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RESEARCH

Long-term outcomes in children with idiopathic nephrotic syndrome: a single center experience

İdiyopatik nefrotik sendromlu çocuklarda uzun dönem sonuçlar: tek merkez deneyimi

Gönül Parmaksız[1]

[1]Başkent University School of Medicine, Adana Dr. Turgut Noyan Training and Research Center, Pediatric Nephrology Department, Adana, Turkey

Abstract

Purpose: Idiopathic nephrotic syndrome (INS) is a common glomerular disease observed in children. Depending on their response to steroids, patients can be classified either as having steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome (SRNS). Whereas SSNS patients respond favorably to steroid treatment and achieve a complete remission with normal renal functions, SRNS patients do not, and are at high risk of developing end-stage renal diseases (ESRD). The aim of this study was to analyze the long-term outcomes of patients with INS.

Materials and Methods: In our medical center, records of children diagnosed with INS were evaluated. Demographic information, laboratory results, response to treatment, and clinical progression were analyzed.

Result: Ninety-one children (64% male) with a mean age of 11.1±4.1 years (3.5-18) were included in the patient cohort, with a mean age of diagnosis of 5.2±3.8 years (1-16.2) and a mean follow-up period of 5.7±2.8 years (2-12). Sixty-eight (75%) patients had SSNS, and 23 (25%) patients had SRNS. Among the SSNS patients, 18 (31%) were steroid-dependent, 12 (20%) were frequently relapsing, and 29 (49%) were infrequently relapsing. Renal biopsy was performed on 29 (32%) patients, 59% had focal segmental glomerulosclerosis. The complete remission rate was 94% for all patients, with 100% for SSNS and 74% for SRNS. ESRD was developed for 9% of patients with SRNS.

Conclusion: The response to steroid treatment serves as a valuable prognostic indicator for INS as it plays a pivotal role in mitigating the risk of progression toward end-stage renal failure.

Keywords:. Nephrotic syndrome, steroid response, children

Öz

Amaç: İdiyopatik nefrotik sendrom (İNS) çocuklarda yaygın bir glomeruler hastalıktır. Steroid tedavisinin yanıtına göre steroide hassas nefrotik sendrom (SHNS) veya steroid dirençli nefrotik sendrom (SDNS) olarak sınıflandırılır. SHNS hastaları steroid tedavisinde normal böbrek fonksiyonları ile tam remisyon elde ederken, SDNS hastaları bunun aksine olumlu yanıt vermez ve son dönem böbrek hastalığı gelişme riski yüksektir. Bu çalışmanın amacı İNS'li çocukların uzun dönem sonuçlarını değerlendirmektir.

Gereç ve Yöntem: Merkezimizde İNS tanısı alan çocukların tıbbi kayıtları geriye dönük olarak değerlendirildi. Demografik bilgileri, laboratuvar bulguları, tedavi yanıtları ve klinik seyri analiz edildi.

Bulgular: Çalışmaya ortalama yaşı 11.1±4.1 (3.5-18) olan 91 çocuk (%64, erkek) dahil edildi. Ortalama tanı yaşı 5.2±3.8 yıl (1-16.2) ve ortalama izlem süreleri 5.7±2.8 yıl (2-12) idi. Hastaların 68 (%75)'i steroide hassas, 23 (%25)'ü steroide dirençli idi. Steroide hassas olanların 18 (%31)'i steroide bağımlı, 12 (%20)'si sık tekrarlayan, 29 (%49)'u seyrek tekrarlayan idi. Böbrek biyopsi 29 (%32) hastaya yapıldı, %59'unun histopatolojik bulgusu fokal segmental glomeruloskleroz idi. Tüm hastaların %94'ünde tam remisyon sağlandı, SHNS hastalarının tamamı, SDNS hastaların %74'ü tam remisyonda idi. SDNS hastalarının %9'unda son dönem böbrek yetmezliği gelişti.

Sonuç: Steroid cevabı İNS'da son dönem böbrek yetmezliğine ilerlemeyi azalttığından iyi prognoz göstergesidir.

Anahtar kelimeler: Nefrotik sendrom, steroid yanıtı, çocuklar

Address for Correspondence: Gönül Parmaksız, Department of Pediatric Nephrology, Baskent University School of Medicine, Adana, Turkey E-mail: gonulped1@hotmail.com
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INTRODUCTION

Idiopathic nephrotic syndrome (INS) is one of the most common manifestations of glomerular disease in childhood. It is characterized by severe proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. The International Study of Kidney Disease in Children (ISKDC) has documented an annual incidence rate for INS ranging from 2 to 7 cases per 100.000 children[1].

As an initial therapeutic approach for INS, steroids are used. Following treatment initiation, patients are classified into either steroid-sensitive or steroid-resistant categories.

Steroid-sensitive nephrotic syndrome (SSNS) accounts for approximately 80% of patients who exhibit a favorable response to steroid treatment. A significant proportion of these patients present histopathological findings consistent with minimal lesion disease (MLD)[2]. Among the children diagnosed with SSNS, a notable number experience one or more relapses. However, most of these patients maintain a positive response to subsequent courses of steroid treatment and they exhibit a promising long-term prognosis, with the potential for complete recovery and restored renal function[3].

On the other hand, in cases of steroid-resistant nephrotic syndrome (SRNS), which accounts for 20% of the patients, focal segmental glomerulosclerosis (FSGS) emerges as the primary histopathological finding. The outcome of SRNS can be uncertain, as there is a considerable risk of progression to end-stage renal disease (ESRD) within a 10-year timeframe, with reported progression rates ranging from 36% to 64%[4]. Numerous studies have been conducted to identify the morphological and clinical indicators that may serve as predictors of renal failure progression of SRNS. However, a definitive conclusion has yet to be reached[5,6]. Current treatment approaches have demonstrated promising outcomes in managing the disease, but long-term side effects and sustainability of remission are still being questioned.

The objective of this study is to investigate the potential influence of steroid response and clinical characteristics on the progression of INS in children. The primary aims are to ascertain the demographic information, treatment responses, and clinical trajectory of children diagnosed with INS within a single center over a period of 12 years. Furthermore, the study seeks to assess the long-term outcomes associated with the disease.

MATERIALS AND METHODS

Sample

This retrospective study was conducted at the Pediatric Nephrology Department of Başkent University, Adana Dr. Turgut Noyan Research and Teaching Center between January 2010 and December 2022. This study was approved by an institutional ethics committee (Başkent University Institutional Review Board and Ethics Committee (Date: 3 January 2023, Project no: KA22/520)). All patients provided written informed consent. Patient data were collected from the hospital's electronic patient registry (Nucleus Automation System) and individual patient files. The patients were closely monitored and treated by a pediatric nephrologist working in the Department of Pediatric Nephrology.

Patients included in the study according to the following criteria: (1) onset of INS at age >1 year, (2) onset of INS at age <18 years, (3) a minimum follow-up period of 24 months. Patients were excluded from the study if they met specific conditions such as inadequate availability of data, a diagnosis of congenital nephrotic syndrome, presence of secondary causes of nephrotic syndrome (such as systemic lupus erythematosus and IgA nephropathy), and known genetic causes such as NPHS1, NPHS2, WT1, or LAMB2.

Definitions

Remission was defined as the absence of proteinuria (less than 4 mg/m^2/h) or a negative or trace urine protein dipstick for 3 consecutive days. Relapse was defined as the presence of urinary protein excretion ≥ 40 mg/m^2/h or a urine dipstick of ≥ 3+ protein for 3 consecutive days. Steroid-sensitive nephrotic syndrome (SSNS) was diagnosed when remission was achieved using steroid therapy alone within a period of 4-8 weeks. Steroid-dependent nephrotic syndrome (SDNS) was diagnosed when the patient relapsed while tapering the steroid dose or within 2 weeks after stopping the steroid therapy. Frequent relapsing nephrotic syndrome (FRNS) was diagnosed when ≥ 4 relapses occurred within 12 months or ≥2 relapses occurred within 6 months. Steroid-resistant nephrotic syndrome (SRNS) was defined as the

absence to reach remission despite 8 weeks of steroid therapy.

Treatment protocols

All patients diagnosed with INS were initially treated with prednisone (PRD) at a dose of 60 mg/m²/d or 2 mg/kg/d (maximum: 60 mg/d) for a period of 4-8 weeks. This was followed by a tapering alternate-day dose for 12 weeks. Relapses were treated with the same doses but for a shorter duration. Children diagnosed with FRNS, SDNS, and SRNS were prescribed steroid-sparing agents. The second-line agents used included levamisole, cyclophosphamide (CYC), cyclosporine A (CsA), and mycophenolate mofetil (MMF). In cases where the second-line agents were ineffective or not tolerated, the third-line agent rituximab (RTX) was employed.

Clinical and renal pathology management

Renal biopsies were performed on patients who met the following criteria: (1) onset age over 10, (2) presence of macroscopic hematuria, (3) hypertension, (4) resistance to steroids, or (5) renal failure and complement deficiency. The study evaluated various factors including age at the onset of INS, response to steroid treatment, number of INS relapses, results of renal biopsies, and immunosuppressive treatments. Patients were classified into two groups, SSNS and SRNS, based on their steroid response. These two groups were then compared in terms of gender, age at diagnosis, consanguinity, family history of nephrotic syndrome, hypertension, presence of microscopic hematuria, and serum albumin level. Furthermore, the SSNS group was further divided into subgroups based on the frequency of relapse, and these subgroups were compared in terms of predictors, including gender, age at diagnosis, hypertension, microscopic hematuria, and serum albumin level.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows v.23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including measures of central tendency (mean, median) and variability (standard deviation, range) were used to summarize the data. Student's t-test was employed for comparing continuous variables, while the Pearson's chi-square test was utilized for categorical variables. The threshold for statistical significance was set at $p<0.05$.

RESULTS

A total of 285 patients diagnosed with idiopathic nephrotic syndrome were initially in the database. After excluding the 194 patients who did not meet the aforementioned criteria, 91 patients were included in the analysis. The mean age of the patients was 11.1±4.1 years (range 3.5-18) and the average follow-up period was 5.7±2.8 years (range 2-12). Among the patients, 68 (75%) were classified as steroid-sensitive (SSNS), and 23 (25%) were classified as steroid-resistant (SRNS). Table 1 provides a summary of the patient characteristics based on their steroid response.

In the entire cohort, there were 58 males and 33 females (ratio of 1.8:1). Within the SSNS group, there were 46 males and 22 females (ratio of 2.1:1), while in the SRNS, there were 12 males and 11 females (ratio of 1.1:1). Males were predominant in both groups, and there was no statistical difference in gender distribution between the two groups ($p=0.33$).

Among the 91 children included in the analysis, the average age of diagnosis was 5.2±3.8 years (range 1-16.2 years). A majority of the children, 58 (64%), were diagnosed before the age of 5, while 33 (36%) were diagnosed after the age of 5. Comparing the age at diagnosis between SSNS and SRNS patients, it was found that the SSNS patients were diagnosed at a younger age (4.4±2.9 years) compared to SRNS patients (7.7±5 years), with a statistically significant difference ($p=0.003$).

In terms of family history, 18 (20%) of all patients had a history of consanguinity, but there was no statistically significant difference observed between SSNS and SRNS patients ($p = 0.13$). Additionally, a history of nephrotic syndrome was present in 7 (8%) of all patients, and it was found to be more frequent in the SRNS group ($p = 0.04$).

At the onset of the disease, 15 (16%) patients exhibited hypertension, and 20 (22%) had microscopic hematuria. The average serum albumin level was initially 19.2±7.0 g/L (range 8.8-46). Hypertension was significantly more prevalent in SRNS patients compared to SSNS patients (43% vs. 7%, $p<0.0001$). There were no significant differences between the two groups in terms of the presence of microscopic hematuria ($p = 0.08$) and serum albumin levels (0.13).

Table 1. Characteristics of patients according to their response to steroid therapy

	All patients (n=91)	SSNS (n=68)	SRNS (n=23)	*p* value
Gender (Male/Female), n	58/33	46/22	12/11	0.33
Age of Diagnosis (years)	5.2±3.8	4.4±2.9	7.7±5.0	0.003
Consanguinity, n, (%)	18 (20)	11(16)	7 (30)	0.13
Family history of NS, n (%)	7 (8)	3 (4)	4 (17)	0.04
Hypertension, n (%)	15 (16)	5 (7)	10 (43)	0.0001
Microscopic hematuria, n (%)	20 (22)	12 (18)	8 (35)	0.08
Serum albumin (g/L)	19.2±7.0	18.1±5.6	22.2±9.4	0.13
Renal pathology, n	29	6	23	
FSGS, n (%)	17 (59)	2 (33)	15 (65)	
DMP, n (%)	7 (24)	2 (33)	5 (22)	
MLD, n (%)	4 (14)	2 (33)	2 (9)	
MPGN, n (%)	1 (3)	0	1 (4)	
Immunosuppressive treatment, n				
PRD	91	68	23	
Levamisole	7	7	0	
CYC	19	15	4	
CsA	38	19	19	
MMF	7	1	6	
RTX	7	4	3	

Data are presented as the mean or n (%). NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; DMP, diffuse mesangial proliferation; MLD, minimal lesion disease; MPGN, membranoproliferative glomerulonephritis; PRD, prednisone; CYC, cyclophosphamide; CsA, cyclosporine A; MMF, mycophenolate mofetil; RTX, rituximab.

Renal biopsy was conducted on 29 patients (32%). FSGS was observed in 17 (59%) cases, DMP in 7 (24%) cases, MLD in 4 (14%) cases, and MPGN in 1 (3%) case. Out of the 29 biopsies, 6 were performed on SSNS patients, and among them, 2 patients were diagnosed after the age of 10 years, and 4 patients exhibited a delayed initial response to steroid treatment.

Among the SSNS patients, 18 (31%) were classified as steroid-dependent (SDNS), 12 (20%) had frequent relapses (FRNS), 29 (49%) had infrequent relapses and 9 (13%) had no relapses (Figure). The median time to the first relapse onset was 8.4 months, and a total of 211 relapses were observed. Of these relapses, 46% occurred following an upper respiratory infection. The SSNS patients were further divided into two groups: SDNS/FRNS and infrequent/non-relapsing, based on their relapse status. Comparative analysis of these groups with respect to predictive parameters including gender, age at diagnosis, hypertension, microscopic hematuria, and serum albumin levels revealed no statistically significant differences in any of the parameters (p=0.053, p=0.37, p=0.42, p=0.27, p=0.84, respectively).

During the treatment process, various medications were administered. PRD was given to 91 patients, levamisole to 7, CYC to 19, CsA to 38, MMF to 7, and RTX to 7.

In the final check-up, the overall complete remission rate was 94% for all patients, and specifically, it was 100% for SSNS patients. Among the SSNS patients, 38 (56%) achieved sustained remission after discontinuing immunosuppressive treatments, while the remaining 30 (44%) continued therapy. Among them, 21 patients used prednisone alone, and 9 patients used a combination of prednisone and CsA. For the SRNS patients, the complete remission rate was 74% (17 children). Among these patients, 12 remained in remission after their immunosuppressive treatments were terminated and the remaining 5 continued their therapy with a combination of prednisone and CsA. Among the 6 SRNS patients who did not achieve remission, 4 (17%) continued to experience nephrotic-level proteinuria, and 2 (9%) progressed to end-stage renal failure (Figure). Kidney transplantation was performed for those who developed ESRD. Furthermore, 19 (21%) of all patients received antihypertensive therapy.

During the treatment, a few complications were observed in the patients. These included hypertensive encephalopathy (n=1), sinus venous thrombosis (n=1), hepatitis (n=1), pyelonephritis (n=1), pneumonia (n=1), peritonitis (n=1) and cellulitis in the arm (n=1). It is noteworthy that both patients who developed end-stage renal failure had a history of consanguineous marriage and their renal biopsy findings were consistent with FSGS.

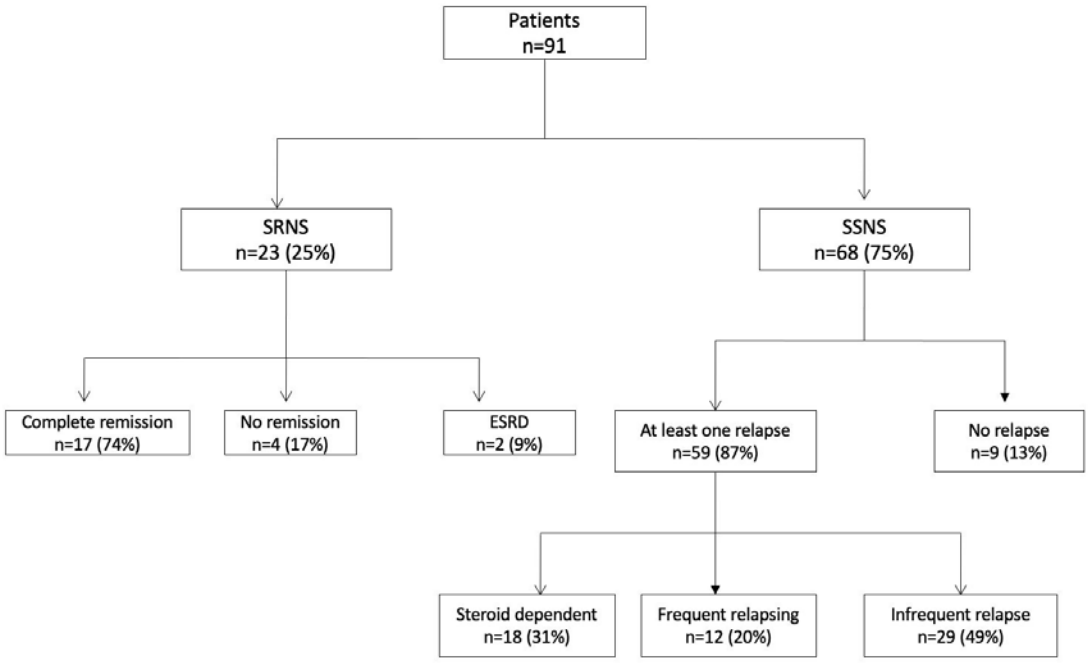

Figure. Response of the patients to steroid therapy.

SRNS, steroid-resistant nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; ESRD, end-stage renal disease.

DISCUSSION

A significant proportion of children with nephrotic syndrome have INS with an estimated 80% of cases being steroid-sensitive and 20% being steroid-resistant[7]. In this study, we observed a distribution of 75% SSNS, and 25% SRNS patients, which aligns with the established literature.

In young children, the proportion of males is greater, with a male-to-female ratio of 2:1, although this gender disparity completely disappears by adolescence[2]. In the present study, the ratio of males to females diagnosed with INS was 1.8:1, consistent with numerous other national and international studies, which have reported a higher incidence of INS in males compared to females[8,9]. Approximately 70-80% of all cases of INS occur in children who are younger than 6 years old. In the study conducted by Özlü et al., the mean age of the 372 children evaluated was 4.7 years old, with many of the patients, 69%, being younger than 5 years old[10]. In our study, the mean age at the disease onset was 5.2 years, with 64% of the patients being younger than 5 years old. A negative correlation exists between the age of diagnosis and the frequency of a relapse. In our study, the median time to the first relapse was 8.4 months, consistent with a study conducted in France reporting a median time of 8.3 months[11]. Some studies suggest that earlier age of onset predicts a higher likelihood of relapse continuing into adulthood[12,13].

The mechanisms underlying the etiopathogenesis of INS remain unclear, despite some studies suggesting

that there may be a genetic aspect to the etiology of INS[14]. The risk of developing INS is higher in individuals with a family history of the condition[1]. Previous studies have identified human lymphocyte antigen linkage to various antigens for SSNS[15]. Both dominant and recessive inherited forms of familial nephrotic syndrome have been identified[16]. In our study, due to the prevalence of cousin marriages in Turkey, 20% of patients had consanguinity, and 8% had a family history of nephrotic syndrome. Lipska et al. reported that 16% of SRNS patients showed an autosomal recessive gene in their genetic screening, while 4% had an autosomal dominant gene[17]. In the study by Santin et al., it was reported that 67% of SRNS patients with a family history had a podocyte gene mutation[18]. In our study, there was a higher frequency of familial disease in SRNS patients, however, we excluded patients with detected mutations, and none of the included SRNS patients underwent genetic screening.

Hypertension is observed in 5-20% of the children with INS and its prevalence is lower in those with MLD compared to other diagnoses[19]. Steroid-resistant patients (66.7%) have a much higher prevalence compared to steroid-sensitive patients (14.3%)[20]. In this study, hypertension was identified to be more prevalent in patients with SRNS at a rate of 43%.

Approximately 20-30% of children with SSNS have microscopic hematuria at the time of diagnosis[19]. Some studies have shown that microscopic hematuria is more frequently found in SRNS than in SSNS[21,22]. In this study, 60% of the patients with microscopic hematuria had SSNS, while the rest 40% had SRNS. This distribution is likely influenced by the larger number of SSNS patients in our cohort.

In the present study, the three most common histological findings on the renal biopsy were FSGS, DMP, and MLD. The ISKDC reported that MLD accounted for 76.4% of renal biopsies in INS cases, while FSGS was identified in 6.9% and DMP in 2.3% of biopsy specimens[23]. Further, Moustafa et al. performed renal biopsies in children diagnosed with SRNS, SDNS, and FRNS, and found that FSGS and MLD accounted for 38.5% of the renal specimens each[24]. Nammalwar et al. reported 35-55% FSGS, 25-40% MLD, and 10-15% DMP as histological findings of SRNS patients[25]. In this study, 79% of the patients who underwent biopsy had SRNS, and FSGS was the most common histological finding in this subgroup. Biopsies were performed on only 6 patients with SSNS, 2 of whom were over 10 years old and 4 had delayed response to steroids. It is worth noting that while the clinical presentations of patients with FSGS, MLD, and DMP were similar, the histological findings may change over time. The PodoNet Registry has provided information on the outcomes of a large group of children with SRNS[5]. Repeated biopsies revealed that the diagnosis changed from MLD to FSGS in 55% of the cases, and from DMP to FSGS in 48% of the cases[5]. However, in this study, repeated biopsies were not performed.

In general, children with SSNS have a favorable long-term prognosis, with many experiencing resolutions of the disease and maintaining normal renal function. Follow-up studies have indicated that 80-90% of children with SSNS will have one or more relapses[26]. Among those who experience relapses, approximately 50% may have frequent relapses or become dependent on steroids[26]. A study by Carter et al. reported that 80% of INS patients achieved long-term remission, with different patterns observed within this group. Of the patients in remission, 25% achieved complete remission after the initial course of steroids, 40% had an infrequently relapsing disease, and 30% had frequently relapsing disease[27]. In this study, remission was achieved in 94% of patients, with 33% being FRNS/SDNS, a result consistent with the literature. Of the patients who achieved remission, 55% had their treatment discontinued and 43% had been in drug-free remission for over 12 months, indicating successful management of the disease.

Numerous predictive studies have been conducted to identify factors that may indicate a higher likelihood of recurrent or steroid-dependent courses in children with SSNS[28,29]. Some of these predictors include young age, male sex, a shorter time between first remission and first relapse, the number of relapses in the first 6 months after presentation, and the presence of infection at presentation or relapse. In our study, we did not identify any predictive factors for relapse among SSNS patients.

A viral prodrome is present in approximately half of the cases of relapse. The exact nature of this association is still uncertain, whether it is simply a symptom of cytokine relapse or if there is a viral agent that triggers nephrotic syndrome. However, it has been established that infections can serve as triggers for relapses in children with FRNS[30]. According to the KDIGO guidelines, administering steroids daily for 5-7 days at the onset of an upper respiratory tract

infection in children with FRNS and SDNS who are either not currently taking steroids or are taking alternate-day steroids may potentially decrease the risk of relapses[31]. In this study, it was found that upper respiratory tract infections were a significant factor contributing to recurrences in patients. As a result, our department has implemented practices to address this trigger.

Resistance to steroids has been demonstrated to be the strongest and the most consistent predictor of progression to ESRD[32]. A study by Abeyagunawardena et al. evaluated the 10-year outcomes of 66 children with SRNS and found that 90% of children who responded to therapy had renal survival, while nearly 50% of non-responders progressed to ESRD3[3]. In a multicenter international study involving French-Belgian-Swiss patients with SRNS, it was reported that 25% of patients required renal replacement therapy within 5 years and 42% within 10 years[34]. Several factors were identified to have a significant impact on the outcome, including the presence of genetic cause, histological findings of the kidney, response to immunosuppressive treatment, level of renal function impairment at the onset of nephrotic syndrome, the onset of the disease after the age of 10, and duration of follow-up. In the studies conducted by Pokrajac et al. and Özlü et al., ESRD developed in 13.6% and 7.1% of the patients, respectively[35,10]. In the current study, ESRD was observed in 2 patients (7.6%), both of whom had FSGS histology, one developing it within 5 years of diagnosis and the other within 8 years.

Before concluding, several limitations of the present study should be addressed. Firstly, it is a retrospective study conducted at a single center, which may limit the generalizability of the findings to a broader population. Multi-center studies involving diverse patient populations can provide more comprehensive insights into the disease course and outcomes. Secondly, the limited number of patients included in the study may affect the statistical power and precision of the results. A larger sample size would enhance the reliability and robustness of the findings. Thirdly, the study duration is relatively short, which may limit the ability to assess the long-term course of nephrotic syndrome and evaluate the durability of treatment responses. However, despite these limitations, our study still contributes valuable information to the existing body of knowledge on INS.

In conclusion, INS in children has a generally favorable prognosis, especially in SSNS cases where patients respond well to steroid therapy. Although relapses requiring long-term steroids are common in SSNS, these children typically have normal kidney function, and the gravity of the disease primarily relates to the side effects of the therapies required to keep the remission. On the other hand, SRNS poses a greater challenge and has a poorer outcome, with a higher risk of progression to chronic kidney disease and ESRD, potentially necessitating dialysis or transplantation. Identifying patients with SRNS who are at higher risk of morbidity and mortality can help tailor appropriate treatments and improve prognosis. Future research is needed, particularly larger-scale, multi-center studies with longer follow-up periods, to enhance the generalizability of findings and gain a deeper understanding of the long-term course of the disease. Future investigations should focus on genetic factors, histopathological findings from renal biopsies, optimized treatment approaches, management of complications, and identification of predictors for renal progression and relapse patterns to further improve patient outcomes. By addressing these areas, we can advance our knowledge and enhance the care provided to children with INS.

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