from onset to end-stage kidney disease, time on dialysis, age at kidney transplantation, donor type, and the proportion of patients who underwent bilateral nephrectomy and prophylactic maneuver consisting of rituximab and/or plasmapheresis.

Table 1
Comparison of clinical characteristics of patients with and without post-transplant recurrence

	Recurrent (n = 9)	Non-recurrent (n = 6)	*P* value
Previously described risk factors			
Sex: male	5/9 (56%)	6/6 (100%)	0.09
Age at onset (years)	3.8 (1.6, 4.8)	5.1 (2.2, 6.7)	0.24
Initial histological diagnosis: MCD	7/9 (78%)	4/6 (67%)	0.54
CR with initial steroid therapy	5/9 (56%)	2/6 (33%)	0.38
Time from onset to ESKD (years)	2.4 (1.0, 6.6)	2.0 (0.3, 6.7)	0.56
Time on dialysis (years)	3.4 (1.8, 5.1)	4.2 (2.6, 5.8)	0.64
Age at KT (years)	9.6 (7.6, 17.2)	12.8 (8.9, 15.4)	0.60
Donor type: living-donor	5/9 (56%)	6/6 (100%)	0.09
Bilateral nephrectomy	2/9 (22%)	2/6 (33%)	0.54
Any prophylactic maneuver[a]	4/9 (44%)	3/6 (50%)	0.62
Factors which have not been previously described as risk factors of recurrence			
Nephrotic syndrome	9/9 (100%)	6/6 (100%)	-

[a]The prophylactic maneuver includes any dose of rituximab infusion and/or at least one session of plasmapheresis

[b]Three patients from each of the recurrent and non-recurrent groups had available data.

[c]Immunosuppressive therapies include calcineurin inhibitors, antimetabolites, and methylprednisolone pulse therapy.

CR, complete remission; ESKD, end-stage kidney disease; KT, kidney transplantation; MCD, minimal change disease; PR, partial remission

	Recurrent (n = 9)	Non-recurrent (n = 6)	*P* value
Edema	9/9 (100%)	6/6 (100%)	-
Diffuse foot process effacement[b]	3/3 (100%)	3/3 (100%)	-
CR or PR with initial steroid therapy	6/9 (67%)	2/6 (33%)	0.23
CR with initial steroid therapy and/or additional therapies with immunosuppressive agents and/or plasmapheresis[c]	7/9 (78%)	3/6 (50%)	0.29
CR or PR with initial steroid therapy and/or additional therapies with immunosuppressive agents and/or plasmapheresis[c]	9/9 (100%)	3/6 (50%)	0.04
[a]The prophylactic maneuver includes any dose of rituximab infusion and/or at least one session of plasmapheresis			
[b]Three patients from each of the recurrent and non-recurrent groups had available data.			
[c]Immunosuppressive therapies include calcineurin inhibitors, antimetabolites, and methylprednisolone pulse therapy.			
CR, complete remission; ESKD, end-stage kidney disease; KT, kidney transplantation; MCD, minimal change disease; PR, partial remission			

All patients presented with nephrotic syndrome and edema. The kidney specimens of all patients with available data had diffuse foot process effacement on electron microscopy evaluation, with effacement of more than 80% of the glomerular capillary surface. The proportion of patients who achieved complete or partial remission with initial steroid therapy and/or additional therapies with immunosuppressive agents and/or plasmapheresis was significantly higher in the recurrent FSGS group than in the non-recurrent group ($P = 0.04$).

Table 2 compares patients who achieved complete or partial remission with initial steroid therapy and/or additional immunosuppressive therapies with those who did not achieve remission. There were no significant differences observed between the two groups regarding sex, age at onset, histological diagnosis based on initial kidney biopsy specimens, time from onset to end-stage kidney disease, time on dialysis, age at kidney transplantation, donor type, and the proportion of patients who underwent bilateral nephrectomy and prophylactic maneuver consisting of rituximab and/or plasmapheresis.

Table 2
Comparison of clinical characteristics between patients who achieved CR or PR with initial steroid therapy and/or additional immunosuppressive therapies[a] and those who did not

	CR or PR with initial steroid therapy and/or additional therapies[a] (n = 12)	No response (n = 3)	*P* value
Previously described risk factors			
Sex: male	8/12 (67%)	3/3 (100%)	0.36
Age at onset (years)	3.9 (1.8, 5.1)	5.9 (2.3, 6.6)	0.35
Initial histological diagnosis: MCD	10/12 (83%)	1/3 (33%)	0.15
Time from onset to ESKD (years)	2.5 (0.8, 7.2)	1.5 (0.1, 2.4)	0.25
Time on dialysis (years)	3.7 (1.4, 4.9)	5.8 (3.2, 5.8)	0.22
Age at KT (years)	11.3 (8.0, 17.2)	12.4 (7.8, 13.3)	0.83
Donor type: living-donor	8/12 (67%)	3/3 (100%)	0.36
Bilateral nephrectomy	2/12 (17%)	2/3 (67%)	0.15
Any prophylactic maneuver[b]	6/12 (50%)	1/3 (33%)	0.55
Factors which have not been previously described as risk factors			
Nephrotic syndrome	12/12 (100%)	3/3(100%)	-
Edema	12/12 (100%)	3/3(100%)	-
Diffuse foot process effacement[c]	5/5 (100%)	1/1 (100%)	-

[a]Additional therapies include calcineurin inhibitors, antimetabolites, methylprednisolone pulse therapy, and/or plasmapheresis.

[b]Prophylactic maneuver includes any dose of rituximab infusion and/or at least 1 session of plasmapheresis

[c]There were 6 patients with available data.

CR, complete remission; ESKD, end-stage kidney disease; KT, kidney transplantation; MCD, minimal change disease; PR, partial remission

Post-transplant recurrence rate in patients stratified by responses to initial steroid therapy and additional treatment with immunosuppressive agents and/or plasmapheresis

Because the proportion of patients who responded to initial steroid therapy and/or additional therapies was significantly higher in the recurrent FSGS group than in the non-recurrent group, we next examined recurrence rates in patients stratified by responses to initial steroid therapy and additional treatment (Fig. 2). Eight patients achieved complete or partial remission with initial steroid therapy, of which six (75%) patients had post-transplant recurrence. Four patients achieved complete or partial remission with additional therapies after initial steroid resistance, which consisted of cyclosporine and plasmapheresis for one patient and methylprednisolone pulse therapy, cyclosporine, cyclophosphamide, and mizoribine treatment for three patients, of which three (75%) patients had post-transplant recurrence. In contrast, none of the three patients who were unresponsive to any treatment with steroid, immunosuppressive agents, and/or plasmapheresis experienced post-transplant recurrence (Fig. 2).

Discussion

Because the majority of the patients with mutations in the genes associated with FSGS do not develop recurrent disease after kidney transplantation, potential risk factors associated with FSGS recurrence should be re-analyzed in genetic-testing-negative patients. In this study, we examined the risk factors associated with post-transplant recurrence in presumed primary FSGS or CFs-mediated FSGS patients by excluding secondary FSGS, familial/syndromic FSGS, and genetic FSGS patients, who were identified based on a comprehensive clinicopathological evaluation and genetic testing. As a result, the overall post-transplant recurrence rate was high at 60% in our study, whereas the recurrence rate has been reported to be 6–55% in the previous studies, which did not perform comprehensive genetic testing [11, 12, 14, 21]. In our analysis of stringently selected patients, previously described risk factors were not shown to be associated with post-transplant recurrence. In contrast, our study suggested that complete or partial remission achieved by initial steroid therapy and/or additional therapies with immunosuppressive agents and/or plasmapheresis may predict post-transplant recurrence of FSGS, although confounding factors could not be evaluated due to small sample size.

Initial steroid sensitivity has recently been described as a risk factor for post-transplant recurrence [23, 24]. In our study, no significant differences were observed in the proportion of patients who achieved complete or partial remission with initial steroid therapy between recurrent and non-recurrent FSGS groups; however, the statistical power of our assessment may have been insufficient because of the small sample size. On the other hand, no study has assessed whether response to treatment with additional therapies, including immunosuppressive agents and/or plasmapheresis after initial steroid resistance, is associated with post-transplant recurrence. Studies have shown that a higher proportion of genetic-testing-negative patients achieve remission with immunosuppressive agents than those with genetic FSGS [26, 27]. This finding suggests that those who respond to immunosuppressants are likely to have primary FSGS or CFs-mediated FSGS [26, 27]. As shown in Fig. 2, response to initial steroid therapy and

additional immunosuppressive agents and/or plasmapheresis therapies may predict post-transplant recurrence of FSGS.

Our study has several limitations. This was a retrospective study and the sample size was too small to analyze confounding factors, although patients who achieved remission with initial steroid therapy and/or additional therapies and those who did not had similar baseline characteristics (Table 2). Additionally, despite the stringent inclusion criteria applied, some patients included in the analysis may have as yet undiscovered genetic mutations associated with FSGS. Further, there was heterogeneity regarding immunosuppressive agents used to treat each patient. Finally, selection bias may exist because decisions regarding whether or not genetic testing is performed depend on the discretion of each physician.

In conclusion, this study suggests that the response to steroid and additional immunosuppressive agents and/or plasmapheresis therapies may predict post-transplant recurrence of FSGS. Further studies that include a greater number of patients with presumed primary FSGS who are stringently selected based on a comprehensive clinicopathological evaluation and genetic testing are needed to validate this finding.

Materials And Methods

Study Population

Patients with secondary FSGS (i.e., adaptive, virus-associated, and drug-induced FSGS) and those who had a previous kidney transplantation were excluded. A total of 59 patients with a clinical diagnosis of steroid-resistant nephrotic syndrome or nephrotic range proteinuria with kidney histology of FSGS, who were 1–25 years at onset of symptoms and underwent kidney transplantation between 2002 and 2018 at seven tertiary centers for pediatric kidney transplantation in Japan, were enrolled in the study (Fig. 1). No organs were procured from prisoners. All transplantations were performed at Tokyo Women’s Medical University, Tokyo Metropolitan Children's Medical Center, Hokkaido University Graduate School of Medicine, Japanese Red Cross Nagoya Daini Hospital, Kyushu University, Toho University, and Aichi Children's Health and Medical Center. Patients with congenital nephrotic syndrome and infantile nephrotic syndrome were excluded because genetic abnormalities have been identified in 70–80% of these patients [8, 24]. Nine patients with familial or syndromic FSGS and 28 patients who did not undergo genetic testing were also excluded. In the remaining 22 patients, whole exome sequencing with a focus on 53 genes associated with FSGS or targeted next-generation sequencing for 60 genes associated with FSGS were performed as previously reported (Supplementary Tables 1 and 2) [28, 29]. Pathogenic mutations in FSGS genes were identified in seven patients, who were thus excluded from the study. Consequently, 15 patients who did not have pathogenic mutations in genes currently known to cause FSGS were analyzed (Fig. 1). This study was approved by the ethical committees of all institutions which participated in the study, including Tokyo Women’s Medical University (approval number: 4866), and performed in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective nature of the study.

Data Analysis

Previously reported risk factors for post-transplant recurrence were extracted from medical records, including sex, age at onset, initial histological diagnosis, initial steroid sensitivity (complete remission achieved by initial steroid therapy), time from onset to end-stage kidney disease, time on dialysis, age at kidney transplantation, donor type (living and deceased), bilateral nephrectomy, and prophylactic maneuver. Additionally, clinical data that have not been previously described as potential risk factors for post-transplant recurrence were also extracted, including the presence or absence of nephrotic syndrome and edema at onset, degree of foot process effacement in native kidney biopsy specimens, partial remission achieved by initial steroid therapy, and complete or partial remission achieved by additional therapies with immunosuppressive agents and/or plasmapheresis.

To examine risk factors for post-transplant recurrence, we compared clinical characteristics of patients with and without recurrent FSGS.

Definitions

Nephrotic syndrome was defined by the presence of hypoalbuminemia (serum albumin < 2.5 g/dL) and nephrotic range of proteinuria (≥ 40 mg/m^2/h) [30]. The degree of foot process effacement was calculated as previously reported [25]. Immunosuppressive therapy included calcineurin inhibitors, antimetabolites, and methylprednisolone pulse therapy. Complete remission was defined as proteinuria < 0.2 g/g or < 1 + of protein on urine dipstick for three consecutive days [31]. Partial remission was defined as proteinuria between 0.2 and 2.0 g/g or ≥ 1 + of protein on urine dipstick and 50% reduction from baseline or greater [31]. No response was defined as the failure to achieve complete or partial remission [31]. Prophylactic maneuvers included rituximab infusion and/or plasmapheresis.

The diagnosis of post-transplant recurrence of FSGS was based on the presence of at least one of the following criteria: 1) development of nephrotic range of proteinuria (urine protein excretion > 2.0 g/day); 2) graft biopsy showing diffuse effacement of podocyte foot processes via electron microscopy; and 3) histological identification of FSGS via light microscopy, in the absence of transplant glomerulopathy [32].

Statistical Analyses

Data are expressed as number (proportion) and median (interquartile range), if not otherwise specified. Comparisons of clinical characteristics between recurrent and non-recurrent patients were made using the Mann–Whitney U test. Categorical data were analyzed using the Fisher's exact test. Statistical evaluations were performed using the JMP Pro statistical package 15.0.0 (SAS Institute, Cary, NC, USA). *P*-values < 0.05 were considered statistically significant.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Acknowledgments

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Author contributions

K.M. participated in research design, the writing of the paper, the performance of the research, and data analysis. T.A. participated in the performance of the research and data analysis. S.K. participated in research design and critically reviewed the manuscript. T.H. and N.K. performed genetic analysis and critically reviewed the manuscript. R.H., H.H., K.H., Y.G., K.N., Y.H., S.S., and N.F. participated in the performance of the research and critically reviewed the manuscript. M.H. participated in research design, the writing of the paper, and data analysis. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

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Figures

Fig. 1

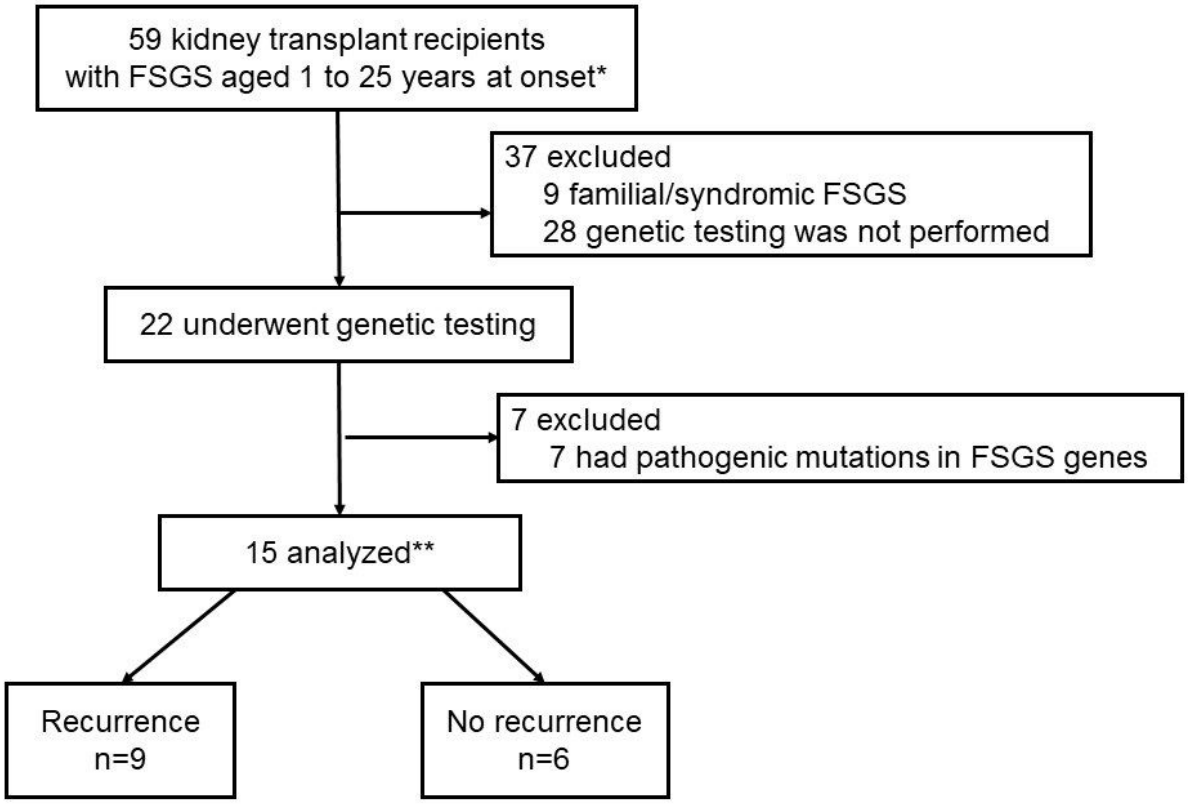

Figure 1

Flowchart describing patient enrollment in this study. *Patients with congenital nephrotic syndrome and infantile nephrotic syndrome were excluded because of the association of this patient group with genetic abnormalities. **No pathogenic mutations were identified in the genes currently known to cause FSGS via whole exome sequencing. FSGS, focal segmental glomerulosclerosis.

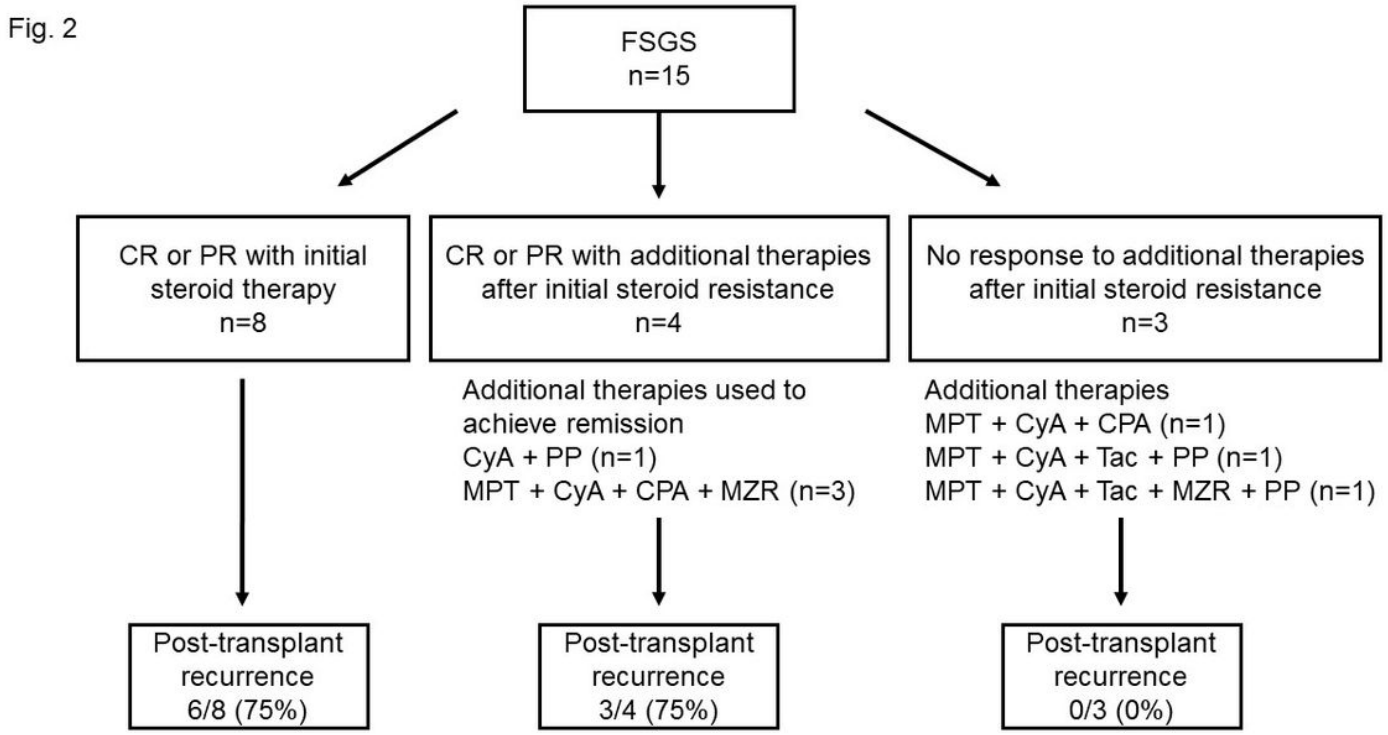

Figure 2

Post-transplant recurrence rate in patients stratified by responses to initial steroid therapy and additional treatment with immunosuppressive agents and/or plasmapheresis. CPA, cyclophosphamide; CR, complete remission; CyA, cyclosporine; FSGS, focal segmental glomerulosclerosis; MPT, methylprednisolone; MZR, mizoribine; PP, plasmapheresis; PR, partial remission; Tac, tacrolimus.

Supplementary Files

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