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# A Systematic Review and Meta-Analysis of the Rate and Risk Factors for Post-transplant Disease Recurrence in Children With Steroid Resistant Nephrotic Syndrome



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**Introduction:** Posttransplant disease recurrence is a feared and severe complication in children with steroid resistant nephrotic syndrome (SRNS), but little is known about its incidence. Recent data suggest relapse is exceptional in patients with genetic SRNS, and initial steroid sensitivity may represent a risk factor for recurrence.

**Methods:** Systematic review and meta-analysis were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to describe the post-transplant relapse rate among children with SRNS; as well as the association between recurrence and all potential risk factors, including the presence of causative genetic mutations, initial steroid sensitivity, underlying histology, and gender. The inclusion criteria were as follows: (i) children with SRNS who are undergoing kidney transplant, (ii) available data on post-transplant recurrence, (iii) no patient selection according to the underlying histology, (iv) available data on genetic testing, and (v) prospective or retrospective cohort design.

**Results:** Of the 5818 records identified, 8 studies including 581 children with SRNS met the inclusion criteria. Overall posttransplant recurrence rate was 39% (95% confidence interval [CI] 34%–44%). No genetic patient relapsed, whereas the recurrence rate in patients with no causative genetic mutation identified was 61% (95% CI 53%–69%). Children with initial steroid sensitivity were at a higher risk for recurrence with a 1.91 relative risk (RR) (95% CI 1.48–2.46) compared with those with primary SRNS (PSRNS). Gender and histology did not significantly affect relapse rate.

**Conclusion:** Post-transplant recurrence is a common event in children with idiopathic non-genetic SRNS, complicating the clinical course in over 60% of patients. The presence of a causative genetic mutation virtually excludes a recurrence. Initial steroid sensitivity is the only other significant risk factor, doubling the risk of relapse.

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SRNS is a frequent cause of end-stage kidney disease (ESKD) in children. Unfortunately, the disease has a significant incidence of post-transplant recurrence (PTx-REC), which also represents a major cause of graft loss despite the intensification of the immunosuppressive treatment.[1–3] Initial studies have identified variable recurrence rates, ranging from 30% to 50%.[4,5]

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The diffusion of a widespread and reliable genetic testing has allowed for the identification of causative genetic mutations in one-third of SRNS cases.[6] In a multicenter national study of 101 children with SRNS transplanted in Italy during more than a decade, we have previously reported no recurrence in all 41 patients with a genetic form of the disease.[7] The presence of underlying pathogenic genetic mutations was associated with a low risk of disease recurrence in other reports.[4,8,9]

On the contrary, the etiology of non-genetic SRNS remains unidentified and is supposed to involve an unknown immune-related circulating permeability factor, possibly responsible for PTx-REC.[10] Moreover,

initial steroid sensitivity has been associated with a higher rate of PTx-REC compared with primary steroid-resistant patients.[11,12]

Considering the variability of the recurrence rate reported by previous studies and the lack of the identification of consistent risk factors for relapse, we performed a systematic review and a meta-analysis of the topic.

### Objectives

We reviewed all existing literature and performed a meta-analysis to describe the rate of PTx-REC in children with SRNS, the association between recurrence and causative genetic mutations, and the impact of other risk factors (initial steroid sensitivity, gender, kidney histology, time to ESKD, age at onset, type of donor, prophylactic plasmapheresis).

## METHODS

### Data Sources and Search Strategy

The Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement were used.[13]

A literature search was conducted using 4 electronic databases (Medline via PubMed, EMBASE, Web of Science and Cochrane Library) from inception to 30 January 2022 (date last searched). The search methodology was tailored to each database as follows: Medline via PubMed: "Glomerulosclerosis, Focal Segmental" (Mesh) or steroid resistant nephrotic syndrome or minimal change disease or MCD AND (recurrence or relapse); EMBASE: ("focal segmental glomerular sclerosis"/exp or "focal segmental glomerular sclerosis" or "minimal change disease"/exp or "minimal change disease" or "mcd" or "steroid resistant nephrotic syndrome") and ("recurrence" or "relapse"); Web of science: ("FSGS" or "Focal Segmental Glomerulosclerosis" or "MCD" or "minimal change disease" or "steroid resistant nephrotic syndrome") and ("recurrence" or "relapse"); and Cochrane: "steroid-resistant nephrotic syndrome" or "focal segmental glomerular sclerosis" or "minimal change disease" or "mcd" all text and ("recurrence" OR "relapse") all text. In addition, the reference lists of the included studies were searched and examined.

### Study Selection and Eligibility criteria

Studies were included if they met the following criteria: (i) enrolled population of children with SRNS (age <21 years) undergoing kidney transplant, (ii) available data on PTx-REC, (iii) no selection of patients according to the underlying histology, (iv) available data on genetic testing, and (v) prospective or retrospective cohort design. Articles with both pediatric and adult patients were included if age-specific data were available. The search was conducted with no time restriction and papers in all languages were considered.

Two reviewers (WM and EP) independently evaluated the titles and abstracts according to the predetermined criteria. For every eligible study, the 2 reviewers assessed the full text. When there was disagreement, the final decision was achieved by consensus or, if necessary, a third reviewer (GM) was involved.

### Data Extraction

A standardized data extraction form was used from 2 independent reviewers to retrieve all patients' relevant information. In the eventuality of multiple publications of the patient cohort, the most updated information was extracted.

### Definitions

SRNS was defined as the lack of remission (i.e., persistent proteinuria) after the initial steroid therapy. In most studies, the initial treatment comprised oral prednisone or prednisolone 60 mg/m$^2$/d or 2 mg/kg/d, for 4 to 6 weeks.

Late SRNS (LSRNS) was defined as an initial steroid sensitivity, followed by a subsequent steroid-resistant disease relapse.

PTx-REC was defined as the development of nephrotic proteinuria any time after transplant when other causes were excluded.

Genetic SRNS was defined by either the documentation of a pathogenic gene mutation, the presence of congenital nephrotic syndrome, a first-degree family member with nephrotic syndrome or syndromic presentation.

### Risk of Bias Assessment

Bias within each study was evaluated by 2 independent reviewers. The assessment of data quality was performed by means of the Joanna Briggs Institute checklist for prevalence studies, which is composed of 9 items.[14] The answers for each item can be "yes," "no," "unclear" or "not applicable." The score is 1 for yes and 0 for the rest. Results are expressed as the percentage of the maximum possible score. The risk of bias is considered low when the total score is $\geq$70%, moderate when between 50% and 69%, and high when between 0% and 49%. Funnel plots were drawn to assess publication bias across studies.

### Data Synthesis and Analysis

Data were reported as rate of recurrence in the included population. This choice was due to the lack of

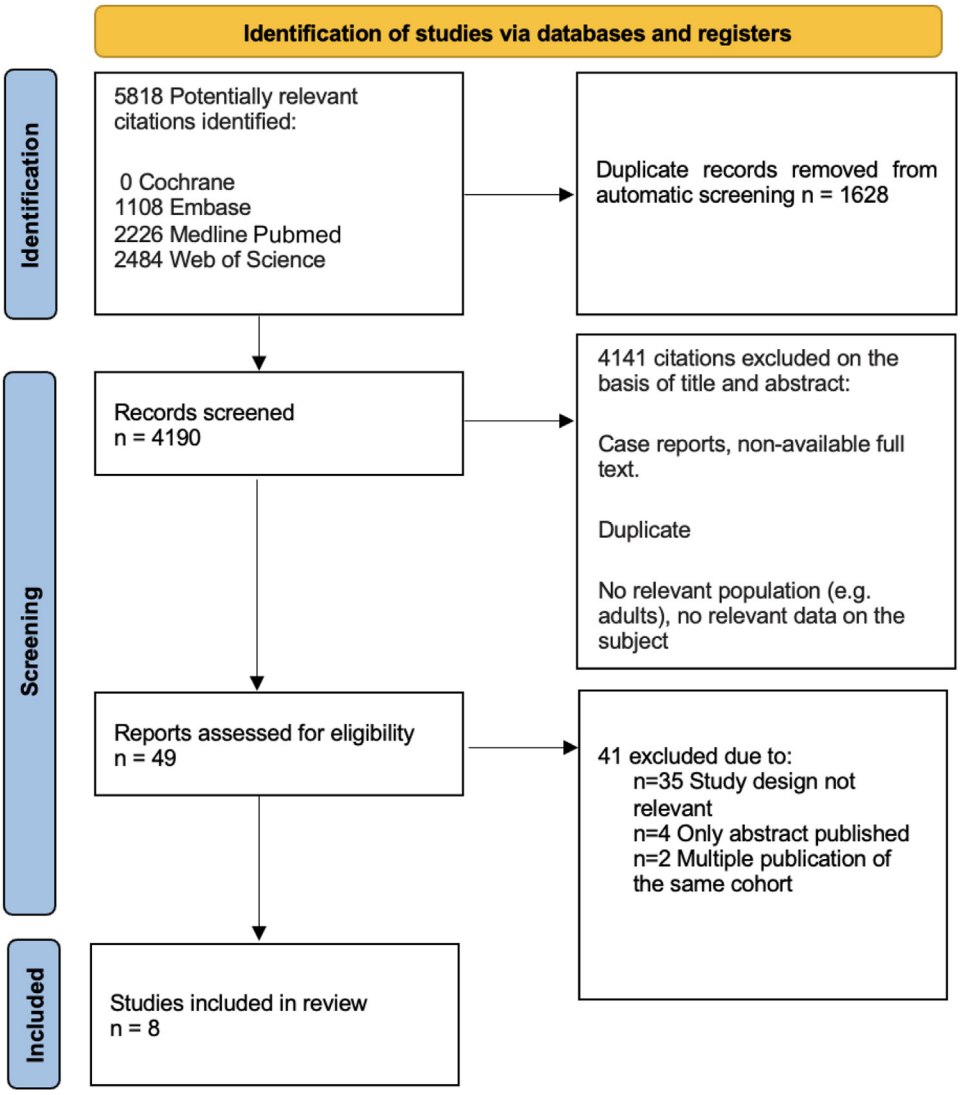



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the included studies. Modified with permission from Page et al.[16]

follow-up duration in most studies that made it impossible to evaluate the incidence. For dichotomized outcomes, RRs are shown. In addition, the estimates using random effect models are reported. Heterogeneity was quantified using the tau$^2$ and $I^2$ statistics, and according to $I^2$ index it was classified as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $<75\%$), or high ($I^2 \geq 75\%$).[15] In addition, Q-statistic was used to evaluate the presence of heterogeneity. *P*-values from Q-statistic were provided in the forest plots. All statistical analyses were performed using the open source software R (R Core Team, 2014. R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

The search strategy identified 5818 references. After removing duplicate records and the initial screening based on titles and abstracts, the full texts of 49 articles were retrieved and further evaluated. After full-text assessment, 41 studies were excluded. The remaining 8 articles were included in the review and meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is shown in Figure 1.

### Characteristics of the Included Studies

In total, 581 children with SRNS who underwent kidney transplant were included from 8 different studies.[7,11,12,17–21] All but one studies were retrospective. The main features of the included studies are summarized in Table 1.

Though the rate of recurrence was reported by all studies, as per inclusion criteria, not all the data needed for every substratification were available for each cohort of patients. We therefore performed a different meta-analysis for each risk factor.

**Table 1.** Main characteristics of the included studies

| Study | Yr | Study dates | Country | Study design | Total patients (n) | Recurrences (n) | Genetic patients (n) | PSRNS patients (n) | LSRNS patients (n) | Age range (Yrs) |
|---|---|---|---|---|---|---|---|---|---|---|
| Ding *et al.*[12] | 2014 | 1981–2012 | France-UK | Retrospective | 139 | 52 | 25 | 86 | 28 | <16 |
| Saeed and Mazloum[21] | 2016 | 2002–2013 | Syriia | Retrospective | 12 | 4 | 5 | NA | NA | <14 |
| Kitzler *et al.*[19] | 2018 | NA | Canada | Retrospective | 13 | 4 | 6 | NA | NA | <18 |
| Pelletier *et al.*[11] | 2018 | 2006–2015 | USA | Retrospective | 158 | 64 | 22 | 109 | 27 | <21 |
| Morello *et al.*[7] | 2020 | 2005–2017 | Italy | Retrospective | 101 | 32 | 41 | NA | NA | <18 |
| Miura *et al.*[18] | 2021 | 2002–2018 | Japan | Retrospective | 36 | 22 | 0 | 22 | 14 | 1–15 |
| Mason *et al.*[17] | 2021 | 1995–2017 | UK | Prospective | 52 | 21 | 21 | 26 | 5 | <18 |
| Francis *et al.*[20] | 2022 | 2000–2019 | Australia- New Zeland | Retrospective | 70 | 36 | 15 | 50 | 20 | 1–18 |

LSRNS, late steroid resistant nephrotic syndrome; NA, not applicable; PSRNS, primary steroid resistant nephrotic syndrome.

## Risk of Bias

According to the Joanna Briggs Institute quality assessment, all studies were considered at low risk of bias (Table 2), therefore, all the studies were included. Funnel plots (Figure 2) did not show a specific pattern suggesting publication bias. Quantitative tests (Begg, Egger, Thompson, Harbord, Macaskill, Peters, Schwarzer, and Deeks) were similarly nonsignificant.

## General PTx-REC Rate in Children With SRNS

Data from 7 studies, including 545 subjects, contributed to the meta-analysis on the overall rate of PTx-REC. The study from Miura *et al.*[18] was not considered because of the exclusion of children with a known genetic disease.

The overall recurrence rate was 39%, with a 95% CI of 34% to 44%. Heterogeneity was 21% (Figure 3). The unpredictable presence of both genetic and non-genetic patients led to a variability in recurrence rates, but the heterogeneity was low.

## Association Between Genetic Background and Disease Recurrence

Different meta-analyses were performed according to the genetic background of patients.

We first addressed the recurrence rate of patients with a known genetic form of SRNS. Overall, 135 patients from 7 different studies contributed to the meta-analysis; the report from Miura was not considered because of the exclusion of patients with a known genetic SRNS. The general requirements for being listed as "genetic" were similar in all studies. Recurrence rate in all these patients was 0%, with no documented recurrence in any of the included studies.

Following the evidence of such a substantial impact of a genetic mutation on the risk of recurrence, we evaluated the rate of disease relapse excluding children with a proven genetic disease, in patients that either had a negative result or did not undergo any genetic test. Data was available in all the articles except the paper from Ding *et al.*[12] A total of 332 patients developped 214 recurrences with a 56% recurrence rate (95% CI 50%−62%). Overall, the heterogeneity was moderate (29%) (Figure 3). However, in this population some genetic forms were reasonably present, 208 patients not being assessed for a genetic disease.

To ascertain the precise risk of relapse in patients with a non-genetic PSRNS, we further evaluated the incidence of disease recurrence in children with an available genetic screening and no mutations detected. These data were available for 6 studies, but only in a subgroup of patients. A total of 129 children were considered with 79 recurrences, with a recurrence rate of 61%, with a very low heterogeneity (0%), and a 95% CI of 53% to 69% (Figure 3). In this subgroup of patients, the risk of recurrence was the highest.

## Recurrence Rates Based on the Initial Steroid Sensitivity

Information on initial steroid response was available only in the most recent studies, because it is a newly identified risk factor for disease recurrence. Data from 5 studies, including 282 patients with PSRNS and 90 with LSRNS were taken in consideration for this meta-analysis.

The definition of PSRNS was slightly different between the studies, but it constantly included the persistence of proteinuria after a full cycle of steroid therapy at the onset. The article from Mason *et al.*[17] had a subcategory of partial responders, who had a persistent proteinuria (>0.2 mg/mg) despite a higher serum albumin level (>2.5 g/dl). Therefore, these patients were classified as PSRNS. The heterogeneity between studies was moderate (67%), nonetheless the RR of recurrence for patients with LSRNS was 1.91 (95% CI 1.48−2.46) compared with those with a PSRNS, confirming initial steroid sensitivity as a main risk factor for recurrence (Figure 4).

## Gender and Disease Recurrence

Data from 5 studies, including 423 subjects, of whom 225 were males and 198 were females, contributed to

**Table 2.** Risk of bias assessment for included studies by means of the Joanna Briggs Institute checklist

| Study | Was the sample frame appropriate to address the target population? | Were study participants sampled in an appropriate way? | Was the sample size adequate? | Were the study subjects and the setting described in detail? | Was the data analysis conducted with sufficient coverage of the identified sample? | Were valid methods used for the identification of the condition? | Was the condition measured in a standard, reliable way for all participants? | Was there appropriate statistical analysis? | Was the response rate adequate, and if not, was the low response rate managed appropriately? | N (%) Total quality score | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Morello *et al.*[7] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | NA | 8 (88.8%) | Low |
| Pelletier *et al.*[11] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | NA | 8 (88.8%) | Low |
| Ding *et al.*[12] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | NA | 8 (88.8%) | Low |
| Miura *et al.*[18] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | NA | 8(88.8%) | Low |
| Mason *et al.*[17] | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | NA | 7 (77.8%) | Low |
| Francis *et al.*[20] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | NA | 8 (88.8%) | Low |
| Kitzler *et al.*[19] | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | NA | 7 (77.8%) | Low |
| Saeed and Mazloum[21] | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | NA | 7 (77.8%) | Low |

Evaluation Criteria (yes/ no/ unclear/ NA). NA, not applicable.

the meta-analysis of the effect of the patients' gender on the incidence of PTx-REC. The RR for males was 1.15 (95% CI 0.90−1.48). The heterogeneity was very low (0%) (Figure 4).

### Association Between Kidney Histology and Disease Recurrence

Data from 3 studies, including 273 subjects, contributed to the meta-analysis of the effect of kidney histology on PTx-REC. The RR of recurrence of patients with a histology of focal segmental glomerulosclerosis (FSGS) when compared with the ones with MCD was 0.91 (95% CI 0.41−1.99). The heterogeneity was high (78%) (Figure 4). The RR appeared to be lower for the FSGS group, but the analysis was not statistically significant.

### Age at Onset, Time to ESKD, Donor Type and Prophylactic Plasmapheresis

We analyzed other patient's characteristics such as age at disease onset and time to ESKD that have been advocated as risk factors for disease recurrence in previous studies.[2,4,5,22,23] These data were not reported as an average value with standard deviations and therefore we could not perform a proper meta-analysis.

However, mean age at onset, reported by 3 studies,[12,18,19] was higher in patients with recurrence (Table 3). Similarly, mean values of time to ESKD from 3 studies[7,12,18] were longer in patients developing recurrence (Table 3). We did not assess the impact of donor type and prophylactic plasmapheresis on PTx-REC because of the lack of this information in most studies.

### Graft Loss and SRNS Recurrence

Data on graft loss after PTx-REC of SRNS were incomplete and fragmentary, preventing a specific meta-analysis. Nonetheless, most studies reported a significantly higher percentage of graft loss during follow-up in patients developing recurrence compared with the ones who did not. The incidence of graft loss because of recurrence was 37.5% and 33.3%, after a median follow-up of 4.9 years and 7.6 years, respectively, in our study[7] and the one from Francis *et al.*[20] Ding found an almost double rate of complications, graft loss, and retransplantation in patients developing recurrence compared with patients who did not (28% vs. 16.5%).[12] Similarly, after a post-transplant follow-up of 6 months, Pelletier reported the occurrence of ESKD and the need for dialysis in 13.3% of patients who relapsed compared with 3.3% of those who did not relapse.[11]

## DISCUSSION

PTx-REC is the most feared complication in children with SRNS undergoing kidney transplantation and its pathogenesis is not entirely understood.

To date, most of the available literature is focused on adult patients with a pretransplant diagnosis of FSGS,[24] with little data available on pediatric patients. This fact is luckily changing in the last few years. A consensus on the management of PTx-REC in the pediatric population has been recently published, providing recommendations on its treatment.[25] Nonetheless, the rate and risk factors of PTx-REC in children still need to be properly addressed. Our goal was to perform a meta-analysis focusing on this topic, including all children with a clinical diagnosis of SRNS, all

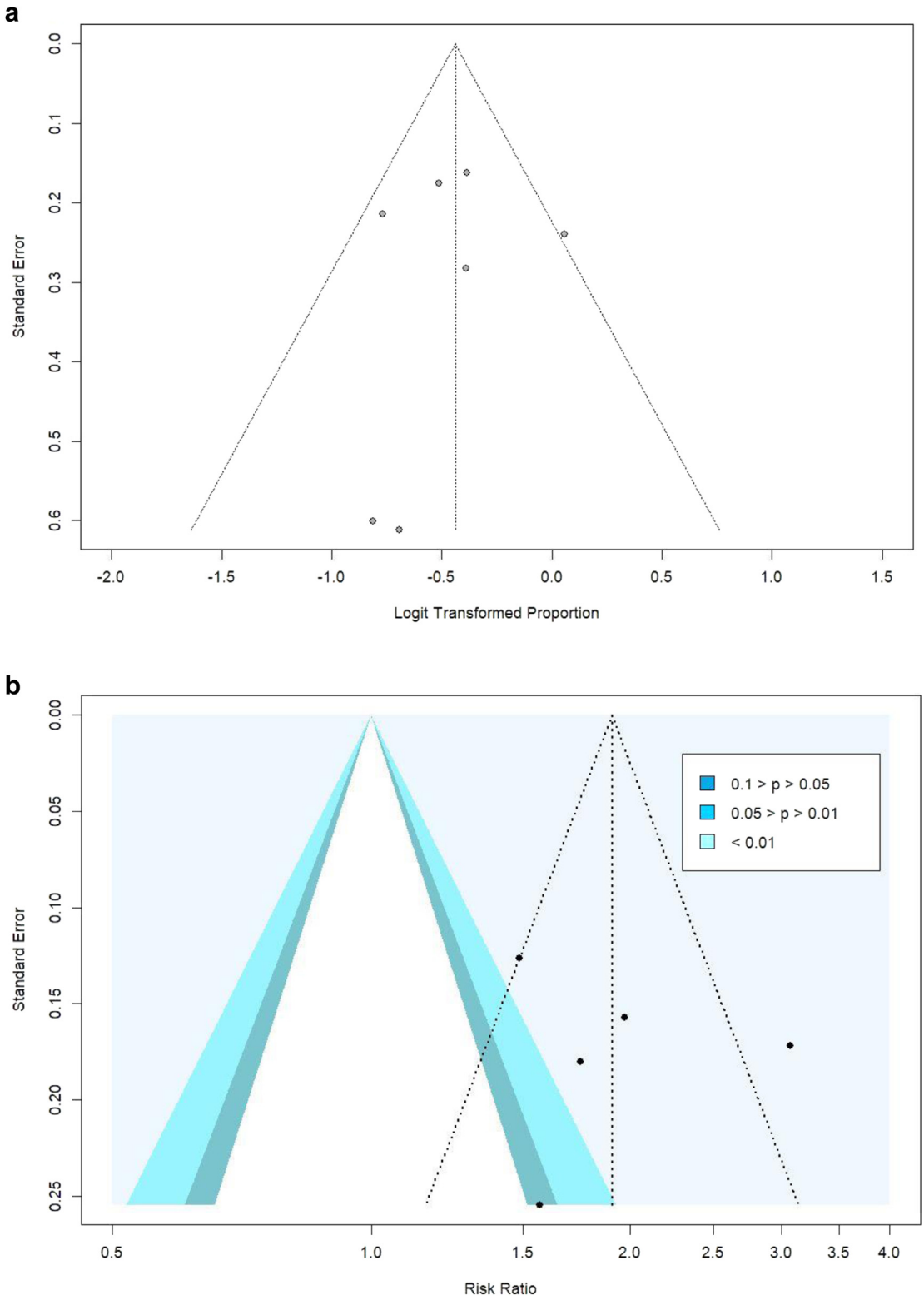
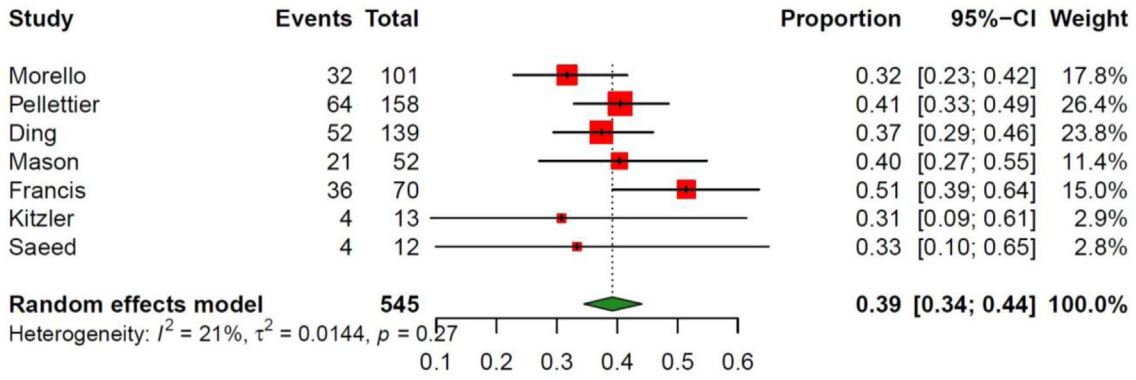



**Figure 2.** (a) Funnel plot for the overall relapse rate; (b) Funnel plot for initial steroid sensitivity as risk factor for recurrence.

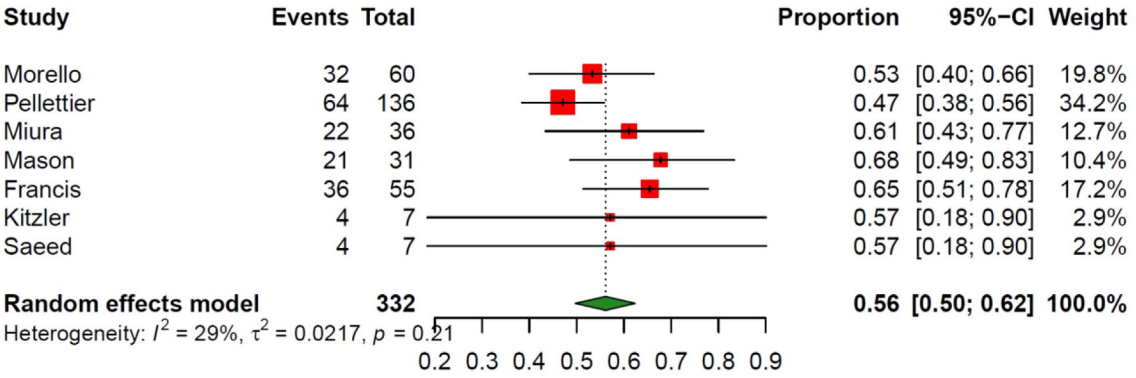
underlying histologies, and addressing the impact of a genetic disease.

Of a total of 545 subjects from 7 studies, the overall PTx-REC rate was 39%. The presence of a different proportion of genetic and non-genetic patients led to a certain variability between the studies, but the meta-analysis showed a limited heterogeneity. Therefore, in an unselected population of children with SRNS undergoing kidney transplant, the expected recurrence rate is about 40% and it is comparable with the one reported in older studies before the routine clinical use of genetic testing.[5] This is a key information to guide post-transplant management in children with SRNS.

**a** **Overall** post-transplant recurrence rate in children with SRNS.




**b** Subgroup analysis of disease recurrence rate **excluding children with a genetic SRNS.**




**c** Subgroup analysis of disease recurrence rate in **children with a negative genetic test.**

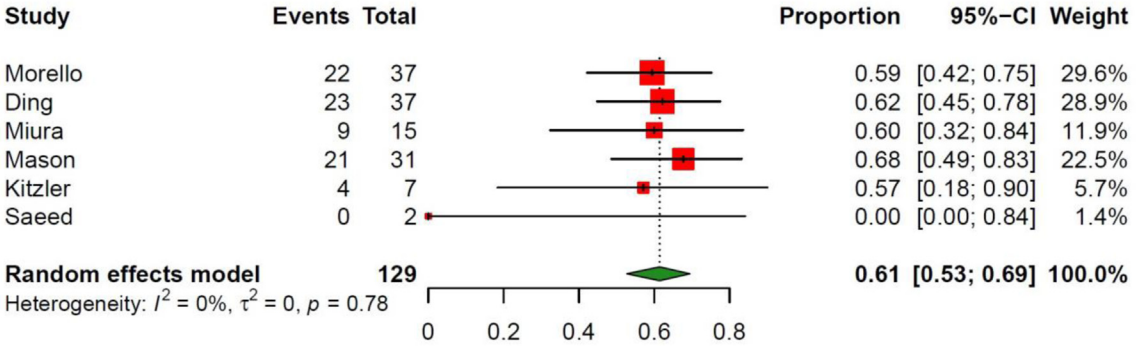
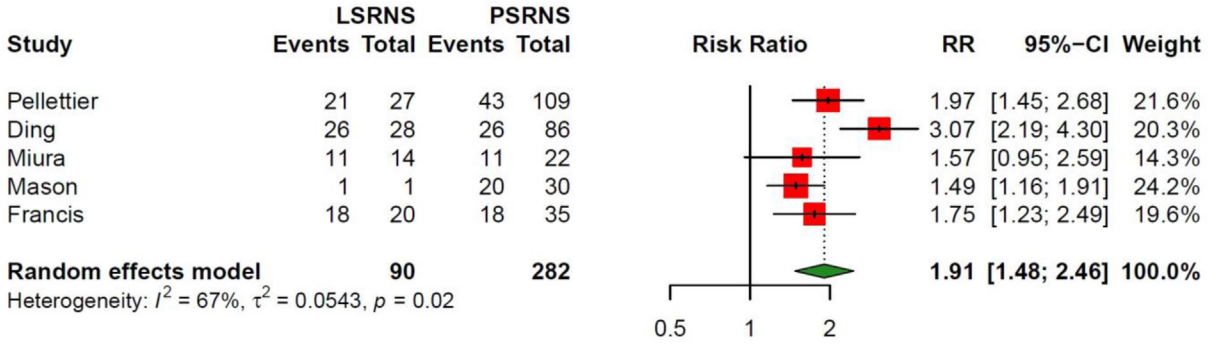
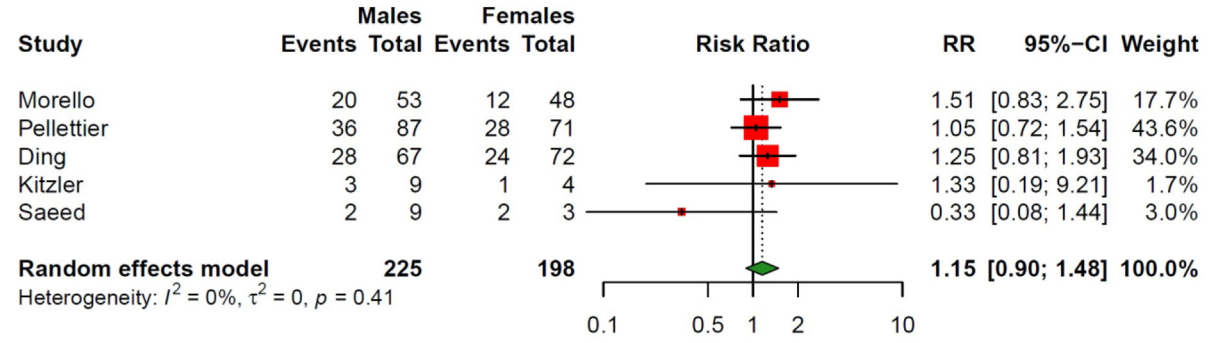



**Figure 3.** (a) Overall post-transplant recurrence rate in children with SRNS. (b) Subgroup analysis of disease recurrence rate excluding patients with a genetic SRNS. (c) Subgroup analysis of disease recurrence rate in patients with a negative genetic test. Error bars indicate 95% CIs. The dotted vertical line drawn through the diamond represents the summary measure with its CIs (lateral tips of diamond). Heterogeneity assessment: $I^2$, tau.$^2$ $P$ value is derived from Q-statistics. Effect size pooling method: the DerSimonian Leird method. Tau estimation method: Paule-Mandel. CI, confidence interval; SRNS, steroid resistant nephrotic syndrome.

**a** Relative risk of post-transplant disease recurrence rate based on **initial steroid sensitivity.**




**b** Relative risk of post-transplant disease recurrence rate based on **gender.**




**c** Relative risk of post-transplant disease recurrence rate based on **kidney histology.**

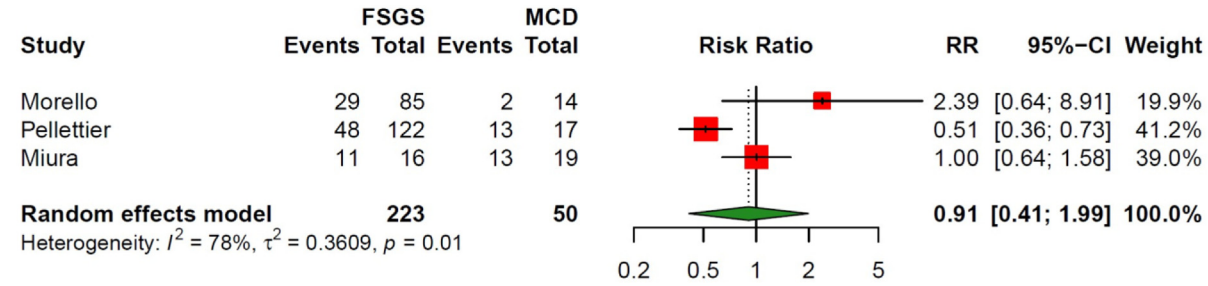



**Figure 4.** (a) Relative risk of post-transplant disease recurrence rate based on initial steroid response. (b) Relative risk of post-transplant disease recurrence rate based on gender. (c) Relative risk of post-transplant disease recurrence rate based on kidney histology. Error bars indicate 95% CIs. Solid vertical line represents no effect, the dotted vertical line drawn through the diamond represents the summary measure with its CIs (lateral tips of diamond). Heterogeneity assessment: $I^2$, tau.$^2$ $P$ value is derived from Q-statistics. Effect size pooling method: the DerSimonian Leird method. Tau estimation method: Paule-Mandel. CI, confidence interval; FSGS, focal segmental glomerulosclerosis; LSRNS, late steroid resistant nephrotic syndrome; MCD, minimal change disease; PSRNS, primary steroid resistant nephrotic syndrome; RR, relative risk.

**Table 3.** Age at onset and time to end-stage kidney disease in patients with and without recurrence

| Study | Patients with recurrence | Patients without recurrence |
|---|---|---|
| Age at onset (yr) | | |
| Ding *et al.*[12] | 4.5 (0.7–12.5) | 3.5 (0.3–15.5) |
| Kitzler *et al.*[19,a] | 9.94 | 3.1 |
| Miura *et al.*[18] | 3.9 (2.5–6.5) | 3.5 (2.3–6.7) |
| Time to ESKD (yr) | | |
| Ding *et al.*[12] | 4 (0–17) | 3 (0–16) |
| Morello *et al.*[7] | 4.6 (0–12) | 2.7 (0–13) |
| Miura *et al.*[18] | 6.1 (2.0–8.6) | 2.5 (0.4–3.7) |

[a]No confidence intervals available.

More importantly, we were able to perform a meta-analysis of recurrence rates based on the genetic background. Of a total cohort of 135 genetic patients, with similar definition between studies, no recurrence was reported. This is in line with the hypothesis of a different pathogenesis of genetic and idiopathic SRNS. The structural and functional genetic anomalies found in the former are completely resolved with kidney transplantation. It must be noted that exceptions have been reported. Mason *et al.*,[26] in their critical re-analysis of all reported PTx-REC in genetic patients, identified 10 cases of genetic patients with a true pathogenic variant developing PTx-REC. Nonetheless, 7 of 10 developed only a "possible" recurrence, defined as a recurrence occurring either after at least 3 months or when information was incomplete. The authors themselves, therefore, suggested the extraordinariness of these cases.

In contrast, on a total of 129 children with a negative genetic test from 6 studies, the recurrence rate was 61% with no heterogeneity (0%). This rate is almost 2 times higher than the one reported on an unscreened population. This information has crucial clinical implications for the planning of kidney transplantation in patients with idiopathic SRNS and for providing adequate information to the patient and the family. A comprehensive genetic evaluation must become part of the basic work-up of all patients with SRNS. The substantial difference in recurrence risk between genetic and idiopathic SRNS may indeed help in evaluating a living donation. Conversely, no solid data are available on the effect of the type of donor on the rate of recurrence.[11,12,27] According to our results, there should be no restriction to living donations in patients with genetic SRNS, once proven that the donor is not a carrier of the family mutation. Living donation in children with a negative genetic result, instead, has to be considered only after a careful risks and benefits analysis. Before proceeding, the clinician must accurately inform the families of the risk of recurrence exceeding 60%.

The response to the initial steroid therapy also significantly influenced the likelihood of developing disease recurrence. Children with LSRNS had a higher risk of relapse, with a RR of 1.91. This data is in accordance with the hypothesis of a substantial difference in the pathogenesis of genetic and idiopathic SRNS. The total lack of steroid response may indeed be related to a still unknown underlying genetic or structural alteration. In contrast, initial sensitivity to therapy could be linked to the presence of a circulating permeability factor, which would linger after transplantation, resulting in recurrence.

Often being advocated as an important prognostic factor for disease severity,[28] underlying histology did not affect PTx-REC rates with FSGS children apparently having a slightly lower, but not significantly different rate of recurrence from those with MCD. The timing of biopsy and the presence of genetic FSGS may have had a role in this finding. Further data are needed to reach solid conclusions on this topic.

Inconclusive and different data were available regarding patients' gender. We analyzed a total of 423 subjects (225 males and 198 females) finding a small but not-significant difference in recurrence rates between males and females (RR 1.15; 95% CI 0.90−1.48). Nonetheless, a minor impact cannot be completely ruled out.

Even if the available data was not sufficient to perform a meta-analysis, the mean age at onset in patients with recurring disease was higher in all studies. This is probably linked to the fact that genetic and congenital patients are comprised in the non-recurring group, and usually have a younger age at disease onset.

Previous studies have suggested that a shorter time to ESKD could be related to higher rates of PTx-REC.[1] We were not able to perform a meta-analysis of this risk factor because of the lack of reported data. Nevertheless, in the 3 available studies, time to ESKD was slightly longer in patients later developing PTx-REC.

This study has some limitations. First, the overall findings may have been affected by publication bias. Indeed, despite the funnel plots indicating minimal publication bias, these approaches are considered limited by their qualitative nature. Second, the statistic strength of the different observational studies was somehow limited because of the low number of articles and patients, partially further reduced because of the availability of data from each different report. Even so, considering the rarity of the disease, this meta-analysis encompasses the largest number of pediatric patients with SRNS undergoing transplantation (581). Finally, we could not test the role of possible confounders, and the presence of genetic patients may have partially biased the analysis of other risk factors.

In conclusion, our review and meta-analysis indicates that PTx-REC is a common event in idiopathic non-genetic SRNS children, complicating the clinical course in over 6 out of 10 patients. The presence of a causative genetic mutation virtually excludes the chance of recurrence, whereas the only other significant risk factor is the presence of an initial response to steroid therapy, with LSRNS having an almost double risk of relapse. These characteristics may help clinicians in the identification of children with the higher risk of relapse, in planning and managing kidney transplantation (living vs. deceased) and to adequately inform the patients and their families.

## DISCLOSURE

All the authors declared no competing interests.

All coauthors have seen and agree with the contents of the manuscript and there is no financial interest to report.

We certify that the submission is original work and is not under review at any other publication.

The authors received no financial support for the research, authorship, and publication of this article. Registration to PROSPERO was not possible because database search was already ongoing at the time of registration.

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